

Thymic neoplasm: a rare disease with a complex clinical presentation

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ABSTRACT

Thymic neoplasms constitute a broad category of rare lesions with a wide spectrum of pathologic characteristics and clinical presentations which therefore require a high index of suspicion to diagnose. The natural history of the disease is seldom predictable, anywhere from an indolent to an aggressively malignant course. Although the classification and staging of these lesions are complex and controversial, complete radical surgical resection remains the gold standard of therapy. Radiation and chemotherapy are important elements of the multimodality approach to treating these patients and it is important for thoracic surgeons to work closely with their colleagues in other disciplines in the management of and future research endeavors in thymic neoplasm. In this review, we discuss the evaluation of the patient with an anterior mediastinal mass, the classification and staging of thymic neoplasms, the role of surgery, radiation and chemotherapy in treating this disease, as well as future directions in research for novel targeted therapies.

KEY WORDS

Thymic neoplasm; thymoma; thymic carcinoma

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Introduction

Thymic neoplasms, thymoma and thymic carcinoma, are a rare heterogenous category of lesions with a broad spectrum of pathologic characteristics and clinical presentations. Thymoma is the most common primary anterior mediastinal mass, with an incidence of 1.5 cases per million, and the overall incidence of thymic neoplasms is 0.13 per 100,000 person years (1). Thymic carcinoma is much more rare than thymoma, but much more likely to spread. In fact, the five year survival rate for all stage thymoma is 78%, whereas only 40% for thymic cancer (2-4). Because of the rarity of these lesions, it is important to have a high index of clinical suspicion and to thoroughly consider the differential diagnosis of the anterior mediastinal mass.

Evaluation of the patient with an anterior mediastinal mass

Evaluation of a patient with an anterior mass must include

the consideration of both malignant and benign processes. Neoplasms include thymoma, lymphoma, thymic carcinoma, thymic carcinoid, thymolipoma, germ cell tumors and lung metastases (5-7). Non-neoplasms include intrathoracic goiter, thymic cysts, lymphangiomas and aortic aneurysms (5-7). Although the etiology and risk factors for thymic tumors are unknown, previous irradiation and Epstein-Barr virus infections have been thought to play a role (8,9). There have also been reports of Class I and II HLA proteins being highly expressed in thymic epithelial cells and there may be an increased risk among Asians and Pacific Islanders (10), as well as an association with malignant fibrous histiocytoma among the Japanese (1). However, more research is required to determine a genetic predisposition to thymic tumors. Many of these masses are benign, especially in asymptomatic cases. However, most patients with symptoms present with malignant disease. Although most mediastinal malignant tumors are lung cancer metastases, most primary neoplasms in the anterior mediastinum are actually thymomas (11).

Because of the difference in the management of these lesions, it is important to differentiate between thymic malignancies and the other listed possibilities prior to initiating treatment. Lymphomas commonly present with generalized lymphadenopathy, but they can also present as primary anterior mediastinal lesions (6,12). Examples include nodular sclerosing Hodgkin's disease and non-Hodgkin's lymphomas, such as diffuse large B-cell lymphoma and acute lymphoblastic lymphoma (6,12). Thymic carcinoids are rare, but they present

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in association with multiple endocrine neoplasia type 1 syndrome (13,14). Although cases of thymoma usually have an indolent presentation, the presentation for lymphoma and germ cell tumors, for example, is much more rapid in onset (15).

Thymoma patients often present at a younger age (5th-8th decade of life) and better physiologic condition than those with other thoracic malignancies, often thus enabling thymoma patients to undergo more aggressive surgical and medical therapy when indicated (11). Of patients with thymoma, 30% are asymptomatic (16) and 30-50% present with Myasthenia Gravis (MG), but only 10-15% of MG patients have thymoma (16,17). MG is usually diagnosed by history (drooping eyelids, double vision, drooling, difficulty climbing stairs, hoarseness, dyspnea) and/or serum anti-acetylcholine receptor antibody levels, and they will require neurological treatment prior to surgical resection of the tumor (16,17). Even if they do not have clinical signs of MG, because of the perioperative risks associated with untreated MG, it is recommended to screen all these patients for MG prior to pursuing treatment for the thymoma (18). Pure red cell aplasia and hypo-gamma-globulinemia are the most common conditions associated with thymoma after MG, 2-6% of patients (16,19).

Other less commonly associated conditions include chronic ulcerative colitis, regional enteritis, systemic lupus erythematosus, sarcoidosis, scleroderma, rheumatoid arthritis, polymyositis, dermatomyositis, pericarditis, Sjogren syndrome, Raynaud's disease, thyroiditis, T-cell deficiency syndrome, pemphigus, alopecia, chronic candidiasis, Cushing's syndrome, hypopituitarism, Addison's disease, hypertrophic osteoarthropathy, macrogenitosomia praecox, nephrosis, minimal change nephropathy, red cell hypoplasia, pernicious anemia, erythrocytosis, agranulocytosis, multiple myeloma, hemolytic anemia, acute leukemia, and T-cell lymphocytosis (16,19). Although extremely rare with only one other case reported in the literature (20), we recently experienced a thymoma case who presented with ANA positive autoimmune hepatitis. Complete biochemical remission of his autoimmune hepatitis with a concomitant weaning of his steroids was achieved with thymectomy.

Local symptoms include pain, cough, hoarseness, and dyspnea (16,19,21). Superior Vena Cava syndrome and weight loss only occur in a small percentage of thymoma patients (16,19,21). It is uncommon for patients with thymoma to have metastatic disease at presentation (4,17), with the pleura being the most frequent site and extra-thoracic disease accounting for <10% of cases (22-24). Thymic carcinoma does present with distant metastasis more frequently than thymoma (6). Thymic tumors can rarely present as primary lesions outside the anterior mediastinum, such as the middle and posterior mediastinum, pleura, neck, and as intra-thyroidal lesions with histological characteristics of thymoma (SETTLE: spindle cell epithelial

tumors of thymic-like epithelium) (10). It has been reported that 17-28% of patients with thymoma present with a second synchronous or metachronous malignancy, including lung, thyroid, gastrointestinal, prostate, lymphoma, brain, sarcoma, and leukemia, especially non-Hodgkin's lymphoma, with an overall risk 1.5-7.1 times greater than population controls (25-27). Therefore, it is important to consider these factors in the evaluation of the patient with a possible thymic neoplasm.

To further evaluate the broad diagnostic spectrum of the anterior mediastinal mass, Chest computed tomography (CT) with intravenous contrast, serum beta-HCG, alpha fetoprotein (AFP), complete blood count, thyroid stimulating hormone (TSH), triiodothyronine (T3) and thyroxine (T4) levels should be obtained (5-7). Beta-HCG and AFP levels can be used to rule out germ cell tumors, and TSH, T3, and T4 levels to rule out mediastinal goiter (5-7). Because so many of these lesions are asymptomatic, they are often incidentally discovered on chest imaging for other diagnostic and screening purposes. For patients who cannot receive iodinated contrast, magnetic resonance imaging of the chest may play a role. Combined PET-CT may play a role for determining whether distant metastases are present, and it provides the benefit of correlation with anatomic structures as opposed to PET scan alone (28).

On CT scan, thymoma usually appears as a well-defined round or oval mass located anterior to the great vessels and heart, below the left innominate vein (15). Features suspicious for malignancy include vascular invasion, encasement, and pleural dissemination (15) (Figure 1). It has been reported that smooth contours and round shape suggest type A thymoma; irregular margins and enlarged lymph nodes suggest thymic carcinoma; calcifications suggest B1, B2 and B3 types; and the combination of homogenous enhancement and a high degree of enhancement suggest type A or AB thymoma; however, the false negative and false-positive rates are too high to apply these correlations broadly (29). There have been similar reports between the correlation of MRI characteristics and thymoma subtypes (29). On PET, there have been reports of higher maximum standard uptake value for B2 and B3 compared to A, AB, and B1, but still lower than C; that a value of 6.2 can differentiate thymoma from thymic carcinoma, and >7.1 completely differentiates the two (29,30). Therefore, combining these modalities may provide diagnostic value before considering biopsy (29).

In situations where clinical presentation and imaging cannot establish a diagnosis, where a patient requires induction chemotherapy, or where a metastatic lesion is suspected, tissue diagnosis is required (31-33). However, the biopsy should not violate the pleural space because of the propensity for pleural dissemination in thymic neoplasia (31-33). Although CT-guided needle biopsy is an option, the aspirated sample is often difficult to distinguish by cytology from other subtypes with a sensitivity of less than 60% (31-33). Core cutting biopsy that obtains

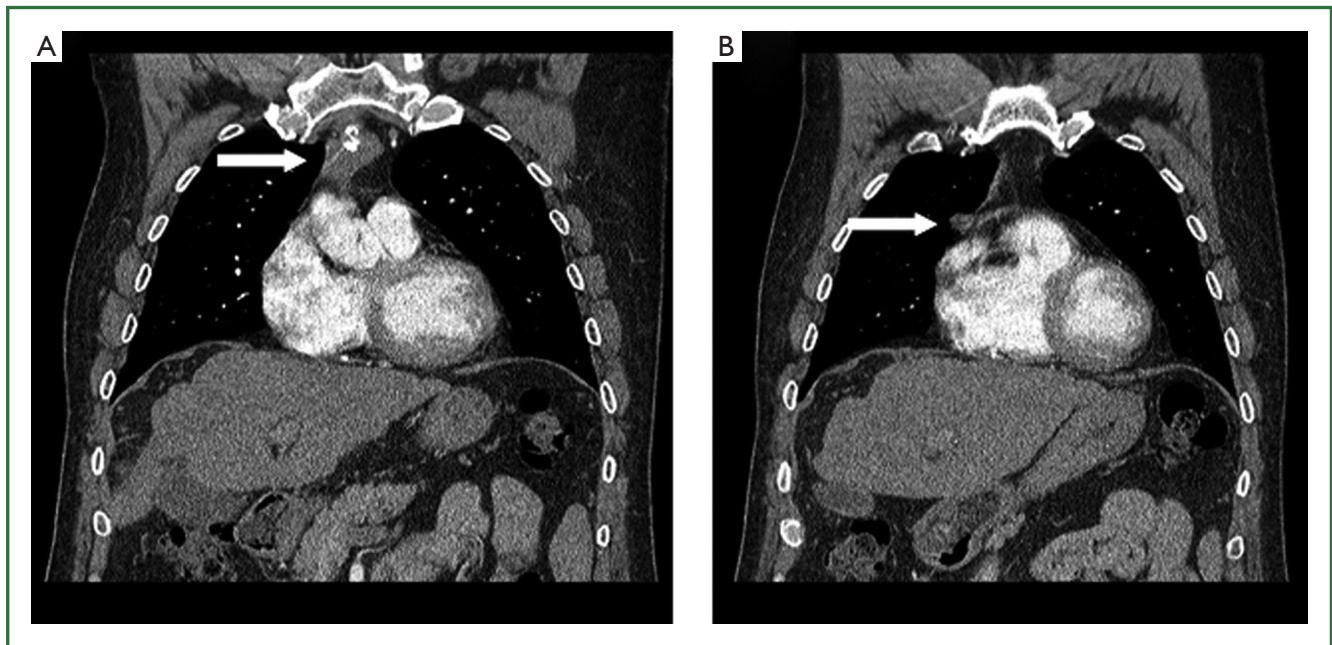


Figure 1. A. Chest CT angiogram demonstrates an anterior mediastinal mass with calcifications (arrow); B. Chest CT scan demonstrates enlarged mass adjacent to the right atrium suspicious for metastatic spread versus contiguous extension (arrow).

Table 1. TNM classification.

T	Primary tumor
TX	Primary cannot be assessed
T0	No primary tumor present
T1	Completely encapsulated tumor
T2	Pericapsular connective tissue tumor invasion
T3	Surrounding structure tumor invasion
T4	Pleural or pericardial tumor dissemination
N	Regional lymph nodes
NX	Lymph nodes cannot be assessed
N0	No lymph node metastasis
N1	Anterior mediastinal lymph node metastasis
N2	Intra-thoracic lymph node metastasis outside of the anterior mediastinum
N3	Scalene and/or supraclavicular lymph node metastasis
M	Distant metastasis
MX	Metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis present

Table 2. TNM Staging system.

Stage I	T	N0	M0
Stage II	T	N0	M0
Stage III	T	N1	M0
	T	N1	M0
	T	N0, I	M0
Stage IV	T	Any N	M0
	Any T	N2, 3	M0
	Any T	Any N	M1

Staging and classification of thymic neoplasms

One of the challenges in managing patients with a thymic neoplasm is the controversy of the histology and staging classification systems of these lesions. Part of the reason is that there has been difficulty in correlating histological characteristics with clinical outcome (34). It is generally agreed that thymoma and thymic carcinoma originate from thymic epithelial cells and that the variable amount of lymphocytes present within the tumor is considered reactive (23). Historically, the Benatz classification defined 4 subtypes: lymphocytic, predominantly epithelial, mixed, and spindle cell; however, it provided no significant prognostic information on the course of the disease associated with these subtypes (35). There have also been multiple attempts to establish a TNM classification which correlated with outcome (23,36) (Tables 1,2); however, the

multiple samples can improve the accuracy of the diagnosis (31-33). Larger samples can be obtained by incisional biopsy (e.g., anterior mediastinotomy or video-assisted thoracoscopy) with a diagnostic sensitivity >90% (31-33).

Table 3. Modified Masaoka staging system.

Stage I	Macroscopically and microscopically completely encapsulated
Stage II	(I) Microscopic transcapsular invasion (II) Microscopic invasion into surrounding tissues but not through mediastinal pleura or pericardium
Stage III	Microscopic invasion into adjacent organs (III) Without great vessel invasion (IV) With great vessel invasion
Stage IV	(V) Pleural or pericardial dissemination (VI) Metastasis lymphogenous or hematogenous

Table 4. WHO histological classification system.

Type	Synonyms
Type A	Spindle cell or medullary thymoma
Type AB	Mixed thymoma
Type B1	Lymphocyte-rich or lymphocytic or predominantly cortical thymoma
Type B2	Cortical thymoma
Type B3	Well-differentiated thymic carcinoma or epithelial thymoma or squamoid thymoma
Type C	Heterogenous thymic carcinoma

system most widely accepted is the one proposed by Masaoka *et al.* in 1981 and modified by Koga in 1994 (4,37) (Table 3).

The Masaoka-Koga staging system takes into account direct tumor invasion into the capsule and surrounding structures, intra- versus extra-thoracic spread, including lymphatic dissemination, and this system does so while having been validated and correlated with the World Health Organization (WHO) histological classification system (16,38-40) (Tables 1-4). This combination relates thymoma epithelial cells to the differentiation process in the medullary and cortical areas of the normal gland (16,38-40). The WHO system categorizes the morphology of the epithelial cells and the lymphocytic/epithelial ratio into 3 types: A, B, and C (41) (Table 4). In fact, as lesions progress from A to C, there is also a progressive deterioration of the prognosis. However, the problem with this system is that there is a low intra- and inter- observer correlation of actually implementing the WHO classification system, resulting in poor reproducibility, especially among pathologists with limited experience in staging thymic neoplasms (23). Because a meta-analysis has demonstrated significant survival differences between four groupings of these categories (i.e. A+AB+B1 versus B2 versus B3 versus C) (23), Suster and Moran proposed to simplify the WHO system to define lesions as well-differentiated tumors for the traditional thymoma, poorly differentiated tumors for the traditional thymic carcinoma, and atypical thymoma for lesions with intermediate features (42,43).

Aside from staging and histology, there are other important

prognostic factors to consider. First, completeness of resection is extremely important for prognosis, even for Stage III and IV lesions (44). Second, although MG once was associated with worse prognosis, advances in managing MG are such that most patients are diagnosed as stage I and II, and have a better outcome (19,24,45), whereas hypogammaglobulinemia and red blood cell aplasia are associated with a worse prognosis (46). Third, although the presence of lymph node metastasis worsens prognosis, it only occurs in <2% of cases and therefore its applications for staging all patients has thus been limited (46). Fourth, great vessel involvement worsens prognosis and increases the risk of recurrence with some even arguing that stage III be further subdivided based upon this criterion (45,47,48). Fifth, early recurrence has also been reported to be a poor prognostic indicator of overall survival (16).

Multimodality approach to thymic neoplasms: surgery, radiation, and systemic therapy

The gold standard for the management of all thymic neoplasms regardless of stage remains complete surgical resection (16). The operation is usually performed through a median sternotomy (Figure 2) and the entire thymus gland with all the surrounding mediastinal fat bordered laterally by the phrenic nerves should be removed (49) (Figure 3). Complete thymectomy is favored even in cases of only partial thymic gland involvement because of

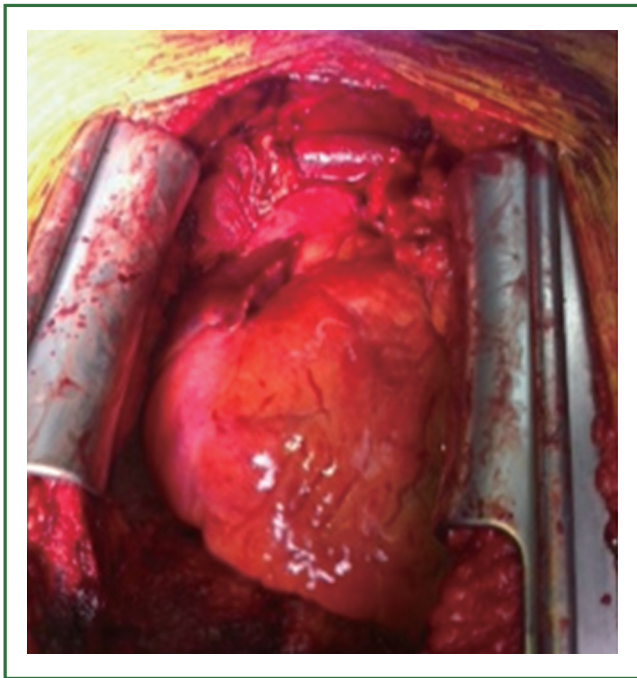


Figure 2. The surgical field after radical complete thymectomy via median sternotomy.

some reports of improved survival and multifocal thymoma (39). The oncologic equivalency of thoracoscopic and robotic assisted approaches has been reported, so long as capsule integrity has been maintained and tumor seeding has been prevented (49-52). However, it should be noted that 40% invade surrounding structures which may limit the ability to achieve R0 margins (16). Operative morbidity and mortality are generally reported as 20% and 2% respectively, with the 10-year overall survival and disease free survival rates of 90% and 94% for stage I; 70% and 88% for stage II; 55% and 56% for stage III; and 35% and 33% for stage IV, respectively (16).

Stage I lesions are managed by resection alone, with annual surveillance for recurrence by Chest CT for at least 10 years; however, for Stages II-IV, adjuvant therapy is an important consideration (47,53,54). Stage II lesions with capsular and mediastinal fat involvement have been reported to have recurrence and metastatic dissemination rates as high as 11%, even despite radiotherapy (55). Stage II B2, B3 and C lesions demonstrate a high extra-mediastinal recurrence rate and thus may require systemic therapy (56).

The oncologic principles of managing stage III lesions rest upon *en bloc* resection as a cornerstone, but only 50% achieve R0 margins due to the structures involved, ranging from 0-89% as

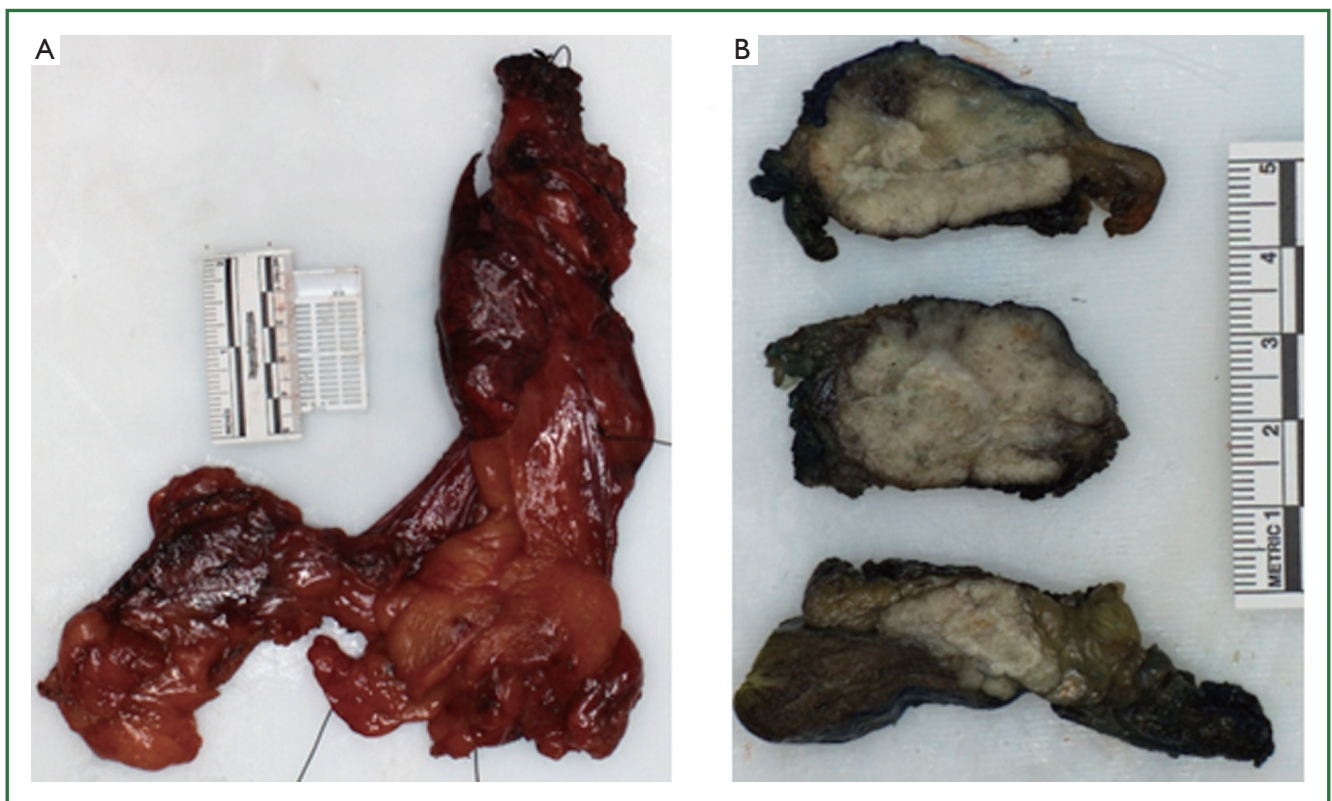


Figure 3. A. The gross surgical specimen demonstrating the thymic neoplasm resected *en bloc* with all the adjacent fat; B. The gross cross section demonstrates the mass was resected with surrounding fat tissue.

determined by surgeon philosophy, judgment, experience and skill (57,58). Even with R0 resection, 10-year survival ranges from 35-53% with a 50% recurrence rate within 5 years, even with adjuvant radiotherapy, and chemotherapy is often also considered (16,59).

Stage IV lesions are also approached surgically in the setting of a multimodality approach. Because initial 5 yr and 10 yr survival rates were 50% and 0%, respectively, with the pleura being the favored host site, some have advocated a more aggressive approach including pleurectomy and extra-pleural pleuropneumectomy (EPP), systemic or intra-pleural chemotherapy, photodynamic therapy, and irradiation, with some improved results (4,60-62). In fact, because 75% of recurrences are in the form of multiple pleural implants, some advocate not opening the mediastinal pleura and that minimally invasive transpleural approaches be used when possible (19,21). When recurrence occurs, complete resection, such as with EPP, has been reported to produce 72% survival at 5-years (63,64). Patients with a second recurrence are also offered surgery, but in the setting of multimodality therapy (63).

Radiotherapy is an important component of the multimodality approach to thymic neoplasms. For patients with unresectable disease, a dose of 60-70 Gy is recommended, whereas adjuvant radiotherapy doses range from 45-50 Gy for clear or close margins, 54 Gy for R1 margins, and 60 Gy or greater for R2 margins, 1.8 to 2.0 Gy per daily fraction (65-68). To prevent extra-mediastinal recurrence within the thorax, hemi- or entire thorax irradiation in addition to mediastinal irradiation, as opposed to mediastinal irradiation alone, has been advocated after Uematsu *et al.* reported 5 year relapse-free and survival rates of 100% and 96% versus 74% and 66%, respectively (69). However, this more aggressive approach did produce a 13% rate of symptomatic irradiation pneumonitis (69). It should be noted that care must be taken to adjust the dose when considering adjacent structures such as the heart (limit ≤ 30 Gy) as these patients as a population are younger and thus will potentially endure more of the long term effects of radiation than, for example, patients with non-small cell lung cancer from whom those dose limits for surrounding normal tissue are derived (65-68). In either case, the clinical target volume for adjuvant radiotherapy should be carefully reviewed with the thoracic surgeon to target the field and any potential sites of residual disease. Neoadjuvant radiation has not been advocated because reports have not demonstrated a survival advantage and because of the concerns of postoperative sternal and respiratory complications (21,58).

Although the role of radiotherapy has not been evaluated in prospective randomized trials, thymic neoplasms are radiosensitive and there are many retrospective reports which guide treatment. Stage I tumors completely resected do not require adjuvant radiotherapy. Because stage IIB tumors have a

higher recurrence rate, especially WHO B2, B3 and C, there are reports of decreasing recurrence from 29-36.4% to 0-8% with radiotherapy, but 92% of the recurrences in the irradiated group were pleural dissemination (57,70,71). However, the role of radiation in stage II disease remains controversial and increasing evidence may be suggesting a lack of a benefit (47,53,54,72). For stages III and IVA, there are reports of adjuvant radiation reducing recurrence after complete resection from 50-53% down to 0-20% (73-75). After incomplete resection, studies have reported 5-year recurrence rates of 79% as opposed to 0% mediastinal failure rates at 5 years with adjuvant radiotherapy (21,73).

Patients with unresectable or recurrent thymic neoplasms are considered candidates for systemic chemotherapy; however, because of the rarity of these lesions, prospective trials comparing the different agents in the literature are rare (16,21,76-81). Patients who present with locally advanced disease can be restaged after treatment with chemotherapy to either undergo surgery if they are resectable, or to consider further radiotherapy and chemotherapy if they did not respond adequately (16,21,76-81). Patients with solitary metastasis should be evaluated for metastasectomy if complete resection can be achieved in the context of complete radical thymectomy with multimodality therapy.

First line therapy regimens include cisplatin, doxorubicin and cyclophosphamide (CAP); CAP with prednisone; cisplatin, doxorubicin, vincristine, and cyclophosphamide (ADOC); cisplatin and etoposide (PE); etoposide, ifosfamide, and cisplatin (VIP), or carboplatin and paclitaxel (16,21, 76-81). The last regimen is preferred for thymic cancer because it has demonstrated the highest response rate (82,83). Despite having 6 options for thymoma, the best outcomes have been reported using cisplatin/doxorubicin-based regimens, and many recommend CAP (53,84). However, PE, VIP, and carboplatin/paclitaxel may provide better options for those who cannot tolerate the more aggressive regimens (83). Second line therapy usually includes etoposide, ifosfamide, pemetrexed, octreotide, prednisone, 5-fluorouracil and leucovorin, gemcitabine, and paclitaxel (16,21,76-81); however, it should be noted that strong data are lacking regarding these regimens for thymic cancer (76).

Because of the importance of complete resection for prognosis, these agents have been employed in the setting of induction chemotherapy to convert unresectable tumors to resectable, but the exact selection criteria for induction chemotherapy have yet to be determined. Response rates have been reported as high as a 20% for complete pathologic response in the final specimen and 43% for radiological response and it is well tolerated in MG, with reports of producing MG remission in same cases (85). However, it should be noted that these studies are limited by small sample size. Thymic cancer is less responsive

to systemic chemotherapy and its inclusion in some of the studies may have contributed to decreased survival (86-88). There is some evidence that steroids and octreotide may have a role in treatment as well; however, these agents have not been fully evaluated and are still under investigation (70,89).

In the era of targeted therapy, there have been investigations into specific targets in thymic neoplasms which may improve response to therapy. The presence of epidermal growth factor receptor (EGFR) mutations in thymic tumors is rare and is thought to explain why there have been poor responses reported to EGFR inhibitors (90). However, with the identification of HRAS/KRAS mutations that predict anti-EGFR drug resistance, there is a potential to determine which patients may respond to such agents (91-126). There is also a small subset of *kit* mutation containing thymic neoplasms which may respond to tyrosine kinase inhibitors (91,127-139). Similarly, insulin-like growth factor-1R expression in thymic tumors has led to ongoing Phase II trials to determine the efficacy of antibodies to this receptor (140).

There is also promise in the utilization of multi-kinase inhibitors, including those that target the vascular endothelial growth factor receptors (141). Because of the third and fourth pharyngeal pouch embryonic endodermal derivation of the thymus, it has been hypothesized that there may be oncogenic and therapeutic relationships to other pharyngeal neoplasia, and therefore, experimental studies targeting the COX-2 system which demonstrated promise on hypopharyngeal tumor cell lines may show future promise in thymic neoplasms (138,142). However, other markers which are over-expressed in thymic neoplasms that predict sensitivity to 5-fluoruracil-based agents, namely thymidine synthase and dihydropyrimidine dehydrogenase, failed to produce encouraging results in clinical studies (143). Therefore, it is important for a multidisciplinary approach to the study and treatment of this complex disease which includes basic scientists, oncologists, radiotherapists, pathologists and thoracic surgeons.

Conclusions

In summary, thymic neoplasms are a rare group of heterogeneous lesions of the anterior mediastinum with a broad range of presentations and clinical courses, which require a high index of suspicion to appropriately diagnose and treat. Although diagnosis can often be made by clinical presentation and imaging alone, biopsy may be required to make the diagnosis or prior to the initiation of multimodality therapy. Surgical complete radical resection remains the gold standard of therapy, but it is important to consider it in the context of multimodality therapy, especially for stage II-IV disease. While thymic neoplasms are radiosensitive, these lesions do not respond as well to chemotherapy, and yet systemic therapy still does play

an important role. Although there is no magic bullet in the treatment of systemic disease, as research continues there are some interesting possibilities for the future management of thymic neoplasms, especially in the era of targeted therapy.

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