Natural History and Treatment of Malignant Thymoma

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Thymomas are rare, slow-growing neoplasms that are considered to be malignant because of their potential invasiveness. The most widely used staging system is that of Masaoka and colleagues, which takes into account

Introduction

Thymomas are rare neoplasms that arise from tissue elements of the thymus and develop in the anterior mediastinum. Although usually slow-growing tumors, thymomas are considered to be malignant because of their potential invasiveness: Invasion beyond the capsule is a major prognostic factor that correlates with a worse outcome.

Surgery is usually the first step in the management of thymomas, and radiotherapy is used widely for invasive thymomas and by some authors for noninvasive thymomas. Chemotherapy is no longer controversial and should be used more in the future.

Normal Thymus Development

The thymus gland is a lymphatic organ involved in lymphoid cell development and maturation. However, its embryologic origins come from the endoderm as epithelial outgrowths of the lower portion of the third pharyngeal pouches. Cells of these epithelial outgrowths grow into the surrounding mesenchyma and subsequently constitute the medullary areas of the lobules of the thymus.

In some areas, epithelial cells accumulate and undergo keratinization and degeneration, leading to distinct structures called Hassall's corpuscles, which are localized in the medulla of the lobules. Lymphocytes derived from hematopoietic stem cells of the bone marrow are secondarily localized within the spaces between the epithelial cells of the cortex of the lobules. The lymphoid cells are generally concentrated in the periphery of the cortex, while medullary areas of the lobules of the mature thymus contain mostly epithelial cells and few lymphocytes. These epithelial cells have a major role in the production of humoral factors necessary for lymphoid differentiation, which occurs in fetal and early postnatal life.

The thymus gland reaches its maximal size in the adolescent, weighing 30 to 40 g. Lymphoid components gradually disappear after puberty and the gland involutes, leading to a fatty residue. Hassall's corpuscles remain, and the thymus never completely disappears. Although the gland is usually situated beneath the upper part of the sternum, thymic tissue can be found in ectopic areas, such as the retrocarinal adipose tissue.

Pathology

Thymomas emerge from the epithelium of the thymus. The tumors always arise from the epithelial elements, although lymphocytic cells may be present, sometimes in a high percentage. Although epithelial neoplastic cells usually grow slowly and do not show cytologic characteristics of malignancy, all thymomas are considered to be malignant neoplasms because of their potential for invasion.

Immunohistochemical studies of thymomas have shown that the thymic epithelium expresses hormones, HLA antigens, acetylcholine receptor epitopes, and cytokeratin. Such studies have also investigated the tumors' lymphocytic cells and have substantiated the nonneoplastic nature of these cells.

Classification Systems

Several pathologic classifications of thymomas have been proposed. Rosai and Levine System--The most widely used classification system is that of Rosai and Levine,[1] which defines thymomas as neoplasms of thymic epithelial cells, regardless of the
presence of a lymphoid component. In 1978, Rosai and Levine modified the definition such that thymic tumors containing cells with the cytologic aspect of malignancy were separately classified as thymic carcinomas,[2] which have a very different clinical outcome.[3,4] Walker et al recently[5] summarized the classification system of Rosai and Levine. Thymomas are divided into three types depending on the predominant cell-type. The tumor is called a lymphocytic thymoma or epithelial thymoma if the predominant cells derive from the lymphocytes or epithelial cells, respectively. If these two cellular components are found in equal parts, the tumor is designated a lymphoepithelial, or mixed, thymoma. In all cases, the number of mitotic cells is low.[6,7] Some also suggest a spindle-shaped type[8] and an oval-cell type, which are thought to be variants of the principal types.

The prognostic significance of pathologic classification is controversial. Histologic aspects of noninvasive and invasive tumors can be identical,[9-12] and the division into lymphocytic, epithelial, or lymphoepithelial types may remain subjective. The supposed influence of histologic subtypes disappears when linked with strong prognostic factors, such as stage or extent of surgical resection.[4,13] Whereas some reports demonstrate that epithelial[7,14] or lymphoepithelial subtypes have a poor outcome,[3] others associate lymphocytic or spindle-cell subtype with a favorable outcome.[15-17]

**Classification by Malignant Cell Ontogeny**--Another system classifies thymomas according to malignant cell ontogeny. When neoplastic cells look like those found in the cortex of the normal thymus, the thymoma is designated a cortical thymoma. Otherwise, the term "medullary lymphoma" is used to describe a proliferation of cells thought to represent the neoplastic equivalents of normal thymic medullary cells. When both cortical and medullary cells are present in the malignant proliferation, the tumor is called a mixed corticomedullary thymoma.[18]

**Staging**

**Masaoka Staging System**

Staging of thymomas is usually based on invasiveness, as considered in the classifications of Bergh et al,[19] Wilkins et al,[20] Curran et al,[21] and Verley and Hollmann.[7] However, the most widely used system is that devised by Masaoka and colleagues,[22] which takes into account the anatomic extent of involvement, as defined clinically and histopathologically (Table 1). The invasiveness of the tumor is one of the most important prognostic factors in thymomas. Tumor invasion beyond the capsule is associated with an unfavorable outcome.[3,7,13,15,21-27] Noninvasive thymomas have a very low[26] or zero[21,23-25] relapse rate, and an extensive review[28] reported an average 80% survival rate for noninvasive thymomas, as compared with < 50% for invasive tumors. Pleural or pericardial effusion of the tumor is the most common form of metastatic involvement. Involvement of regional nodes is rare. Metastasis to distant organs is very unusual (< 10% at presentation), and the most common extrathoracic sites of disease involvement are the liver, kidney, brain, and spleen.

**GETT Staging System**

Among invasive tumors, disease-free survival is usually worse with higher stages although the differences are not always statistically significant.[3,7,21,22] However, because the extent of surgery is a prognostic factor of major importance, a staging system based on the surgical and pathologic features of the tumor was described by the French Study Group on Thymic Tumors (GETT) (Table 2).[29,30] In the GETT staging system, the predominant feature is the extent of surgical resection: completely resected, noninvasive tumors are stage I and completely resected invasive tumors are stage II tumors, whereas incompletely resected tumors are stage III tumors. In the Masaoka staging system, contiguous spread to the pericardium is a stage III tumor, whereas in the GETT system, in case of total resection, it becomes a stage II tumor. Conversely, an encapsulated totally resected GETT stage I tumor is designated a stage II tumor in the Masaoka system if there is microscopic invasion of the capsule.

In a series of 163 patients,[23] our group studied the correspondence of the two staging systems and showed that they were concordant in 88% of cases. However the Masaoka system tended to upgrade GETT stage I and II tumors; 61% and 20% of GETT stage I and II tumors, respectively, were Masaoka stage II and III thymomas. Analysis of disease-free survival showed that the Masaoka II-GETT I patients experienced a better outcome than the Masaoka II-GETT II patients and should be managed differently. Similarly, the Masaoka III-GETT II patients had a better prognosis than the
Masaoka III-GETT III patients. The disease-free survival of GETT I thymomas differs significantly from the disease-free survival of GETT II thymomas, and the disease-free survival of GETT II differs significantly from the disease-free survival of GETT III. These findings indicate that the GETT classification seems to be the best staging system.

**Management**

**Surgery**

**Total vs Subtotal Resection**--Complete surgical resection remains the first-line therapy for all thymomas regardless of invasiveness, except for rare cases that have metastasized. All of the published reports have shown higher rates of overall and disease-free survival in patients who underwent total re-section,[8,21,23,31] as compared with those treated with partial excision,[4,13,22,23,29,32] although the observed differences were not always statistically significant.[3,26,27] With total resection, 5-year survival rates range from 74% to 98%.[23,28]

Progress in the field of vascular surgery may help enhance the number of total resections, especially in cases of associated vena caval obstruction.[13]

**Subtotal Resection vs Biopsy**--In published reports, subtotal resections seemed to produce higher survival rates than simple biopsies (5-year survival rates of 64% to 71% vs 25% to 40%).[4,13,23,26] However, the number of patients who underwent a biopsy was small--10% to 20%--even in the series reporting more than 100 patients,[4,7,13,21,26,32] and the data should therefore be viewed cautiously.

Other problems complicate the analysis of studies of subtotal surgery: The use of radiotherapy differs from one report to another, the extent of surgery is not always precisely described,[4] the number of patients studied is often small, and the studies were performed over periods of up to 40 years.

The advantage of partial surgery over biopsy alone remains a subject of controversy for several authors.[21,29,33] Like other investigators,[3,27] we have observed more metastases and more local recurrences after simple biopsies than after subtotal resections.[23]

**Radiotherapy**

**After Subtotal Resection or Biopsy**--Experts generally agree about the value of postoperative radiotherapy after subtotal resection or biopsy alone.[3,21,26,28,33-35] The published literature on this topic, which includes series of 11 to 55 patients, reports local control rates of 50% to 80%,[3,21,23,27,33-35] with more local failures among patients who undergo biopsy.[23,27]

To reduce the rate of out-field failure (ie, failure outside of the radiation field), the use of prophylactic pleural and pulmonary irradiation has been advocated,[13,17] as well as the use of radioactive phosphorus-32.[6] Both approaches seem questionable when one considers the low doses delivered. Furthermore, although out-field recurrences appear to be more frequent in patients with stage IV-A disease, they are often associated with in-field mediastinal recurrences.

Due to the small size of the samples reported in the literature, no conclusions can be drawn about the usefulness of radiotherapy.[23,26,32] We observed local failures in one-third of patients treated with radiotherapy after subtotal resection or simple biopsy; 61% of these were in-field recurrences. Local control was achieved in one-half of patients after biopsy alone. Chemotherapy did not influence local control. In accordance with the findings of others,[33,34] our data suggest that there may be no relationship between the dose of radiation and local relapses, although pooled data[36] suggest that doses of 60 Gy or more may improve local control.

**After Total Resection**--The value of radiotherapy after total resection is more controversial and should be considered according to the invasiveness of the thymoma. In a review of eight reports involving 115 completely resected invasive tumors, Curran et al reported a 5% recurrence rate with the use of postoperative irradiation vs 28% without radiotherapy.[21] Nakahara et al found that completely resected noninvasive thymomas had the same outcome as did completely resected and irradiated invasive tumors.[13]

Although the issue of radiotherapy after total resection for invasive tumors is still open to debate,[27,37] our data showing equal survivals for stages I and II treated with postoperative radiation provide additional support for its use. According to most of the literature and our results, a dose of 50 Gy should be sufficient in such cases,[3,7,21,38] although Nakahara et al suggested that 40 Gy could achieve a 93% local control rate for completely resected stage II and III disease.

In contrast, analysis of the published literature does not favor the use of adjuvant radiotherapy in patients with completely resected noninvasive thymomas. In such patients, Curran et al and Fujimura et al reported no local failures after irradiation,[21,24] whereas Nakahara et al have been
using surgical treatment alone for stage I disease since 1988.[13] However, Pollack et al argued that an exception should be made for patients with large stage I disease in whom pleural or pericardial adhesions (GETT stage I-B) are suspected during surgery. Since an adequate microscopic examination for sites of discontinuity through the capsule and microscopic invasion into adherent pleura or pericardium is often impossible because of the thinness of the capsule and its propensity for being broached during handling or preparation, Pollack et al advocate the use of postoperative radiation in these stage I patients.[3] Since we have observed no failures among irradiated stage I-B patients in our series, we share this viewpoint.

**New Approaches to Enhance** - Local Control -- Possible approaches to enhance local control include the use of intraoperative radiotherapy, due to its ability to deliver a high dose in a reduced volume, as well as conformal radiotherapy, due to the advent of three-dimensional (3D) imaging procedures and their accuracy in delineating target volumes. These approaches may also help avoid radiation-related complications. Although unusual, such complications are difficult to avoid with high-energy photon beams because of the closeness of the heart and lungs.

**Treatment Recommendations** -- Therefore, we advise against the use of fraction sizes exceeding 2 Gy or cardiotoxic chemotherapy, when possible. The recommended radiation dose for thymomas after complete resection is 50 Gy in 25 to 28 fractions; this is sufficient to control 98% to 100% of completely resected noninvasive or invasive thymomas.[23] Patients who undergo a subtotal resection or simple biopsy should receive a dose of 60 Gy using the most sophisticated radiation technique available, ie, a 3D treatment planning system. The volume to be treated includes the entire mediastinum and part of the adjacent lung when there is parenchymal involvement, or otherwise, as delineated by CT scan or surgical clips plus a 2-cm margin.

The treatment of supraclavicular lymph nodes is controversial, and no firm recommendations can be given at present. We found no difference in outcome between 97 patients who received a median dose of 40 Gy to both supraclavicular fossae and 52 patients who received no treatment to this region.[23]

**Chemotherapy**

In the past, chemotherapy was reserved for invasive thymomas that could not be totally resected or that progressed after surgery or radiation therapy. In such cases (defined as Masaoka stage III or IV), the 5-year survival rate achieved with surgery and radiation therapy was 25%.[17]

Single Agents -- Hu and Levine[39] reviewed published results achieved with single-agent chemotherapy or combination chemotherapy in malignant thymomas. Corticosteroids alone were sometimes used regardless of their immunosuppressive effect, especially when thymoma-associated systemic syndromes were present, but the results were poor.[40] Similarly, alkylating agents or alkaloids such as vincristine have been used as single agents with unsatisfactory results.[41]

Although results of cisplatin (Platinol) and doxorubicin as single agents were also poor, these two drugs showed greater efficacy than previously used agents.

**Combination Regimens** -- To enhance results, some groups have used combination regimens including cisplatin and/or doxorubicin. Hu and Levine suggested classifying these combination chemotherapy programs as cisplatin- or non-cisplatin-containing regimens.[39] Many case reports and small series have suggested the chemosensitivity of thymoma to combination chemotherapies, such as cyclophosphamide, Oncovin, procarbazine and prednisone (COPP) or cyclophosphamide, vincristine, and prednisone.

The role of anthracyclines is less clear. In a small series of five patients with malignant thymoma and myasthenia gravis who received cyclophosphamide, doxorubicin, and vincristine, the authors observed one complete and two partial responses, and two patients were long-term survivors.[42] Platinum-containing regimens have shown better results, with an overall response rate of 70% to 80%, half of which were complete responses.[43,44] Using a 4-day course of cisplatin (50 mg/m²) and doxorubicin (40 mg/m²) on day 1, vincristine on day 3, and cyclophosphamide on day 4 (700 mg/m²), Chahinian et al treated 11 patients with invasive or metastatic thymoma. They observed a 91% rate of overall clinical responses and a 47% rate of complete clinical responses.[45]

In another report, seven patients with stage III thymomas were treated with cisplatin (75 mg/m²) and etoposide (100 mg/m²) on day 1 and etoposide (120 mg/m² on days 1, 3, and 5. All seven patients responded to three cycles of this chemotherapy program and subsequently underwent resection and radiation therapy.[46]

The Radiation Therapy Oncology Group (RTOG) initiated a trial testing neoadjuvant chemotherapy (cyclophosphamide, doxorubicin, cisplatin, and prednisone) prior to radiotherapy for unresectable thymoma. Unfortunately, the study closed because of poor accrual.

In one of the largest series of patients,[47] Fornasierie et al treated 37 patients with stage III or IV
invasive thymoma with a monthly chemotherapy regimen consisting of cisplatin (50 mg/m²) and doxorubicin (40 mg/m²) on day 1, vincristine (0.6 mg/m²) on day 3, and cyclophosphamide (700 mg/m²) on day 4. The overall clinical response rate was close to 92%, with 43% complete remissions. Subsequent thoracotomy confirmed 7 of the 16 complete remissions. The median duration of remission was 12 months (range, 2 to 96+ months), and the median survival was 15 months (range, 5 to 96+ months).

Except for a lower objective response rate, results published by Patrick et al were similar. They treated 29 patients with metastatic or recurrent thymoma with the combination of cisplatin, doxorubicin, and cyclophosphamide. The median duration of response was 11.8 months (range, 0.9 to 70.5+ months), time to treatment failure was 18.4 months (range, 0.8 to 91.9+ months), and median survival was 37.7 months (range, 2 to 91.9+ months).[48]

In our multicenter, retrospective series of 149 patients with nonmetastatic thymomas, all 149 patients received radiotherapy, and 74 (68%) were also given postoperative chemotherapy with cyclophosphamide, doxorubicin, and cisplatin. Multivariate analysis showed that the use of chemotherapy was associated with higher survival rates (P < .001), especially in patients with stage III-IV disease and mediastinal compression at diagnosis.[23]

Summary—Malignant thymomas are chemosensitive tumors. Chemotherapy can improve the outcome of invasive Masaoka stage III and IV thymomas or recurrent thymomas. Only platinum-containing regimens show consistent efficacy.

Conclusions

The treatment of choice for thymomas is always surgery followed by radiotherapy, except in patients with stage I-A disease, for whom surgery alone is sufficient. Chemotherapy is no longer a controversial treatment, and platinum-containing regimens should be used in patients with invasive Masaoka stage III-IV thymomas or recurrent tumors.

Since thymomas are rare tumors, there are insufficient numbers of patients to conduct prospective randomized trials. Only multicenter studies will help evaluate new therapeutic strategies, such as intraoperative radiotherapy.

References:


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