Induction Therapy for Thymoma

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KEYWORDS

• Thymic tumors • Induction treatment • Neoadjuvant • Chemotherapy • Chemoradiation

KEY POINTS

- Although surgery is the mainstay of treatment of most thymic tumors, they are also chemosensitive and radiosensitive.
- Locally advanced thymic tumors may pose challenges to complete resection given the anatomic confines of the mediastinum.
- Induction therapy with chemotherapy or radiation therapy prior to surgery may improve surgical resectability.
- Although response to induction chemotherapy or chemoradiotherapy seems comparable, greater tumor necrosis has been observed after chemoradiotherapy, albeit at a potential cost of higher toxicity.

INTRODUCTION

Thymic neoplasms are rare malignancies with an incidence of approximately 2.2 to 2.6/million/y for thymomas and even less for thymic carcinomas (0.3–0.6/million/y).[1] They represent, however, the most common tumors of the mediastinum encountered by thoracic surgeons, and a notable proportion of these tumors present at an advanced stage. Local invasion into surrounding mediastinal structures (Masaoka-Koga stage III)[2] or intrathoracic metastases to the pleura or pericardium (stage IVA) can pose a challenge to complete resection. In a worldwide data set of 4987 cases assembled by the International Thymic Malignancy Interest Group,[3] approximately 30% of the tumors were Masaoka-Koga stages III and IVA, and 11% of the tumors reported by the Japanese Association for Research on the Thymus were stage III thymomas.[4]

The stage of the tumor and completeness of resection have been consistently found the most significant prognostic factors.[5] Early-stage, localized tumors (Masaoka-Koga stages I and II) are typically treated with surgical resection alone, with prolonged survival outcomes and 10-year overall survival rates of 80% to 90%.[6] The poorer outcomes historically associated with locally advanced stage thymic tumors have led clinicians to use multimodality strategies with the addition of chemotherapy and radiotherapy to surgery.

GENERAL APPROACH TO THE TREATMENT OF LOCALLY ADVANCED THYMIC TUMORS

Thymic tumors are generally considered a surgical disease and a complete resection is the primary goal. Successful treatment of locally advanced tumors requires careful selection of patients and surgical approach and consideration of neoadjuvant therapies that may improve the likelihood of a complete resection.

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The general approach to patients with locally advanced thymic tumors should involve a multidisciplinary evaluation, including the thoracic surgeon, medical oncologist, radiation oncologist, radiologist, pathologist, and neurologist (for patients with concomitant myasthenia gravis). Discussion of the treatment plan in the setting of a multidisciplinary tumor board can greatly facilitate the coordination of care for these challenging cases.

Radiographic evaluation with a high-resolution CT scan with intravenous contrast (preferentially given through the left or right upper extremity to opacify the innominate vein or right brachiocephalic vein if there is concern for invasion of these structures) is essential for delineating the anatomic relationships of the tumor and adjacent organs.[7] The value of PET scanning in these patients remains unclear but may be more helpful in patients with thymic carcinomas to evaluate the extent of disease, given their more aggressive nature and higher propensity towards distant metastasis.[8]

If preoperative therapy is planned, tissue diagnosis is needed before initiating induction treatment. This can generally be obtained through needle biopsy, preferentially a core biopsy.[9] The risk of seeding by the needle is extremely low and certainly no higher than attempts at biopsy via mediastinotomy (Chamberlain procedure) or by thoracoscopy, where cells can be shed into the open pleural space in the course of biopsying the mass. After completion of induction therapy, the patient is restaged with another contrast CT scan to evaluate response to treatment and extent of disease.

INDUCTION CHEMOTHERAPY IN THYMOMA

Thymomas are considered chemosensitive tumors and a variety of combinations of chemotherapy regimens have been reported with varying response rates.[5] The sensitivity of thymomas to chemotherapy was well established by 2 cooperative group trials, 1 examining the cisplatin, doxorubicin, cyclophosphamide (CAP) regimen led by Eastern Cooperative Oncology Group[10] and 1 examining etoposide-cisplatin (EP) led by the European Organisation for Research and Treatment of Cancer[11] in patients with metastatic or unresectable disease. Response rates were notable and comparable with acceptable toxicity across both regimens.[10,11]

In general, the literature on induction therapy is comprised largely of small retrospective case series, but these collectively suggest that combination regimens are well tolerated and a majority of the patients in the reported studies were able to proceed to resection with promising resection rates (**Table 1**). In these studies thymomas have demonstrated marked chemosensitivity with clinical response rates of approximately 62% to 100% and complete resection rates of 22% to 92%.

Unsurprisingly there are no randomized controlled trials on induction therapy in this rare disease, but a few prospective single-arm trials have been conducted and are worth noting. The CAP regimen was used as induction therapy in patients with unresectable thymoma in a single-arm prospective trial published by Kim and colleagues,[12] which included 22 patients with locally advanced disease. Patients received neoadjuvant chemotherapy with CAP and prednisone, followed by resection, postoperative radiotherapy (PORT), and consolidation chemotherapy; 17 patients had some radiographic response and 6 of 16 patients had greater than 80% tumor necrosis on pathologic evaluation. At 5 years, disease-free survival was 77% and overall survival was 95%.

In a phase II study conducted by the Japan Clinical Oncology Group, either dose-dense chemotherapy (cisplatin, vincristine, doxorubicin, and etoposide) or radiation was administered followed by resection. Resectable patients underwent surgery and PORT whereas unresectable patients received radiation only. In the chemotherapy group, 62% of patients had radiographic response and 14% had complete pathologic response.[13]

Lucchi and colleagues[14] reported a prospective analysis of 30 stages III and IVA thymoma patients who underwent induction with cisplatin, epirubicin, and etoposide. They noted 73% response rate and 77% complete resection rate.

More recently multi-institutional collaborations have led to large retrospective database analyses. In a recent report from the Japanese Association for Research of the Thymus, 441 patients with clinical stage III thymoma were evaluated. Among those, 113 received induction treatment. Induction treatment response was 52%; however, induction was associated with worse prognosis. The investigators concluded that this is likely because patients with more advanced disease received induction treatment.[4]

In a report from the European Society of Thoracic Surgeons database,[15] 370 stage III thymoma patients were reported. Induction and adjuvant treatments were administered at the discretion of the multidisciplinary team. Induction was generally administered, however, to patients deemed to have unresectable disease. Most common chemotherapy regimen was cisplatin,