Staging System of Thymoma

Akira Masaoka, MD, PhD

Introduction: Thirty years have gone by since the Masaoka staging system of thymoma was proposed in 1981. Although the Masaoka staging system has been accepted by many surgeons and pathologists, some proposals of revision and improvements have been suggested. At this time, I reinvestigated the Masaoka staging system based on the recent follow-up study of the thymomas resected at Nagoya City University.

Methods: Using the follow-up results of 211 thymomas in Nagoya, I analyzed the following aspects: (1) evaluation of the Masaoka staging system as a prognostic factor in the Nagoya series and (2) critical assessment of the proposals of revision to the Masaoka staging system.

Results: (1) Univariate analysis showed that Masaoka stages were significantly prognostic for overall survival ($p < 0.0001$). (2) The difference of survivals between stage I and II was not significant, but progression-free survival of stage I was 100% for up to 20 years, whereas one tumor death case in stage II was found. (3) Differences of survival between the cases with and without great vessel invasion in stage III were not significant. (4) Prognosis of N^+ tumors was yet better defined.

Conclusion: (1) The Masaoka staging system remains a valuable prognostic factor. (2) Combination of stage I with II and separation of stage III into subgroups are not recommended. (3) At the moment, it is better to include N^+ tumors in stage IVb.

Key Words: Thymoma, Staging system, TNM classification, Follow-up study.

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In the 1960s, thymomas were classified into two categories: noninvasive and invasive. Bernatz et al.[1] proposed a histologic classification and described four histologic subtypes: predominantly lymphocytic type, predominantly epithelial type, predominantly mixed type, and predominantly spindle cell type. Tumors belonging to the first three categories consisted of round epithelial cells and lymphocytes with differences in the ratio of the two components determining the category that the tumor belonged to. Bernatz et al. found that the predominantly epithelial subtype of thymoma was the most dominant among invasive thymomas.

To quantify the ratio of epithelial cells and lymphocytes, we[2] calculated the numbers of these cells and determined the lymphocytes to epithelial cells ratio (L/E ratio). In our series of 22 cases, L/E ratios ranged from 0.27 to 4.10 with a mean value of 1.93 (Figure 1).

We also found a significant difference in the L/E ratios of invasive and noninvasive thymomas (Figure 2) with invasive thymomas having a lower ratio than noninvasive thymomas. This had also been recognized by Bernatz et al. In our series, we found three cases of recurrent thymoma with L/E ratios that were strikingly lower as compared with tumors at the time of diagnosis (Figure 3). Hence, it seemed that the L/E ratio changed based on the biologic behavior of the tumor: a decrease in the L/E ratio seemed to correlate with a change in the nature of the tumor from encapsulated thymoma to invasive thymoma. This finding led to propose a staging system for thymomas.

MASAOKA STAGING SYSTEM

To establish a new staging system for thymomas, we took into consideration a few basic characteristics of the disease:

1. Thymoma is a very slow growing tumor. In our experience, it could take as long as 30 years for a noninvasive thymoma to become invasive if it was not surgically resected.
2. Some noninvasive thymomas that had been resected completely recurred in the same region.
3. Some patients with completely resected invasive thymomas could survive.
4. Pleural dissemination is a frequent site of progression.
5. Some patients develop lymphogenous or hematogeneous metastases.

Two other staging systems were developed by Bergh et al.[3] and Wilkins and Castleman[4] (Table 1). The difference between the two systems was limited to one point: stage II Wilkins thymoma involved pleura and pericardial invasion.

In our opinion, there were some major inadequacies in the staging systems of Bergh et al. and Wilkins and Castleman: (1) the actual sites of intrathoracic metastasis were not clear, (2) the description of invasion was inadequate, (3) stage III includes too broad spectrum of disease, and (4) hematogenous and lymphogenous metastases were not well represented.

Emeritus Professor of Surgery, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan.

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Address correspondence to: Akira Masaoka, MD, PhD; Emeritus Professor of Surgery, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan. E-mail: tenpaku@med.nagoya-cu.ac.jp

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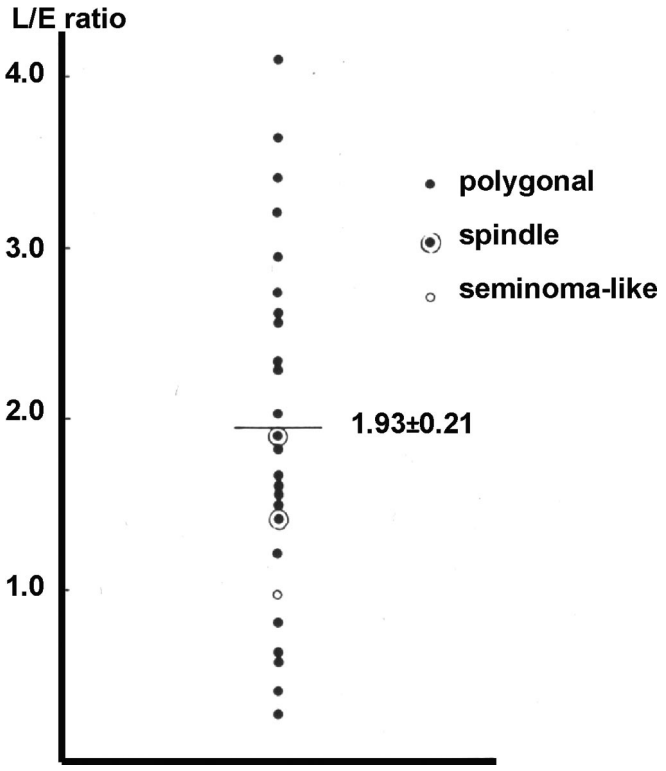

FIGURE 1. L/E ratio of thymomas. Reprinted with permission from *Cancer* 1977;40:1225.

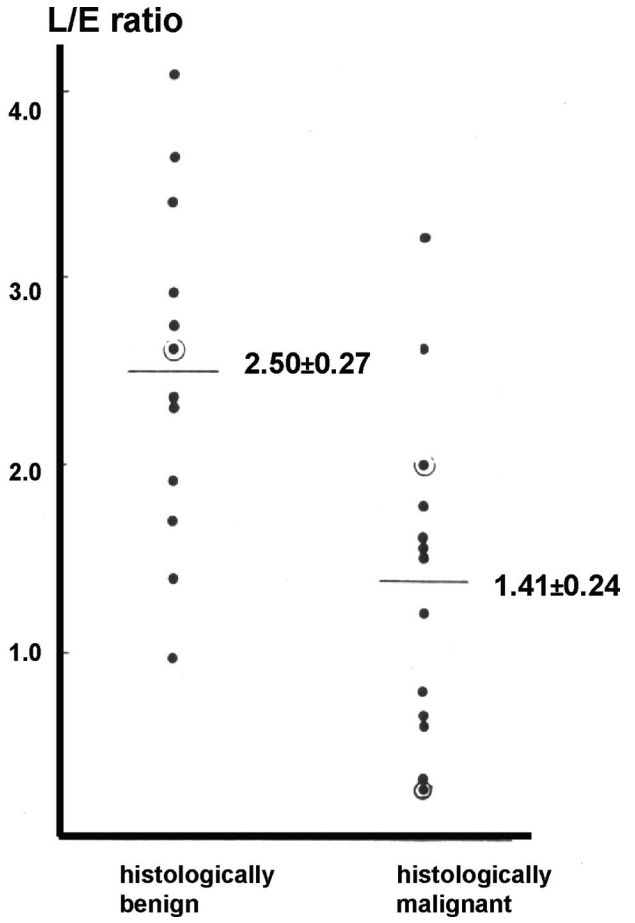

FIGURE 2. L/E ratios of noninvasive and invasive thymomas. Reprinted with permission from *Cancer* 1977;40:1226.

We proposed a surgical and pathologic staging system based on the extent of disease in 1981 (Table 2).[5] We defined tumor extent as follows: (1) stage I: completely encapsulated, (2) stage II: invasion by the second layer surrounding the tumor (defined below), (3) stage III: direct invasion beyond the second layer, and (4) discontinuous progression.

The anatomic layers surrounding the tumor are depicted in Figure 4. Invasion into the pleural cavity is preceded by breaching of anatomic barriers in the following sequence: capsule, mediastinal pleura, visceral pleura, and finally lung. On the other hand, when the tumor invades the mediastinum, it invades through the capsule, mediastinal adipose tissue, pericardium or great vessels, and finally heart. Accordingly, the second layer surrounding the tumor is either the mediastinal pleura or mediastinal adipose tissue.

There are two points that need to be stressed. First, stage II disease involves invasion into the mediastinal pleura at perioperative inspection, even if histologic invasion could not be proved. We believe that this finding precedes histologic invasion.

Second, stage IV disease is divided into two categories IVa and IVb. Stage IVa consists of serosal dissemination, i.e., involvement of the pleura and pericardium. Stage IVb consists of metastasis via lymphogenous and hematogenous routes. Accordingly, stage IVb includes cases with lymph node metastasis at any station.

In 1981, we reviewed 93 thymoma cases at Osaka University.[5] The stage of disease is shown in Table 3. All three cases of stage IVb disease had hematogenous metastasis involving the liver, lung, and rib. Survival curves associated with these four stages are shown in Figure 5.

CHANGE IN THE OPERATIVE PROCEDURE FOR THYMOMA

In 1970s, an important problem for thoracic surgeons was the operative route in thymectomy for myasthenia gravis. Whether transsternal or transcervical, the target of resection was the intracapsular thymus. I call it simple thymectomy.

However, we became aware that the results of transcervical thymectomies were inferior to those of transsternal thymectomies. We suspected that parts of the thymic tissues might be left in the transcervical thymectomies. So, we investigated the presence and distribution of thymic tissues in the anterior mediastinum systematically.[6] As a result of this study, we found many foci of thymic tissues in the extrathymic anterior mediastinal adipose tissues in most cases.

I thought that to eliminate the thymic tissues, en bloc resection of the anterior mediastinal adipose tissues including the thymus gland is necessary. So, I advocated to apply this procedure in the treatment of myasthenia gravis, and named it "extended thymectomy".[7] It could improve the operative results for myasthenia gravis.

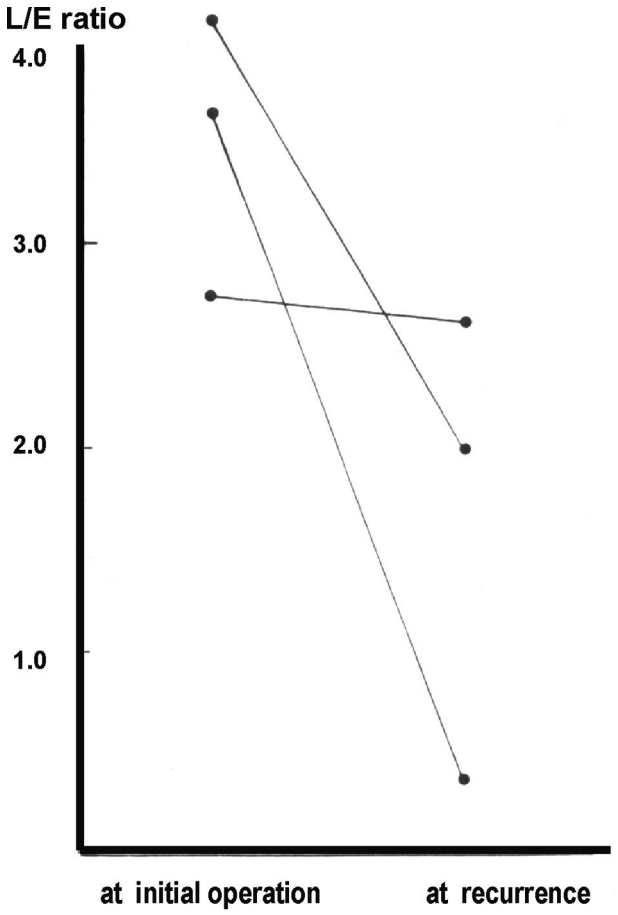

FIGURE 3. L/E ratios of initial and recurrent tumors in three thymomas. Reprinted with permission from *Cancer* 1977;40:1227.

TABLE 1. Staging System by Bergh et al. and Wilkins and Castleman[3,4]

Stage	Description
Staging system by Bergh et al.	
Stage I	Intact capsule or growth within the capsule
Stage II	Pericapsular growth into the mediastinal fat tissue
Stage III	Invasive growth into the surrounding organs, intrathoracic metastases, or both
Staging system by Wilkins and Castleman	
Stage I	Intact capsule or growth within the capsule
Stage II	Pericapsular growth into the mediastinal fat tissue or adjacent pleura or pericardium
Stage III	Invasive growth into the surrounding organs, intrathoracic metastases, or both

On the other hand, at that time, another problem concerning thymomectomy was pointed out. It was the occurrence of myasthenia gravis after thymomectomy for nonmyasthenic patients.[8] In this era, resection of only the thymoma was the standard operation for thymoma. I call it simple thymomectomy. I thought, to prevent the occurrence of postthymomectomy myasthenia gravis, surgeons should perform the extended thymectomy, instead of simple thymomectomy for the thymoma patients, too.[5]

The aim of this procedure was prevention of the postthymomectomy myasthenia gravis, and its conduct in all thymoma patients was supported by finding of lack of immunologic deficiency in the myasthenic patients, who had undergone these operations.

Table 4 shows transition of operative procedures in Nagoya City University occurring every 5 years. In early 1980s, simple thymomectomy was dominant, but later the extended thymectomies were performed in most patients. After the extended thymectomy became a routine operation for thymoma, we encountered lymphnode metastases, which

TABLE 2. Masaoka Staging System[5]

Stage I	Macroscopically completely encapsulated and microscopically no capsular invasion
Stage II	1. Macroscopic invasion into surrounding fatty tissue or mediastinal pleura, or
	2. Microscopic invasion into capsule
Stage III	Macroscopic invasion into neighboring organ, i.e., pericardium, great vessels, or lung
Stage IVa	Pleural or pericardial dissemination
Stage IVb	Lymphogenous or hematogenous metastasis

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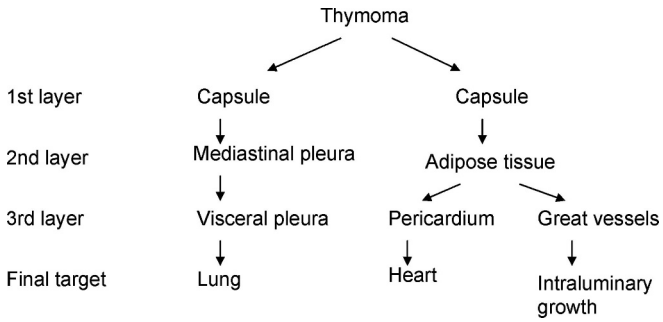

FIGURE 4. Process of invasion of thymoma. Left lane indicates course to pleural cavity. Right lane indicates course to deep mediastinum.

TABLE 3. Masaoka's Stages and Patients Distribution (Osaka University, 1981)

Stages	No. of Patients
Stage I	37
Stage II	13
Stage III	32
Stage IVa	8
Stage IVb	3[a]
Total	93

[a] Liver, lung, and rib metastasis.

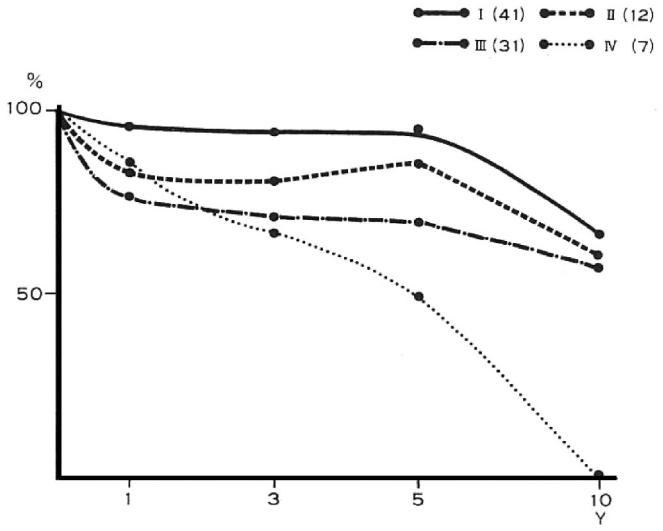

FIGURE 5. Survival curves of each stage in thymoma (Osaka University, 1981). Reprinted with permission from *Cancer* 1981;48:2491.

TABLE 4. Transition of Operative Procedures

	Exploratory Thoracotomy	Subtotal Resection	Simple Thymomectomy	Extended Thymectomy	Total
1971–1975	1	0	1	0	2
1976–1980	1	0	5	2	8
1981–1985	1	2	8	6	17
1986–1990	2	3	6	9	20
1991–1995	0	3	1	19	23
1996–2000	0	8	0	22	30
2001–2005	0	8	3	43	54
2006–2008	2	6	9	30	47
Total	7	30	33	131	201

were found in the anterior mediastinal adipose tissues resected by this operation. This let us propose our tumor, node, metastasis (TNM) classification system.

TNM CLASSIFICATION SYSTEM

In 1991, we proposed a TNM classification system for thymoma (Table 5).[9] T factors mimicked the staging criteria. N1 corresponds to anterior mediastinal, N2 other mediastinal, and N3 extrathoracic lymphnode metastasis. M1 means hematogenous metastasis in any organ.

However, the staging system was not revised. All N-positive and M-positive cases were included in stage IVb.

EVALUATION OF THE MASAOKA STAGING SYSTEM AS A PROGNOSTIC FACTOR

Many authors investigated the relationship between the Masaoka stage and survival. Major articles on these investigations since 1990 are listed in Table 6.[10–26] Almost all authors except Wilkins et al.[13] recognized a significant correlation between staging and survival.

TABLE 5. TNM Classification of Thymoma (Yamakawa, Masaoka)[9]

T factor	
T1	Macroscopically completely encapsulated and microscopically no capsular invasion
T2	Macroscopically adhesion or invasion into surrounding fatty tissue or mediastinal pleura, or microscopic invasion into capsule
T3	Invasion into neighboring organs, such as pericardium, great vessels, and lung
T4	Pleural or pericardial dissemination
N factor	
N0	No lymph node metastasis
N1	Metastasis to anterior mediastinal lymph nodes
N2	Metastasis to intrathoracic lymphnodes except anterior mediastinal lymph nodes
N3	Metastasis to extrathoracic lymphnodes
M factor	
M0	No hematogenous metastasis
M1	Hematogenous metastasis

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REINVESTIGATION OF THE MASAOKA STAGING SYSTEM

In 1980, I was transferred to Nagoya City University from Osaka University. In 2010, we performed a follow-up study of thymomas in Nagoya City University and reinvestigated the relationship between stages and survival after an interval of 30 years from the Osaka series.[27]

The series consists of 211 thymomas treated in Nagoya City University Hospital from 1971 to 2008. Of these, 201 patients underwent operations: exploratory thoracotomy in 7, subtotal resection of tumor in 30, simple thymomectomy in 33, and extended thymectomy in 131 patients. Stage distribution is as follows: stage I 76 (36.0%), stage II 61 (28.9%), stage III 31 (14.7%), stage IVa 33 (15.6%), and stage IVb 10 (4.7%). Two survival parameters were adopted: overall survival and progression-free survival.

The overall survivals of each stage are shown in Figure 6 and Table 7. The curves are arranged stepwise according to the stages. Survival of IVb seems somewhat superior to that of IVa. Significant differences are found in I versus III, I versus IVa, I versus IVb, II versus III, II versus IVa, II versus IVb.

The progression-free survivals are shown in Figure 7 and Table 8. The survival curves of I and II become much closer and have high percentage of survival (stage I: 100%, stage II: 94.1%). The survival curves of stage IVa and IVb are nearly superimposed. Overall survival curves seem to fall into three groups; stage I and II, stage III, and stage IVa and IVb.

The reason why the progression-free survival rates of stage I and II lie higher than the overall survival curves is that most of the deaths in stage I and II are due to the associated disease or complication of therapies, but not the tumor. Indeed, only one patient with stage II died due to tumor recurrence. In contrast, the progression-free survival rates of stage IVb were lower than the overall survival rates. This

TABLE 6. The *p* Values of Stage vs. Survival

Author	City	Publish	No. of Case	Survival	*p*	Remarks
Pescarmona et al.[10]	Rome	1990	83	Overall	<0.001	
Regnard et al.[11]	Le Plessis- Robinson	1996	307	Disease free	<0.00001	
Gripp et al.[12]	Düsseldorf	1998	70	Disease free	0.0001	
Wilkins et al.[13]	Baltimore	1999	136	Overall	0.123	
				Thymoma related	0.290	
Lardinois et al.[14]	Lausanne	2000	71	Overall	<0.05	
				Disease free	<0.0001	
Ogawa et al.[15]	Multi institutional	2002	103	Overall	<0.0001	
				Disease free	<0.0001	
Okumura et al.[16]	Osaka	2002	273	Tumor specific	<0.0001	
Nakagawa et al.[17]	Tokyo	2003	130	Overall	0.000	Modified Masaoka
Kondo et al.[18]	Tokushima	2004	100	Disease free	0.002	
Park et al.[19]	Seoul	2004	150	Overall	<0.001	Thymic EP tumor
Rea et al.[20]	Padua	2004	132	Overall	0.003	Thymic EP tumor
Zhu et al.[21]	Shanghai	2004	175	Overall	<0.0001	
				Disease free	<0.0001	
Kim et al.[22]	Seoul	2005	108	Tumor specific	0.000	
Rena et al.[23]	Torino	2005	178	Overall	0.036	
				Disease free	0.012	
Mineo et al.[24]	Rome	2005	88	Overall	0.001	
				Disease free	0.0001	
Wright et al.[25]	Boston	2005	179	Tumor specific	<0.0001	Thymic EP tumor
Bedini et al.[26]	Milan	2005	123	Progression free	0.0001	

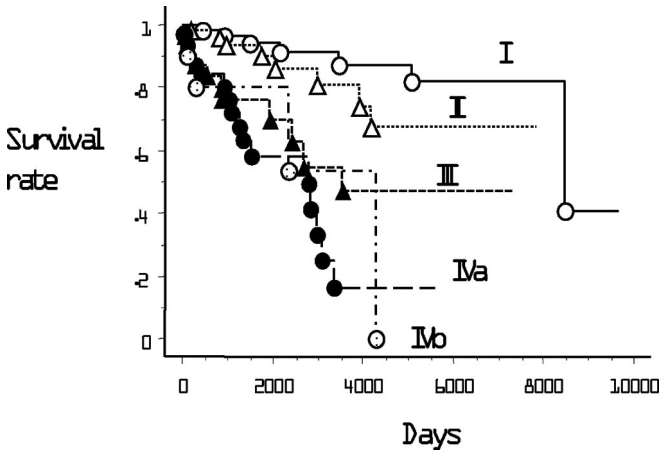

FIGURE 6. Masaoka stages and overall survival. Survival curves are ranged stepwise. Survival curve of IVb seems somewhat superior to that of IVa. I versus II: $p = 0.1162$; I versus III: $p = 0.0001$; I versus IVa: $p < 0.0001$; I versus IVb: $p < 0.0001$; II versus III: $p = 0.0094$; II versus IVa: $p < 0.0001$; II versus IVb: $p = 0.0116$; III versus IV: $p = 0.3319$; IVa versus IVb: $p = 0.7042$.

finding was due to the presence of persistent tumor in surviving patients with stage IVb.

Univariate analysis proved that the relationship between overall survival and stage is significant ($p < 0.0001$). However, we could not show a relation between progression-free survival and stage, because the progression-free survival in stage I remained 100% up to 20-year follow-up.

TABLE 7. Masaoka Stage and Overall Survival

	Survival Rate (%)/Patients at Risk Postoperative Time (ys)				
	1	3	5	10	20
I/76	100/62	96.4/48	94.0/36	87.1/20	81.7/6
II/61	98.2/49	93.3/35	89.7/24	80.6/14	67.2/1
III/31	85.3/22	72.5/15	72.5/13	44.9/6	44.9/1
IVa/33	87.4/24	70.4/16	55.9/9	20.0/2	
IVb/10	77.8/7	77.8/5	77.8/3	51.9/1	

COMPARISON OF THE RESULTS OF THE OSAKA SERIES AND THE NAGOYA SERIES

I compared the results of the Osaka series ($n = 93$) and the Nagoya series ($n = 211$). Both were investigated with 30 years follow-up. Differences are as follows; (1) the overall survivals in stage I and II of the Nagoya series are superior to those of Osaka series (10-year survival rates of stage I: 87.1% versus 66.7%, those of stage II: 80.6% versus 60.0%), (2) the overall survivals in stage IV of Nagoya series are superior to that of Osaka series (10-year survival rates of stage IV: IVa 20.0%, IVb 51.9% versus IV 0%).

These differences might be caused by the change in the operative procedures. In the Osaka series, a majority of patients underwent simple thymomectomies, whereas a majority of patients in the Nagoya series underwent extended thymectomies. The extended thymectomies could reduce tumor recurrence, particularly in stage I and II, and increase incidence of N^+ cases classified in stage IVb.

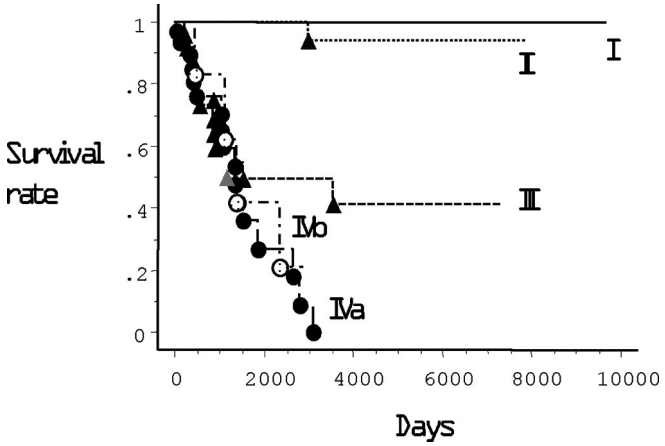

FIGURE 7. Masaoka stages and progression-free survival. Those of stage IVa and IVb become nearly superimposed. I versus any stage: not available; II versus III: $p < 0.0001$; II versus IVa: $p < 0.0001$; II versus IVb: $p < 0.0001$; III versus IVa: $p = 0.1028$; III versus IVb: $p = 0.7426$; IVa versus IVb: $p = 0.6021$.

TABLE 8. Masaoka Stage and Progression-Free Survival

	Survival Rate (%)/Patients at Risk Postoperative Time (ys)				
	1	**3**	**5**	**10**	**20**
I/76	100/62	100/48	100/36	100/20	100/6
II/61	100/49	100/35	100/24	94.1/15	94.1/1
III/31	91.7/22	68.8/12	59.6/8	49.7/5	41.4/1
IVa/33	85.1/20	75.9/11	53.7/4	0/0	
IVb/10	100/7	83.3/4	41.7/2	0/0	

Indeed, in the Osaka series, recurrences occurred in two of 37 of stage I and three of 13 of stage II. On the other hand, in the Nagoya series, recurrence occurred only in one of 61 of stage II, who had undergone simple thymomectomy.

Furthermore, in the Nagoya series, nine N^+ cases were detected, whereas no N^+ cases were observed in the Osaka series. There were five cases of T3N1M0. Although the mean follow-up period was only 4.3 years, two T3N1M0 cases had recurrences. Prognosis of N^+ thymoma is a significant problem.

PROPOSALS OF REVISION OF THE MASAOKA STAGING SYSTEM

Although the Masaoka staging system was in general recognized as a valuable prognostic indicator, some proposals for its revision have been suggested.

Combination of Stage I and II

Gupta et al.[28] reviewed 21 papers published in the 21st century and performed a metaanalysis of the results of stage I and II cases. Because they did not find significant differences between them, they proposed to combine stage I and II, and collapse the staging system into three stages.

I had read these 21 articles in detail and found two issues that are important and need to be mentioned. The first is divergence of the definition of stage II among reports. Some include the cases with histologic invasion to mediastinal pleura into stage II, whereas others include them into stage III. Such confusion might originate from the insufficient description of stage II that I wrote myself. The paragraph in the definition of stage II 1 (Table 2) should be read as follows: with or without histologic invasion.

The second issue to be mentioned is the lack of description of operative procedures in many of these 21 reports. As mentioned earlier, the operative procedure might affect the results. Whether extended thymectomy or simple thymomectomy was used is an important issue. However, many authors did not describe it in their reports. The results of stage I and II should be reinvestigated after addressing these two issues.

Furthermore, there is a trend to use thoracoscopic surgery for stage I and II thymoma, which does not allow to perform an extended thymectomy. The prevalence of thoracoscopic surgery could affect the survival of stage I and II thymomas.

However, some reports recognized a significant difference between the results of stage I and II, as described by Haniuda et al.,[29] Mineo et al.,[24] Maggi et al.,[30] and Lardinois et al.[14]

I did not observe significant differences between stage I and II in overall survival. However, progression-free survival of stage I remained at 100% for a long time in our series. In such circumstance, the presence of a tumor death case in stage II might be meaningful, even if the number of cases is very small.

Based on the above mentioned reasons, I think, it is better to keep the separation of stage I and II at the moment.

Separation of Subgroups in Stage III

Okumura et al.[31] suggested to divide stage III into two subclasses, i.e., IIIa: without great vessel invasion and IIIb: with great vessel invasion, based on his own data.

However, we did not find significant differences in survival between the group with great vessel invasion and that without great vessel invasion in our Nagoya series.

There are scarce reports concerning this subdivision.

Introduction of Other Factors Into the Staging System

Asamura et al.[32] proposed to add tumor size, based on his own data, considering that large tumors (>10 cm in diameter) have a worse prognosis. However, tumor extent, as proposed in the Masaoka staging system seems to be more relevant than dimension. Furthermore, the fact that some types of thymomas can be dramatically reduced in size rapidly after administration of steroids argues against this proposal for change.[33]

There have been proposals to include completeness of operation in the staging system.[11,34] Needless to say, complete resection is the best prognostic factor. However, I think, that a staging system should offer a guideline to select the therapeutic modality. Completeness of resection could be

designated by a separate parameter. I propose the following criteria for results of surgery:

R0a = complete resection by extended thymectomy,
R0b = complete resection by simple thymomectomy,
R1 = microscopically incomplete resection,
R2 = macroscopically incomplete resection.

The subdivision of R0 cases should be useful to analyze the results.

TNM CLASSIFICATION AND STAGE

In 2004, the World Health Organization (WHO) proposed a system of TNM classification and staging (Table 9).[35] This system is similar except for two points: (1) histologic invasion into mediastinal pleura is categorized into T3, (2) T1N1M0, T2N1M0, and T3N1M0 belong to stage III.

In 2005, Bedini et al.[26] proposed a new system named Istituto Nazionale Tumori TNM-based staging system (Table 10). I think, the system by Bedini et al. is too complicated and limitation of the involved area by dissemination might cause confusion in this staging system.

A major difference between the WHO system and mine focuses on the allocation of N1. In the WHO staging system, N1 is included in stage III, whereas it is included in stage IVb in my classification. My system respects the concept of invasion by contiguity (stage III) versus discontinuous progression (stage IV). On the contrary, the WHO staging system respects localization of the involved area, giving priority to the results of operation.

Staging systems of cancers of other organs use progression of metastasis to lymphnode stations as an important part of stage definition. However, lymphnode metastasis is a rare situation in thymoma, and its progression stages are poorly defined. Kondo and Monden[36] collected follow-up data of 1064 thymomas in Japan and there were only 19 (1.8%) cases of N^+ thymomas. This is a low incidence compared with the cancers of other organs. Also in our series, the incidence of N^+ tumor was low: nine of 211 (4.3%). The behavior of lymphogenous metastasis of thymoma warrants further investigation. Until more information is obtained, it might be better to include the N^+ thymomas in IVb stage.

EPILOGUE

The Masaoka staging system still remains a valuable and reproducible prognostic factor of thymoma. However, some proposals of revision of the staging system have been offered, to identify significant differences in survival between each identified stage. In my opinion, the staging system should obey the following principles:

1. It should be logically justified.
2. It should be simple to use.
3. Frequent revisions should be avoided.

TABLE 9. WHO Staging System: TNM Classification

T-Primary tumor			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
T1	Tumor completely encapsulated		
T2	Tumor invades pericapsular connective tissue		
T3	Tumor invades into neighboring structures, such as pericardium, mediastinal pleura, thoracic wall, great vessels, and lung		
T4	Tumor with pleural or pericardial dissemination		
N-Regional lymph nodes			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Metastasis in anterior mediastinal lymph nodes		
N2	Metastasis in other intrathoracic lymph nodes excluding anterior mediastinal lymph nodes		
N3	Metastasis in scalene and/or supraclavicular lymph nodes		
M-Distant metastasis			
MX	Distant metastasis cannot be assessed		
M0	No distant metastasis		
M1	Distant metastasis		
Stage grouping			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1	N1	M0
	T2	N1	M0
	T3	N0, 1	M0
Stage IV	T4	Any N	M0
	Any T	N2, 3	M0
	Any T	Any N	M1

TABLE 10. The Istituto Nazionale Tumori TNM-Based Staging System (Bedini et al.[26])

T1	No capsular invasion			
T2	Microscopic invasion into the capsule, or extracapsular involvement limited to the surrounding fatty tissue or normal thymus			
T3	Direct invasion into the mediastinal pleura and/or anterior pericardium			
T4	Direct invasion into neighboring organs, such as sternum, great vessels, and lungs; implants to the mediastinal pleura or pericardium, only if anterior to phrenic nerves			
N0	No lymph node metastasis			
N1	Metastasis to anterior mediastinal lymph nodes			
N2	Metastasis to intrathoracic lymph nodes other than anterior mediastinal			
N3	Metastasis to prescalene or supraclavicular nodes			
M0	No hematogenous metastasis			
M1a	Implants to the pericardium or mediastinal pleura beyond the sites defined in the T4 category			
M1b	Hematogenous metastasis to other sites, or involvement of lymph nodal stations other than those described in the N categories			
Stage grouping				
I	Locally restricted disease	T1–2	N0	M0
II	Locally advanced disease	T3–4	N0	M0
		Any T	N1–2	M0
III	Systemic disease	Any T	N3	M0
		Any T	Any N	M1
Classification of residual disease				
R0	No residual tumor			
R1	Microscopic residual tumor			
R2a	Local macroscopic residual tumor after reductive resection (>80% of the tumor)			
R2b	Other features of residual tumor			

Adapted from *Ann Thorac Surg* 2005;80:1994–2000.

Since modalities of diagnosis and treatment are progressing day by day, a staging system should be as comprehensive as yet as simple as possible.

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