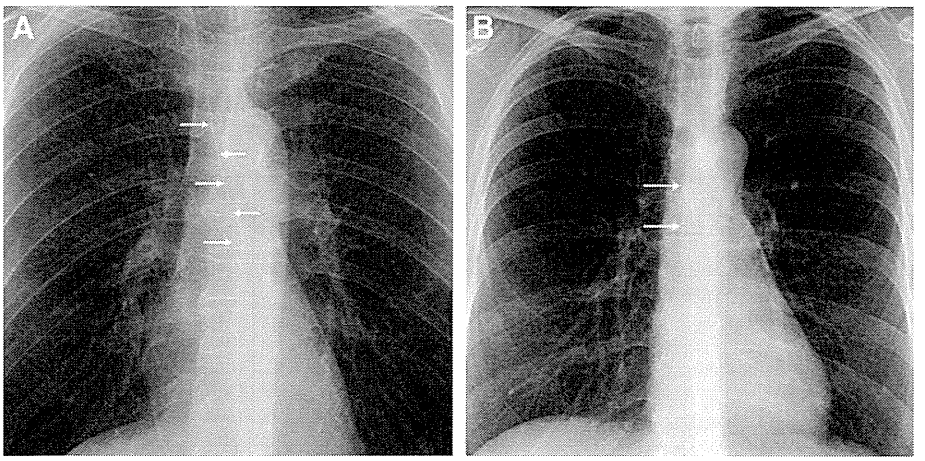

FIGURE 2. Normal and abnormal anterior junction line. *A*, Coned-down posteroanterior chest radiograph demonstrates the normal anterior junction line (arrows), representing the point of contact between the anterior lungs and their pleural surfaces anterior to the cardiovascular structures. *B*, Coned-down posteroanterior chest radiograph of a different patient demonstrates thickening of the anterior junction line (arrows) consistent with a biopsy-proven thymoma in the anterior mediastinum.

to therapy and in some cases can help distinguish between certain malignancies. However, it is important to note that imaging with FDG-PET can be misleading, given that normal and hyperplastic thymus and inflammatory lesions in the mediastinum are often FDG-avid.

IMAGING APPROACH TO AN ANTERIOR MEDIASTINAL MASS

Evaluation of an anterior mediastinal mass may seem difficult because of the number of different entities and the rarity with which most of them are encountered by the average radiologist. A discussion between the clinician and the radiologist is exceedingly important, and it is best if this happens at the time the images are interpreted. The degree of confidence in the presumptive diagnosis depends on how well it fits from a variety of viewpoints (imaging, demographics, and clinical presentation) and has significant bearing on the need for biopsy and if so, which type of biopsy approach is best.

To structure the approach to patients with an anterior mediastinal mass, we begin with identification of certain imaging characteristics that allow a fairly certain diagnosis to be made on imaging alone. Then we discuss imaging features that are fairly common, and, while not definite by imaging appearance alone, can nevertheless lead to a fairly reliable presumptive diagnosis in the appropriate clinical setting. We focus initially on the more commonly seen features and tumors, in order to present a practical way of structuring an approach to patients. Unusual tumors and features are discussed last; because of the rarity of such tumors the degree of certainly of the presumed diagnosis will always be somewhat limited.

A highly reliable clinical diagnosis of an anterior mediastinal lesion can be made when certain characteristic features are found on cross-sectional imaging and/or are noted in the clinical presentation (Table 1). Specific findings such as hyperdense and enhancing lesions that communicate with the thyroid gland, intralesional fat, cystic components, and soft tissue attenuation may be used to narrow the differential diagnosis. The presence of calcifications, whether punctate, coarse, or curvilinear, cannot discriminate benign from malignant anterior mediastinal masses and may be seen in a benign lesion (such as a benign teratoma) as well as in a malignant lesion (such as a thymoma or treated lymphoma).[18]

Lesions Identifiable on Imaging

A heterogeneous anterior mediastinal mass that is intrinsically hyperdense, enhances following the administration of IV contrast, and demonstrates continuity with the cervical thyroid gland can reliably be diagnosed as a mediastinal goiter. Most mediastinal goiters demonstrate high attenuation on non-contrast CT, with Hounsfield Units measuring 70–85, due to the presence of iodine (Figure 3*A*). Following the administration of IV contrast, prolonged and sustained enhancement is typically seen. Regions of low attenuation within goiters are commonly seen and represent cystic changes. Calcifications may also be present. The majority of substernal goiters can be reliably diagnosed by CT imaging alone. However, it is important to note that mediastinal goiters are not always connected to the thyroid gland; nevertheless, when they are separate, they often demonstrate similar imaging features. As thyroid goiters may result in compression and deviation of the trachea, evaluation of the airways should be performed. When a goiter exhibits loss of distinct mediastinal fascial planes or is associated with cervical or mediastinal lymphadenopathy, the possibility of thyroid malignancy should be investigated.[19] Although patients may be asymptomatic, symptoms related to compression of mediastinal structures (particularly the airways) should be reported.

The presence of visible areas of intralesional fat (which typically measures between −40 and −120 Hounsfield Units on CT) within a heterogeneous anterior mediastinal mass is highly suggestive of a benign teratoma, as these lesions characteristically demonstrate varying amounts of fat, fluid, calcification (including bone and tooth-like elements), and soft tissue.[20,21] Fat is identified in approximately 50% of cases[21] (Figure 3*B*). Although a fat–fluid level is highly specific for teratoma, this finding is much less common, and formation of bone or a tooth is rare.[22] Benign teratomas can sometimes be mostly cystic. Most benign teratomas are sufficiently characteristic to be diagnosed reliably based on imaging characteristics alone by an experienced thoracic radiologist. Benign teratomas are typically seen in younger patients and account for approximately 25% of anterior mediastinal masses in ages 10–19, 10–15% in ages 20–49, and less than 5% over age 50 in both men and women. Patients are typically asymptomatic, but may report symptoms due to compression of mediastinal structures.

TABLE 1. Imaging Algorithm for Anterior Mediastinal Masses

	% of Anterior Mediastinal Masses	Level of Confidence	Diagnosed With[a]	Confirm With/Next Steps
Highly Characteristic Lesions				
Hyperdense and enhancing lesion with connection to thyroid → Goiter	20-40% age >40	Certain	Imaging	-
Heterogeneous with fat, fluid, soft tissue, & calcification → Benign teratoma	25% age 10-19 10-15% age 20-49	Very high	Imaging	-
Well-circumscribed, round/oval/saccular, and homogeneous mass located near thymic bed on CT → Consider thymic cyst and evaluate with MRI				
If purely cystic → Thymic cyst and follow-up with MRI	<5%	Very high	Imaging	MRI
If cystic but with soft tissue components → Multilocular cyst or cystic thymoma	<5%	Uncertain	Imaging, Clinical	Resection
If purely cystic and located in cardiophrenic angle → Pericardial cyst	Low	Very high	Imaging	-
Suggestive on Imaging; Requires Clinical Context				
Lobular, homogeneous or slightly heterogeneous mass→ Thymoma	15-25% age 20-39 ~50% age >40	Moderate	Imaging	± Biopsy
Context: Pt with Myasthenia gravis or other paraneoplastic syndrome	5-10% age 20-39 ~20% age >40	Certain	+Clinical	± Biopsy
Multiple markedly enlarged or matted lymph nodes / masses in anterior mediastinum ± neck, ± encasing but respecting vessels → HD, MLC-NHL	20-50% ♀ age <40 20-25% ♂ age <40 <10% ♂♀ age >40	High	Imaging	Core biopsy
Context: "B" symptoms and ↑ LDH	Same	Very high	+ Clinical	Core biopsy
Large mass with pleural effusion, rapid onset, "B" symptoms → LB-NHL	15% age 10-19 5-10% age 20-39	High	Imaging, Clinical	Cytology
Large heterogeneous mass, especially with lung metastases → NSGCT *Context: Young ♂ with rapid onset of symptoms*	10-25% ♂ age <40 < 5% ♂ age >40 2-5% ♀ age <40	Moderate	Imaging, Clinical	Labs, ± biopsy
Homogeneous or slightly hetrogeneous mass ± lung metastases → Seminoma *Context:: young ♂, intermediate onset*	5-10% ♂ age <40 0-2% ♀ age <40	Moderate	Imaging, Clinical	Biopsy
Large heterogeneous mass, local invasion, lymphadenopathy, ± distant metastases → Thymic carcinoma or carcinoid	<2% age 20-39 ~5% age >40	Uncertain	Imaging	Biopsy
Low attenuation, symmetric enlargement of thymus *Context:: Pt treated with chemo, RT, or steroids → Thymic hyperplasia*	Uncommon	Very high	Clinical, Imaging	± MRI
Rare Characteristic Features				
Lobular, homogeneous or slightly heterogeneous mass and with subpleural implants → Thymoma (invasive)	<5%	Very high	Imaging	Biopsy
Large fatty mass with small amount of soft tissue & vessels, connection with thymus → Thymolipoma	<5%	Very high	Imaging	-
Lobulated, encapsulated lesion consisting almost entirely of fat → Lipoma	2%	Very high	Imaging	-
Fatty lesion with aggressive features such as soft tissue components, invasion, lymphadenopathy, or metastatic disease → Liposarcoma	Very rare	Moderate	Imaging	Biopsy

A proposed structured approach for radiologists in evaluating patients with an anterior mediastinal mass. This table focuses on the most common entities first and on entities in which imaging is often particularly helpful. However, the incidence varies according to age and gender, and the level of confidence in a presumptive clinical diagnosis varies according to whether the radiographic features are seen with a congruent clinical setting.

[a]This refers to which factors play a prominent role in establishing the presumptive clinical diagnosis.

"B" symptoms, fever, sweats, and weight loss; HD, Hodgkin disease; LB-NHL, lymphoblastic non-Hodgkin lymphoma; LDH, lactose dehydrogenase; MLC-NHL, mediastinal large cell non-Hodgkin lymphoma; MRI, magnetic resonance imaging; NSGCT, nonseminomatous germ cell tumor.

When well-circumscribed, round/oval/saccular, and homogeneous lesions are present in the anterior mediastinum near the thymic bed, the possibility of thymic cyst should be considered. Although thymic cysts may measure water or fluid attenuation (between 0 and 20 Hounsfield Units) on CT (Figure 3*C*), they can manifest as higher density lesions. This feature is responsible for CT's inability to reliably distinguish cystic lesions from solid masses. In the case of suspected thymic cyst, MRI should be performed. Purely cystic lesions in the anterior mediastinum with no soft tissue nodules and

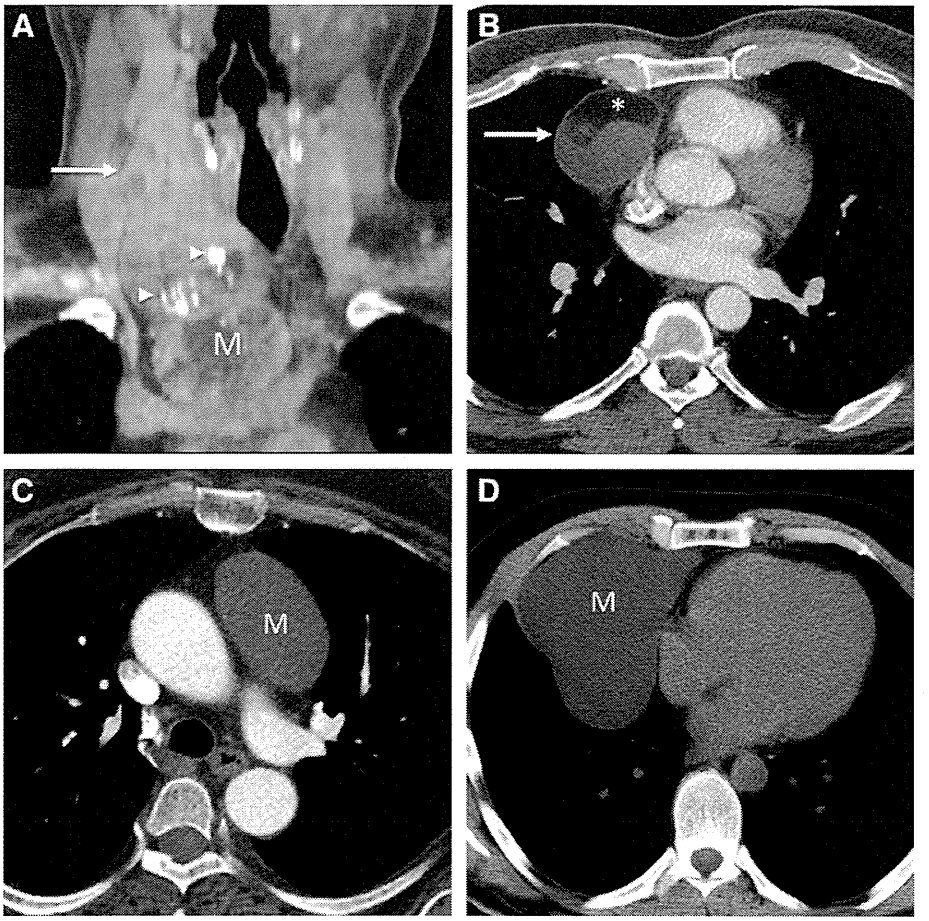

FIGURE 3. Lesions identifiable on imaging. *A*, Coronal reformatted contrast-enhanced coned-down CT of an asymptomatic 54-year-old man demonstrates a high attenuation and enhancing mass (M) in the anterior mediastinum that is contiguous with the right lobe of the thyroid gland (arrow) and extends substernally, consistent with a goiter. Note the presence of coarse calcifications (arrowheads). *B*, Coned-down contrast-enhanced axial CT of an asymptomatic 34-year-old man demonstrates a well-circumscribed mass (arrow) in the right anterior mediastinum that contains both fat (asterisk) and fluid. This appearance is highly suggestive of a benign teratoma. *C*, Coned-down contrast-enhanced axial CT of an asymptomatic 49-year-old woman demonstrates a well-defined mass (M) in the anterior mediastinum that is fluid attenuation. No soft tissue components or internal septations are present in this lesion, which represents a thymic cyst. *D*, Coned-down noncontrast axial CT of an asymptomatic 51-year-old man shows a lobular fluid attenuation mass (M) in the right cardiophrenic angle, consistent with a pericardial cyst.

no internal septations on MRI can reliably be diagnosed as unilocular thymic cysts.[23] Cystic lesions that contain soft tissue components may represent mulitlocular thymic cysts or cystic thymoma. The diagnosis of cystic thymoma should be strongly considered in patients with a cystic anterior mediastinal lesion and symptoms related to myasthenia gravis or other paraneoplastic syndromes, especially men and women older than 40 years of age. A well-circumscribed lesion measuring water or fluid density with thin or imperceptible walls in one of the cardiophrenic angles can be confidently diagnosed as a pericardial cyst[24,25] (Figure 3*D*).

Lesions Identifiable by a Combination of Imaging and Clinical Context

Normal thymic tissue is usually seen in young patients and should decrease in prominence with age. By age 40, the thymus should be replaced by fat. Thymic hyperplasia should be considered in young patients with uniform enlargement of the thymus compared with prior imaging, or in patients over the age of 40 with soft tissue in the thymic bed without focal mass or contour abnormality similar to normal thymus. In patients who have been treated with chemotherapy, radiation therapy, or corticosteroids, have been exposed to stresses such as burns or injuries, or who have known disorders such as myasthenia gravis, hyperthyroidism, collagen vascular diseases, or HIV, thymic hyperplasia should be considered when a low attenuation anterior mediastinal mass is identified. Although the most common manifestation of thymic hyperplasia is diffuse, symmetric enlargement of the thymus on CT, intralesional fat may be present and result in ill-defined regions of low attenuation (Figure 4*A*). In most patients, thymic hyperplasia can be diagnosed reliably when there is a typical CT appearance (e.g., enlarged but maintaining the shape of the thymus) in a patient following stress. However, sometimes the CT appearance is not straightforward and it may appear more nodular or bulky in configuration, resembling a thymoma or lymphoma. When the findings are not classic for thymic hyperplasia, one can either re-image after a sufficiently long period (~3 months) to let the thymus decrease in size on its own or perform chemical shift MRI with in- and out-of-phase gradient echo sequences. Thymic hyperplasia and the normal thymus demonstrate loss of signal on out-of-phase images due to the suppression of microscopic fat interspersed between nonneoplastic thymic tissue, whereas thymic malignancies and lymphoma do not suppress on out-of-phase imaging[26,27] (Figure 4*B–D*). With either confirmatory approach an unnecessary biopsy or surgery can be avoided.

A homogeneous or slightly heterogeneous anterior mediastinal mass in men and women older than 40 years of age likely represents a thymoma[28] (Figure 5*A*). When this appearance is combined with symptoms of myasthenia gravis or other paraneoplastic syndrome (such as pure red cell

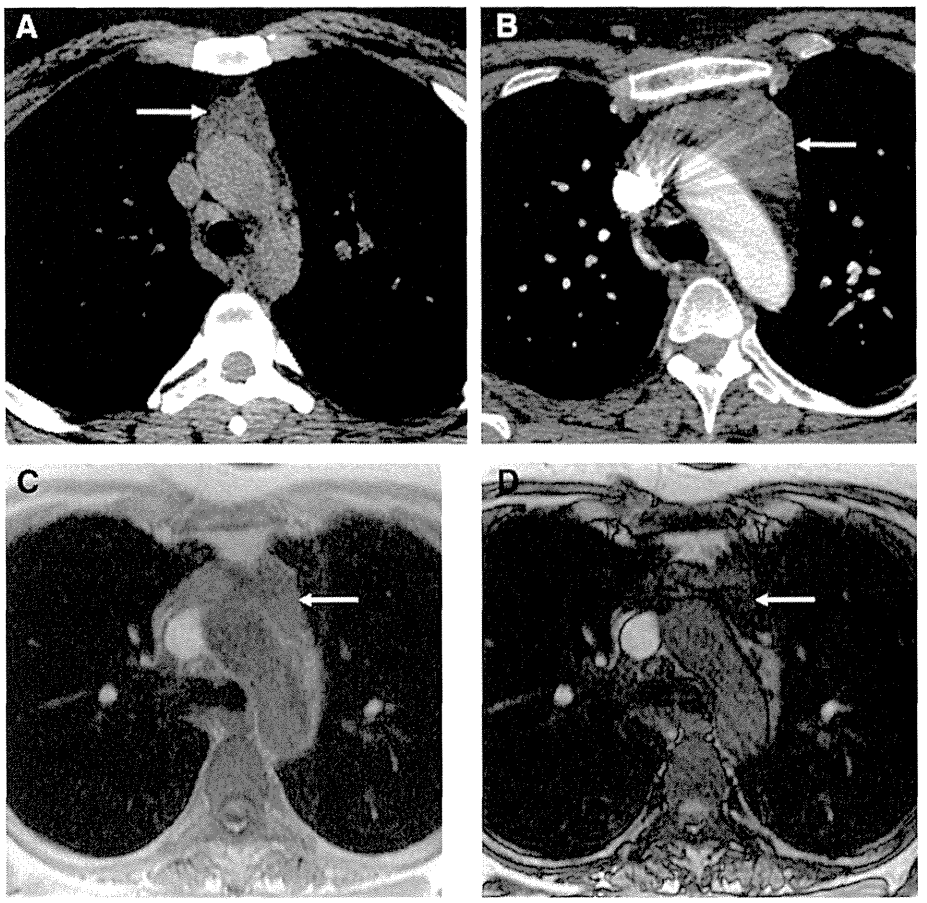

FIGURE 4. Thymic hyperplasia. *A*, Coned-down contrast-enhanced axial CT of a 23-year-old woman treated with chemotherapy for lymphoma demonstrates foci of low attenuation within hyperplastic thymic tissue (arrow), consistent with thymic hyperplasia. *B–D*, Coned-down contrast-enhanced axial CT (*B*) of a 38-year-old woman with chest pain and shortness of breath shows a soft tissue mass (arrow) in the anterior mediastinum. Because fat was difficult to detect by the CT alone to confirm the diagnosis of thymic hyperplasia, an MRI with chemical shift sequences was ordered. Axial in-phase (*C*) and out-of-phase (*D*) T1-weighted MRI of the same patient demonstrate soft tissue (arrow) in the anterior mediastinum that is similar in signal intensity to muscle on the in-phase image but shows complete loss of signal intensity on the out-of-phase image, compatible with thymic hyperplasia. Thymic hyperplasia and normal thymus (as opposed to thymoma or other soft tissue masses in this region) demonstrate loss of signal on out-of-phase imaging secondary to the suppression of microscopic fat interspersed between normal thymic tissue.

aplasia/Diamond-Blackfan syndrome or hypogammaglobulinemia), there is little doubt about the diagnosis. As more than 80% of thymomas are accurately diagnosed on CT or MRI due to their typical cross-sectional appearance, tissue diagnosis is typically unnecessary.[14] Lymphadenopathy is typically absent, but pleural and/or pericardial spread may be identified in advanced (stage IV) disease and is often quite pathognomonic for thymic malignancy. In the setting of a large anterior mediastinal mass with features such as heterogeneity, local invasion, lymphadenopathy, and pleural effusion, thymic epithelial neoplasms other than thymoma such as thymic carcinoma (Figure 5*B*) and carcinoid should be considered.[29] On ^{18}F-FDG PET/CT, thymic carcinomas and carcinoids typically demonstrate greater FDG uptake than thymomas.[30,31]

In patients with enlarged lymph nodes or lobulated soft tissue masses in the mediastinum on cross-sectional imaging, which may or may not be seen in association with lymphadenopathy in the lower neck or axilla, a lymphoma such as Hodgkin disease and mediastinal large cell non-Hodgkin lymphoma should be considered. Although it may be difficult to distinguish lymphoma from other soft tissue lesions in the mediastinum, the infiltrative nature of some lymphomas helps distinguish it from thymic epithelial neoplasms. Mediastinal lymphomas often encircle but "respect" the great vessels. When this is seen in the right age cohort, lymphoma being the most common anterior mediastinal mass in young patients, and especially when combined with "B" symptoms such as fever, weight loss, and night sweats (present in ~50% of mediastinal lymphomas), one can be quite confident of the clinical diagnosis. Further evaluation is typically performed with core needle biopsy combined with aspiration for flow cytometry or surgical biopsy.

For patients diagnosed with lymphoma, FDG-PET/CT has become the modality of choice for staging. FDG-PET/CT is more accurate than CT at detecting lymphomatous involvement of lymph nodes, with a sensitivity of 94% and a specificity of 100%, respectively, compared with 88% and 86% for CT.[32] FDG-PET/CT is also effective at identifying intranodal and extranodal disease within the remainder of the body. The sensitivity and specificity of FDG-PET/CT in detecting organ involvement are 88% and 100%, respectively, compared with 50% and 90% for CT.[32]

When patients present with a large anterior mediastinal mass, pleural effusion, "B" symptoms, and elevated serum levels of lactate dehydrogenase, then lymphoblastic non-Hodgkin lymphoma should be considered (Figure 5*C*). A rapid onset of symptoms is characteristically seen. Cytology of the pleural effusion (when present) or bone marrow biopsy is almost always sufficient to confirm the presumptive diagnosis.

When a large, lobular homogeneous anterior mediastinal mass is identified on cross-sectional imaging in a young man 10–39 years of age, seminoma should be considered[33] (Figure 5*D*). These lesions may be indistinguishable from

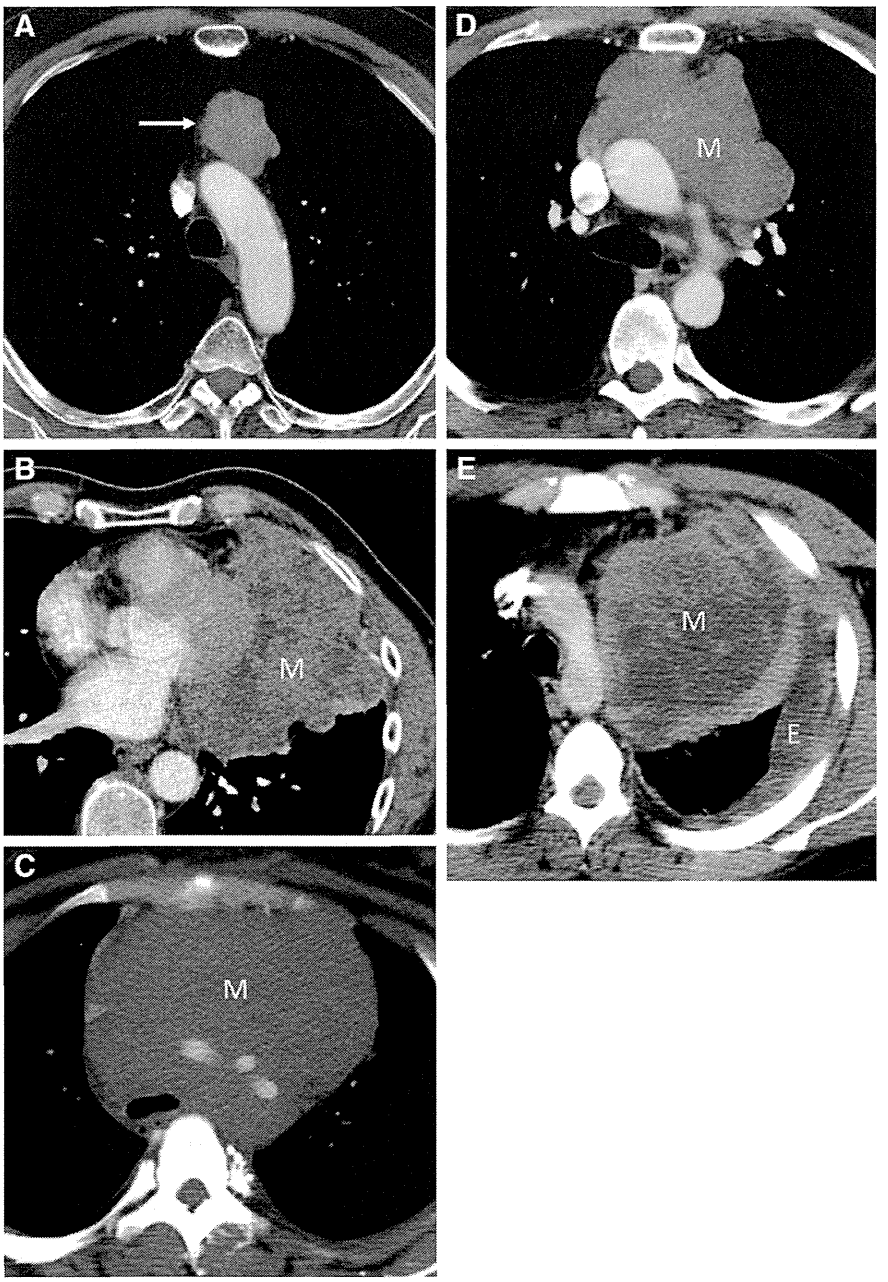

FIGURE 5. Lesions identifiable on imaging with clinical context. *A*, Coned-down contrast-enhanced axial CT of a 43-year-old man with myasthenia gravis demonstrates a well-defined, lobular soft tissue mass (arrow) in the anterior mediastinum. In a patient older than 40 years of age, the imaging appearance and clinical history are typical of a thymoma, which was confirmed at the time of surgery. *B*, Coned-down contrast-enhanced axial CT of a 38-year-old with chest pain demonstrates a large, lobular mass (M) originating in the left anterior mediastinum. The central regions of low attenuation represent necrosis. Note the extension of tumor around the left heart with obliteration of the adjacent fat plane. CT-guided biopsy revealed thymic carcinoma and cardiac invasion was confirmed at the time of surgery. *C*, Coned-down contrast-enhanced axial CT of a 33-year-old woman presenting with fever and weight loss demonstrates a large soft tissue mass (M) in the anterior mediastinum that extends into the middle mediastinum and insinuates itself around the great vessels. The infiltrative nature of this mass is characteristic of lymphoma and enables differentiation from other anterior mediastinal masses, such as thymoma. *D*, Coned-down contrast-enhanced axial CT of a 37-year-old man presenting with chest pain demonstrates a large, homogeneous, lobular mass (M) in the anterior mediastinum. Elevated serum lactate dehydrogenase and slightly elevated serum β-HCG levels were present and seminoma was confirmed at biopsy. *E*, Coned-down contrast-enhanced axial CT of a 28-year-old man presenting with chest pain, weight loss, and elevated serum α-FP demonstrates a large heterogeneous mass (M) originating in the left anterior mediastinum and extending into the left hemithorax. Regions of low density represent tumor necrosis. Biopsy revealed NSGCT. Note the loculated left pleural effusion (E), which was found to represent metastatic disease to the left pleura at the time of surgery.

lymphoma.[33] Although pleural effusions are rare, pulmonary metastases are relatively common (this is distinctly unusual for Hodgkin disease or mediastinal large cell non-Hodgkin lymphoma). Approximately 10% of patients with seminoma demonstrate slightly elevated serum β-HCG but α-FP is typically normal.[34,35] Serum lactate dehydrogenase levels are usually elevated, but this is true for many lymphomas as well.[36,37] Further evaluation with core needle or surgical biopsy is usually performed. When a heterogeneous anterior mediastinal mass is present with lung metastases in women and men below the age of 40, NSGCTs should be included in the differentiation diagnosis[38,39] (Figure 5*E*). Markedly elevated serum α-FP or β-HCG levels are present in 90% of patients and are pathognomonic for this diagnosis.[35,36,40,41] Primary mediastinal seminoma or NSGCTs are well-recognized entities; there is no documented reason to search for an occult testicular primary lesion via testicular ultrasound.

Evaluation of Rare Tumors

When an anterior mediastinal mass contains intralesional fat, several rare tumors can be clinically diagnosed with a high degree of confidence. In the setting of a large fat-containing mass in the anterior mediastinum or at one of the cardiophrenic angles, thymolipoma should be considered. These benign encapsulated lesions usually contain 50–85% fat (although up to 95% has been reported) and a small amount of solid tissue and fibrous septa, and are typically very large with an average size of 20 cm.[42,43] Direct connection with the thymus may be visualized and confirms the diagnosis.[44] Patients may have symptoms related to mass effect such as dyspnea or be asymptomatic, and anecdotal cases of associations between thymolipomas and myasthenia gravis, Grave's disease, and hematological disorders have been reported.[44] Thymolipomas are relatively uncommon (<5% of anterior mediastinal masses in all age groups); but when they consist almost entirely of fat the diagnosis can be made quite reliably by imaging alone.

Additional rare tumors with intralesional fat include lipomas and liposarcomas. Lipomas account for approximately 2% of all primary mediastinal neoplasms and appear as encapsulated lesions primarily composed of fat with a small amount of soft tissue and vessels in the anterior mediastinum.[45] Liposarcomas may be distinguished from lipomas by aggressive features such as increased soft tissue components, local invasion, lymphadenopathy, and metastatic disease.[45,46] Ectopic parathyroid adenomas may rarely occur in the mediastinum, typically in the anterior compartment. In one study, 81% of these tumors were identified in the anterior mediastinum.[47] Parathyroid adenomas manifest as small soft tissue lesions with or without calcification[48]; while this appearance is relatively nonspecific, these tumors should be suspected in the setting of hyperparathyroidism. Technetium-99 sestamibi single-photon emission computed tomography scans are typically more effective for making the diagnosis of ectopic parathyroid adenoma.[48]

Many anterior mediastinal masses may be reliably diagnosed by a combination of clinical and imaging features. However, when characteristic radiographic features are absent or seen in an atypical clinical setting, a presumptive diagnosis with reasonable confidence is not possible. In such scenarios, extensive speculation is usually not helpful; acquisition of tissue through core needle, surgical biopsy, or resection is generally of greater benefit to guide subsequent management than additional imaging studies.

CONCLUSION

Certain anterior mediastinal tumors can be reliably identified by imaging alone, including substernal goiters, benign teratoma, and benign cysts. However, many anterior mediastinal tumors exhibit suggestive but inconclusive imaging features; when the imaging correlates with the typical clinical features a presumptive diagnosis can be quite reliable. This underscores the need for a discussion between the clinician and the radiologist when evaluating most anterior mediastinal tumors. The suggested approach, therefore, is to initially rule in or out those lesions that can be reliably identified purely on the basis of characteristic imaging features. Less conclusive imaging features should be correlated with specific clinical features; in many cases this will strongly suggest a particular diagnosis and a further evaluative or treatment strategy. Additional detail regarding clinical features, evaluation and treatment is provided in the companion paper *Approaching the Patient with an Anterior Mediastinal Mass: A Guide for Clinicians*.[2] This approach provides structure to the radiologic evaluation of anterior mediastinal masses, and facilitates a more streamlined and efficient discussion and further workup of these patients.

REFERENCES

1. Henschke CI, Lee IJ, Wu N et al. CT screening for lung cancer: prevalence and incidence of mediastinal masses. *Radiology* 2006;239:586–590.
2. Carter BW, Marom EM, Detterbeck FC. Approaching the patient with an anterior mediastinal mass: a guide for clinicians. *J Thorac Oncol* 2014.
3. Davis RD Jr, Oldham HN Jr, Sabiston DC Jr. Primary cysts and neoplasms of the mediastinum: recent changes in clinical presentation, methods of diagnosis, management, and results. *Ann Thorac Surg* 1987;44:229–237.
4. Levasseur P, Kaswin R, Rojas-Miranda A, et al. Apropos of a series of 742 operated patients. *Nouv Presse Med* 1976; 5:2857–2859.
5. Cohen AJ, Thompson L, Edwards FH, Bellamy RF. Primary cysts and tumors of the mediastinum. *Ann Thorac Surg* 1991;51:378–384; discussion 385.
6. Rubush JL, Gardner IR, Boyd WC, Ehrenhaft JL. Mediastinal tumors. Review of 186 cases. *J Thorac Cardiovasc Surg* 1973;65:216–222.
7. Wychulis AR, Payne WS, Clagett OT, Woolner LB. Surgical treatment of mediastinal tumors: a 40 year experience. *J Thorac Cardiovasc Surg* 1971;62:379–392.
8. Mullen B, Richardson JD. Primary anterior mediastinal tumors in children and adults. *Ann Thorac Surg* 1986;42:338–345.
9. Takeda S, Miyoshi S, Minami M et al. Clinical spectrum of primary mediastinal tumors: a comparison of adult and pediatric populations (Abstract). *Chest* 2000;118:206S.
10. Whooley BP, Urschel JD, Antkowiak JG, Takita H. Primary tumors of the mediastinum. *J Surg Oncol* 1999;70:95–99.
11. Azarow KS, Pearl RH, Zurcher R, Edwards FH, Cohen AJ. Primary mediastinal masses. A comparison of adult and pediatric populations. *J Thorac Cardiovasc Surg* 1993;106:67–72.
12. Carter BW, Tomiyama N, Bhora FY, et al. A modern definition of mediastinal compartments. *J Thorac Oncol* 2014;9:S99–S103.
13. Fujimoto K, Hara M, Tomiyama N, Kusumoto M, Sakai F, Fujii Y. Proposal for a new mediastinal compartment classification of transverse plane images according to the Japanese Association for Research on the

Thymus (JART) General Rules for the Study of Mediastinal Tumors. *Oncol Rep* 2014;31:565–572.
14. Tomiyama N, Honda O, Tsubamoto M, et al. Anterior mediastinal tumors: diagnostic accuracy of CT and MRI. *Eur J Radiol* 2009;69:280–288.
15. Ackman JB, Wu CC. MRI of the thymus. *AJR Am J Roentgenol* 2011;197:W15–W20.
16. Inaoka T, Takahashi K, Mineta M, et al. Thymic hyperplasia and thymus gland tumors: differentiation with chemical shift MR imaging. *Radiology* 2007;243:869–876.
17. Takahashi K, Al-Janabi NJ. Computed tomography and magnetic resonance imaging of mediastinal tumors. *J Magn Reson Imaging* 2010;32:1325–1339.
18. Rosado-de-Christenson ML, Templeton PA, Moran CA. From the archives of the AFIP. Mediastinal germ cell tumors: radiologic and pathologic correlation. *Radiographics* 1992;12:1013–1030.
19. Naidich DP, Webb WR, Muller NL, Krinsky GA, Zerhouni EA, Siegelman SS (Eds). Mediastinum. In Computed Tomography and Magnetic Resonance of the Thorax, 3rd Ed. Philadelphia, PA: Lippincott Williams and Wilkins, 1999. Pp. 82–83.
20. Molinari F, Bankier AA, Eisenberg RL. Fat-containing lesions in adult thoracic imaging. *AJR Am J Roentgenol* 2011;197:W795–W813.
21. Rosado-de-Christenson ML, Templeton PA, Moran CA. From the archives of the AFIP. Mediastinal germ cell tumors: radiologic and pathologic correlation. *Radiographics* 1992;12:1013–1030.
22. Wright C. Germ cell tumors of the mediastinum. In Pearson F, Cooper J, Deslauriers J, Ginsberg RJ, Hiebert C, Patterson G, Urschel H (Eds.), Thoracic Surgery. New York: Churchill Livingstone, 2002. Pp. 1711–1719.
23. Choi YW, McAdams HP, Jeon SC, et al. Idiopathic multilocular thymic cyst: CT features with clinical and histopathologic correlation. *AJR Am J Roentgenol* 2001;177:881–885.
24. Feigin DS, Fenoglio JJ, McAllister HA, Madewell JE. Pericardial cysts. A radiologic-pathologic correlation and review. *Radiology* 1977;125:15–20.
25. Jeung MY, Gasser B, Gangi A, et al. Imaging of cystic masses of the mediastinum. *Radiographics* 2002;22 Spec No:S79–S93.
26. Inaoka T, Takahashi K, Mineta M, et al. Thymic hyperplasia and thymus gland tumors: differentiation with chemical shift MR imaging. *Radiology* 2007;243:869–876.
27. Takahashi K, Inaoka T, Murakami N, et al. Characterization of the normal and hyperplastic thymus on chemical-shift MR imaging. *AJR Am J Roentgenol* 2003;180:1265–1269.
28. Benveniste MF, Rosado-de-Christenson ML, Sabloff BS, Moran CA, Swisher SG, Marom EM. Role of imaging in the diagnosis, staging, and treatment of thymoma. *Radiographics* 2011;31:1847–1861; discussion 1861.
29. Rosado-de-Christenson ML, Strollo DC, Marom EM. Imaging of thymic epithelial neoplasms. *Hematol Oncol Clin North Am* 2008;22(3):409–431.
30. Endo M, Nakagawa K, Ohde Y, et al. Utility of 18FDG-PET for differentiating the grade of malignancy in thymic epithelial tumors. *Lung Cancer* 2008;61:350–355.
31. Inoue A, Tomiyama N, Tatsumi M, et al. (18)F-FDG PET for the evaluation of thymic epithelial tumors: Correlation with the World Health Organization classification in addition to dual-time-point imaging. *Eur J Nucl Med Mol Imaging* 2009;36:1219–1225.
32. Schaefer NG, Hany TF, Taverna C, et al. Non-Hodgkin lymphoma and Hodgkin disease: coregistered FDG PET and CT at staging and restaging–do we need contrast-enhanced CT? *Radiology* 2004;232:823–829.
33. Strollo DC, Rosado-de-Christenson ML. Primary mediastinal malignant germ cell neoplasms: imaging features. *Chest Surg Clin N Am* 2002;12:645–658.
34. Lemarié E, Assouline PS, Diot P, et al. Primary mediastinal germ cell tumors. Results of a French retrospective study. *Chest* 1992;102:1477–1483.
35. Economou JS, Trump DL, Holmes EC, Eggleston JE. Management of primary germ cell tumors of the mediastinum. *J Thorac Cardiovasc Surg* 1982;83:643–649.
36. Bokemeyer C, Nichols CR, Droz JP, et al. Extragonadal germ cell tumors of the mediastinum and retroperitoneum: results from an international analysis. *J Clin Oncol* 2002;20:1864–1873.
37. Bukowski RM, Wolf M, Kulander BG, Montie J, Crawford ED, Blumenstein B. Alternating combination chemotherapy in patients with extragonadal germ cell tumors. A Southwest Oncology Group study. *Cancer* 1993;71:2631–2638.
38. Rosado-de-Christenson ML, Templeton PA, Moran CA. From the archives of the AFIP. Mediastinal germ cell tumors: radiologic and pathologic correlation. *Radiographics* 1992;12(5):1013–1030.
39. Lee KS, lm J-G, Han CH, Han MC, Kim C-W, Kim WS. Malignant primary germ cell tumors of the mediastinum: CT features. *AJR* 1989;153:947–951.
40. Wright CD, Kesler KA, Nichols CR, et al. Primary mediastinal nonseminomatous germ cell tumors. Results of a multimodality approach. *J Thorac Cardiovasc Surg* 1990;99:210–217.
41. Kesler KA, Rieger KM, Ganjoo KN, et al. Primary mediastinal nonseminomatous germ cell tumors: the influence of postchemotherapy pathology on long-term survival after surgery. *J Thorac Cardiovasc Surg* 1999;118:692–700.
42. Gaerte SC, Meyer CA, Winer-Muram HT, Tarver RD, Conces DJ Jr. Fat-containing lesions of the chest. *Radiographics* 2002;22 Spec No S61–S78.
43. Molinari F, Bankier AA, Eisenberg RL. Fat-containing lesions in adult thoracic imaging. *AJR Am J Roentgenol* 2011;197:W795–W813.
44. Nishino M, Ashiku SK, Kocher ON, et al. The thymus: a comprehensive review. *Radiographics* 2006;26:335–348.
45. Munden RF, Nesbitt JC, Kemp BL, Chasen MH, Whitman GJ. Primary liposarcoma of the mediastinum. *AJR Am J Roentgenol* 2000;175:1340.
46. Hahn HP, Fletcher CD. Primary mediastinal liposarcoma: clinicopathologic analysis of 24 cases. *Am J Surg Pathol* 2007;31:1868–1874.
47. Clark OH. Mediastinal parathyroid tumors. *Arch Surg* 1988;123:1096–1100.
48. Juanpere S, Cañete N, Ortuño P, Martínez S, Sanchez G, Bernado L. A diagnostic approach to the mediastinal masses. *Insights Imaging* 2013;4:29–52.

Thymoma Patients With Pleural Dissemination: Nationwide Retrospective Study of 136 Cases in Japan

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Background. Thymoma is a rare mediastinal tumor with relatively slow growth. However, advanced-stage cases with pleural dissemination are occasionally encountered. The outcome of surgical resection for thymomas with pleural dissemination has not been clearly determined.

Methods. We retrospectively investigated the clinical records of 2,835 patients with thymic epithelial tumors that were treated from 1991 to 2010 in 32 institutions that participated in the Japanese Association for Research on the Thymus. In this study, we analyzed the clinicopathologic factors and prognosis of thymoma patients with pleural dissemination who underwent surgical resection.

Results. The thymomas with pleural disseminations numbered 148 cases (5.2% in the 2,835 thymic epithelial tumors). Surgical resection was performed in 136 cases. Pathologic Masaoka stages were classified as IVA (n = 118) and IVB (n = 18). In Masaoka stage IVA disease, the small number of disseminated pleural nodules (10 or fewer) was related to the curative resection. The prognosis was also better in these cases than in those with greater than 10 disseminated pleural nodules (certified during the operation; $p = 0.0057$). Patients who underwent macroscopic total resection of disseminated nodules had a better prognosis than those with residual tumors ($p = 0.037$). In stage IVA cases with complete resection (n = 42), the efficacy of adjuvant chemotherapy, radiotherapy, or both was not demonstrated.

Conclusions. Macroscopic total resection of tumors appears to be a promising prognostic factor in Masaoka stage IVA thymomas. The number of disseminated pleural nodules correlated with resectability.

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Thymoma is a rare mediastinal tumor, and because its progression is relatively slow, a large number of patients and long (>5 years) follow-up are required to determine the effect of any treatment. In the treatment for thymoma, only complete surgical resection has been considered as potentially curable [1, 2]. For the early-stage cases, there is no doubt that surgical resection is the treatment of choice. For the cases with pleural dissemination, there is a lack of consensus on treatment strategy, and complete surgical resection is generally considered difficult. Multimodality therapy (surgery, chemotherapy, and radiation) has been used for advanced thymomas. However, the efficacy of chemotherapy and radiotherapy for advanced or recurrent thymomas has not been determined [3–7]. In addition, it is difficult to plan clinical trials because of the rarity of thymomas with pleural dissemination.

The progression pattern for thymoma is different from that for tumors of other organs, which metastasize by lymphogenous or hematogenous routes. Thymomas often recur locally or as pleural dissemination. To improve survival, adjuvant therapies including preoperative or postoperative chemotherapy and radiotherapy for advanced thymomas have been suggested. However, the efficacies of adjuvant chemotherapy and radiotherapy have been controversial [1, 8–13].

In this retrospective study, the clinicopathologic factors and the prognosis of thymoma with pleural dissemination were studied using the data from multiple centers of the Japanese Association for Research on the Thymus for evaluating the efficacy of surgical resection and multimodality therapy.

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Patients and Methods

Patients

A retrospective review of clinical records was conducted at 32 institutions that participated in the Japanese Association for Research on the Thymus. The present study was approved by the Institutional Review Board of Nagoya City University Hospital and other institutions, and individual patient consent was not required for this retrospective study. There were 2,835 thymic epithelial tumors collected that were treated between 1991 and 2010. They included 2,423 thymomas, 306 thymic carcinomas, 64 neuroendocrine carcinomas, and 42 unknown thymic epithelial tumors.

In this study, 148 thymoma patients with pleural dissemination were extracted. They included 128 and 20 patients in Masaoka stages IVA and IVB, respectively. To clarify the efficacy of surgical resection, 12 patients who underwent biopsy only were excluded. We used the most recent revision of the World Health Organization histologic TNM classification and stage grouping of thymic epithelial tumors in 2004 [14] and the Masaoka staging system [15, 16]. In cases with disseminated pleural nodules (stage IVA) or lymph node involvement (stage IVB), if all of the pleural nodules or involved lymph nodes were completely resected, the operation was considered a macroscopically complete resection (MCR).

Statistical Analysis

Survival curves were analyzed by the Kaplan-Meier method and univariate log-rank test. Overall survival was calculated from the date of surgery to death. Disease-free survival was calculated from the date of surgery to the date of identification of the recurrent disease or death for any cause. The frequency distributions between groups were tested with the χ^2 test. Significance was defined as a probability value of less than 0.05. All of the data were analyzed with EZR software [17].

Results

The 136 patients ranged in age from 23 to 83 years, with a mean age of 52. They consisted of 51 men and 85 women. Using World Health Organization histopathologic classification of the tumors [12], thymomas were diagnosed as

Table 1. Prognostic Factors in Thymoma With Pleural Dissemination (n = 136)

Factor	Subgroup	Numbers	5-Year Survival	10-Year Survival	Log-Rank Test *p* Value
Sex	Male	51	87.3%	68.2%	0.572
	Female	85	81.3%	59.8%	
Age	≤60 y	95	89.3%	60.5%	0.462
	>60 y	41	68.4%	68.4%	
PS	0	98	83.8%	62.8%	0.823
	≥1	33	84.5%	57.1%	
WHO classification	A, AB, B1	31	73.1%	53.3%	0.371
	B2, B3	105	86.0%	65.4%	
Extrapleural pneumonectomy	−	128	85.3%	62.5%	0.633
	+	8	70.0%	70.0%	
MG	−	97	79.4%	58.0%	0.125
	+	39	92.6%	71.9%	
Adjuvant chemotherapy	−	93	84.5%	62.3%	0.690
	+	43	82.2%	62.2%	
Adjuvant radiotherapy	−	75	83.5%	60.6%	0.759
	+	61	81.9%	62.2%	
Adjuvant chemoradiotherapy	−	120	82.8%	61.7%	0.515
	+	16	84.8%	60.6%	
Preoperative Masaoka stage	I–III	27	87.0%	77.3%	0.173
	IVa, IVb	75	83.7%	56.6%	
Maximal tumor size	≤70 mm	68	85.1%	63.0%	0.762
	>70 mm	60	86.0%	60.8%	
Number of pleural dissemination	1–10	64	84.2%	80.2%	0.090
	≥11	35	85.0%	52.2%	
Resectability	MCR	46	82.6%	82.6%	0.064
	MRT	86	83.2%	53.9%	
Postoperative Masaoka stage	IVA	118	86.7%	62.5%	0.255
	IVB	18	67.8%	59.4%	

MCR = macroscopic complete resection; MG = myasthenia gravis; MRT = macroscopic residual tumor; PS = performance status; WHO = World Health Organization.

type A (n = 2), type AB (n = 8), type B1 (n = 21), type B2 (n = 62), and type B3 (n = 43). The preoperative clinical staging showed the following composition of patients: 5 in stage I, 8 in stage II, 14 in stage III, 76 in stage IVA, 12 in stage IVB, and 21 unknown. Associated complications were myasthenia gravis (n = 39), pure red cell aplasia (n = 10), and Sjögren's syndrome (n = 1). Median follow-up duration for the 136 patients was 4.4 years.

Thymoma With Pleural Dissemination

Clinical and pathologic data of the 136 patients are shown in Table 1. Briefly, B2 and B3 thymomas were the main types and made up 77.2% of the total. Tumor resection was performed in 128 patients (94.1%), and only 8 patients underwent extrapleural pneumonectomy (5.9%). Resectability was not high as reflected by only 46 cases that were evaluated as MCR (33.8%), and adjuvant chemotherapy, radiotherapy, or both were often selected. There were no standard therapeutic courses as adjuvant therapy, and the therapeutic course after surgery was decided by each institution.

In the present study, no relationship was detected between clinicopathologic factors and the prognosis in the 136 cases with pleural dissemination (Table 1). The 5-year survival of the thymomas with pleural dissemination was 83.5%. In the analysis of numbers of disseminated pleural nodules, the cases with 10 or fewer tended to have a better prognosis (Fig 1A; $p = 0.090$). Also in the analysis of resectability, the MCR cases tended to show a better prognosis (Fig 2A; $p = 0.064$). The number of disseminated pleural nodules was correlated with resectability ($p = 0.0016$). Extrapleural pneumonectomy was performed in 8 patients. One patient had a recurrence 30 months after surgery and died 50 months after surgery. One patient died 14 days after surgery because of heart failure. Three patients were alive without recurrence, and 3 patients were alive with recurrent tumor.

Thymoma With Pleural Dissemination Without Systemic Metastasis or Lymph Node Involvement (Pathologic Masaoka Stage IVA)

In the next step, prognosis of the patients with postoperative Masaoka IVA disease was analyzed (Table 2). Masaoka IVB disease was excluded because it is no longer a local disease. The 5-year survival of the thymomas in stage IVA was 86.7%. The cases with 10 or fewer pleural nodules had a better prognosis than those with 11 or

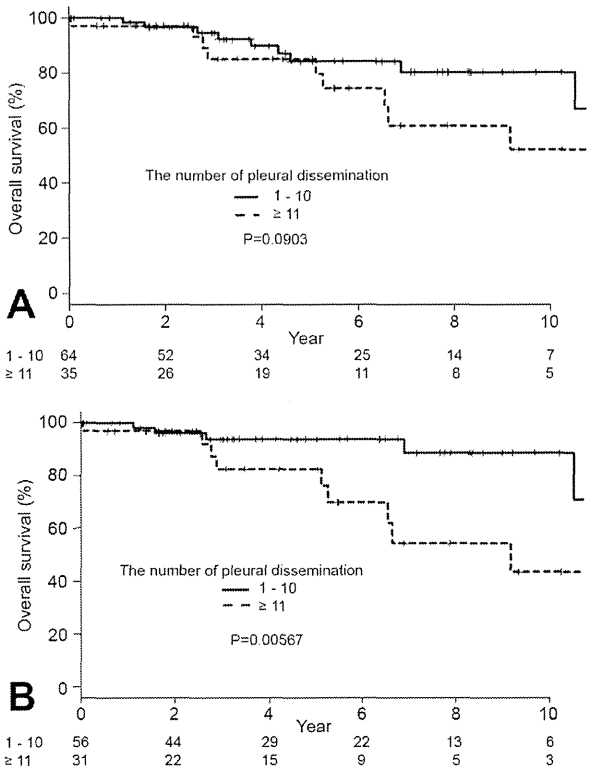

Fig 1. (A) Overall survival of thymoma with pleural dissemination divided by the number of pleural dissemination (n = 136; p = 0.090). (B) Overall survival of Masaoka stage IVA thymoma with pleural dissemination divided by the number of pleural dissemination (n = 118; p = 0.0057).

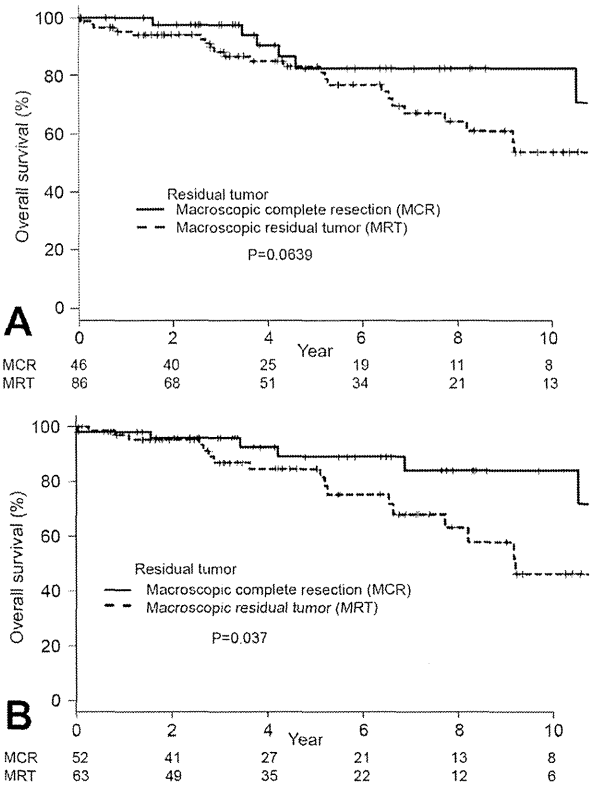

Fig 2. (A) Overall survival of thymoma with pleural dissemination divided by the macroscopic complete resection (MCR) or macroscopic residual tumor (MRT; n = 136; p = 0.064). (B) Overall survival of Masaoka stage IVA thymoma with pleural dissemination divided by the macroscopic complete resection or macroscopic residual tumor (n = 118; p = 0.037).

Table 2. Prognostic Factors in Thymoma With Pleural Dissemination (Masaoka Stage IVA, n = 118)

Factor	Subgroup	Numbers	5-Year Survival	10-Year Survival	Log-Rank Test p Value
Sex	Male	46	85.5%	63.9%	0.894
	Female	72	87.6%	62.4%	
Age	≤60 y	81	92.7%	57.0%	0.742
	>60 y	37	71.3%	71.3%	
PS	0	87	86.6%	63.0%	0.783
	≥1	27	90.7%	54.9%	
WHO classification	A, AB, B1	27	88.3%	64.4%	0.948
	B2, B3	91	86.0%	62.7%	
Extrapleural pneumonectomy	−	110	89.5%	62.7%	0.497
	+	8	70.0%	70.0%	
MG	−	83	84.5%	58.0%	0.268
	+	35	91.3%	71.5%	
Adjuvant chemotherapy	−	83	85.9%	62.3%	0.611
	+	35	89.1%	64.3%	
Adjuvant radiotherapy	−	65	90.0%	62.0%	0.633
	+	53	83.3%	60.9%	
Adjuvant chemoradiotherapy	−	103	87.4%	64.5%	0.987
	+	15	83.6%	55.7%	
Preoperative Masaoka stage	I–III	21	95.0%	79.2%	0.123
	IVa, IVb	75	83.3%	55.8%	
Maximal tumor size	≤70 mm	63	89.4%	64.1%	0.744
	>70 mm	49	88.1%	54.6%	
Number of pleural dissemination	1–10	56	93.6%	88.4%	0.0057
	≥11	31	82.3%	43.3%	
Resectability	MCR	52	88.6%	88.6%	0.037
	MRT	63	84.5%	46.3%	

MCR = macroscopic complete resection; MG = myasthenia gravis; MRT = macroscopic residual tumor; PS = performance status; WHO = World Health Organization.

more (Fig 1B; $p = 0.0057$). The cases that had all of the pleural nodules resected (MCR) had a better prognosis than those with residual tumors (Fig 2B; $p = 0.037$). The number of disseminated pleural nodules correlated with resectability ($p = 0.00065$).

Thymoma With Pleural Dissemination With Systemic Metastasis or Lymph Node Involvement (Pathologic Masaoka Stage IVB)

The cases with Masaoka IVB disease (Table 3) were analyzed to determine the efficacy of the surgical resections that were performed. The 5-year survival of the thymomas in stage IVB was 67.8%. In stage IVB patients, those with type A, AB, or B1 had a poorer prognosis than those with type B2 or B3 ($p = 0.027$), but this analysis was based on a very small number (n = 4) of type A, AB, or B1 patients. Other clinicopathologic factors did not affect the prognosis of stage IVB thymoma patients with pleural dissemination (Table 3).

Adjuvant Therapy for Masaoka Stage IVA Thymoma With No Macroscopic Residual Tumor

The overall survival and disease-free survival of patients who had adjuvant chemotherapy, adjuvant radiotherapy, or adjuvant chemoradiotherapy were not better than patients who did not undergo postoperative adjuvant therapy (Fig 3; $p = 0.477$, $p = 0.366$).

Comment

A large-scale retrospective analysis was conducted of thymoma patients with pleural dissemination. The therapeutic strategy and prognostic factors for thymomas with pleural dissemination have not been determined. Surgical resection has been recommended as the principal treatment, and completeness of resection is considered to be the most important determinant of long-term survival in thymomas. However, in thymoma cases with pleural dissemination, complete surgical resection of disseminated pleural nodules is difficult. In this study 136 thymomas with pleural disseminations were investigated for the relationship between clinicopathologic factors and prognosis. We have demonstrated the importance of complete surgical resection of tumors even in cases with disseminated nodules in Masaoka IVA disease. There was an interaction between the numbers of disseminated pleural nodules and resectability in Masaoka IVA disease. This interaction was not found in Masaoka IVB disease. It is difficult to determine the number of disseminated nodules by preoperative imaging because our patients

Table 3. Prognostic Factors in Thymoma With Pleural Dissemination (Masaoka Stage IVB, n = 18)

Factor	Subgroup	Numbers	5-Year Survival	10-Year Survival	Log-Rank Test *p* Value
Sex	Male	5	100%	100%	0.054
	Female	13	56.6%	45.3%	
Age	≤60 y	13	74.1%	63.5%	0.871
	>60 y	5	40.0%	40.0%	
PS	0	11	70.1%	58.4%	0.883
	≥1	6	62.5%	62.5%	
WHO classification	A, AB, B1	4	0%	0%	0.027
	B2, B3	14	85.1%	74.5%	
Extrapleural pneumonectomy	−	18	67.6%	59.1%	−
	+	0	−	−	
MG	−	14	55.9%	55.9%	0.227
	+	4	100%	75.0%	
Adjuvant chemotherapy	−	10	77.1%	61.7%	0.617
	+	8	57.1%	57.1%	
Adjuvant radiotherapy	−	10	60.0%	60.0%	0.690
	+	8	75.0%	62.5%	
Adjuvant chemoradiotherapy	−	17	65.5%	56.2%	0.460
	+	1	100%	100%	
Preoperative Masaoka stage	I–III	6	66.7%	66.7%	0.707
	IVa, IVb	10	67.5%	54.0%	
Maximal tumor size	≤70 mm	5	60.0%	60.0%	0.611
	>70 mm	12	77.1%	64.3%	
Number of pleural dissemination	1–10	8	43.8%	43.8%	0.100
	≥11	4	100%	100%	
Resectability	MCR	3	33.3%	33.3%	0.340
	MRT	14	76.6%	65.7%	

MCR = macroscopic complete resection; MG = myasthenia gravis; MRT = macroscopic residual tumor; PS = performance status; WHO = World Health Organization.

included many who were diagnosed with diseases in clinical stages I to III (20 of 94; 21.3%). Yano and colleagues [3] also reported the discrepancy between the numbers of disseminated nodules that were diagnosed preoperatively and those counted intraoperatively.

The present data demonstrated that the prognosis of thymoma patients with stage IVA disease is not as dismal as expected (Figs 1, 2). When the dissemination is found during the operation, it is suggested that the operation be continued and the nodules resected if there are 10 or fewer disseminated nodules. The appropriateness of using the number of 10 nodules should be determined by prospective studies. Yano and colleagues [18] reported that a small number of recurrent lesions of thymoma showed better prognosis. The number of disseminated nodules may be a prognostic factor in Masaoka IVA disease.

Some authors have stated that extrapleural pneumonectomy was effective for complete resection of pleural dissemination [19–21]. In this study 8 patients underwent extrapleural pneumonectomy, but the 5-year survival was only 70%. Although extrapleural pneumonectomy may be an option for thymoma cases with pleural dissemination, the procedure should be limited because of the high operative mortality and the low postoperative quality of life.

In the cases of thymoma patients in Masaoka stage IV disease, no significant improvement in overall survival and disease-free survival was noted for patients who were treated with postoperative radiation, chemotherapy, or both compared with those without adjuvant therapy. Although a variety of chemotherapeutic regimens such as adjuvant chemotherapy after surgery for thymoma have been reported, there is no standard chemotherapeutic protocol for thymoma [9–11]. Thymoma is a rare tumor, and advanced stages of thymoma are much rarer. Even in the present relatively large-scale study, efficacy of adjuvant therapy could not be demonstrated. A prospective, worldwide, randomized, controlled trial of chemotherapy or radiotherapy for advanced thymoma is eagerly awaited.

The present study has several limitations, other than the small number of advanced-stage patients. During the two decades of this study, newer surgical devices and techniques have been introduced including thoracoscopic surgery and robotic surgery. Chemotherapeutic agents, apparatuses for radiotherapy, and radiographic imaging technologies have also been improved. The chemotherapeutic agents and regimens, as well as devices and techniques, varied by the period and among the institutions.

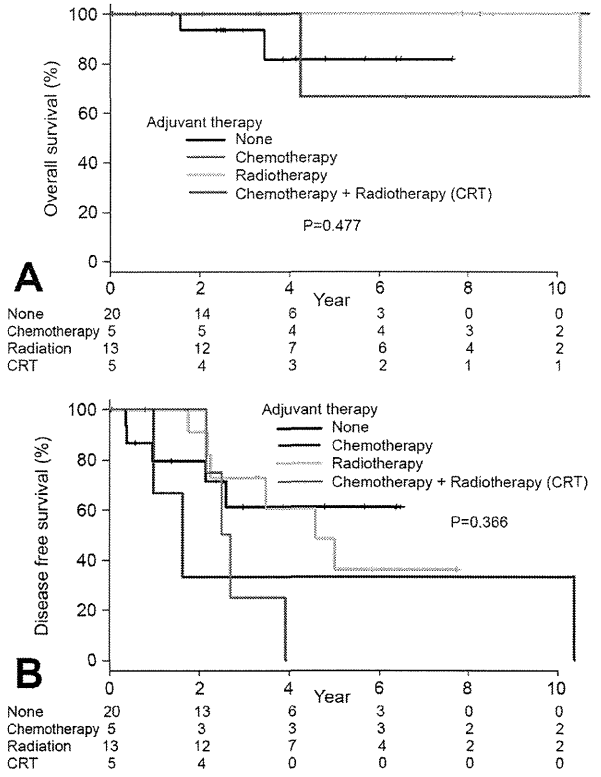

Fig 3. (A) Overall survival of Masaoka stage IVA thymoma with macroscopic complete resection divided by the adjuvant therapy (none, chemotherapy, radiotherapy, or chemoradiotherapy [CRT]; n = 42; p = 0.477). (B) Disease-free survival of Masaoka stage IVA thymoma with macroscopic complete resection divided by the adjuvant therapy (none, chemotherapy, radiotherapy, or chemoradiotherapy; n = 42; p = 0.366).

In conclusion, resection of disseminated pleural nodules of thymoma appears to be an acceptable therapeutic option for Masaoka stage IVA diseases.

References

1. Kondo K, Monden Y. Therapy for thymic epithelial tumors: a clinical study of 1,320 patients from Japan. Ann Thorac Surg 2003;76:878–85.
2. Regnard JF, Magdeleinat P, Dromer C, et al. Prognostic factors and long-term results after thymoma resection: a series of 307 patients. J Thorac Cardiovasc Surg 1996;112:376–84.
3. Yano M, Sasaki H, Yukiue H, et al. Thymoma with dissemination: efficacy of macroscopic total resection of disseminated nodules. World J Surg 2009;33:1425–31.
4. Kim ES, Putnam JB, Komaki R, et al. Phase II study of a multidisciplinary approach with induction chemotherapy, followed by surgical resection, radiation therapy, and consolidation chemotherapy for unresectable malignant thymomas: final report. Lung Cancer 2004;44:369–79.
5. Lucchi M, Ambrogi MC, Duranti L, et al. Advanced stage thymomas and thymic carcinomas: results of multimodality treatments. Ann Thorac Surg 2005;79:1840–4.
6. Haniuda M, Miyazawa M, Yoshida K, et al. Is postoperative radiotherapy for thymoma effective? Ann Surg 1996;224:219–24.
7. Uematsu M, Yoshida H, Kondo M, et al. Entire hemithorax irradiation following complete resection in patients with stage II–III invasive thymoma. Int J Radiat Oncol Biol Phys 1996;35:357–60.
8. Ogawa K, Uno T, Toita T, et al. Postoperative radiotherapy for patients with completely resected thymoma: a multi-institutional, retrospective review of 103 patients. Cancer 2002;94:1405–13.
9. Utsumi T, Shiono H, Kadota Y, et al. Postoperative radiation therapy after complete resection of thymoma has little impact on survival. Cancer 2009;115:5413–20.
10. Sugie C, Shibamoto Y, Ikeya-Hashizume C, et al. Invasive thymoma: postoperative mediastinal irradiation, and low-dose entire hemithorax irradiation in patients with pleural dissemination. J Thorac Oncol 2008;3:75–81.
11. Venuta F, Rendina EA, Longo F, et al. Long-term outcome after multimodality treatment for stage III thymic tumors. Ann Thorac Surg 2003;76:1866–72.
12. Lucchi M, Melfi F, Dini P, et al. Neoadjuvant chemotherapy for stage III and IVA thymomas: a single-institution experience with a long follow-up. J Thorac Oncol 2006;1:308–13.
13. Yokoi K, Matsuguma H, Nakahara R, et al. Multidisciplinary treatment for advanced invasive thymoma with cisplatin, doxorubicin, and methylprednisolone. J Thorac Oncol 2007;2:73–8.
14. Travis WD, Brambilla E, Müller-Hermelink HK, Harris CC, eds. World Health Organization classification of tumours. Pathology and genetics of tumours of the lung, pleura, thymus and heart. Lyon: International Agency for Research on Cancer Press; 2004:146–51.
15. Masaoka A, Monden Y, Nakahara K, Tanioka T. Follow-up study of thymomas with special reference to their clinical stages. Cancer 1981;48:2485–92.
16. Yamakawa Y, Masaoka A, Hashimoto T, et al. A tentative tumor-node-metastasis classification of thymoma. Cancer 1991;68:1984–7.
17. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant 2013;48:452–8.
18. Yano M, Sasaki H, Moriyama S, et al. Number of recurrent lesions is a prognostic factor in recurrent thymoma. Interact Cardiovasc Thorac Surg 2011;13:21–4.
19. Wright CD. Pleuropneumonectomy for the treatment of Masaoka stage IVA thymoma. Ann Thorac Surg 2006;82:1254–9.
20. Ishikawa Y, Matsuguma H, Nakahara R, et al. Mulimodality therapy for patients with invasive thymoma disseminated into the pleural cavity: the potential role of extrapleural pneumonectomy. Ann Thorac Surg 2009;88:952–7.
21. Yang HC, Yoon YS, Kim HK, et al. En bloc extended total thymectomy and extrapleural pneumonectomy in Masaoka stage IVA thymomas. J Cardiothorac Surg 2011;6:28.

INVITED COMMENTARY

Okuda and colleagues [1] report on a relatively large number of patients with Masaoka stage IVA thymoma (136) who had resection of their tumor and the pleural implants. These rare patients were accumulated from a national Japanese database, The Japanese Association for Research on the Thymus, which covered 32 institutions over 19 years to produce this number of patients, further emphasizing just how uncommon this

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ORIGINAL ARTICLE

Differences in the prognosis of resected lung adenocarcinoma according to the histological subtype: a retrospective analysis of Japanese lung cancer registry data

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Abstract

OBJECTIVES: This study intended to assess the clinicopathological features of the histological subtypes of adenocarcinoma of the lung in a large registry population.

METHODS: The Japanese Joint Committee of Lung Cancer Registry performed a nationwide retrospective registry study on the prognosis and clinicopathological profiles of 11 663 patients who underwent resection for primary lung neoplasm in 2004. The registry data of 7921 (62.5%) patients with adenocarcinoma were analysed regarding the prognosis and clinicopathological features according to the histological subtype of adenocarcinoma. The histological subtypes were defined according to the 1999 World Health Organization classification (third edition), where bronchioloalveolar carcinoma (BAC) is defined as adenocarcinoma with a pure bronchioloalveolar growth pattern without invasion.

RESULTS: The distribution of the histological subtype was acinar in 471 patients (7.5%), papillary in 2004 (32.2%), BAC in 1385 (22.3%), solid adenocarcinoma with mucin in 103 (1.7%) and adenocarcinoma with mixed subtypes (AMS) in 2257 (36.3%). The 5-year overall survival rates according to histological subtype were 63.4% for acinar, 72.9% for papillary, 90.3% for BAC, 54.4% for solid adenocarcinoma with mucin and 73.7% for AMS. While the survival rate in patients with BAC was significantly better than those for the other histological subtypes, acinar and solid adenocarcinoma with mucin had significantly worse prognoses than the other histological subtypes. The histological subtype was an independent predictor of survival in a multivariate analysis ($P < 0.001$). Regarding BAC, the pathological stage included not only Stage IA/IB ($n = 1275$; 92.1%), but also Stage II–IV ($n = 110$; 7.9%). One hundred twenty-five patients (9.0%) with BAC had recurrence, including both local and distant recurrence.

CONCLUSIONS: The histological subtype in adenocarcinoma significantly correlated with the prognosis. In BACs with recurrence or pathological stage II–IV, these tumours might have been classified as invasive adenocarcinoma rather than as BAC. The need for the rigorous pathological evaluation of adenocarcinomas that are considered to be a preinvasive or minimally invasive tumour should be addressed in the new lung adenocarcinoma classification to be proposed by the International Association for the Study of Lung Cancer, the American Thoracic Society and the European Respiratory Society.

Keywords: Database • Histology • Lung cancer surgery • Lung pathology • Outcomes

INTRODUCTION

Adenocarcinoma of the lung is the most common histology of lung cancer in Japan, and the proportion of adenocarcinoma has been increasing in many countries [1, 2]. Adenocarcinomas frequently exhibit a heterogeneous histology, while combining bronchioloalveolar (lepidic), papillary, acinar and solid growth patterns [1]. The histological subtyping of lung adenocarcinoma has

developed over the past several decades as reflected in the World Health Organization (WHO) classification. The most significant change was introduced in the third edition of the latter in 1999 [3]. In the third edition, the histological subtype of adenocarcinoma consisted of five subtypes based on the histological growth pattern, i.e. four pure forms [acinar, papillary, bronchioloalveolar carcinoma (BAC) and solid adenocarcinoma with mucin] and one heterogeneous form [adenocarcinoma with mixed subtypes (AMS), which shows a variable admixture of more than one histological subtype pattern]. In particular, BAC was strictly defined as a noninvasive tumour with a pure lepidic growth pattern [3].

Several important prognostic factors have been identified, such as tumour-node-metastasis (TNM) stage, performance status, gender, age, histology and so forth [4, 5]. Although it has been speculated that the particular biological behaviour likely influences the presence of specific histological growth patterns of adenocarcinoma [6], the relationship between the histological subtype of adenocarcinoma and prognosis has not been clearly demonstrated in a large cohort. For BACs, an excellent prognosis should be expected based on the definition of BAC as a noninvasive tumour. Nevertheless, in previous reports based on the 1999 WHO classification, resected BACs were not necessarily associated with satisfactory prognosis even if they were in stage I [6–8].

In Japan, the task force committee of the Japanese Joint Committee of Lung Cancer Registry has periodically performed nationwide registry studies on the prognosis and clinicopathological profiles of lung neoplasms [2, 4]. Recently, the committee reported a retrospective registry study that focused on 11 663 cases of lung cancer resected in 2004 after a 5-year follow-up period [2]. The present study deals with this retrospective registry for patients with lung cancer resected in 2004. This registry data has been used in other publications previously without direct overlap with the present study [9].

The aim of this study was to evaluate the clinicopathological characteristics and prognostic implications according to the histological subtypes of lung adenocarcinoma based on the 1999 third edition of the WHO classification [3], and furthermore to investigate the pattern of recurrence in BAC, which has been defined as a noninvasive adenocarcinoma.

PATIENTS AND METHODS

Registry

In 2010, the Japanese Joint Committee of Lung Cancer Registry performed a nationwide retrospective registry study on the prognosis and clinicopathological profiles of resected lung neoplasms in Japan. The committee received the registries of 11 663 patients from 253 teaching hospitals. The registered data included the clinicopathological and prognostic items, which had been described previously [2]. Recurrent or multiple lung cancers were not included in this registry. Cancer recurrence was divided into three categories according to the site of the initial relapse: loco-regional, distant and at both sites simultaneously. Loco-regional recurrence was defined as any recurrent disease within the ipsilateral hemithorax, mediastinum or supraclavicular lymph nodes. All other sites of recurrence were considered distant recurrence. The cause of death was recorded as either lung-cancer-related, other disease or unknown. The data relating to survival time, recurrence, and cause of death were collected from a medical chart or a national death registry in the respective teaching hospitals. Although the method of data collection for the postoperative follow-up was not standardized because of a retrospective study, the postoperative follow-up was regularly scheduled in the respective teaching hospitals. All patients were staged on the basis of the seventh edition of the Union for International Cancer Control TNM Classification of the malignant tumour staging system published in 2009 [10]. Tumour histology was described according to the third edition of the WHO classification published in 1999 [3], where lung adenocarcinomas were subclassified into the following five histological subtypes: acinar, papillary, BAC, solid adenocarcinoma with mucin and AMS, and variants such as well-differentiated foetal adenocarcinoma, colloid adenocarcinoma, mucinous cystadenocarcinoma, signet-ring adenocarcinoma or clear cell adenocarcinoma. In addition, BAC was cytologically subdivided into three groups: non-mucinous, mucinous and mixed mucinous and non-mucinous or indeterminate.

Patients

The study focused on patients with an adenocarcinoma histology. Of the 11 663 registered patients, 7921 (62.5%) had adenocarcinoma. Patients with variants such as well-differentiated foetal adenocarcinoma ($n = 3$), colloid adenocarcinoma ($n = 4$), mucinous cystadenocarcinoma ($n = 3$), signet-ring adenocarcinoma ($n = 9$) or clear cell adenocarcinoma ($n = 11$) and those ($n = 1671$) with incomplete data regarding the histological subtype of adenocarcinoma were excluded. The remaining 6220 patients were analysed in terms of prognosis and clinicopathological characteristics according to the histological subtype of adenocarcinoma.

Statistical analysis

The χ^2 test and one-way analysis of variance were used to evaluate the differences in categorical variables and continuous variables, respectively. The survival time was defined as the time between the date of surgery and the last follow-up date. The survival curves were estimated by the Kaplan–Meier method, and differences in survival were assessed by the log-rank test. Overall survival was defined as the time between the operation and death from any cause. Disease-free survival was defined as the time between the operation and disease recurrence, lung cancer-related death or the last follow-up. A multivariate analysis by a Cox proportional hazards model was used to test the significance of prognostic factors, including gender, age, smoking status, operative mode, surgical curability, histological subtype of adenocarcinoma, tumour size, p-T status and p-N status. Significance was defined as a P-value of <0.05. All statistical analyses were performed with the SAS version 9.1.3 (SAS Institute, Inc., Cary, NC, USA) or with IBM SPSS version 19 (IBM Corporation, NY, USA).

RESULTS

Clinicopathological features

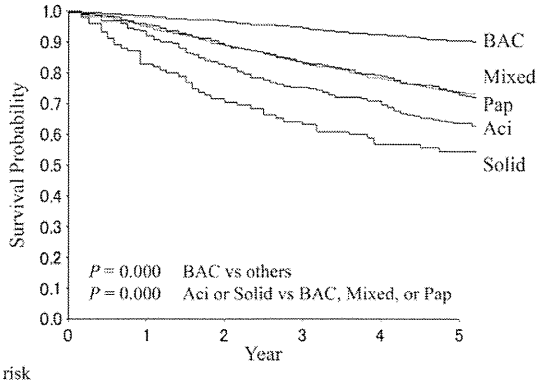
The distribution of histological subtypes in adenocarcinoma is as follows. The most common subtype was AMS ($n = 2257$; 36.3%), followed by papillary ($n = 2004$; 32.2%), BAC ($n = 1385$; 22.3%), acinar ($n = 471$; 7.5%) and solid adenocarcinoma ($n = 103$; 1.7%). Of the 1385 patients with BAC, 1110 (80.1%) had non-mucinous

type, 102 (7.4%) had mucinous type and 173 (12.5%) had mixed mucinous and non-mucinous or indeterminate type. The clinicopathological features according to the histological subtype are summarized in Table 1. The mean age at surgical resection for patients with solid adenocarcinoma was significantly younger than that for patients with other subtypes. With regard to gender, the proportion of females in BAC was significantly greater than that in other subtypes, whereas the proportion of males in solid adenocarcinoma was significantly greater than that in other subtypes. The proportion of smokers was significantly higher in those with acinar and solid adenocarcinoma than in those with other subtypes, whereas it was significantly lower in patients with BAC than in those with other subtypes. One hundred fifty-seven patients (2.5%) of all the 6220 patients received neoadjuvant therapy. The neoadjuvant therapy included chemotherapy ($n = 111$; 1.8%), radiotherapy ($n = 4$; 0.1%), chemoradiotherapy ($n = 34$; 0.5%) and others ($n = 8$; 0.1%). The proportion of patients who received neoadjuvant therapy was significantly higher in patients with solid adenocarcinoma than in those with other subtypes, whereas it was significantly lower in patients with BAC than in those with other subtypes. With regard to the operative mode, the proportion of pneumonectomy was higher in patients with solid adenocarcinoma than in those with other subtypes, whereas the proportion of segmentectomy/wedge resection was higher in patients with BAC than in those with other subtypes. Regarding tumour size, BAC was significantly smaller and solid

Table 1: Clinicopathological features of patients with resected adenocarcinoma of the lung according to the histological subtype

Characteristic	BAC ($n = 1385$)	Acinar ($n = 471$)	Papillary ($n = 2004$)	Solid ($n = 103$)	AMS ($n = 2257$)	*P*
Age (year)						
Mean	65.1 ± 10.3	66.0 ± 10.0	66.6 ± 9.7	63.9 ± 9.7	65.9 ± 9.7	<0.001
Sex						
Male	551 (39.8%)	309 (65.6%)	1024 (51.1%)	76 (73.8%)	1186 (52.5%)	<0.001
Female	834 (60.2%)	162 (34.4%)	980 (48.9%)	27 (26.2%)	1071 (47.5%)	
Smoking status						
Non-smoker	834 (65.3%)	158 (36.8%)	964 (51.7%)	23 (22.8%)	1093 (50.8%)	<0.001
Ex-smoker	223 (17.4%)	93 (21.7%)	341 (18.3%)	21 (20.8%)	456 (21.2%)	
Current smoker	221 (17.3%)	178 (41.5%)	560 (30.0%)	57 (56.4%)	602 (28.0%)	
Serum CEA level						
Normal	1217 (87.9%)	308 (65.4%)	1488 (74.3%)	59 (57.3%)	1616 (71.6%)	<0.001
High	168 (12.1%)	163 (34.6%)	516 (25.7%)	44 (42.7%)	641 (28.4%)	
Clinical stage						
IA	1189 (85.8%)	248 (52.7%)	1226 (61.2%)	40 (38.8%)	1374 (60.9%)	<0.001
IB	150 (10.8%)	113 (24.0%)	494 (24.7%)	28 (27.2%)	545 (24.1%)	
IIA	4 (0.3%)	5 (1.1%)	30 (1.5%)	6 (5.8%)	48 (2.1%)	
IIB	12 (0.9%)	39 (8.3%)	81 (4.0%)	10 (9.7%)	108 (4.8%)	
IIIA	13 (0.9%)	41 (8.7%)	96 (4.8%)	12 (11.7%)	113 (5.0%)	
IIIB/IV	17 (1.2%)	25 (5.2%)	77 (3.8%)	7 (6.8%)	69 (3.1%)	
Neoadjuvant therapy						
No	1374 (99.2%)	450 (95.5%)	1952 (97.4%)	93 (90.3%)	2194 (97.2%)	<0.001
Yes	11 (0.8%)	21 (4.5%)	52 (2.6%)	10 (9.7%)	63 (2.8%)	
Operative mode						
Pneumonectomy	2 (0.1%)	8 (1.7%)	27 (1.4%)	8 (7.9%)	31 (1.4%)	<0.001
Lobectomy	844 (61.2%)	382 (82.4%)	1680 (84.6%)	74 (73.3%)	1900 (85.4%)	
Segmentectomy/wedge resection	533 (38.6%)	74 (16.0%)	279 (14.1%)	19 (18.8%)	295 (13.2%)	
Curability						
R0	1364 (99.3%)	482 (92.0%)	1887 (94.8%)	98 (95.1%)	2134 (95.5%)	<0.001
R1	4 (0.3%)	15 (3.2%)	56 (2.8%)	3 (2.9%)	45 (2.0%)	
R2	6 (0.4%)	22 (4.7%)	48 (2.4%)	2 (1.9%)	56 (2.5%)	
Tumour size						
Mean	1.9 ± 1.6	3.0 ± 1.6	2.7 ± 1.5	3.5 ± 2.0	2.8 ± 1.7	<0.001
Pleural invasion						
pl0	1297 (93.8%)	286 (61.4%)	1328 (66.6%)	62 (60.2%)	1588 (71.0%)	<0.001
pl1/pl2	82 (5.9%)	139 (29.8%)	559 (28.0%)	29 (28.2%)	512 (22.9%)	
pl3	4 (0.2%)	41 (8.8%)	107 (5.4%)	12 (11.6%)	138 (6.2%)	
Pathological stage						
IA	1143 (82.5%)	165 (35.0%)	883(44.1%)	31 (30.1%)	1046 (46.4%)	<0.001
IB	132 (9.5%)	118 (25.1%)	502 (25.1%)	18 (17.5%)	489 (21.7%)	
IIA	25 (1.8%)	42 (8.9%)	135 (6.7%)	11 (10.6%)	142 (6.3%)	
IIB	32 (2.3%)	36 (7.7%)	83 (4.1%)	14 (13.6%)	106 (4.7%)	
IIIA	40 (2.9%)	84 (17.8%)	297 (14.8%)	25 (24.3%)	367 (16.2%)	
IIIB/IV	13 (1.0%)	26 (5.5%)	104 (5.2%)	4 (3.9%)	107 (4.7%)	
Adjuvant chemotherapy						
No	1235 (91.4%)	295 (65.0%)	1403 (72.3%)	61 (61.0%)	1604 (74.0%)	<0.001
Yes	116 (8.6%)	159 (35.0%)	538 (27.7%)	39 (39.0%)	565 (26.0%)	

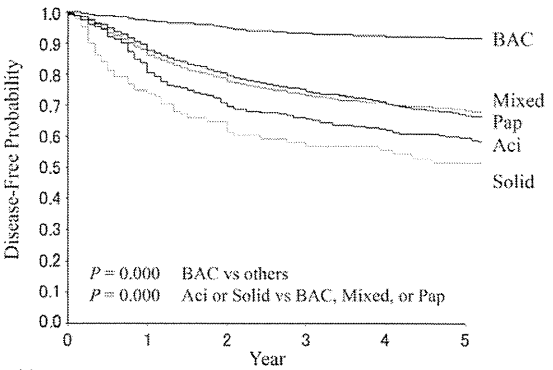
BAC: bronchioloalveolar carcinoma; Solid: solid adenocarcinoma with mucin; AMS: adenocarcinoma with mixed subtypes.



No. at risk

BAC	1385	1321	1269	1220	1131	922
Mixed	2257	2099	1921	1729	1543	1278
Pap	2004	1856	1686	1505	1347	1121
Aci	471	424	363	318	282	223
Solid	103	81	69	60	53	45

Figure 1: Overall survival curves based on the histological subtype of adenocarcinoma. There is a significant difference in survival between BAC and the other subtypes ($P < 0.001$) and between acinar or solid and BAC, mixed subtypes or papillary ($P < 0.001$). BAC: bronchioloalveolar carcinoma; Mixed: adenocarcinoma with mixed subtypes; Aci: acinar; Pap: papillary; Solid: solid adenocarcinoma with mucin.



No. at risk

BAC	1385	1283	1217	1160	1073	886
Mixed	2257	1847	1601	1436	1295	1099
Pap	2004	1646	1419	1266	1127	930
Aci	471	354	286	251	221	187
Solid	103	68	57	48	45	37

Figure 2: Disease-free survival curves based on the histological subtype of adenocarcinoma. There is a significant difference in survival between BAC and the other subtypes ($P < 0.001$) and between acinar or solid and BAC, mixed subtypes or papillary ($P < 0.001$). BAC: bronchioloalveolar carcinoma; Mixed: adenocarcinoma with mixed subtypes; Aci: acinar; Pap: papillary; Solid: solid adenocarcinoma with mucin.

adenocarcinoma was significantly larger, compared with the other subtypes. Pleural invasion was significantly infrequent in BAC compared with the other subtypes. With regard to the pathological stage, BAC had significantly more cases in Stage IA and solid adenocarcinoma had more cases in Stage IIIA, compared with the other subtypes.

Survival according to the histological subtype of adenocarcinoma

The postoperative follow-up was complete in 87% of all the patients. The overall 5-year survival rates according to the histological subtype of adenocarcinoma were 90.3% in BAC, 73.7% in AMS, 72.9% in papillary, 63.4% in acinar and 54.4% in solid adenocarcinoma. The survival curves are shown in Fig. 1. Patients with BAC had significantly better overall survival than those with other subtypes ($P < 0.001$). Patients with acinar or solid adenocarcinoma had significantly worse overall survival than those with BAC, AMS or papillary subtype ($P < 0.001$). Disease-free 5-year survival rates according to the histological subtype in adenocarcinoma were 91.4% in BAC, 68.3% in mixed subtypes, 66.6% in papillary, 59.4% in acinar and 51.5% in solid adenocarcinoma with mucin (Fig. 2). Patients with BAC had significantly better disease-free survival than those with other subtypes ($P < 0.001$). Patients with acinar or solid adenocarcinoma with mucin had significantly worse disease-free survival than those with BAC, mixed subtypes or papillary subtype ($P < 0.001$).

In a Cox proportional hazards model to predict overall survival, the following factors persisted as important prognostic factors: gender, age, operative mode, histological subtype of adenocarcinoma, surgical curability, tumour size, p-T status and p-N status (Table 2). With regard to histological subtype of adenocarcinoma, BAC had a significantly better prognosis, whereas solid adenocarcinoma and acinar subtype had significantly worse prognoses.

The prognosis among histological subtypes was further examined with regard to each pathological stage. In patients with pathological stage IA, BAC had significantly better overall survival than other subtypes ($P < 0.001$) (Fig. 3A). In patients with pathological stage IB, BAC had significantly better survival than acinar or solid adenocarcinoma (Fig. 3B). In patients with pathological stage II, solid adenocarcinoma had significantly worse survival than BAC, AMS or papillary subtype (Fig. 3C). In patients with pathological stage IIIA, there were no significant differences among histological subtypes (Fig. 3D).

Death was observed in 139 (10.0%) of the 1385 patients with BAC, 168 (35.7%) of the 471 patients with acinar, 538 (26.8%) of the 2004 patients with papillary, 44 (42.7%) of the 103 patients with solid adenocarcinoma and 597 (26.5%) of the 2257 patients with AMS in their clinical course. The distribution of cause of death in patients with adenocarcinoma according to the histological subtype is given in Table 3. With regard to cause of death, patients with BAC significantly had more death from diseases other than lung cancer ($P < 0.001$) more frequently.

The recurrence was observed in 125 (9.0%) of the 1385 patients with BAC, 198 (42.0%) of the 471 patients with acinar, 658 (32.8%) of the 2004 patients with papillary, 46 (44.7%) of the 103 patients with solid adenocarcinoma and 738 (32.7%) of the 2257 patients with AMS in their clinical course. The distribution of mode of recurrence in patients with adenocarcinoma according to the histological subtype is given in Table 4. There were no significant differences in mode of recurrence among the histological subtypes ($P = 0.089$).

Prognosis of bronchioloalveolar carcinoma

Regarding the mode of recurrence, 71 (56.8%) were distant, 38 (30.4%) were loco-regional and 7 (5.6%) were both simultaneously as given in Table 4. The distribution of pathological stage in BAC patients with recurrence was 40 patients in Stage IA, 19 in Stage IB, 25 in Stage II and 41 in Stage III/IV. The recurrence in BACs in

Table 2: Multivariate analysis of overall survival for resected cases of adenocarcinoma of the lung: Cox proportional hazard model (n = 6220)

Variable	HR	95% CI	P
Gender			
Men	1.000		
Women	0.665	0.568–0.778	<0.001
Age (year)			<0.001
<50	1.000		
50–70	1.177	0.902–1.537	0.230
>70	2.000	1.562–2.620	<0.001
Smoking status			0.052
Non-smoker	1.000		
Ex-smoker	1.151	0.962–1.376	0.124
Current smoker	1.227	1.040–1.446	0.015
Operative mode			<0.001
Pneumonectomy	1.000		
Lobectomy	0.633	0.461–0.868	0.005
Segmentectomy	0.951	0.653–1.386	0.795
Wedge resection	1.160	0.804–1.674	0.427
Surgical curability			
Complete	1.000		
Incomplete	1.772	1.449–2.166	<0.001
Histological subtype			<0.001
Acinar	1.000		
Papillary	0.844	0.697–1.023	0.084
BAC	0.508	0.393–0.656	<0.001
Solid with mucin	1.146	0.808–1.625	0.445
Mixed subtypes	0.817	0.676–0.988	0.037
Tumour size	1.099	1.064–1.134	<0.001
p-T status			<0.001
T1a	1.000		
T1b	1.445	1.204–1.734	<0.001
T2a	1.895	1.605–2.237	<0.001
T2b	1.701	1.228–2.355	0.001
T3	2.757	2.210–3.439	<0.001
T4	2.431	1.716–3.444	<0.001
p-N status			<0.001
N0	1.000		
N1	2.251	1.883–2.691	<0.001
N2	3.462	3.058–3.919	<0.001
N3	6.166	3.805–9.990	<0.001

HR: hazard ratio; CI: confidence interval; BAC: bronchioloalveolar carcinoma.

Stage I accounted for 3.5% of all BACs in Stage IA and 14.4% of those in Stage IB.

DISCUSSION

In this Japanese Lung Cancer Registry Study of 6,220 patients with resected lung adenocarcinoma, we showed that the histological subtype was a significant predictor of prognosis, independent of T- or N-factor in staging for lung cancer. In the WHO classification, the histological subtype of lung adenocarcinoma is classified according to the histological growth pattern. In our study, BAC had a significantly better prognosis, whereas solid adenocarcinoma and acinar subtype had significantly worse prognoses. In addition, the proportion of patients with advanced stage (Stage II–III) was higher in solid subtype than in other subtypes. We supposed that this could be the reason why the proportion of patients with pneumonectomy or patients who received neoadjuvant therapy was higher in patients with solid subtype than those with other subtypes.

In the present study, we investigated the clinicopathological features of histological subtypes of lung adenocarcinoma based on the 1999 WHO histological classification [3]. AMS is likely to be the most common histological subtype of lung adenocarcinoma because most lung adenocarcinomas are histologically heterogeneous and consist of more than one subtype even if they are small [1, 11, 12]. According to recent reports [12, 13], >80–90% of adenocarcinomas were classified as AMS when qualified expert pathologists re-reviewed the tumour histology in surgically resected adenocarcinoma using the 1999 WHO classification. However, AMS accounted for only 36.3% of adenocarcinomas in the present study. This may expose potential problems in the reproducibility of diagnosis with regard to the histological subtyping of lung adenocarcinoma among pathologists. Poor interobserver concordance regarding interpretation of the histological pattern in lung adenocarcinoma has been pointed out for some time [14].

BAC was once considered a well-differentiated adenocarcinoma that grew along the alveolar wall or underwent aerogenous spread [1]. The clinical manifestations varied, such as a single pulmonary nodule, multiple pulmonary nodules, localized infiltrates and diffuse pulmonary involvement (pneumonic-type) [1, 6]. In the 1999 WHO classification, the term BAC was newly defined as adenocarcinoma that showed the lepidic growth without evidence of stromal, vascular or pleural invasion. Thus, there should be no evidence of invasion for a diagnosis of BAC. If an invasive component is identified, the tumour is classified as AMS rather than BAC. Naturally, patients with BAC might be expected to have early stage without lymph node metastasis, and thus would have an excellent prognosis without recurrence. However, of the 1385 patients with BAC in the present study, 7.9% were in pathological stage II–IV and 9.0% had recurrence, including both local and distant recurrence. This recurrence was seen even in Stage I BACs. Consequently, the disease-free 5-year survival rate in BAC reached no further than 91.4%. Perhaps these BACs with recurrence or a positive-node should have been classified as invasive adenocarcinoma, i.e. AMS, rather than as BAC, although it is not possible to perform a detailed histological review to confirm the diagnosis in each case with such a large number of BAC patients from a variety of hospitals. In past reports on BAC as determined based on the 1999 WHO classification, resected BACs were not necessarily associated with excellent survival, as given in Table 5 [6–8, 11, 15–22]. In addition, these reports on BAC also included patients with distant as well as loco-regional recurrence. Surprisingly, reports that refer to BAC with N1 and N2 disease are still being published [23]. The issue of a strict pathological evaluation of 'invasion' must be clarified. The increasing importance of the precise definition and education on interpretation of pathological 'invasion' is also advocated in the recent report [24].

On the other hand, despite recent remarkable advances in our understanding of lung adenocarcinoma in the fields of medical oncology, molecular biology and radiology, there remains a need for a universally accepted classification of adenocarcinoma subtypes. Many reports have demonstrated a correlation between the predominant histological growth pattern of adenocarcinoma and survival [6, 13]. Tumours with a predominant lepidic growth pattern are associated with a better prognosis [6, 13], while those with a predominantly solid pattern or papillary pattern are more aggressive [5, 13]. Molecular markers such as epidermal growth factor receptor (EGFR) mutation, K-ras mutation or fusion of anaplastic lymphoma kinase (ALK) rearrangement are likely to be

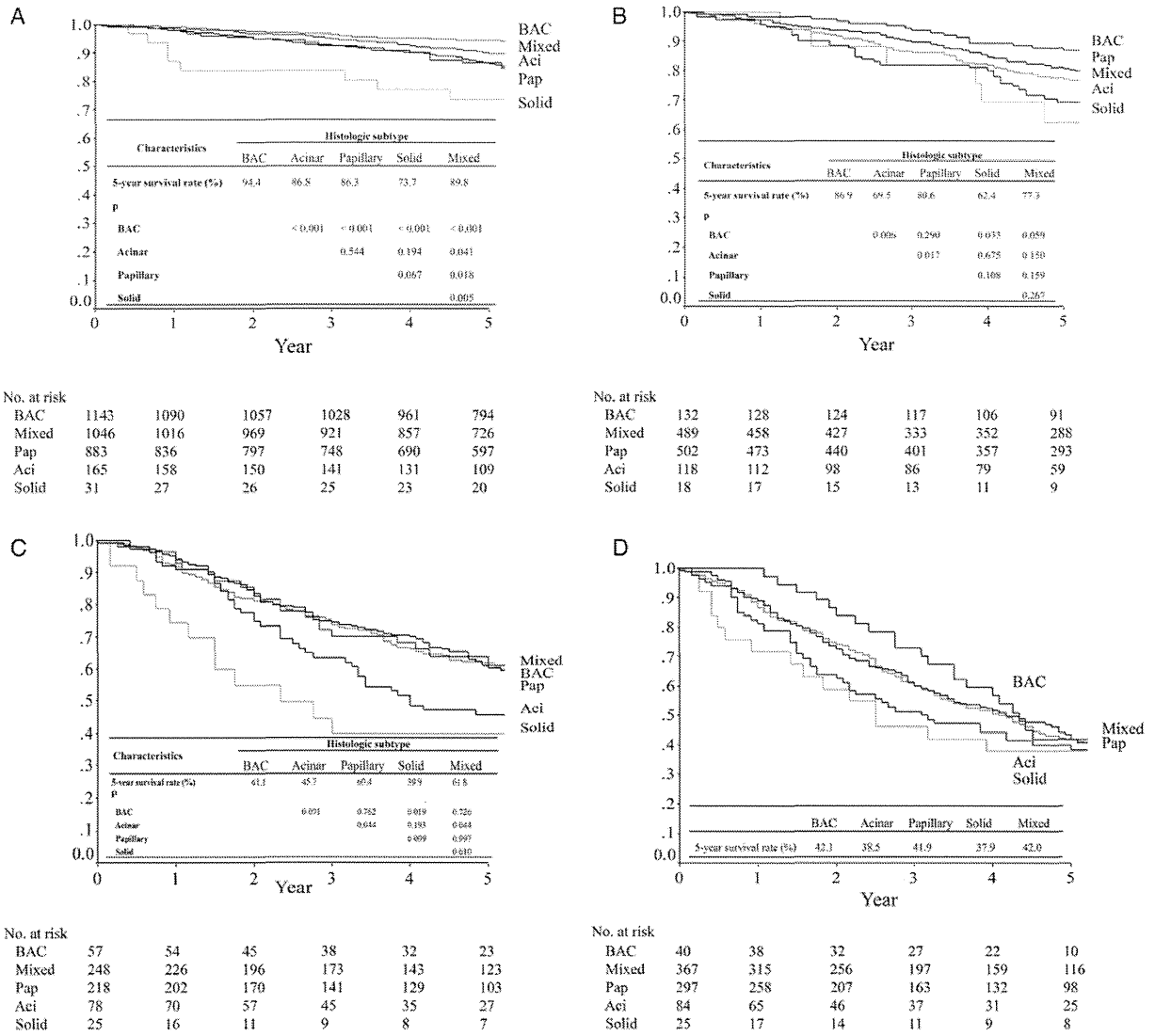


Figure 3: (**A**) Overall survival curves based on the histological subtype of pathological stage IA in adenocarcinoma. The 5-year survival rates according to the histological subtype and *P* values in survival differences among histological subtypes are shown in the cross-table. BAC: bronchioloalveolar carcinoma; Mixed: adenocarcinoma with mixed subtypes; Aci: acinar; Pap: papillary; Solid: solid adenocarcinoma with mucin. (**B**) Overall survival curves based on the histological subtype of pathological stage IB in adenocarcinoma. The 5-year survival rates according to the histological subtype and *P* values in survival differences among histological subtypes are shown in the cross-table. (**C**) Overall survival curves based on the histological subtype of pathological stage II in adenocarcinoma. The 5-year survival rates according to the histological subtype and *P* values in survival differences among histological subtypes are shown in the cross-table. (**D**) Overall survival curves based on the histological subtype of pathological stage IIIA in adenocarcinoma. The 5-year survival rates according to the histological subtype and *P* values in survival differences among histological subtypes are shown in the cross-table.

Table 3: Cause of death in patients with resected adenocarcinoma according to the histological subtype

Cause of death	BAC	Acinar	Papillary	Solid	AMS
Lung-cancer-related	69 (49.6%)	132 (78.6%)	418 (77.7%)	34 (77.3%)	467 (78.2%)
Other disease	67 (48.2%)	34 (20.2%)	115 (21.4%)	10 (22.7%)	117 (19.6%)
Unknown	3 (2.2%)	2 (1.2%)	5 (0.9%)	0 (0%)	13 (2.2%)
Total number of death	139	168	538	44	597

BAC: bronchioloalveolar carcinoma; Solid: solid adenocarcinoma with mucin; AMS: adenocarcinoma with mixed subtypes.

Table 4: Mode of recurrence in patients with resected adenocarcinoma according to the histological subtype

Mode of recurrence	BAC	Acinar	Papillary	Solid	AMS
Loco-regional	38 (30.4%)	53 (26.8%)	202 (30.7%)	14 (30.4%)	210 (28.5%)
Distant	71 (56.8%)	112 (56.6%)	328 (49.8%)	29 (63.0%)	384 (52.0%)
Both simultaneously	7 (5.6%)	21 (10.6%)	98 (14.9%)	2 (4.3%)	105 (14.2%)
Unknown	9 (7.2%)	12 (6.1%)	30 (4.6%)	1 (2.2%)	39 (5.3%)
Total number of recurrence	125	198	658	46	738

BAC: bronchioloalveolar carcinoma; Solid: solid adenocarcinoma with mucin; AMS: adenocarcinoma with mixed subtypes.
No statistical significant difference in mode of recurrence among the histological subtypes ($P = 0.089$).

Table 5: Postoperative 5-year survival rates for patients with BAC diagnosed according to the 1999 WHO classification

Author (year)	Number of patients	Pathological stage	5-year survival rate
Breathnach and colleagues (2001)	33	I	74%/83%, DFS/OS
Volpino and colleagues (2001)	34	IA	74.9%, OS
Ebright and colleagues (2002)	47	I	83.3%, OS
Rena and colleagues (2003)	28	I	81%, DFS
Furak and colleagues (2003)	67	All (IA/IB)	61.9%, OS (71%/77%, OS)
Sakurai and colleagues (2004)	85	IA (≤2 cm)	100%, DFS
Campione and colleagues (2004)	54	IA	88%, OS
Zell and colleagues (2007)	627	I	65%, OS
Koike and colleagues (2009)	46	I	93%, DFS
Casali and colleagues (2010)	40	All (I)	51%/64%, DFS/OS (69%/79%, DFS/OS)
Ebbert and colleagues (2010)	78	All	83.5%, OS
Whitson and colleagues (2012)	5532	All (lobectomy cases)	59.5%, OS
Present study	1385	All	91.4%/90.3%, DFS/OS

BAC: bronchioloalveolar carcinoma; WHO: World Health Organization; DFS: disease-free survival; OS: overall survival.

associated with a particular histological growth pattern of adenocarcinoma [1]. Moreover, these molecular markers can be used to predict the response to targeted therapy, particularly after the discovery of EGFR mutations and their association with sensitivity to EGFR tyrosine kinase inhibitors (EGFR TKIs) such as gefitinib [1]. It has been reported that EGFR mutations are more prevalent in the lepidic growth predominant subtype and ALK rearrangement in the acinar predominant subtype [1]. According to radiological-pathological studies, tumours that show ground-glass opacity on high-resolution computed tomography seem to be BACs or adenocarcinomas like BAC with a lepidic growth pattern accompanied by minimal invasion [1]. However, most of these adenocarcinomas will be classified as 'AMS' based on the 1999 WHO classification despite having such widely varied clinical behaviours. Therefore, the 1999 WHO classification has limited clinical utility. Ultimately, AMS includes tumours that are minimally invasive to overtly invasive. Additionally, with regard to BAC tumours, a discrepancy still exists between the rigorous pathological definition of BAC according to the 1999 WHO classification and the clinical use of the term. To address these issues, a new adenocarcinoma classification has recently been proposed by international multidisciplinary lung cancer experts including medical oncologists, respiratory physicians, pathologists, surgeons, molecular biologists and radiologists, who are sponsored by the International Association for the Study of Lung Cancer (IASLC), the American Thoracic Society (ATS), and the European Respiratory Society (ERS) [1]. This was published as the new IASLC/ATS/ERS International Multidisciplinary Lung Adenocarcinoma Classification in 2011. Although we had too much incomplete data on histological subtype in adenocarcinoma in the present study, detailed pathological evaluation of histological subtype is becoming more important for clinical practice in the future. Pathologists need to put the focus on identifying the histological subtype of adenocarcinoma.

Regarding EGFR mutations in lung adenocarcinoma for a matter peculiar to a Japanese, EGFR TKIs have been developed as a targeted therapy in this disorder. East-Asians and patients with bronchioloalveolar pathological subtype have been shown to be significantly associated with a favourable response to EGFR TKIs [1]. Although the proportion of BAC in adenocarcinoma was ~20% in this Japanese registry data, it was reportedly lower in Western countries. Actually, the proportion of BAC in adenocarcinoma, even if it includes bronchioloalveolar-growth predominant subtype, has been reported to be only ~8% in Western countries [12, 13]. The distribution of the histological subtype in adenocarcinoma could be quite different among countries. The difference might affect the future drug development of targeted therapy among countries.

In the new proposed classification [1], the terms BAC and AMS were made obsolete. A BAC is called 'adenocarcinoma *in situ*' as a preinvasive lesion and the category of 'minimally invasive adenocarcinoma' was added, whereas invasive tumours other than minimally invasive adenocarcinoma are classified according to their