Thyroid epithelial tumors mainly consist of thymoma, thymic carcinoma, and thymic carcinoid. Thyroid carcinoma and carcinoid are very rare neoplasms [1]. The classification of thyroid epithelial tumors has remained a subject of controversy for many years [2]. The outline of thyroid epithelial tumors has been clarified by “Atlas of Tumor Pathology: Tumors of the Mediastium (AFIP)” and “Histological Typing of Tumours of the Thymus (WHO),” published recently [3, 4]. The clinical staging system for thymoma was introduced first by Bergh and associates in 1978 and subsequently was modified by Masaoka and associates in 1981 [5, 6]; the Masaoka classification is the most widely accepted now [7]. In treatment for thyroid epithelial tumor, surgery remains the mainstay of treatment, and radiation and chemotherapy also have been applied widely as adjuvant and palliative procedures.

Methods. We compiled records of 1,320 patients with thyroid epithelial tumors who were treated from 1990 to 1994 in 115 institutes certified as special institutes for general thoracic surgery by The Japanese Association for Chest Surgery.

Results. Patients with stage I thymoma were treated with only surgery, and patients with stage II and III thymoma and thymic carcinoid underwent surgery and additional radiotherapy. Patients with stage IV thymoma and thymic carcinoma were treated with radiation or chemotherapy. The Masaoka clinical stage is an excellent predictor of the prognosis of thymoma and thymic carcinoma, but not thymic carcinoid. In stage III and IV thymoma, the 5-year survival rates of total resection, subtotal resection, and inoperable groups were 93%, 64%, and 36%, respectively. On the other hand, in thymic carcinoma, the 5-year survival rates of total resection, subtotal resection, and inoperable groups were 67%, 30%, and 24%, respectively. Prophylactic mediastinal radiotherapy could not prevent local recurrences effectively in patients with totally resected stage II and III thymoma. Adjuvant therapy including radiation or chemotherapy did not improve the prognosis in patients with totally resected III and VI thymoma and thymic carcinoma.

Conclusions. Total resection is the most important factor in the treatment of thyroid epithelial tumors. There is value in debulking surgery in invasive thymoma, but not in thymic carcinoma. We doubt that adjuvant therapy is valuable for patients with totally resected invasive thymoma and thymic carcinoma.

Material and Methods

Patients

We sent a questionnaire on thyroid epithelial tumors to 185 institutes certificated as special institutes by The Japanese Association for Chest Surgery, and received replies from 115 institutes (62%). We compiled records of 1,320 patients with thyroid epithelial tumors (1,093 thymomas, 186 thymic carcinomas, and 41 thymic carcinoids) who were treated between 1990 and 1994. The thymoma patients consisted of 495 men and 590 women. The patients’ ages ranged from 8 to 94 years, with a mean age of 53.7 ± 14.0 (SD). The thymic carcinoma patients consisted of 111 men and 73 women, with ages ranging from 19 to 89 years and a mean age of 57.9 ± 13.2 years. The thymic carcinoid patients consisted of 30 men and 11 women, with ages ranging from 13 to 70 years and a...
mean age of 53.5 ± 12.4 years. Thymoma was subclassified according to a modification of Bernatz’s classification into the following types: predominantly lymphocytic thymoma (n = 344), predominantly epithelial thymoma (n = 226), mixed thymoma (n = 428), and spindle cell thymoma (n = 41) [14]. Thymic carcinoma included 115 squamous cell carcinomas, 27 undifferentiated carcinomas, five adenocarcinomas, four adenosquamous carcinomas, two mucoepidermoid carcinomas, two lympho-epithelioma-like carcinomas, one clear cell carcinoma, one carcinoma combining squamous cell carcinoma and small cell carcinoma, and one tumor combining small cell carcinoma and thymoma. In this study, pathologists certified by the Japanese Society of Pathology in each institute diagnosed thymoma, thymic carcinoma, or thymic carcinoid. Final pathologic staging was performed based on Masaoka’s staging system [6]. Myasthenia gravis was associated with 270 cases (24.8%) of thymoma, four cases (2.2%) of thymic carcinoma, and none of thymic carcinoid. Pure red cell aplasia (PRCA), hyper- or hypoglobulinemia, and Sjögren’s syndrome were associated with 28 cases (2.6%), seven cases (0.65%), and five cases (0.46%) of thymoma, respectively. Thymic carcinoid had two Cushing syndrome and one MEN type I.

### Table 1. Therapeutic Modalities of Thymic Epithelial Tumors

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Operation Method</th>
<th>No. of Patients</th>
<th>Recurrence</th>
<th>Treatment Modality</th>
<th>Adjuvant Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Surgery</td>
<td>Radiotherapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Surgery + adjuvant</td>
<td>Chemoradiotherapy</td>
</tr>
<tr>
<td>Thymoma</td>
<td>Total</td>
<td>522 (100)</td>
<td>4/462 (0.9)</td>
<td>491 (94.4)</td>
<td>82.1%</td>
</tr>
<tr>
<td></td>
<td>I Subtotal</td>
<td>0</td>
<td></td>
<td>29 (5.6)</td>
<td>3.6%</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>12.4%</td>
<td>14.3%</td>
</tr>
<tr>
<td></td>
<td>Inop Total</td>
<td>0</td>
<td>9/217 (4.1)</td>
<td>Nonsurgery</td>
<td>87.9%</td>
</tr>
<tr>
<td></td>
<td>II Subtotal</td>
<td>247 (100)</td>
<td></td>
<td>107 (43.3)</td>
<td>5.6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Nonsurgery</td>
<td>6.5%</td>
</tr>
<tr>
<td></td>
<td>Inop Total</td>
<td>0</td>
<td>24/148 (28.4)</td>
<td>Nonsurgery</td>
<td>72.4%</td>
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<tr>
<td></td>
<td>III Subtotal</td>
<td>170 (84.6)</td>
<td></td>
<td>152 (74.5)</td>
<td>19.7%</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Nonsurgery</td>
<td>7.9%</td>
</tr>
<tr>
<td></td>
<td>Inop Total</td>
<td>13 (6.4)</td>
<td>12/35 (34.3)</td>
<td>Nonsurgery</td>
<td>3.0%</td>
</tr>
<tr>
<td></td>
<td>IV Subtotal</td>
<td>42 (41.6)</td>
<td></td>
<td>105 (57.7)</td>
<td>38.0%</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Nonsurgery</td>
<td>14.0%</td>
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<td></td>
<td>44.0%</td>
<td>16.5%</td>
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<td></td>
<td></td>
<td></td>
<td>Surgery + adjuvant</td>
<td>38.0%</td>
</tr>
<tr>
<td>Thymic carcinoma</td>
<td>Subtotal</td>
<td>37 (20.3)</td>
<td></td>
<td>24 (13.2)</td>
<td>48.0%</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>Surgery + adjuvant</td>
<td>16.5%</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Nonsurgery</td>
<td>14.0%</td>
</tr>
<tr>
<td></td>
<td>Inop Total</td>
<td>53 (29.1)</td>
<td>18/28 (64.3)</td>
<td>Nonsurgery</td>
<td>37.5%</td>
</tr>
<tr>
<td></td>
<td>Thymic carcinoid Subtotal</td>
<td>2 (5.0)</td>
<td></td>
<td>53 (29.1)</td>
<td>52.1%</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>Surgery + adjuvant</td>
<td>6.3%</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Nonsurgery</td>
<td>16.5%</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>62.8%</td>
<td>9.1%</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Surgery + adjuvant</td>
<td>22.7%</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Nonsurgery</td>
<td>16.5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>50.0%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

* A number in a parenthesis is a percentage.

**Statistical Analysis**

Prognostic factors were analyzed by the Kaplan-Meier method with respect to survival and recurrence, and deaths due to the complications (myasthenia gravis and pure red cell aplasia, etc) or unrelated disease were
excluded from analysis. The comparisons between survival curves were carried out by the log-rank test. Significance was defined as a $p$ value less than 0.05.

**Results**

**Stage of Disease**

The stages and the histologic types of thymic epithelial tumors are shown as follows. In thymoma, 522 patients (48.3%) were in stage I, 247 (22.8%) in stage II, 204 (18.9%) in stage III, 73 (6.8%) in IVA, and 35 (3.2%) in IVB. In thymic carcinoma, 10 patients (5.3%) were in stage I, 11 (5.9%) in stage II, 74 (39.0%) in stage III, 26 (13.9%) in IVA, and 61 (32.6%) in IVB. In thymic carcinoid, 8 patients (19.5%) were in stage I, 4 (9.8%) in stage II, 12 (29.3%) in stage III, 4 (9.8%) in IVA, and 11 (26.8%) in IVB.

**Resectability of Thymic Epithelial Tumors**

Surgery for thymic epithelial tumors was classified into three groups: total resection (no tumor remained macroscopically), subtotal resection (almost all of the tumor was resected macroscopically), and inoperable (including partial resection, exploratory thoracotomy and simple biopsy) groups. The resectability rates of stage I, II, III, and IV thymomas were 100%, 100%, 85%, and 42%, respectively. Fifty-one percent of patients with carcinoma and 88% of patients with carcinoid underwent a total resection (Table 1).

**Recurrence of Totally Resected Thymic Epithelial Tumors**

Of 981 patients with thymoma who underwent macroscopically total resection, 862 patients had information on recurrence. Of these, 67 patients (7.8%) developed recurrence. The recurrence rates in stages I, II, III, and IV were 0.9%, 4.1%, 28.4%, and 34.3%, respectively. In thymic carcinoma, 51% of patients developed recurrence, whereas, in thymic carcinoid, 64% of patients had recurrence (Table 1).
Treatment for Thymic Epithelial Tumors

Treatments for thymic epithelial tumors were divided into three groups: only surgery, surgery plus adjuvant therapy including radiotherapy or chemotherapy, and nonsurgery groups including exploratory thoracotomy and simple biopsy (Table 1). Most of patients with stage I thymoma underwent only surgery. About half of the patients with stage II thymoma and three-fourths of the patients with stage III thymoma underwent surgery with adjuvant therapy. Most of the adjuvant therapy in stages I, II, and III thymomas consisted of radiotherapy. Seventy-one percent of patients with stage IV thymoma and 58% of patients with carcinoma underwent surgery with adjuvant therapy. In more than half, adjuvant therapy included chemotherapy. In thymic carcinoid, 54% of patients underwent surgery with adjuvant therapy. In sixty-eight percent of this group, adjuvant therapy consisted of radiation therapy only.

Survival Rate of Thymic Epithelial Tumor Patients

Figure 1 shows the survival curves for 924 thymomas, 154 thymic carcinomas, and 35 thymic carcinoids. The 5-year survival rates for thymoma, thymic carcinoid, and thymic carcinoma, including inoperable cases, were 94.4%, 84.4%, and 50.5%, respectively. There were significant differences in survival rate between thymoma and thymic carcinoma (p < 0.0001), thymoma and thymic carcinoid (p = 0.0032), and thymic carcinoid and thymic carcinoma (p = 0.0017).

Survival Rate of Patients With Thymoma, Thymic Carcinoma, and Thymic Carcinoid According to Masaoka Clinical Staging System

Figure 2a shows the survival curve of thymoma according to the clinical stage. The 5-year survival rates of stage I, II, III, IVA, and IVB thymomas were 100%, 98.4%, 88.7%, 70.6%, and 52.8%, respectively. Significant differences in survival rate were observed between stages II and III (p < 0.0001), and between stages III and IVA (p = 0.0011). There was no significant difference in survival rate between stages I and II, or stages IVA and IVB. As the case numbers in stage I (n = 9) and II (n = 10) were small in thymic carcinoma, stage I cases were combined with stage II cases. The 5-year survival rates of stage I plus II, III, and IV thymic carcinoma were 88.2%, 51.7%, and 37.6%, respectively (Fig 2b). Significant differences in survival rate were observed between stage I plus II and III (p = 0.0178), and between stages III and IV (p = 0.0485). Figure 2c shows the survival curves of stage I plus II, III, and IV thymic carcinoid, with the 5-year survival rates of 88.9%, 90.9%, and 72.9%, respectively. No significant difference in survival rate was observed among these three groups.

Survival Rate in Stage III and IV Thymomas and Thymic Carcinoma According to Operation Modes

All stage I and II thymomas were totally resected and their prognosis is excellent (Fig 3). In stage III and IV thymoma, the 5-year survival rates of total resection, subtotal resection, and inoperable groups were 92.9%, 64.4%, and 35.6%, respectively. There were significant differences in survival rates between the total resection and subtotal resection groups (p < 0.0001), and between the subtotal resection and inoperable groups (p = 0.0028). On the other hand, in thymic carcinoma, the 5-year survival rates of total resection, subtotal resection, and inoperable groups were 66.9%, 30.1%, and 24.2%, respectively. There were significant differences in survival rates between the total resection and subtotal resection groups (p = 0.0066), and between the total resection and inoperable groups (p < 0.0001). No significant difference in survival rates between subtotal resection and inoperable group was observed (p = 0.2066).
Survival Curve of Stage III-IV Thymoma and Thymic Carcinoma According to the Therapeutic Modalities

The 5-year survival rates of patients with totally resected stage III-IV thymoma with chemotherapy, with radiochemotherapy, with radiotherapy, and with no adjuvant therapy were 81.5%, 46.6%, 73.6%, and 72.2%, respectively. There was a significant difference in survival between patients with radiochemotherapy and those with radiotherapy ($p = 0.0213$), and between those with radiochemotherapy and those with no adjuvant therapy ($p = 0.0397$).

Recurrence of Stage II and III Thymomas

Of the patients with stage II thymoma, 122 were treated by surgery alone, and 86 underwent surgery with radiotherapy. The doses of radiation therapy in 80 of 86 patients were more than 40 Gy (43.7 ± 7.7 Gy [mean ± SD]). Five (4.1%) of 122 patients without additional radiotherapy and 4 (4.7%) of 86 patients with additional radiotherapy had recurrence. In local recurrence, 2 (1.6%) patients without additional radiotherapy and no patient with additional radiotherapy relapsed.

Of the patients with stage III thymoma, 31 underwent surgery alone, and 78 patients underwent surgery with radiotherapy. The doses of radiation therapy in 73 of 78 patients were more than 40 Gy (45.4 ± 8.4 Gy). Eight (26%) of 31 patients without additional radiotherapy and 18 (23%) of 78 patients with additional radiotherapy had a recurrence. In local recurrence, 1 (3.1%) patient without additional radiotherapy and 4 (5.1%) patients with additional radiotherapy relapsed. There was no significant difference in incidence in the recurrence between the surgery alone and surgery with radiotherapy groups in stage II and III thymoma.

Comment

The Masaoka staging system is advocated as the appropriate one to adopt [7, 15]. In this study, the rates of stage I, II, III, and IV thymoma were 48%, 23%, 19%, and 10%, respectively. The treatment of thymoma depends upon its clinical stage. Most patients with stage I thymoma were treated by surgery alone, and patients with stage II and III thymomas were treated by surgery with radiotherapy. Patients with stage IV thymomas were treated by surgery with adjuvant therapy including chemotherapy. Our therapeutic strategy for thymoma was similar to that in other reports [7, 9]. The recurrence rates in this study were low compared with previous reports (stage I, 3% to 12%; II, 13% to 33%; III, 27% to 47%) [7, 15, 16]. In this study, the 5-year survival rates of stage I, II, III, IV, and IVB thymoma were 100%, 98%, 89%, and 71%, respectively. Several large series reported 5-year survival rates in thymoma (stage I, 89% to 100%; II, 70% to 100%; III, 50% to 87%; and IV, 46% to 50%) [3, 11, 17–19]. We demonstrated that a clear-cut distinction of survival rates between stage I and II thymomas is not always feasible, whereas the distinctions between stage II and III and stage III and IV thymomas are more obvious.

The thymic carcinomas already had invasion to neighboring organs, dissemination (about 90%), and lymph node metastases or distant metastases (about 30%) at
diagnosis, as our and other studies mentioned [20, 21]. The total resection rate (51%) in this study was high compared with previous reports (35% to 39%) [20, 22, 23]. The rate (58%, 33%) of surgery with adjuvant therapy or chemotherapy in this study was similar to the previous data (62% to 79%, 38% to 42%) [22, 23]. Thymic carcinoma has a significantly worse prognosis than thymoma and thymic carcinoma. This study revealed that the Masaoka clinical stage is an excellent indicator predicting the prognosis not only of thymoma but also of thymic carcinoma.

Most thymic carcinoids were treated by surgery with radiotherapy. Although most thymic carcinoids can be completely resected by surgery (88%), they frequently show recurrence (64%). Moran and associates and Fukai and associates reported that although most patients were treated by complete surgical excision (100% and 87%), the recurrence rate was relatively high (36% and 77%) [24, 25]. The Masaoka clinical stage is not a good predictor of the prognosis of thymic carcinoid.

Our data demonstrated that total resection of the tumor is the most important factor in survival rate in invasive thymoma and thymic carcinoma. Maggi and associates [10] found that the type of surgery affected the survival in invasive thymoma. Patients with invasive thymoma who received radical surgery survived 80% at 5 years and 73% at 10 years, compared with 59% and 44% for patients who had subtotal resection, and 42% and 21% (at 8 years) for those who had only a biopsy, respectively [10]. The data in this study are in agreement with Maggi’s data. We reported that the 5-year survival rates of total resection, subtotal resection, and inoperable groups were 93%, 64%, and 36%, respectively, in III and IV thymoma. There were significant differences in survival rate among the three surgical types. Subtotal resection of invasive thymoma may yield a surprisingly high survival rate compared with inoperable cases, including partial resection or biopsy. We think that the surgeon must attempt to remove a thymoma as much as possible, even if complete resection could not be carried out. On the other hand, in thymic carcinoma, the 5-year survival rates of total resection, subtotal resection, and inoperable groups were 67%, 30%, and 24%, respectively. No significant difference in survival rate between the subtotal resection and inoperable groups was observed. These data suggest that there is a value of so-called “debulking procedures” in invasive thymoma, but not in thymic carcinoma.

In this study, the recurrent rates of completely resected stage II and III thymomas were 4.7% and 23% in patients with postoperative radiotherapy and 4.1% and 26% in patients without radiotherapy, respectively. Quintanilla-Martinez and associates reported that 28% and 13% of patients with postoperative radiotherapy and 8% and 13% of patients without postoperative radiotherapy relapsed in completely resected stage II and III thymomas, respectively [19]. Haniuda and associates reported that 23% and 30% of patients with postoperative radiotherapy and 25% and 25% of patients without postoperative radiotherapy relapsed in completely resected stage II and III thymomas, respectively [26]. These studies, including our data, demonstrated that the recurrence rates of completely resected stage II and III thymomas were not significantly decreased by postoperative radiotherapy. Furthermore, our data revealed that the local recurrence rates of stage II and III thymomas were not significantly decreased by postoperative radiotherapy. The local recurrence rates of completely resected stage II and III thymomas were 0% and 5.1% in patients with postoperative radiotherapy and 1.6% and 3.1% in patients without radiotherapy, respectively. On the other hand, several reports suggest the utility of postoperative mediastinal radiotherapy in preventing recurrence in patients with invasive thymoma [15, 27]. Our coworker reported in a previous study that 8% and 24% of patients with postoperative radiotherapy and 29% and 40% of patients without postoperative radiotherapy relapsed in stage II and III thymoma, respectively [15]. Curran and associates reported that no patient with postoperative radiotherapy and 42% of patients without postoperative radiotherapy relapsed in stage II and III thymoma [27]. Most authors do not recommend radiotherapy after totally resected stage I (noninvasive) thymoma [7, 9]. We doubt that postoperative radiotherapy is valuable in patients with totally resected stage II and III thymoma, although we believe in the value of postoperative radiotherapy in patients with incompletely resected stage II and III thymoma.

This study also demonstrated that adjuvant radiotherapy did not improve the prognosis of invasive thymoma, although most cases with radiation therapy received a sufficient dose of radiation. In patients with completely resected III and VI thymoma, there was no significant difference in survival rate between surgery alone and surgery with radiotherapy (5- and 10-year survival: 100% and 95% vs 93% and 78%). Cohen and associates were unable to demonstrate any significant difference in survival between patients with postoperative radiotherapy and those without it in completely resected thymoma [28]. Although several reports have demonstrated that patients with invasive thymoma benefited from application of postoperative irradiation, these studies were not a controlled and had insufficient numbers of patients [12, 17, 27, 29]. Nakahara and associates reported that patients with stage III thymoma who underwent complete resection followed by postoperative irradiation survived 100% at 5 years and 95% at 10 years [17]. However, they did not show the prognosis of patients with stage III thymoma who underwent surgery alone. Whether or not postoperative mediastinal radiotherapy reduces the rate of local recurrence and improves the prognosis in completely resected invasive thymoma is controversial. Prospective randomized control studies will be necessary in order to determine the true role of additional radiotherapy for patients with completely resected stage II and III thymoma.

In this study, there was no significant difference in survival between surgery alone and surgery with radiotherapy in completely resected thymic carcinoma (5-year survival, 72% vs 74%). There are few reports on the effect of adjuvant radiotherapy in completely resected thymic
carcinoma [29]. Considering the small number of patients, no conclusion can be drawn concerning the effect of radiotherapy.

This study demonstrated that chemotherapy does not bring any survival benefits to patients with completely resected stage III and IV thymomas and thymic carcinoma. However, as this study included the results of 115 institutes, the cycle, regimen, and dose of chemotherapy were varied. Large-scale and prospective randomized trials with a constant regimen of chemotherapy should elucidate the true effect of chemotherapy for invasive thymoma and thymic carcinoma.

In conclusion, complete resection is the most important factor in the treatment of thymic epithelial tumor. Surgery alone is sufficient for patients with noninvasive thymoma (stage I thymoma). Prophylactic radiotherapy can not prevent local recurrence effectively in patients with totally resected stage II and III thymoma. There is a value of so-called “debulking procedures” in invasive thymoma, but not in thymic carcinoma.

References

INVITED COMMENTARY
The classification and treatment of thymic epithelial tumors has been in evolution over the last 40 to 50 years. New systems of histologic classification have been proposed by Levine and Rosai in 1978, Muller-Hermelink in 1985, and Suster and Moran in 1999. The Masaoka system was introduced in the 1970s and 1980s and is based on the presence or absence of capsular invasion, direct extension into surrounding structures, and metastatic disease. This classification system is fairly easily interpreted from the surgical perspective, considering that previous differentiation between invasive and noninvasive thymomas was primarily based not on histological criteria but on surgical interpretation of intraoperative findings.

The W.H.O. classification was introduced in 1999 and represents an attempt to standardize histologic classification of thymic epithelial tumors and to provide guidelines to assess invasiveness on histologic as well as surgical parameters. It provides a more consistent ap-