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Thymoma

Treatment of Early Stage Thymic Tumors: Surgery and Radiation Therapy

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Opinion statement

Tumors of the thymus are an uncommon entity, constituting 30% and 15% of anterior mediastinal masses in adults and children, respectively. The majority of these tumors are thymomas, with thymic carcinomas less common, and thymic carcinoids exceedingly rare. Recognition of the distinct clinicopathologic behavior of various thymic neoplasms is crucial to providing optimal treatment. Evidence guiding the treatment of early stage thymic tumors is limited secondary to the low incidence and resulting lack of randomized data. Proper management requires a careful analysis of the available literature with particular attention paid to limitations of the existing studies. This article provides a discussion of the presentation, evaluation, diagnosis, surgical techniques, and treatment outcomes relevant to early stage thymomas, thymic carcinomas, and thymic carcinoid tumors. The role of radiation therapy in the management of early stage thymic tumors remains controversial and is discussed in detail.

Thymic neoplasms

Although lymphomas, carcinoid tumors, and germ-cell tumors all may arise within the thymus, only thymomas, thymic carcinomas, and thymolipomas arise from true thymic elements.

Thymic neoplasms constitute 30% and 15% of anterior mediastinal masses in adults and children, respectively, with thymomas being the most common [1, 2]. Ninety percent of thymomas occur in the anterior mediastinum, and the remainder arise in the neck or other areas of the mediastinum including, rarely, the heart [3].

Thymomas grossly are lobulated, firm, tan-pink to gray tumors that may contain cystic spaces, calcification, or hemorrhage. They may be encapsulated, adherent to surrounding structures, or frankly invasive. To unify the pathology of thymic neoplasms, the World Health Organization (WHO) adopted a new classification system for thymic neoplasms (Table 1)

Table 1. World Health Organization classification system for thymic epithelial tumors

Tumor type	Cells	Clinicopathologic classification	Histologic terminology
A	Spindle or oval	Benign thymoma	Medullary
B	Epithelioid or dendritic	Category I malignant thymoma	Cortical; organoid
B1			Lymphocyte-rich; predominately cortical
B2			Cortical
B3			Well-differentiated thymic carcinoma
AB		Benign thymoma	Mixed
C		Category II malignant thymoma	Nonorganotypic; thymic carcinoma, epidermoid keratinizing and nonkeratinizing carcinoma, lymphoepithelioma-like carcinoma, sarcomatoid carcinoma, clear cell carcinoma, basaloid carcinoma, mucoepidermoid carcinoma, undifferentiated carcinoma

[4–6]. WHO-type A-B2 tumors are more likely to present with loco-regional disease, compared to WHO-type B3-C tumors [7, 8•]. Based on the Masaoka thymoma staging system, stage I and II are considered early stages. In stage I, the tumor is macroscopically encapsulated and without microscopic capsular invasion. In stage II, the tumor invades into the surrounding fatty tissue or mediastinal pleura or exhibits microscopic capsular invasion.

Thymoma

Presentation

- Nearly one-half of thymomas are asymptomatic and discovered incidentally. In symptomatic patients, 40% have symptoms of myasthenia gravis whereas others complain of chest pain and symptoms of hemorrhage or compression of mediastinal structures [9].

Associated systemic syndromes

- Myasthenia gravis (MG) is the most common autoimmune disorder associated with thymoma, occurring in 30–50% of patients [10, 11]. Symptoms include diplopia, ptosis, dysphagia, and fatigue. Ocular symptoms are the most frequent initial complaint, eventually progressing to generalized weakness in 80%. Some improvement in myasthenic symptoms almost always occurs after thymectomy, but complete remission rates vary from 7% to 63% [12]. Patients with MG and thymomas do not respond as well to thymectomy as do MG patients without thymomas. Other less commonly associated systemic syndromes include red cell aplasia and hypogammaglobulinemia.

Radiographic imaging studies

- Radiological studies play a central role in the evaluation of thymoma. Since many patients are asymptomatic at presentation, a widened mediastinum or loss of the normal anterior clear space on the lateral film of a routine chest radiogram may be the first sign of disease. In such a patient, an intravenous contrast-enhanced spiral computed

tomography (CT) scan should be obtained as the next step to accurately assess the nature of the lesion (cystic vs. solid), detect fat and calcium, determine the relationship to surrounding anatomic structures, and, in some instances, predict invasiveness of tumors [13, 14].

- Recent advances in EKG-gating and real-time magnetic resonance imaging (MRI) and angiography (MRA) have dramatically increased the usefulness of this modality in the evaluation of mediastinal masses. Not only superior to CT in defining vascular involvement, MRI can detect subtle differences in tumor contour, capsule clarity, and intratumoral signal (low) that correlate with the WHO classification of thymomas [15].
- Positron emission tomography (PET) is well established for the assessment of mediastinal lymphoma, and its utility in clarifying the invasiveness of thymoma is gaining general acceptance [16, 17].

Serology and chemistry

- All young male patients with an anterior mediastinal mass should have serum testing for α-fetoprotein (AFP), human chorionic gonadotropin-β (β-HCG), and lactate dehydrogenase (LDH). Although these levels are normal in mature teratoma, malignant germ-cell tumors will have significant elevations and thus establish this diagnosis and thereby excluding the diagnosis of thymoma.

Invasive diagnostic tests

- Generally, biopsy of a discrete anterior mediastinal mass that is suspected to be thymoma is unnecessary. Theses situations include: (1) patient over 40 years of age without clinical symptoms or signs of lymphoma, and with normal AFP and β-HCG and (2) the mass is associated with MG. When the anterior mediastinal mass cannot be distinguished from one of the other malignant tumors of the anterior mediastinum (e.g., a lymphoma, germ-cell tumor, or metastatic cancer) or is potentially nonresectable, a biopsy is indicated to establish the diagnosis before making any decision regarding therapy.
- CT- or ultrasound-guided percutaneous needle biopsy is now a standard in the initial evaluation of mediastinal masses [10]. Although fine-needle specimens are often adequate to distinguish carcinomatous lesions, core biopsies are recommended for most mediastinal neoplasms, especially lymphoma and thymoma. Recent series report diagnostic yields for percutaneous needle biopsy in excess of 90% [18]. Complications include simple pneumothorax (25%), hemoptysis (7–15%), and pneumothorax requiring chest tube placement (5%) [18].
- Surgical procedures occasionally are still required in the diagnosis of mediastinal tumors. Mediastinoscopy is a relatively simple procedure with a diagnostic accuracy of more than 90% for biopsies of the upper middle and, in some hands, the anterior and posterior mediastinum [19]. Anterior parasternal mediastinotomy (Chamberlain procedure) yields a diagnosis in 95% of anterior mediastinal masses and may be accomplished under local anesthesia [19, 20]. Thoracoscopy is a minimally invasive procedure that provides a diagnostic accuracy of nearly 100% in most areas of the mediastinum; however, transpleural biopsy of mediastinal masses is generally not recommended due to

risks of tumor seeding of the pleural space [19]. Currently, thoracotomy is rarely necessary as a diagnostic procedure.

Treatment

- Thymomas are slow-growing neoplasms that should be considered potentially malignant-acting (i.e., capable of invasion and distant spread). Depending on the stage, surgery and radiation all may play a role in their management. For early stage thymoma (Masaoka Stage I and II), complete surgical resection is the mainstay of therapy, and it is the most important predictor of long-term survival [21••–23].

Surgery

Transcervical thymectomy

While transcervical thymectomy has been well described in patient with MG without thymoma, it is generally not recommended in patients with thymic tumors.

Median sternotomy

This is the most widely employed approach to thymectomy. Although full sternotomy is typical, partial upper sternotomy with extension of the bony incision into the third or fourth intercostals space also has its advocates [24]. Bilateral anterolateral thoracotomies with transverse sternotomy, or "clam-shell procedure," is preferred with laterally displaced larger tumors.

Minimally invasive thymectomy

Video-assisted thoracoscopy. Experience has been gained with minimally invasive approaches for performance of thymectomy in patients with MG and thymoma since the early 1990s [25–28]. The advantages of this approach include less postoperative pain, less pulmonary dysfunction, no chest tubes are required, better cosmesis, and shorter hospitalization. Video-assisted thoracoscopic technique includes right-sided or bilateral approach. The right-sided approach is more commonly performed because more room is available for maneuvering within the right thoracic cavity. Also, the superior vena cava serves as a landmark for initiation of the surgical dissection and for identification of the phrenic nerve and nominate vein.

Robotic-assisted thymectomy. More recently, robotic-assisted surgery has been used for thymectomy and various centers have shown that it can be performed safely and effectively [29•–32]. In addition to the benefits of video-assisted thoracoscopic approach, robotic-assisted approach provides added advantages: (1) improved dexterity of instruments with 7 degree of freedom and 360 degree rotation, (2) high-resolution and real-time video image with stereoscopic view, and (3) filtering of hand tremors allowing greater technical precision. The harmonic scalpel is also an available accessory instrument for the robot, which provides further versatility in tissue handling, dissection, and superior hemostasis. In an anatomic area such as the anterior mediastinum with limited and finite space, the added dexterity and improved visualization allows for complete removal of all possible thymic tissue with minimally invasive techniques and maximal cosmetic results.

It is generally accepted that whatever approach is used, completeness of thymectomy is mandatory to obtain optimal clinical results. During surgery, a careful assessment of areas of possible invasion and adherence should be made. Extended total thymectomy, including all tissues anterior to the pericardium from the diaphragm to the neck and laterally from phrenic nerve to phrenic nerve, is recommended in all cases.

Treatment outcomes

- Complete surgical resection is associated with an 82% overall 7-year survival rate, whereas survival with incomplete resection is 71% and with biopsy alone is only 26% [33]. Survival after complete tumor resection has been similar in patients with noninvasive and invasive thymomas in several studies [21••, 22]. Patients with MG and thymoma have a 56–78% 10-year survival rate and a 3% recurrence rate with 4.8% (1.7% since 1980) operative mortality after extended thymectomy [23, 34•].

Radiation therapy

- The place of radiotherapy (RT) in the adjuvant treatment of thymic neoplasms remains controversial. The rarity of these tumors precludes large-scale prospective trials, and as a result, treatment recommendations are based upon retrospective reviews and consensus opinion. Here, we review the role of external beam radiation in the adjuvant therapy of early stage thymoma.
- Stage I thymomas are encapsulated tumors without macroscopic spread or microscopic capsular invasion. A complete surgical resection is nearly always achievable, yielding a local control rate that approaches 100% [21••, 35•–37••]. Histologic analysis reveals that most stage I thymomas are WHO subtype A or AB; these tumors tend to exhibit indolent clinical behavior [36]. The excellent local control and overall survival obtained with surgery alone render adjuvant RT unnecessary.
- The optimal management of stage II thymomas is a subject of ongoing debate. It is widely acknowledged that stage II lesions with positive margins should receive post-operative RT. Defining a consensus for completely resected tumors (R0) has been difficult. Some endorse treating all stage II lesions with adjuvant RT. Support for this recommendation comes in two forms. Some authors, such as Curran, note unacceptably high rates of local recurrence after surgery alone. Curran reported an actuarial recurrence rate of 47% at 5 years in 18 stage II patients not receiving RT after R0 resection. Curran goes on to note that the single R0, stage II patient who received RT did not fail [35•]. The second type of evidence interpreted to support adjuvant RT after R0 resection of stage II thymoma is found in series where all patients received post-op RT. After complete resection and adjuvant RT, excellent local control rates ranging from 90% to 98% have been reported [23, 38–40]. However, the necessity of adjuvant therapy has been questioned in contemporary series. The largest series by Kondo et al. consists of 1,320 patients from 115 institutions. Contained

within this series are 206 patients with completely resected stage II thymoma. Eighty-six patients received RT, 120 did not, and recurrence rates were 4.7% vs. 4.1%, respectively [21••]. Mangi et al. reviewed 49 patients with completely resected stage II thymoma; 35 received adjuvant RT, 14 did not. Local recurrence rates were 2.9% vs. 0%, respectively [41]. Singhal et al. published an analysis of 40 patients with completely resected stage II thymoma; 20 received adjuvant RT. There were no local failures in either group [37••]. Rena et al. reported on 58 patients, 32 treated with complete resection alone, and 26 with resection plus adjuvant RT. Local recurrence was 6.2% vs. 11.5%, respectively; this difference did not reach statistical significance [42•].

- The recent literature suggests that RT does not confer additional local control when added to a meticulous R0 resection for stage II thymoma [21••, 37••, 41, 42•]. Hence, recommending adjuvant RT for all stage II thymomas is discouraged. High-risk histologic subtypes (B2 and B3), pleural invasion, and adhesions are factors that demand attention; if present there may be a role for adjuvant RT [36, 38]. In summary, adjuvant RT should be recommended for all patients with stage II thymoma and positive/questionable margins. RT should also be considered for patients with pleural adhesions or high-risk histology. Patients who undergo an R0 resection and do not have high risk features should be observed.
- Modern radiotherapy techniques are essential to maximize treatment benefit while minimizing toxicity. Utilization of 3D conformal therapy or IMRT allows clinicians to respect normal tissue guidelines without compromising target coverage. The organs at risk include the heart, lungs, esophagus, and spinal cord. The following tolerances assume standard fractionation. Spinal cord dose should be kept <45–50 Gy. The volume of lung receiving 20 Gy should be kept < 37% and mean lung dose should be <20 Gy. Mean esophageal dose should be kept <34 Gy, but short segments (10 cm or less) can tolerate up to 60 Gy. Up to 1/3 of the heart can receive 60 Gy, up to 2/3 can receive 45 Gy, and the entire heart can tolerate 40 Gy.
- The optimal dose to deliver to the tumor is unclear. Multiple studies have failed to prove a dose response beyond 40–45 Gy. A recent publication noted that doses in excess of 50 Gy were significantly associated with improved survival. It should be noted, however, that local control was unaffected by dose, rendering it likely that the survival advantage observed was a statistical anomaly rather than a genuine dose response [43•]. It is generally accepted that doses of 45–50 Gy are sufficient for the control of microscopic disease. Doses of 60 Gy or more are considered appropriate for gross disease/definitive treatment.

Other thymic neoplasms

Thymic carcinoma

- Thymic carcinoma is a rare aggressive thymic neoplasm. Extensive local invasion and distant metastases are common. The prognosis of thymic carcinoma is poor because of early metastatic involvement of pleura, lung, mediastinal, cervical and axillary lymph nodes, bone, brain, and liver [44, 45]. The overall survival rate at 5 years is approximately 35% [44, 46]. Surgical resection remains the mainstay of treatment. Multimodality therapy including chemotherapy is often employed secondary to the high rates of local recurrence and distant

metastases. Recent series illustrate the poor prognosis of these neoplasms as well as the ability of multimodality treatment to achieve reasonable local control. Mornex et al. report on a series of 90 patients treated with varying combinations of surgery, RT, and chemotherapy. All patients received either partial resection or biopsy. Five- and ten-year survivals were 51% and 39%, with local control achieved in 66% of patients at 8 years. Extent of resection was found to correlate strongly with survival [47]. Ogawa et al. published a series of 40 patients with thymic carcinoma. All patients received radiation, 27 received a resection of some sort. Of the 16 patients who underwent an R0 resection, local control was 100%. Despite reasonable local control, 5- and 10-year survival for the whole cohort was 38% and 28%, respectively. Again, extent of resection was a significant predictor of survival [48]. Hsu et al. reported results for their cohort of 26 patients, 17 of whom received R0 resection and all of whom received post-operative radiotherapy. Five-year overall survival was 73%, and 5-year local control was 91% [49]. Based on these results, radiotherapy to a dose between 50 and 60 Gy is deemed beneficial in the adjuvant setting. The optimal combination of surgery, chemotherapy, and radiation has yet to be defined, but treatment of thymic carcinoma within a multimodality paradigm is recommended.

Thymic carcinoid

- Thymic carcinoid tumors are rare, male predominant tumors that are associated with Cushing's syndrome, multiple endocrine neoplasia, and, rarely, carcinoid syndrome [50–56]. Thymic carcinoids represent 2–4% of anterior mediastinal tumors [57]. Approximately 200 cases have been reported to date since first being described in 1972 by Rosai and Higa [50]. Outcome data is limited, with virtually all reports consisting of small series of patients. It has been recognized that thymic carcinoids represent a distinct clinicopathologic entity from their counterparts of the same name arising elsewhere in the body. Whereas carcinoid tumors of the lung tend to be indolent and unlikely to metastasize, thymic carcinoids have a poor prognosis, are locally aggressive, and have demonstrated metastatic rates ranging from 40% to 82% [57–61]. In the largest series to date, overall 5- and 10-year survival was 28% and 10%, respectively [58].
- It is known that completeness of resection is a strongly prognostic factor for overall survival [57, 59–61]. As such, surgical resection is a fundamental component of treatment. The evidence supporting radiotherapy in the adjuvant, neoadjuvant, or definitive setting is extremely limited. There are series and case reports suggesting that the addition of post-operative radiotherapy may improve local control following complete resection. Tiffet et al. illustrates this point with a series of 12 patients treated with maximal resection. In nine patients, an R0 resection was achieved; three of nine received adjuvant radiotherapy and none experienced a local recurrence. There were four local recurrences in the six patients following R0 resection who did not receive adjuvant RT. This evidence is anecdotal, but the general trend of improved local control is seen in other small series as well [57]. Hence, maximal resection followed by adjuvant radiotherapy appears to be a reasonable local management strategy.

- The aggressive nature of thymic carcinoid mandates aggressive therapeutic paradigms. Surgery followed by radiation appears to offer a reasonable probability of local control, but these patients remain at high risk for metastatic disease. A multimodality approach to treatment is worth considering. For early stage patients that are resectable at presentation, chemotherapy either before or after adjuvant radiotherapy deserves strong consideration. For patients with locally advanced disease, neoadjuvant treatment with chemoradiation may offer the potential for downstaging and increased resectability. There are no studies investigating the use of neoadjuvant chemoradiotherapy followed by aggressive resection, but there are reports establishing feasibility. A case report by Filosso et al. describes treating a patient with bulky thymic carcinoid to 45 Gy concurrently with four cycles of cisplatin and etoposide; complete resection was achieved [62•].
- In summary, thymic carcinoid is a rare and dangerous clinicopathological entity prone to local progression and metastatic spread. Few patients survive beyond 5–10 years. Treatment should best be approached in a multidisciplinary fashion. Patients resectable at presentation should undergo maximum resection followed by chemotherapy and radiation therapy as the clinical context permits. The optimal radiation dose has not been determined, but doses similar to those employed for thymic epithelial tumors represent a reasonable choice. Patients with locally advanced disease unlikely to achieve an R0 resection may benefit from neoadjuvant chemotherapy and radiation. Optimal agents have not been elucidated, but platinum/etoposide is reasonable.

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