Review Article

Endovascular interventions in cancer patients with compromise of the mediastinal vasculature: a review

Steven Yevich[1]^, Nicolas Cardenas[2], Rahul Sheth[1], Joshua Kuban[1], Milan Patel[1], Ketan Shah[1], Koustav Pal[1], Stephen R. Chen[1], Alda Tam[1]

[1]Department of Interventional Radiology, Division of Diagnostic Imaging, University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Department of Radiology, University of Texas Health Science Center at Houston, Houston, TX, USA

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Correspondence to: Steven Yevich, MD, MPH. Department of Interventional Radiology, Division of Diagnostic Imaging, University of Texas MD Anderson Cancer Center, 1400 Pressler Street, FCT14.6016, Houston, TX 77030, USA. Email: syevich@mdanderson.org.

Abstract: The mediastinal vasculature can be affected by various etiologies in cancer patients. Both direct and indirect sequela of cancer may result in life-threatening clinical presentations. Tumor growth may cause vessel narrowing and decreased blood flow from either extrinsic mass effect, invasion into the vascular wall, or tumor thrombus within the lumen. In addition, cancer patients are predisposed to indirect sequela to the mediastinal vasculature from an increased risk of benign thromboembolic events, tumor thrombus, or iatrogenic complications during cancer treatments. Benign thrombus may result in partial or complete occlusion of the superior vena cava (SVC) or pulmonary artery. Vascular damage such as pseudoaneurysm or stricture may result from iatrogenic complications from radiation therapy, surgery, or other interventions. The clinical presentation of the vascular compromise is dictated by the vascular anatomical structure that is affected and the type of injury. In the appropriate clinical scenario, endovascular treatments may be pursued. These minimally invasive procedures include balloon venoplasty and angioplasty, stent placement, catheter-directed thrombolysis, embolectomy, and embolization. This review discusses the most common endovascular interventions for vascular compromise based on the great vessel affected: the SVC, pulmonary artery, pulmonary vein, bronchial arteries, or the aorta and supra-aortic arteries. Indications for treatment are discussed, with particular attention to disease etiology and clinical presentation.

Keywords: Stent; stenosis; pseudoaneurysm; embolism; thrombectomy

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Introduction

Endovascular interventions have emerged as a critical tool for treating various vascular diseases. For cancer patients, vascular compromise can occur from extrinsic or intrinsic tumor compression, tumor erosion of the vascular wall, and malignant tumor or bland thrombus. Such vascular issues can lead to a wide variety of severe symptoms and signs, which include facial swelling, cerebral edema, poor cardiac output, or bleeding, to name a few. When compared to conventional surgical options, minimally invasive interventions offer quicker recovery periods, fewer side effects, and rapid symptomatic relief.

Endovascular procedures exploit the body's preexisting vasculature to reach the mediastinum, where specialists

^ ORCID: 0000-0002-8313-7568.

use catheters in combination with other devices to provide treatment. The majority of endovascular procedures for mediastinal vascular compromise will involve treatment for vascular obstruction. Balloon dilatation, termed angioplasty or venoplasty depending on the vessel, is performed to dilate the stenotic or occluded vessel. A self-expanding stent can be placed to maintain the vessel's patency. Depending on the clinical scenario, other treatment options include cytoreduction of thrombus with catheter-directed thrombolysis, mechanical thrombectomy, or embolectomy, which are minimally invasive interventions to remove thrombus or embolus from the mediastinal vasculature. Lastly, some endovascular procedures are performed for damaged vasculature in the setting of active bleeding or concern for impending bleeding risk. For this scenario, endovascular procedures include embolization and covered stent placement.

This review aims to highlight and address the most common endovascular interventions for vascular compromise based on the vessel or site affected within the mediastinum.

Section 1: characterization and planning

When clinical symptoms suggest concern for mediastinal vascular compromise, the first step to endovascular treatment is to characterize the vessel injury with imaging (1). While two-view chest radiographs may be diagnostic, cross-sectional imaging provides additional important details that assist treatment planning. The proceduralist typically requests a contrast-enhanced computed tomography (CT) to confirm the diagnosis, assess the extent of injury, validate the necessity for intervention, and ensure that all appropriate equipment is available. If compromise of the superior vena cava (SVC), heart, or pulmonary vasculature is suspected, then a CT pulmonary embolus protocol is most helpful so as to time the contrast bolus for opacification of the SVC and pulmonary vasculature. If compromise of the aorta or supra-aortic vessels are suspected, then a CT angiogram is most helpful to time the contrast bolus for opacification of these arteries. Occasionally, contrast-enhanced magnetic resonance imaging (MRI) can be helpful to better evaluate the cardiac and aortic walls, or characterize flow dynamics. Lastly, a fluoroscopic venogram or angiogram may be performed; however with advancements in cross-sectional imaging over the last few decades, the traditional diagnostic fluoroscopic study is typically reserved for situations where cross-sectional imaging is non-diagnostic, indications for endovascular treatment are uncertain, or when the patient cannot obtain cross-sectional imaging due to rapid clinical deterioration (2). When fluoroscopic imaging is indicated, an adjunctive intravascular ultrasound can be helpful during the venogram or angiogram to help characterize and measure vascular stenosis and possibly assist in treatment (*Figure 1*) (3).

Once the affected vessel is identified, endovascular treatment selection largely depends on the nature and degree of injury (*Table 1*). At times, more than one endovascular treatment may be applied. In these situations, selecting the most appropriate treatment can be confusing if the technical considerations are not understood. One treatment might be favored over another depending on the specifics of the cancer, anticipated response of systemic or radiation therapies, patient comorbidities, or proceduralist experience. The following three comparative scenarios provide some examples of common clinical considerations when tailoring endovascular treatments.

Clinical scenarios

(I) In one comparative treatment scenario, active bleeding from tumor erosion or damage to the vascular wall can be treated with either embolization or placement of a covered stent. Embolization is highly effective for small vessel damage, such as bronchial artery injury or peripheral pulmonary artery pseudoaneurysms, as embolization provides occlusion of the injured small vessels with precise injection of particles or liquid embolic (4-7). While small and low-profile stents are manufactured and more readily available, the physical constraints of the small diameter vessel may prevent satisfactory positioning of the stent and may even increase the risk of bleeding complications after stent deployment. For large vessel damage, however, such as a central pulmonary artery or thoracic aorta pseudoaneurysm, covered stents are the main endovascular method to isolate the damaged portion of the vessel with a stent of specified diameter and length (4).

(II) In another comparative treatment scenario, vascular compression caused by an extrinsic tumor can be treated with endovascular balloon dilatation and placement of a stent or by embolization of the extrinsic tumor. If the compression of the vasculature

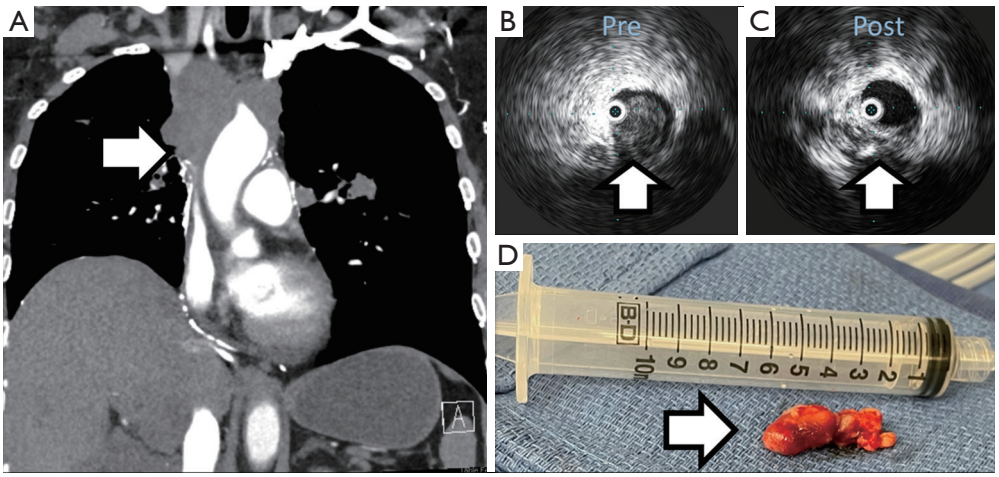

Figure 1 Contrast enhanced CT image in the coronal view demonstrates a mediastinal mass with compression of the SVC (A, arrow). Removal of the intraluminal tumor thrombus may be performed with the use of intravascular ultrasound and mechanical thrombectomy. For example, in another patient with hepatic IVC compression and concern for tumor thrombus, intravascular ultrasound images confirmed tumor thrombus within the IVC (B, arrow) and absence of the thrombus after successful endovascular mechanical thrombectomy (C, arrow). The gross specimen was consistent with tumor thrombus from the patient's known prostate cancer (D, arrow). CT, computed tomography; SVC, superior vena cava; IVC, inferior vena cava.

results in life-threatening or severe symptoms, or if the tumor is hypovascular, then embolization might not be appropriate. In this scenario, immediate symptomatic relief can be achieved with endovascular balloon dilation of the stenotic region and stent placement to provide a physical framework to prevent repeat stenosis (8). Stent placement, however, can also have drawbacks depending on the clinical presentation. Stents are generally non-retrievable once deployed and may occlude with time, both factors which might not be ideal if the extrinsic tumor is expected to decrease in size with chemotherapy or radiation, if the patient has a long life expectancy or in the setting of contradiction to the anticoagulation that is often recommended to prevent future occlusion of the stent (9-11). In these settings, the alternative treatment of tumor embolization may provide sufficient symptomatic relief, particularly if the extrinsic compressive tumor is hypervascular and hence expected to respond well to embolization, and symptoms are mild and not immediately life-threating as the symptomatic relief after embolization often requires weeks to be achieved. After embolization of the tumor arteries, patients expect to have symptomatic improvement over 2 months as the tumor volume responds to devascularization (12).

(III) In a third comparative treatment scenario, intravascular thrombus can be treated with either thrombolysis, vacuum aspiration, mechanical retrieval, or stent placement (13-16). Thrombolysis involves the injection of a potent thrombolytic agent, which might be highly effective but contraindicated in cancer patients with coagulopathy or intracranial lesions. Alternatively, vacuum retrieval of thrombus might be highly effective for acute thrombus, but less ideal for benign chronic thrombus or tumor thrombus both of which can adhere firmly to the vessel wall to the vessel wall (15,17). For benign chronic thrombus or tumor thrombus, mechanical retrieval or placement of a covered stent may be appropriate for definitive treatment (13,18,19). In consideration for stent placement, this treatment option often requires the patient to maintain lifelong anticoagulation to prevent future stent occlusion, which again might not be appropriate in contraindications to anticoagulation or long life expectancy (20).

The above three scenarios are meant to convey a general sense of the multitude of considerations that an interventionalist will weigh during triage of a patient with mediastinal vascular compromise. The access and type of treatment varies greatly based upon the type and location of injury, the injury characteristic, and patient comorbidities.

Table 1 Summary of site-based considerations and treatments

Site affected	Recommended treatments	Potential side effects
Superior vena cava	• Venoplasty and stent placement for severe symptoms or cancers unresponsive to chemotherapy and radiation	• Stent migration, tumor invasion, early post-stent thrombosis, hemoptysis
	• Removal of indwelling central line if related to vascular compromise	• Fatal complications: hemoptysis, ruptured SVC, hemopericardium, respiratory failure
	• Chemotherapy or radiation for SVCS caused by lymphoma and germ cell tumors	
Right atrium	• Endovascular retrieval of foreign bodies such as fragmented central catheters	• Permanent cardiac dysfunction, damage to cardiac valves
	• Arterial embolization for tumor thrombus extending from IVC or SVC	• Life-threatening pericardial hemorrhagic effusion
	• Covered stent placement in SVC or IVC to trap tumor embolus	• Delayed effects, as the tumor slowly revascularizes
		• Improved long-term patency but potential for tumor overgrowth of the stent
Acute thromboembolism	• Catheter-directed thrombolysis	• Major bleeding complications when thrombolytics are used
	• Catheter-directed mechanical fragmentation	
	• Thrombectomy without thrombolytics for patients with contraindications to thrombolytic agents	
Pulmonary stenosis	• Percutaneous angioplasty and stenting for patients with right ventricular dysfunction, severe pulmonary valvular regurgitation, or hemodynamic instability	• Vessel rupture, balloon rupture, and stent embolization
Pulmonary pseudoaneurysm	• Endovascular embolization with coils or liquid embolic agents; covered stent placement for more proximal locations	• High mortality due to risk for rupture; multidisciplinary precautions essential
Bronchial arteries	• Embolization with particles or metallic coils and plugs for bronchial artery injury	• High rate of bleeding recurrence, may require repeat embolization
	• Occlusive embolization for pseudoaneurysms in the mediastinal segment of the bronchial arteries	• Collateral circulation will not revascularize the aneurysm post-embolization
	• Thoracic aorta stent graft for pseudoaneurysms close to the aorta	• It is challenging to complete embolization, specific to cases near the aorta
Aorta	• Placement of a covered stent accessed via common femoral arteries. Anticoagulation post-procedure	• Stent migration, endovascular leak, arterial dissection. Need for lifelong antiplatelet therapy, which may conflict with other cancer treatments

SVCS, superior vena cava syndrome; SVC, superior vena cava; IVC, inferior vena cava.

The article has been structured based upon anatomical site of vascular compromise, as this often is the first factor that affects the treatment triage and technical approach.

Access and approach

The percutaneous access is planned once the most appropriate endovascular treatment is selected. Most endovascular treatments are performed with 5–8 French access sheaths due to their low profile and broad availability. Larger access sheaths of up to 24 French may be required for venous mechanical endovascular thrombectomy or stent placement. An assist from vascular surgery for open arterial access may be necessary to place large stents within the aorta. The location of vascular access is planned based upon the mediastinal vessel affected, any patient-specific anatomical variants, and preference of the proceduralist. Interventions in the SVC or pulmonary arteries are performed from venous access through the internal jugular, brachial, or femoral veins. Pulmonary venous interventions

are also typically performed via a transvenous approach, but may require a trans-septal cardiac puncture (21). Endovascular procedures for the aorta or supra-aortic vessels are typically performed with percutaneous access via the common femoral artery, but can also be approach via radial or brachial artery access.

Contraindications

Absolute and relative contraindications to endovascular procedures should be considered within the clinical context. Treatments are typically postponed in the event of active infection; however, exceptions are made for life-saving interventions in the event of severe vascular compromise. For instance, active hemorrhage caused by a fungal pseudoaneurysm may warrant emergent embolization. Other relative contraindications that can frequently present in cancer patients include significant thrombocytopenia or other bleeding disorders, which might warrant pre-procedure correction of bleeding diathesis with infusion of platelets, fresh frozen plasma, or packed red blood cell blood products. Typically acceptable lab parameters for venous access procedures are platelet count greater than 20,000 and an international normalized ratio (INR) below 2–3 (22). Arterial access procedures are safer for patients with a platelet count greater than 50,000 and an INR below 1.5–1.8. Finally, standard contraindications for thrombolytics apply for thromboembolism treatment with catheter-directed thrombolytic injection, including absolute contraindications for intracranial hemorrhage, cerebral neoplasm, recent stroke, and active bleeding or bleeding diathesis (23).

SVC syndrome (SVCS)

As the major draining vein of the upper body, obstruction of the SVC can lead to a constellation of symptoms known as SVCS. Until 50 years ago, infectious diseases such as syphilis and tuberculosis accounted for the majority of SVCS. With advancements in the prevention and treatment of these infectious etiologies over the last few decades, most SVCS today result from iatrogenic factors and cancer. Approximately 40% of SVCS cases are caused by thrombosis or stenosis secondary to central venous catheters and other medical devices, while malignant tumors are the cause of the majority of the remaining 60% of cases (24).

In cancer patients, SVCS can be caused by external tumor compression, direct tumor invasion, tumor thrombosis, benign thrombosis, or iatrogenic lines and devices. The most common malignant causes for SVCS are non-small cell lung cancer (NSCLC; 50%), small-cell lung cancer (SCLC; 25%), non-Hodgkin's lymphoma (NHL; 12%), metastases (9%), germ-cell tumor (3%), thymoma (2%), mesothelioma (1%), and other cancers (1%) (12,25-27).

Compression of the SVC leads to decreased venous return to the heart and resultant increased venous pressure in the upper torso. The severity of symptoms is directly related to the degree of venous obstruction and inversely related to the presence of venous collaterals (18,28,29). If the compression occurs gradually, collateral veins may redirect venous return to the heart, and symptoms may be limited to mild swelling and distended subcutaneous vessels in the upper torso, upper extremities, and neck that may be partially or completely relieved with inclined or upright positioning. If the collateral circulation cannot compensate for the obstruction or if SVC obstruction is rapid in onset, the patient may experience debilitating and potentially life-threatening sequela.

The constellation of clinical symptoms associated with SVCS can initially include upper extremity and facial swelling but, in more severe cases, may progress to include cyanosis, plethora, or functional compromise of the larynx and pharynx that manifests as cough, hoarseness, dysphagia, stridor, and respiratory distress. In severe cases, cerebral edema may lead to headaches, visual disturbances, and altered mental status. Although the presentation of severe SVCS can be striking and debilitating, most cases are not fatal. Ahmann *et al.* documented only one death in 1986 patients with SVCS (19). Patients tend to develop symptoms over two weeks or longer, which can afford time to receive treatment.

The multidisciplinary approach to SVCS is tailored based on the etiology of the obstruction and the patient's clinical presentation. A clinical exam identifies the urgency for intervention and allows the provider to track the progression of clinical symptoms. Cross-sectional imaging is important to identify the etiology of disease. Optimally, CT or MRI is performed with contrast. A fluoroscopic venogram can be performed for definitive diagnosis and also allows for measurement of blood flow gradients across the stenosis and treatment planning.

Various classification schemes have been advanced to help guide the clinical discussion for endovascular intervention. Some of these classification systems rely upon imaging findings. For example, the Stanford and Doty classification system stratifies patients based on the degree

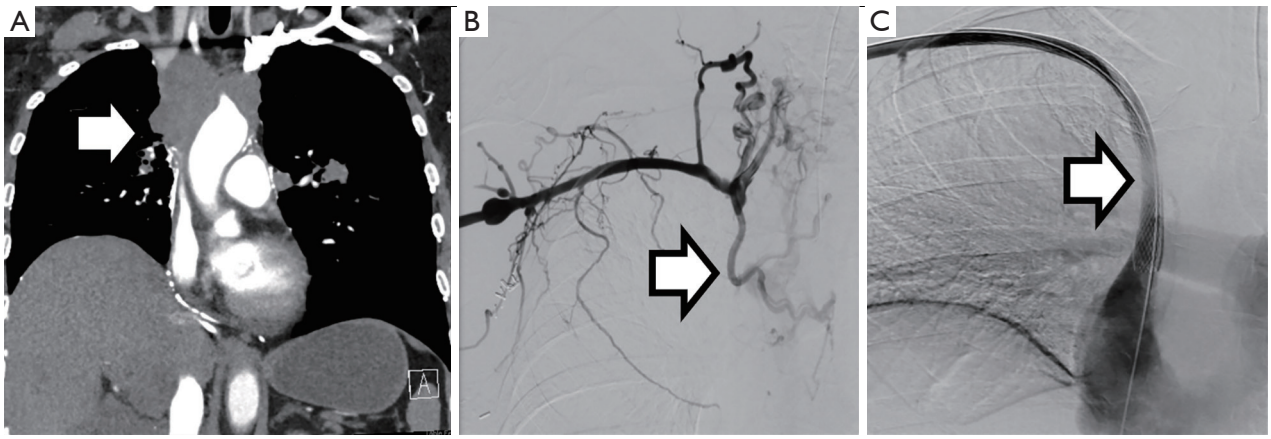

Figure 2 A 61-year-old woman with lung adenocarcinoma. A mediastinal metastasis caused compression upon the SVC (A, arrow) that was initially planned to be treated with radiation therapy. Unfortunately, the patient developed worsening headaches, shortness of breath, and dysphasia that were all exacerbated when the patient reclined. A venogram performed from the right upper extremity confirmed complete occlusion of the SVC with minimal collateral venous development (B, arrow). The obstruction was crossed with an endovascular catheter and a non-covered stent was placed across the SVC to improve venous return to the heart (C, arrow). The patient's symptoms improved overnight. SVC, superior vena cava.

of SVC obstruction and flow within the azygous vein (30). Most recommendations, however, focus predominantly on the clinical presentation to guide the indication for endovascular treatment, while radiologic imaging provides invaluable information to identify the etiology of the stenosis and assist the proceduralist in treatment planning.

Several causes for symptomatic SVCS might not warrant endovascular intervention. If the vascular compromise is related to an indwelling central line, this offending device can be removed to improve venous flow (31,32). If a mediastinal or lung tumor is the cause for SVCS compression, then biopsy is critical for triage as the underlying malignancy plays a large part in identifying the optimal treatment plan. For example, in patients with SVCS caused by lymphoma and germ cell tumors, SVCS is often relieved with chemotherapy or radiation alone (18). It is important to note that the initial clinical response to chemotherapy or radiation therapy does not obviate the need for endovascular procedures in the future. In patients with SVCS treated with chemotherapy, radiation, or both, approximately 20% can have symptomatic recurrence (33).

Endovascular intervention for SVCS includes venoplasty and stent placement. Stent placement is indicated for thrombus in the case of severe acute symptoms such as respiratory compromise or altered mental status (*Figure 2*) (1). Stent placement is also indicated to treat symptomatic SVCS caused by cancers such as mesothelioma that are known to not respond well to chemotherapy and radiation (34). Balloon venoplasty is typically performed during stent placement rather than as a standalone treatment. Venoplasty alone can be insufficient to provide long-term patency to a vessel, particularly if tumor compression is the etiology for SVCS, as continued tumor growth can overcome the temporary effects of venoplasty. Conversely, venoplasty may be attempted as a first-line measure in focal or short-segment stenosis from a prior central line (35). In addition, venoplasty alone might be preferred in patients who are not good candidates for anticoagulation or those with long life expectancy, as stent deployment often necessitates life-long anticoagulation to prevent future thrombosis and occlusion.

Stenting for SVCS with life-threatening symptoms has been well documented to have good immediate and long-term effectiveness and a low complication rate. In a review of 44 studies with a total of 1,437 patients, Léon *et al.* found immediate clinical effectiveness within 48–72 hours of 90.50% (95% CI: 88.86–91.97%) (24). Symptomatic recurrences occurred in 11%, of which 78% were successfully treated with repeat intravascular intervention. The non-fatal complication rate was 8.28% (95% CI: 6.91–9.83%), which consisted of stent migration (18.80%), tumor invasion of the stent (13.68%), early post-stent thrombosis (10.26%), and hemoptysis (7.69%). The overall fatal complication rate was 1.46% (95% CI: 0.91–2.23%), nearly all occurring immediately or within 24 hours

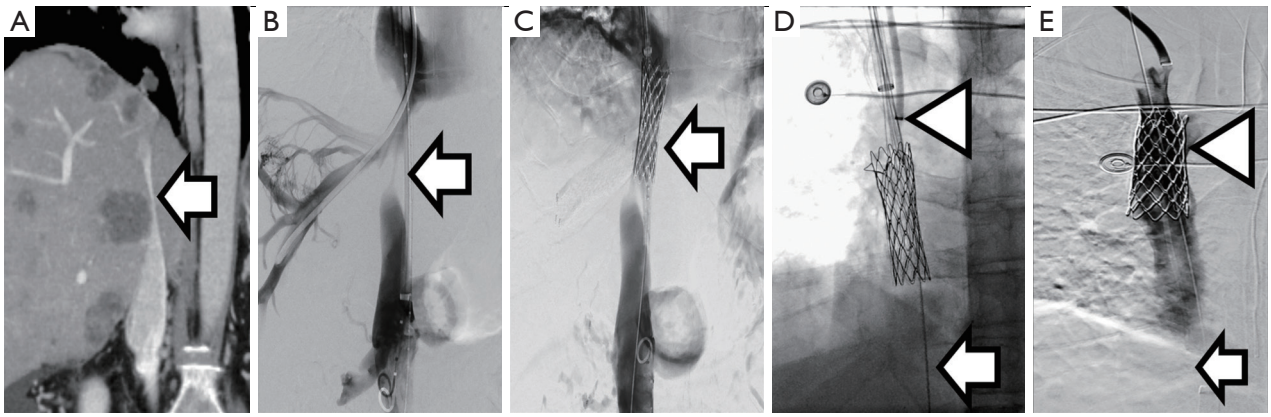

Figure 3 A 59-year-old man with history of metastatic rectal cancer presented with severe stenosis of the IVC due to liver metastasis (A, arrow), which resulted in recurrent high volume ascites despite multiple paracenteses. Simultaneous venograms through catheters in the IVC and the right middle hepatic vein redemonstrated the stenosis (B, arrow). A metallic stent was placed at the location of stenosis (C, arrow). Unfortunately, the metallic stent migrated to the right atrium. The stent was retrieved with snares from an internal jugular approach (D, arrow maintains location of IVC stenosis comparable to prior imaging, while the arrowhead identifies snare capture of the stent). The stent could not be removed through a sheath, and was instead safely deployed in the SVC (E, arrow maintains location of IVC stenosis, while the arrowhead identifies stent deployed in SVC). IVC, inferior vena cava; SVC, superior vena cava.

post-intervention. The most common fatal complications included hemoptysis (19.05%), ruptured SVC (19.05%), hemopericardium (9.25%), and respiratory failure (9.52%).

Right atrium

Cancer patients can present with pathology that extends or propagates from the SVC or inferior vena cava (IVC) into the right atrium. For example, iatrogenic devices such as fragmented central catheters or thromboembolic filters may migrate from the SVC or IVC (36). Similarly, tumor thrombus may extend from the SVC or IVC into the right atrium (37). Yet again, cross-sectional imaging is helpful for the diagnosis of the pathology and to ascertain the presence of damage to the cardiac wall or pericardial effusion. A transthoracic or transesophageal echocardiogram can be obtained to identify the impact on cardiac function and characterize flow dynamics.

Foreign bodies within the heart can be treated with endovascular retrieval (*Figure 3*). The indications and risks are determined based on the foreign body material composition, size, and shape. Fragments of central catheters are generally easily removed under fluoroscopic guidance via access through the internal jugular or femoral veins (38). Attempts to retrieve metallic objects can be more challenging, and a multidisciplinary discussion that includes representatives from surgery and cardiology is recommended. During the retrieval of metallic objects, damage to the cardiac valves or wall may result in permanent cardiac dysfunction or life-threatening hemorrhagic pericardial effusion.

Tumor thrombus may extend from the IVC or SVC into the right atrium, compromising venous return to the heart and potentially resulting in tumor emboli to the pulmonary artery or lung parenchyma. The most common tumor emboli originate from renal cell carcoma and hepatocelluar carcinoma extension into the IVC (39). Treatment of the tumor thrombus can be approached through three different mechanisms. The tumor can be embolized, with resultant decrease in the size and extent of the tumor and the associated tumor thrombus. Alternatively, stent deployment can be used to trap the tumor between the stent and the vessel wall (IVC *vs.* SVC). Lastly, mechanical thrombectomy can be used to aspirate or snare any residual uncontained tumor. Arterial embolization can be performed with selective, catheter-directed injection of small particles or liquid embolic into the arteries supplying the tumor (40). The treatment effects are typically realized up to 2 months after embolization, as the tumor slowly responds to devascularization. Embolization can be performed as an adjunctive therapy before surgical resection or as a standalone treatment when surgery is contraindicated. Placement of a covered stent of a covered stent into the SVC or IVC may be undertaken to trap the tumor embolus

along the vascular wall, effectively decreasing obstruction and mitigating the risk for embolization to the atrium and pulmonary arteries. When placed within vessels compromised by tumors, covered stents have been suggested for improved long-term patency at 3, 6, and 12 months compared to uncovered stents due to decreased tumor overgrowth of the stent (41).

Acute pulmonary artery embolism

In the United States, venous thromboembolism with pulmonary embolism (PE) is estimated to result in 150,000–250,000 hospitalizations and 60,000–100,000 deaths yearly (42). Non-endovascular treatments include systemic anticoagulation, peripheral thrombolysis, surgical embolectomy, and mechanical circulatory support. The endovascular interventions are catheter-directed thrombolysis and catheter embolectomy (43). Triage within a multidisciplinary group setting is recommended to provide the most appropriate therapy depending on the patient's symptoms, cardiac strain, and contradictions to anticoagulation such as thrombocytopenia, recent surgery, or brain metastases (44).

Catheter-directed thrombolysis for pulmonary artery thromboembolism is performed by inserting a 4–6 French catheter via the right atrium and ventricle into the pulmonary artery (*Figure 4*). The thrombolytic agent is thus delivered directly into the embolus. Most commonly, tissue plasminogen activator is infused at a rate of 0.5–1.0 mg/hour for a total dose of 12–24 mg over a 12–24 hour infusion. Catheter-directed mechanical fragmentation or thrombectomy can be performed immediately before or after catheter-directed thrombolysis (*Figure 5*) (45). Fragmentation is performed by mechanical agitation of a major thrombus in the main pulmonary arteries using a catheter or wire. It is typically followed by attempts to quickly push the fragmented small clots from the main pulmonary artery into distal segmental branches to restore blood flow through the larger mainstem pulmonary artery and decrease right heart strain. Thrombectomy typically involves a larger diameter catheter (8–24 French), with either vacuum aspiration and/or nitinol metallic discs that capture the clot to allow mechanical retrieval (46,47). Thrombectomy can be performed without thrombolytics, which provides a means to treat patients with contraindications to thrombolytic agents.

Clinical outcomes for catheter-directed PE treatment vary based on clinical presentation, underlying patient factors, and technique employed. In a multicenter study that treated 101 patients with massive or submassive PE, clinical success as defined by stabilization of hemodynamics, improvement in pulmonary hypertension or right heart strain, and survival to hospital discharge was achieved in 86% and 97%, respectively (48). Notably, patients with massive PE were treated with the addition and combination of catheter-directed fragmentation and aspiration immediately before and after catheter-directed infusion. In a multicenter registry with 137 patients and a meta-analysis with 860, the catheter-directed thrombolysis complication rate included intracerebral hemorrhage in 1.5% and 0.35%, respectively and major complications in 9.4% and 4.65%, respectively. Major complications included fatality, intracranial hemorrhage, and any bleeding that required transfusion or surgical repair (49). Lastly, the use of ultrasound-accelerated thrombolysis has been pursued as a potential means to improve outcomes with some suggestions of similar treatment efficacy with reduced thrombolytic infusion time and treatment-related complications (50).

Pulmonary artery stenosis (PAS)

PAS is primarily seen in children with congenital heart disease but has been reported in adults. Rarely, mediastinal tumors cause extrinsic compression of the pulmonary arteries to produce hemodynamically significant obstruction. Teratomas and Hodgkin's disease are the most common causes of extrinsic pulmonary artery compression in cancer patients (51). Additional causes for PAS include inflammatory processes such as Takayasu arteritis and Behcet disease, mediastinal fibrosis (most commonly seen after Histoplasma infection) and chronic thromboembolism (52,53). Clinical manifestations are often nonspecific and include chest pain and dyspnea. Cross-sectional imaging with contrast-enhanced CT or MRI often provides a definitive diagnosis. Transthoracic echocardiogram (TTE) can provide a useful non-invasive modality to measure blood velocity within the pulmonary arteries. A pulmonary angiogram with pressure measurements can also be pursued for a definitive diagnosis if cross sectional imaging is inconclusive (54).

Due to very limited data, the decision to treat PAS with an endovascular approach should be made on a case-by-case basis. Percutaneous angioplasty and stenting can be considered in patients with severe PAS that results in right ventricular dysfunction, severe pulmonary valvular regurgitation, or hemodynamic instability (55). In these

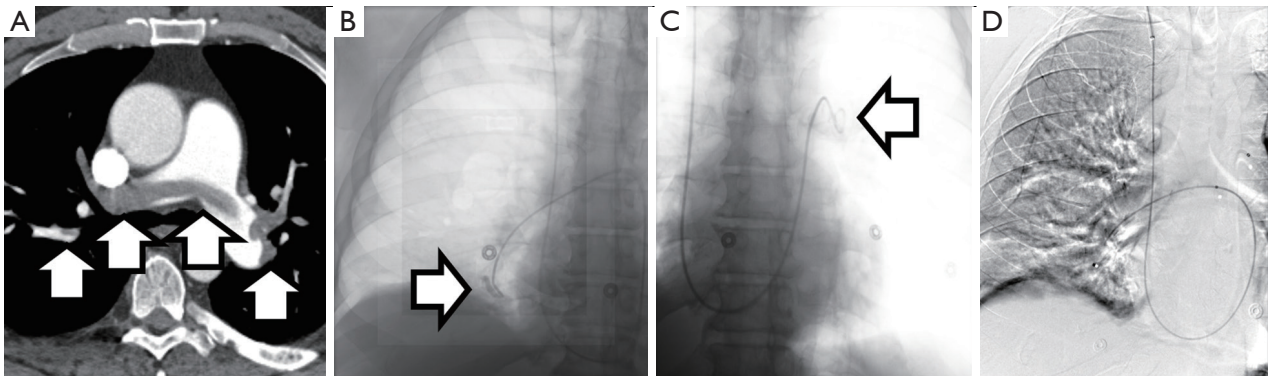

Figure 4 A 60-year-old man with multiple myeloma presented with bilateral pulmonary embolus in the mainstem and segmental branches (A, arrows). Endovascular access was performed via right internal jugular access. Pulmonary artery pressures were 70/22 mmHg with mean of 37 mmHg (B and C, arrows designate right and left pulmonary artery catheters respectively). Overnight infusion of tissue plasminogen activator via both catheters provided symptomatic relieve, decreased thrombus burden on subsequent pulmonary angiogram the next afternoon (D), and decreased pulmonary artery pressures to 51/22 mmHg with mean of 33 mmHg.

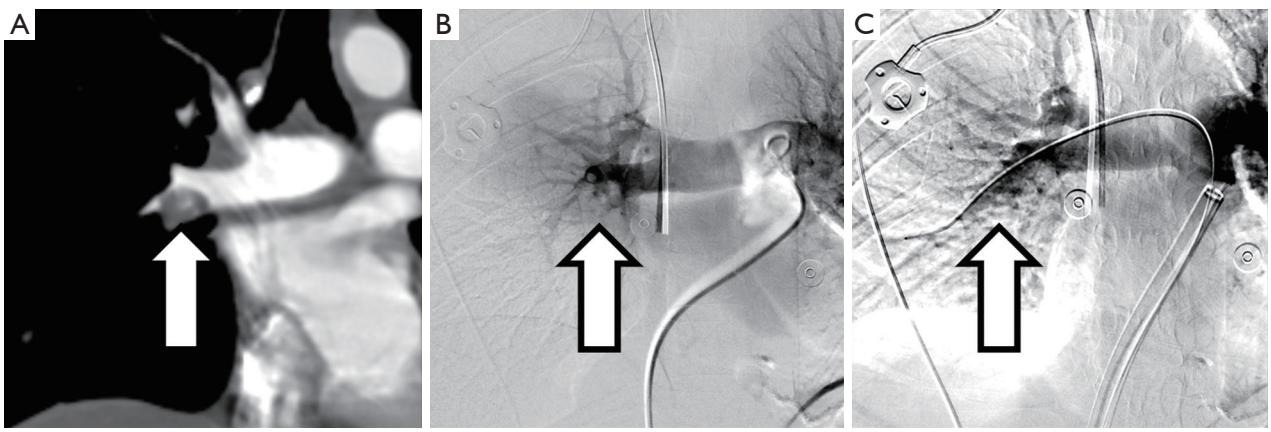

Figure 5 A 46-year-old woman with history of metastatic colon cancer presented with bilateral segmental pulmonary emboli within the lower lobes, greater in the right (A, arrow). She was determined to be a high-intermediate risk with tachycardia, elevated troponin-T and BNP, and enlarged right ventricle on CT-angiogram. Catheter directed angiogram confirmed absence of blood flow to the bilateral lower lobes (B, arrow demonstrates right segmental artery cut off) and main pulmonary artery pressure measured 25 mmHg. Mechanical thrombectomy was performed bilaterally with restoration of the blood flow (C, arrow demonstrated reconstituted right pulmonary artery). BNP, b-type natriuretic peptide; CT, computed tomography.

patients, stenting provides rapid symptom relief compared to radiation and chemotherapy. Gutzeit *et al.* describe a case of NSCLC-causing PAS that manifested as severe shortness of breath and orthopnea (56). Angioplasty and stenting of the pulmonary artery resulted in immediate improvement of symptoms. Similarly, Fierro-Renoy *et al.* describe a case of bilateral PAS in a patient with NSCLC who was treated with bilateral angioplasty and stenting, resulting in the resolution of symptoms (55). Two additional case reports by Hirota *et al.* and Meckel *et al.* describe similar clinical scenarios with successful pulmonary artery stenting in right-sided heart failure due to malignant pulmonary artery obstruction (57,58).

Pulmonary artery pseudoaneurysm

A pulmonary artery pseudoaneurysm can develop in cancer patients as a sequela of prior treatments, including

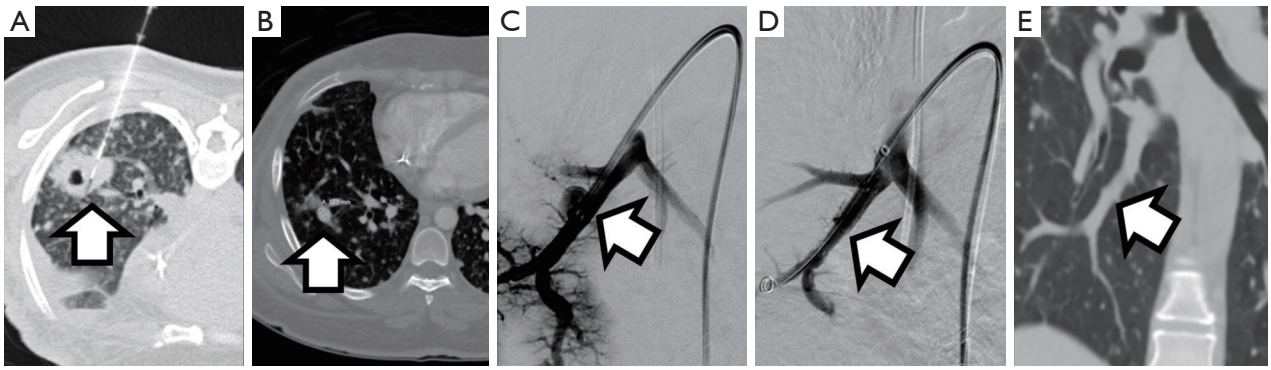

Figure 6 A 28-year-old woman with a cavitary right lower lobe lung lesion that was biopsied at an outside hospital (A, arrow). Approximately 3 months after the biopsy, the patient presented with progressively worsening shortness of breath and chest imaging confirmed pneumonia. An incidental finding of a pseudoaneurysm was noted in the right lower lobe (B, arrow), which was likely a complication of the prior biopsy. After completion of antibiotics and resolution of pneumonia, the patient presented for endovascular treatment given the risk for life-threatening bleeding if the pseudoaneurysm were to rupture. A selective angiogram in the right lower lobe pulmonary artery demonstrated the pseudoaneurysm arose from the basilar segmental branch and contained a large neck (C, arrow). A covered stent was placed across the pseudoaneurysm to provide complete occlusion of the pseudoaneurysm while maintaining distal patency of the artery (D, arrow). A follow up CT scan 6 years later confirms complete resolution of the pseudoaneurysm and persistent patency of the stent (E, arrow). CT, computed tomography.

cardiac catheterization, surgery, radiation therapy, or percutaneous lung biopsy and ablation (59-63). In addition, pseudoaneurysms in the pulmonary artery may arise in immune-compromised cancer patients with fungal or tuberculosis lung infections, termed Rasmussen aneurysms.

Pseudoaneurysms are associated with a high mortality rate due to the potential to rupture and cause massive hemoptysis. The patient may present clinically with new or intermittent hemoptysis or asymptomatic with an incidental imaging finding. Cross-sectional contrast-enhanced CT is diagnostic; however, pulmonary arteriography may identify pseudoaneurysms not well seen on cross-sectional imaging (64).

Endovascular treatment options include embolization with coils or liquid embolic agents and covered stent placement. While embolization is often the most convenient and safest treatment option, particularly for pseudoaneurysms in distal pulmonary artery segments, stent placement may be pursued for more proximal locations to preserve distal pulmonary artery perfusion (*Figure 6*). A high mortality rate is reported due to the high risk for rupture of the pseudoaneurysm during instrumentation (65). Multidisciplinary precautions should be coordinated between the proceduralist, anesthesiology, and thoracic surgery. In the event that endovascular access is challenging and deemed too high a risk, then pseudoaneurysms in distal segments can also be treated with injection of an embolic agent via a CT-guided percutaneous access (66).

Pulmonary vein stenosis (PVS)

PVS is a rare entity that primarily occurs in young children with congenital heart disease. Malignant causes are rare, but have been reported for bronchogenic carcinoma, esophageal tumors, lymphoma, and metastases (67). Non-malignant etiologies can also present in cancer patients, such post-radiation damage or from inflammatory and infectious causes such as fibrosing mediastinitis, sarcoidosis, or tuberculosis. Iatrogenic causes have also been documented from cardiology radiofrequency ablation procedures to treat atrial fibrillation (68,69).

Patients with PVS present with shortness of breath and radiographic evidence of localized pulmonary edema. Delayed diagnosis is common as the symptoms and radiographic findings are similar to those seen with pneumonia or cardiac disease. Cross-sectional imaging with contrast-enhanced CT or MRI can provide the definitive diagnosis and characterize the degree of vascular compromise. Normal pulmonary vein diameter is 10–15 mm. For symptoms of PVS to manifest, compression of the vessel diameter to 4–6 mm, or 60% vessel narrowing, is often necessary (68). When the diagnosis is uncertain, a pulmonary artery wedge angiography can be pursued for

definitive diagnosis.

Although PVS is rare and data is limited, percutaneous angioplasty and stenting via trans-septal puncture has been pursued for acute symptomatic relief. In 34 patients with a benign etiology of PVS, balloon venoplasty alone provided immediate symptomatic relieve in 42%, while the combination of venoplasty and stenting provided acute symptomatic relief in 95% (70). The rate of re-stenosis has been reported between 33–72% and depends on the etiology of the stenosis, reference diameter of the pulmonary vein, and initial stent diameter. Complication rates range from 0–25% and include pulmonary vein perforation, stent dislodgment, hemoptysis, pulmonary hemorrhage, ST-elevation, and transient neurological deficits (71). In a series of 98 patients requiring 145 catheterizations, only two vein perforations and one stent dislodgement were reported (68). While the predominant experience with PVS stenting has been performed in patients with non-cancerous etiology, this endovascular option can be pursued in cancer patients in the appropriate clinical setting.

Bronchial arteries

Bronchial artery damage in cancer patients can result in hemorrhage into the mediastinum, lung parenchyma, or pleura. Patients can present with hemoptysis, chest pain, dyspnea, and fatigue. Both primary lung and metastatic tumors can precipitate this injury (72-74). In addition, bronchial artery injury can be the sequela of fungal or microbacterial infection in immunocompromised cancer patient, or a result of cancer related therapy including radiation therapy, surgery, or percutaneous ablation (75,76). Cross-sectional imaging with CT can help localize the pathology, although an angiogram may be necessary for definitive diagnosis due to the small caliber of the bronchial arteries. The endovascular treatment of bronchial artery injury is embolization with either particles or metallic coils and plugs. The immediate success rate is high, albeit recurrence of bleeding is common and repeat embolization may be required. In 21 cancer patients treated with bronchial artery embolization, immediate bleeding control was achieved in 96%, but the median time to recurrence of bleeding was 66 days, and recurrence-free survival was 34% after 1 year (77).

Vascular erosion or pseudoaneurysm of the bronchial arteries occurs most commonly within the lung parenchyma. Endovascular treatment with embolization can be performed with selective injection of small particles for partial to complete occlusion of the artery. Bleeding typically resolves immediately after embolization, although the patient may continue to have some hemoptysis for days after the procedure as the blood that accumulated before the embolization is cleared from the lung parenchyma. Embolization can also provide secondary benefits if a tumor caused the bronchial artery injury, as embolization can result in tumor necrosis (74,78). In rare situations, embolization of a distal pseudoaneurysm may not be possible due to the anatomy and distortion from a lung tumor. In these cases, percutaneous embolization under CT guidance or a combination of fluoroscopic and US guidance may be attempted (79).

Pseudoaneurysms in the mediastinal segment of the bronchial arteries can be treated with occlusive embolization. Typically, metallic coils or plugs are used to completely occlude the arterial component distal to and proximal to the pseudoaneurysm. Thus, collateral circulation that develops after embolization will not revascularize the aneurysm from the distal arterial component. Rarely, the pseudoaneurysm is located within the mediastinum in close proximity to the aorta. In this case, complete embolization may be challenging, and a thoracic aorta stent graft may be necessary to occlude the arterial flow to the pseudoaneurysm completely (62,80).

Aorta and supra-aortic arteries

Damage to the aorta or supra-aortic vessels can present in various mechanisms in cancer patents. Unlike for venous structures, extrinsic tumor growth does not typically cause compression of large diameter arteries in the mediastinum. Tumor expansion between the supra-aortic vessels can displace these vessels, which may present as imaging abnormalities. While the tumors themselves might not directly damage the supra-aortic arteries, cancer treatments such as radiation or surgery can result in arterial or cardiac valvular damage (81). Although rare, tumor invasion can result in pseudoaneurysm development, as seen in a lung cancer erosion case report into the aortic arch (7). Pseudoaneurysms can also be caused by fungal or mycobacterial infections, which are not uncommon in immunocompromised cancer patients. Historically, these patients were treated surgically, but there is growing evidence that endovascular treatments provide a minimally invasive treatment alternative (82).

Endovascular treatment of arterial pathology in the aorta and supra-aortic vessels is predominantly performed with the placement of a covered stent. Arterial access is typically

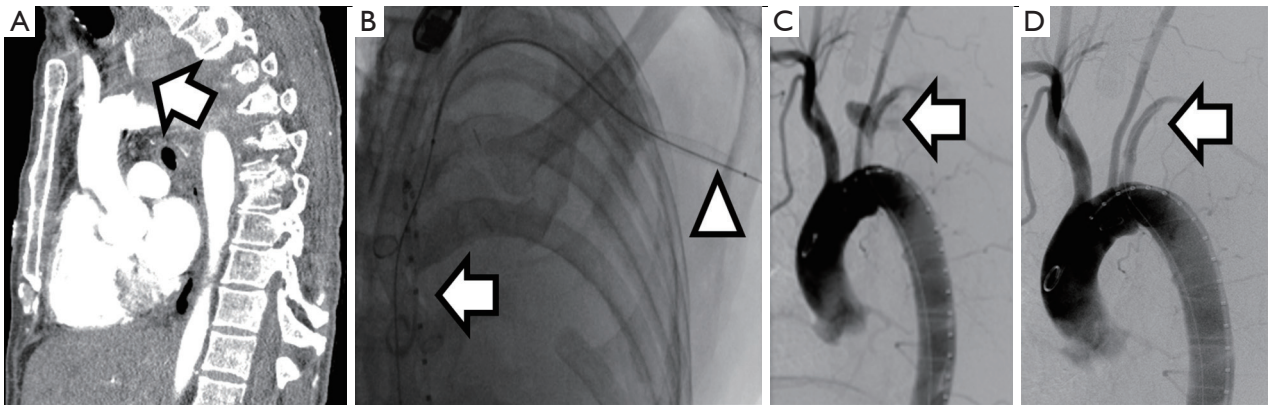

Figure 7 A 60-year-old man with epithelioid malignant mesothelioma status post left pleurectomy decortication, resection of the diaphragm, and posterior mediastinal lymph node dissection with adjuvant radiation to the left hemithorax. The patient presents to the emergency room with large volume hemoptysis, left shoulder pain, and left upper extremity pallor and numbness. A CT demonstrated a pseudoaneurysm in the left subclavian artery with bronchial fistula and pleural cutaneous fistula (A, arrow identifies pseudoaneurysm with adjacent mediastinal and parenchymal hematoma). Arterial access was achieved via both a femoral and left brachial access (B, arrow and arrowhead respectively). Angiograms through the bilateral accesses confirmed and further characterized the pseudoaneurysm (C, arrow). A stent was successfully placed via the left brachial artery access, with occlusion of the pseudoaneurysm and reconstitution of blood flow (D, arrow). CT, computed tomography.

obtained via the common femoral arteries. An open surgical access to the common femoral arteries was traditionally necessary to advance the thoracic aorta stents. Percutaneous access has evolved with new closure devices that can facilitate stent advancement to a certain size without open surgical access (83). Injury or stenosis in the supra-aortic arteries can also be approached through brachial or radial artery access in certain situations, again depending upon the size of the stent required (*Figure 7*) (84).

Stent deployment for the aorta or supra-aortic arteries is performed under fluoroscopy, similar to stent deployment in other vascular locations. For complex aortic arch treatment, intra-procedural cross-sectional imaging can be used for additional information to confirm successful stent deployment (85). Complications include stent migration, endovascular leak, and arterial dissection (86). After stent placement, recommendations include anticoagulation with dual antiplatelet medications for several weeks to months and typically at least one antiplatelet lifelong (87,88). This need for anticoagulation is an important consideration when planning stent placement in cancer patients who might develop intracranial metastases or bleeding diathesis from tumor growth or systemic treatments in the near future. Follow-up with contrast-enhanced CT, MRI, or duplex ultrasound is routinely scheduled to monitor for endovascular leaks around the stent (88,89).

Conclusions

Compromise of mediastinal vasculature in cancer patients can be caused by a myriad of etiologies, including extrinsic tumor compression, erosion of the vascular wall, benign or malignant thrombus, and iatrogenic injury. While this review is comprehensive, the current level of evidence for the described treatment outcomes is limited due to the lack of large cohort studies or randomized control studies, data heterogeneity necessary to achieve high levels of literature evidence. This is perhaps due to the relative rarity of various disease processes affecting the mediastinum and the relative novel and burgeoning field of endovascular and interventional radiology. Furthermore, patients present with marked clinical variety based on the location, type, and degree of vascular injury. The decision for endovascular treatment is best pursued with a multidisciplinary discussion to tailor the treatment for the patient's presenting symptoms, comorbidities, and future cancer treatment considerations.

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Footnote

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Review Article

Benign disorders of the mediastinum: a narrative review

Saad Farooq[1], Sabiha Armin[2], Daniel Ocazionez[3], Rosa M. Estrada-Y-Martin[1], Sujith V. Cherian[1]^

[1]Divisions of Critical Care, Pulmonary and Sleep Medicine, Department of Internal Medicine, McGovern Medical School, The University of Texas Health Science Center (UTHealth), Houston, TX, USA; [2]Department of Internal Medicine, McGovern Medical School, The University of Texas Health Science Center (UTHealth), Houston, TX, USA; [3]Department of Diagnostic and Interventional Radiology, McGovern Medical School, The University of Texas Health Science Center (UTHealth), Houston, TX, USA

Contributions: (I) Conception and design: S Farooq, S Armin, RM Estrada-Y-Martin, SV Cherian; (II) Administrative support: SV Cherian, D Ocazionez, RM Estrada-Y-Martin; (III) Provision of study materials or patients: D Ocazionez, RM Estrada-Y-Martin, SV Cherian; (IV) Collection and assembly of data: S Farooq, S Armin, SV Cherian; (V) Data analysis and interpretation: S Farooq, SV Cherian, RM Estrada-Y-Martin; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Sujith V. Cherian, MD, FCCP. Divisions of Critical Care, Pulmonary and Sleep Medicine, Department of Internal Medicine, McGovern Medical School, The University of Texas Health Science Center (UTHealth), 6431 Fannin Street, Houston, TX 77030, USA. Email: sujithvcherian@gmail.com; sujith.v.cherian@uth.tmc.edu.

Background and Objective: There are several benign processes that affect the mediastinum with considerable morbidity that may range from reactive entities to neoplastic disorders. This review article will focus on non-neoplastic benign mediastinal diseases which include large vessel vasculitis such as Takayasu and giant cell arteritis, mediastinal granulomas, fibrosing mediastinitis and mediastinal infections. These diseases can cause significant morbidity and mortality; therefore, we aim to familiarize readers with the pathophysiology, epidemiology and diagnosis of these mediastinal diseases and provide an update on the treatment options available.

Methods: We searched various databases such as PubMed and Google Scholar from August 2023 until January 2024 for the various benign mediastinal disorders we wanted to discuss. Relevant articles that were written in English were shortlisted and used to help write this narrative review.

Key Content and Findings: We will briefly discuss the anatomy of the mediastinum along with some of the more common benign mediastinal disorders. We will discuss epidemiology, etiology, clinical features, and treatment. Relevant laboratory, and imaging findings important to make the diagnosis will be included as well.

Conclusions: Prompt diagnosis of these diseases is of the utmost importance as delay in care may be associated with increased mortality. Our article aims to provide an up-to-date review and summarize the current literature regarding these diseases.

Keywords: Mediastinum; vasculitis; infection; mediastinitis

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Introduction

The mediastinum is the central part of the thoracic cavity bounded by the sternum anteriorly, the pleurae laterally and the thoracic vertebral spine posteriorly. It contains several vital structures including the pericardium, heart, aorta, trachea, esophagus, and the thoracic duct which may all be affected by different diseases (1,2). For the purposes of this article, we focus on causes of mediastinitis, granulomas and

^ ORCID: 0000-0003-0177-9979.

Table 1 The search strategy summary

Items	Specification
Date of search	08-2023 till 01-2024
Databases and other sources searched	PubMed, Google Scholar
Search terms used	Mediastinitis; benign mediastinal disorders vasculitis
Timeframe	1980–2023
Inclusion criteria	English only
Selection process	Independently. All selected articles were reviewed by all authors

vasculitides that involve the structures in the mediastinum.

The main blood vessels contained within the mediastinum include the aorta, superior and inferior vena cava, and pulmonary arteries (1). Involvement of these vessels often occurs due to vasculitides which results in inflammation of the vessel wall and may cause perfusion to vital structures. Giant cell and Takayasu arteritis (TA) are the main vasculitides affecting large vessels. While some of these processes are not clinically apparent and may be found incidentally on imaging, others are found when patients present with symptoms secondary to mass effect. We present this article in accordance with the Narrative Review reporting checklist (available at https://med.amegroups.com/article/view/10.21037/med-24-14/rc).

Methods

We conducted a comprehensive literature review of relevant articles on databases such as PubMed and Google Scholar that were written in English. The literature review was conducted from August 2023 until January 2024. The articles were shortlisted by the authors and used to help write this review (*Table 1*).

Vasculitides

Takayasu and giant cell arteritis (GCA)

TA and GCA are both large vessel vasculitides that can affect the aorta and its major branches. Inflammation can lead to loss of vascular wall integrity and cause bleeding, ischemia, and thrombosis (3).

TA was first described in 1908 by a Japanese ophthalmologist (4). It is also described as a pulse-less disease due to the absence of radial pulse in some patients. It is the most common vasculitis to affect the aorta in patients under the age of 50 years. The inflammation may be limited to a particular part of the vessel, or it may be diffuse (4). Other arteries that may be involved include the coronaries, pulmonary and renal arteries which can lead to vascular aneurysms, thrombosis, wall rupture, dissection, and obstruction of the vascular lumen (5).

GCA (also called Hortons disease) is the most common primary systemic vasculitis which can affect both extra or intra-cranial vessels (6). The similarities between these two large vessel vasculitides have led some to question whether they represent varying phenotypes within the same spectrum of disease (7).

Epidemiology

TA is predominantly seen in young women of reproductive age and mainly in Asian countries such as Japan. It is nine times more common in females than males (8). Although data on incidence in the United States (US) is limited, it is estimated to effect 0.9 people per million but there is considerable heterogeneity between different populations (9).

On the other hand, GCA affects older population, usually more than 50 years of age. Peak incidence is typically in the 7th decade of life. Northern Europeans and women are more commonly affected. In the US, GCA is the most frequent primary vasculitis with an incidence of 18/100,000 in one study (10).

Etiology

It is unclear what exactly causes TA and GCA and what the initial triggering event is. Vascular injury occurs primarily by cell mediated mechanisms. A genetic association with human leukocyte antigen (HLA) alleles has been reported and specific HLA alleles may be associated with more severe forms of the disease (11). It is believed that cell-mediated

Table 2 Classification criteria for Takayasu arteritis [modified with permission from the reference (13)]

Takayasu arteritis classification criteria	Points
Clinical criteria	
Arm or leg claudication	2
Reduced pulse in upper extremity	2
Ischemic cardiac pain or angina	2
Female gender	1
Vascular bruit	2
Carotid artery abnormality	2
Difference of ≥20 mmHg in systolic blood pressure	1
Imaging criteria	
Systemic involvement of paired arteries	1
Abdominal aorta involvement with renal and mesenteric artery involvement	3
One arterial territory involved	1
Two territories involved	2
Three arterial territories involved	3

Absolute requirements: (I) age ≤60 years at the time of diagnosis; (II) evidence of vasculitis on imaging. Score ≥5 is needed for the diagnosis of Takayasu arteritis.

mechanisms cause an inflammatory process that involves the aorta and its major branches and lead to vascular damage, fibrosis, and scarring (10).

Under microscopic examination, cytotoxic T lymphocytes which cause vascular injury by releasing various cytokines are observed. The inflammatory pattern is granulomatous and giant cells along with well-formed granulomas containing clusters of activated macrophages may be seen in some patients (5).

Severe adventitial scarring may be seen in TA whereas in GCA inflammation is most severe in the inner media of blood vessels and adventitia is relatively spared. Intimal hyperplasia may be present as well. In GCA, compact granulomas are usually absent whereas giant cells and epithelioid macrophages may be seen. Furthermore, vascular smooth muscle and elastic fibers may be lost due to vasa vasorum involvement (5).

Clinical features and diagnosis

Due to ongoing inflammation, both TA and GCA can cause non-specific symptoms like fatigue, fever, lethargy, weight loss, and hypertension. More specific symptoms are upper extremity or chest pain. Once the damage to the aorta and its major branches occur, weakness and neurological manifestations such as strokes and seizures may be present due to arterial insufficiency (8). In some patients, tenderness around the region of the carotid artery may be seen. However, some patients may be asymptomatic only to be diagnosed on autopsy (5).

On examination, high or discordant blood pressure between limbs, arterial bruits and decreased or absent pulses may alert a clinician to the possibility of this diagnosis. Rashes resembling erythema nodosum or pyoderma gangrenosum may be seen in a few patients.

Clinical symptoms often reflect the end-organ whose perfusion is affected, for example visual impairment may result from involvement of retinal vessels. Other symptoms may include unilateral headache, jaw pain, scalp tenderness, vision loss, and myalgias.

Importantly, GCA is associated with polymyalgia rheumatica (PMR) in 40% to 60% of patients at diagnosis which can cause myalgia of various parts such as shoulder, pelvic, and back muscles; therefore, a diagnosis of GCA should be considered in all patients with PMR (10). TA and GCA diagnosis can be made with the 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology (ACR/EULAR) criteria which scores the probability of having these vasculitides by using absolute and additional criteria (12,13). For GCA importance is given to laboratory parameters such as elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) as well. A score of 5 or greater is needed for diagnosis of TA whereas a score of 6 or greater is needed for GCA (*Tables 2,3*) (12,13).

Laboratory data

There are no specific lab markers that indicate large vessel vasculitides. Acute phase reactants such as ESR, CRP, and interleukin-6 (IL-6) may be elevated which helps support the diagnosis in patients with other features of the disease. Anemia of chronic disease and thrombocytosis may also be seen (12,13).

Imaging

Imaging studies involving computed tomography (CT) angiograms and magnetic resonance imaging (MRI) can help in determining the extent of the disease. Sometimes the diagnosis may be incidentally discovered based on imaging done for some other cause (14). Imaging may show vascular

Table 3 Giant cell Arteritis classification criteria [modified with permission from the reference (12)]

Giant cell arteritis classification criteria	Points
Clinical criteria	
Sudden vision loss	3
Jaw or tongue claudication	2
New temporal headache	2
Shoulder/neck morning stiffness	2
Scalp tenderness	2
Abnormal temporal artery examination	2
Lab, biopsy and imaging criteria	
ESR ≥50 mm/hour or CRP ≥10 mg/liter	3
Halo sign on temporal artery ultrasound or positive temporal artery biopsy	5
Bilateral axillary involvement	2
FDG-PET avid activity throughout the aorta	2

Absolute requirement: age ≥50 years at the time of diagnosis. A score of 6 or greater needed for diagnosis. ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; FDG-PET, fluorodeoxyglucose positron emission tomography.

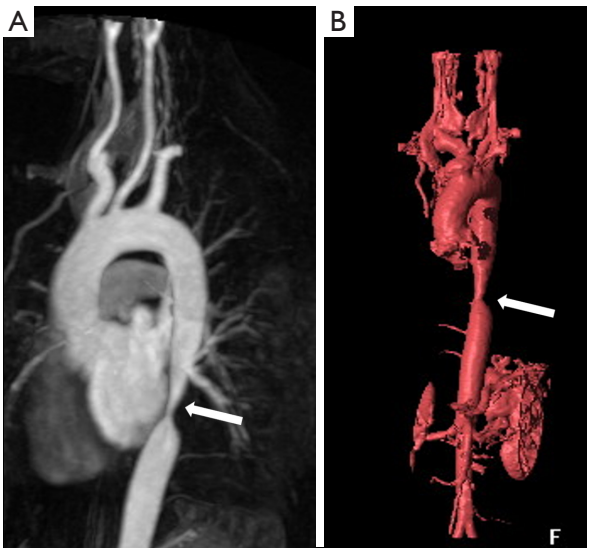

Figure 1 A 27-year-old woman with Takayasu arteritis. (A) Magnetic resonance angiography showing severe narrowing of the descending thoracic aorta (white arrow). (B) 3-dimensional volume-rendered magnetic resonance image showing severe narrowing of the descending thoracic aorta (white arrow).

wall thickening, luminal narrowing and aneurysms (15) (*Figure 1*). Positron emission tomography (PET) scans are also being used to differentiate large vessel vasculitis from clinical mimickers and to monitor disease remission (16).

EULAR recommends MRI as the initial diagnostic modality to investigate mural inflammation or stenosis in patients with suspected TA, with PET and CT scans as alternative imaging modalities if MRI is not promptly available (17). PET scan is particularly useful in patients with non-specific symptoms as it helps rule out alternative diagnoses. Ultrasound is of limited utility in assessment of thoracic aorta (17). Conventional angiography used to be the gold standard for diagnosis but is not recommended now due to availability of more advanced imaging techniques and the invasive nature of the procedure. EULAR recommends that in cases where diagnosis cannot be confirmed via clinical history, laboratory tests and imaging, additional tests (biopsy) and further imaging should be obtained to confirm the diagnosis. Importantly, treatment should not be delayed while waiting to obtain imaging studies if the large vessel vasculitis is suspected as the consequences of untreated vasculitis may cause irreversible damage (17).

For GCA, EULAR recommends ultrasound of temporal or axillary arteries for predominantly intracranial suspected GCA whereas ACR recommends an initial long segment (>1 cm) unilateral temporal artery biopsy. ACR recommends contralateral biopsy in cases of negative initial biopsy or if symptoms are not unilateral. Treatment with-corticosteroids should be initiated as soon as the diagnosis is suspected and a biopsy should be obtained within 2 weeks of starting steroids (13,18). Temporal artery biopsy is recommended over performing ultrasound or MRI to aid in diagnosis but in patients with newly diagnosed GCA, it is recommended to obtain non-invasive imaging to assess for large vessel involvement (18).

Treatment

Corticosteroids form the backbone of treatment for large vessel vasculitides. For TA, EULAR recommends starting 40–60 mg/day of prednisone or equivalent and once disease is controlled, taper to 15–20 mg/day over 2–3 months (19). Tocilizumab and methotrexate may be used as adjuncts in select cases (19). Occasionally, for life or organ threatening disease pulse dose steroids (500–1,000 mg IV) may be used for the first few days and then tapered to oral prednisone. Steroids sparing agents are commonly used and include methotrexate, azathioprine, and mycophenolate; however, there is no good quality data to favor one over the other (20).

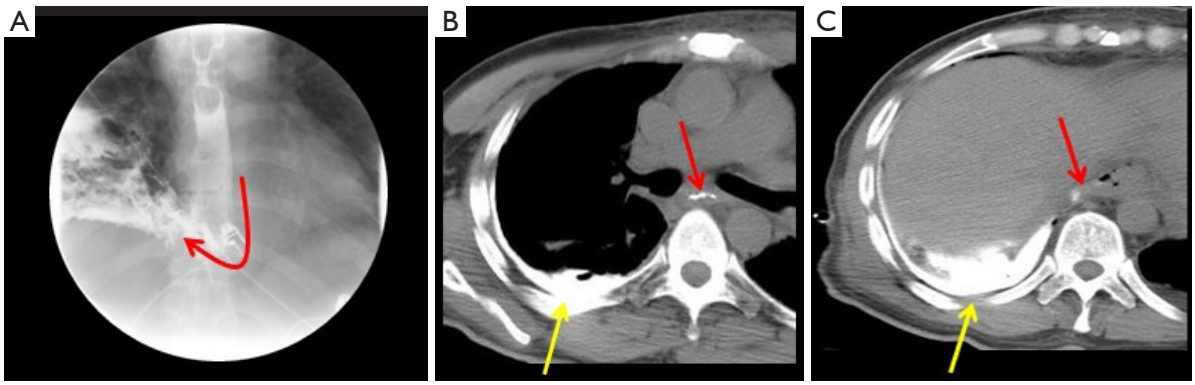

Figure 2 A 50-year-old man with esophageal rupture. (A) Fluoroscopic image showing a defect in the left esophageal wall with the red arrow pointing towards contrast tracking into the right pleural space. (B) Axial views of chest CT scan showing contrast in the esophagus (red arrow) and extravasation into the right pleural space (yellow arrow). (C) Axial views of chest CT scan showing contrast in esophagus (red arrow) and extravasation into the right pleural space (yellow arrow). CT, computed tomography.

ACR also recommends starting tocilizumab in addition to corticosteroids in patients with newly diagnosed GCA whereas EULAR recommends it in selected patients only (18,19).

For existing vascular stenosis, endovascular and other surgical procedures may be used to help relieve vascular narrowing and reduce symptoms. Regular follow-ups and imaging studies are needed to ensure that there is no ongoing subclinical vasculitis.

The optimum duration of treatment is not defined by ACR whereas EULAR recommends to slowly taper steroids over 2–3 months once the disease is controlled. Neither society recommends the addition of antiplatelets or anticoagulants unless other indications for their use exist (18,19).

Mediastinitis

Mediastinitis refers to infection within the connective tissue of the mediastinum. It may occur in the form of (I) acute mediastinitis due to descending necrotizing infection or esophageal rupture and (II) post-surgical mediastinitis (PSM) or chronic mediastinitis as (I) mediastinal granulomas (MG) and (II) fibrosing mediastinitis (FM) (21). Due to involvement of several vital structures within the mediastinum, prompt diagnosis and management is of paramount importance.

Acute mediastinitis

Acute mediastinitis is an infectious process typically caused by bacteria. These infections can spread rapidly and cause significant morbidity and mortality. They may result from direct contamination, post-surgery, lymphangitic or hematogenous spread, extension from the head and neck or extension from nearby structures such as lung, pericardium, or esophagus (22). While in the past, most cases of mediastinitis were due to esophageal rupture or extension of infections from the head and neck, currently, most cases of mediastinitis are post-surgical.

Esophageal perforation (Boerhaave's syndrome) is commonly due to forceful retching or vomiting and can cause acute mediastinitis (*Figure 2*). Esophageal perforation may also be iatrogenic, for example during endoscopy or failed surgical anastomosis, trauma, or from foreign body ingestion. The underlying esophagus is usually normal although some patients may have esophagitis or preexisting ulcers. Mortality is 21% to 50 % and any delay in recognition and treatment increases mortality risk substantially (23).

Descending necrotizing mediastinitis (DNM) is an infection which starts from above the mediastinum and then descends towards the mediastinum (*Figure 3*) (24). Sources include dental and tonsillar abscess, epiglottitis, and neck infections, which can spread through the facial planes and track downward into the mediastinum. DNM is often polymicrobial with both aerobic and anaerobic bacteria involved. In a report of 17 patients with DNM, all patients required surgery along with antibiotics. Mortality rates are variable and range from 6% to 40% with more recent studies suggesting a lower mortality rate than observed in prior studies (22,25).

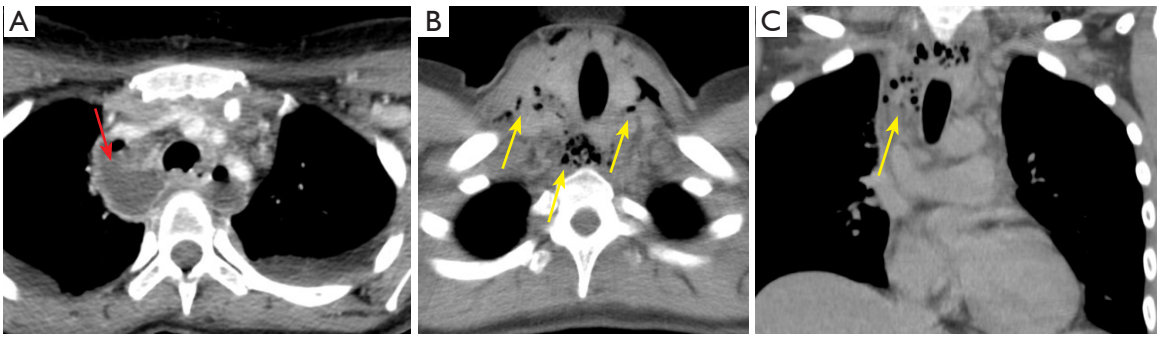

Figure 3 A 60-year-old man with odontogenic infection who developed neck and mediastinal infection as seen by foci of gas. (A) Axial view chest CT scan showing upper mediastinal involvement and rim-enhancing fluid collections (red arrow). (B) Axial view chest CT scan showing multiple foci of gas because of infection in the neck (yellow arrows). (C) Coronal view chest CT scan showing gas in the mediastinum (yellow arrow). CT, computed tomography.

Epidemiology

Risk factors for DNM include immunodeficiency, smoking, alcohol use, use of glucocorticoids diabetes and poor dentition. Men and women appear equally affected and mean age of presentation is around 50 years (25).

Esophageal perforation is rare with an incidence of 3.1/million per year. The majority is iatrogenic whereas the rest are spontaneous or due to foreign body ingestion (26). Spontaneous rupture is associated with the poorest survival (27).

Clinical features

Patients may present with signs and symptoms of infection such as fever, chills, night sweats and more acute presentation may be due to septic shock. In esophageal perforation, patients may have dysphagia, odynophagia, severe chest pain and may have a preceding history of retching and/or vomiting. On exam, crepitus due to subcutaneous emphysema may be present (28).

Clinical features for DNM were established by Estrera *et al.* and include clinical manifestation of severe infection, characteristic imaging, evidence of necrotizing mediastinitis on surgery and/or autopsy or both and establishment of relationship between an oropharyngeal or cervical infection and development of DNM (29).

Lab markers

Acute inflammatory markers such as ESR, CRP, procalcitonin and white cell count will be raised but are non-specific. Blood cultures should also be obtained. Some patients may have evidence of disseminated intravascular coagulation (DIC) (25).

Imaging

CT scan with contrast is often the modality of choice for acute mediastinitis. Widening of mediastinum, mediastinal fluid collection, extraluminal gas bubbles, increased fat attenuation, lymphadenopathy all support the diagnosis (30).

Findings suggestive of esophageal perforation on chest imaging include esophageal wall thickening, free peritoneal air or subcutaneous emphysema, pleural effusions, pneumothorax or hydropneumothorax, widened mediastinum and pneumomediastinum. A contrast esophagogram establishes the location and extent of the rupture but false negative may occur in up to 10% of cases (27).

Treatment

Management of mediastinitis depends on the underlying cause. Often patients require intensive care unit (ICU) level of care as they may be in septic shock. Airway compromise should also be anticipated and plan to manage airway should be discussed with the anesthesia team, particularly in cases of DNM. Antibiotics with additional anerobic coverage are indicated in all patients. Surgical debridement in surgical candidates is often indicated. For DNM, surgical drainage of the deep neck infection along with mediastinal drainage should be performed as soon as possible (31).

In cases of esophageal perforation, it is important to avoid all oral intake. Total parenteral nutrition is often initiated along with proton pump inhibitors and possible addition of antifungals. Endoscopic techniques are also being increasingly used, especially in patients who are not candidates for open surgery (32).

PSM

PSM can manifest in two primary forms: superficial, which involves the skin and subcutaneous tissue (occurring above the fascial line), and deep, affecting the sternum, ribs, and retrosternal tissues (occurring below the fascial line). A key diagnostic indicator is the presence of subcutaneous emphysema, which is detectable through imaging techniques (33).

Postoperative infections, particularly following cardiothoracic or esophageal procedures, have become the most common etiology associated with mediastinitis. PSM carries an alarmingly high mortality rate, estimated between 14% and 47%, and is associated with numerous challenges, including the need for repeated surgical interventions, prolonged stays in intensive care units, extended hospitalization, and the potential development of other postsurgical complications (33-35). These complications can encompass pericarditis, sepsis, multiorgan failure, airway obstruction, and bleeding diathesis, underscoring the urgency of a multidisciplinary approach to its management.

Pathogenesis

The precise pathogenesis of PSM remains a subject of ongoing research, but several factors are believed to contribute such as sternal separation or instability arising from chest wall issues such as obesity, underlying obstructive lung diseases, or poor wound healing. Additionally, preoperative colonization and the migration of bacteria from other body sites into the mediastinal space play a role, as do the specific procedural and surgical techniques employed. In obese patients, the greater presence of adipose tissue provides a potential environment for microbial growth, while issues related to antibiotic dosage adjustments may arise in patients with larger volumes of distribution. Patients with underlying chronic obstructive pulmonary disease (COPD) face an increased risk of PSM, primarily due to mechanical stress on the sternum resulting from frequent coughing, which can lead to sternal instability and dehiscence. Postoperative respiratory complications and prolonged mechanical ventilation further compound this risk (34,35).

Epidemiology

Despite its relatively low overall incidence, ranging from 0.4% to 7% across most medical institutions, PSM is a life-threatening complication (36). The development of both superficial and deep mediastinitis is influenced by various risk factors, encompassing patient-related and surgical technical factors. Patient-related risk factors include older age (age >65 years), obesity (defined as >20% of ideal body weight or body mass index >30 kg/m^2), a history of smoking, diabetes mellitus, chronic infection, chronic obstructive lung disease, the presence of ventricular assist devices, preoperative hemodynamic instability, preoperative renal failure necessitating hemodialysis, sepsis, multiple transfusions (>4 units), prolonged postoperative ventilation, and perioperative immunosuppression (37-39). Surgical technical factors related to PSM include emergency surgery, bilateral internal mammary artery use, prolonged operating room time (>200 minutes), excessive use of electrocautery, and median sternotomy incision.

Microbiology

As is often the case for surgical site infections, most cases of PSM stem from a patient's endogenous flora. Among the culprits for postoperative mediastinitis, Gram-positive *Staphylococcus* (*S.*) species are the most common, with methicillin-sensitive *S. aureus* (MSSA) being prevalent in cases where preoperative nasal MSSA colonization exists (40). Conversely, postoperative mediastinitis involving methicillin-resistant *S. aureus* (MRSA) appears to be linked to nosocomial transmission (40). In a study evaluating intensive care units admissions of 316 patients of PSM in a 10-year period, the most common micro-organisms isolated were MSSA (45%), MRSA (16%), Gram-negative bacilli (17%), coagulase-negative staphylococci (13%) and streptococci (5%) (41). Rarely other micro-organisms associated with PSM include fungi and mycobacteria including *Mycobacterium tuberculosis* (42-44).

Clinical features and diagnosis

Diagnosing PSM poses challenges as it is often difficult to clinically distinguish between superficial and deep sternal wound infections. Diagnosis typically relies on a combination of factors, including clinical history, radiographic features, serologic markers for infection, and microbiologic culture growth. Patients may exhibit signs of superficial or deep PSM for up to a year after surgery, although most cases arise within 30 days postoperatively (33,34). The Centers for Disease Control and Prevention define mediastinitis by the presence of one or more of the following criteria: (I) isolation of microorganisms from mediastinal tissue or fluid culture; (II) evidence of mediastinitis upon gross anatomic or histopathologic examination; or (III) the presence of chest pain, sternal

instability, or fever (>38 ℃), accompanied by purulent drainage from the mediastinum or mediastinal widening on chest imaging (36). Common physical examination findings associated with PSM include wound dehiscence, wound discharge, and sternal instability, particularly when accompanied by fever (41).

Laboratory data

Laboratory tests may reveal leukocytosis, thrombocytosis, electrolyte imbalances, elevated lactic acid levels, increased ESRs, elevated CRP levels, and positive blood cultures. However, no single test is sufficiently sensitive or specific for diagnosing PSM. Given the strong association between PSM and bacterial infections, blood cultures should always be obtained in addition to surgical wound-based culture collections (45,46).

Imaging

Chest radiography may reveal pleural effusions, pneumomediastinum, mediastinal widening, displacement of suture wires, and air-fluid levels (preferably observed on lateral films), suggestive of PSM. However, it is essential to note that these radiographic signs can also be present in cases of postoperative edema, lymphadenopathy, and hemorrhage. For more accurate diagnosis CT and MRI are preferred over radiography or nuclear imaging due to their higher sensitivity and specificity (47). These modalities are particularly valuable for detecting air-fluid levels several weeks after surgery and assessing the depth of dehiscence and infection. CT scans are the preferred choice for evaluating suspected mediastinitis, especially in patients 14 days post-operatively with fever and leukocytosis but without evident signs of infection or sternal wound drainage. CT findings indicative of PSM may include increased attenuation of mediastinal fat, pleural effusions, sternal dehiscence, localized mediastinal fluid collections, and free gas bubbles. However, less than 50% of PSM cases exhibit mediastinal lymphadenopathy, pericardial effusions, lung infiltrates, or mediastinal fistula on CT scans. It is worth noting that obtaining an MRI for PSM diagnosis can be limited by artifact issues caused by sternal wires and the presence of metallic devices in postoperative patients, especially those requiring prolonged mechanical ventilation (30,47,48).

Management of PSM

The treatment of PSM primarily involves early surgical debridement and sternal irrigation, along with culture-directed antibiotic therapy and prolonged antibiotic treatment. Many different surgical strategies have been described including primary closure, revision with open dressings and sternal reconstruction with muscle flaps (either pectoralis major or rectus abdominis or omental flaps). Vacuum assisted closure with application of negative pressure facilitates drainage and tissue granulation which help with wound healing (33,49). The optimal surgical approach however remains unknown, and approach varies depending on operator and institutional experience and expertise. The focus rather should be on prevention which should include a collective approach including preoperative screening for microbes, administration of prophylactic antibiotics, preoperative skin preparation, avoiding wound contamination, proper surgical technique and optimizing conditions for wound healing and correcting hyperglycemia (50-52).

Regarding antimicrobial therapy, it typically extends from 4 to 6 weeks for most patients and can extend to months for those requiring sternal resection and flap use. Initial empiric therapy involves broad-spectrum coverage against both Gram-positive cocci and Gram-negative bacilli. In cases where MRSA is a concern, intravenous vancomycin, and a third-generation cephalosporin, such as ceftazidime or cefotaxime, or alternatives like fluoroquinolones or aminoglycosides may be appropriate choices (53). However, the treatment regimen should be adjusted based on local antibiograms and the results of blood and mediastinal wound cultures.

MG and FM

MG may appear as a mass in the mediastinum and can result from a variety of etiologies. Histoplasmosis is the most common etiology in the US whereas other causes include tuberculosis (TB), sarcoidosis, other fungal infections, actinomyces and syphilis. These organisms may also cause mediastinal adenitis (2,54). MGs are clusters of necrotic lymph nodes which are filled with semi liquid necrotic debris and surrounded by a thin capsule due to the host cellular immunity attempt to contain possible infection (54).

FM is characterized by an excessive, progressive fibrotic reaction which often compresses nearby structures such as the esophagus and mediastinal vascular structures such as pulmonary artery, pulmonary veins, superior vena cava (SVC) (55). In the US, FM is almost always due to an idiosyncratic response to histoplasma exposure, though the initial infection may not always be apparent (56). Other rare causes include TB, other fungal infections such as

aspergillosis, sarcoidosis, silicosis, immunoglobulin G4 (IgG4) related disease, prior mediastinal radiation, or autoimmune diseases (55).

Epidemiology

Histoplasma is endemic in the Ohio and Mississippi river valleys. Although, many persons are histoplasma seropositive, MG and FM do not develop in most patients (56). As mentioned previously other infections that may cause MG and FM like fungi, syphilis, actinomyces and TB are also present in the US. There is a lack of data on the exact incidence and prevalence of MG and FM and further epidemiological studies are needed. FM is extremely rare, the largest study on FM just described 94 patients over a 9-year period (57).

Etiology

It is not known why certain individuals are predisposed to granuloma formation or FM. Initial infection is often subclinical, and granulomas can form in the affected organ which may eventually necrose and calcify. Occasionally, the involved lymph node can enlarge and coalesce to form granulomas (54).

FM may result from leakage of fungal antigens which can lead to a progressive hypersensitivity response. Certain genotypes may increase the odds of developing FM over granulomas for example, HLA-A2 is associated with more than a 3-fold increase in risk of developing FM (58). It is thought that TB may cause FM in a similar way but mechanisms for other causes of FM are yet unknown. While MG and FM have been speculated as continuums of the same disease; there remains no evidence that this is indeed the case.

The causes of MG and FM may be different outside the US. In a French study 31 patients with FM and pulmonary hypertension were evaluated. Thirteen patients had FM due to sarcoid, 9 due to TB, 2 had prior radiation and 3 had idiopathic FM (59). Interestingly, no patient was thought to have had prior histoplasmosis, likely due to low incidence of histoplasmosis in France.

Clinical features and diagnosis

Patients with MG are often asymptomatic and may have an incidentally discovered mass on imaging performed for other reasons. Patients may have a remote history of histoplasmosis. If the granulomas become large, they can compress adjacent structures and causes symptoms, for example SVC syndrome, dysphagia, odynophagia, cough, pneumonia, or hemoptysis. A fistula may develop between the granuloma and neighboring structure and lead to symptoms as well (54).

FM causes symptoms due to compression of neighboring structures. Symptoms are often progressive over a few years as the growth of fibrous tissue is usually slow at around 1 mm/year (55). SVC syndrome, pulmonary artery or vein obstruction, airway compression and esophageal compression may occur. Obstruction of pulmonary artery or vein may also lead to pulmonary hypertension (59).

If imaging is not characteristic, a biopsy is indicated to rule out any other causes of a mediastinal mass such as lung cancer or lymphoma. However, most patients with malignancies have a more rapid clinical course and calcifications are absent. If the lesion is accessible, endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) can be performed to obtain tissue samples.

Imaging

Chest CT should be done in patients suspected of having a granuloma and it may show a well-defined mass with some scattered or diffuse calcifications. There may be other signs of prior histoplasma infection such as calcifications in the lymph nodes, spleen, and/or liver. A history of residence in a histoplasma or TB endemic region may be present.

Circumferential compression of structure with a dense infiltrate which often traverses fat planes is more typical of FM whereas lymphadenopathy and lack of calcifications raise concern for adenitis (*Figure 4*) (2). Contrast enhancement is variable. This process is typically unilateral although it can be bilateral as well. Other features seen in FM include mediastinal widening, lymphadenopathy, atelectasis, and pleural effusion. Imaging features are characteristic enough to suggest the diagnosis in the right clinical context (56). PET scans are often non-specific and not routinely performed.

Laboratory data

Histoplasma antigen testing and serologic tests should be performed. If other infections such as TB, aspergillus or sarcoidosis is suspected, testing for them should be performed as well.

Treatment

Asymptomatic patients with classic history and imaging findings can be monitored by serial CT scans. The frequency of imaging is not well established but may

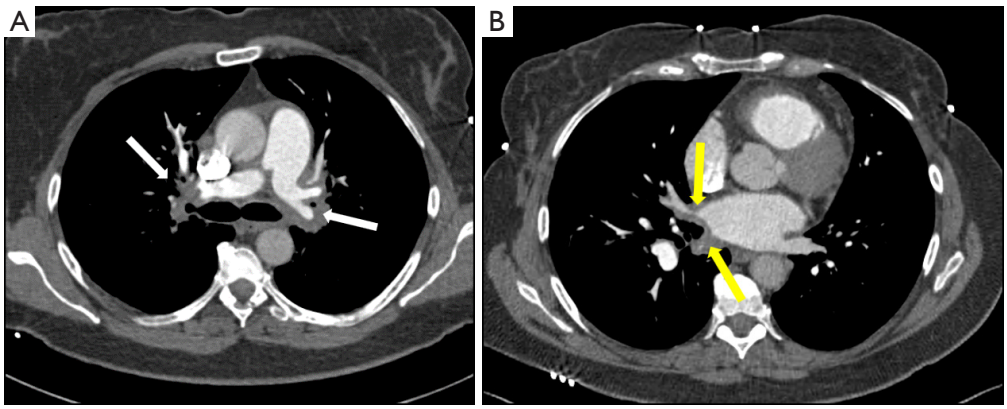

Figure 4 A 60-year-old woman with a known history of fibrosing mediastinitis. (A) Axial view chest CT scan showing diffuse mediastinal soft tissue thickening around the pulmonary artery (white arrows). (B) Axial view chest CT scan showing diffuse mediastinal soft tissue thickening around the pulmonary veins (yellow arrows). CT, computed tomography.

be obtained at 6-month intervals initially and spaced out to yearly scans afterwards. Surgical excision may be recommended if the mass grows. In some patients, MG may resolve spontaneously without any specific treatment. In symptomatic patients the definitive therapy is surgical excision with the removal of the free wall. Sometimes, it may not be possible to completely excise the granuloma as the free wall may be adherent to critical mediastinal structure (54). Infectious Disease Society of America (IDSA) guidelines does not recommend treatment for MG due to histoplasmosis. However, in symptomatic patients itraconazole may be used (60).

For FM, there is no evidence that antifungals or glucocorticoids improve symptoms. There may be some benefit by using rituximab although, further studies are needed to see if it is truly beneficial (54). IDSA only recommends itraconazole if findings cannot differentiate between MG and FM (60). For vascular and airway stenosis, stents may be used to relieve obstruction although, durability of airway stents for FM is poor (54).

Conclusions

There are several causes of benign mediastinal pathologies, which include but are not limited to masses, cystic lesions, benign neoplasms, vasculitis, and infections—of which a few have been reviewed within this article. While some of these entities are discovered incidentally, others are diagnosed when patients present with symptoms secondary to pressure effect on several vital structures within the mediastinum. Furthermore, infections pose an important benign cause due to the several catastrophic consequences associated with them if not diagnosed or managed in time. We hope our article will enable readers to recognize these mediastinal disorders and initiate prompt treatment. Further research is needed on several of these pathologies to improve diagnostic ability and treatment options.

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Footnote

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Review Article

Current immunotherapy for thymic epithelial tumors: a narrative review

Yoko Yamamoto[1,2,3], Kota Iwahori[3,4]^, Yasushi Shintani[2]

[1]Department of General Thoracic Surgery, Sakai City Medical Center, Osaka, Japan; [2]Department of General Thoracic Surgery, Graduate School of Medicine, Osaka University, Osaka, Japan; [3]Department of Clinical Research in Tumor Immunology, Graduate School of Medicine, Osaka University, Osaka, Japan; [4]Department of Respiratory Medicine and Clinical Immunology, Graduate School of Medicine, Osaka University, Osaka, Japan

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Correspondence to: Kota Iwahori, MD, PhD. Department of Clinical Research in Tumor Immunology, Graduate School of Medicine, Osaka University, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan; Department of Respiratory Medicine and Clinical Immunology, Graduate School of Medicine, Osaka University, Osaka, Japan. Email: iwahori@climm.med.osaka-u.ac.jp.

Background and Objective: Thymic epithelial tumors (TETs) are the most common neoplasm of the prevascular mediastinal compartment and are characterized by their rarity and variable clinical presentation. The present study aimed to explore the current management of patients with TET with a special focus on immunotherapy for advanced disease.

Methods: Relevant studies published between 1981 and 2024 were searched in PubMed using search terms "Thymoma", "Thymic cancer", "Myasthenia gravis", "Radiation therapy", "Surgery", and "Immunotherapy".

Key Content and Findings: The International Thymic Malignancy Interest Group and the International Association for the Study of Lung Cancer established the tumor-node-metastasis (TNM) staging system for TET based on an overall survival (OS) analysis of a retrospective international database. While complete surgical resection is the mainstay for resectable TET, there are currently no clear guidelines on systemic treatments for advanced TET because of the complexity, rarity, and heterogeneity of this disease and the lack of *in vivo* and *in vitro* models. With the development of immunotherapy, the application of the anti-programmed cell death-1 (anti-PD-1) antibody is expanding and includes TET. Clinical trials on immune checkpoint inhibitors (ICIs) are ongoing, and the acceptable clinical efficacy of the anti-PD-1 antibody for TET has been reported. On the other hand, there have been reports of a heightened frequency of severe immune-related adverse events (irAEs) in TET.

Conclusions: ICIs have the potential for patients with TET. The benefit-toxicity ratio of ICI treatment needs to be carefully evaluated for those patients.

Keywords: Thymoma; thymic carcinoma; immunotherapy; tumor microenvironment

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^ ORCID: 0000-0002-9891-6003.

Introduction

The majority of prevascular mediastinal compartment tumors are thymic epithelial tumors (TETs) and include thymoma, thymic carcinoma, and neuroendocrine tumors, which originate in the thymus (1). These tumors are malignant tumors and have unique biological behaviors. Thymoma is histologically comprised of various percentages of epithelial and lymphocytic components. These lymphocytes are comprised mainly of immature T lymphocytes, namely, double-positive T (DPT) cells that resemble the normal cells of the thymus. However, these cells are nearly absent in type A thymomas (2). Thymomas often invade adjacent organs, disseminate within the thoracic cavity, and rarely metastasize lymphogenously or hematogenously. Thymic carcinoma is a more aggressive malignant TET with clear nuclear atypia and no immature T cells and is often diagnosed in the advanced stage because of a lack of evident symptoms during its initiation and early progression. Thymoma is associated with autoimmune complications, such as myasthenia gravis, pure red cell aplasia, hypogammaglobulinemia, and the absence of B cells. Myasthenia gravis is attributed to the incomplete induction of tolerance to self-antigens in T cells that mature within thymic tumors due to the function of thymoma epithelial cells (3). On the other hand, thymic carcinoma that has lost epithelial cell function is not only associated with myasthenia gravis, but also not with other autoimmune conditions.

The detailed etiology of TET remains unclear. Difficulties are associated with generating cell lines from the tumor cells of TET because of their rarity, histological diversity, and the presence of intra-tumoral lymphocytes to varying degrees, and animal experiments are also challenging. Therefore, basic research on TET is insufficient, and, as a consequence, a standard treatment has not yet been established.

A recent study reported that the 10-year overall, disease-specific, and recurrence-free survival rates of thymoma and thymic carcinoma were 88.1% and 54.3%, 96.5% and 62.1%, and 89.2% and 51.1%, respectively (4). Complete surgical resection reportedly represents the solitary opportunity for achieving a curative outcome in cases of TET (5,6). Nonetheless, achieving complete resection remains an elusive goal in instances of advanced TET, and notwithstanding successful resection, the rates of recurrence for type B3 and thymic carcinoma stand at 27.5% and 50.0%, respectively (7). Furthermore, surgical intervention may not be viable for certain patients afflicted by tumors infiltrating adjacent vital structures such as the heart and major vasculature, or those manifesting metastatic dissemination across multiple organs. TET of more aggressive histological subtypes frequently manifests at an advanced disease stage, precipitating poorer overall survival (OS) outcomes. Complementary therapeutic modalities including chemotherapy, radiation therapy, and molecular-targeted agents constitute viable adjuncts in the treatment armamentarium (8,9). The advent of immune checkpoint inhibitors (ICIs) heralds a paradigm shift in cancer immunotherapy. Notably, the anti-programmed cell death-1 (anti-PD-1) antibody confers discernible benefits upon a select subset of cancer patients. Ongoing clinical trials investigating the efficacy of ICI are underway, with reports delineating the favorable clinical outcomes associated with the anti-PD-1 antibody in TET cases (10-17). According to the recent National Comprehensive Cancer Network (NCCN) guidelines (18), pembrolizumab has been approved as a second-line treatment for thymic carcinoma because of its promising antitumor activity.

This review provides an overview of the current management of patients with TET with a special focus on immunotherapy for advanced disease. We discussed the future direction of development for immunotherapy of TET. We present this article in accordance with the Narrative Review reporting checklist (available at https://med.amegroups.com/article/view/10.21037/med-24-24/rc).

Methods

Relevant studies published between 1981 and 2024 were searched using the search terms “Thymoma”, “Thymic cancer”, “Myasthenia gravis”, “Radiation therapy”, “Surgery”, and “Immunotherapy”. Prospective and retrospective studies, meta-analyses, review articles, and case studies were included as references. Papers were chosen based on relevance because the current study is not a systematic review. The biggest limitation of this study is the lack of randomized clinical trials because of tumor rarity. We excluded studies that we considered with low reliability, such as no mention of the stage, clinical data, treatment details, and without full texts, or those not written in English. The search strategy is summarized in *Table 1*.

Histopathological classification and staging

According to the histopathological classification delineated

Table 1 The search strategy summary

Items	Specification
Date of search	April 3, 2024 to May 4, 2024
Databases and other sources searched	PubMed
Search terms used	"Thymoma", "Thymic cancer", "Myasthenia gravis", "Radiation therapy", "Surgery" and "Immunotherapy"
Timeframe	1981–2024
Inclusion and exclusion criteria	Prospective studies, retrospective studies, meta-analyses, and case studies were included
	Papers that we considered with low reliability and non-English papers were excluded
Selection process	Y.Y. conducted the literature search. All the authors subsequently discussed and agreed on the literature

by the World Health Organization (WHO), TETs are categorized into thymoma (including types A, AB, B1, B2, and B3) or thymic carcinoma, predicated upon the morphology of epithelial tumor cells and the degree of intratumoral lymphocytic infiltration (2,19). Thymic carcinoma encompasses various subtypes, with squamous cell carcinoma standing out as the most prevalent among them. The WHO classification reflects the characteristics of each tumor, correlates with myasthenia gravis as a complication, the degree of tumor invasion, and prognosis, and has become a clinically valuable classification that is now widely used (20).

Masaoka *et al.* proposed a clinicopathological staging system (21) that is used worldwide and is accepted as the standard because it accurately reflects the oncological behavior of TET, particularly in thymoma (22). In recent years, the International Thymic Malignancy Interest Group and the International Association for the Study of Lung Cancer established a tumor-node-metastasis (TNM) staging system for TET based on OS analysis of a retrospective international database (23-26). It is important to note that the Masaoka staging system is based on surgical pathology and TNM staging may be desirable in the presence of lymph nodal and distant metastasis.

Current management of TET

Before commencing any therapeutic intervention, it is imperative to ascertain the serum levels of anti-acetylcholine receptor antibodies in all individuals suspected of harboring thymoma, irrespective of symptomatic presentation, to discern the presence of myasthenia gravis and avert the onset of myasthenic crises (27,28). The management of patients with TET requires a multidisciplinary team involving oncologists, thoracic surgeons, radiologists, neurologists, and pathologists. Surgical intervention assumes a pivotal role in the therapeutic management of TET due to the curative potential associated with complete surgical excision. As delineated in the latest directives from the NCCN, the therapeutic pathway for resectable thymic neoplasms (Masaoka I–II) entails initial surgical intervention, with subsequent therapeutic modalities such as systemic therapy or radiotherapy being contingent upon factors such as the adequacy of resection, histological subtype, and tumor staging. Minimally invasive approaches, such as unilateral trans-thoracic, trans-subxiphoid, video-assisted thoracoscopic, and robotic-assisted thoracoscopic surgeries, are options for early-stage TET (29-32), but not advanced TET. Therefore, the surgical approach needs to be carefully selected based on the tumor size, location, and whether the combined resection of other organs is required (33-35).

The efficacy of postoperative radiotherapy (PORT) for TET is controversial. A recent meta-analysis revealed that PORT was beneficial for Masaoka II and III thymoma (36). However, Omasa *et al.* reported the effectiveness of PORT for thymic carcinoma, but not for Masaoka II and III thymoma (37). PORT was also found to be effective for patients with positive surgical margins (38). Contemporary guidelines advocate for radiotherapy dosage and fractionation protocols predicated upon the rationale for radiation utilization and the extent of surgical excision achieved in postoperative scenarios.

The completeness of resection is a crucial factor affecting the prognosis of patients, even for stage III and IV tumors. Adjacent organ invasion, including great vessels, pericardium, heart, lung, and chest wall, as well as pleural dissemination, make complete resection difficult to

achieve. When complete resection cannot be anticipated, the treatment requires a tumor biopsy and the confirmation of the histological type followed by chemotherapy or chemoradiotherapy as the initial treatment before surgery. Although a standard chemotherapy regimen has not yet been established, previous studies demonstrated that multidisciplinary treatment improved complete resection outcomes and increased survival rates (39,40). High-dose methylprednisolone is also reportedly effective against B1 thymoma, which is rich in immature T lymphocytes that differentiate and mature within the tumor due to the effects of tumorigenic thymic epithelial cells (41), suggesting its potential as a preoperative treatment (42,43). In addition, since steroid receptors are present in tumor thymic epithelial cells, steroids may directly affect the tumor cells themselves as a treatment for thymoma (44).

The most frequent site of recurrence for thymoma is the pleura (45). Re-resection was previously reported as an acceptable option for the recurrent pleural dissemination of thymoma (46-48). Although the standard management of recurrent TET has not yet been established, prolonged survival is expected for patients with surgical indications.

Chemoradiotherapy or chemotherapy alone is considered for unresectable TET. According to the guidelines established by the NCCN, the prevailing standard therapeutic protocol encompasses platinum-based chemotherapy regimens in conjunction with anthracycline (CAP or ADOC regimens) or etoposide for thymoma (49) and paclitaxel for thymic carcinoma (50,51). The second line of systemic therapy comprises etoposide, everolimus, 5-fluorouracil (5-FU) and leucovorin, gemcitabine, ifosfamide, octreotide, paclitaxel, and pemetrexed for thymoma, while pembrolizumab (10), sunitinib (52), and lenvatinib (53) are recommended for thymic carcinoma. Lenvatinib, functioning as a multi-targeted inhibitor targeting VEGFR, FGFR, RET, c-kit, and other kinases, demonstrates favorable therapeutic efficacy. The REMORA trial underscored the safety and efficacy of lenvatinib in patients afflicted with advanced and metastatic thymic carcinoma, with a notable response rate of 38% [90% confidence interval (CI): 25.6–52.0%; P<0.0001] (53).

Immunotherapy for TET

The advent of ICI heralded a paradigm shift in the landscape of cancer immunotherapy. The efficacy of the anti-PD-1 antibody extends to a select cohort of cancer patients. Its indications are progressively broadening, now encompassing TET. Ongoing clinical trials investigating ICI are underway, with reports indicating the favorable clinical outcomes associated with the anti-PD-1 antibody in TET cases (10-17). Furthermore, Yang *et al.* showed a single case report that a patient with thymic carcinoma and multiple lung metastases responded well to anti-PD-1 therapy (54). According to the recent NCCN guidelines, pembrolizumab has been approved as a second-line treatment for thymic carcinoma because of its promising antitumor activity.

Table 2 summarizes the outcomes of clinical trials on patients with advanced TET who were treated with immunotherapy. Between 2018 and 2023, eight clinical studies (one phase I trial and seven phase II trials) investigated the effects of immunotherapy in patients with TET. The administered drug was pembrolizumab in two, nivolumab in two, atezolizumab in one, avelumab in one, the combination of avelumab and axitinib in one, and a WT1 peptide vaccine in one. All patients had stage III or IV disease. The overall response rate (ORR) ranged between 0 and 38.5% for all patients, while median progression-free survival (PFS) was 3.8 to 11.7 months. Median OS was 14.1 to 26.6 months. Treatment-related severe immune-related adverse events (irAEs) occurred in 0 to 71.4% of patients.

In more detail, Rajan *et al.* conducted a phase 1 trial of the anti-programmed cell death-ligand 1 (anti-PD-L1) antibody avelumab, including seven patients with relapsed thymoma and one patient with thymic carcinoma treated with at least one prior standard therapy (14). The ORR of thymoma and thymic carcinoma were 28.5% and 0%, respectively. Grade ≥3 irAEs were reported in five out of eight patients (62.5%). This study initially provided the efficiency of immunotherapy for thymoma. Cho *et al.* reported a single-center, phase 2 study of anti-PD-1 antibody, pembrolizumab in 26 patients with thymic carcinoma and 7 patients with thymoma whose disease progressed after at least one line of platinum-based chemotherapy (11). Notably, this study included three patients who were previously diagnosed with myasthenia gravis without receiving immunosuppressive treatment at least 1 year before enrollment. This report showed the ORR of thymoma and thymic carcinoma were 28.6% and 19.2%, respectively. The median PFS was 6.1 months for both thymoma and thymic carcinoma, the median OS was not reached for thymoma, and 14.5 months for thymic carcinoma. Five patients with thymoma (71.4%) and three patients with thymic carcinoma (11.5%) discontinued pembrolizumab treatment because of grade 3 or 4 irAEs. Moreover, three patients who had a previous history of

Table 2 Summary of clinical trials

Author	Treatment	Disease	N	Median age (years)	Response rate (%)	Median PFS (95% CI) (months)	Median OS (95% CI) (months)	Severe irAEs (%)
Giaccone (10)	Pembrolizumab	TC	40	57	22.5	4.2 (2.9–10.3)	24.9 (15.5–not reached)	14.6
Cho (11)	Pembrolizumab	T	7	57	28.6	6.1 (4.3–7.9)	Not reached	71.4
		TC	26	57	19.2	6.1 (5.1–7.1)	14.5	11.5
Oji (12)	WT1 peptide vaccine	T	4	57	0	Not reported	Not reported	25.0
		TC	11	53	0	Not reported	Not reported	0
Katsuya (13)	Nivolumab	TC	15	55	0	3.8 (1.9–7.0)	14.1 (11.1–not estimated)	13.3
Rajan (14)	Avelumab	T	7	53	28.5	Not available	Not available	62.5
		TC	1		0	Not available	Not available	
Tabernero (15)	Atezolizumab	T	13	61	38.5	11.7 (3.22–37.22)	Not estimated	35.7
Conforti (16)	Avelumab + axitinib	T	3	62	34.4	7.5 (3.7–10.0)	26.6 (17.0–30.3)	12.5
		T or TC	2					
		TC	27					
Girard (17)	Nivolumab	T	10	58	14.3	6.2 (3.1–10.4)	21.3 (11.6–not estimated)	34.0
		TC	43					

N, number; PFS, progression-free survival; CI, confidence interval; OS, overall survival; irAEs, immune-related adverse events; TC, thymic carcinoma; T, thymoma.

myasthenia gravis developed serious irAEs, including myasthenia, autoimmune hepatitis, and myocarditis, leading to discontinuation after the first cycle of pembrolizumab. Giaccone *et al.* reported a single-center, phase 2 study of pembrolizumab in 40 patients with recurrent thymic carcinoma who had progressed after at least one line of chemotherapy (10). The median follow-up was 20 months and the ORR was 22.5%. This report also demonstrated that PFS and OS were longer in patients with high PD-L1 expression than in those with low or no PD-L1 expression. Although patients without a history of autoimmune disease were enrolled, six patients (14.6%) developed serious irAEs including myocarditis, hepatitis, pancreatitis, bullous pemphigoid, and myasthenia gravis. In the PRIMER study, a Japanese multi-center phase 2 study of the anti-PD-1 antibody nivolumab in the same patient population, showed that 15 patients were enrolled, and no objective responses were observed, two out of 15 (13.3%) patients observed serious irAE [grade 3 aspartate aminotransferase (AST) increase and grade 2 adrenal insufficiency] (13). In this study, nivolumab did not demonstrate similar efficacy to pembrolizumab. On the other hand, the NIVOTHYM study from Europe, a phase 2 trial of nivolumab in 53 patients with advanced or relapsed type B3 thymoma and thymic carcinoma failed after at least one line of platinum-based chemotherapy, showed the ORR was 14.3% and grade ≥3 irAEs were observed in 18 cases (34.0%) including myocarditis, transaminitis, and neutropenia (17). Tabernero *et al.* reported that a phase 2 multicohort study of anti-PD-L1 antibody atezolizumab in multiple solid cancers progressed after one or more lines of systemic treatment (15). In this study, 13 thymoma patients were efficacy evaluable and the ORR was 38.5%. The point to note is that the thymoma cohort showed the highest rate of irAEs (35.7%) among the other solid cancers.

In the CAVEATT study, a multicenter phase 2 trial of a combined use of avelumab and the anti-angiogenic agent axitinib in 32 pre-treated patients (27 thymic carcinoma, three B3 thymoma, two mixed-type thymic carcinoma and thymoma B3) with at least one line of platinum-based chemotherapy received (16). The ORR was 34.4% and four out of 32 patients (12.5%) developed serious irAEs including interstitial pneumonitis and polymyositis. This study provided a positive outcome of the

combination of anti-angiogenic therapy and ICI. Oji *et al.* reported a phase 2 trial of the WT1 peptide vaccine in 11 patients with thymic carcinoma and four patients with thymoma (12). Fourteen patients received chemotherapy and the remaining one received radiation therapy alone due to complications with a hemostatic defect. Although the majority of patients demonstrated a WT1-specific immune response, no objective responses were observed. Although these immunotherapy clinical trials have shown efficacy in patients with advanced TET, additional biomarkers research to identify patients who can benefit from immunotherapy and develop serious irAEs is warranted.

To underpin the rationale for employing immunotherapy in the context of TET, a preclinical investigation conducted phenotypic and functional assessments of T cells derived from surgically excised TET specimens, focusing on the single-positive T cells therein. Utilizing flow cytometric data, a cluster analysis of T-cell phenotypes revealed that type B3 thymoma and thymic carcinoma pertained to the "hot" cluster, characterized by a notable prevalence of Tim-3^+ and $CD103^+$ expression within CD4 and CD8 single-positive T cells. Significant amplifications in cytokine secretion and cytotoxicity elicited by T cells upon exposure to the anti-PD-1 antibody were notably conspicuous in these histological subtypes. These observations underscore the potential utility of immunotherapeutic approaches for patients with type B3 thymoma and thymic carcinoma (55). On the other hand, Furuya *et al.* reported that the majority of PD-1^+ T cells in type AB/B1/B2 thymomas were intratumoral developing T cells and not tumor-infiltrating lymphocytes (56). Genetic differences have been reported between type B3 thymoma/thymic carcinoma and type AB/B1/B2 thymoma tumor cells in TET (57-59) and significant increases in the tumor mutation burden have been observed in type B3 thymoma and thymic carcinoma, particularly thymic carcinoma (58,60). These findings provide a rationale for the application of immunotherapy to type B3 thymoma and thymic carcinoma.

However, the high incidence of severe irAEs in TET remains a concern. Tabernero *et al.* demonstrated that the thymoma cohort exhibited the highest incidence of adverse events, with 35.7% of patients experiencing severe irAEs in their cohort study. Notably, two patients each presented with hepatitis and myasthenia gravis, the latter proving fatal in one patient (15). This observation could potentially be elucidated by the immune microenvironment, characterized by the presence of immature T cells, which may underlie autoimmune reactions and subsequent irAEs (61). Fenioux *et al.* reported that ICIs were more frequently associated with ICI myotoxicity in patients with TET than in those with other cancers, and myocarditis occurred earlier after the initiation of ICI in the former than in the latter and was more severe in terms of life-threatening arrhythmias and concurrent myositis (62). Furthermore, the presence of anti-acetylcholine-receptor antibodies was more prevalent in patients with than in those without ICI-related myocarditis. This study also suggested the potential of anti-acetylcholine-receptor antibodies as a predictive biomarker for severe myotoxicity (62). Therefore, due to the high incidence of severe irAEs in TET, particularly in thymoma, the indication of ICI remains a critical issue for patients with thymoma or those with a previous history of autoimmune syndrome. In addition to patients who will benefit from immunotherapy, it is important to identify those who are most likely to develop serious irAEs.

Limitations

In this narrative review, we focused on immunotherapy for TET. Although there have been clinical trials of TET that showed favorable clinical outcomes associated with ICI, the high incidence of severe irAEs was also reported. There were limitations in the present study. Because of the rarity and heterogeneity of TET, the patient cohort size in each clinical trial was relatively modest. Specifically, a substantial cohort size is requisite for the assessment of irAEs in TET. We must deliberate on immunotherapy for TET based on forthcoming extensive clinical studies involving large cohorts.

Conclusions

Complete surgical resection is the mainstay for resectable TET; however, there are no clear guidelines on systemic treatments for advanced TET. Regarding immunotherapy, ICIs have potential for patients with TET; however, a higher incidence of ICI-related myocarditis and myositis was reported in these patients. Therefore, the benefit-toxicity ratio of ICI treatment needs to be carefully evaluated. Future studies are needed to establish the efficacy and safety of immunotherapy.

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Review Article

Surgical management of thymic tumors: a narrative review with focus on robotic-assisted surgery

Robin Deckarm[1#], Dominik Valentin Flury[1,2#^], Sarah Deckarm[1,3], Sebastian Ott[1,2^], Gregor Jan Kocher[1,2,3^]

[1]University of Bern, Bern, Switzerland; [2]Department of Thoracic Surgery, St. Claraspital, Basel, Switzerland; [3]Department of Thoracic Surgery, Hirslanden Clinic Beau-Site (Hirslanden Group) & Lindenhof Hospital (Lindenhof Group Bern), Bern, Switzerland

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[#]These authors contributed equally to this work as co-first authors.

Correspondence to: Gregor Jan Kocher, MD. Department of Thoracic Surgery, Hirslanden Clinic Beau-Site (Hirslanden Group) & Lindenhof Hospital (Lindenhof Group Bern), Schaenzlihalde 1, 3013 Bern, Switzerland; Department of Thoracic Surgery, St. Claraspital, Basel, Switzerland; University of Bern, Bern, Switzerland. Email: gregor.kocher@hin.ch.

Background and Objective: Thymic epithelial tumors, including thymomas and thymic carcinomas, represent the most common mediastinal tumors and account for up to 50% of all anterior mediastinal tumors. For early stages of these thymic tumors, complete resection of the entire thymus is the recommended treatment. The transition from open surgery to video-assisted thoracoscopic surgery (VATS) and recently to robotic-assisted thoracic surgery (RATS) has fundamentally altered the treatment of thymic tumors. While RATS has been widely implemented due to its many advantages including good visualization with magnification and three-dimensional vision, improved maneuverability and precise instrument control, different techniques have been described. This narrative review focuses on the main approaches and outcomes of RATS thymectomy. It compares the technical, perioperative and clinical outcomes of RATS thymectomy, in particular, with VATS and open thymectomy.

Methods: A non-systematic review for full text studies written in the English language was conducted using the PubMed search engine and literature was summarized.

Key Content and Findings: We present an overview of robotic-assisted resection for thymomas and review the main approaches and outcomes of RATS thymectomy. Critical points of the RATS approach, including surgical specifics and pitfalls, are presented. Technical advantages and disadvantages of each technique are discussed. The perioperative and clinical outcomes of RATS thymectomy are compared, where possible, to those for VATS and open thymectomy. Currently, retrospective analyses demonstrate comparable or even more favorable outcomes following a RATS approach in comparison to VATS and open approaches in terms of operating time, conversion rates, intraoperative complications, completeness of resection and mortality. Certain analyses also report better outcomes for patients undergoing RATS thymectomy in terms of blood loss, postoperative complications, duration of pleural drainage and length of hospital stay compared to VATS and open thymectomy.

Conclusions: Overall, RATS has shown promising results and could become the preferred technique for resection of thymic tumors. It shows good outcomes compared to VATS and open thymectomy in the current literature. However, especially for extended tumors with the need for extended resection and reconstruction, open thymectomy remains a valuable approach.

^ ORCID: Dominik Valentin Flury, 0000-0002-5829-4692; Sebastian Ott, 0009-0008-6884-3430; Gregor Jan Kocher, 0000-0001-6531-2919.

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Introduction

The thymus is a primary lymphatic organ engaged in the proliferation and maturation of T-lymphocytes (1). It is comprised of two asymmetrical lobes that lie between the phrenic nerves and communicate in the midline, located behind the sternum and ventral to the pericardium, aortic arch, pulmonary artery, superior vena cava and brachiocephalic vein. During the course of adolescence, the thymus gland typically undergoes involution and recedes, becoming macroscopically indistinguishable from retrosternal fibrous adipose tissue (2).

Despite its normal involution, the thymic gland can sometimes harbor altered or abnormal cellular proliferation. This deviation from the typical cellular behavior can manifest as various conditions, including thymic tumors. Thymic epithelial tumors, including thymomas and thymic carcinomas, represent the most common mediastinal masses and account for around 20% of all mediastinal tumors and up to 50% of all anterior mediastinal tumors (3). Nevertheless, thymic tumors are very rare tumors, accounting for only around 0.2% up to 1.5% of all malignancies (4).

Thymomas may present with varied clinical manifestations. Slow, indolent growth is typical for thymomas, leading to around a third of all thymomas being diagnosed incidentally in radiological examinations of the chest (5). Occasionally symptoms including pain, cough, hoarseness, dyspnea can occur. Patients tend to present with symptoms once the tumor infiltrates or displaces surrounding structures. In cases of larger tumors, this infiltration may lead to complications such as superior vena cava syndrome due to local tumor compression (6,7).

As thymomas play a critical role in autoimmune pathogenesis, certain patients with tumors of the thymus may present with associated paraneoplastic syndromes. One of the most well-known associations is that between myasthenia gravis and thymomas, which was first identified by Alfred Blalock in the late 1930s. Blalock observed that resection of thymic tumors in patients with myasthenia gravis led to a striking improvement in their symptoms (8). Approximately 30–50% of all patients with thymomas show symptoms of myasthenia gravis (6,9).

It is critical that these patients receive treatment by a specialist and are carefully evaluated by experienced neurologists before undergoing surgical resections, in order to effectively evaluate the risk of a postoperative myasthenic crisis (10,11). Therefore, it is recommended, that all patients with thymomas should be evaluated for symptoms of myasthenia gravis both by detailed history taking and, if necessary, a laboratory analysis of serum anti-acetylcholine receptor antibodies (12).

Diagnostic procedures

Diagnosis is frequently incidental on a chest radiograph or computed tomography (CT) of the chest. An intravenous contrast-enhanced chest CT scan is the imaging modality of choice, and is essential for evaluating the precise configuration, margins, density, location and extension of the lesion (13). In CT scans, thymomas present as well-defined, homogeneous retrosternal soft tissue attenuation, which may appear round or lobulated (14). Typically, thymomas are located ventral to the great vessels and superior pericardium, however, various locations within the anterior-superior compartment of the mediastinum have been described (15). Irregular contours, necrotic or cystic components as well as focal calcification are associated with invasive thymomas (14).

Magnetic resonance imaging (MRI) of the chest is not routinely used in evaluation of thymic tumors. However, due to the absence of radiation exposure compared to CT scans, MRI can assist in the evaluation of subtle local invasion as well as cystic components. Furthermore, the ability to discriminate between thymic cysts and thymic malignancy can potentially help to avoid unnecessary thymectomy (6,13,16).

Additionally, fluorodeoxyglucose (FDG)-positron emission tomography CT (PET-CT) scans can be used to differentiate between subtypes of thymic epithelial tumors, with thymic carcinoma showing higher FDG uptake

compared to thymomas. However, PET-CT is not routinely used in the staging of thymic tumors, as thymic hyperplasia might also present with hypermetabolism (13,17). PET-CT scans have a role in the detection of local and distant metastasis for FDG-avid tumors as well as in evaluation of tumor recurrence (13,17,18).

As radiologic diagnostics have a high accuracy and can often differentiate thymomas based on imaging characteristics, pretreatment biopsy is not required if the probability of thymoma is high. Therefore, upfront surgical resection is both diagnostic and therapeutic. In all other cases and if a thymic tumor is unlikely, tissue biopsy is recommended (6,17,19). Additionally, as thymomas are usually encapsulated, biopsy, especially transpleural biopsy, risks tumor cell seeding and dissemination, which can convert an early stage thymoma into a stage IV disease with pleural dissemination (6,17,20,21).

Tumor stage and treatment

Treatment strategies must be carefully adapted to each tumor stage. For most diagnosed unclear anterior mediastinal masses, surgical resection is the primary therapeutic approach. However, for cases where a thymic carcinoma is suspected or the mass appears to be not completely resectable due to local extension or infiltration, a multimodal therapeutic strategy should be evaluated in a multidisciplinary case discussion.

Employing the tumor, node, metastasis (TNM) staging system preoperatively enhances the efficacy in evaluating the extent and resectability of thymomas, thereby guiding upfront surgical resection as the primary diagnostic and therapeutic approach (6,17). Well-encapsulated tumors or tumors that are limited to the mediastinal fat and pleura are considered resectable tumors (TNM stage I including cT1a cN0 cM0 and cT1b cN0 cM0) (22). In contrast, locally advanced tumors with invasion of the pericardium (TNM stage II including cT2 cN0 cM0) or the unilateral phrenic nerve and even those tumors showing involvement of the lung (TNM stage IIIa including cT3 cN0 cM0) can be potentially resectable. Therefore, the indication for complete resection should be discussed in a multidisciplinary board (6,23). As TNM stage IIIa includes a very heterogeneous group of tumors, ranging from potentially resectable to unresectable tumors (e.g., those with involvement of the great vessels, myocardium, trachea, esophagus), a multimodal treatment approach should be considered for these cases as well as for TNM stage IIIb (cT4 cN0 cM0) and above. In highly selected cases, surgery might even be indicated in TNM stage IVb tumors with easily resectable pleural and pericardial metastases (23,24).

Postoperatively, the Masaoka-Koga classification is employed to further stratify thymomas based on their pathological findings, thereby providing additional prognostic information and assisting in tailoring further adjuvant therapies (6,17,22-24).

Thymectomy

Despite the evolving surgical approaches over the past decades, certain core principles remain fundamental to thymectomy. Foremost among these is the necessity for complete resection, which serves as the primary goal when determining indications for surgery, as completeness of resection is an independent prognostic factor (25-31). It is important to resect all thymic tissue including the primary bulk of the thymoma, the cranial horns of the thymus, any thymic tissue invading adjacent structures and ectopic of thymic tissue that may be contained in the surrounding mediastinal adipose tissue, especially for patients with myasthenia gravis, to prevent recurrence of disease (28,32). Simultaneously, it is important to avoid tumor disruption, thereby reducing the potential risks associated with tumor spillage and pleural dissemination. Emphasizing a minimal or "no-touch" technique and ensuring *en-bloc* resection remains key across all surgical approaches (33,34). If the tumor is not deemed completely resectable during surgery or potential tumor involvement close to the resection margins cannot be excluded, metallic clips can be placed at the margins of the surgical bed to mark the area of tissue removal. This allows for concentrated postoperative radiation in case of an incomplete resection. Incomplete resections or tumor debulking are not reported to improve prognosis, however, they may be an option in individual cases (17,35).

Historically, there are several established techniques for thymectomy. Traditional open approaches have been employed in the management of anterior mediastinal tumors and were considered the standard for numerous decades (36,37). The most common open surgical approach for thymomas is the transsternal approach (38). Other approaches have been described and include transcervical approaches, as well as thoracotomies (39-41).

After the first minimally invasive thymectomy performed in the 1990s (42), video-assisted thoracoscopic surgery (VATS) has established itself as a safe and widely applied

Table 1 Search strategy summary

Items	Specification
Date of search	December 01, 2023 to January 06, 2024
Databases/sources searched	PubMed
Search terms used	Thymectomy, robotic thymectomy, robot thymectomy, robotic thymoma, robotic anterior mediastinum, RATS thymectomy, RATS thymoma, RATS anterior mediastinum, da vinci thymectomy, da vinci thymoma, da vinci anterior mediastinum, minimally invasive thymectomy, surgery anterior mediastinum, VATS thymectomy, VATS thymoma, VATS anterior mediastinum, open thymectomy, transsternal thymectomy, open surgery thymoma
Timeframe	January 01, 2003 to December 31, 2023
Inclusion and exclusion criteria	Inclusion: English language, full text articles (case studies, case reports, retrospective cohort series, systematic reviews, meta-analyses), studies of historical relevance or background
	Exclusion: studies on other compartments of the mediastinum (non-anterior), non-thymomas or non-surgical treatment
Selection process	Both co-first authors screened the titles and abstracts of all articles identified in the search. Full-text articles were retrieved for all potentially relevant studies. The reviewers then independently assessed the full-text articles for inclusion in the review. Disagreements were resolved through discussion and consensus

RATS, robotic-assisted thoracic surgery; VATS, video-assisted thoracoscopic surgery.

approach for thymectomy due to advancements in surgical instrumentation and video technology (43,44). Currently, no standard approach for VATS thymectomy exists. Trocar positioning, number of trocars used as well as side of approach (left, right, bilateral, subxiphoidal) depend on various factors, such as tumor size and location, need for optimal exposure of several anatomical structures as well as surgeons' preference (45-48). While the introduction of VATS was a major milestone in the development of minimally invasive surgery, it still shows limitations such as limited maneuverability, two-dimensional view, amplified tremor due to long stiff instruments as well as a long learning curve. The use of a robotic platform can overcome these limitations, offering greater maneuverability of instruments (endo-wrist instruments), precise manipulation with tremor suppression, better ergonomics, three-dimensional visualization and an overall shorter learning curve. Since its first implementation robotic-assisted thoracic surgery (RATS) has gained more and more popularity in the field of minimally invasive thoracic surgery in the last 20 years. We present this article in accordance with the Narrative Review reporting checklist (available at https://med.amegroups.com/article/view/10.21037/med-24-17/rc).

Methods

The literature research was conducted using the PubMed search engine. A comprehensive review of the English-language literature on RATS thymectomy was performed including case reports, retrospective and prospective cohorts, meta-analyses, systematic reviews and randomized controlled trials where available. Literature published between January 1, 2003 and December 31, 2023 was included, with some older, landmark references or cornerstone studies also cited. The search strategy is summarized in *Table 1*.

Surgical treatment of thymomas

Robotic-assisted thymectomy

The first reported robotic-assisted thymectomy took place in December 2000 (49). Similar to VATS, RATS approaches exhibit variations in trocar positioning and the number of trocars used. The subsequent section outlines the distinct approaches employed in RATS thymectomy.

In many centers that regularly conduct RATS thymectomies, patient positioning is standardized. For the resection of anterior mediastinal masses, the patient

is commonly positioned in a 30 to 45 degree semi-supine position with elevated hemithorax ipsilateral to the side of the approach (3,50). The ipsilateral arm is positioned lower than the operating table on an armrest, providing extensive space for the robotic arms. Meanwhile, the contralateral arm is supported on an additional armrest, abducted away from the chest, enabling a contralateral approach if necessary, which could be beneficial, for example, in case of massive bleeding, affording easier access for a median sternotomy (51).

While a unilateral three-trocar technique is frequently employed with incisions typically ranging between the third and fifth intercostal spaces (3,50-53). Some groups have adopted a four-trocar approach for extra mobility and flexibility (32,54).

The optimal side for RATS thymectomy remains a subject of debate. In practice, the dominant side of the tumor often dictates the side of the approach to ensure optimal visualization of the ipsilateral phrenic nerve and to manage potential pleural, pericardial or pulmonary involvement, as well as any adhesions (33). Typically, a left-sided approach is preferred, as it provides easier access to a larger portion of the thymic gland. Moreover, a composite anatomical analysis based on 50 consecutive resections of the thymus gland for myasthenia gravis by Jaretzki *et al.* revealed that in 72% of resected cases (55), the thymus gland is located laterally beneath the left phrenic nerve, offering improved identification and safer dissection around the nerve when directly visualized from the left side. Additionally, a major disadvantage of the right-sided approach, is the difficulty in identifying the left phrenic nerve, which increases the risk of intraoperative injury (33). Furthermore, since the right phrenic nerve runs near the superior vena cava, its path is more predictable and can be traced further along its caudal section (56). This allows for easier identification of the right phrenic nerve during a left-sided approach to thymectomy and reduces the risk of injury (33,57). Conversely, a right-sided approach may be helpful in reducing the risk of injuries to the heart and pericardium resulting from trocar and robotic arm insertion, given the absence of the cardiac apex (33). Further, the larger amount of space provided when entering the mediastinum from the right (due to the less prominent position of the heart and aorta on the right), is especially valuable in patients with mediastinal adiposity, left cardiac hypertrophy or a smaller thoracic cavity (e.g., in patients with Pectus excavatum) (33). In addition, the easier identification of the confluence of the superior vena cava and thus the right brachiocephalic vein, may reduce the risk of injury to these structures through better visualization (33). Thus, as these approaches offer distinct advantages, it is critical that the operating team determines the optimal approach based on their experience and their favored technique while also considering individual patient anatomy.

In addition to the left- and right-sided approaches for RATS thymectomy described above, a subxiphoid approach has recently emerged as an alternative to the lateral approaches (58). The subxiphoid approach involves establishing surgical access to the patient's thoracic cavity via a subxiphoid incision for the camera trocar (59). Once observational access is established, the instrument trocars and robotic arms are inserted either subcostally (60) or intercostally bilaterally (51,58,59,61,62). Several authors have described placing the bilateral instrument trocars below the costal arches (subcostally), reducing the risk of intercostal damage and postoperative pain (60). Groups performing subxiphoid RATS thymectomies using multiple ports have suggested that the surgical view is superior to unilateral approaches, with some comparing it favorably to the perspective achieved through a transsternal approach (60). This approach offers a favorable surgical view of the upper mediastinum and the borders of the bilateral phrenic nerves (62). However, several groups have shown that the operative time, excluding console time, was notably greater in the subxiphoid group compared to the right- and left-sided groups due to the additional time required for subxiphoid incision, tissue dissection, bilateral pleura opening, and trocar placement (51). In light of these challenges, single-port RATS thymectomy has gained attention for its minimally invasive nature, primarily utilizing a subxiphoid technique. The single-port, or uniportal, subxiphoid approach involves a single incision below the sternum and offers the advantage of avoiding intercostal nerve injury, potentially reducing postoperative pain and improving cosmetic outcomes (63,64). Park *et al.* reported their experiences with uniportal subxiphoid RATS thymectomy, highlighting its technical feasibility and satisfactory patient outcomes. However, they also acknowledged that the uniportal subxiphoid approach has limitations, such as its current inability to perform complex procedures or remove particularly large tumors (63).

In multi-port RATS thymectomy, enlarging incisions for specimen retrieval and preventing specimen disruption is crucial, necessitating additional procedural steps. In contrast, uniportal RATS and VATS enable specimen extraction

through the same incision used for access, minimizing the need for incision enlargement and potentially reducing postoperative discomfort. Ensuring meticulous specimen orientation remains essential for precise pathological assessment and surgical accuracy in both multi-port and uniportal approaches, aligning with principles of no-touch technique and *en-bloc* resection (33,34,65,66).

Outcomes after thymectomy (RATS *vs.* VATS *vs.* open)

Over the past decades, the evolution of thymectomy techniques from open surgery to VATS, and most recently to RATS, has been paralleled by significant improvements in patient outcomes. VATS holds a slight advantage due to its longer history of clinical use and wider adoption compared to RATS. Consequently, surgeons have accumulated more extensive experience and familiarity with VATS techniques (67). Additionally, certain surgeons favor the hands-on and tactile feedback offered by conventional VATS instruments over robotic instruments (68). However, several studies have indicated that VATS exhibits a less steep learning curve. This phenomenon is mainly linked to the challenge of developing essential skills, such as depth perception and video-hand-eye coordination, which are crucial for achieving competence in VATS procedures (68,69).

From a technical perspective, RATS offers several advantages over VATS. The RATS approach provides a genuine three-dimensional view and up to seven degrees of freedom for most instruments (70). It allows for adjusting the ratio of instrument movements and freezing instruments during repositioning (71). VATS instruments, which exhibit stiffness and elongation, have a tendency to amplify the motion of surgical instruments. Conversely, RATS offers a notable benefit owing to its sophisticated tremor filtering capabilities (50,72,73). These factors have led to rapid learning curves for RATS thymectomies, often requiring only 15 to 20 cases (74). However, it is essential to acknowledge that the RATS technique also has certain disadvantages, including longer setup times (which improve markedly with operating room experience) and longer intraoperative instrument change intervals. Additionally, the acquisition of new robotic instruments is costlier (50).

Open thymectomy was originally favored for its superior visualization of the situs, as it offers unparalleled visibility of the surgical field due to the wide access provided (75). For patients undergoing transsternal thymectomy, a rapid emergency response is feasible in the event of intraoperative complications, such as significant bleeding. Although, there has been a shift toward minimally invasive approaches in the past two decades, the open approach nevertheless remained a cornerstone for the resection of particularly large thymomas with major invasion of adjacent structures (76).

During the late 2000s, many authors advised against routinely employing minimally invasive surgery for thymomas exceeding 4 cm in size, favoring an open approach instead (77). More recently, several studies have shown that thymomas exceeding 5 cm can be successfully resected in a minimally invasive manner (3,53,76,78). Currently there is no consensus regarding the maximum tumor size for minimally invasive surgery (79).

In-depth comparative outcomes between RATS, VATS, and open thymectomy are summarized in *Table 2*, with a detailed comparison of the outcomes discussed in the following paragraphs.

Duration of operation

In addition to the aforementioned technical differences, operative, perioperative and short-term results vary between the techniques. In extensive meta-analyses conducted by Hess *et al.*, O'Sullivan *et al.*, and Shen *et al.*, the mean duration of surgery for thymectomies performed using RATS, VATS, and open approaches showed no statistically significant differences among the examined studies (80-82). The mean operating time among the examined studies for RATS thymectomies ranged from 71 minutes (n=51) (87) to 224.5 minutes (n=14) (89). For VATS thymectomies mean operating time ranged from 79 minutes (n=35) (87) to 198 minutes (n=79) (95) and for open thymectomies, mean operating time ranged from 88 minutes (n=44) (96) to 243.8 minutes (n=22) (89). Nevertheless, a high degree of heterogeneity in recorded operating times was noted by numerous authors and can potentially be attributed to differences in the experience of surgeons across various centers. Additionally, it was noted by several authors that various studies included in these meta-analyses may define operating times differently. Commonly these are skin incision to skin suture, or procedure time (either including or excluding docking time of the robotic system), or even total operating room occupation (81,87,97-99). In many cases, the operating time may not be defined within the text,

Table 2 Comparative outcomes: RATS *vs.* VATS *vs.* open thymectomy

Outcome	Approach for thymectomy		
	RATS	VATS	Open
Duration of operation	Meta-analyses show no statistically significant differences in mean duration of surgery between RATS, VATS, and open thymectomies. Operating times differ significantly among studies due to variations in surgical expertise and particularly in the definitions used for measuring operating time (80-82)		
Intraoperative complications	No significant differences in intraoperative complication rates were found among the three thymectomy approaches, suggesting comparable safety with appropriate patient selection (81)		
Intraoperative blood loss	RATS results in significantly lower intraoperative blood loss compared to open thymectomy (173 mL). The reported significant difference in blood loss compared to VATS thymectomy is minimal (24 mL) (81-83)	Compared to open thymectomy, VATS results in lower blood loss, while showing a slightly higher blood loss (24 mL) compared to RATS (81-83)	Open thymectomy's higher blood loss is primarily due to sternotomy's invasiveness. RATS demonstrates significantly lower blood loss compared to open thymectomy, while VATS also shows reduced blood loss, underscoring the benefits of minimally invasive approaches (81-83)
Conversion rate	Statistical analysis indicates minimal heterogeneity and no significant difference in conversion rates between RATS and VATS approaches (81); low conversion rates highlight the impact of precise patient selection, intraoperative vigilance, surgical skill, and technological advances in reducing open procedures		
Complete resection rate	There was no difference in the rate of complete resection between minimally invasive and open thymectomy approaches. Complete resection rates are consistently high across all approaches (81,84-86)		
Duration of pleural drainage	RATS shows lower (87) to significantly lower (82) drainage duration compared to VATS	VATS shows higher (87) to significantly higher (82) drainage duration compared to RATS	Minimally invasive approaches also demonstrate shorter (88) to significantly shorter (80,87) drainage durations compared to open thymectomy
Volume of pleural drainage	RATS exhibits significantly lower (82,87) pleural drainage volume compared to VATS	VATS exhibits significantly higher (82,87) pleural drainage volume compared to RATS	Minimally invasive approaches also show lower (88) to significantly lower (87) drainage volumes compared to open thymectomy
Length of hospital stay	RATS shows comparable (81) up to significantly shorter LOS compared to VATS (82,87) and shorter (89) to significantly shorter (81) LOS compared to open thymectomy	VATS shows comparable (81) up to significantly longer LOS compared to RATS (82,87) and shorter (88) to significantly shorter (87,90) LOS compared to open thymectomy	Open thymectomy shows longer (88,89) to significantly longer (81,87,90) LOS compared to minimally invasive approaches
Postoperative complications	RATS consistently shows low complication rates (81-84,87) and significantly lower rates compared to open thymectomy (81,87,91). Furthermore, RATS demonstrates comparable (87) or marginally lower (81,82,84) postoperative complication rates than VATS, with certain studies indicating significantly reduced rates (82)	VATS shows low complication rates overall (81,87). VATS and open thymectomy generally exhibit comparable complication rates (88). Moreover, VATS shows postoperative complication rates that are comparable (87) to or slightly higher (81,82,84) than those of RATS, with some studies indicating significantly higher rates (82)	Open thymectomy also demonstrates low complication rates (83,92), comparable to minimally invasive approaches (80,88), although some studies indicate significantly higher rates of postoperative complications compared to RATS thymectomy (81,87,91,92)
Mortality	All three approaches report minimal or no mortality within the first 30 days after thymectomy (80,81), indicating comparable safety and efficacy in minimizing short-term risks		
Recurrence	Data comparing recurrence rates among RATS, VATS, and open thymectomy are limited. Studies indicate no significant differences in recurrence rates between minimally invasive and open thymectomy (78,80,88), while RATS studies report no recurrences with small sample sizes (93,94)		

RATS, robotic-assisted thoracic surgery; VATS, video-assisted thoracoscopic surgery; LOS, length of hospital stay.

making interpretation difficult.

Robotic surgery safety measures

While the robotic arms allow for a greater range of motion in highly confined spaces, the lack of tactile feedback has been a concern for some surgeons (100,101). Recent developments highlight the potential for future integration of haptic feedback systems into robotic-assisted surgery, which may be immensely beneficial (101).

As described above a left-sided approach poses challenges in visualizing and identifying the right phrenic nerve and vice-versa (56). Nevertheless, due to the vena cava's prominent position as a leading structure in the right hemithorax, identifying the right phrenic nerve from the left is comparatively more straightforward (33,57). To minimize the risk of phrenic nerve injury, contralateral thoracoscopic surveillance of the contralateral nerve during VATS thymectomy has been described (102). However, this is rarely implemented in clinical practice due to increased surgical trauma, and need for a larger operating team and material, as well as only limited benefits (103).

In addition, the risk for intraoperative injury to vascular structures, and consequent minor or major bleeding must always be considered. Bleeding is primarily caused by injuries to the internal mammary vessels and the thymic veins (104,105). Significant bleeding can furthermore occur in cases of accidental injury to the left brachiocephalic vein, the superior vena cava or the ascending aorta (105,106). As they can be potentially catastrophic, all precautions to prevent injury and to control significant bleedings must be taken. Continuous identification of veins throughout the operation is crucial, as strands of tissue may unexpectedly contain smaller branches of thymic veins. As there is no tactile feedback in robotic-assisted interventions, the surgeon must pay close attention to any visual indications of tissue strain. It may be possible to control bleeding by compression, clipping, stitching or application of a vascular patch. A strategy for addressing and mitigating massive bleeding must always be at hand during RATS thymectomies and the surgical team must be prepared for open surgery. In RATS, emergency conversions to open surgery pose a challenge. This occurs because the surgeon, while operating from the control console, is not in a sterile environment. Additionally, the presence of robotic arms can significantly hinder access to the patient (107). Therefore, it is necessary to have an additional surgeon who remains consistently sterile and stays close to the patient at all times. Furthermore, thorough instruction of the entire operating team regarding procedures and intraoperative complications is necessary (108).

Intraoperative complications

The rate of intraoperative complications for RATS thymectomies was comparable to those reported for the VATS approach with pooled analysis demonstrating a range of 0% to 9% versus 0% to 11%, respectively (81,84). Among the twelve studies analyzed by O'sullivan *et al.*, which reported intraoperative complications in RATS thymectomies, seven studies indicated a 0% rate of intraoperative complications (81). The rate of complications is reported by several studies, however precise information on the occurrence of specific intraoperative complications is limited in the available studies, making it challenging to provide a quantitative overview of individual complication rates.

While a 0% intraoperative complication rate was reported for VATS thymectomy by Kamel *et al.* (n=7) (83), higher rates of intraoperative complications were reported at 5.7% by Qian *et al.* (n=35) (87) and at 11% by Rowse *et al.* (n=45) (84). Qian *et al.* describe one case of hemorrhage due to pleural adhesions in their VATS group, however, they do not relate the second case of intraoperative complication (87). The complications observed by Rowse *et al.* where small pericardiotomies of 2–3 mm in four patients and an injury to the internal mammary artery in one patient undergoing VATS thymectomy (84).

The systematic review by O'sullivan *et al.* further examined six separate studies for intraoperative complications during open thymectomy (81). Four studies reported a 0% intraoperative complication rate (89,99,109,110). Before statistical matching, Kamel *et al.* reported a 17% intraoperative complication rate (83). The importance of this value must be questioned as an outlier; however, the number of cases was only twelve and after propensity-matching the rate decreases to 4.5% (83). The specific intraoperative complications are not described. Qian *et al.* observed a 5.4% intraoperative complication rate for open thymectomy, whereby, among 37 patients, two cases of intraoperative hemorrhage occurred (87).

Summarily, these results indicate that there is no statistically significant difference in the rates of intraoperative complications between the three approaches for thymectomy. While this may be surprising considering

the intrinsic invasiveness of open thymectomy and the ostensible advantages of minimally invasive surgery, this indicates primarily that all three approaches are safe relative to one another when patients are well selected. Further research will be necessary to specify the rates of individual intraoperative complications. Additionally, increased experience with the robotic platform could potentially lead to a reduction in intraoperative complication rates, making it comparatively more advantageous in the future.

Intraoperative blood loss

Intraoperative blood loss is reported to be low for RATS thymectomy, though heterogeneity in data is very high. Across the available literature, estimated mean blood loss during RATS thymectomy ranged from less than 10 mL (n=6) reported by Renaud *et al.* (110) to 103.6 mL (n=117) as described by Kang *et al.* (92). Kamel *et al.* also reported very low mean blood loss of 20 mL among 70 patients (83). Among the studies included for blood loss in pooled analyses by O'sullivan *et al.*, this parameter did not exceed 100 mL in seven of nine studies (81).

In contrast, among the seven studies focused on comparing RATS and open thymectomy, six revealed mean blood loss of over 100 mL for open thymectomy (transsternal approach). Hereby, median blood loss ranges from 150 mL as reported by Kamel *et al.* (n=22) (83) and Kneuertz *et al.* (n=34) (76) to a mean blood loss of 466.1 mL reported by Ye *et al.* (n=51) (94) for transsternal thymectomies.

For the VATS approach, Kamel *et al.* reported a median intraoperative blood loss of 10 mL for seven cases (83). Shen *et al.* included seven studies with a total of 253 cases in their analysis for intraoperative blood loss among VATS procedures (82). Five of these seven studies indicate a mean intraoperative blood loss of less than 100 mL. O'sullivan *et al.* similarly found that among four studies, three studies reported less than 100 mL of blood loss during VATS thymectomy (81). Pooled-analysis of the seven studies that compared RATS and open thymectomy specifically indicates that mean blood loss is significantly lower for RATS groups (P=0.01) (81). However, analysis by O'sullivan *et al.* found no significant difference in terms of blood loss between RATS and VATS (81). Contrastingly, in their 2022 meta-analysis of seven studies that compared RATS versus VATS thymectomies, Shen *et al.* found that pooled analysis demonstrates that the RATS (n=196) approach yielded significantly less blood loss than VATS (n=253) (P=0.009) (82). The weighted mean difference for blood loss for RATS versus open thymectomy lay at 173 mL according to the analysis by O'sullivan *et al.*, and 24 mL for RATS versus VATS according to Shen *et al.* (81,82). The higher intraoperative blood loss observed for open thymectomy is predominantly attributable to the invasiveness of sternotomy, as opposed to the reduced incisions employed in minimally invasive techniques. While O'sullivan *et al.* question the clinical relevance of a 173 mL reduced blood loss and one may question the relevance of a 24 mL difference as well, these results nevertheless reinforce the advantages of minimally invasive surgery.

Conversion rates

In addition to significant intraoperative blood loss or vascular injury, conversion was necessary for marked pleural adhesions or significant local tumor invasion of vascular structures, the phrenic nerve or pericardium (80). Nevertheless, conversion rates during RATS thymectomies reported in literature are relatively low. Nine out of thirteen studies analyzed by O'sullivan *et al.* reported a 0% conversion rate (81). Higher conversion rates were reported by several authors, whereby the highest conversion rate reported was 7.1% by Balduyck *et al.* (n=14) (89) and Kamel *et al.* (n=70) (83). One patient reported by Balduyck *et al.* required conversion to a median sternotomy due to invasion into the subclavian vein (89). Kamel *et al.* reported a total of five conversions to an open approach out of 70 patients with three conversions attributed to advanced local invasion into surrounding structures (including the aorta and innominate vein) and two conversions for dense pleural adhesions (83). Similarly, Marulli *et al.* documented two cases where the decision to convert was made due to the size of the specimen and the suspected infiltration into the pericardium (99). Wilshire *et al.* performed one conversion due to challenges in accurately defining tumor margins (111).

Similarly, low rates of conversion to open thymectomy were reported by groups performing VATS thymectomies. Hereby, the reported conversion rates ranged from 0% (n=45) (87) to 1.3% (n=79) (95) and 4% (n=25) (85).

The specific reasons for transitioning to an open procedure were not extensively detailed in the aforementioned studies, except in one case reported by Ye *et al.*, where the reason was an intraoperative injury to the left innominate vein (85). Statistical analysis of these results indicates minimal heterogeneity and no significant

difference in conversion rates between RATS and VATS approaches (81). The low conversion rates for both RATS and VATS thymectomy indicate that with meticulous patient selection, careful intraoperative monitoring, high expertise from surgical teams, and the advancements in technology available today, an optimized response to intraoperative challenges is possible and the need for conversion to open procedures is decreased significantly.

Complete resection

Complete resection is the cornerstone of surgical treatment for thymoma. The resection boundaries for thymectomy should encompass all thymic and perithymic tissue located between the phrenic nerves, extending from the innominate vein superiorly to the diaphragm inferiorly (84). The meta-analysis by O'sullivan *et al.* includes nine studies that compare complete resection rates between RATS and open thymectomy (81). Among these studies, seven reported a 100% complete resection rate for RATS among a total of 267 patients. Kneuertz *et al.* indicate the lowest complete resection rate at 90% among 20 patients for RATS thymectomy and 85% for open thymectomy among 34 cases (76). It must be noted however that this study specifically focused on large thymomas with a median size of 6.0 cm, which may have made complete resection more challenging. In 2017, Burt *et al.* provided data from their large international registry study. Hereby, complete resection was achieved in 92% of 146 patients undergoing RATS thymectomy (86). Also, among 2028 patients that underwent open thymectomy, complete resection was achieved in 86% of patients (86). However, Burt *et al.* report that after propensity matching and balancing of all variables, the rate of complete resection did not differ between minimally invasive or open thymectomy (86). Similarly, O'sullivan *et al.* concluded after pooled analysis that no statistically significant difference in complete resection rate and decreased positive margin rate could be demonstrated between open and RATS thymectomy (81). With regard to the VATS approach, Burt *et al.* reported a 95% complete resection rate among 315 patients that underwent VATS thymectomy (86). Rowse *et al.* and Ye *et al.* furthermore reported a 100% complete resection rate among all patients undergoing RATS (n=11 and 21) and VATS thymectomy (n=45 and 25) (84,85). Subsequent statistical analysis indicates that there is no significant difference in complete resection rates between RATS and VATS thymectomy (81). The absence of statistically significant differences in complete resection rates should not come as a surprise. Each of the approaches (transsternal, VATS and RATS) offers unique benefits in terms of surgical technique and visualization. Rather than relying solely on tradition or personal preference, clinicians should meticulously evaluate individual anatomical and pathoanatomical factors that favor a specific surgical technique. Ultimately, the resection rates achieved across all three methods are comparable.

Duration and volume of pleural drainage

In terms of postoperative parameters, limited data comparing duration and volume of pleural drainage between RATS, VATS and open thymectomy is available. In the pooled analysis of seven studies conducted by Shen *et al.*, comparing RATS and VATS among a total of 603 patients, it was observed that postoperative duration of pleural drainage was lower for RATS compared to VATS (82). Specifically, the weighted mean difference indicates a shortening of approximately one day for patients undergoing RATS thymectomy (82). The shortest mean duration of postoperative pleural drainage was reported at 1.1 days by Ye *et al.* (n=21) (85) and the longest was 3.1 days as reported by Şehitogullari *et al.* (n=21) (112). Six of seven studies reported a duration of less than three days for RATS thymectomy (82).

Among VATS thymectomies, Li *et al.* reported a mean duration of postoperative pleural drainage of 2.34 days for 35 patients, the lowest mean of postoperative pleural drainage duration reported for this approach (113). Şehitogullari *et al.* reported the longest mean duration of postoperative pleural drainage for the VATS thymectomy at 5.1 days for 24 cases (112). Only two of seven studies reported an average duration of under three days for patients undergoing VATS thymectomy (82). Though, pooled analysis by Shen at al. indicates significantly shorter duration of postoperative pleural drainage for RATS compared to VATS (P<0.001), the clinical significance of this discrepancy might be debatable, particularly given the considerable heterogeneity observed in the available data on this parameter. However, when contrasting this parameter between minimally invasive and open surgical approaches, the difference becomes more apparent and, therefore, potentially more clinically significant. Among ten studies analyzed by Hess *et al.* in a meta-analysis comparing minimally invasive and open thymectomy, none of the authors reported a median duration of postoperative pleural drainage of less than 2.4 days after open thymectomy (80,114). In the open thymectomy groups, the mean duration

of postoperative pleural drainage extended beyond three days in eight out of ten studies, with Lee *et al.* reporting a mean duration of 5.3 days for 59 patients undergoing extended transsternal thymectomy (80,115). Consequentially, in seven out of ten studies, a statistically significant reduction in pleural drainage duration was noted when comparing minimally invasive and open approaches (80).

In thymectomy patients, an additional valuable metric for assessing tissue damage and postoperative healing is the total volume of pleural drainage. This metric reflects the quantity of fluid accumulated over the entire duration of pleural drainage. Shen *et al.* conducted an analysis of data from five studies involving 217 patients who underwent RATS thymectomy and 225 patients undergoing VATS thymectomy. The findings revealed that the pleural drainage volume was 80.81 mL lower in patients undergoing RATS compared to VATS (82). Among the studies included in the meta-analysis, Li *et al.* reported the lowest mean volume of drainage for RATS with 209.5 mL (n=60) (113), with Wang *et al.* documenting the highest mean volume of pleural drainage of 398.02 mL (n=58) (82,116).

In VATS thymectomy, Li *et al.* observed low median volume of pleural drainage of 217.04 mL (n=60) (113), while Qian *et al.* reported the highest mean volume of pleural drainage of 613.9 mL (n=35) (87).

While comprehensive meta-analyses comparing volume of pleural drainage across RATS, VATS and open thymectomies are scarce, Qian *et al.* report that the mean volume of pleural drainage was 352.2 mL for RATS (n=51), 613.9 mL for VATS (n=35) and 980.00 mL for open thymectomy (n=37) (87). Similarly, in a systematic review conducted by Xie *et al.* comparing VATS and open thymectomy, it was found that among three studies involving a total of 424 patients, weighted mean volume of pleural drainage was lower in VATS (408.4 mL) compared to open thymectomy (732.1 mL) (88).

The duration and volume of pleural drainage provide valuable insights into fluid dynamics within the pleural space following thoracic surgery. These parameters serve as indicators of healing, inflammation, infection, or residual fluid. Reductions in both drainage volume and duration are favorable outcomes associated with minimally invasive surgery, including RATS, suggesting decreased tissue trauma and improved postoperative recovery. It is important to acknowledge that traditional open surgical techniques are significantly more invasive and tissue-damaging. However, it is worth noting that open surgery is often necessary for particularly large thymomas, which may confound the interpretation of these parameters. Nevertheless, minimizing pleural drainage duration and volume may positively impact postoperative hospital stays for patients.

Length of hospital stay (LOS)

There is significant heterogeneity in the mean LOS reported among groups, reflecting variations in postoperative care protocols, differences in hospital policies or resources, insurance policies and patient comorbidities. Qian *et al.* reported statistically significant differences in the mean hospital stay with 4.3 days for RATS, 5.5 days for VATS and 6.6 days for open thymectomy (87). Similarly, Xie *et al.* showed an average hospital stay of 9.8 days for open thymectomy, compared to 7.0 days for VATS (88), and Friedant *et al.* noted a significantly shorter LOS for minimally invasive thymectomy (RATS and VATS) with a mean LOS of 8 days compared to open thymectomy with a mean LOS of 9 days (90). Additionally, the meta-analysis by O'sullivan *et al.* demonstrated that among 382 RATS thymectomies and 442 open thymectomies a mean weighted difference in LOS of over two days between RATS and open thymectomies, with RATS having a significantly shorter LOS (81). However, the shorter LOS (0.81 days) for RATS compared to VATS was not statistically significant (81). In a more recent meta-analysis by Shen *et al.*, RATS (n=688) showed a significantly shorter LOS, with a mean difference of 1.07 days less compared to VATS (n=730) (82). In terms of trends for LOS, among the 13 studies analyzed by O'sullivan *et al.*, 9 reported a LOS of 4 or less days for RATS, while only 3 reported the same for open thymectomy (81). Furthermore, 10 of 13 studies reported average LOS of 5 or more days after open thymectomy, while only 1 study reported such values for RATS (81). Similarly, among the 11 studies analyzed by Shen *et al.*, 8 reported LOS of 4 or more days after VATS thymectomy (82). It is conceivable that studies with larger sample sizes would be necessary to detect a more pronounced difference in LOS between RATS and VATS. An outlier among the RATS groups was the study by Balduyck *et al.* whereby mean LOS was 9.6 days for 14 patients undergoing RATS thymectomy and 11.8 days for 22 patients undergoing transsternal thymectomy (89). While it is stated that patients were released from the hospital once they were able to move around independently and when postoperative pain was effectively managed with oral analgesic medication, no specific reasoning for the extended LOS for RATS could

be found (89). Considering the intrinsic invasiveness of the open approach, open thymectomies tend to result in higher surgical trauma due to the performed sternotomy and may require the use of an epidural catheter or similar for pain management as well as more intensive monitoring, support and physiotherapeutic aid, which may be associated with a longer hospital stay.

Postoperative complications

Postoperative complications are a significant concern following thymic surgery, warranting careful monitoring and management. Current research suggests that the rate of postoperative complications is highly heterogeneous between various centers and types of complications that arise can be very diverse. Thirteen studies examined by O'sullivan *et al.* included data comparing rates of postoperative complications for RATS and open thymectomy. In these studies, 382 patients underwent RATS thymectomy and 442 had an open approach (81). Statistical analysis demonstrated a significantly lower postoperative complication rate in the RATS group with low heterogeneity (P<0.0001) (81). The lowest rates of postoperative complications after RATS thymectomy were reported at 0% by Qian *et al.*, Renaud *et al.* and Seong *et al.* for a total of 91 patients (87,93,110). In contrast, higher rates of postoperative complications after RATS were reported by Wilshire *et al.* and Balduyck *et al.* (89,111). Wilshire *et al.* state that five minor and one major event occurred among 23 patients (26%) while Balduyck *et al.* describe phrenic nerve paralysis in two patients and a deep-vein thrombosis in one, among 14 patients (21.4%) (89,111). Kamel *et al.* reported an 8% postoperative complication rate for a larger case number of 70 patients undergoing RATS thymectomy (83). Hereby, three patients experienced a myasthenic crisis, three suffered postoperative pneumonia, and two patients had prolonged air leakage (83). Other postoperative complications that have been described after RATS thymectomy include tension pneumothorax, hemorrhage, wound infection, atelectasis of the lung, pleural effusion, among others (80). Extensive trials are essential to specify the rates of complications, particularly for RATS, given its comparatively less established status and the limited accumulated experience.

For open thymectomy, no postoperative complications were observed by Kamel *et al.* for 22 patients (83). The study by Weksler *et al.* reported particularly high postoperative complication rates for the open approach (91). Among 35 open thymectomies, 20 postoperative complications arose (57%), while only one complication was observed after fifteen RATS thymectomies (6.7%) (91). These included seven cases of supraventricular arrhythmia (six patients in the transsternal group and in one in the RATS group), sternal dehiscence, atelectasis, renal failure, respiratory failure, change in mental status, severe subcutaneous emphysema, and chylothorax (91). Furthermore, Kang *et al.* reported a lower postoperative complication rate of 14% (12% after propensity score matching) for a particularly large number of open thymectomies (n=312) (92). Major complications included postoperative bleeding and reintubation, pleural or pericardial effusion, diaphragmatic paralysis and vocal cord palsy (92). Other common postoperative complications after open thymectomy were impaired wound healing and wound infection (80). In addition, sternal instability and dehiscence, respiratory infections (especially pneumonia), and in the long term, pathological scarring are reported (10,80).

Both O'sullivan *et al.* and Shen *et al.* have performed statistical analysis comparing rates of postoperative complications between RATS and VATS thymectomy. O'sullivan *et al.* reported that pooled analysis of five studies, with 212 RATS and 244 VATS thymectomies from the period 2011 to 2017, showed no statistically significant differences in postoperative complication rates (81). However, the more recent analysis by Shen *et al.*, that incorporates eight studies from a broader and more recent time frame (2013–2020), showed that the rate of postoperative complications was significantly lower in the RATS group (n=260) than in the VATS group (n=338) (P=0.02) (82). This observation suggests that the improved outcomes in RATS may be attributed to the increased accumulation of surgical expertise and advancements in robotic technology over time, reflecting a learning curve and refinement in RATS techniques that have resulted in better postoperative outcomes compared to earlier studies. With regard to the specific postoperative complications reported after VATS thymectomy, these are tendentially similar to those reported for RATS thymectomy. For instance, Rowse *et al.* reported seven postoperative complications among 45 patients, including phrenic nerve palsy, pericarditis, atrial fibrillation and pleural effusion (84). Myasthenic crises are feared complications after all forms of thymic surgery and special attention must be paid postoperatively for stigmata of respiratory failure. Strategically optimizing pharmacotherapy (including parasympathomimetics, corticosteroids, immunomodulators

and biologicals) is crucial for facilitating successful patient adaptation during and after surgery. This approach aims to detect and manage myasthenic crises effectively. While data for RATS is sparse, a meta-analysis conducted by Geng *et al.* with fifteen studies and 2,626 patients undergoing surgery for myasthenia gravis, found that the risk of a myasthenia crisis is increased with lengthier surgeries and more blood loss (117). This observation suggests that myasthenic crises may occur more frequently after open thymectomy, likely due to the observed increased blood loss. However, robust large-scale studies are needed to establish more definitive evidence. The higher incidence of postoperative complications following open thymectomy, compared to minimally invasive approaches, is anticipated due to the greater tissue trauma inherent in open procedures. Factors such as larger incisions (including sternotomy), heightened blood loss, and increased tissue manipulation contribute to the elevated rate of complications after open thymectomy. Given that managing complications can be intricate and discomforting for patients, minimizing these complications remains a notable advantage of minimally invasive techniques, particularly RATS.

Mortality

For all three approaches to thymectomy, there were few or no reported mortalities in the first 30 days after surgery (80,81). The meta-analysis by O'sullivan *et al.* indicates that of ten studies comparing mortality between RATS and open thymectomy, no deaths were recorded among 342 RATS thymectomies, and only one death was recorded within one study in the open cohort among a total of 453 open thymectomies (81). Similarly, in three studies comparing RATS and VATS, no deaths were recorded among 136 RATS thymectomies and 159 VATS thymectomies (81). Pooled analysis showed equivalent results between all of the groups and minimal heterogeneity (81). Hess *et al.* report similar findings for mortality in their meta-analysis comparing minimally invasive and open approaches for thymectomy (80). Specifically, while no deaths after minimally invasive surgery were recorded (80), Jurado *et al.* (n=186) and Weksler *et al.* (n=35) reported one death after open thymectomy (91,118). Jurado *et al.* report a pulmonary embolism on the third postoperative day as the cause of death, while Weksler *et al.* do not specify the cause of death in their reported case (91,118). After statistical analysis by Hess *et al.*, the 30-day mortality did not differ significantly between minimally invasive and open thymectomy (80). The uniformity in 30-day postoperative mortality rates across all three surgical approaches suggests comparable safety profiles and overall efficacy in terms of short-term outcomes. This indicates that while each approach may differ in terms of technique and invasiveness, they are all similarly effective in minimizing the risk of mortality within the immediate postoperative period in well selected patient groups.

Recurrence

While comprehensive data comparing recurrence rates among all three surgical approaches are scarce, insights can be gained through the examination of specific comparative studies. The systematic review by Hess *et al.* compares the recurrence rates following minimally invasive thymectomy, specifically VATS (n=764) and RATS (n=74) as one group against open thymectomy (n=1,230). Analysis of the twenty studies included, showed no statistically significant difference in recurrence. Pleural recurrence or dissemination was more frequently observed than local recurrence in both groups (80). Similarly, Xie *et al.* compared recurrence for VATS (n=540) and open (n=521) thymectomies in their systematic review. Hereby, recurrence-free survival was tracked for up to ten years among 14 studies. VATS was associated with 5-year overall survival and 10-year recurrence-free survival that were similar to or higher than those seen with open thymectomy (88). Agatsuma *et al.* also observed no statistically significant difference in recurrence-free survival and overall survival rates between their propensity score-matched VATS (n=140) and open thymectomy (n=140) groups (78). Additionally, Ye *et al.* (RATS, n=23) and Seong *et al.* (RATS, n=34) specifically compared recurrence rates between RATS and open thymectomies (93,94). Thymoma recurrence was monitored using chest CT scans at 6 and 12 months post-surgery, followed by annual scans in the study by Ye *et al.* (94). In the study by Ye *et al.*, no recurrences were observed during the postoperative follow-up period, which extended for 16.9 months (range, 1–48 months) in the RATS group and 18.1 months (range, 1–48 months) in the open thymectomy group (94). Additionally, Seong *et al.* reported no recurrences in either study group during a mean follow-up duration of 1.11±0.21 years for the RATS group and 1.85±0.19 years (range, data not specified) for the open thymectomy group (93). These studies, however, have relatively small sample sizes.

Data on recurrence rates after RATS thymectomy are

currently limited, and long-term follow-up is not yet widely available, likely due to the recent adoption of this approach in thymic surgery. Nevertheless, existing data suggests that RATS thymectomy shows comparable local and pleural recurrence rates to both VATS and open thymectomy.

Limitations

Our narrative review encountered several limitations, and the findings necessitate cautious interpretation. The studies under review predominantly followed a retrospective, non-randomized, and purely observational design, given the absence of prospective, multicenter trials. Consensus among all authors underscores the need for additional investigation, particularly through larger, robustly designed randomized trials, to comprehensively assess oncological outcomes and long-term patient outcomes in this field.

Conclusions

Meticulous staging and diagnostics as well as an efficient multidisciplinary approach to therapeutic decisions are critical for the successful treatment of patients with thymomas. Complete resection of the entire thymus is the preferred primary treatment approach and each surgical approach to thymectomy, whether open, VATS, or RATS, presents unique technical, perioperative and clinical advantages, as well as disadvantages depending on tumor stage and local extension of disease. Minimally invasive thymectomy using RATS is frequently performed from the left side as many thymomas are located left-sided of the patient's median. Additionally, right-sided and subxiphoidal approaches are feasible alternatives. Open, VATS and RATS thymectomies showed comparable operating times, and achievement of complete resection with similar conversion rates between VATS and RATS. In terms of LOS, estimated intraoperative blood loss and postoperative complications, significant differences favoring RATS are reported. Despite ongoing debate regarding the optimal approach, current research supports the feasibility and safety of RATS techniques in achieving excellent outcomes. Future studies and advancements in technology may further refine the role of RATS thymectomy in the management of thymomas.

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Footnote

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Review Article

Managing recurrent thymic epithelial tumors after resection: outcomes and role of re-resection

Tetsuya Mizuno, Toyofumi Fengshi Chen-Yoshikawa

Department of Thoracic Surgery, Nagoya University Graduate School of Medicine, Nagoya, Japan

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Correspondence to: Toyofumi Fengshi Chen-Yoshikawa, MD. Department of Thoracic Surgery, Nagoya University Graduate School of Medicine, Tsurumai-cho 65, Showa-ku, Nagoya, 466-8550, Japan. Email: tyoshikawa@med.nagoya-u.ac.jp.

Abstract: Thymic epithelial tumors (TETs) are rare neoplasms that include thymomas, thymic carcinomas (TCs), and thymic neuroendocrine neoplasms (TNENs). These three tumor categories differ in aggressiveness, the incidence of recurrence after resection, the pattern of recurrence, and survival outcomes. Owing to the tumor's rarity, randomized trials have not been performed in the initial treatment setting. Furthermore, such trials have never been performed in recurrent cases after the initial resection. Thymomas have indolent characteristics, with a wide range of biological spectra compared to TCs and TNENs; therefore, several authors have reported favorable outcomes after re-resection for recurrent thymomas. Common recurrent sites are the local site and pleura, and recurrent disease progresses slowly after detection. Additionally, long-term survivors are sometimes observed after recurrence, and whether re-resections contribute to post-recurrent and cause-specific survival remains unclear. Multimodal therapies are indicated in patients with locally or regionally advanced recurrence, similar to those performed in the initial treatment settings. TCs and TNENs exhibit more aggressive behavior than thymomas. Surgical resection was performed on selected patients who experienced recurrence. Currently, there are no guidelines on selecting patients for re-resection. Therefore, it is most likely that each physician selects based on favorable factors, including the extent of disease, disease-free intervals, and histology. No evidence of nonsurgical treatments, such as radiotherapy or chemotherapy, has yet to be established. This review article summarizes the limited evidence on managing recurrent TETs after resection compared to thymomas, TCs, and TNENs, focusing on re-resection.

Keywords: Thymic epithelial tumors (TETs); recurrence; re-resection

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Introduction

Thymic epithelial tumors (TETs) are rare neoplasms, with an incidence of 0.15 per 100,000 person-years (1), although they are the most common tumors arising from the anterior mediastinum. Although both the National Comprehensive Cancer Network (NCCN) guidelines and the European Society for Medical Oncology (ESMO) guidelines suggested that recurrent TETs should be managed following the same strategy as newly diagnosed tumors (2,3), due to the low incidence of the disease, and limited knowledge of its biology, the establishment of standard treatment based on prospective studies has not yet been achieved. Treatments, including surgery, have been recommended for resectable cases, and induction therapies are considered for locally advanced cases. In selected cases of thymomas that initially appear with pleural disease, surgical resection has been indicated to achieve complete macroscopic resection due to their indolent characteristics.

Table 1 Study characteristics

Authors	Year	Patients with Rec.	Thymoma	TC	TNEN	Rec. after initial surgery (%)	MG (%)	Surgery for Rec. (%)	CR in re-resected cases (%)
Bott (4)	2011	25	15	10	NA	22.3	NA	44.4	50.0
Hamaji (5)	2012	48	30	9	9	13.9	13.0	83.3	NA
Mizuno (6)	2015	405	243	156	NA	14.8	13.3	38.6	71.0
Margaritora (7)	2011	43	43	0	0	13.7	93.0	69.8	73.0
Yano (8)	2011	24	24	0	0	15.1	20.8	50.0	100 (MCR)
Bae (9)	2012	41	41	0	0	13.4	53.7	36.6	87.0
Sandri (13)	2014	81	81	0	0	NA	66.7	75.3	73.0
Marulli (10)	2016	103	103	0	0	9.3	61.2	63.4	68.5 (MCR)
Fiorelli (11)	2017	53	53	0	0	10.3	56.0	71.7	60.0
Chiappetta (14)	2019	155	155	0	0	NA	69.0	87.0	70.4
Chiappetta (15)	2021	160	135	0	0	NA	66.6	84.3	80.7
Miyata (12)	2021	60	0	38	16	39.4	NA	27.0	NA

Rec., recurrence; TC, thymic carcinoma; TNEN, thymic neuroendocrine neoplasm; MG, myasthenia gravis; CR, complete resection; NA, not available; MCR, macroscopic complete resection.

Despite efforts by physicians, not a small proportion, 10–40% of patients with TET experience recurrence, those are 13.9–22.3% in all TETs (4-6), 36.6–87.0% in thymomas (7-11), 39.4% in thymic cancers (TCs) and thymic neuroendocrine neoplasms (TNENs) (12) (*Table 1*), and treatment is required after complete resection. In cases of recurrence of other malignant neoplasms, surgical resection has been indicated for limited and/or pleural disease based on previous studies, which mainly consisted of retrospective cohort studies, including a small series.

In this literature, we review previous literature regarding the treatment of recurrent TETs, including thymomas, TCs, and TNENs, and aim to provide a perspective on current treatment strategies, especially those focusing on surgical resections. We searched articles published after 2010 using the terms recurrence, thymic tumor, and resection in the PubMed database. Articles including 20 or more treated patients with recurrence were selected for discussing re-resection for TETs.

Initial treatment course of TETs and afterward

The current World Health Organization (WHO) classification divides this entity into thymomas, TCs, and TNENs (16). They have a wide range of histological characteristics and malignant potentials. Surgical resection is considered the mainstay of treatment for these tumors if they are resectable. Preoperative treatment is considered for complete resection during surgery for locally advanced diseases with invasion of neighboring structures, including the great vessels. After complete resection is achieved, the disease control and prognosis of patients are usually favorable. However, a significant proportion of patients experience disease recurrence, which sometimes develops at a later stage and is subsequently diagnosed late. A mean recurrence-free interval (RFI) of more than 5 years after initial resection was documented (7,13,14) (*Table 2*). The WHO histological type, tumor size at initial treatment, pathological stage, and completeness of initial resection have been suggested as potential risk factors for recurrence after resection. There are various disease statuses at the time of recurrence diagnosis. Treatment strategies are planned based on factors including extent of disease, disease-free interval (DFI), WHO histological type, patient symptoms, and presence of comorbidities, including autoimmune myasthenia gravis (MG).

Incidence and mode of recurrence of TETs after initial resection

Owing to their indolent biological nature, disease control of thymomas is comparatively favorable after initial resection.

Table 2 Summarized outcomes of studies

Authors	Year	RFI (months)	Rec. site	OS, %		OS (surgery), %		Prognostic factors
				5-year	10-year	5-year	10-year	
Bott (4)	2011	NA	No distant 76.0%, distant 24.0%	58.0	41.0	82.0	58.0	None
Hamaji (5)	2012	Median 45	Local 23.7%, pleura 73.7%, lung 26.3%, distant 26.8%	37.4	11.6	NA	NA	Histology (thymoma)
Mizuno (6)	2015	Mean 32	Local 14.7%, pleura 54.1%, lung 21.0%	59.9	42.5	82.7	68.2	Non-TC, RFI
Margaritora (7)	2011	Mean 34.6	Local 4.2%, pleura 87.4%, lung 4.2%, distant 4.2%	73.3	25.1	NA	NA	Small NRL
Yano (8)	2011	Mean 92.7	Local 28%, pleura 58%, lung 12%	64.0	51.0	77.0	NA	CR, surgery
Bae (9)	2012	Median 41	Local 26.8%, regional 70.7%, distant 2.5%	59.7	33.2	90.9 (CR)	NA	Histology, CR
Sandri (13)	2014	Mean 86.5	Local 18.5%, pleura/pericardium 58%, lung 16.0%	68.7	52.0	82.4 (CR)	65.4 (CR)	CR, Rec. site
Marulli (10)	2016	Median 50	Local 19.4%, regional 69.9%, distant 22.3%	63.0	37.0	NA	NA	MCR, single rec.
Fiorelli (11)	2017	Mean 55	Local 24.0%, regional 49.0%, distant 27.0%	52.0	32.0	NA	NA	CR, reresection
Chiappetta (14)	2019	Mean 78	Pleura 49.6%, parenchyma 6.4%, both 13.5%	70.2	44.4	70.5	67.3	MG, long RFI
Chiappetta (15)	2021	NA	Local 12.5%, regional 71.8%, distant 15.7%	91.0	67.0	91.0	67.0	Locoregional single, intrathoracic single
Miyata (12)	2021	Median 17.5	Local 41.7%, distant 58.3%	23.0	NA	30.0	NA	Initial stage, RFI, treatment/CTx for Rec.

RFI, recurrence-free interval; Rec., recurrence; OS, overall survival; NA, not available; TC, thymic carcinoma; NRL, number of recurrent lesions; CR, complete resection; MCR, macroscopic complete resection; MG, myasthenia gravis; CTx, chemotherapy.

Recurrence rates have been reported to be 10.3–15.1% in resected thymoma cases (7-11) (*Table 1*). According to the Japanese Association of Research for Thymus (JART), the recurrence rate after resection was 10.0% (6). Differential recurrence rates were reported according to the WHO Health Organization histologic type and initial stage. According to a report by Bae *et al.*, the recurrence rates of types A, AB, B1, B2, and B3 were 0, 6.3, 4.2, 18.2, and 20.7%, respectively, indicating high recurrence rates of Type B2–3 thymoma. Regarding the initial stage, Masaoka stages I, II, III, and IV recurrence rates were 6.0%, 11.4%, 26.8%, and 50%, respectively, and higher recurrence rates were identified in advanced stages (9).

The modes of recurrence of resected thymomas are distinctive compared to those of other malignancies, including TCs and TNENs. Sandri *et al.* reported that 58% of the pleural/pericardium sites and 18.5% of the mediastinum were recurrent sites in thymomas (13). Chiappetta *et al.* documented 12.5% of local sites, 71.8% of regional sites, including the pleura, and 15.7% of distant sites, following the definition proposed by the International Thymic Malignancy Interest Group (ITMIG) (15). This proposal defines local recurrence as a disease in the anterior mediastinum or tissues contiguous with the resected primary thymoma, regional recurrence as intrathoracic recurrence, and distant recurrence as extrathoracic recurrence and intraparenchymal pulmonary nodules (17). Considering the trends in recurrence sites with a low incidence of distant recurrence, we have acknowledged that we often indicate local therapies such as surgery and/or radiotherapy to treat recurrent thymoma after resection.

Higher recurrence rates have been observed in patients with resected TCs. Ruffini *et al.* documented 28% (18), Hamaji *et al.* did as high as 40.9% (5), and Hishida *et al.* did 39.1% of recurrent rate after R0 resection (19). In these reports on TCs, the incidence and the modes of recurrence were different from those of thymomas. Many patients experience recurrence at distant sites in the lungs, bone, brain, and liver, and local therapies are unfavorable (5,20).

In recurrent thymoma cases, the proportion of patients indicated for re-resection ranged from 36.6% to 87.0% (7-11,13-15) (*Table 1*). These differences were assumed to be due to the treatment period, different modes of recurrence by cohort, and the treatment policies of physicians. In the

JART cohort, one of the largest series, resections were indicated in 49.8% of recurrent thymoma cases and 24.4% of recurrent TCs cases, showing frequent indications for re-resection in thymoma cases (6). In the combined analyses of recurrent TCs and TNENs, surgery was performed for limited cases, as low as 27% (12).

Prognosis of TETs after recurrence

Most studies have reported the long-term outcomes of 5- and 10-year overall survival (OS) after thymoma recurrence. These values ranged from 52.0–91.0% and 25.1–67.0%, respectively, and included patients treated with re-resection and nonsurgical treatment. In cases of re-resection, the 5- and 10-year OS rates range from 70.5–91.0% and from 58.0–67.3%, respectively (4-15) (*Table 2*). These are more favorable outcomes than those in non-surgically treated patients, although the survival differences were insignificant in several reports (9,13,14). Better survival of patients with thymomas after recurrence has been documented (5,13). Regarding progression-free survival (PFS) after initial recurrence, for which reports are limited, an identical trend to that in post-recurrent survival (PRS) was observed, and the PFS of TC patients was extremely poor (5).

The effect of recurrence sites on patient outcomes remains controversial. Sandri *et al.* noted the disease-free survival (DFS) advantages of patients after initial recurrence with local recurrence compared to those with pleural or lung recurrence (13). At the same time, Chiappetta *et al.* did not show a significant difference in PRS by recurrent sites proposed by ITMIG (15). In cases of pleural recurrence, Choe *et al.* documented a 5-year OS rate of 73% and a 10-year OS rate of 51% after re-resection in a combined analysis of thymomas and TCs (21). In comparison, Aprile *et al.* documented 59.9% and 77.0% 10-year-OS rate after re-resection and resection and hyperthermic intrathoracic chemotherapy (HITHOC) in thymoma cases, suggesting the efficacy of HITHOC in combination with surgical resection to prolong the survival of thymoma patients with pleural recurrence (22).

Surgical treatment for recurred disease

For treating recurrent thymic tumors, tumor resection is indicated based on the extent of the disease. The efficacy of perioperative treatments for recurrent disease has not been proven, and their indications have not been fully discussed. They are sometimes used as an initial treatment for locally advanced diseases (9,13-15). The indications may differ among reports; according to Chiappetta *et al.*, perioperative chemotherapy/radiotherapy was indicated in 49% and 57.7% of patients who underwent re-resection (14,15). Conversely, Sandri *et al.* found that perioperative treatment was indicated for no more than one-fourth of re-resected cases (13).

Furthermore, most studies did not include patient selection for perioperative treatment. The ESMO guidelines recommend cisplatin-based regimens in combination with doxorubicin and cyclophosphamide (CAP) or etoposide (2). CAMP (cisplatin, doxorubicin, cyclophosphamide, methylprednisolone) and ADOC (adriamycin, vincristine, cyclophosphamide, cisplatin) are also being used for advanced cases. In cases of pleural metastases, Choe *et al.* used CAP regimens in 60% of patients with preoperative treatment, cisplatin and paclitaxel in 13%, and cisplatin and etoposide in 10% (21). After two to four cycles, surgical resection was performed to achieve complete resection, especially for locally recurrent disease. Chemoradiotherapy is sometimes indicated with a better response and subsequent complete resection.

Regarding surgical procedures for pleural disease, partial pleurectomy and pleural decortication are mainly performed, and extrapleural pneumonectomy (EPP) and pleurectomy/decortication (P/D) are indicated for selected patients (23). Nakamura *et al.* reported six cases of pleural recurrence in six thymoma patients treated with multimodality therapy. Two of the six patients underwent EPP, and the remaining four patients underwent pleural resection after CAMP therapy (24). As previously mentioned, the combination of HITHOC with surgery is a treatment option for disseminated diseases of the pleural cavity. Aprile *et al.* documented better local DFS in patients with HITHOC than in those who underwent surgery alone; however, a significantly favorable OS was not observed (22).

Prognostic factors after re-resection

The PRS has been widely used as a standard outcome measure for factors associated with outcomes after recurrence. In cases of thymoma recurrence, most studies have identified surgical treatment and complete resection as favorable prognostic factors (5-7). Mizuno *et al.* previously reported that macroscopic complete resection (R0–1) provided a better PRS than macroscopic incomplete resection (R2) and nonsurgical cases from the Japanese

database (6). Other studies have suggested that the initial stage, WHO histology, single recurrence, and locoregional recurrence are favorable factors (5,10,13) (*Table 2*). In DFS analyses, complete resection and the site of recurrence are also potential prognostic factors (13,15). TCs are often evaluated in combination with other types of thymoma. These included limited TCs series, and prognostic factors were not reported (4,5,20).

Role of repeated resection

Thymomas have indolent characteristics and exhibit a less aggressive progression. However, they sometimes develop locally or exhibit pleural recurrence rather than distant metastases. Fiorelli *et al.* documented 53 cases of thymoma recurrence after complete resection. Among the 38 patients who underwent repeated resection for the first recurrence, 22 (57.9%) experienced a second recurrence. They performed surgery in 3 cases of a fourth recurrence (11). Chiappetta *et al.* treated 160 patients with thymoma with initial recurrence, and re-resection was indicated in 135 cases (84.3%). A second recurrence developed in 60 cases (37.5%), and multivariable analysis documented that the only independent prognostic factor for OS after the second recurrence was complete surgical resection (14). Their results may indicate that repeated surgeries for recurrence are associated with better survival. These modalities are considered options for thymomas with resectable recurrence. Whether surgical interventions prolong survival has not been proven.

Impact of MG on post-recurrent outcomes

Thymomas are unique neoplasms associated with autoimmune disorders. MG is the most common autoimmune disease accompanied by thymomas, and up to 30% of patients are reported to have the disease. In patients with recurrent disease after thymoma resection, a wide range of patients (13.3–93%) had MG (6,7,11,13,14). Intensive surgical and/or nonsurgical treatment may worsen their symptoms, and sufficient treatment could not be given. However, the effect of MG on post-recurrence survival remains controversial. Fiorelli *et al.* reported better survival in patients without MG than in those with MG (11). Chiappetta *et al.* reported opposite outcomes of better OS and DFS in patients with MG (14). They commented on the potential associations between MG and early disease and the impact of intensive surveillance performed by oncological and neurological physicians. They concluded that the relationship between MG and thymoma prognosis remains unclear. Other studies have not demonstrated significant associations between MG and the outcomes of patients with recurrent thymoma and TETs (6,7,13).

Nonsurgical treatment for recurrence

Although surgical resection is recommended for resectable recurrent TETs, nonsurgical treatment is indicated for cases of unresectable recurrence owing to the extent of the disease or medical reasons. In patients without a history of chemotherapy, cisplatin-based combination regimens are indicated: a combination of cisplatin, doxorubicin, and cyclophosphamide, and cisplatin and etoposide as the primary chemotherapy for advanced disease. In patients with a history of chemotherapy, re-administration of a previously effective regimen was considered. Other second-line treatment options include carboplatin plus paclitaxel or cisplatin plus etoposide (2,25). In TC cases, immune checkpoint inhibitors (ICIs), which block the programmed cell death-1 (PD-1) pathway (PD-1 and PD-L1), have changed the treatment. Several phase II trials have shown improved objective response rates (ORRs) and median PFS after ICI monotherapy with pembrolizumab or nivolumab (26-28). Specifically, Cho *et al.* reported a median PFS of 6.1 months with pembrolizumab therapy in the pretreated TETs cohort. They also reported including one third of enrolled patients experienced recurrence following resection (27). Recently, a phase II trial was conducted to establish the safety and efficacy of atezolizumab in combination with carboplatin and paclitaxel (29). As for molecular targeted therapy, the mammalian target of rapamycin (mTOR) inhibitor everolimus and the multi-kinase inhibitor lenvatinib showed promising outcomes in patients previously treated with cisplatin. The median OS was 28.3 months, and the OS rate at 36 months was 35.7% (30).

Radiotherapy has been an option for treatment in combination with chemotherapy in cases with unresectable local or limited extent of the disease. Recent intensity-modulated radiotherapy (IMRT) techniques have shown advantages in target coverage and avoidance of normal tissue. This modality provides good local control for patients with pleural disease and can be an option for patients for whom surgery is unfeasible (31,32).

Conclusions

The recurrence of TETs after resection is a heterogeneous disease in terms of the malignant potential of the tumor itself and the mode of recurrence. In recurrent TCs and TNENs, DFIs are commonly shorter than those in thymomas, and rapid progression and extension are observed. Re-resections may be indicated for localized disease, and prolonged PRS is expected in selected TC/TNEN patients for re-resections. Conversely, thymomas rarely present with distant metastases, and recurrent diseases often develop at local and pleural sites. We frequently recommend re-resection for patients with recurrent thymoma because of these tumor characteristics.

Furthermore, the PRS of thymomas with re-resection was more favorable than that of TCs and TNENs. As potential prognostic factors, WHO histological type, stage, and DFI have been proposed, and indications for re-resection have been decided, considering the presence of those factors. However, the effect of MG on the outcomes of patients with recurrent thymomas is controversial. For locally invasive and pleural diseases, especially thymomas, a multimodal approach might be an option for complete re-resection and disease control. Although survival in patients with re-resected TETs of a less aggressive nature is favorable compared with that of nonsurgical ones, how the surgical interventions themselves prolong PRS has not yet been proven. Further exploration and debate are required regarding the efficacy of re-resection for recurrent TETs.

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Footnote

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Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://med.amegroups.com/article/view/10.21037/med-24-26/coif). The authors have no conflicts of interest to declare.

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Review Article

Transesophageal endosonography in the diagnosis of sarcoidosis: a narrative review

Yuka Shinohara, Masahide Oki

Department of Respiratory Medicine, NHO Nagoya Medical Center, Nagoya, Japan

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

Correspondence to: Masahide Oki, MD. Department of Respiratory Medicine, NHO Nagoya Medical Center, 4-1-1 Sannomaru, Naka-ku, Nagoya 460-0001, Japan. Email: masahideo@aol.com.

Background and Objective: Transesophageal endosonography, including endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) and endoscopic ultrasound with bronchoscope-guided fine-needle aspiration (EUS-B-FNA), has been applied to the diagnosis of benign as well as malignant diseases. This narrative review summarizes the recent use of EUS-(B)-FNA in diagnosing sarcoidosis.

Methods: A comprehensive and systematic online literature search of PubMed was conducted using the keywords ("sarcoidosis"), and ("EUS" OR "EUS-FNA" OR "EUS-B" OR "EUS-B-FNA" OR "endoscopic ultrasound guided fine needle aspiration" OR "endoscopic ultrasound using the EBUS scope guided fine needle aspiration" OR "endoscopic ultrasound using the EBUS bronchoscope" OR "transesophageal" OR "transesophageal endoscopic ultrasound guided fine needle aspiration" OR "transesophageal bronchoscopic ultrasound guided fine needle aspiration").

Key Content and Findings: Most EUS-FNA procedures were performed under moderate sedation, primarily using midazolam, with 22-gauge needles. The diagnostic sensitivity of sarcoidosis in mediastinal lymph node sampling is as high as 75–100% for EUS-FNA and 70–86% for EUS-B-FNA, much higher than that of traditional bronchoscopic procedures, such as transbronchial lung biopsy (TBLB) and conventional transbronchial needle aspiration (TBNA). The complications associated with EUS-(B)-FNA have thus far included only a few cases of mediastinitis, successfully treated with antibiotics, as well as lymph node hematoma, and sore throat.

Conclusions: EUS-FNA and EUS-B-FNA provide high diagnostic yields in patients with sarcoidosis. The safety profile is acceptable, although there is a slight risk of infectious complications. EUS-B-FNA, a minimally invasive and well-tolerated procedure, offers a viable alternative to endobronchial ultrasound-guided TBNA (EBUS-TBNA) for the diagnosis of sarcoidosis, particularly in patients with cough and poor respiratory function; this procedure can easily be performed by pulmonologists.

Keywords: Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA); endoscopic ultrasound with bronchoscope-guided fine-needle aspiration (EUS-B-FNA); sarcoidosis

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Introduction

The clinical manifestations of sarcoidosis are often non-specific. The granulomatous inflammation seen in sarcoidosis is also associated with other diseases that present with similar findings, including tuberculosis, fungal infections, lymphoma, lung cancer, and berylliosis, all of which must be excluded (1,2). Thus, to avoid false-positive results, a definitive diagnosis requires both clinical and

radiologic confirmation, including evidence of noncaseating granuloma of the involved tissue (3).

In patients with lesions that do not involve the skin or peripheral lymph nodes and thus cannot be easily sampled, transbronchial lung biopsy (TBLB) was recommended in the previous American Thoracic Society guidelines published in 1999 (2). However, the diagnostic yield of this procedure is only ~65% (40–90%) and a pathological diagnosis cannot be made in one-third of the cases (4,5). In addition, TBLB is occasionally associated with pneumothorax (incidence of 1–5%) and bleeding (9%) (6). Transbronchial needle aspiration (TBNA), as a conventional bronchoscopic approach, has a diagnostic yield similar to that of TBLB (42–76%) (7-9). Mediastinoscopy was once the next step in patients not diagnosed by TBLB or TBNA, as the reported diagnostic yield is as high as 82–97% (10-12), but the procedure is invasive and requires hospitalization and general anesthesia.

The development of endosonography, including endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) and endobronchial ultrasound-guided TBNA (EBUS-TBNA), has dramatically changed the evaluation of hilar-mediastinal lesions. The high accuracy and safety of endosonography for diagnosing benign as well as malignant lesions is now well established (13,14). As sarcoidosis is characterized by enlarged hilar and mediastinal lymph nodes, endosonography has proven useful in obtaining tissue specimens for its diagnosis, as demonstrated in several studies. The advantages of EBUS-TBNA are that it allows real-time TBNA and the locations of the needle and the target lesion on ultrasound images can be simultaneously confirmed. Given its high diagnostic yield (71–94%) and excellent safety (15-23), EBUS-TBNA is now recommended as the first-line method of tissue sampling in patients with suspected sarcoidosis (3). Although the reported diagnostic accuracy of EUS-FNA for accessible mediastinal lesions is comparable to that of EBUS-TBNA, a recent guideline (3) did not refer to its use for tissue sampling in sarcoidosis. This narrative review summarizes the current application of EUS-FNA and endoscopic ultrasound with bronchoscope-guided fine-needle aspiration (EUS-B-FNA) in diagnosing thoracic sarcoidosis. We present this article in accordance with the Narrative Review reporting checklist (available at https://med.amegroups.com/article/view/10.21037/med-24-37/rc).

Methods

A comprehensive and systematic online literature search of PubMed was conducted using the keywords ("sarcoidosis"), and ("EUS" OR "EUS-FNA" OR "EUS-B" OR "EUS-B-FNA" OR "endoscopic ultrasound guided fine needle aspiration" OR "endoscopic ultrasound using the EBUS scope guided fine needle aspiration" OR "endoscopic ultrasound using the EBUS bronchoscope" OR "transesophageal" OR "transesophageal endoscopic ultrasound guided fine needle aspiration" OR "transesophageal bronchoscopic ultrasound guided fine needle aspiration"). From the initially identified 35,324 articles related to sarcoidosis, 296 articles were retrieved. After the exclusion of those that did not include mediastinal disease, 258 articles remained. Editorials, comment, letters, proceedings, books, and abstracts were also excluded. The majority of the articles were related to EBUS-TBNA. After the list was narrowed to articles with at least 10 cases of sarcoidosis diagnosed by EUS-FNA and EUS-B-FNA, 15 articles were finally reviewed. The search strategy is summarized in *Table 1*.

Procedures

The results regarding the use of EUS-FNA and EUS-B-FNA in diagnosing sarcoidosis are summarized in *Table 2* (18,24-35) and *Table 3* (36-38). In most studies, EUS-FNA was performed with the patients under moderate sedation, mainly using midazolam, but in a few studies the patients were placed under deep sedation using propofol. Because EUS endoscopes have a larger working channel than EBUS bronchoscopes, a variety of needles are available. The reliability of the cytological diagnosis of sarcoidosis has been well established. In most studies, 22-gauge needles were used, but a few studies used 19-gauge needles. In a prospective study, Iwashita *et al.* prepared cytological and histological specimens obtained using a 19-gauge needle, and each specimen was blindly evaluated by pathologists (29). The sensitivity of histological specimens in EUS-FNA was significantly higher than that of cytological specimens (94.4% *vs.* 77.8%, P=0.0444). The subcarinal lymph nodes were the most frequently examined, followed by the left paratracheal lymph nodes. The subaortic, para-esophageal, and intra-abdominal lymph nodes, which are inaccessible by EBUS-TBNA, were evaluated only rarely.

Diagnostic performance of EUS-FNA

In 1999, Mishra *et al.* published the first report of the

Table 1 Search strategy summary

Items	Specification
Date of search	May 18, 2024
Databases and other sources searched	PubMed
Search terms used	("sarcoidosis"), and ("EUS" OR "EUS-FNA" OR "EUS-B" OR "EUS-B-FNA" OR "endoscopic ultrasound guided fine needle aspiration" OR "endoscopic ultrasound using the EBUS scope guided fine needle aspiration" OR "endoscopic ultrasound using the EBUS bronchoscope" OR "transesophageal" OR "transesophageal endoscopic ultrasound guided fine needle aspiration" OR "transesophageal bronchoscopic ultrasound guided fine needle aspiration")
Timeframe	January 1, 1938 to May 18, 2024
Inclusion and exclusion criteria	Inclusion criteria: original article, research article, full paper, English language
	Exclusion criteria: editorial, comments, letters, proceedings, books, abstracts, non-English papers, less than 10 cases of sarcoidosis diagnosed
Selection process	First author conducted the selection process, initial literature review, assessed all of the identified studies based on the eligibility criteria. Both authors reviewed the final list of studies included in the review

EUS, endoscopic ultrasound; EUS-FNA, endoscopic ultrasound-guided fine-needle aspiration; EUS-B-FNA, endoscopic ultrasound with bronchoscope-guided fine-needle aspiration; EBUS, endobronchial ultrasound.

usefulness of EUS-FNA in diagnosing sarcoidosis (39), based on the cytological diagnosis of sarcoidosis in 6 of 108 patients who underwent EUS-FNA of the mediastinal lymph nodes. Subsequently, several investigators reported the diagnostic efficacy of EUS-FNA in patients with sarcoidosis. In 13 studies, 4 involving patients with mediastinal lymphadenopathy (24,26,31,33) and 9 limited to patients with suspected sarcoidosis (18,25,27-30,32,34,35), the reported sensitivities ranged from 75% to 100% (*Table 2*). The results are comparable to those obtained with EBUS-TBNA [71–94% (15-22)] or mediastinoscopy [82–97% (10-12)].

Three studies evaluated the diagnostic yield of EUS-FNA in patients with negative bronchoscopy results. Tournoy *et al.* performed EUS-FNA in 18 patients with negative bronchoscopy [TBLB, TBNA, endobronchial biopsy (EBB)] for sarcoidosis and reported a sensitivity of 94% in 16 patients (18). In a crossover study, Gnass *et al.* performed EUS-FNA in 21 patients with negative TBNA or EBUS-TBNA results; sarcoidosis was diagnosed in 9 patients whereas EBUS-TBNA did not identify any additional cases among 5 patients with negative EUS-FNA results (34). In a crossover study, Kocoń *et al.* reported that EUS-FNA was of diagnostic utility in 7 of 8 patients with negative bronchoscopy results (combined EBUS-TBNA, TBLB, EBB and TBNA), and EBUS-TBNA in 2 of 8 patients with negative bronchoscopy results (combined EUS-FNA, TBLB, EBB and TBNA) (35).

As granulomatous inflammation is associated with many diseases besides sarcoidosis, including tuberculosis and fungal infections, there is a risk of false-positive results, but such cases are rare. In a study investigating the usefulness of EUS-FNA in differentiating between tuberculosis and sarcoidosis, including 30 cases of sarcoidosis and 28 cases of tuberculosis, 3 tuberculosis cases were initially misdiagnosed as sarcoidosis based on the cytology obtained with EUS-FNA (31).

Diagnostic performance of EUS-B-FNA

Despite the high diagnostic utility of mediastinal lymph node biopsy by EUS-FNA, the procedure is limited by the need for a skilled endoscopist and specialized equipment, such as an ultrasound endoscope and needle. An EBUS bronchoscope, equipped with a miniaturized convex probe at its tip, shares a mechanism similar to an EUS endoscope. Therefore, the transesophageal EUS-FNA procedure can be performed using an EBUS bronchoscope; this technique is termed EUS-B-FNA (40). Considering the familiarity of pulmonologists with EBUS bronchoscopy, they may find it easier to perform EUS-B-FNA than to perform EUS-FNA. In addition, EUS-FNA is better tolerated and less invasive than EBUS-TBNA (41).

The results obtained with EUS-B-FNA in diagnosing

Table 2 Studies using EUS-FNA in patients with suspicion of sarcoidosis

Author	Year	Study design	Sedation	Needle size (G)	Size of LN, mm[†]	No. of passes	LN examined	Stage	No. of patients examined	No. of patients with sarcoidosis	No. of patients with sarcoidosis diagnosed by EUS-FNA	Sensitivity for diagnosing sarcoidosis, %	Complications	Other
Fritscher-Ravens (24)	2000	Retrospective	Moderate sedation	22	NA	NA	NA	NA	153	16	16	100	No	False positive result: 1
Fritscher-Ravens (25)	2000	Prospective	NA	22	24 [10–41]	NA	#4R, #5, #7, #8	I, II, III	19	18	18	100	No	False positive result: 1
Wildi (26)	2004	Retrospective	NA	22	18 [5–40]	≥4	Subcarinal, AP window, paratracheal, para-aortal	NA	124	28	25	89	No	
Annema (27)	2005	Prospective	Moderate sedation	22	25 [5–40]	Mean 3	Lt paratracheal, AP window, subcarinal, para-esophageal	I, II	51	50	41	82	No	
Michael (28)	2008	Retrospective	Moderate/ deep sedation	22/25	NA	Mean 5.3 per lesion	Subcarinal/ mediastinal/ intra-abdominal	NA	21	21	18	86	Mild sore throat: 1	Intra-abdominal LN: 7
Iwashita (29)	2008	Prospective	Moderate sedation	19	19 [5–42]	Mean 2.4	Subcarinal, left/ right hilar, left paratracheal	I	41	36	34	94.4	Mediastinitis: 1	
Tournoy (18)	2010	Prospective	Moderate/ deep sedation	22	NA	NA	NA	NA	18	17	16	94	No	TBB + EBB/ TBNA: 121; EBUS-TBNA: 54
von Bartheld (30)	2010	Retrospective	Moderate sedation	22	NA	Mean 3.9	#2R, #4L, #4R, #5, #7, #8	I, II	100	91	79	87	Mediastinitis: 1; local hematoma: 1; sore throat: 1	
Fritscher-Ravens (31)	2011	Prospective	NA	22	[5–42]	≥3 (2 for cytology, 1 for bacteriological analysis)	Mostly subcarinal, AP window	I, II	71	30	30	100	No	False positive result: 3
von Bartheld (32)	2013	Randomized	Moderate/ deep sedation	22	NA	Mean 5.21	NA	I, II	102	NA	NA	88	Mediastinal abscess	EBUS-TBNA: 56; bronchoscopy: 149
Jamil (33)	2014	Retrospective	NA	19/22/25	15 [7–33]	Median 3	NA	NA	160	32	25	78.1	NA	
Gnass (34)	2015	Randomized	Moderate sedation	22	≥10	3–5	NA	I, II	36	35	31	88.6	No	EBUS-TBNA: 36; TBNA: 43
Kocoń (35)	2017	Randomized	Moderate sedation	22	NA	3–6	#4L, #7	I, II	51	NA	NA	75	No	EBUS-TBNA: 55

[†], mean or median [range]. #2R, right upper paratracheal; #4R, right lower paratracheal; #4L, left lower paratracheal; #5, subaortic; #7, subcarinal; #8, paraesophageal. EUS-FNA, endoscopic ultrasound-guided fine-needle aspiration; G, gauge; LN, lymph nodes; NA, not available; AP, aortopulmonary; Lt, left; TBB, transbronchial biopsy; EBB, endobronchial biopsy; TBNA, transbronchial needle aspiration; EBUS-TBNA, endobronchial ultrasound-guided-transbronchial needle aspiration.

Table 3 Studies on EUS-B-FNA in patients suspected of sarcoidosis

Author	Year	Study design	Sedation	Needle size (G)	Size of LN, mm†	No. of passes	LN examined	Stage	No. of patients examined	No. of patients with sarcoidosis	No. of patients with sarcoidosis diagnosed by EUS-FNA	Sensitivity for diagnosing sarcoidosis, %	Complications	Other
Oki (36)	2013	Prospective	Moderate sedation	21	13.6 [6.8–28.7]	Mean 3.3 per lesion	#2L, 3p, #4R/L, #7, #8, #10L	I, II	33	29	25	86	No	
Filarecka (37)	2020	Prospective	Moderate sedation	22	15.2	3–5	#2R/L, #4R/L, #7, #8	I, II	50	47	33	70.21	No	
Crombag (38)	2022	Randomized	Moderate/ deep sedation	22/25	18 [15–22]	≥5	#2R, #4R/L, #7, #8, #9	I, II	358	141	115	82	No	EBUS-TBNA: 185

†, mean or median [range]. #2L, left upper paratracheal; #2R/L, right/left upper paratracheal; 3p, retrotracheal; #4R/L, right/left lower paratracheal; #7, subcarinal; #8, paraesophageal; #9, pulmonary ligament; #10L, left hilar. EUS-B-FNA, endoscopic ultrasound with bronchoscope-guided fine-needle; G, gauge; LN, lymph node; EUS-FNA, endoscopic ultrasound-guided fine-needle aspiration; EBUS-TBNA, endobronchial ultrasound-guided-transbronchial needle aspiration.

sarcoidosis are summarized in *Table 3*. Oki *et al.* evaluated the diagnostic utility of EUS-B-FNA in a prospective study of 33 patients with suspected stage I/II sarcoidosis; they reported a diagnostic yield of 86% (36). Filarecka *et al*. evaluated EBUS-TBNA followed by EUS-B-FNA in 50 patients with suspected stage I/II sarcoidosis. The sensitivity of EBUS-TBNA, EUS-B-FNA, and its combination was 76.6%, 70.2%, and 91.7%, respectively (37). Crombag *et al.* published a large multicenter international randomized trial in 2022 that included 358 patients with suspected stage I/II sarcoidosis. The study randomized 185 patients to EBUS-TBNA and 173 to EUS-B-FNA; 306 patients (86%) were ultimately diagnosed with sarcoidosis. The detection rate and sensitivity based on the detected granulomas were 70% and 78% for EBUS-TBNA and 68% and 82% for EUS-B-FNA, respectively; the differences between the two groups were not significant (38).

Safety of EUS-FNA and EUS-B-FNA

Of the 13 studies on EUS-FNA, a small number of cases reported serious complications, including mediastinitis (2 cases) and mediastinal abscess (1 case) (29,30,32). Although the safety of EUS-FNA has been well established, the risk of infectious complications in sarcoidosis patients should be kept in mind. In a case series of 252 patients with sarcoidosis who underwent EUS-FNA, 5 developed mediastinal abscess, with 4 patients requiring surgical treatment (42). The other reported complications associated with EUS-FNA were all minor ones, such as sore throat and hematoma.

In three studies of EUS-B-FNA, no complications were reported. Severe cough or oxygen desaturation, which often occur during EBUS-TBNA, are less common during EUS-B-FNA. In the study by Oki *et al.*, oxygen desaturation occurred in only 6% of patients (36). Pulmonologists unfamiliar with transesophageal procedures should be cautious when performing EUS-B-FNA in patients with suspected esophageal varices, esophagitis, and esophageal stenosis (43). These conditions may increase the risk of complications during the procedure.

Will EUS-FNA become the method of choice for tissue sampling in sarcoidosis?

As sarcoidosis often involves the hilar-mediastinal lymph nodes and lungs, patients are often managed by pulmonologists. However, while pulmonologists are able

to easily perform bronchoscopy, including EBUS-TBNA, TBLB, TBNA, and EBB, they are often not familiar with the handling of an EUS endoscope. The diagnostic performance of EUS-FNA is comparable to that of EBUS-TBNA; consequently, under certain circumstances, such as the availability of experienced endoscopists and an EUS-endoscope or sampling from EUS- but not EBUS-accessible lesions, it is a useful alternative to EBUS-TBNA when diagnosing sarcoidosis. EUS-B-FNA overcomes the limitation of EUS-FNA and offers an alternative to EBUS-TBNA (44,45). Although there is a learning curve, pulmonologists experienced in EBUS-TBNA can learn and perform EUS-B-FNA relatively easily (46,47). Pulmonology trainees should gain experience with EBUS, EUS-B-FNA, and EUS-FNA techniques (40). EUS-B-FNA offers the advantages of being minimally invasive and well-tolerated, even in patients with cough and poor respiratory function. Given the high tolerability and diagnostic efficacy of EUS-B-FNA, it is an effective technique available to pulmonologists when mediastinal sampling is required.

Conclusions

EUS-FNA and EUS-B-FNA are highly accurate procedures for diagnosing sarcoidosis. The reported safety profile is acceptable, although the risk of infectious complications should be considered. In particular, given its ease of performance by pulmonologists, EUS-B-FNA offers a useful alternative to EBUS-TBNA in the diagnosis of sarcoidosis.

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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-24-37/rc

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Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://med.amegroups.com/article/view/10.21037/med-24-37/coif). M.O. reports receiving speaker fees from Olympus Corporation and Fujifilm Corp. as a guest speaker at academic medical meetings. The other author has no conflicts of interest to declare.

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Review Article

Diagnostic modalities in the mediastinum and the role of bronchoscopy in mediastinal assessment: a narrative review

Yonatan Dollin[1]^, Jorge A. Munoz Pineda[1]^, Lily Sung[2]^, Farnaz Hasteh[3], Monica Fortich[4]^, Amanda Lopez[4]^, Keriann Van Nostrand[1]^, Niral M. Patel[1]^, Russell Miller[1]^, George Cheng[1]^

[1]Division of Pulmonary, Critical Care and Sleep Medicine, University of California San Diego, San Diego, CA, USA; [2]Departement of Radiology, University of California San Diego, San Diego, CA, USA; [3]Division of Pathology, University of California San Diego, San Diego, CA, USA; [4]Division of Internal Medicine, University of California San Diego, San Diego, CA, USA

Contributions: (I) Conception and design: Y Dollin, G Cheng, JA Munoz Pineda; (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: Y Dollin, G Cheng, JA Munoz Pineda; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Yonatan Dollin, DO. Division of Pulmonary, Critical Care and Sleep Medicine, University of California San Diego, 9500 Gilman Dr., La Jolla, San Diego, CA 92093, USA. Email: ydollin@health.ucsd.edu.

Background and Objective: Diagnosis of pathology in the mediastinum has proven quite challenging, given the wide variability of both benign and malignant diseases that affect a diverse array of structures. This complexity has led to the development of many different non-invasive and invasive diagnostic modalities. Historically, diagnosis of the mediastinum has relied on different imaging modalities such as chest X-ray, computed tomography (CT), magnetic resonance imaging, and positron emission topography. Once a suspicious lesion was identified with one of these techniques, the gold standard for diagnosis was mediastinoscopy for diagnosis and staging of disease. More recently, many minimally invasive techniques such as CT-guided biopsy, endobronchial ultrasound with transbronchial needle aspiration, and endoscopic ultrasound with fine needle aspiration have revolutionized the diagnosis of the mediastinum. This review provides a comprehensive analysis of all the modalities available for diagnosing mediastinal disease with an emphasis on bronchoscopic techniques.

Methods: Literature search was performed via the PubMed database. We included all types of articles and study designs, including original research, meta-analyses, reviews, and abstracts.

Key Content and Findings: Minimally invasive techniques such as endobronchial ultrasound-transbronchial needle aspiration (EBUS-TBNA) and endoscopic ultrasound-fine needle aspiration (EUS-FNA) have demonstrated high diagnostic yield and low complication rate and have made a significant difference in the time to diagnosis and lives of patients. There continues to be innovation in the field of bronchoscopy with the development of new technologies such as confocal laser endomicroscopy, optical coherence tomography, and artificial intelligence.

Conclusions: Bronchoscopy is and will continue to be an integral modality in minimally invasive diagnosis of the mediastinum.

Keywords: Endobronchial ultrasound-transbronchial needle aspiration (EBUS-TBNA); endoscopic ultrasound-fine needle aspiration (EUS-FNA); mediastinal modalities; mediastinal bronchoscopy

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^ ORCID: Yonatan Dollin, 0000-0001-8754-1800; Jorge A. Munoz Pineda, 0009-0007-6664-8765; Lily Sung, 0009-0002-3439-3490; Monica Fortich, 0009-0007-7309-1889; Amanda Lopez, 0009-0009-1894-4847; Keriann Van Nostrand, 0009-0002-8388-355X; Niral M. Patel, 0000-0003-1360-2767; Russell Miller, 0000-0002-4690-4748; George Cheng, 0000-0001-6859-8705.

Introduction

Mediastinum, as a thoracic compartment, encompasses critical structures including the heart, esophagus, trachea, main bronchi, thymus and major arteries and veins (1-3). A wide array of pathologies can occur in the mediastinum, most commonly lymphomas, lymphadenopathies, thymic masses, germ cell tumors and cystic lesions (4,5). Benign conditions such as sarcoidosis and atypical infections, including tuberculosis and fungal infections, also frequently affect the mediastinum.

Given the diverse range of diseases and anatomical structures within the mediastinum, numerous imaging modalities have been developed for its evaluation. These include chest X-ray (CXR), computed tomography (CT), magnetic resonance imaging (MRI), diffuse weighted imaging (DWI), and positron emission tomography (PET). While these imaging modalities have proven useful for evaluating mediastinal disease, they have notable limitations, such as exposure to contrast agents and radiation, and often fall short in providing a definitive diagnosis.

To overcome these limitations, invasive diagnostic modalities are essential. Among these, endobronchial ultrasound-transbronchial needle aspiration (EBUS-TBNA) has gained prominence for its efficacy in tissue sampling and lymph node biopsy. Historically, surgical exploration of the mediastinum with biopsy was the gold standard for diagnosis. However, the high diagnostic yield, accuracy, and safety profile of EBUS-TBNA has led to its rapid adoption and inclusion in guidelines as the first-line diagnostic modality.

This review explores the various imaging and invasive modalities for diagnosing mediastinal diseases, with a particular focus on bronchoscopic methods. We present this article in accordance with the Narrative Review reporting checklist (available at https://med.amegroups.com/article/view/10.21037/med-24-32/rc).

Methods

A literature search was performed via the PubMed database see *Table 1*. We included all types of articles and study design, including original research, meta-analyses, reviews, and abstracts.

Radiographic techniques in the mediastinum

The International Thymic Malignancy Interest Group (ITIMG) classification was created to standardize localization of mediastinal masses on imaging and is widely accepted in clinical practice. ITIMG divides the mediastinum into three compartments: prevascular (anterior), visceral (middle), and paravertebral (posterior) (5). This classification system is used in various imaging modalities including CT, MRI, and fluorine-18-2-fluoro-2-deoxy-D-glucose-positron emission tomography (FDG-PET).

In 2020, the American College of Radiology (ACR) published appropriateness criteria recommending a step-wise approach to diagnosing a mediastinal mass. This approach begins with chest radiograph for general localization, followed by a CT chest for further characterization, FDG-

Table 1 The search strategy summary

Items	Specification
Date of search	06/01/2024 and 06/08/2024
Database searched	PubMed
Search terms used	Examples of search terms used are: “Mediastinum Review”, “EBUS-TBNA Review”, “mediastinoscopy review”, “imaging modalities in the mediastinum review”, “radiographic techniques in the mediastinum review”, “EUS-FNA in the mediastinum review”, “confocal laser endomicroscopy in the mediastinum”, “optical coherence tomography in the mediastinum”
Timeframe	2009–2024
Inclusion and exclusion criteria	We included all types of articles and study design, including original research, meta-analyses, reviews, and abstracts. All articles used were in English. Studies performed prior to 2009 were excluded
Selection process	All senior authors (Y.D., J.A.M.P., G.C.) consented to inclusion of each article in manuscript preparation. Only articles with complete consensus were included

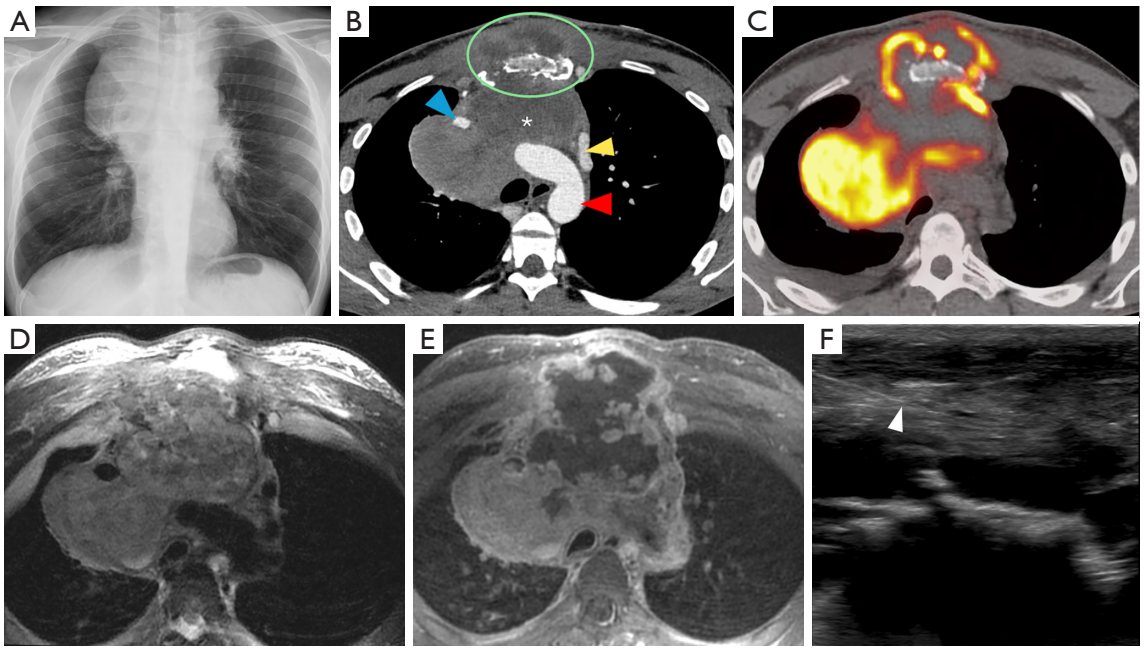

Figure 1 Lymphoma imaging with different radiographic modalities. (A) Frontal chest radiograph shows a large superior mediastinal mass. (B) Subsequent contrast-enhanced chest computed tomography shows a corresponding large, heterogeneously enhancing soft tissue mass (*) in the anterior and middle mediastinum, which exerts mass effect on the adjacent soft tissue structures narrowing the right brachiocephalic vein (blue arrowhead), occluding the left brachiocephalic vein with enlargement of the left superior intercostal vein (yellow arrowhead), and posteriorly displacing the aortic arch (red arrowhead). The mass invades the anterior chest wall and results in osseous destruction of the sternum (green circle). (C) Fluorine-18-2-fluoro-2-deoxy-D-glucose-positron emission tomography demonstrates avid associated radiotracer uptake with areas of photopenia corresponding to necrosis. (D) Axial T2-weighted magnetic resonance imaging images show heterogeneous T2 hyperintensity. (E) T1-weighted post-contrast magnetic resonance imaging images show heterogeneous enhancement with an area of nonenhancement corresponding to the area of central necrosis. (F) Ultrasound-guided biopsy (white arrowhead) was performed with pathology revealing large cell lymphoma.

PET is considered for additional metabolic information, leading to further diagnostic intervention if necessary. The ACR also recommends MRI of the chest to avoid unnecessary biopsy or surgery and to assist in planning for necessary procedures (6).

CXR

CXR is an imaging modality that utilizes X-rays that are absorbed by the structure of interest which causes attenuation of each ray and then exposes a film with different pixel values depending on that attenuation (see *Figures 1*,*2*). This results in a two-dimensional representation of a three-dimensional anatomical structure (7). Due to its simplicity and inexpensive nature, it is the most common initial modality used globally (7). This modality is recommended by ACR as the initial modality to localize a mediastinal mass and narrow the differential (6). Limitations of CXR include assessing smaller structures such as lymph nodes, further characterization of lesions is limited due to the composite attenuation of each X-ray beam, and image quality is often affected by patient positioning, degree of inspiration, medical devices, and body habitus (7).

CT

CT imaging is the key modality for imaging the mediastinum because it is effective at localizing both malignant and benign disease in the mediastinum, is readily available, and can be performed rapidly. CT allows for increased resolution leading to more accurate assessment of location, size, presence of fat or calcification, attenuation, and relationship/involvement of surrounding and nearby organs (5,8). CT imaging uses a series of X-rays rotated around the patient, producing computer-generated additive cross-sectional images. This

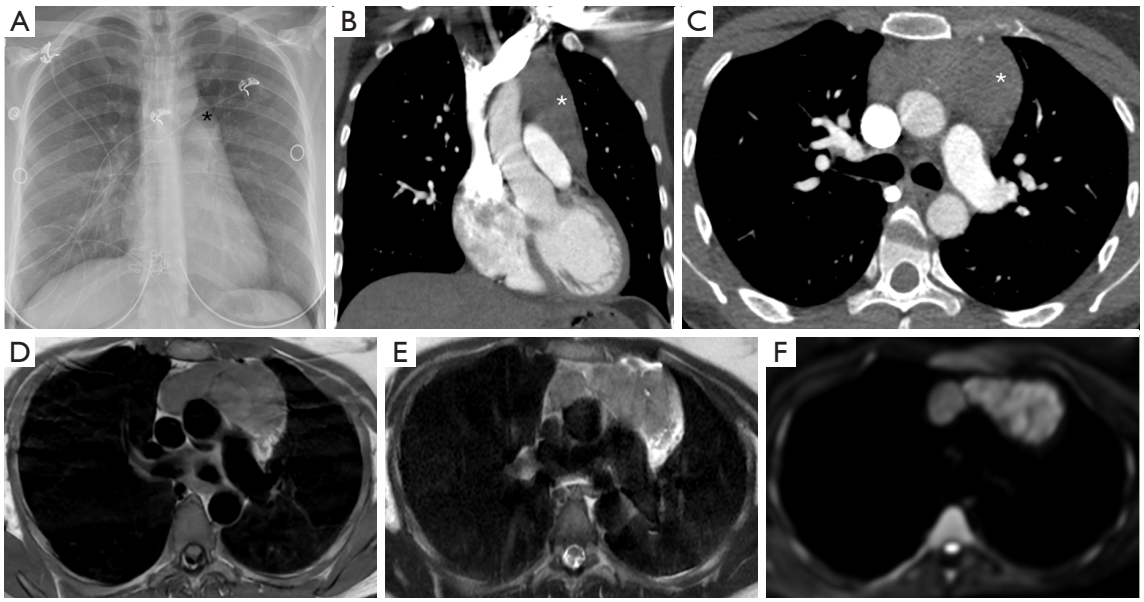

Figure 2 Hodgkin's lymphoma imaging with different radiographic modalities. (A) Frontal chest radiograph shows a mass in the anterior-posterior window (*). (B,C) Coronal and axial contrast-enhancing chest CT show a corresponding homogeneous, lobulated soft tissue mass (*) in the anterior mediastinum, which abuts the superior vena cava, aorta, and main pulmonary artery. The mass demonstrates (D) T1 iso- to hyperintensity on T1-weighted axial magnetic resonance imaging images, (E) heterogeneous T2 hyperintensity on T2-weighted axial magnetic resonance imaging images, and (F) restricted diffusion on diffusion-weighted images with suggestion of septations. Subsequently, ultrasound-guided biopsy revealed Hodgkin lymphoma. CT, computed tomography.

technique eliminates the superimposition of structures seen in CXR, removing noise and improving resolution (9). This increased resolution can be used to further characterize lymphomas, thymic neoplasms, and thyroid tumors (*Figures 1-4*) (4). There are several limitations to CT imaging of the mediastinum. CT imaging is less sensitive and specific than tissue diagnosis from more invasive techniques (10); one study showed CT was inferior to invasive techniques in both sensitivity and specificity in diagnosing small cell lung cancer (10). It is also often difficult to differentiate between solid and cystic lesions on CT especially if the cyst contains proteinaceous material or hemorrhage with high attenuation (11). CT also exposes the patient to higher radiation levels and is not suitable for patients that have allergies to iodinated contrast (6).

MRI

While MRI is not the initial diagnostic modality of choice in the mediastinum, it allows for further tissue characterization of mediastinal masses beyond that of CT (6). MRI has greater soft tissue resolution than CT, which is uniquely useful in revealing characteristics of mediastinal tumors (*Figures 1-3*). These features include cystic changes, hemorrhage, fat, fibrous capsules, and septa (12). MRI is also superior to CT in detection of mass invasion across tissue planes (6).

The key to these advantages is utilizing T1 and T2 weighted imaging available with MRI. T1 shows high signal intensity when imaging hemorrhage while T2 shows high signal intensity with cystic changes and myxoid tissue. Both are superior to CT when imaging fibrous capsules or septa in thymic tumors (12). Limitations of MRI include cost, patient claustrophobia, availability, lack of definitive diagnosis, and length of time needed to complete the exam.

DWI

DWI is a technique that generates signal contrast using principles of Brownian motion (i.e., motion of water molecules). A magnetic field gradient is produced by the MRI machine and a sensor measures the movement of random water molecules in response. This signal is then quantified

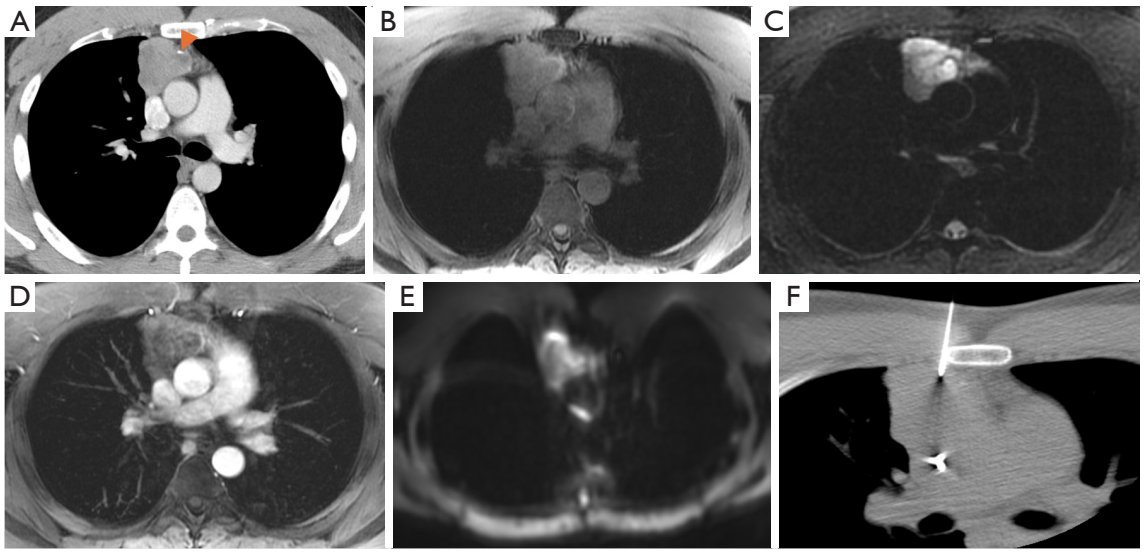

Figure 3 Thymoma imaging with different radiographic modalities. (A) Axial chest computed tomography shows a smoothly marginated, heterogeneously enhancing soft tissue mass in the anterior mediastinum with a punctate calcification (orange arrowhead). Magnetic resonance imaging signal characteristics of the mass demonstrate (B) T1 iso-intensity on axial T1-weighted images, (C) heterogeneous T2 hyperintensity on T2-weighted images, (D) heterogeneous enhancement on axial T1 post-contrast images, and (E) restricted diffusion on diffusion-weighted imaging. (F) Computed tomography-guided biopsy resulted thymoma.

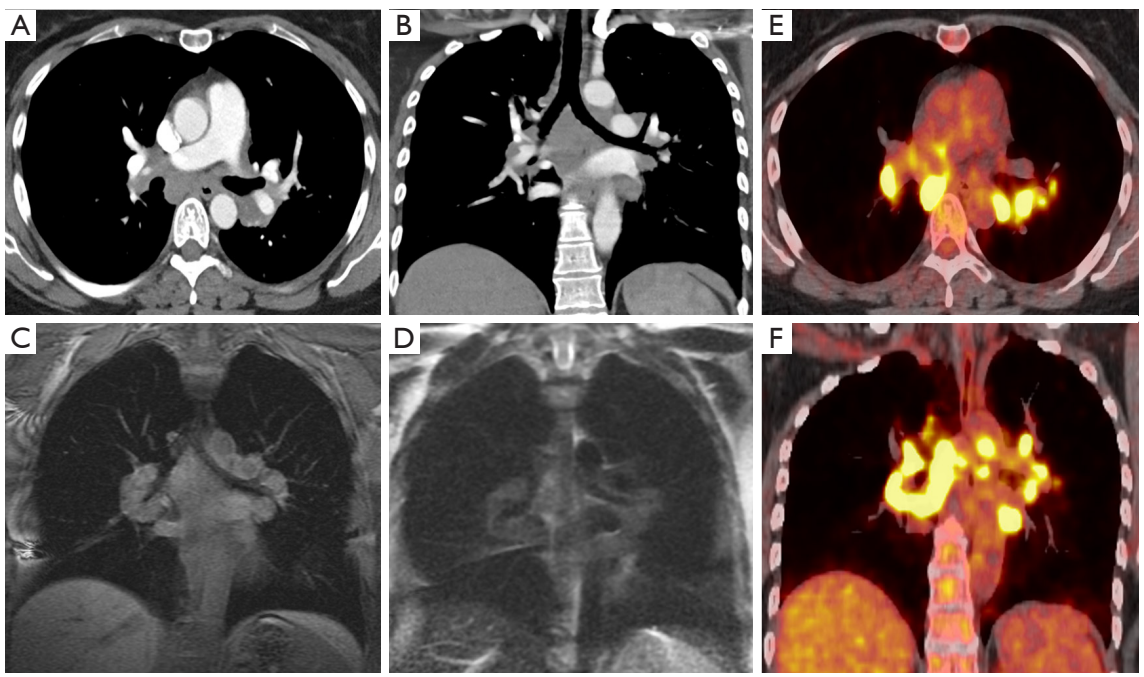

Figure 4 Sarcoidosis imaging with different radiographic modalities. (A,B) Axial and coronal contrast-enhanced computed tomography images show symmetric mediastinal and hilar lymphadenopathy, in a pattern characteristic for sarcoidosis. The lymphadenopathy demonstrates (C) T1 iso-intensity on coronal T1-weighted images and (D) T2 hyperintensity on T2-weighted images. (E,F) Axial and coronal fluorine-18-2-fluoro-2-deoxy-D-glucose-positron emission tomography images demonstrate corresponding avid radiotracer uptake within the lymph nodes.

into apparent diffusion coefficient (ADC) maps. Malignancies have been shown to have lower ADC values than surrounding tissue. These ADC values rise after treatment (13). A meta-analysis done by Santos *et al.* evaluated the role of DWI in differentiating mediastinal lymph nodes between benign and malignant, which showed a pooled sensitivity of 92% and specificity of 93% (14). Limitations of DWI include susceptibility to motion and arterial pulse artifact, nearby implants that can degrade study quality, and overlapping ADC values between malignant and benign lymph nodes (15).

Functional imaging

FDG-PET

FDG PET/CT is a functional imaging modality that utilizes radiotracers to measure active metabolic processes in the body (*Figures 1*,*3*,*4*). The role of FDG-PET in the mediastinum is primarily detection, staging, and surveillance of lymphadenopathy (6). In the case of malignancy or infection, it can also be useful in assessing response to treatment. FDG-PET has been shown to be more useful in excluding malignancy, while a positive FDG-PET is less helpful, as both benign and malignant processes can be PET avid (*Figure 4*) (6). This was illustrated by Tatci *et al.* who evaluated the ability of FDG PET/CT to differentiate malignant *vs.* benign masses; FDG PET/CT had a high sensitivity of 90%, but a low specificity at 55.16% (16).

Invasive techniques

The limited diagnostic capability of imaging modalities necessitates the use of invasive techniques to obtain tissue samples for pathological testing. This section summarizes some of the most common invasive techniques for obtaining tissue such as image-guided percutaneous core needle biopsy (CNB), endoscopic ultrasound (EUS), mediastinoscopy, and video-assisted thoracoscopy surgery (VATS). Mediastinoscopy is an open surgical approach, while EUS and VATS are considered minimally invasive surgeries.

Image-guided percutaneous CNB

Image guided CNB utilizes different imaging techniques (CT, CT-fluoroscopy, cone beam CT, ultrasonography, or MRI) to guide a needle for biopsy of a mediastinal lesion (*Figure 3*). This technique is minimally invasive and has less complications than the surgical procedures mentioned below (17). The diagnostic accuracy of CNB is variable across studies as there are different definitions of diagnostic accuracy. In one meta-analysis that pooled data from eighteen studies found the diagnostic accuracy was 92% while the total complication rate was 13%, and major complication rate was 2% (17). Major complications considered were pneumothorax requiring intervention, hemothorax, hemoptysis requiring intense care unit admission, air embolism, needles seeding of cancer, and death. The primary limitation of CNB is the inaccessibility of the target via percutaneous approach due to safety concerns arising from crowded anatomical space. Additional limitations include patient positioning challenges, navigation guidance relying on two-dimensional images, and patient allergies to iodinated contrast in the case of CT-guided procedures.

Endoscopic ultrasound-fine needle aspiration (EUS-FNA)

EUS-FNA is a minimally invasive technique that utilizes a high frequency ultrasound transducer incorporated into the tip of the endoscope to locate biopsy targets in the mediastinum with subsequent biopsy with a needle passing through the endoscope's working channel. EUS refers to the introduction of the endoscope into the esophagus and thus is specifically suited for diagnosis of the middle and posterior mediastinum over an airway-centered approach, as the esophagus is located posteriorly to the trachea. Lymph node stations accessible with EUS include stations 1, 2L, 2R, 3P, 4L, 5–9, and 10L. Of these accessible stations, 5, 6, 8, and 9 are usually inaccessible to endobronchial ultrasound (EBUS) (18). EUS has been shown to be effective at diagnosing mediastinal disease in the locations it can access. In lung cancer, a meta-analysis analyzed 11 studies (n=313) and the pooled diagnostic yield was 90% (19). In diagnosing lymphadenopathy, other observational studies have shown a sensitivity of 88–95.3% and specificity of 96–100% (19). Other applications of EUS include pericardial effusion drainage, biopsy of pericardial masses, diagnosis of sarcoidosis, lymphoma, infections, and para-esophageal abscess drainage (19). There is a similar technique called endoscopic ultrasound with bronchoscope-guided fine-needle aspiration (EUS-B-FNA) where instead of using an endoscope, the EBUS bronchoscope is used sequentially to perform airway exam and then esophageal exam (20). Limitations of both EUS-FNA and EUS-B-FNA include, technical skills of the operator, expense, availability of endoscopy suite, constrained access to the anterior mediastinum, and narrow field of view (19).

VATS

VATS is a minimally invasive surgical procedure which

involves small incisions in the chest wall and insertion of a thoracoscope to access the thoracic cavity. The goal of this approach is to minimize trauma to surrounding tissues. Similar to mediastinoscopy, it has been used for mediastinal tumor removal and lymph node biopsy allowing for staging. As VATS is a minimally invasive technique, it offers many advantages over open surgical procedures such as reduced post-operative pain, shorter hospital stays, and quicker recovery time (21). Despite these advantages, VATS carries significant risks such as hemorrhage, air embolism, pneumothorax, pleural effusion, wound infection, and postoperative pulmonary edema (21).

Mediastinoscopy

Mediastinoscopy is a surgical procedure which requires a small incision just above the manubrium and utilizes a mediastinoscope to examine the mediastinum, obtain tissue samples, remove tumors, and perform lymph node biopsy and staging. Most commonly, it has been utilized for diagnosing, treating, and staging non-small cell lung carcinoma (22). A study performed by Diebels *et al.* evaluated the utility of mediastinoscopy in mediastinal lymph node staging for non-small cell lung cancer (NSCLC). The study reported that mediastinoscopy had 81.8% sensitivity, 100% specificity, and 94.1% diagnostic accuracy (23). Due to the 100% specificity, mediastinoscopy was historically considered the gold standard for diagnosing the mediastinum especially for staging; however, it does carry significant risks similar to VATs such as hemorrhage, air embolism, injury to surrounding structures such as the recurrent laryngeal nerve, wound infection, and postoperative pulmonary edema (22). These risks result in morbidity rate of between 1.5% and 3%, and an overall mortality rate of 0.09% (22). Mediastinoscopy is best served for anterior mediastinal structures; accessing posterior mediastinum structures with mediastinoscopy is difficult.

Video-assisted mediastinal lymphadenectomy (VAMLA) and transcervical extended mediastinal lymphadenectomy (TEMLA)

Two surgical techniques were developed to supplement VATS in order to systematically stage the lymph nodes in the mediastinum and work by systematically removing all mediastinal lymph nodes along with the associated adipose tissue. VAMLA is achieved entirely through video assistance via insertion of a mediastinoscope through a small incision allowing for visualization and removal of most lymph nodes in the mediastinum. TEMLA is an open procedure where a 5–8 cm collar incision is made in the neck and then a Cooper retractor is used to lift the sternum allowing for visualization and complete dissection of all mediastinal lymph nodes. The main difference between the two techniques is that TEMLA has a higher negative predictive value (98.7%) because more lymph node stations are accessible (prevascular, paraaortic, subaortic and paraesophageal) but also has a higher rate of morbidity and mortality (24). Some studies suggest that these techniques have a high accuracy (96% and 98%) and a negative predictive value of 97–99% due to their increased sensitivity for micro metastases (25). Complications of VAMLA/TEMLA are similar to mediastinoscopy (mainly damage to surrounding structures, pneumothorax, pleural effusions, hemorrhage, and infection) and happen in less than 5% of patients. Data on the use of VAMLA and TEMLA has been mixed, and thus the routine use of these techniques is controversial. The latest European Society of Thoracic Surgery (ESTS) guidelines [2014] evaluated these two techniques and determined the data was scarce and thus did not recommend their use (26).

Advanced bronchoscopic imaging techniques

EBUS

The main role of EBUS in diagnosing the mediastinum is the real-time imaging of lymph nodes. There are three modes available with current EBUS technology to image lymph nodes; gray scale (B-mode), elastography, and blood flow Doppler (27). The most common and accepted mode is B-mode in combination with transbronchial needle aspiration (TBNA) (27). This section breaks down the utilization of these different techniques and the evidence supporting them.

Gray scale (B-mode) with EBUS-TBNA

Differentiating malignant and benign lymph node targets with B-mode imaging has both qualitative and quantitative methods. Qualitative methods include shape, size, echogenicity, margin, absence or presence of central hilar structure, nodal conglomeration, presence of coagulation necrosis sign, and presence of calcification (*Figure 5*) (27). The quantitative method uses gray scale texture to measure echogenicity the details of which are beyond the scope of this review (27).

EBUS-TBNA involves bronchoscopic guidance of an ultrasound probe with adjacent working channel to different lymph node stations through the airways. The operator uses real-time gray scale ultrasound imaging to confirm the

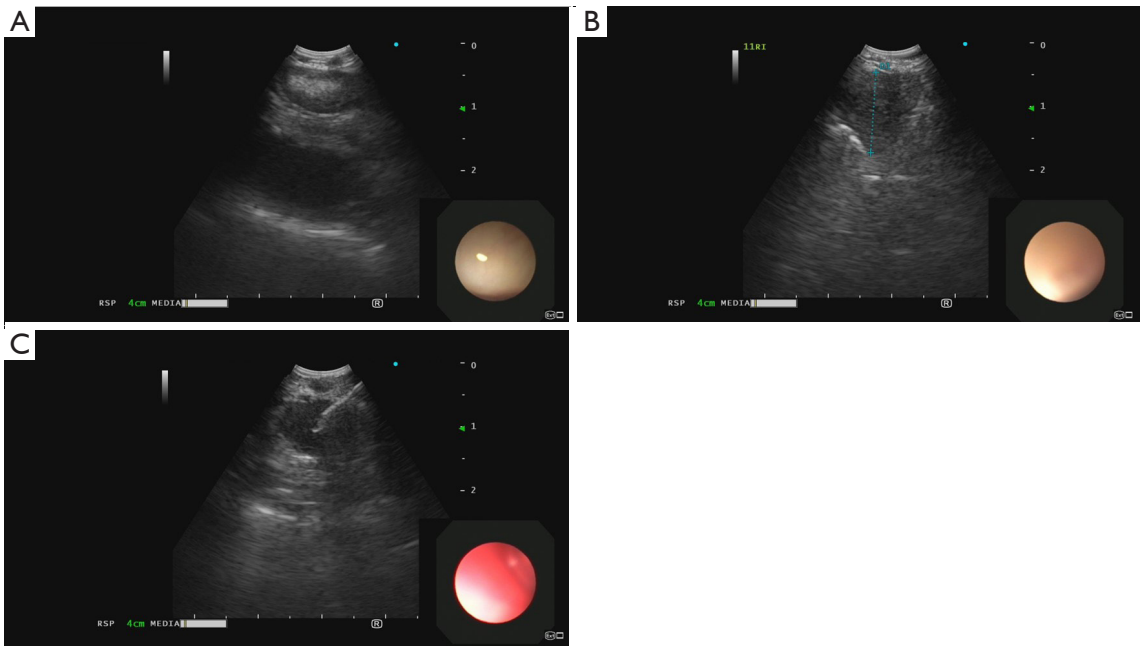

Figure 5 Characteristics of malignant lymph nodes on EBUS. (A-C) Examples of B-mode (gray scale) lymph nodes that are greater than 1 cm on the short axis, round/heterogenous shape, and a distinct margin, all concerning qualitative signs of malignancy. (A) EBUS 2D mode view of mediastinal lymph node. (B) EBUS 2D mode view with measurements of mediastinal lymph node. (C) Realtime EBUS view of the needle during TBNA of a mediastinal lymph node. EBUS, endobronchial ultrasound; 2D, two dimensional; TBNA, transbronchial needle aspiration.

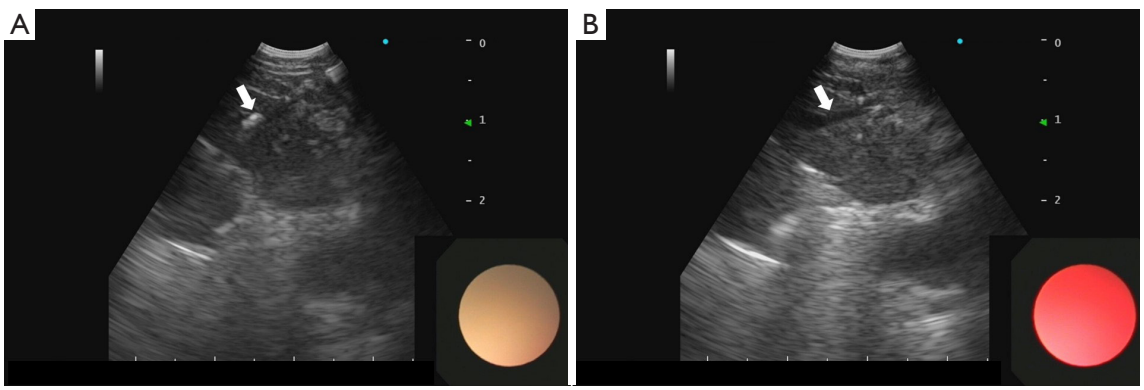

Figure 6 EBUS with utilization of cryoprobe. (A) EBUS visualization of 1.1 mm cryoprobe (white arrow) in lymph node. (B) EBUS visualization of anechoic shadow of 1.1 mm cryoprobe (white arrow) after cryoextraction of lymph node biopsy. EBUS, endobronchial ultrasound.

target. A fine needle is then used to make a transbronchial puncture into the lesion with subsequent aspiration of sample (*Figures 5*,*6*) (28). The decision of which lymph node to sample is based on size and morphology of the lymph node target. Lymph node locations accessible by EBUS are 2R, 2L, 3P, 4R, 4L and 7 as well as 10R, 10L, 11R, and 11L (28). In addition to lymph node targets, any other mediastinal pathology accessible from the bronchus, such as a mass, that can be identified on ultrasound can also be targeted. The advantages of this technique include its minimally invasive nature, does not necessitate general anesthesia, cost of procedure, does not require hospitalization, lower risk of complications such as pneumothorax compared to CT-guided biopsy, ability to target lymph nodes not accessible to other invasive techniques, decreased time to diagnosis, real-time imaging, ability to sample multiple lymph nodes and

lesions in the same procedure, and high diagnostic yield.

Many mediastinal diseases can be diagnosed by EBUS-TBNA. Malignant diseases include intrathoracic cancers (i.e., lung, thyroid, thymic, esophageal, lymphomas) as well as metastases from intrathoracic or extra-thoracic malignancies (29). Infectious causes of mediastinal lymphadenopathy diagnosed by EBUS-TBNA include *Mycobacterium*, fungi (*Coccidioides*, *Histoplasma*), other bacteria (*F. tularensis*, *B. anthracis*), and viruses (human immunodeficiency virus, Epstein-Barr virus) (29). Inflammatory causes include sarcoidosis, rheumatoid arthritis, and hypersensitivity pneumonitis (29).

EBUS-TBNA has now become standard of care for diagnosing and staging lung cancer, diagnosing and staging other mediastinal malignancies, and diagnosing infectious and benign mediastinal diseases. The American College of Chest Physicians (CHEST) recommends EBUS-TBNA as the initial diagnostic modality in mediastinal lung cancer staging, lymphadenopathy, sarcoidosis, tuberculosis, and lymphoma (30). The modality was recommended because of its high diagnostic yield and its minimally invasive safety profile.

In many studies prior to 2016, mediastinal staging of lung cancer with EBUS-TBNA had an overall diagnostic yield of 89% and negative predictive value of 91% (30). This high diagnostic yield led to a recommendation of using EBUS-TBNA as the initial mediastinal staging modality of choice over surgical staging. This was further supported by a more recent 2020 meta-analysis Kuijvenhoven *et al.* which analyzed 14 additional studies and reported a diagnostic yield of 89%, a sensitivity of 91%, with EBUS associated complications of only 5.4% (31).

For sarcoidosis, TBNA can be useful in providing histologic confirmation of non-caseating granulomatous inflammation. The 2016 CHEST guidelines reference the Agarwal *et al.* meta-analysis which included 15 studies which reported a diagnostic yield for sarcoidosis of 54–93% with a pooled diagnostic yield of 79% [95% confidence interval (CI): 71–86%] (32). Further analysis of 10 additional studies lead to a pooled diagnostic yield of 78.2% (95% CI: 75.6–80.4%) (32). The high diagnostic yield led to the CHEST recommendation of EBUS-TBNA as the initial diagnostic modality in suspected sarcoidosis in patients who have mediastinal or hilar lymphadenopathy. A more recent meta-analysis from Trisolini *et al.* reported a diagnostic yield of 79% (33).

For tuberculosis, the 2016 CHEST guidelines analyzed three studies. The diagnosis of tuberculosis via lymph node sampling was made by the presence of acid-fast bacilli smears on aspirate, or presence of necrotizing granuloma with positive tuberculosis skin test and right clinical context. The first two studies Garcia-Olivé *et al.* and Cetinkaya *et al.* had a high diagnostic yield of 80% and 79% respectively (34,35). The third study, Madan *et al.*, showed a diagnostic yield of 84.8% (36). Based on these data, the CHEST guidelines recommended EBUS-TBNA as the initial diagnostic modality in suspected tuberculosis in patients that require lymph node sampling.

For lymphoma, the 2016 CHEST guidelines mention five studies with a total of 212 patients that evaluated the diagnostic yield of EBUS-TBNA. The two studies showing the highest diagnostic yield reported 91% and 89%; while the study showing the lowest diagnostic yield reported 38% (37) with an average diagnostic accuracy of 68.7% when all combined (30). The variability between the reported diagnostic yield between those studies was explained by differing definitions of diagnostic yield. Despite this variability, the data was sufficient to support the recommendation of EBUS-TBNA as the initial diagnostic modality (30).

Limitations of EBUS-TBNA

For mediastinal staging in lung cancer, EBUS is not able to stage the entire mediastinum. EBUS is limited to the anterosuperior mediastinum in areas accessible from larger bronchi. It is also technically difficult to access some anatomic areas such as the superior lung lobes due to the steep angle required for access. This limitation has been significantly decreased with the development of navigational bronchoscopy, but this topic is beyond the scope of this review. Effective EBUS requires a program including specially trained support staff, the proceduralist, and access to a pathology program that has the appropriate expertise. This can limit access to EBUS from hospitals that cannot field the cost (28).

EBUS elastography

Ultrasound elastography indirectly measures the stiffness and compressibility of lymph node tissue by assessing the speed of compression or shear waves penetrating the lymph node tissue and translating that into a color scale (*Figure* 7), allowing the operator to determine the stiffness of the lymph node (38). Malignant lymph node tissue has been shown in many studies to be stiffer than benign lymph node tissue (39,40).

The best evidence suggesting diagnostic value of using elastography to differentiate between benign and malignant

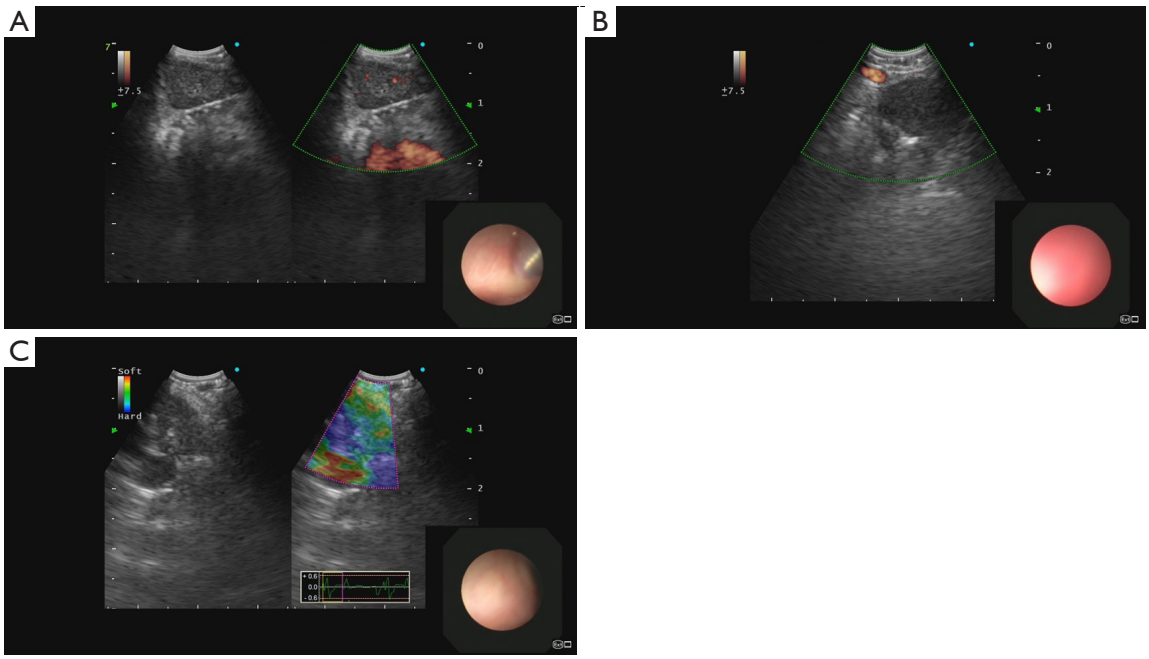

Figure 7 Advanced EBUS techniques: EBUS-TBNA, blood flow Doppler, and elastography. (A) Dual screen view of EBUS 2D mode (left) and corresponding color Doppler mode (right) of lymph node and vessel. (B) Color Doppler mode EBUS view of lymph node and adjacent vessel. (C) Dual screen view of EBUS 2D mode (left) and corresponding elastography mode (right) of lymph node. EBUS, endobronchial ultrasound; TBNA, transbronchial needle aspiration; 2D, two dimensional.

lymph nodes was a meta-analysis performed by Wu *et al.* (41). This study incorporated 17 studies and found a pooled sensitivity of 90% (95% CI: 0.84–0.94), and a specificity of 78% (95% CI: 0.74–0.81) for diagnosing mediastinal and hilar lymph nodes. These data led the authors of this study to recommend elastography as an adjunct to EBUS-TBNA to improve diagnostic accuracy. Of note, the studies analyzed in this meta-analysis were heterogenous and all elastography methods were included (quantitative, semi-quantitative, and qualitative). Thus, while these data are promising, the need for validating randomized trials as well as standardized elasticity measurement protocols remains.

Limitations of elastography

There are several limitations to elastography. False positives have been shown in benign diseases that cause increased stiffness such as sarcoidosis, pneumoconiosis, and tuberculosis as elastography cannot differentiate between stiff fibrotic lymph nodes and stiff malignant lymph nodes (42). False negatives have also been documented as necrosis, hemorrhage, or liquification of malignant lymph nodes also appear less stiff and thus may be incorrectly characterized as benign (42). Finally, there is a lack of standardization of elastography protocols; thus, further studies validating best practice protocols are still needed for wide-spread adoption.

Doppler imaging via EBUS

EBUS with flow Doppler takes advantage of the "Doppler effect" in physics where mass (red blood cells) moving toward or away from the detector (probe) changes the frequency of signal received (*Figure 7*). If the frequency detected increases, the flow is moving toward the probe and if the frequency decreases, away from the probe (43).

There are several qualitative methods for differentiating benign from malignant lymph nodes on color Doppler. One method described by Wang *et al.* classifies lymph nodes into three flow pattern distributions avascular, hilar vascular, and non-hilar vascular (44). Based on previous data showing that metastatic lymph nodes tend to have vascular supply but destroyed central hilar vasculature, they diagnosed malignant lymph nodes in the non-hilar vascular category. Using this classification system, the study cited a diagnostic accuracy of 79.69% (44). Another method described by Nakajima *et al.* (45) combined a similar flow pattern distribution with a graded vascular image pattern system where Grades 0 and I were benign and Grades II and III were

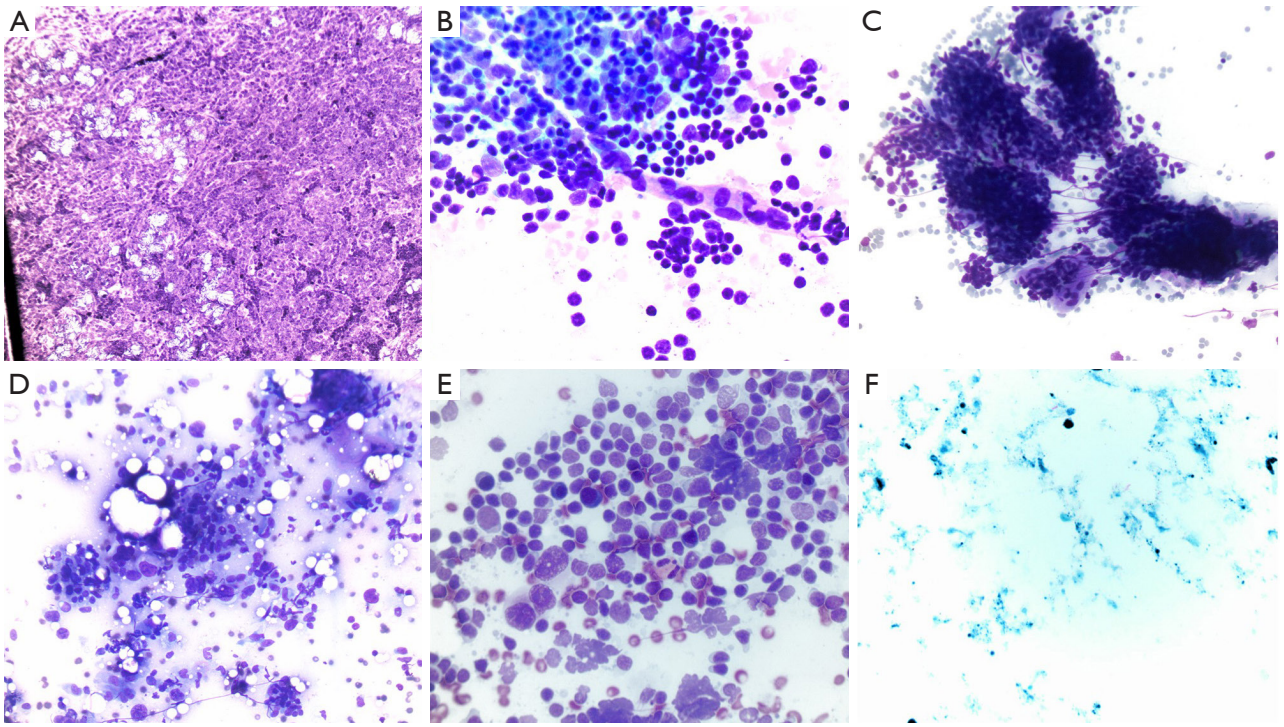

Figure 8 Rapid on-site evaluation: the preparations and corresponding stains are either air-dried slide with Diff-quick stain or alcohol fixed slide with Papanicoalou stain. (A) Thymoma (Pap stain, ×40); (B) Castleman's disease (Diff-quick stain, ×40); (C) thymoma (Pap stain, ×40); (D) diffuse large B-cell lymphoma (Diff-quick stain, ×40); (E) Hodgkin's lymphoma (Diff-quick stain, ×40); (F) acid fast bacilli (acid fast stain on the cell block, ×40).

malignant (45). The grades were determined by the number of blood vessels and the signal's strength. Additionally, presence of positive bronchial artery (BA) inflow sign (blue signal towards a lymph node) was considered malignant regardless of grade. This system yielded a similar diagnostic accuracy of 78.0% (45). This grading system was further supported by a single-center prospective cohort trial in 2015 performed by Nosotti *et al.* who reported a diagnostic accuracy of 81% (46). No studies of quantitative methods of blood flow Doppler were found in our literature review. This diagnostic technique shows promise; however, more randomized studies as well as the development of quantitative techniques should be performed.

The limitation of Doppler flow imaging is no large studies have been performed to validate the Nakajima vascular pattern and because of the qualitative nature of the classification system, there is inherent subjectivity leading to inter-operator variability (46). Despite this limitation, this technology is already broadly integrated as an adjunct to EBUS-TBNA due to its precise identification of blood flow. The use of color Doppler to explicitly avoid vascular structures for needle sampling is widely used and enhances the safety profile of EBUS-TBNA.

Real time imaging and rapid on-site evaluation (ROSE)

ROSE is the process where a cytopathologist is present adjacent to the bronchoscopy suite and can provide real-time feedback on quality and quantity of the biopsy sample and sometimes provide an initial diagnosis (*Figure 8*). ROSE allows the cytopathologist to identify blood, necrosis, bronchial epithelial cells, lymphocytes, malignant cells, and atypical cells and relay that feedback to the operator (47). Chen *et al.* performed a meta-analysis, the pooled diagnostic yield of 18 studies showed improvement of 14% (95% CI: 0.09–0.18) when ROSE was used (47). There are conflicting studies on whether ROSE improves diagnostic yield. For instance, the Sehgal *et al.* meta-analysis analyzed five studies and showed no difference in diagnostic yield with the addition of ROSE [risk difference 0.04 (95% CI: –0.01 to 0.09)] (48). Despite the disagreement on diagnostic yield, most studies performed showed data supporting that

ROSE decreases the number of needle passes; Chen *et al.* showed (–0.99, 95% CI: –1.89 to –0.09) and Sehgal *et al.* showed a mean difference of –1.1 (95% CI: –2.2 to –0.005; P<0.001) (47,48). However, neither study saw a difference in complication rate. While ROSE does not significantly alter diagnostic yield, it does reduce the number of needle passes needed.

Comparative analysis

EBUS and traditional imaging/surgical modalities

Many guidelines recommend EBUS-TBNA as a first line modality for mediastinal diagnosis. These guidelines were supported by comparison studies between EBUS-TBNA, CT-guided biopsy, and mediastinoscopy.

EBUS-TBNA and FDG-PET

Several studies have shown EBUS-TBNA to have higher diagnostic accuracy than PET. One study showed that EBUS-TBNA has a higher accuracy (87.5% *vs.* 79.2%), positive predictive value, and specificity as PET (49). More recently, the SEISMIC study found that systematic endoscopic mediastinal staging was more accurate with addition of EBUS-TBNA than FDG-PET alone in diagnosing NSCLC (50). While the diagnostic accuracy has been shown to be higher in EBUS-TBNA, the two techniques are both involved in the staging of mediastinum. According to the ESTS guidelines [2014], suspicion for nodal disease on CT chest or FDG-PET prompts mediastinal staging with EBUS/EUS (26).

EBUS-TBNAs and CT-guided biopsy

Many studies have compared diagnostic accuracy and complication rate between EBUS-TBNA and CT-guided biopsy. A study by Uchimura *et al.* explored EBUS with elastography analysis of lymph nodes that were considered negative by CT. The results showed EBUS with elastography using an SAR cutoff had a sensitivity of 88%, specificity 80.2%, and diagnostic accuracy of 83.9% (51). This study suggested that even in radiographically negative lymph nodes, EBUS with elastography still predicted malignant lymph nodes with high diagnostic accuracy (51). While EBUS with elastography can catch some radiographically negative lymph nodes, when directly comparing the two techniques, the diagnostic yield has been shown to be similar. A meta-analysis by Fu *et al.* analyzed nine studies and found that both diagnostic yield [odds ratio (OR): 0.23; P<0.001] and diagnostic accuracy (OR: 0.43; P=0.002) was higher with CT guided biopsy than with EBUS-TBNA with similar rates of procedural success. However, the complication rate of CT guided biopsy was substantially higher (OR: 7.27; P<0.001) (52). The authors also noted that there was large heterogenicity in the way studies defined diagnostic yield. Sub-group analysis performed showed that CT guided biopsy was particularly superior in diagnostic yield when the lesions were small or close to the pleura. When reviewing the data, both EBUS-TBNA and CT-guided biopsy have utility in diagnosing the mediastinum, but CT-guided biopsy does have a higher complication rate.

EBUS-TBNA and mediastinoscopy

Historically, mediastinoscopy has been considered the gold standard for invasive diagnosis of mediastinal disease. This changed around 2016 with data supporting the use of EBUS-TBNA as the first-line diagnostic modality due to being more cost-effective, lower complication rate, and a similar to better (in some studies) diagnostic yield (53). Many studies have shown that EBUS-TBNA is equivalent to or better than mediastinoscopy in terms of diagnostic yield in lymph node staging of NSCLC. Um *et al.* showed accuracy of 92.9%, sensitivity of 88%, and specificity 100% compared to mediastinoscopy which showed 89%, 81.3%, and 100% respectively (54). Yasufuku *et al.* showed sensitivity, specificity, and diagnostic accuracy for EBUS-TBNA was 81%, 100%, and 93% and for mediastinoscopy 79%, 100%, and 93% respectively (55). No complications were seen in EBUS patients and 2.6% had complications in mediastinoscopy (55). A more recent 2020 meta-analysis performed by Figueiredo *et al.* analyzed five studies and found that no statistically significant differences were observed in sensitivity, specificity, positive predictive value, or negative predictive value between the two modalities, but they did not assess diagnostic accuracy (56).

Even though the data does support EBUS-TBNA as a first-line modality over mediastinoscopy due to similar diagnostic yield with lower complication rate, there remains a role for mediastinoscopy in diagnosis of the mediastinum in select patients that are EBUS-TBNA negative or have no pulmonary manifestations of disease. For example, Zhu *et al.* found that in patients with lymphadenopathy but without pulmonary abnormalities, mediastinoscopy had a much higher diagnostic accuracy than EBUS-TBNA (96% *vs.* 62%) (57).

Synergistic use of EBUS with other modalities

While EBUS-TBNA has revolutionized the diagnosis of the

mediastinum, its ability to achieve a definitive diagnosis can be further augmented by combining it with elastography, EUS-FNA, and mediastinoscopy.

EBUS-TBNA with EUS-FNA

There are several advantages to combining these two modalities including ability to access inferior mediastinal lymph nodes, reaching para-esophageal masses not normally accessible to EBUS-TBNA, and increased diagnostic yield (58). Further, if EBUS-TBNA is combined with EUS-B-FNA (inserting the EBUS scope into the esophagus to perform the EUS exam), then there are many other advantages such as decreased cost, lower doses of sedatives, less incidence of oxygen desaturation in low reserve patients, operator satisfaction, shorter procedural time, ability to be performed by a single operator, and ability to perform procedure in a single setting (58). A meta-analysis performed by Hong *et al.* analyzed studies with combined EBUS-TBNA and EUS-B-FNA in diagnosing and staging lung cancer and sarcoidosis. In lung cancer, 10 prospective studies involving greater than 1,000 patients, all showed a significant increase in both diagnostic yield and sensitivity with the combination (58). In sarcoidosis, Hong *et al.* reported there were no prospective head-to-head studies comparing combination EBUS-TBNA/EUS-B-FNA to EBUS-TBNA alone, but there were two studies that reported a diagnostic yield of 88% and 66% respectively for EBUS-TBNA alone (59,60). This was then compared to a third study which reported, for the combination modality, a diagnostic yield of 92.16% (61). This suggests that the combination modality produced a higher yield (58).

Another meta-analysis performed by Shen *et al.* analyzed 10 studies that compared EBUS-TBNA with EUS-FNA, and six studies that compared EBUS-TBNA with EUS-B-FNA all in diagnosing general mediastinal disease. They concluded that diagnostic accuracy was slightly better in the EBUS-TBNA/EUS-FNA combination (62). In summary, the combination of EBUS-TBNA with either EUS-B-FNA or EUS-FNA can significantly improve the diagnostic yield in appropriate cases.

EBUS-TBNA with mediastinoscopy

While current guidelines recommend EBUS-TBNA for first line diagnosis of lung cancer and lymph node staging, there is significant data supporting the use of video-assisted mediastinoscopy (VAM) in patients with EBUS-TBNA negative lymph nodes. A meta-analysis performed by Sanz-Santos *et al.* analyzed 28 studies of patients with EBUS-TBNA negative lymph nodes. Of those patients, 2,472 came from studies without confirmatory VAM and 2,721 came from studies with confirmatory VAM. The meta-analysis reported that sensitivity and negative predictive value were improved in patients with confirmatory VAM (66.9% increased to 96.7% and 79.2% increased to 91.8% respectively) (63). Despite these significant improvements, the number needed to treat (NNT) was high (23.8). The authors concluded confirmatory VAM after negative EBUS-TBNA reduced the rate of unforeseen N2/N3 disease, but the NNT was high (63). With the high NNT, only certain patient populations should be offered confirmatory VAM (63). While Sanz-Santos *et al.* did not comment on which patient populations this should be, many different studies and current guidelines suggest those patients with negative EBUS-TBNA lymph nodes with high pre-test probability of malignancy should receive confirmatory VAM.

EBUS-TBNA with forceps and cryobiopsy

Staging and diagnosis of the mediastinum with EBUS continues to improve as new tools allow for larger tissue samples. Forceps biopsy has been shown to increase diagnostic yield especially in sarcoidosis or lymphoma due to the large tissue sample acquired (64). Transbronchial biopsy with the 1.1 mm cryoprobe has also been shown to increase diagnostic yield with a larger tissue sample and the added benefit of preserving tissue architecture. This has been particularly useful in diagnosing interstitial lung disease (64). Several studies have shown augmented diagnostic yield with these tools over EBUS-TBNA. Two RCTs showed an augmented diagnostic yield with cryobiopsy (93% from 81% and 91.6% from 85.7%) (64,65). Additionally, a study showed cryobiopsy yielded tissue more qualified for lung cancer molecular testing then forceps (64). A meta-analysis performed by Mathew *et al.* (N=844), showed the cryobiopsy augmented EBUS-TBNA from diagnostic yield of 81% to 91% with no significant increases in complications (66). The development of advanced tools such as the cryo probe, continues to increase the efficacy of EBUS as a diagnostic technique in the mediastinum.

Future directions in mediastinal diagnosis with bronchoscopy

The field of bronchoscopy is continuously advancing, and new techniques and technologies are showing promise in advancing the field of mediastinal diagnosis. Some of these new techniques/technologies include confocal laser

endomicroscopy (CLE), optical coherence tomography (OCT), and artificial intelligence (AI).

CLE

CLE is a novel technique that is minimally invasive and provides real-time, microscopic analysis of tissue structure (67). This procedure involves advancing a flexible mini-probe (pCLE) using transbronchial or trans-esophageal procedures or transbronchial/trans-esophageal biopsy needles (nCLE). Once located at the specimen of interest, a low power laser is shined on the specimen and the reflected light travels back up a pin hole to the detector. Out of focus light is thus blocked by the pin hole allowing for microscopic imaging (67). This technology has been useful in diagnosing lung disease, but it can equally be applied to mediastinum. There have been preliminary observational studies that have shown promise in CLE diagnosis of mediastinal lymph nodes. Benias *et al.* performed an observational study during EUS procedures and found that clusters of dark pleomorphic cells could be seen on nCLE and correlated well with histologic proven tumor cells (68). Wijmans *et al.* (69) also performed an observational study where they used three nCLE criteria (dark enlarged pleomorphic cells, dark clumps, and directional streaming) to detect malignancy. A study by Zuo *et al.* found that combining nCLE with EBUS resulted in a higher sensitivity, specificity, and positive predictive value, than either modality alone (70). While this technology has shown promise in preliminary studies in diagnosing malignancy in mediastinal lymph nodes, confirmatory larger randomized trials are needed before widespread adoption.

OCT

OCT is a near infra-red light-based technique that allows for high resolution images of target tissues. The OCT probe can be advanced through the working channel of the EBUS scope or regular bronchoscope allowing for real-time high-resolution images of lymph nodes of interest in the mediastinum (71). These images are produced by generating pull backs from distal to proximal, and then taking the resultant circumferential two-dimensional images and reconstructing them to three dimensional images (71). While there have been a few *ex-vivo* preliminary studies using OCT, we were unable to find any published *in-vivo* studies in our literature review. Hariri *et al.* developed OCT criteria in an *ex-vivo* study for differentiating solitary pulmonary nodules (SPN) and lung parenchyma (72). Shostak *et al.* later further observed characteristics that distinguished carcinoma from benign lymph node tissue in another *ex-vivo* study (73). Future studies are needed to be able to distinguish lymph node tissue from bronchial or lung parenchyma, but this technology shows promise in enhancing future EBUS-TBNA procedures.

AI

With the widespread adoption of AI, there have been many preliminary studies applying AI to bronchoscopy. A subset of AI called "machine learning" is the process of building computer models that can learn and then make predictions from data without being explicitly programmed. The main application of AI in bronchoscopy has been using intraluminal bronchial images that has allowed the "deep learning" AI to identify bronchial segments with a high degree of accuracy. Additionally, EBUS images have been utilized to instruct the AI on how to recognize benign *vs.* malignant disease (74). Another subset of AI termed "artificial neural networks" or "convolutional neural networks (CNN)" uses sensory "neurons" as data inputs which then connect to a hidden layer of computer programming and then transferred to an output layer that renders the decision (74). These CNN models may be helpful for training future bronchoscopists since the CNN can provide real time bronchial anatomy feedback to the operator. Cold *et al.* studied bronchoscopy training between a group using the CNN model for real time feedback *vs.* written instructions. The group using the CNN model showed significantly higher performance in segment identification (75). These studies are small and preliminary and larger confirmatory trials are needed before widespread adoption.

Deep learning models also shows promise in expanding access to ROSE. Yan *et al.* compared diagnostic accuracy of a deep learning model to a cytopathologist during flexible bronchoscopy with transbronchial biopsy (76). Their model showed comparable to slightly inferior accuracy to the pathologists in both image identification as well as in cancer diagnosis (76). This capability could make ROSE more available to healthcare facilities that do not have access to ROSE pathologists (76). While this is an exciting potential application of AI, further confirmatory studies are needed before widespread adoption.

Limitations of the review

Our review has several limitations. This is a "narrative"

review and thus the data presented is not comprehensive. Not all data presented comes from prospective randomized controlled trials and no analysis for bias was performed; thus, there may be inherent bias in the data presented. Studies presented had different definitions of diagnostic accuracy and diagnostic yield so comparison between these studies should be made with caution. Studies presented were performed in many different countries in heterogeneous patient populations, so comparison between patient populations should be made with caution.

Conclusions

Bronchoscopy with its versatility, recent advancement, and high diagnostic yields with relatively low complication rate has revolutionized invasive diagnosis of the mediastinum. In both benign and malignant diseases, bronchoscopy has given patients and providers unprecedented cost savings, decreased time to diagnosis, decreased complications, and has led to better health outcomes. Bronchoscopy has also been proven to have even better diagnostic yield and outcomes when combined with classic imaging and diagnostic modalities such as CT, PET, MRI, EUS, and surgical mediastinoscopy. Bronchoscopy continues to advance mediastinal diagnosis with innovative technologies such as elastography, CLE, OCT, and AI. In conclusion, bronchoscopy is and will continue to be an integral modality in invasive diagnosis of the mediastinum.

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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-24-32/rc

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://med.amegroups.com/article/view/10.21037/med-24-32/coif). The authors have no conflicts of interest to declare.

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. 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 was obtained from the patient for the publication of this study and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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Case Report

Resection of shrinking secondary thymic cyst during follow-up—a case report

Taekyung Kang[1]^, Mi-Jin Kang[2]^

[1]Department of Emergency Medicine, Inje University Sanggye Paik Hospital, Seoul, Korea; [2]Department of Radiology, Inje University Sanggye Paik Hospital, Seoul, Korea

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

Correspondence to: Mi-Jin Kang, MD. Department of Radiology, Inje University Sanggye Paik Hospital, 1342, Dongil-ro, Nowon-gu, Seoul 01757, Korea. Email: s2621@paik.ac.kr; cooky52@paran.com.

Background: Thymic cysts can be classified as congenital or acquired. Most thymic cysts do not change in size over a short period of time. Although very rare, thymic cyst rupture is associated with serious complications, such as mediastinal hemorrhage and hemothorax. We experienced a case of partial rupture of a secondary thymic cyst, in an asymptomatic patient.

Case Description: A 60-year-old woman visited Inje University Sanggye Paik Hospital with left hilar bulging detected on routine chest radiograph. A chest computed tomography (CT) scan revealed a 6 cm well-defined cystic mass with partial septation in the prevascular mediastinum. Thus, secondary thymic cyst was suggested. On the follow-up chest CT scan taken 3 months later, the size of the thymic cyst decreased, while the solid portion increased slightly, suggesting the potential presence of malignancy. Consequently, surgery was conducted. Adhesion to the lung and aorta was observed, but they were relatively well separated. The pathological findings revealed a partially ruptured thymic cyst with fat necrosis and multifocal granulomas.

Conclusions: There are controversies in the treatment of thymic cysts. Some clinicians prefer strict medical supervision to avoid unnecessary surgery, while others advocate immediate excision to avoid complication. However, if any changes are observed during the follow-up of the thymic cyst, it may indicate malignant transformation or rupture, necessitating prompt surgical excision.

Keywords: Case report; secondary thymic cyst; impending rupture; video-assisted thoracoscopic surgery resection (VATS resection)

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Introduction

Thymic cysts can be classified as congenital or acquired. Congenital cysts are typically thin-walled unilocular lesions, whereas acquired thymic cysts are typically thick-walled multilocular lesions (1). Most thymic cysts do not change in size over a short period of time.

Thymic cyst rupture rarely occurs; however, when it does happen, it is associated with serious complications, such as mediastinal hemorrhage or hemothorax (2). We experienced a case of partially ruptured thymic cyst without symptoms or complications. We present this article in accordance with the CARE reporting checklist (available at https://med.

^ ORCID: Taekyung Kang, 0000-0002-4573-9007; Mi-Jin Kang, 0000-0001-8510-3268.

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Case presentation

A 60-year-old woman visited Inje University Sanggye Paik Hospital with an abnormality detected during routine chest radiography. Chest radiography revealed a bulging contour in the left hilar region (*Figure 1*). Chest computed tomography (CT) with contrast enhancement revealed a 6 cm well-defined cystic mass in the prevascular mediastinum (*Figure 2A,2B*). There were multiple septations in the inferior portion of the cyst, and both the wall of the cyst and septa were enhanced. As the patient was asymptomatic and laboratory findings were unremarkable, we suspected an acquired thymic cyst rather than an abscess. Incidentally, a mixed ground-glass nodule (GGN) was detected in the right middle lobe (RML). Three months later, the patient underwent a follow-up CT scan with contrast enhancement for the GGN. On the follow-up CT scan, the 2 cm mixed GGN in the RML was stable. However, the prevascular mediastinal mass had changed in size and shape (*Figure 3A,3B*). The size of the mass decreased from 6 to 5 cm, and the attenuation of the internal fluid content increased, suggesting a complication. Furthermore, the lower part of the mass transformed into to a solid component and exhibited enhancement. The possibility of a malignant tumor in the prevascular mediastinum could not be ruled out. Thus, video-assisted thoracoscopic surgery (VATS) was performed. After surgery, the patient was discharged and is currently doing well.

A surgical examination revealed a large cystic mass in the left prevascular mediastinum. Adhesion to the lung and aorta was observed, but they were relatively well separated (*Figure 4*).

Upon gross macroscopic examination, the mass appeared as a 5 cm encapsulated cystic mass. The inner surface of the mass was relatively smooth, with yellowish plaques. The surrounding tissue exhibited creamy-yellowish necrotic changes. The pathological examination revealed a partially ruptured thymic cyst with fat necrosis and multifocal granulomas.

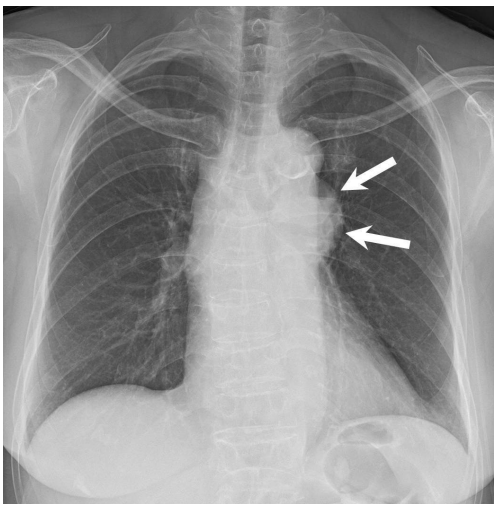

Figure 1 Chest radiograph shows bulging contour at the left hilar area (arrows) with hilar overlay sign.

Highlight box

Key findings

- We experienced a case of partial rupture of a secondary thymic cyst in an asymptomatic patient.

What is known and what is new?

- Most thymic cysts do not change in size over a short period of time, and their rupture, although rare, presents serious complications.
- Our findings indicate that thymic cysts with decreased size and increased solid mass can potentially signal early rupture.

What is the implication, and what should change now?

- Our findings provide a valuable basis for further scientific and clinical research on thymic cyst changes that may indicate early rupture and aid rupture prevention.

Ethical statement

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). Publication of this case report and accompanying images was waived from patient consent according to the Sanggye Paik Hospital institutional review board.

Discussion

There are controversies in the treatment of thymic cysts (3,4). Some clinicians prefer strict medical supervision, while others advocate immediate excision to establish a diagnosis and prevent complications. However, if there is a change in the imaging findings during follow-up, it is possible that it has transformed into a malignant condition, necessitating surgery (5).

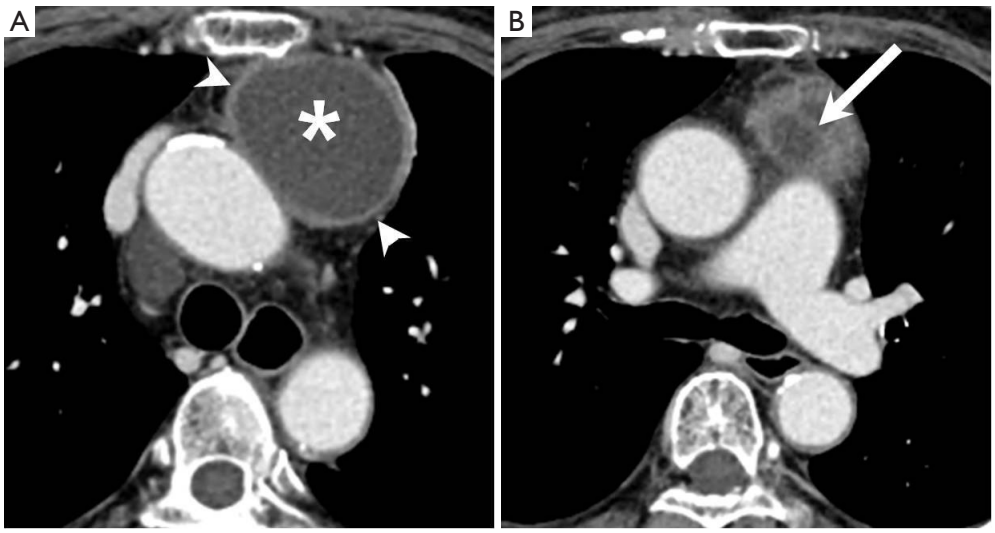

Figure 2 CT scans reveal a well-defined cystic lesion (asterisk in A) with an enhanced wall (arrowheads in A) in the left prevascular mediastinum. A small septum is suspected at the inferior portion of the cystic mass (arrow in B). CT, computed tomography.

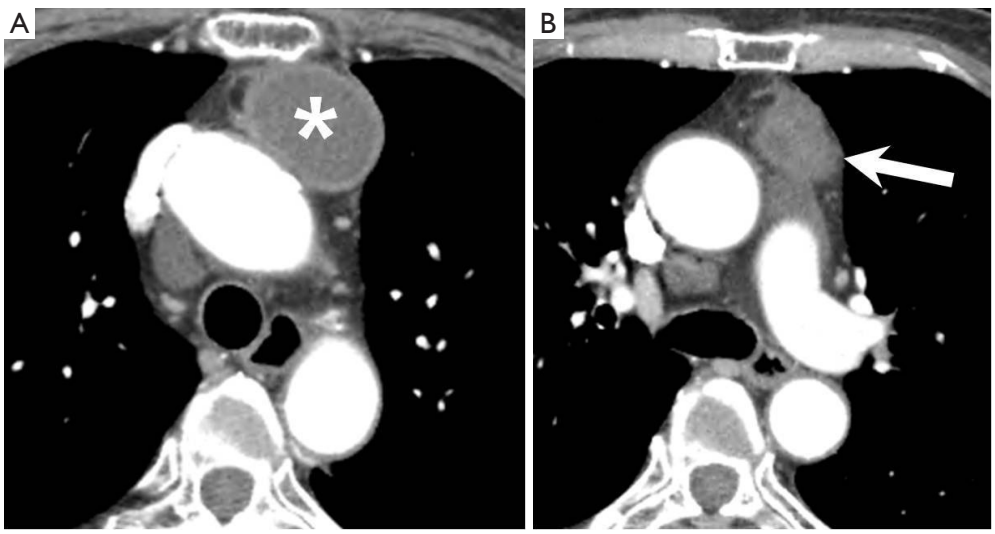

Figure 3 Follow-up CT scans reveal that the size of the cystic mass was decreased. The attenuation of the internal fluid is increased (asterisk in A), and the far inferior portion of the mass has changed to a solid component (arrow in B). CT, computed tomography.

Thymic cyst rupture is reported very rarely; however, when it occurs, it is accompanied by a variety of complications. In Tsuda *et al.*'s report, the ruptured thymic cyst presented with mediastinal hemorrhage and hemothorax (6). Upon histopathological examination, a hematoma observed due to partial destruction of the epithelial lining. And in Lachanas *et al.*'s report, the thymic cyst ruptured into the pleural cavity (7). Our patient had neither symptoms nor complications. However, if the operation is delayed, complications, such as fluid leakage from the thymic cyst into the pleural cavity due to overt rupture, and formation of a hematoma and hemothorax, could occur.

Conclusions

In conclusion, this decrease in size may also lead to an increase in the solid portion of the thymic cyst, potentially signaling early rupture. However, additional investigations

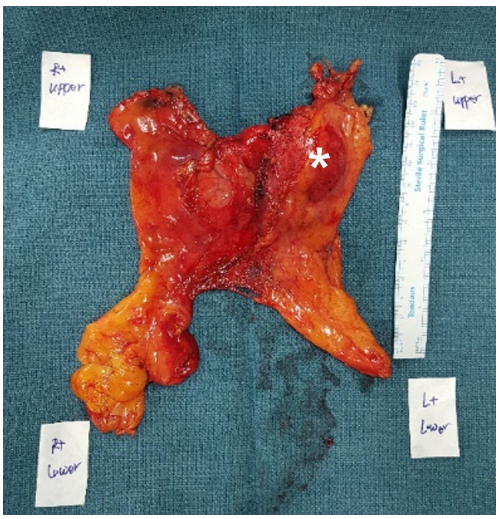

Figure 4 Thymectomy specimen image shows a 5 cm sized cyst (asterisk) in the upper portion of the left lobe of the thyroid gland. Grossly, no rupture was noted.

and analyses are necessary to confirm this hypothesis.

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Footnote

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Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://med.amegroups.com/article/view/10.21037/med-24-13/coif). The authors have no conflicts of interest to declare.

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. 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). Publication of this case report and accompanying images was waived from patient consent according to the Sanggye Paik Hospital institutional review board.

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Conservative management of emphysematous esophagitis—a case report

Taekyung Kang[1]^, Mi-Jin Kang[2]^

[1]Department of Emergency Medicine, Inje University Sanggye Paik Hospital, Seoul, Korea; [2]Department of Radiology, Inje University Sanggye Paik Hospital, Seoul, Korea

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

Correspondence to: Mi-Jin Kang, MD. Department of Radiology, Inje University Sanggye Paik Hospital, 1342, Dongil-ro, Nowon-gu, Seoul 01757, Korea. Email: s2621@paik.ac.kr; cooky52@paran.com.

Background: Emphysematous esophagitis is a very rare disease and there are only a few previous reports in the literature. Previously reported cases have resulted in emphysematous esophagitis following anterior cervical procedures or ingestion of hydrogen peroxide (HP). In this report, we describe a case in which a patient with emphysematous esophagitis accompanied by gastritis without the above predisposing factors was treated with conservative treatment.

Case Description: A 65-year-old woman was admitted to Inje University Sanggye Paik Hospital with general weakness, abdominal discomfort, nausea and chest discomfort. On chest and abdominal radiographs, there were abnormal air density in upper mediastinum and abdomen. Chest and abdomen computed tomography (CT) revealed mural air at entire esophagus and stomach. The patient managed with proton pump inhibitor (PPI), broad spectrum antibiotic therapy, and total parenteral nutrition (TPN).

Conclusions: Emphysematous gastritis occurs mainly along with emphysematous gastritis, with a mortality rate of up to 62%. It is mainly known to be caused by infection of the esophageal wall by gas forming bacteria, but there are also cases where there is no ingestion or exact cause. There is still controversy about treatment methods due to the high death rate, but if detected early like the reported patient, a good outcome can be expected with conservative treatment alone.

Keywords: Emphysematous esophagitis; conservative management; intramural gad; case report

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Introduction

Emphysematous esophagitis is a very rare and severe disease with only a few case reports (1,2). In one paper, there was a report on emphysematous esophagitis occurring after hydrogen peroxide (HP) ingestion (1). In another paper, a case of emphysematous esophagitis was reported with no clear preceding factors other than acupuncture at anterior cervical region (2).

In this paper, we report a case of emphysematous esophagitis in a 65-year-old female patient with no history of trauma or toxic ingestion. In the early stage of the disease, the patient's esophageal necrosis was so severe that even an attempt to enter the endoscope was not possible, but our patient recovered with appropriate conservative treatment and was discharged. We present this article in accordance with the CARE reporting checklist (available at

^ ORCID: Taekyung Kang, 0000-0002-4573-9007; Mi-Jin Kang, 0000-0001-8510-3268.

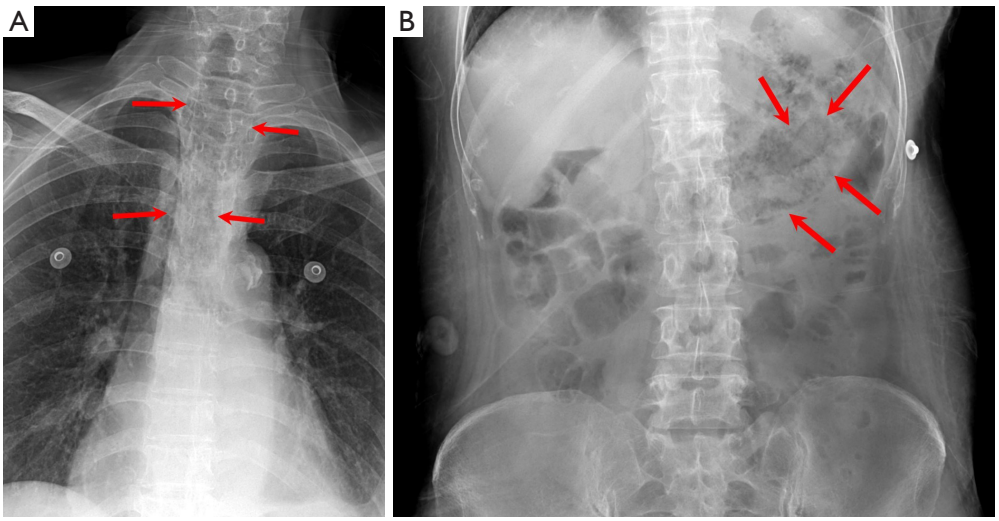

Figure 1 Plain radiographs of a patient with emphysematous esophagitis with gastritis taken in the emergency room. There are liner or dot-like air density gathered in the upper mediastinum (arrows) on a chest radiograph (A). There are air shadows along the border of the stomach (arrows) on an abdominal radiograph (B).

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Case presentation

A 65-year-old woman was admitted to Inje University Sanggye Paik Hospital with general weakness. She complained abdominal discomfort, nausea and loss of appetite for 1 week. And she also complained chest discomfort started 3 days ago. She had a history of atrial fibrillation and mitral stenosis and was taking warfarin. Initial laboratory studies revealed increased white blood cell 13,150/μL, C-reactive protein 23.1 mg/dL, and prolonged prothrombin time 31.9 (international normalized ratio 3.18). These findings suggested that there was some type of inflammation in the body. For further evaluation chest and abdominal radiographs were obtained. A chest radiograph showed abnormal air shadows in upper mediastinum (*Figure 1A*). An abdominal radiograph also showed abnormal air shadows in the left upper quadrant of the abdomen (*Figure 1B*). Thus, the patient underwent chest and abdomen computed tomography (CT) scan with contrast enhancement (CE). Chest CT scan showed intramural gas in the mural layer of the entire esophagus and stomach (*Figure 2A*,*2B*). Thus, emphysematous esophagitis and gastritis were suspected. In addition, there were no findings of pneumomediastinum or portal vein gas, and there was no intraperitoneal free air.

Endoscopy was attempted for a more accurate diagnosis. Bluish-gray mucosa was observed from the entrance to the esophagus and was judged to be necrosis. Therefore, the examination was discontinued due to the risk of perforation. On blood culture, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* were grown. The patient received conservative management with proton pump inhibitors (PPIs), broad spectrum antibiotic therapy, fluid resuscitation and total parenteral nutrition (TPN). On follow-up CE chest CT scan, obtained 12 days later, intramural gas in esophagus and stomach was decreased (*Figure 3A*).

The patient received antibiotic treatment for about

Highlight box

Key findings

- We experienced a case of emphysematous esophagitis with gastritis that was managed conservatively.

What is known and what is new?

- Emphysematous esophagitis with gastritis is very rare and fatal, with a mortality rate exceeding 60%.
- We successfully treated a patient with emphysematous esophagitis with gastritis using a proton pump inhibitor, broad-spectrum antibiotic therapy, and total parenteral nutrition.

What is the implication, and what should change now?

- Emphysematous esophagitis is a very dangerous disease, but if detected early, it can be treated with conservative management.

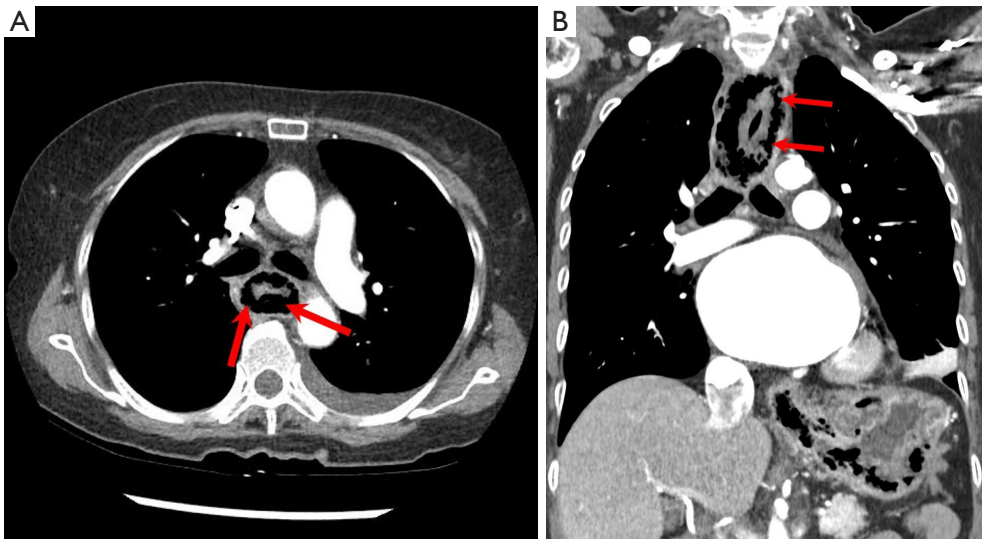

Figure 2 CT scans of a patient with emphysematous esophagitis with gastritis taken in the emergency room. Axial (A) and coronal (B) view of contrast enhanced chest CT show intramural gas of the esophagus (arrows). CT, computed tomography.

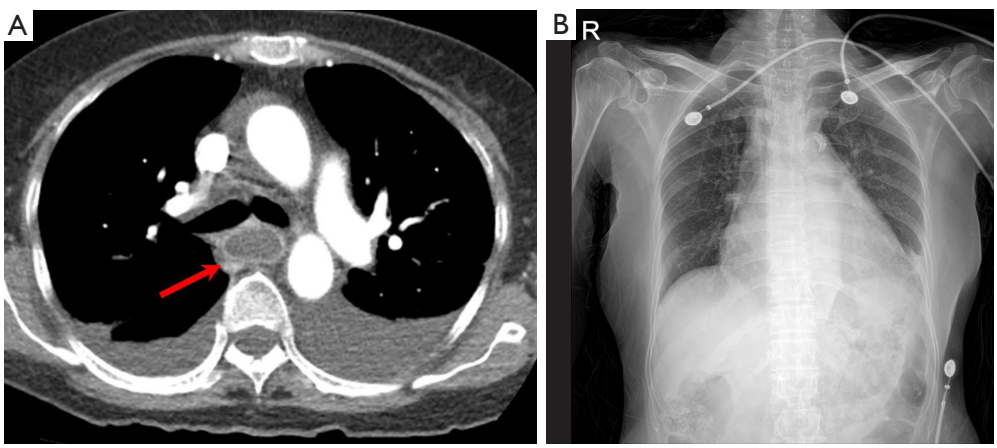

Figure 3 Follow-up CT scan and chest radiograph of a patient with emphysematous esophagitis with gastritis. A follow-up chest CT (A) performed 12 days later shows that all intramural air in the esophagus had disappeared, and there was mild wall thinning and fluid retention in the esophagus (arrow). Bilateral pleural effusion is also observed. A follow-up chest radiograph obtained 2 months later (B) shows no unusual findings other than subsegmental atelectasis in the left lower lung zone. CT, computed tomography.

a month, and then went on a diet. The patient's symptoms improved and she was discharged. A chest CT performed on the 12th day of hospitalization revealed a thrombus in the left atrium (LA), and the patient was discharged with a prescription for anticoagulants. Two months after discharge, the patient returned to Inje University Sanggye Paik Hospital with hematemesis. Plain chest radiograph before discharge showed improved air shadows in upper mediastinum and upper abdomen (*Figure 3B*).

Ethical statement

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). Publication of this case report and accompanying images was waived from patient consent according to the Sanggye Paik Hospital institutional review board.

Discussion

Emphysematous esophagitis is thought to be an infection of the esophageal wall caused by gas forming bacteria and is usually accompanied by emphysematous gastritis (1).

If there is air shadow within the esophageal or stomach wall but there is no sign of systemic toxicity, this should be classified as esophageal or gastric emphysema as it is self-limiting (3). Endoscopy shows erosion of the esophageal wall or severe necrosis, similar to the reported cases. Plain chest X-ray shows additional mediastinal air shadows other than those caused by the esophageal lumen along the path of the esophagus. On CT, it is more clearly visible as circular or linear air density located within the esophageal wall.

The mortality rate of emphysematous gastritis is 62%, and increases to 75% when portal vein gas is present (4). The mortality rate of emphysematous esophagitis itself is unknown, but since it is mainly accompanied by emphysematous gastritis, it can be assumed to be similar to or slightly higher.

If emphysematous esophagitis is detected early, it is possible to try conservative management with TPN and broad-spectrum antibiotics to provide adequate nutrition while resting the gastrointestinal system (1,2). However, when esophageal or gastric perforation occurs, surgical management must be performed first, followed by supportive management (4).

Conclusions

In conclusion, emphysematous esophagitis is a severe disease, but if the clinical and radiological findings are known, such patients can be detected quickly and adequate therapy can be started.

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Footnote

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Unusual outcome of treatment of thymoma with immunotherapy: case report

Mohamed Shanshal[1]^, Joseph Maakaron[2], Kaushal Parikh[1], Jenesse Nicole Moffett[1], Ailsa G. Luce[1], Anna J. Schwecke[1], Julian Molina[1], Konstantinos Leventakos[1]

[1]Department of Oncology, Mayo Clinic, Rochester, MN, USA; [2]Division of Hematology, Oncology and Transplantation, University of Minnesota, Minneapolis, MN, USA

Contributions: (I) Conception and design: M Shanshal, K Leventakos; (II) Administrative support: None; (III) Provision of study materials or patients: M Shanshal, K Leventakos; (IV) Collection and assembly of data: M Shanshal, K Leventakos; (V) Data analysis and interpretation: M Shanshal, K Leventakos; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Mohamed Shanshal, MD. Department of Oncology, Mayo Clinic, 200 First Street, Rochester, MN 55902, USA.
Email: shanshal.mohamed@mayo.edu.

Background: Thymoma is a rare mediastinal neoplasm originating from thymic epithelial cells, often associated with paraneoplastic syndromes. These syndromes can manifest as a range of autoimmune disorders, including myasthenia gravis, pure red cell aplasia, and aplastic anemia. Clinical trials involving the use of immune checkpoint inhibitors (ICIs) in thymoma have been complicated by a high incidence of immune-related adverse effects (irAEs). As a result, the use of ICIs in the treatment of thymoma is not currently recommended.

Case Description: We present a case of thymoma with paraneoplastic aplastic anemia that showed a remarkable response to atezolizumab following the discontinuation of cyclosporine. The patient was initially treated with cisplatin, doxorubicin, and cyclophosphamide (CAP), achieving a short-term partial response. However, this response was not sustained, and she developed aplastic anemia characterized by worsening anemia, reticulocytopenia, and thrombocytopenia. A bone marrow biopsy revealed erythroid hypoplasia without dysplasia, linked to her thymoma. Cyclosporine was initiated to manage the aplastic anemia, but the disease continued to progress, leading to a switch to capecitabine and gemcitabine. Restaging scans revealed further advancement, with extensive pleural metastasis. To manage the progressing disease, atezolizumab was introduced. Initially, no response was seen while on cyclosporine, but after discontinuing cyclosporine, the patient experienced a significant therapeutic response. Despite this success, immune-related dermatitis and hematological complications developed, requiring careful management. In clinical trials, ICI use alongside immunosuppressants is common for managing paraneoplastic manifestations in thymoma.

Conclusions: This case highlights the potential efficacy of ICI in thymoma treatment, emphasizing the delicate balance required between immunosuppression and immunotherapy for optimal outcomes. Achieving this delicate balance is vital for optimizing patient outcomes while minimizing the risk of severe complications and ensuring that both the paraneoplastic syndrome and the tumor itself are adequately managed. This consideration is particularly important when developing future clinical trials for thymoma, where the complex interplay between these therapies must be carefully evaluated to design effective and safe treatment protocols.

Keywords: Thymoma; immunotherapy; paraneoplastic syndromes; case report

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^ ORCID: 0009-0005-0775-2680.

Introduction

Thymoma is a rare neoplasm arising from the thymic epithelial cell and present with paraneoplastic syndrome in up to 50% of cases (1). Use of immune check point inhibitors (ICIs) is particularly challenging given high incidence of immune-related adverse effects (irAEs) (2). In clinical trials, the utilization of ICI alongside concurrent immunosuppressant therapies is a frequent practice for addressing the paraneoplastic manifestations associated with thymoma. Here we report a case of thymoma associated with paraneoplastic aplastic anemia that exhibited remarkable response to immunotherapy atezolizumab when cyclosporine held. This case highlights the potential efficacy of ICI in treatment of thymoma and suggesting a careful balance between immunosuppression and immunotherapy for optimal patient outcomes. We present this case in accordance with the CARE reporting checklist (available at https://med.amegroups.com/article/view/10.21037/med-24-20/rc).

Case presentation

A 63-year-old female presented with progressive shortness of breath who underwent computed tomography (CT) scan and found to have an anterior mediastinal mass. The patient has a medical history of hypertension and mitral valve regurgitation. Physical exam was negative with exception of decrease air entry at the left upper lung. Positron emission tomography (PET) scan showed mass with invasion of left upper lung, left pericardial and left pleural metastasis i.e., stage IVB thymoma. Blood testing was significant for normocytic anemia with mild thrombocytopenia. Biopsy results revealed a predominant epithelial type, with few immature T lymphocytes. The tumor cells exhibited palisading around the perivascular space, displaying mild to moderate cellular atypia. Immunohistochemical (IHC) stains were positive for Oscar keratin, Pax8, and P40, with background thymocytes marked with TdT, CD5, CD3, and programmed death ligand-1 (PD-L1) at 95%. These findings were consistent with thymoma World Health Organization (WHO) class B3.

Following the initiation of treatment with CAP, the patient experienced a short-term partial response. However, she subsequently developed aplastic anemia characterized by worsening anemia, reticulocytopenia and thrombocytopenia. A bone marrow biopsy revealed erythroid hypoplasia without dysplasia, attributed to her thymoma. Consequently, she started treatment with cyclosporine.

In response to disease progression, capecitabine and gemcitabine initiated. Restaging scans indicated ongoing disease advancement in the mediastinum, accompanied by extensive pleural metastasis (*Figure 1A*).

The decision was then to start atezolizumab in early 2022, while cyclosporine continued for aplastic anemia. However, restaging scans after three cycles showed ongoing disease progression (*Figure 1B*). It was then suggested that cyclosporine might be blunting her ICI response. Consequently, the decision made to hold cyclosporine in May 2022, given stable blood counts. After the fourth cycle, a repeat CT chest revealed a remarkable response to immune therapy (*Figure 1C*). However, the patient developed immune-related dermatitis, worsening anemia, and thrombocytopenia. Atezolizumab held, yet she maintained good overall disease control for around 15 months with a small area of progression in the mediastinum (*Figure 1D*). Her blood counts responded to eltrombopag, and she remained stable and transfusion independent. A graph of her hemoglobin and platelets counts is shown in *Figure 1* (lower panel).

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 was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Highlight box

Key findings

- We report a case of thymoma with paraneoplastic aplastic anemia that showed a significant response to atezolizumab after discontinuation of cyclosporine.

What is known and what is new?

- Thymomas often present with paraneoplastic syndromes, and immune checkpoint inhibitors (ICIs) are associated with high immune-related adverse events.
- This case demonstrates improved efficacy of atezolizumab after discontinuation of cyclosporine in thymoma treatment.

What is the implication, and what should change now?

- Balancing immunosuppression and immunotherapy is crucial for optimizing thymoma treatment.
- Further studies are needed to refine treatment strategies and confirm these findings.

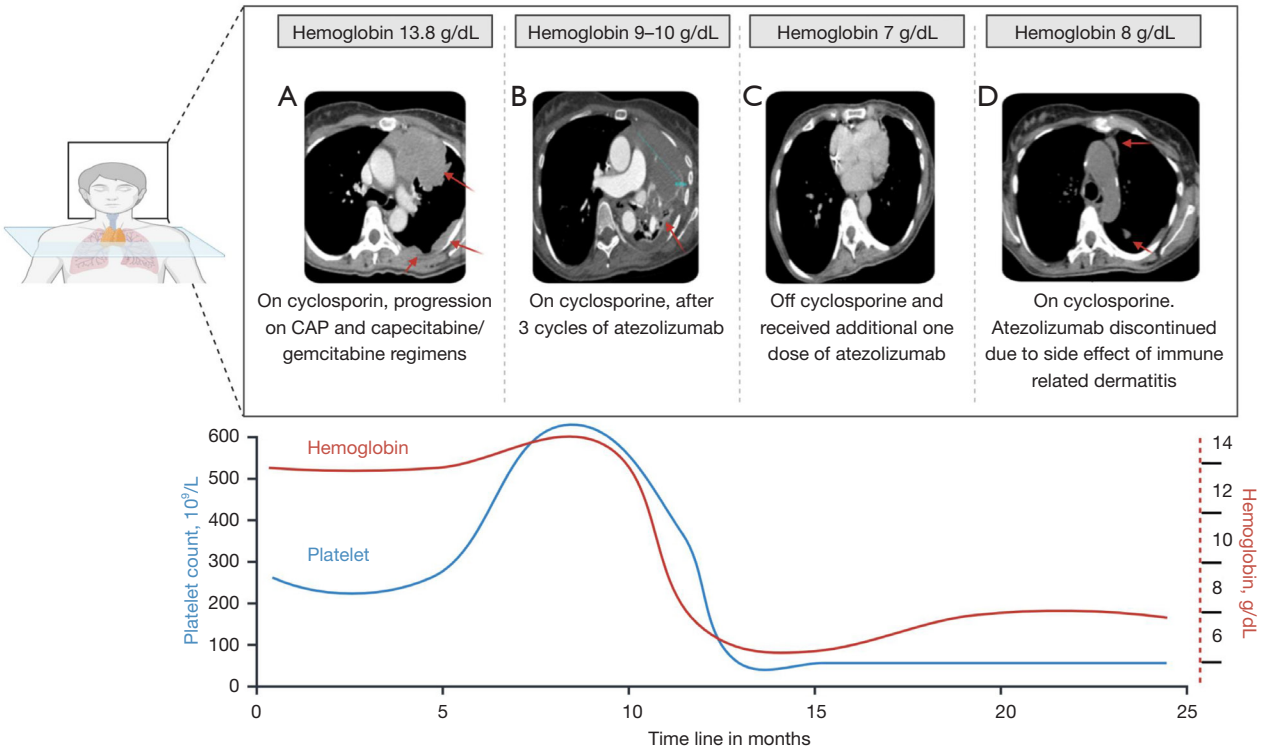

Figure 1 Imaging and hematological response to treatment with atezolizumab in relation to cyclosporine use. The upper panel illustrates the treatment timeline and imaging results, while the lower panel presents the patient's platelet count and hemoglobin levels during treatment. (A) Imaging shows the treatment timeline with CAP, highlighting a disease progression as indicated by red arrows. (B) Imaging continues to indicate the lack of response and disease progression on atezolizumab while on cyclosporine treatment. (C) Imaging depicts a significant and positive response to atezolizumab treatment after the discontinuation of cyclosporine. (D) Disease recurrence is evident in the imaging upon the reintroduction of cyclosporine, marked by red arrows. The lower panel presents the patient's platelet count and hemoglobin levels throughout the treatment period. This figure was created with BioRender.com. CAP, cisplatin, doxorubicin, and cyclophosphamide.

Discussion

Treatment of recurrent thymoma remains challenging due to rarity of disease and low response rate with using chemotherapeutic agents (3). Multiple immune check points inhibitors assessed for safety and efficacy such as pembrolizumab which was evaluated for safety and efficacy in open label phase II trial that included seven patients with thymoma. Two of them had B3 thymoma and the rest were B2 thymoma. The overall response rate was 28.6% with duration of response not reached at 15 months. Five of seven patients with thymoma reported grade ≥3 immune-related adverse events, including hepatitis, myocarditis, thyroiditis, glomerulonephritis, and colitis (4).

Avelumab was evaluated for efficacy and safety in phase 1 trial that included 7 patients with thymoma, the objective response rate (ORR) was 57% (5). The trial did analysis of tumor infiltrate post treatment with avelumab which revealed predominance of lymphocytes with a mature CD8 positive T-cell phenotype and low level of T regulatory cell, raising the question of the rule of CD8 T-cell in development of immune related side effect as well as explaining the robust response to ICI.

Despite the low baseline tumor mutational burden (TMB) and the rarity of microsatellite instability-high (MSI-H) thymomas compared to other cancers, a study suggests a higher-than-expected response rate to ICIs for TMB-high or MSI-H thymomas. This enhanced response is likely attributed to the unique role of the thymus in T-cell development and the associated immune microenvironment (6).

This case shed the light on the rule and potential reduction of efficacy of ICI with concomitant use of

immunosuppressant agents that is frequently used in treatment of paraneoplastic syndrome associated with thymoma such as myasthenia gravis and aplastic anemia. Immunosuppressant agents such as steroid or cyclosporine blunts the effect of CD8 T-cell and is associated with reduced efficacy of ICI therapy.

Conclusions

In our case, patient with WHO type B3 thymoma had no response to 3 cycles atezolizumab when used with concomitant cyclosporine, however, a profound response to atezolizumab within one cycle occurred when cyclosporine was held. This case highlights the efficacy if ICI in treatment of thymoma and it also shed light into the negative impact of concomitant use immunosuppressant that are frequently used concomitantly in treatment of paraneoplastic manifestations of thymoma.

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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. All procedures performed in this study were in accordance with the ethical standards of the institutional and national research committees and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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