THYMIC CARCINOMA: CURRENT STAGING DOES NOT PREDICT PROGNOSIS

David Blumberg, MD
Michael E. Burt, MD, PhD†
Manjit S. Bains, MD
Robert J. Downey, MD
Nael Martini, MD
Valerie Rusch, MD
Robert J. Ginsberg, MD

Background: **Thymic carcinomas are currently staged by Masaoka classification, a staging system for thymomas. We retrospectively evaluated surgical patients with thymic carcinoma to determine prognostic factors and to evaluate the usefulness of Masaoka staging in this disease.** ***Methods:*** **Our computerized tumor registry yielded 118 patients with thymoma. Review of pathologic material revealed 43 cases of thymic carcinoma. Collection of data was by review of hospital and physician charts and telephone contact with patients. Analysis of prognostic factors was performed in patients undergoing complete resection by the method of Kaplan-Meier and Cox proportional hazards regression.** ***Results:*** **Between 1949 and 1993, 43 patients underwent surgery for thymic carcinoma. Overall survival was 65% at 5 years and 35% at 10 years. Overall recurrence was 65% at 5 years and 75% at 10 years. On univariate analysis, survival was not dependent on age, sex, tumor size, or Masaoka stage but was dependent on innominate vessel invasion. By multivariate analysis, survival was dependent only on innominate vessel invasion.** ***Conclusions:*** **Patients with thymic carcinoma have a high rate of recurrence. Tumor invasion of the innominate vessels is associated with a particularly poor prognosis. Although Masaoka staging is useful in staging patients with thymoma, it does not appear to predict outcome for patients with thymic carcinoma. (J Thorac Cardiovasc Surg 1998;115:303-9)**

Although all thymomas are derived from the epithelial cells of the thymus, they represent a diverse group of tumors with varied histologic findings and biologic behavior. Histologic subtypes include predominantly lymphocytic, predominantly epithelial, mixed lymphoepithelial, or spindle cell thymomas, and thymic carcinomas. Compared with other histologic subtypes, thymic carcinomas have malignant cytologic findings[1-3] and a clinical course characterized by early and frequent metastasis and poor survival.[4-7] Studies to define prognostic variables or to test efficacy of treatment modalities for patients with thymic carcinoma, however, have been limited by the rarity of this tumor. As a result, thymic carcinomas are currently staged and treated by the same guidelines used for thymomas, despite having a more aggressive histologic appearance and clinical course.

In our recent review of 118 patients with thymoma, we reported 43 patients with thymic carcinomas seen over a 45-year period, representing one of the largest single institutional experiences.[8] Similar to other reports, patients with thymic carcinoma typically had advanced disease and had higher recurrence rates and worse survival compared with most thymomas. Because patients with thymic carcinoma have a worse prognosis compared with patients with thymoma, we performed a multivariate analysis to determine unique prognostic factors for patients undergoing complete resection of thymic carcinoma at Memorial Hospital.

Patients and methods

As previously reported, 118 patients with thymoma were surgically treated at Memorial Hospital from 1949 to 1993.[8] Forty-three of these patients were histologically

From the Thoracic Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, N.Y.

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Address for reprints: Robert Ginsberg, MD, Thoracic Service, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY 10021.

† Deceased.

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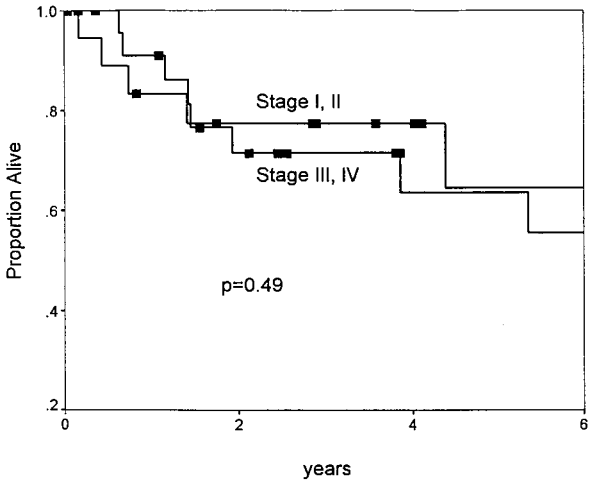

Fig. 1. Survival of patients with thymic carcinoma (n = 43) stratified by Masaoka stage: early stage I, II (n = 18) versus advanced stage III, IV (n = 25).

proven to have thymic carcinomas by review of microscopic sections by one pathologist (Dr. Juan Rosai). The criteria for diagnosis of thymic carcinoma was an epithelial cell thymic tumor with clear-cut cytologic features of malignancy. Thymic carcinomas included tumors defined as type II malignant thymomas, as described by Rosai and colleagues,[9, 10] and well-differentiated thymic carcinomas, as defined by Kirchner, Schalke, Marx, and Müller-Hermelink.[11] Data were collected from medical charts on all 43 patients and follow-up was performed by review of physicians office charts and contact of patients by telephone. Analysis of prognostic factors of patients who had complete resection was performed by the method of Kaplan and Meier[12] and by log rank analysis.[13] Significance was defined as p value less than 0.05.

Results

Patient demographics. Median age of patients was 50 years (range 19 to 72). There were 27 men and 16 women. Thirty-eight patients (88%) were symptomatic at presentation with cough (n = 14), dyspnea (n = 12), chest pain (n = 10), superior vena caval syndrome (n = 4), myasthenia gravis (n = 10), red cell aplasia (n = 3), and hypogammaglobulinemia (n = 1).

Clinicopathologic staging. The operative approach was median sternotomy in 60% and anterolateral thoracotomy in 40%. At operation, 25 patients (58%) had mediastinal invasion involving the pericardium (n = 23), pleura (n = 20), lung (n = 8), phrenic nerve (n = 14), or innominate vessels (n = 9). Final pathologic staging was performed by the Masaoka staging system: stage I, encapsulated tumor; stage II, invasion into surrounding fatty tissue or mediastinal pleura or microscopic invasion of the thymic capsule; stage III, invasion of mediastinal structures (i.e., lung, pericardium, or great vessels); stage IVa, metastasis confined to the intrathoracic cavity; stage IVb, distant metastasis.[4] There were three patients with stage I disease (7%), 15 stage II (35%), 20 stage III (47%), and 5 stage IVa (11%). Of 43 thymic carcinomas, 16 tumors were well-differentiated thymic carcinomas and 27 were type II malignant thymomas.

Patient treatment. Overall, 29 patients (67%) had complete resection and 14 patients had incomplete resection (33%). Of the 14 patients who had incomplete resection, 5 had invasion of great arteries, 1 had synchronous metastasis, 2 had chest wall involvement, and 6 had extensive mediastinal invasion. Patients having incomplete resection were treated postoperatively with chemotherapy (n = 1), radiation (n = 6), and combined chemotherapy and radiation (n = 7). Patients having complete resection received adjuvant chemotherapy (n = 3), radiation (n = 8), and combined chemotherapy and radiation (n = 13).

Factors associated with survival of all patients (n = 43). Of 43 patients, overall survival was 65% at 5 years, and 35% at 10 years. Survival was not dependent on age (p = 0.13), sex (p = 0.9), or tumor size (p = 0.89). Five-year survivals for patients undergoing complete resection (n = 29) and incomplete resection (n = 14) were 68% and 62%, respectively (p = 0.18). Survival was not dependent on Masaoka stage (p = 0.29). There were three stage I patients with survivals of 3.6, 4.1, and 8.2 years. Median survivals of stage II patients (n = 15), stage III patients (n = 20), and stage IV patients (n = 6.7) were 9.2, 5.3, and 6.7 years, respectively. Survival of patients with early stage disease (stage I or II) as defined by Masaoka classification was no different from that of patients with advanced stage disease III or IV (Fig. 1). Survival of patients with well-differentiated thymic carcinomas was similar to that of patients with type II malignant thymomas (Fig. 2). Survival was adversely affected (p = 0.009) by the presence of tumor invasion of the innominate vessels (vein and or artery). Patients with invasion of the innominate vessels (n = 9) had a 5-year survival of 37% compared with a 75% 5-year survival for patients (n = 34) with no innominate vessel invasion (Fig. 3). Survival of patients was not dependent on tumor invasion of mediastinal structures with the exception of the innominate vessels (Table I).

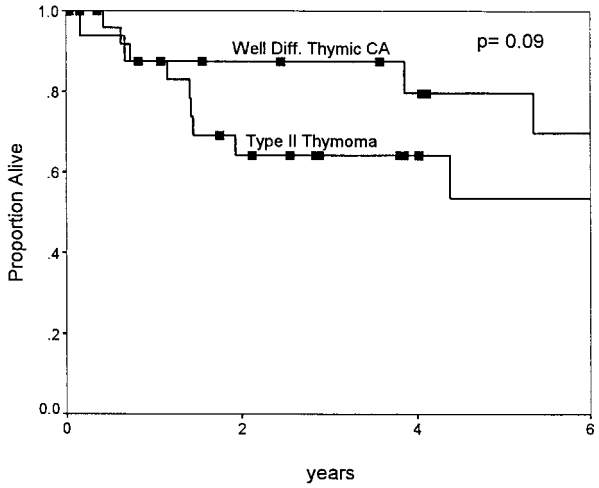

Fig. 2. Survival of patients with thymic carcinoma: well-differentiated thymic carcinoma ($n = 16$) compared with type II malignant thymoma ($n = 27$).

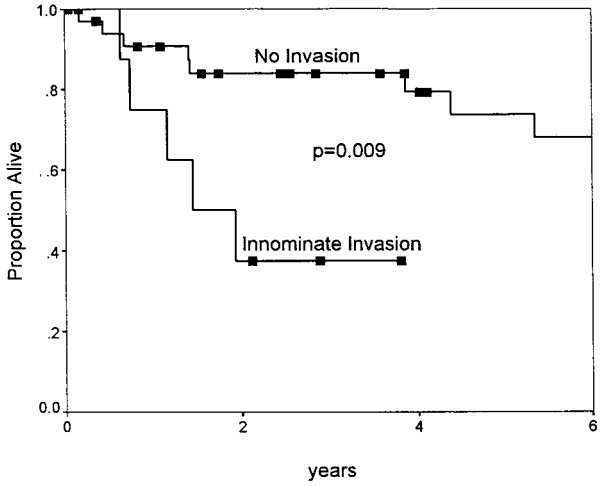

Fig. 3. Survival of patients with thymic carcinoma with innominate vessel invasion ($n = 9$) compared with no vessel invasion ($n = 34$).

Patterns of recurrence. Of 29 patients having complete resection, median follow-up was 3.8 years. There was a total of 16 recurrences, with 11 local recurrences, 2 distant metastases, and 3 local with distant metastases. Overall recurrence was 65% at 5 years and 75% at 10 years (Fig. 4). There were 12 actual long-term survivors (>4 years), with a median survival of 6.7 years (range 4 to 14.2 years). Of these long-term survivors, four patients had no evidence of disease at 4.0, 4.1, 8.2, and 14.2 years, five patients were alive with recurrent disease at 4.1, 6.3, 8.2, 10.1, and 12.9 years, and three patients were dead from progression of disease at 4.4, 6.6, and 6.8 years.

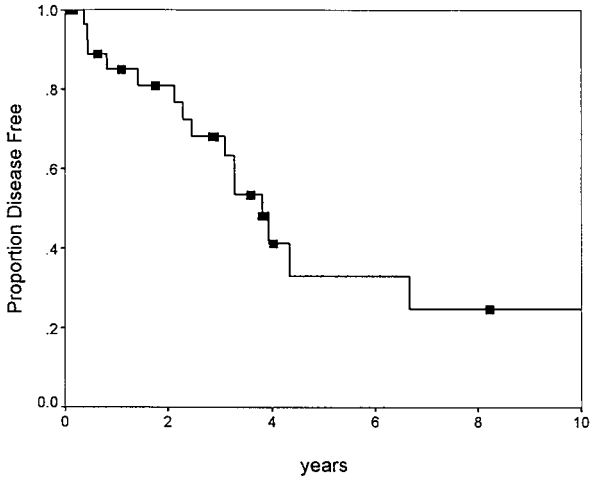

Fig. 4. Overall recurrence in patients having complete resection for thymic carcinoma ($n = 29$).

Table I. *Survival of patients' (n = 43) by site of mediastinal invasion*

Site	*Invasion*	*Survival (5 yr)*	*p Value*
Pericardium	No ($n = 20$)	62%	
	Yes ($n = 23$)	70%	0.31
Pleura	No ($n = 23$)	65%	
	Yes ($n = 20$)	70%	0.2
Lung	No ($n = 35$)	65%	
	Yes ($n = 8$)	62%	0.77
Phrenic nerve	No ($n = 29$)	70%	
	Yes ($n = 14$)	55%	0.43
Innominate vessels	No ($n = 34$)	75%	
	Yes ($n = 9$)	37% (4yr)	0.009

Effect of clinicopathologic factors on recurrence. Recurrence in patients having complete resection was not dependent on age ($p = 0.94$), sex ($p = 0.5$), presentation with symptoms ($p = 0.62$), or tumor size ($p = 0.42$). No difference was found in recurrence in patients based on Masaoka stage (Fig. 5). Recurrence in patients with innominate vessel invasion ($n = 6$) and with no vessel invasion ($n = 23$) were both 45% at 4 years. Patients with well-differentiated thymic carcinomas had a recurrence rate similar to patients with type II thymomas (Fig. 6).

Multivariable models. Survival of patients with thymic carcinoma was dependent only on innominate vessel invasion (95% CI 1.3 to 15.8; $p = 0.02$). Extent of resection (complete vs incomplete; $p = 0.2$), Masaoka stage ($p = 0.8$), and microscopic

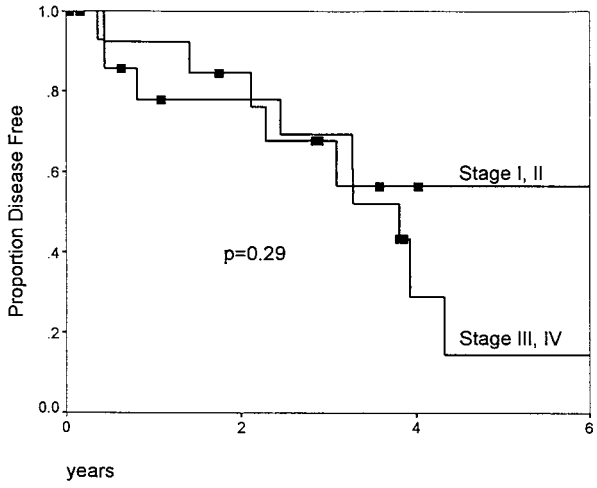

Fig. 5. Recurrence in patients having complete resection for thymic carcinoma ($n = 29$) stratified by Masaoka stage: early stage I, II ($n = 13$) versus advanced stage III, IV ($n = 16$).

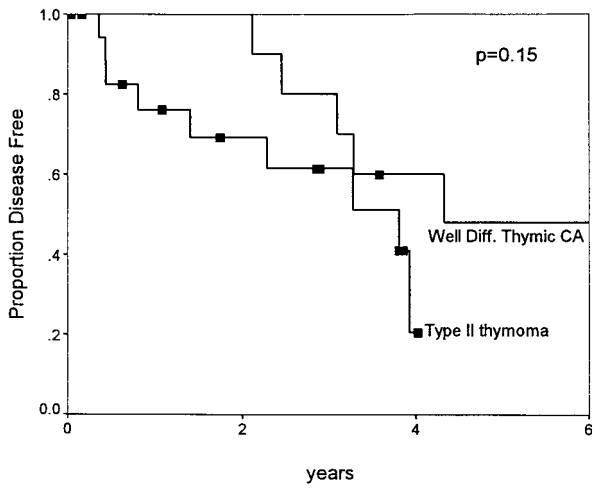

Fig. 6. Recurrence in patients having complete resection for thymic carcinoma ($n = 29$): well-differentiated thymic carcinoma ($n = 10$) compared with type II malignant thymoma ($n = 19$).

subtype (well-differentiated vs type II thymoma; $p = 0.3$) were not factors predictive of survival. Recurrence in patients with thymic carcinoma was not dependent on Masaoka stage ($p = 0.4$), innominate vessel invasion ($p = 0.6$), or microscopic subtype ($p = 0.15$).

Discussion

Until recently the diagnosis of thymic carcinoma as a real clinical entity has been questioned and has been a significant source of confusion for pathologists and clinicians alike. All thymic carcinomas are believed to arise from the epithelial cells of the thymus. Thymic carcinomas or type II malignant thymomas, as originally defined by Rosai and Levine, are epithelial thymic tumors with clear-cut malignant cytologic features, including nucleolar prominence, high nuclear/cytoplasm ratios, and abundant mitoses. In addition, there are seven unique histologic subtypes of thymic carcinoma, including squamous, mucoepidermoid, basaloid, sarcomatoid, small cell, lymphoepithelial, and clear cell.[9, 10] A second classification of epithelial tumors of the thymus by Müller-Hermelink has further complicated the diagnosis of this disease.[11] This classification scheme differentiates thymic carcinomas from thymic carcinomas on the basis of cortical and medullary components, "organotypic differentiation." By this scheme, thymomas are classified as medullary, cortical, or mixed type, whereas thymic carcinomas show a loss of medullary and cortical organization. Among the thymic carcinomas, a subgroup of tumors with only small areas of organotypic differentiation exists and are classified as well-differentiated thymic carcinomas. Thymic carcinomas with complete lack of cortical and medullary features are analogous to the original thymic carcinoma or type II malignant thymoma proposed by Rosai. In our study of 43 thymic carcinomas, there were 16 well-differentiated thymic carcinomas and 27 type II malignant thymomas. By multivariate analysis, survival or recurrence was no different between these two subgroups of thymic carcinomas. Although the diagnosis of thymic carcinoma is clearly complicated for the pathologist, treatment decision-making by the clinician need not take into account the subtype of thymic carcinoma because this variable does not seem to have a significant impact on clinical outcome.

Patients with thymic carcinoma have been staged by the same staging system used for thymoma, the Masaoka classification. No studies, however, have definitively validated the prognostic usefulness of this classification for patients with thymic carcinoma. Previous studies have demonstrated that patients with thymic carcinoma have a worse prognosis compared with patients with thymomas; studies examining prognostic factors unique to thymic carcinoma are sparse. Our objectives were to evaluate the usefulness of Masaoka staging for patients with thymic carcinoma and to determine unique prognos-

tic factors in a sizable cohort of patients compared with other studies.

Prior studies have suggested that the poor outcome of these patients is in part related to the advanced stage (Masaoka) of patients at initial presentation.[4] Our data, however, refute this. In our series, we were unable to confirm that stage as defined by the Masaoka staging system for thymoma was of prognostic usefulness. By actuarial analysis, survival of the entire cohort of 43 patients was not predicted by Masaoka stage. Masaoka stage was also not predictive of survival or recurrence in patients who had complete resection. Of 43 patients, there were 17 actual long-term survivors (>4 years). Approximately one half of these patients ($n = 8$) had advanced-stage disease (stage I, $n = 2$; stage II, $n = 7$; stage III, $n = 5$; and stage IV, $n = 3$), indicating that long-term survival may not be dependent on Masaoka stage. Despite the lack of correlation between Masaoka stage and survival for thymic carcinomas, we have previously shown that Masaoka stage was predictive of survival for patients with thymoma.[8] These differences between thymoma and thymic carcinoma would seem to reflect a true biologic difference in these two diseases and not a result of a small sample size. We found that prognosis for patients with thymic carcinoma was dependent solely on tumor invasion of the innominate vessels. Other sites of tumor invasion within the mediastinum were not associated with a poor outcome. This further illustrates the lack of usefulness of Masaoka classification in thymic carcinoma because all patients with mediastinal invasion would be classified as having advanced stage III disease.

Although patients with innominate vessel invasion have a worse prognosis, patients with thymic carcinoma in general have a high recurrence rate and poor survival. In addition, of those few long-term survivors, only a minority (4/17) were free of disease at last follow-up. Clearly this raises the question of whether patients with thymic carcinoma should be primarily treated by surgery. A lack of efficacy of complete surgical resection for these patients is suggested by similar survival rates for patients who had complete resection compared with those who had incomplete resection. Other reports have also failed to show an improved survival in patients having complete versus incomplete resection.[4]

Clearly other therapeutic modalities should be explored in these patients. Recent studies have shown some encouraging results for the use of chemotherapy in patients with thymic carcinoma. In our series, most patients were treated with adjuvant chemotherapy, the most common drugs being cisplatin, doxorubicin (Adriamycin), and cyclophosphamide (Cytoxan). Unfortunately, analysis of the effect of chemotherapy in our series was limited because of a wide variability of drug regimens administered. Chemotherapy has been used successfully by other investigators. In one study, five patients were treated with cisplatin-based regimens, with three clinical responses and two patients having a complete response.[14] A complete pathologic response was also observed in a report of one patient with thymic carcinoma who showed no pathologic evidence of tumor after chemotherapy with a regimen of cisplatin, vinblastine, bleomycin, and etoposide.[15] This same patient had metastatic disease at initial presentation and was noted to be disease free 5 years later. Thymic carcinoma has also been shown to be somewhat radiosensitive, with an 86% overall response rate and evidence of regrowth in only 17% of responders in one study.[16] Combined radiation and chemotherapy with cisplatin, vindesine, and cyclophosphamide was studied in five patients with partially resected tumors with one patient disease free at 5 years.[17] A more recent prospective study has also shown efficacy for cisplatin-based chemotherapy in patients with advanced thymoma.[18]

Thymic carcinoma comprises a group of thymic tumors with high risk of recurrence and poor overall survival. We were unable to demonstrate that current staging of thymic carcinoma by Masaoka classification for thymoma is prognostically useful. We have demonstrated that survival for patients with thymic carcinoma is adversely affected by tumor invasion of the innominate vessels. All patients with this disease, however, are at significant risk for recurrence and should be considered for novel treatment approaches.

We gratefully appreciate Dr. Juan Rosai's review of all pathologic material. We also thank T. J. Yao of the Department of Blostatistics at Memorial Hospital.

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Discussion

Dr. Paul A. Kirschner *(New York, N.Y.).* Dr. Blumberg and his associates have questioned the validity of the Masaoka staging system as applied to prognosis of thymic carcinoma. My comments will deal with the choice of the staging system and with the definition of thymic carcinoma.

To begin with, Masaoka and associates[1] in 1981 specifically excluded thymic carcinoma from the Masaoka staging system, restricting their cases only to those tumors with bland cytologic features, be they (1) noninvasive, encapsulated tumors, so-called benign thymoma, or (2) invasive tumors ("malignant thymoma") with bland cytologic findings, the latter being category I of Rosai. Invasiveness was the prognostic parameter for Masaoka, not histologic findings.

More confusing has been the definition of the term *thymic carcinoma.* Early on, it was applied to frankly undifferentiated epithelial tumors that were relatively infrequent (usually a single-digit percentage of thymic tumors) and, parenthetically, rarely if ever associated with myasthenia gravis or other autoimmune phenomena.

More recently, the term *well-differentiated thymic carcinoma* was introduced as part of the Müller-Hermelink "cortical/medullary" histologic reclassification of thymic epithelial tumors in 1989,[2] and this new group straddles the category I cytologically blind of Rosai and the cytologically malignant category II of Rosai. It undoubtedly accounts for the astonishing number of cases in Dr. Blumberg's series, 43 cases, or 36% of his total thymic tumor experience at Memorial.

When the Massachusetts General Hospital[3, 4] reclassified their cases according to this classification, they also came up with a very high percentage (28%), not quite the same percentage but a very high one, using the term *well-differentiated thymic carcinoma.*

Parenthetically, the term *thymic carcinoma* was not used in previous Memorial papers reporting on their experience with thymoma.

Further evidence of this overliberal use of the term *thymic carcinoma* is the high incidence of autoimmune disease reported by Dr. Blumberg, which I derived from his manuscript, 14 cases, or 33%, including 10 with myasthenia gravis, an incidence not heretofore noted in true thymic carcinoma. My question is, what was the incidence of myasthenia gravis in the high-grade tumors with innominate vessel invasion?

Shimosato[5] of Japan, in an editorial in 1994, deplored the lack of a standard WHO histologic classification of thymic tumors, as is present in many other types of tumors that we deal with, including lung tumors. He also supported a TNM staging system, the latter having already been proposed by Yamakawa and associates[6] in a paper in which Masaoka was one of the coauthors in 1991 and Tsuchiya and coworkers[7] in 1994 to more properly stage thymic carcinoma by including the N factor. My question is, what was the incidence of lymph node metastasis in this series of cases?

In the current paper, Dr. Blumberg has also demonstrated the need for subclassifying thymic carcinoma by degree of histologic differentiation and invasiveness to explain the discrepancies in recurrence and survivals in this widened spectrum of thymic carcinoma. These discrepancies appear to be derived from the use of a staging system that was never intended to include thymic carcinoma in the first place and an overly broad interpretation of the term *thymic carcinoma* proper. The true situation will probably be a balance between histology and invasiveness to more accurately stage all thymic epithelial tumors.

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Dr. Willard A. Fry *(Evanston, Ill.).* I have three questions. First, were most of the cases operated by sternotomy or bilateral thoracotomy? Second, was a total thymectomy performed? Third, do you recommend radiotherapy in all cases of thymic carcinoma as a postoperative adjuvant? If yes, do you add chemotherapy?

Dr. Larry R. Kaiser *(Philadelphia, Pa.).* Your series goes back to the 1940s. How complete was your follow-up?

Dr. Blumberg. I thank Dr. Kirschner for his poignant comments and acknowledge that he is clearly a recognized authority in this area.

In response to your question regarding the definition of thymic carcinoma and the large experience of these tumors we are reporting, I would like to make several comments. We have previously reported our experience with 118 patients with thymoma treated at Memorial Hospital from 1949 to 1993. In this report, 43 tumors were classified as thymic carcinoma. This study represents a subset analysis with the objectives of defining prognostic factors and determining the usefulness of Masaoka staging in thymic carcinoma. To define a thymic carcinoma, we have used both the classifications of Rosai and Müller-Hermelink. Thymic carcinomas had either clear-cut malignant cytologic features (type II malignant thymoma) or were well-differentiated thymic carcinomas. Our incidence of thymic carcinomas was 43 of 118 (36%), which is similar to other published reports. Hsu reported a 10-year experience with thymic carcinomas in 1994 in this Journal. Of 75 patients with thymic tumors, 20 had thymic carcinomas, representing a 36% incidence. As you note, after reclassifying their cases, the Massachusetts General Hospital group has also reported a relatively high incidence of thymic carcinoma. So clearly we have not been over liberal in our diagnosis of thymic carcinoma. We have, in fact, used the two currently accepted classifications for diagnosing thymic carcinoma. Our study demonstrates that survival and recurrence of patients with thymic carcinoma is similar independent of the classification used for diagnosis of thymic carcinoma. Patients with well-differentiated thymic carcinomas and type II malignant thymomas had a similar poor prognosis. Clearly both classification systems should be used to discriminate thymic carcinoma from benign thymomas to appropriately manage patients with this highly aggressive disease.

The high incidence of myasthenia gravis in our group of thymic carcinomas is clearly related to inclusion of well-differentiated thymic carcinomas in our series. Myasthenia gravis occurred in 10 of 43 patients. Of these 10 patients with myasthenia gravis, 9 had well-differentiated thymic carcinomas. The association of myasthenia gravis with thymic carcinoma has previously been described by Müller-Hermelink.

Dr. Kirschner made the point that Masaoka staging was never intended as a clinical staging system for thymic carcinoma. Despite this fact, studies in the literature, including the experience of Hsu (J Thorac Cardiovasc Surg 1994;107:615-20) have staged patients with thymic carcinoma by Masaoka classification. Because we have a large experience with thymic carcinoma patients, all of whom were clinically staged by Masaoka classification, we had the unique opportunity to evaluate the usefulness of Masaoka classification in this disease. Unlike in patients with thymoma, Masaoka stage is not predictive of prognosis. Use of Masaoka staging in thymic carcinoma should be cautioned against because patients with early-stage disease with no mediastinal invasion (Masaoka stages I and II) do as poorly as patients with advanced stage disease with mediastinal invasion or metastases (Masaoka stages III and IV). As pointed out by Dr. Kirschner, investigators from Japan have advocated a TNM classification for this disease. We do not have specific data on the incidence of mediastinal lymph node metastases but strongly believe that all patients with thymic carcinoma should be treated aggressively because they are all at high risk for recurrence.

Regarding Dr. Fry's question on operative techniques, 60% of patients were explored with median sternotomy and 40% with thoracotomy. All patients underwent a total thymectomy.

In regard to the use of adjuvant therapy, we recommend a multimodality approach in all patients with thymic carcinoma. As we have pointed out, there are data in the literature to support the efficacy of chemotherapy and radiation in this disease. In our series most patients received adjuvant therapy. Radiation was given to 35 patients with a median dose of 5000 rad. Chemotherapy was administered to 24 patients. Cisplatin was the most common agent. Most patients received a combination of cisplatin, doxorubicin, and cyclophosphamide. We were unable to analyze the effect of adjuvant treatment because there was no standard adjuvant regimen. However the usefulness of adjuvant therapy in our series is suggested by the 65% overall 5-year survival of patients, which is significantly higher than other reported series.

In response to Dr. Kaiser: The median follow-up for the entire cohort of 43 patients was 2.9 years and in the completely resected group it was 3.8 years.