Induction Therapy for Thymic Malignancies

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KEYWORDS

• Thymoma • Thymic carcinoma • Induction therapy
• Neoadjuvant therapy

Thymic malignancies (thymoma and thymic carcinoma) are relatively rare tumors of the chest that express a broad range of biological behaviors. Surgery remains the mainstay of therapy, and complete surgical resection is the primary predictor of long-term survival.[1,2] Although stage-specific overall long-term survival for patients with stage III cancers is significantly lower than that for patients with stage I or II disease, in patients with stage III disease who undergo successful, microscopically margin-negative (R0) surgical resection, survival approaches that of patients with stage I disease[3] (**Table 1**). For early-stage tumors (Masaoka stage I–IIB; **Table 2**), initial therapy with surgical resection to microscopically negative margins is feasible and is the recommended definitive therapeutic modality.[4–8] However, for patients with more advanced disease (stage III or greater), complete surgical extirpation (including contiguous resection of lungs, pericardium, and/or great vessels) with negative margins is more challenging. Whereas most patients with early-stage disease can undergo R0 resection, only 50% to 60% of patients with stage III thymomas taken directly to surgery can successfully be resected to microscopically negative margins.[9–12] It is in the latter subset of patients that induction therapy plays a role.

Although paradigms for adjuvant chemotherapy and radiation for advanced-stage thymomas and thymic carcinomas are well described,[13] the specific role of neoadjuvant therapy for these malignancies is unclear. The rarity of these tumors and the role of surgery as the traditional mainstay of therapy have resulted in a paucity of clinical trials assessing the value of induction therapy for these cancers. There are no randomized controlled clinical trials aimed to assess the benefit of induction therapy, either directly comparing rates of R0 resection with or without induction therapy, or assessing the long-term survival benefits, and we have to extrapolate from the literature to generate Category 2A recommendations for treatment. Nevertheless, reasonable conclusions can be gleaned by careful examination of the existing literature.

SHOULD PATIENTS WITH STAGE III OR GREATER THYMIC MALIGNANCIES RECEIVE INDUCTION CHEMOTHERAPY OR RADIATION?

To answer this question on the basis of the existing literature, several important end points must be examined. Because an R0 resection is the single most important factor for long-term success in the treatment of thymic malignancies, the immediate question is whether or not induction therapy increases the chances for R0 resection. This is difficult to glean when reviewing large numbers of nonrandomized trials. In such an assessment, the selection criteria used to proceed to surgical resection in patients with stage III or greater disease are a significant confounding variable. The rates of R0 resection in patients undergoing attempted curative resection seem higher if patients are carefully selected for surgery, as in the case of studies aimed at assessing the value of induction chemotherapy or chemoradiation, as compared with retrospective analyses of surgical

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Table 1
Stage-specific overall 10-year survival and survival after complete (R0) surgical resection

Stage	Overall 10-Year Survival (%)	10-Year Survival After R0 Resection (%)
I	80	80
II	78	78
III	47	75
IVA	30	42

Data from Regnard J-F, 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.

outcomes alone serving as historical controls. Such selection bias variability between studies may be standardized in part by assessing what percentage of patients who receive induction therapy in a given study actually make it to surgery, but this information is not clearly defined in any given study. Another important and immediate end point is the degree of clinical/radiographic response to therapy (complete response, partial response, stable disease, or disease progression). If consistent clinically apparent responses can be obtained with induction therapy, one might assume that this would translate into higher rates of R0 resection and consequently greater overall survival. As for patients who have stable disease through induction therapy, even the more aggressive thymic malignancies are generally more indolent than lung or esophageal cancers, and differentiating stable disease from disease progression may be difficult because of the short course of many of these studies. Distinguishing the relative value of chemotherapy, radiation therapy, or both in the neoadjuvant setting remains a challenge, and there are no studies that stratify the relative value of these interventions. Despite these inherent shortcomings, a brief review of the existing literature might help us to ascertain the value of induction therapy for patients with stage III or greater thymic malignancy.

Table 3 summarizes several existing induction therapy trials and provides a synopsis of the relative value of induction therapy (chemotherapy, radiation therapy, or chemoradiation) based on the clinical/radiographic response rates, rates of R0 resection, and overall survival. This discussion relates only to advanced-stage (III–IVB) thymic malignancies, because the current recommendation for stage I to IIB lesions is to proceed directly to surgical resection.[13] This discussion also treats advanced-stage thymomas and thymic carcinomas as a single entity; although this has inherent shortcomings, the WHO classification[14] suggests that this is a continuum of the same disease, and there is sufficient overlap in the advanced stages of these entities by way of outcomes and available therapies that supports this discussion. A summary of most of the relevant studies is shown in **Table 3**. A study by Bretti and colleagues[15] is discussed in greater detail to highlight the relative value of the conclusions of such studies and their shortcomings.

Bretti and colleagues[15] reported a series of 63 patients with malignant thymoma who were treated

Table 2
Modified Masaoka clinical staging of thymic malignancies

Masaoka Stage	Diagnostic Criteria
I	Macroscopically and microscopically completely encapsulated
II	(A) Microscopic transcapsular invasion (B) Macroscopic invasion into surrounding fatty tissue or grossly adherent to but not through mediastinal pleura or pericardium
III	Macroscopic invasion into neighboring organs (pericardium, great vessels, lungs)
IV	(A) Pleural or pericardial dissemination (B) Lymphogenous or hematogenous metastasis

From Masaoka A, Monden Y, Nakahara K, et al. Follow-up study of thymomas with special reference to their clinical stages. Cancer 1981;48:2485–92; with permission.