Feasibility of multimodality therapy including extended resections in stage IVA thymoma

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Objective: Extended resections for advanced-stage thymomas are not commonly performed because of the potential morbidity in the face of unclear survival or palliative benefit. We reviewed our experience with multimodality treatment for Masaoka stage IVA thymomas for feasibility and outcomes.

Methods: We conducted a retrospective review of a single-institution surgical database. Data included patient demographics, preoperative staging and treatment, perioperative events, pathologic findings, and postoperative outcomes.

Results: During the period from 1996 to 2006, 18 patients who had Masaoka stage IVA thymoma underwent surgical resection. All patients received preoperative chemotherapy. Four patients with extensive pleural involvement underwent concomitant extrapleural pneumonectomy and postoperative hemithoracic radiation. Complete resection was achieved in 12 (67%) patients. There was no operative mortality. With a median follow-up of 32.2 months (range 1.4–129.9 months), 3-year, 5-year, and 10-year survivals were 91%, 78%, and 65%, respectively, and median survival has not yet been reached.

Conclusion: Multimodality therapy including extended surgical resection can be performed in select patients with stage IVA thymoma with low morbidity and mortality and can result in excellent long-term survival.

Surgery is considered the mainstay of treatment for thymoma. The prognosis in thymoma has been consistently established to correspond to the completeness of resection and the Masaoka stage of the tumor.¹⁻⁵ Masaoka stage IVA describes locally advanced disease with pleural or pericardial metastases without

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Abbreviations and Acronyms

CP	= carboplatin and paclitaxel
EP	= cisplatin and etoposide
EPP	= extrapleural pneumonectomy
PAC	= cisplatin, doxorubicin, and cyclophosphamide
RECIST	= Response Evaluation Criteria In Solid Tumors
SSDI	= Social Security Death Index
VIP	= etoposide, ifosfamide, cisplatin

distant metastases. The treatment of advanced thymoma is unclear inasmuch as complete resection may be difficult to attain and no standardized approach to multimodality treatment has been developed. The literature on stage IVA thymoma has been limited owing to its rarity, and series often span several decades, reflecting older histologic classification schemes, therapeutic agents, or surgical techniques.

In stage IVA thymoma, metastatic disease confined to the chest still allows the potential for complete resection of all disease. Extensive resections including extrapleural pneumonectomy (EPP) and resection of the superior vena cava for various thoracic malignant tumors including thymoma have been reported.⁶⁻¹³ Several reports suggest that multimodality therapy in advanced thymoma may improve outcomes by potentially increasing resectability and reducing recurrences.¹⁴⁻¹⁹ The purpose of this study was to determine the feasibility and outcome of multimodality therapy and extended resections in a contemporary series of consecutive patients with Masaoka stage IVA thymoma.

Patients and Methods**Collection of Clinical Data**

We undertook a retrospective review of all patients undergoing resection for thymic epithelial tumors at Memorial Sloan-Kettering Cancer Center between January 1996 and December 2006. The Institutional Review Board granted approval for this study on August 30, 2005. Patients who had undergone prior resection and patients with a diagnosis of thymic carcinoma only or thymic carcinoid were excluded from the analysis. During this time period, 107 patients underwent surgery for the diagnosis of thymoma or well-differentiated thymic carcinoma. Of these, 18 patients had stage IVA thymoma with pleural dissemination and were included in this analysis. Patient records were reviewed for demographic information, treatment details, adverse events, and outcomes.

Pathologic Classification

Microscopic sections from these patients were re-reviewed by one pathologist (W.T.) to confirm the diagnosis of thymoma without prior knowledge of clinical data. Histologic type was classified according to the 2004 revision of the World Health Organization classification of thymic epithelial tumors.²⁰ Resection status was determined from the operative notes and the pathology reports. R0

and R1 resections were collectively considered as complete macroscopic resections. Incomplete resections were defined as those resections in which gross tumor was left behind (R2 resections).

Disease Assessment, Adverse Events, and Follow-up

Response to preoperative therapy was graded according to the RECIST criteria (Response Evaluation Criteria In Solid Tumors). Partial response was defined as a 30% decrease and progressive disease as a 20% increase in the longest diameter of target lesions.²¹ Perioperative adverse events and adverse events arising from adjuvant radiation therapy were identified from the medical record and graded according to the "Common Terminology Criteria for Adverse Events" version 3.0.²² A significant proportion of patients received their chemotherapy outside of this institution and, therefore, data regarding these treatment-related adverse events were not uniformly available. Dates of death were obtained from the medical record and from the Social Security Death Index (SSDI). Surviving patients were censored at the last update of the SSDI on January 24, 2007. Recurrences were dated from the first postoperative radiographic study that demonstrated recurrent disease. Although there was no strict routine for postoperative follow-up, the most common approach was to obtain serial computed tomographic scans of the chest, generally at 6-month intervals. Patients with no evidence of disease were censored at the date of the most recent radiographic study demonstrating absence of disease.

Statistical Analysis

Survival analysis was performed by the Kaplan-Meier method and was calculated from the date of surgery to the date of death or to the last update of the SSDI. Disease-free survival was determined in only those patients who had undergone complete macroscopic resections and was calculated from the date of surgery to the date of the first radiographic study demonstrating recurrent disease or most recent study demonstrating absence of disease.

Results**Clinical and Pathologic Data**

From January 1996 to December 2006, 18 patients with stage IVA thymoma underwent multimodality therapy including surgery. Patient characteristics are shown in [Table 1](#). The median age was 43.5 years (range 26–74 years). Ten patients were female. The majority of patients were white. The most common presentations were pain or dyspnea, although many patients were free of symptoms. None of the patients had any significant cardiac, pulmonary, or renal disease, but 1 patient had insulin-dependent diabetes. There were no cases of myasthenia gravis at diagnosis, although this disease developed postoperatively in 1 patient, and 1 patient had systemic lupus erythematosus. The histologic classification of the tumors was distributed primarily among the B subtypes with half of the patients demonstrating a component of B3 thymoma.

Preoperative Treatment

All 18 patients received preoperative chemotherapy with a platinum-based regimen. Treatment details are noted in

TABLE 1. Patient characteristics (n = 18 patients)

Age (y)	
Median	43.5
Range	26–74
Gender	
Male	8
Female	10
Symptoms on presentation	
Pain	6
Dyspnea	5
Cough	1
None	6
Ethnicity	
White	15
Asian	1
Hispanic	1
African American	0
Other	1
Comorbidities	
Coronary disease	0
Congestive heart failure	0
Renal insufficiency	0
Chronic obstructive pulmonary disease	0
Diabetes	1
Autoimmune disorders	
Myasthenia gravis	0
Red cell aplasia	0
Hypogammaglobulinemia	0
Systemic lupus erythematosus	1
Histology (WHO classification)	
AB	1
B1	2
B2	3
B3	6
B1-B2	2
B2-B3	2
B1-B3	2

WHO, World Health Organization.

Table 2. The majority (n = 10) underwent treatment with PAC (cisplatin, doxorubicin, and cyclophosphamide). Three patients each received VIP (etoposide, ifosfamide, cisplatin), CP (carboplatin and paclitaxel), and 2 were treated with PE (cisplatin and etoposide). One patient taking CP received concurrent radiation. Three patients who failed to respond to initial chemotherapy received additional alternative systemic therapy. There were 12 partial responses and no complete responses, for an overall response rate to chemotherapy of 67%.

Surgical Management

The surgical management, perioperative treatment, and outcomes are shown schematically in [Figure 1](#). The most common approach used either a hemi-clamshell (n = 8) incision or full clamshell (n = 3) to provide adequate

exposure of the mediastinum and pleural space ([Table 2](#)). In 2 cases, the clamshell incision was extended with a partial sternotomy for better exposure of the mediastinum and diaphragm. In 3 cases requiring a thymectomy with en bloc EPP, a median sternotomy was performed to mobilize the thymus followed immediately by a posterolateral thoracotomy to resect the lung and pleura. Pleural and parenchymal involvement was most frequently managed with pleurectomy and wedge resections of involved lung. Extensive pleural involvement necessitated EPP in 4 patients, lobectomy in 2 patients, and pneumonectomy and parietal pleurectomy in 1 patient. Local infiltration also necessitated resection of the superior vena cava or innominate vein in 3 patients and chest wall resection in 2 patients. In patients with disease involving the diaphragm, this was resected and the diaphragm either repaired primarily or reconstructed with prosthetic material. Complete macroscopic resection of all tumor was achieved in 12 (67%) patients. Resections were incomplete in the remaining 6 patients. Four of these had near-total resections, in which all of the tumor was removed but minimal residual disease was left behind on either the great vessels or the phrenic nerve. The other 2 incomplete resections left the gross tumor behind owing to tumor invading the heart in 1 case and inaccessible bilateral disease in the other.

Postoperative Treatment

The 4 patients who underwent EPP received adjuvant hemithoracic radiation (4500–5400 cGy). Three additional patients were treated with postoperative mediastinal radiation to the tumor bed alone (3000–5400c Gy). Five patients were treated with additional postoperative chemotherapy. ([Table 2](#)) Three patients had postoperative instillation of intrapleural brachytherapy with P32 (10–15 mCi) via an intrapleural catheter placed at the time of the operation.

Immediate and Long-term Outcomes

There were no operative deaths and the 30-day mortality was 0%. The median length of hospital stay was 9 days (range 5–17 days). Perioperative adverse events occurred in 7 (39%) of the 18 patients and are noted in [Table 3](#). The most common events were pulmonary (n = 7), followed by gastrointestinal (n = 2). One patient required vocal cord injection for a temporary laryngeal nerve dysfunction, and 1 patient who had been receiving high-dose corticosteroids required rewiring of an unstable sternum. There was one major complication of an intraoperative cardiac arrest of unknown etiology in a patient who was successfully resuscitated and subsequently discharged from the hospital in 9 days with no sequelae. Adjuvant radiation therapy was well tolerated, with adverse events limited to only grade 1 or 2 skin reactions, nausea, and esophagitis. One long-term adverse event was noted in a long-term survivor (112

TABLE 2. Patient treatment

Patient (age, sex)	Histology	Preoperative treatment	Response	Approach	Resection status	Postoperative treatment	Outcome
1 (33, F)	B1-B3	CP	PR	Sternotomy, thoracotomy	Incomplete	CP + RT	Dead, 42 mo
2 (56, F)	B3	PAC	PR	Hemi-clamshell	Incomplete	P32	Alive, 38 mo
3 (37, F)	B2-B3	PAC	PR	Thoracotomy	Complete	N/A	Alive, 130 mo
4 (26, M)	B1	PE + CAV	Stable	Hemi-clamshell	Complete	RT	Alive, 117 mo
5 (32, F)	B2	VIP + OP	PR	Sternotomy, thoracotomy	Complete	RT	Alive, 112 mo
6 (71, F)	B1	VIP	N/A	Clamshell	Complete	N/A	Dead, 73 mo
7 (56, F)	B3	PE	Progressive	Sternotomy, clamshell	Incomplete	None	Alive, 21 mo
8 (41, M)	B1-B2	PAC	PR	Hemi-clamshell	Complete	PAC + P32	Alive, 77 mo
9 (38, F)	B3	CP + PE	PR	Sternotomy, clamshell	Incomplete	None	Alive, 108 mo
10 (41, M)	B1-B3	VIP	PR	Hemi-clamshell	Complete	RT	Dead, 29 mo
11 (53, M)	B2	CP + RT	PR	Hemi-clamshell	Incomplete	CP	Alive, 38 mo
12 (46, M)	B1-B2	PAC	PR	Thoracotomy	Complete	RT	Alive, 32 mo
13 (57, M)	B3	PAC	PR	Sternotomy	Complete	RT	Alive, 24 mo
14 (43, F)	B2	PAC	Stable	Thoracotomy	Complete	P32	Alive, 21 mo
15 (44, M)	B2-B3	PAC	PR	Hemi-clamshell	Incomplete	CP	Alive, 16 mo
16 (74, M)	B3	PAC	Stable	Hemi-clamshell	Complete	None	Alive, 14 mo
17 (39, F)	AB	PAC	Stable	Sternotomy, thoracotomy	Complete	RT	Alive, 4 mo
18 (58, F)	B3	PAC	PR	Hemi-clamshell	Complete	PAC	Alive, 2 mo

CP, Carboplatin, paclitaxel; PAC, cisplatin, doxorubicin, cyclophosphamide; PE, cisplatin, etoposide; CAV, cyclophosphamide, doxorubicin, vincristine; VIP, etoposide, ifosfamide, cisplatin; OP, octreotide, prednisone; RT, radiation; P32, p 32 brachytherapy; PR, partial response; N/A, not available.

months)—radiation-induced breast cancer, which developed 8 years after postoperative hemithoracic radiation.

Disease-free and Overall Survival

Among the 12 patients who had a complete macroscopic resection, recurrences developed in 3 patients who had all undergone pleurectomies (5, 65, and 95 months postoperatively). Of the patients with recurrences, all of which were pleura-based, 1 died of disease at 73 months, 1 who had postoperative chemotherapy and intrapleural brachytherapy had 2 re-resections and is alive with disease at 77 months, and 1 who had postoperative radiation is alive with disease at 117 months. One patient with an initially incomplete resection underwent re-resection of the residual disease 3 months postoperatively with a complete macroscopic resection and remains alive with disease at 108 months.

At the time of latest follow-up, 3 of the 18 patients had died at 29, 42, and 73 months. Four patients have survived more than 9 years. The longest survival in this series is 11 years and the patient is free of disease. The overall survival of these patients was 91% at 3 years, 78% at 5 years, and 65% at 10 years (Figure 2). Median survival has not yet been reached. Median follow-up was 32.2 months (range 1.4–129.9 months). Disease-free survival was 90% at 3 and 5 years and 34% at 10 years, with a median disease-free survival of 95 months. The median follow-up for disease status was 22.8 months (range 0.2–108.7 months) (Figure 2).

Discussion

There are few studies in the literature examining the management of stage IVA thymoma. For thymomas with intrathoracic metastases, the optimal treatment strategy remains undefined. Previous series often have not classified their tumors according to the current World Health Organization histologic scheme and frequently consider stages III and IV together collectively as advanced disease. Series that include patients with stage IV disease may span multiple decades and do not always distinguish between resections for pleural recurrences versus thymomas with pleural involvement at diagnosis. Surgery is considered the mainstay of treatment, but few reports have gone into detail regarding the surgical approaches to advanced thymomas with pleural involvement. In Masaoka's original report, patients with stage IV disease (including IVA and IVB) had a 5-year survival of 50% and a 10-year survival of 0%.³ Since then, several series have observed a wide range of survivals for stage IVA disease (Table 4). Our previous series included a smaller number of patients (n = 9) with stage IVA thymomas treated less uniformly over a period of 44 years (1949 to 1993).¹ This earlier experience suggested that multimodality treatment and complete resection were important in achieving long-term survival. We now present a larger contemporary series of patients who had Masaoka stage IVA thymoma at diagnosis, treated more uniformly with multimodality treatment including extended resections with low morbidity, no mortality, and excellent long-term survival.

Figure 1. Schema showing the preoperative and postoperative treatment, the operations performed, and the outcomes in the 18 patients undergoing surgery for stage IVA thymoma. *RT*, Radiation; *NED*, alive, no evidence of disease; *AWD*, alive with disease; *DOD*, dead of disease. *One patient also received concurrent induction radiation. **One patient received concurrent chemoradiation postoperatively.

Complete resections can be difficult to achieve in the face of a large mediastinal mass with associated pleural disease. Resectability rates of stage IVA thymomas have been reported to range from 0% to 42% without preoperative therapy.^{3,17,18} Induction therapy for advanced thymomas, including stages III and IV, has been advocated by several authors with good clinical response rates and improved resectability rates in the range of 70%.^{17,19} Despite the heterogeneity of chemotherapy regimens in our series, all were platinum based. Three patients who failed to respond to initial chemotherapy underwent a second line of

treatment, and overall we observed a clinical response rate of 67%, emphasizing that thymomas are sensitive to platinum-based chemotherapy. In a series of 21 stage III and IVA thymomas receiving induction therapy with PAC plus prednisone, Kim and associates¹⁵ reported a complete resection rate of 76%. We obtained comparable results in our series with a 67% complete resection rate in our group of stage IVA thymomas.

We consider an aggressive approach toward surgical resection to be warranted. The management of thymoma with pleural involvement depends on whether the pleural disease is limited or extensive. Our experience suggests that disease limited to scattered pleural metastases can be managed by resection of individual pleural lesions and concomitant pulmonary resections as needed. There are no data regarding the use of complete parietal pleurectomy for these patients. Unlike malignant pleural mesothelioma, in which the disease intrinsically involves the entire pleural surface, metastatic thymoma may be a more limited pleural disease process. In the majority of patients, a hemi-clamshell approach provides optimal exposure of the mediastinum as well as the pleural space.^{23,24}

In patients with extensive and confluent pleural disease, an extended resection with EPP is required for complete resection. A median sternotomy followed im-

TABLE 3. Perioperative adverse events*

Adverse event	Grade				
	1	2	3	4	5
Atelectasis	—	3	—	—	—
Pneumonia	—	3	—	—	—
Pleural effusion	—	1	—	—	—
Ileus	—	1	—	—	—
Colitis	—	1	—	—	—
Laryngeal nerve dysfunction	—	—	1	—	—
Wound complication	—	—	1	—	—
Cardiac arrest	—	—	—	1	—

*Analyzed according to CTCAE version 3.0.²²

Figure 2. Overall and disease-free survival.

mediately by en bloc EPP via a posterolateral thoracotomy usually provides the best exposure. Compared with the largest published experience with EPP, our series had less morbidity and no mortality.²⁵ Our results are comparable with a previously reported small series of EPP for thymoma and add to the literature that suggests aggressive approaches with extended resections are feasible with low morbidity and mortality.^{26,27} This may relate to the generally young age and good overall health of patients with thymoma.

TABLE 4. Survival of patients with stage IVA thymoma

First author	Year	n	Five-year survival (%)	Ten-year survival (10%)
Masaoka ^{3*}	1981	11	50	0
Nakahara ^{7*}	1988	15	47	47
Maggi ¹⁷	1991	21	59	40
Pan ^{30*}	1994	12	41	22
Blumberg ¹	1995	9	100	—
Regnard ^{31*}	1996	19	—	30
Yagi ¹²	1996	5	67	33
Wilkins ^{32*}	1999	5	40	40
Kondo ²	2003	67	70	47
Nakagawa ^{4*}	2003	11	47	47
Sperling ^{5*}	2003	10	48	16
Lucchi ¹⁶	2005	16	—	46
Wright ²⁶	2006	5	75	50
MSKCC (current series)	2007	18	78	65

MSKCC, Memorial Sloan-Kettering Cancer Center. *Stage IVA + B.

High-dose hemithoracic radiation has been shown to be feasible after EPP for mesothelioma and reduces local recurrence rates.^{28,29} The absence of the lung in the chest allows delivery of higher doses of radiation without incurring additional toxicity. Drawing from this experience, we have treated all 4 patients who underwent EPP with hemithoracic radiation at a median dose of 5040 cGy. Three other patients received adjuvant mediastinal radiation, 2 in the setting of microscopic diseased margins. There was no major immediate radiotherapy-related toxicity. However, a radiation-induced second malignant tumor in 1 long-term survivor (breast cancer arising on the irradiated side 8 years postoperatively) serves as a cautionary note that all of these patients should be kept under life-long follow-up. The role of adjuvant radiation after pleurectomy and the role of adjuvant chemotherapy remain unclear. Currently no data have been reported regarding the feasibility and efficacy of adjuvant chemotherapy in this setting.

In conclusion, multimodality therapy of stage IVA thymoma incorporating extended resections is feasible and safe with low morbidity and mortality and offers the potential for long-term survival. However, by definition, any retrospective single-institution surgical series will include small numbers of patients who never underwent an operation because induction therapy failed. In addition, there is a need to develop more uniform treatment regimens for this challenging patient population. Our data suggest that prospective multicenter trials in this patient population are warranted to confirm and extend our experience.

References

- Blumberg D, Port JL, Weksler B, Delgado R, Rosai J, Bains MS, et al. Thymoma: a multivariate analysis of factors predicting survival. *Ann Thorac Surg.* 1995;60:908-14.
- Kondo K, Monden Y. Therapy for thymic epithelial tumors: a clinical study of 1,320 patients from Japan. *Ann Thorac Surg.* 2003;75:878-85.
- Masaoka A, Monden Y, Nakahara K, Tanioka T. Follow-up study of thymomas with special reference to their clinical stages. *Cancer.* 1981;48:2485-92.
- Nakagawa K, Asamura H, Matsuno Y, Suzuki K, Kondo H, Maeshima A, et al. Thymoma: a clinicopathologic study based on the new World Health Organization classification. *J Thorac Cardiovasc Surg.* 2003;126:1134-40.
- Sperling B, Marschall J, Kennedy R, Pahwa P, Chibbar R. Thymoma: a review of the clinical and pathological findings in 65 cases. *Can J Surg.* 2003;46:37-42.
- Higashiyama M, Doi O, Kodama K, Yokouchi H. Intrathoracic chemothermotherapy following panpleuropneumectomy for pleural dissemination of invasive thymoma. *Chest.* 1994;105:1884-5.
- Nakahara K, Ohno K, Hashimoto J, Maeda H, Miyoshi S, Sakurai M, et al. Thymoma: results with complete resection and adjuvant postoperative irradiation in 141 consecutive patients. *J Thorac Cardiovasc Surg.* 1988;95:1041-7.
- Nakahashi H, Maeo S, Osaki T, Dobashi K, Horiuchi Y, Miyazaki Y. Complete excision and panpleuropneumectomy resulting in long-term survival for a teenager with invasive thymoma: report of a case. *Surg Today.* 1992;22:558-60.
- Okada Y, Kondo T, Handa M, Saito R, Oura H, Shimada K, et al. [Surgical treatment of stage IVA thymoma.] In Japanese. *Kyobu Geka.* 1993;46:35-40.
- Shinada J, Yoshimura H, Hirai S, Ishihara A, Yanase N, Kameya T. [Pleuropneumectomy with combined resection of diaphragm, superior vena cava, and pericardium, for invasive thymoma with pleural dissemination]. In Japanese. *Kyobu Geka.* 1991;44:949-52.
- Suzuki S, Okada S, Nagamoto N, Handa M, Koike K, Fujimura S. [Pleuropneumectomy with thymectomy for invasive thymoma with pleural disseminations—a case report]. In Japanese. *Nippon Kyobu Geka Gakkai Zasshi.* 1990;38:1371-4.
- Yagi K, Hirata T, Fukuse T, Yokomise H, Inui K, Ike O, et al. Surgical treatment for invasive thymoma, especially when the superior vena cava is invaded. *Ann Thorac Surg.* 1996;61:521-44.
- Yokoi K, Matsuguma H, Nakahara R. [Extrapleural pneumectomy for thoracic malignancies]. In Japanese. *Kyobu Geka.* 2004;57:1000-4.
- Bretti S, Berruti A, Loddio C, Sperone P, Casadio C, Tessa M, et al. Multimodal management of stages III-IVA malignant thymoma. *Lung Cancer.* 2004;44:69-77.
- Kim ES, Putnam JB, Komaki R, Walsh GL, Ro JY, Shin HJ, et al. Phase II study of multidisciplinary approach with induction chemotherapy, followed by surgical resection, radiation therapy, and consolidation chemotherapy for unresectable malignant thymomas: final report. *Lung Cancer.* 2004;44:369-79.
- Lucchi M, Ambrogi MC, Duranti L, Basolo F, Fontanini G, Angeletti CA, et al. Advanced stage thymomas and thymic carcinomas: results of multimodality treatments. *Ann Thorac Surg.* 2005;79:1840-4.
- Maggi G, Casadio C, Cavallo A, Cianci R, Molinatti M, Ruffini E. Thymoma: results of 241 operated cases. *Ann Thorac Surg.* 1991;51:152-6.
- Rea F, Sartori F, Loy M, Calabró F, Fornasiero A, Daniele O, et al. Chemotherapy and operation for invasive thymoma. *J Thorac Cardiovasc Surg.* 1993;106:543-9.
- Venuta F, Rendina EA, Longo F, De Giacomo T, Anile M, Mercadante E, et al. Long-term outcome after multimodality treatment for Stage III thymic tumors. *Ann Thorac Surg.* 2003;76:1866-72.
- Müller-Hermelink HK, Ströbel P, Zettl A, Marx A. Combined thymic epithelial tumours. In: Travis WD, Brambilla E, Müller-Hermelink HK, Harris CC, editors. Pathology and genetics: tumours of the lung, pleura, thymus and heart (WHO classification of tumours). Lyon: IARC Press; 2004. p. 196-201.
- RECIST, the National Cancer Institute. Response Evaluation Criteria In Solid Tumors. 2000. Available from: <http://ctep.cancer.gov/guidelines/recist.html>.
- CTCAE, National Cancer Institute. Common terminology criteria for adverse events v.3.0. 2006. Available from: <http://ctep.cancer.gov/forms/CTCAEv3.pdf>.
- Bains MS, Ginsberg RJ, Jones WG, McCormack PM, Rusch VW, Burt ME, et al. The clamshell incision. An improved approach to bilateral pulmonary and mediastinal tumor. *Ann Thorac Surg.* 1994;58:30-3.
- Lardinois D, Sippel M, Gugger M, Dusmet M, Ris HB. Morbidity and validity of the hemclamshell approach for thoracic surgery. *Eur J Cardiothorac Surg.* 1999;16:194-9.
- Sugarbaker DJ, Jaklitsch MT, Bueno R, Richards W, Lukanich J, Mentzer SJ, et al. Prevention, early detection, and management of complications after 328 consecutive extrapleural pneumonectomies. *J Thorac Cardiovasc Surg.* 2004;128:138-46.
- Wright CD. Pleuropneumectomy for the treatment of Masaoka Stage IV thymoma. *Ann Thorac Surg.* 2006;82:1234-9.
- Haniuda M, Kondo R, Numanami H, Makiuchi A, Machida E, Armano J. Recurrence of thymoma: clinicopathological features, re-operation, and outcome. *J Surg Oncol.* 2001;78:183-8.
- Rusch VW, Rosenzweig K, Venkatraman E, Leon L, Raben A, Harrison L, et al. A Phase II trial of surgical resection and adjuvant high dose hemithoracic radiation for malignant pleural mesothelioma. *J Thorac Cardiovasc Surg.* 2001;122:788-95.
- Yajnik S, Rosenzweig KE, Mychalczak B, Krug L, Flores R, Hong L, et al. Hemithoracic radiation after extrapleural pneumonectomy for malignant pleural mesothelioma. *Int J Radiat Oncol Biol Phys.* 2003;56:1319-26.
- Pan CC, Wu HP, Yang CF, Chen WY, Chiang H. The clinicopathological correlation of epithelial subtyping in thymoma: a study of 112 consecutive cases. *Hum Pathol.* 1994;25:893-9.
- Regnard J-F, Magdeleinat P, Dromer C, Dulmet E, de Montpreville V, Levi J-F, et al. Prognostic factors and long-term results after thymoma resection: a series of 307 patients. *J Thorac Cardiovasc Surg.* 1996;112:367-84.
- Wilkins KB, Shiekh E, Green R, Patel M, George S, Takano M, et al. Clinical and pathologic predictors of survival in patients with thymoma. *Ann Surg.* 1999;230:562-74.

Discussion

Dr Cameron D. Wright (Boston, Mass). Thank you, Dr Huang. That was an excellent presentation. The paper was likewise clear, concise, and quite informative.

The authors describe a relatively modern cohort of patients with locally advanced thymomas, those with stage IVA disease, treated in a fashion relatively similarly, and we all recognize there is no true standard therapy for these particular patients. After receiving induction chemotherapy, these 18 patients had a high complete resection rate, minimal morbidity, and no mortality. The survival was quite good at 78% at 5 years. I have a note of caution, though. The median follow-up was only 32 months, and these tumors do have an ability to recur more than 5 years after resection. Therefore, this information is somewhat guarded. The authors conclude that induction chemotherapy followed by resection is safe and efficacious and probably represents the appropriate therapy.

I have 5 questions for the authors. First, was there any hint as to which chemotherapy was the best? PAC was the most common. That is certainly very popular. Did you have any inkling that that might be the best chemotherapy for this particular disease? Give us the benefit of your experience.

Second, are there any patients on whom you do not operate with stage IVA disease? You told us those on whom you do operate, but not those on whom you do not.

Third, how extensive should the pleurectomy be? Should we just do local pleural resection of the grossly visible metastases or

should we do a complete pleurectomy when we identify even one or two pleural metastases?

Fourth, were there any near-complete responses radiographically or, even more importantly, pathologically, and was there any evidence of necrosis in your pathologic specimens from this induction chemotherapy, signifying some benefit for this chemotherapy?

Finally, why not give chemotherapy postoperatively to the patients who responded preoperatively? Sixty-seven percent responded preoperatively. You identified that biologically. It is an aggressive tumor that has already metastasized. Why not give more chemotherapy to those who have proven to have had some benefit?

Dr Huang. Thank you, Dr Wright. The most frequent combination of chemotherapy used in our series was PAC based on the preferences of the treating oncologist as well as data from Loehrer and associates^{1,2} demonstrating the efficacy of this combination as well as its superiority to alternative regimens such as cisplatin and etoposide and ifosfamide.

As this was a retrospective review of a surgical database, this study includes only those patients who underwent resection. Patients with stage IVA disease who may not have responded to induction therapy or who were otherwise not deemed to be surgical candidates were not included in this analysis; therefore, no conclusions can be drawn regarding contraindications to surgery.

The consensus among the surgeons in our group is to do a local resection of each individual pleural lesion, with the goal of attaining a complete resection while limiting the amount of pulmonary resection needed. We generally do not perform a complete parietal pleurectomy. In cases in which the pleural component is very extensive and confluent, EPP may offer the only possibility of achieving a complete resection.

Although there were no radiographic complete responses based on the RECIST criteria, 5 of the 10 responders did have evidence of treatment effect ranging up to 50% necrosis in the specimens, confirming the chemosensitivity of this tumor. There were no pathologic complete responses, re-emphasizing the point that medical therapy alone is probably insufficient and that surgery remains essential in the treatment of thymoma.

Although several reports have demonstrated the efficacy of induction chemotherapy, there are no data regarding the utility of postoperative chemotherapy in thymoma. It is reasonable to consider postoperative chemotherapy in patients with incomplete resections who responded to induction therapy. Whether postoperative chemotherapy is of any benefit to patients with complete resections is unknown.

Dr Federico Venuta (Rome, Italy) What was the reason for incompleteness of resection? Was it related to the primary tumor or to the pleural dissemination? Were there patients with pleural effusions in the population of patients receiving pleurectomy? Probably it was my fault, but I did not get the survival of patients receiving incomplete resections.

Dr Huang. In 4 of the 6 incomplete resections, only minimal disease was left behind owing to involvement of either the great vessels or both phrenic nerves. In each of these 4 cases, tumor was shaved off the critical involved structures, necessarily leaving minimal residual disease behind. In the other 2 incomplete resections, gross disease remained owing to invasion of the heart in 1 case and the discovery of bilateral pleural disease in the other. Data regarding pleural effusions were not captured in our database.

There was a trend toward a survival benefit for complete resection. The survival was 86% in macroscopically complete resections and 50% in those with incomplete resections. However, with only 3 events, these numbers are not statistically significant.

Dr Philip Linden. (Boston, Mass) Did you make any effort to determine what preoperative factors might influence long-term survival; that is, did the degree of response to chemotherapy correlate with survival, comorbid conditions, or type of operation at all? It would be very useful to know to try to predict which patients might do well long term.

Dr Huang. This cohort clearly represents a preselected group of patients. In general, these were very young and otherwise healthy patients with very little comorbidity. The small number of patients in this cohort precluded the performance of a multivariate analysis of prognosticating factors.

Dr Walter Weder. (Zurich, Switzerland) What was the survival difference between those who underwent EPP compared with pleurectomy?

Dr Huang. With only 3 events for analysis, there was a marginally better survival for pleurectomy than EPP that was not statistically significant.

References

1. Loehrer PJ, Kim K, Aisner SC, Livingston R, Einhorn LH, Johnson D, et al. Cisplatin plus doxorubicin plus cyclophosphamide in metastatic or recurrent thymoma: final results of an intergroup trial. The Eastern Cooperative Oncology Group, Southwest Oncology Group, and Southeastern Cancer Study Group. *J Clin Oncol.* 1994;12:1164-8.
2. Loehrer PJ, Jiroutek M, Aisner S, Aisner J, Green M, Thomas CR, et al. Combined etoposide, ifosfamide, and cisplatin in the treatment of patients with advanced thymoma and thymic carcinoma: an intergroup trial. *Cancer.* 2001;91:2010-5.