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CHEST

Multilobulated thymoma with an acute angle: a new predictor of lung invasion

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Abstract

Objective Imaging features of thymomas such as lobulation, infiltration into lung, and adjacent lung abnormality have been associated with lung invasion but are unreliable. The goal of this study was to develop a more objective and reproducible method for predicting lung invasion by thymomas.

Subjects and methods Fifty-four thymomas resected from 2007 to 2017 were included for analysis. Pre-operative CT scans for these thymomas were reviewed, and multiple features were evaluated, including the interface of each thymoma with the adjacent lung. A multilobulated thymoma with at least one acute angle between lobulations was considered suspicious for lung invasion. Two blinded radiologists then tested this hypothesis by reviewing all 54 CT scans and using this single criterion to predict lung invasion.

Results Twelve thymomas invaded the lung. All lung-invasive thymomas were multilobulated. Twenty-nine thymomas had a multilobulated interface with the lung. Multilobulated thymomas were more likely to invade the lung than thymomas with a single lobulation or no lobulation ($p = 0.0008$). Using the criterion of multilobulation with at least one acute angle between lobulations to predict lung invasion, the two readers achieved a sensitivity of 67–83%, specificity of 93–98%, positive predictive value of 77–89%, and negative predicted value of 91–95%. Nine lung-invasive thymomas also invaded mediastinal structures or disseminated to the pleura.

Conclusions A multilobulated thymoma with at least one acute angle between lobulations predicts lung invasion with a high degree of accuracy. When lung invasion is suspected, the findings are indicative of a locally aggressive tumor, and the pleura and mediastinal structures should also be closely inspected for invasion.

Key Points

- *A multilobulated thymoma with at least one acute angle between lobulations is predictive of lung invasion.*
- *Coronal and sagittal reformations and thin sections are helpful in challenging cases.*
- *Lung invasion indicates a locally aggressive tumor, and the pleura and other mediastinal structures should also be closely inspected for invasion.*

Keywords Thymoma · Multidetector computed tomography · Mediastinum · Neoplasm invasiveness · Lung

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Abbreviations

IASLC	International Association for the Study of Lung Cancer
ITMIG	International Thymic Malignancies Interest Group
LI	Lung invasion
TET	Thymic epithelial tumor
WHO	World Health Organization

Introduction

A thymoma is a rare primary tumor of the thymus with the potential for local invasion of surrounding structures such as the pleura, pericardium, lung, and mediastinal vasculature. It is classified as a thymic epithelial tumor (TET), along with thymic carcinoma and thymic neuroendocrine tumors. Multiple staging systems for TETs, notably the Masaoka-Koga system, have been used in the past to guide management [1, 2]. More recently, the first TNM staging system for TETs was jointly proposed by the International Thymic Malignancies Interest Group (ITMIG) and International Association for the Study of Lung Cancer (IASLC) and is now included in the 8th edition of the *TNM Classification of Malignant Tumors* [3].

As ITMIG/IASLC stage increases, management becomes more complex with progressive increase in recurrence rates [3, 4]. The T component is defined by the direct invasion of surrounding structures and determines stages I, II, IIIa, and IIIb. Lung invasion (LI) is classified as T3 (stage IIIa) [3, 4]. Stage IVa and IVb tumors, such as those with dissemination to the pleura, are decided by the N and M components [5].

The ability to predict LI on pre-operative imaging is potentially valuable for treatment planning. LI necessitates a wedge resection of the involved lung and raises the possibility of diaphragmatic plication due to phrenic nerve involvement. These factors impact the choice between minimally invasive and open surgical approaches [6].

Suspicion for LI also indicates a more locally aggressive tumor that may invade other structures and for which a complete resection may be difficult to achieve. Completeness of surgical resection is the most important predictor of outcome in patients with thymoma [7–10]. For stage III tumors, recurrence rates range from 10 to 60% [3, 11, 12].

Larger size, irregular shape and contour, infiltration of mediastinal fat, calcification, and heterogeneity are imaging features associated with increased likelihood of microscopic invasion and advanced stage [13–17]. Features suggesting LI include a lobulated or irregular interface with lung and adjacent lung abnormality [15–21]. The accuracy of these features for LI, however, is inconsistent.

Zerhouni et al predicted LI in all six patients of a series of ten advanced-stage thymomas, alluding to lobulation as the main morphologic feature suggesting LI without explicitly detailing the criteria [22]. Tomiyama et al analyzed a group of less advanced thymomas and found that an irregular interface with lung was a poor predictor of LI [19]. More recently, Shen et al found that a single lobulation was not predictive of LI but multilobulation yielded a sensitivity of 40%, a specificity of 79%, a positive predictive value (PPV) of 65%, and a negative predictive value (NPV) of 59% [23]. These measures increased to 41%, 91%, 81%, and 62%, respectively, when a lung abnormality (which they defined as patchy inflammation or fibrosis) was identified adjacent to a multilobulated thymoma.

The goal of the current study was to develop a more objective and reproducible method for predicting LI with the hypothesis that a multilobulated thymoma with at least one acute angle between lobulations is predictive of LI.

Methods

Patient selection This retrospective analysis received institutional review board approval. The Department of Pathology provided a list of all resected thymomas from 2007 to 2017 ($n = 106$). Fifty-two patients were excluded because the pre-operative chest CT was not within 3 months of surgery, not of diagnostic quality, or performed at another institution and unavailable. The remaining 54 patients were included for analysis, and their pre-operative chest CT scans, operative reports, and pathology reports were reviewed. No patients received neoadjuvant therapy prior to surgery. Thymic carcinomas and neuroendocrine tumors were not included in this analysis.

CT scan protocol Of the 54 CT scans included for evaluation, 45 were scanned with intravenous contrast and 9 without contrast. Slice thicknesses ranged from 1 to 5 mm. If coronal and/or sagittal reformations were not included in the original scan protocol, they were constructed on a separate workstation and exported to PACS. Protocol differences were due to changes in the standard protocol at our institution over the study period and 13 scans being uploaded from different institutions.

Imaging analysis CT scans were reviewed for thymoma size, calcification, and location within the prevascular mediastinum (midline, left, or right). A thymoma was considered midline if any component was located behind the sternum. Off-midline thymomas characterized as right or left had no midline component. Thymoma heterogeneity was not evaluated because intravenous contrast-enhanced CT scans were not available for all patients.

The interface of the thymoma with adjacent lung was then characterized as having no interface with the lung, a smooth interface, a single lobulation, or multiple lobulations (Fig. 1). If the interface with lung was multilobulated, the angle formed by adjacent lobulations was estimated on lung windows as either acute or obtuse (Fig. 2). Angles between a tumor lobulation and another structure such as the mediastinum, chest wall, or a blood vessel were disregarded (Fig. 3). Angles were estimated rather than quantified because visually distinguishing acute from obtuse angles was considered more feasible for translation into clinical practice. Adjacent lung abnormality was defined as a focal pulmonary opacity along an area of tumor extension toward the lung. Compressive atelectasis occurring over a longer segment of tumor was not considered an adjacent lung abnormality. Elevated ipsilateral hemidiaphragm, pleural effusion, and pleural nodularity were noted when present.

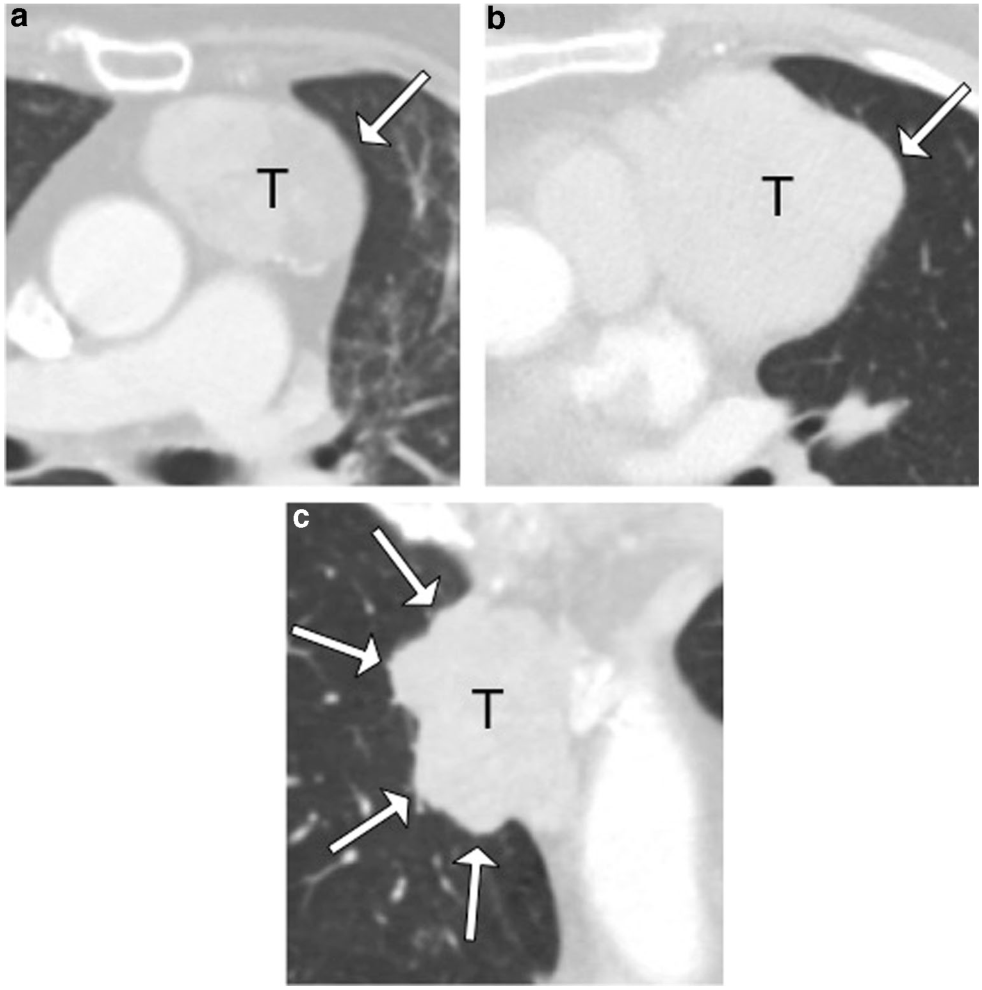

Fig. 1 Example of thymoma interfaces with the lung. **a** A thymoma (T) with a smooth interface with the left lung and no lobulation (arrow); **b** a thymoma (T) with a single lobulation along the left lung interface (arrow); **c** a thymoma (T) with multiple lobulations along the right lung interface (arrows)

These imaging features were then correlated with pathology and operative reports. All of the pathology reports included the Masaoka-Koga stage and World Health Organization (WHO) subtype, and we re-classified tumor stage according to the updated ITMIG/IASLC staging system [3]. Operative reports were screened for thymomas that adhered to the lung (requiring wedge resection) but did not invade the visceral pleura or lung on microscopic evaluation.

After this initial review, a hypothesis was formulated that at least one acute angle between lobulations on CT predicted LI (Fig. 4). A 90° angle did not fulfill the criterion of an acute angle. To test this hypothesis, two cardiothoracic radiologists

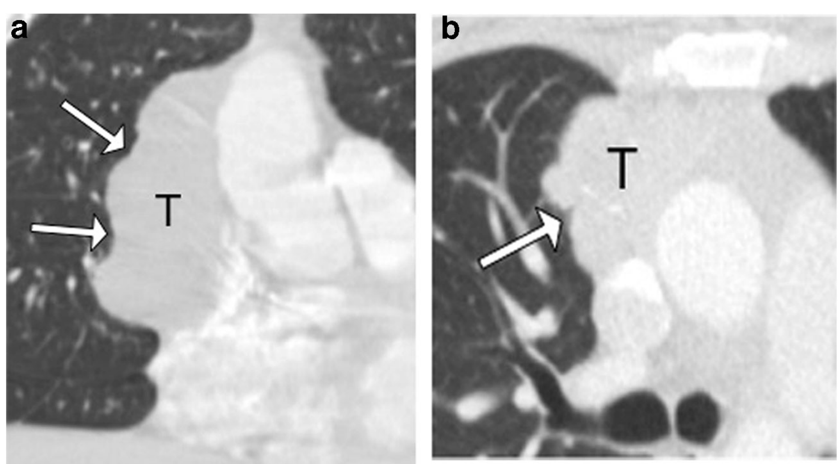

Fig. 2 Examples of multilobulated thymomas with an acute angle versus obtuse angle. **a** A multilobulated thymoma (T) with obtuse angles between lobulations along the right lung interface (arrows); **b** a multilobulated thymoma (T) with an acute angle between lobulations along the right lung interface (arrow)

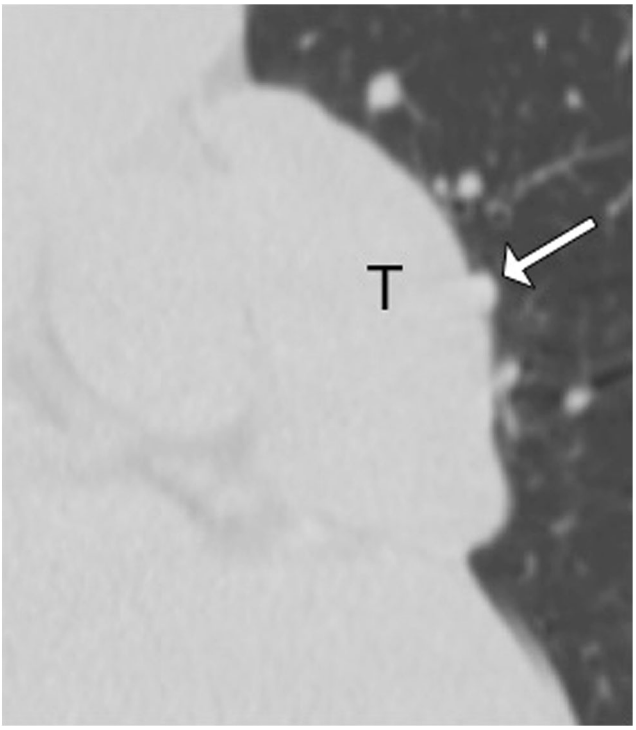

Fig. 3 Pulmonary blood vessel mimicking a lobulation. A 49-year-old female with a thymoma that did not invade the lung (T). A pulmonary blood vessel along the left lung interface mimics a focal projection (arrow). A thymoma and blood vessel may have similar attenuation, particularly on a non-contrast CT scan

(with 12 and 25 years of post-fellowship experience) reviewed all 54 pre-operative CT scans and were blinded to any information in the operative and pathology reports. They were instructed to determine if each thymoma invaded the lung based on the single criterion of its interface with the lung. The presence of at least one acute angle was sufficient for LI. They were also encouraged to review coronal and sagittal reformations in addition to the axial slices (Fig. 5).

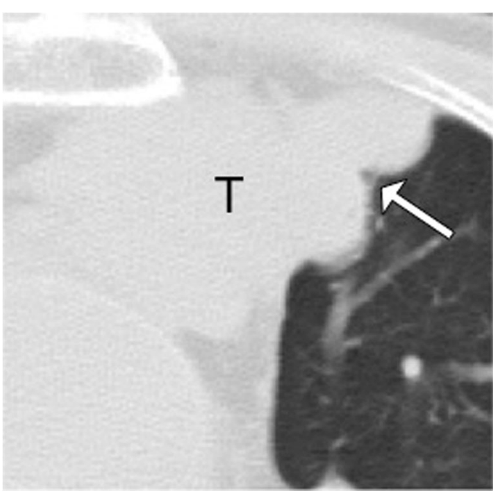

Fig. 4 Lung-invasive thymoma. An 82-year-old man with a thymoma (T) forming an acute angle between lobulations along the left lung interface (arrow). This finding is suggestive of tumor invasion into the lung

Pathologic evaluation Pathologic analysis was performed according to standard of care. If the resected specimens included the lung, they were inspected for gross pleural or lung invasion, while the lung was inked a separate color from the rest of the specimen. LI was diagnosed by microscopic evidence of tumor cells penetrating the thymic capsule into the fibroelastic pleura and/or lung parenchyma.

Statistical analysis The Wilcoxon rank sum test was used to assess the difference in median thymoma size between lung-invasive and non-lung-invasive thymomas. Fisher's exact test was used to assess the association of LI with location (midline versus off-midline) and lobulation (smooth, single lobulation, or multilobulation). Using pathologically proven LI as the gold standard, the sensitivity and specificity of multilobulation were calculated. Cohen's kappa coefficient was used to assess the level of agreement in identifying LI between the two readers. We did not correlate our study findings to recurrence rates, which would have required a larger patient pool and a longer follow-up period.

Results

Clinical information for all study subjects and characteristics of all resected thymomas ($n = 54$) are listed in Table 1. Twelve thymomas (22%) invaded the lung. Clinical information and imaging characteristics of the 12 lung-invasive thymomas are listed in Table 2. Patients with MG were less likely to have a lung-invasive thymoma than patients without MG (12.5% compared to 26.3%), though this relationship was not statistically significant ($p = 0.474$). The Wilcoxon rank sum test showed no statistically significant association between thymoma size and LI ($p = 0.303$).

All lung-invasive thymomas were multilobulated and none were associated with a pleural effusion. Three lung-invasive thymomas were midline and nine were off-midline. In total, 16.7% of patients with midline thymomas had LI compared to 25% of patients with off-midline thymomas ($p = 0.730$).

Overall, 29 thymomas had a multilobulated interface with the lung. Twelve (41%) invaded the lung, while no smooth or single-lobulated thymoma invaded the lung. Multilobulated thymomas were therefore more likely to invade the lung ($p = 0.0008$). The sensitivity and NPV of multilobulation for LI were both 100%. Specificity and PPV were 45% and 34%, respectively. These data are included in Table 3. No thymoma demonstrated overt infiltration into the lung or an associated lung abnormality.

Using multilobulation with at least one acute angle between lobulations to predict LI, reader 1 correctly identified

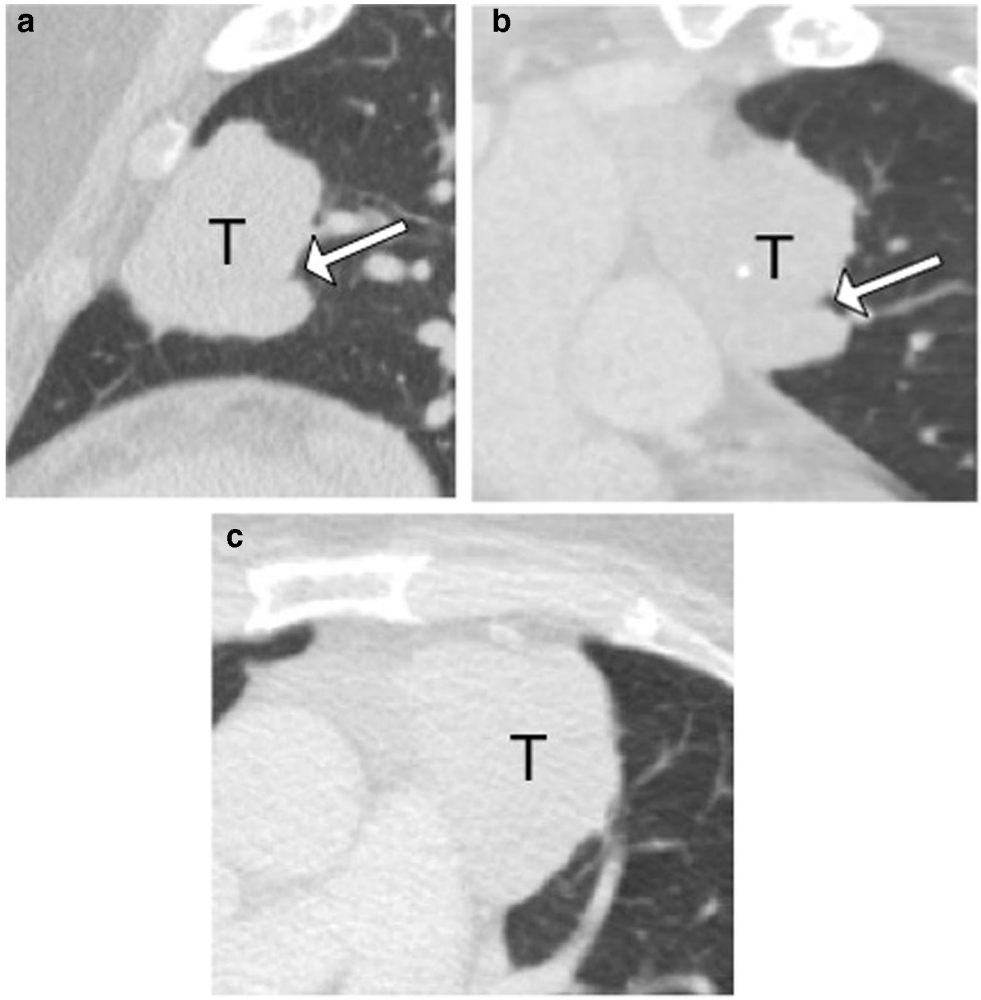

Fig. 5 Example of a lung-invasive thymoma with an acute angle not seen on axial images. A 57-year-old woman with a multilobulated thymoma (T) with an acute angle (arrows) between lobulations seen on (**a**) sagittal and (**b**) coronal images. **c** The acute angle cannot be seen on the corresponding axial image

Table 1 Summary of all patients

Clinical characteristics	
Patients	All; ($n = 54$) MG; ($n = 16$)
Age (years)	All; 28–88 (mean = 57.6) MG; 28–71 (mean = 53.5)
Gender	33 female (61.1%) 21 male (38.9%)
Thymoma characteristics	
Size (cm)	All; 1.5–12 (mean = 5.7) MG; 1.5–8 (mean = 5.0)
Calcification	32 (59.2%)
Multilobulation	29 (53.7%)
Location	18 midline (33.3%) 22 left (40.7%) 14 right (25.9%)
WHO type	5 A (0.9%) 20 AB (37%) 11 B1 (20.4%) 13 B2 (24.1%) 4 B3 (0.7%)

MG myasthenia gravis, *WHO* World Health Organization

10 of 12 lung-invasive thymomas for a total of ten true positives, three false positives, and two false negatives. Reader 2 correctly identified 8 of 12 lung-invasive thymomas for a total of eight true positives, one false positive, and four false negatives. Seven lung-invasive thymomas were correctly identified by both readers, and four were correctly identified by only one reader. One lung-invasive thymoma was not identified by either reader. One thymoma without invasion into the lung or any other structure (IASLC/ITMIG stage I) was suspected to invade the lung by both readers. Of the four lung-invasive thymomas scanned with minimum slice thickness of 5 mm, both reviewers correctly identified two, and one reviewer correctly identified two.

Reader 1 achieved overall sensitivity of 83%, specificity of 93%, PPV of 77%, and NPV of 95%. Reader 2 achieved sensitivity of 67%, specificity of 98%, PPV of 89%, and NPV of 91%. Agreement between the two readers was good (Cohen's kappa coefficient = 0.66). These data are also included in Table 3. Seven of 42 (17%) thymomas adhered to the lung during surgery without invading it. None were suspected to invade the lung by either reader.

Table 2 Summary of lung-invasive thymomas

Patient	Age	Gender	MG	Size (cm)	Calcification	Elevated diaphragm	ITMIG/IASLC stage	Other structure(s) invaded	WHO type	Interface with lung	Adjacent lung abnormality	Location	Pleural effusion	CT slice thickness (mm)
1	82	Male	–	7.2	–	–	3a	Pericardium, innominate vein	B2	Multilobulated	–	Left	–	5
2	45	Male	–	4.2	–	–	4a	Pleura, diaphragm	B2	Multilobulated	–	Midline	–	3.75
3	69	Male	–	6.7	–	+	3a	–	AB	Multilobulated	–	Right	–	3.75
4	68	Female	+	5.4	+	–	3a	Pericardium	B1	Multilobulated	–	Left	–	1.25
5	33	Male	–	7.5	–	–	4a	Pleura, diaphragm	B1	Multilobulated	–	Left	–	5
6	88	Male	–	9.2	+	+	3a	Pericardium, superior vena cava	A	Multilobulated	–	Midline	–	5
7	51	Female	–	5.4	+	–	3b	Pericardium, aorta	B3	Multilobulated	–	Left	–	5
8	57	Female	–	6.1	+	–	4a	Pleura	B1	Multilobulated	–	Left	–	2.5
9	54	Female	–	11.1	–	–	4a	Pleura	B3	Multilobulated	–	Midline	–	2.5
10	45	Female	–	3.7	+	–	3a	–	B2	Multilobulated	–	Left	–	2.5
11	86	Male	–	4.9	–	–	3a	–	A	Multilobulated	–	Left	–	2.5
12	34	Male	+	4.8	+	–	4a	Pericardium, pleura	B3	Multilobulated	–	Right	–	2.5

MG myasthenia gravis, *ITMIG/IASLC* International Thymic Malignancies Interest Group/International Association for the Study of Lung Cancer, *WHO* World Health Organization

Table 3 Accuracy of CT for lung invasion

Multilobulation				
Sensitivity	Specificity	PPV	NPV	
100%	45%	34%	100%	
Acute angle between lobulations				
Sensitivity	Specificity	PPV	NPV	
83%	93%	77%	95%	Reader 1
67%	98%	89%	91%	Reader 2
Inter-reader agreement				
Cohen's kappa coefficient = 0.66 (95% CI 0.41, 0.91)				

PPV positive predictive value, *NPV* negative predictive value, *CI* confidence interval

Discussion

These results show a high degree of accuracy for predicting LI by thymomas. Though all lung-invasive thymomas were multilobulated, multilobulation on its own was not a reliable indicator of LI (45% specific with PPV of 34%). Confident prediction of LI instead required at least one acute angle between lobulations, increasing PPV to 77–89% and NPV to 91–95% with good agreement between the two readers. This method performed well over a range of tumor stages, and we feel it is the most accurate predictor of LI by thymomas. We did not identify overt infiltration of any thymoma into the lung or any clear adjacent lung abnormality. These subjective features are difficult to assess and did not significantly impact our ability to predict LI.

Of the 12 lung-invasive thymomas, nine invaded mediastinal structures with one upgraded to ITMIG/IASLC stage IIIb due to aorta invasion and five upgraded to stage IVa due to disseminated pleural involvement [5]. This highlights the importance of evaluating for direct or distant spread to other structures when LI is suspected.

To evaluate the potential weaknesses of this method for predicting LI, the two reviewers' false positives and negatives were re-reviewed (Fig. 6). The two readers were both incorrect in two cases. The lung-invasive thymoma not identified by either reader was multilobulated and had several angles of about 90°, but no definite acute angle could be identified. The thymoma incorrectly predicted to invade the lung by both readers was multilobulated and appeared to have an acute angle between lobulations on an axial slice but only obtuse angles on coronal and sagittal reformations. The slice thickness for both of these cases was 2.5 mm and therefore not considered a contributing factor.

Seven thymomas in our study adhered to the lung without invading it. Although adherence alone does not affect staging (microscopic invasion is required) [24], advanced knowledge of adherence would potentially be helpful for surgical planning. Unfortunately, no imaging feature correlated with adherence and neither reader suspected LI in any of these cases.

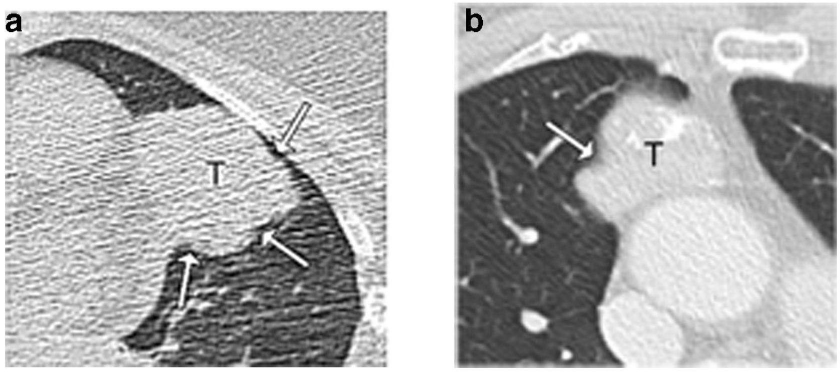

Fig. 6 Incorrectly predicted thymomas. **a** A 71-year-old woman with a lung-invasive thymoma (T) missed by both reviewers. Approximately 90° angles are identified between lobulations along the left lung interface, but no clear acute angle is seen (arrows). **b** A 65-year-old woman with a thymoma (T) thought to invade the lung by both reviewers. Although there was no histologic lung invasion, an acute angle can be seen between two lobulations along the right lung interface (arrow)

Thymomas associated with MG were less likely to invade the lung in this study, although this may reflect earlier detection by screening rather than less aggressive behavior. Some groups have found an association between thymoma calcification and higher stage [16, 19], but we did not find an association between calcification and LI. Our results are similar to Yakushiji et al who found no difference in calcification between low-risk and high-risk groups [25]. We also found no association between LI and thymoma size, which currently has no role in the T component of the ITMIG/IASLC staging system [4].

It is notable that, of the 12 lung-invasive thymomas, two were WHO type A and one was type AB. Though CT is of limited value in predicting WHO classification [26], past studies have shown a more advanced stage in B2 and B3 thymomas [8, 10, 20, 27] and an increased likelihood of regular contours in type A thymomas [28].

Finally, we evaluated whether off-midline thymomas, which grow in closer proximity to the lung than do midline thymomas, were more likely to invade the lung. Though off-midline thymomas were overall more common than midline thymomas, there was no statistically significant increase in LI.

Limitations The main limitation of this study is that we could not confirm that the lobulations forming acute angles were the actual sites of LI. A prospective study could test this hypothesis, though it still may be difficult for the surgeon and pathologist to orient the resection specimen to imaging findings. If the lobulations forming acute angles are not sites of LI, they may alternatively serve as markers for extreme lobulation and advanced stage.

Other limitations are related to the subtlety of findings in some cases. While radiologists have shown excellent agreement with one another for determining multilobulation [28], estimating the angle between small lobulations is more challenging, particularly with inadequate spatial resolution or volume averaging between the tumor and lung. For this reason, we recommend thin slices when evaluating thymomas for LI, though our two reviewers were able to predict LI on scans with minimum slice thickness of 5 mm. It is also unclear if a 90° angle should be considered a sign of LI.

Despite these limitations, our two reviewers were accurate and demonstrated good agreement with one another. We anticipate that accuracy and interobserver agreement will further improve as radiologists gain more experience with this method. Availability of thin slices for all future scans may also improve the ability to predict LI. It is unclear if this method can be applied to the evaluation of the other TETs or other mediastinal masses.

Conclusion

This study shows that a multilobulated thymoma with at least one acute angle between lobulations predicts LI with a high degree of accuracy. Because an acute angle may be subtle and may not be seen in all planes, we recommend that thymomas be carefully evaluated in axial, coronal, and sagittal planes. Thin sections may also improve diagnostic accuracy. When LI is suspected, the findings are indicative of a locally aggressive tumor, and the pleura and other mediastinal structures should also be closely inspected for invasion.

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Daniel Green, MD.

Conflict of interest The authors of this manuscript declare no relationships with any companies, whose products or services may be related to the subject matter of the article.

Statistics and biometry Gulce Askin, MPH, kindly provided statistical advice for this manuscript.

Informed consent Written informed consent was not required for this study because it was a retrospective review of medical records.

Ethical approval Institutional Review Board approval was obtained.

Methodology
• retrospective
• observational
• performed at one institution

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