The Masaoka-Koga Stage Classification for Thymic Malignancies

Clarification and Definition of Terms

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No official stage classification for thymic malignancies has been defined by the Union Internationale Contre le Cancer and the American Joint Commission on Cancer. The International Thymic Malignancy Interest group (ITMIG) has selected the Masaoka system[1] with the modification proposed by Koga et al.[2] as the one that will be used,[3] until a scientifically validated system is defined in the next edition of the international tumor staging manuals in 2017. However, there are details of the Masaoka and Koga classifications that have never been defined clearly. This article addresses this issue to achieve consistency in terms from this point forward for ITMIG initiatives. We hope that this standard will be adopted by all researchers because it will enhance collaboration and definition of a better classification system in the future.

METHODS

The process used in the development of this document was designed to represent a broad consensus within the community of clinicians and researchers interested in thymic diseases. A core work group drafted proposed definitions (Frank C. Detterbeck, Cesar Moran, Andrew Nicholson, Kazuya Kondo, and Paul Van Schil), which were refined by an extended work group (James Huang, Akira Masaoka, Edith Marom, Nicolas Girard, William Travis, Meinoshin Okumura, and Alexander Brunelli). These were further revised at an ITMIG Definition and Terminology workshop on November 16, 2010, which was supported by the International Association for the Study of Lung Cancer. After distribution to all ITMIG members for comment, the final document was approved and adopted by ITMIG members in February 2011.

THE MASAOKA-KOGA STAGING SYSTEM

History of Stage Classification

A three-tiered staging system was proposed by Bergh et al.[4] in 1978 (stage I, within the capsule; stage II, extension into mediastinal fat; and stage III, invasion of surrounding organs or intrathoracic metastases). A similar system was proposed 1 year later by Wilkins et al.,[5] with the difference that stage II specifically mentioned extension into the mediastinal pleura or pericardium. The four-tiered Masaoka staging system was proposed in 1981 (based on 93 patients),[1] and a modification of this classification was suggested by Koga et al.[2] in 1994 (based on 79 patients). This modified classification system has been used most widely. Many institutions and authors who state that they use the "Masaoka system" are actually using the Koga modification when one examines their definitions. Details regarding these two classification schemes are discussed in the next section.

Additional stage classification systems have been proposed. Other suggested modifications of the Masaoka system include subdividing stage I into Ia and Ib groups based on the presence of absence of adherence without microscopic invasion.[6,7] Subdivision of stage III depending on the presence of great vessel invasion is suggested by Association of Directors of Anatomic and Surgical Pathology (ADASP).[8]

Incorporating the completeness of resection into the classification of stage III and IV was also suggested by some authors.[6,7] A French system proposed in 1991 fully incorporated the completeness of resection into the classification.[9] However, this is really a prognostic classification system, because it goes beyond anatomic tumor extent (the focus of stage classification) by including the results of treatment.

Yamakawa et al.[10] proposed a tumor, node, metastasis (TNM) system in 1991 (based on 207 patients), which followed

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TABLE 1. Masaoka-Koga Staging System

Stage	Definition
I	Grossly and microscopically completely encapsulated tumor
IIa	Microscopic transcapsular invasion
b	Macroscopic invasion into thymic or surrounding fatty tissue, or grossly adherent to but not breaking through mediastinal pleura or pericardium
III	Macroscopic invasion into neighboring organ (i.e., pericardium, great vessel, or lung)
IVa	Pleural or pericardial metastases
b	Lymphogenous or hematogenous metastasis

Adapted from *Pathol Int* 1994;44:359–367.

the original Masaoka system for the T descriptor and grouped any N- or M-positive tumor into stage IVb (pleural or pericardial nodules alone are T4, stage IVa). Modifications of this were proposed by Tsuchiya et al.[11] in 1994 and the World Health Organization in 2004.[12] Bedini et al.[13] proposed a modified TNM system in 2005 (based on a sophisticated analysis of 127 patients), which they call the Istituto Nazionale Tumori system. They proposed three stage groupings: stage I (locally restricted disease) essentially includes Masaoka stages I and II with the exception of mediastinal pleural involvement, stage II (locally advanced disease) includes tumors invading local structures or involving intrathoracic lymph nodes, and stage III (systemic disease) involving cervical nodes or distant extrathoracic sites. However, none of the TNM systems have been adopted to any significant degree, and only the Yamakawa system has undergone validation studies.[14,15]

Overview of the System

The Masaoka-Koga classification system is summarized in Table 1. It is focused on the local extension of the primary tumor, with nodal involvement playing a lesser role. This is consistent with the observation that nodal involvement is relatively uncommon with thymomas, although this is not true for thymic carcinoma.

The original Masaoka system and the Koga modification thereof differ in several ways:

- The Koga system defines stage II as involving transcapsular invasion, whereas the Masaoka system refers more vaguely to capsular invasion.
- Microscopic invasion into surrounding fat is stage IIa in the Koga system and IIb in the Masaoka system.
- The Koga system includes an explicit mention of "adherence to without breaking through the mediastinal pleura or pericardium."

There are several nuances that have not been clearly defined in the Masaoka-Koga system:

- Exactly what is meant by transcapsular invasion?
- How should tumors that lack a complete capsule be defined?
- How should "macroscopic invasion" be classified that is shown microscopically not to be present (either of the perithymic fat or neighboring organs)?
- Is there a difference between macroscopic invasion and adherence to the mediastinal pleura or pericardium?
- What is meant by adherence to the mediastinal pleura or pericardium?
- Can we define the difference between "invasion of" and "breaking through" the mediastinal pleura?
- The extent of involvement of the pericardium in stage IIb and stage III is ambiguously worded.
- How do we know when a separate focus of tumor has been spread hematogenously?
- Does the staging system apply to thymic carcinoma as well?

General criticisms that have been raised about the Masoaka and Masaoka-Koga staging systems are that there is little, if any, survival difference between stage I and II and that stage III involves a wide spectrum ranging from transpleural adhesions without invasion to extensive macroscopic and microscopic involvement of the aorta, pulmonary arteries, and heart. The goal of this article is not to define a new and better staging system; this will require prospective study and careful analysis. The goal is to stick to the existing stage classification as closely as possible but to define nuances, so that prospective data are recorded in a consistent manner and thereby facilitate a robust evaluation. However, an awareness of the implications of how nuances are defined is useful despite the approach of remaining consistent with the existing classification for the time being.

Stage I

A stage I thymoma is understood to have no transcapsular invasion. Invasion into but not through the capsule is classified as a stage I, localized thymoma (Table 2, Figure 1). The tumor must breach the capsule to be designated as invasive (and no longer stage I). Details of the process that should be used to determine this is addressed in another article.[16]

A stage I thymoma is not classified as benign, just as carcinoma in situ is not considered a benign condition. Furthermore, all large series with long-term follow-up have demonstrated recurrences and metastases from stage I thymoma of all histologic types.[17] Therefore, because all thymomas exhibit these hallmarks of malignancy, all thymomas are considered malignant (although most are low grade and can be successfully treated).

In some patients, the capsule is partially absent—this should not be interpreted as invasion. This situation should be clearly documented in the report (i.e., thymoma, partially unencapsulated), and it should be indicated in a note that capsular invasion cannot be assessed in the areas devoid of a capsule. However, the tumor should still be designated as stage I unless there is clear evidence of tumor extension into the mediastinal fat. It should be recognized that the capsule is not a native anatomical landmark, rather a reflection of desmoplasia induced by the tumor, hence, areas that are unencapsulated may exist.

Stage II

A tumor showing transcapsular invasion is designated as stage II. If there is limited microscopic extension into tissues surrounding the capsule (i.e., ≤3 mm), the tumor

TABLE 2. ITMIG Definition of Details of the Masaoka-Koga Staging System

Stage	Definition (the ITMIG Interpretation of Details Is in Italics)
I	Grossly and microscopically completely encapsulated tumor *This includes tumors with invasion into but not through the capsule, or …* *Tumors in which the capsule is missing but without invasion into surrounding tissues*
IIa	Microscopic transcapsular invasion *Microscopic transcapsular invasion (not grossly appreciated)*
b	Macroscopic invasion into thymic or surrounding fatty tissue, or grossly adherent to but not breaking through mediastinal pleura or pericardium *Gross visual tumor extension into normal thymus or perithymic fat surrounding the thymoma (microscopically confirmed), or …* *Adherence to pleura or pericardium making removal of these structures necessary during resection, with microscopic confirmation of perithymic invasion (but without microscopic extension into or through the mediastinal pleura or into the fibrous layer of the pericardium)*
III	Macroscopic invasion into neighboring organ (i.e., pericardium, great vessel, or lung) *This includes extension of the primary tumor to any of the following tissues:* *Microscopic involvement of mediastinal pleura (either partial or penetrating the elastin layer); or …* *Microscopic involvement of the pericardium (either partial in the fibrous layer or penetrating through to the serosal layer); or …* *Microscopically confirmed direct penetration into the outer elastin layer of the visceral pleura or into the lung parenchyma; or …* *Invasion into the phrenic or vagus nerves (microscopically confirmed, adherence alone is not sufficient); or …* *Invasion into or penetration through major vascular structures (microscopically confirmed);* *Adherence (i.e., fibrous attachment) of lung or adjacent organs only if there is mediastinal pleural or pericardial invasion (microscopically confirmed)*
IVa	Pleural or pericardial metastases *Microscopically confirmed nodules, separate from the primary tumor, involving the visceral or parietal pleural surfaces, or the pericardial or epicardial surfaces,*
b	Lymphogenous or hematogenous metastasis *Any nodal involvement (e.g., anterior mediastinal, intrathoracic, low or anterior cervical nodes, any other extrathoracic nodes)* *Distant metastases (i.e., extrathoracic and outside the cervical perithymic region) or pulmonary parenchymal nodules (not a pleural implant)*

ITMIG, International Thymic Malignancy Interest group.

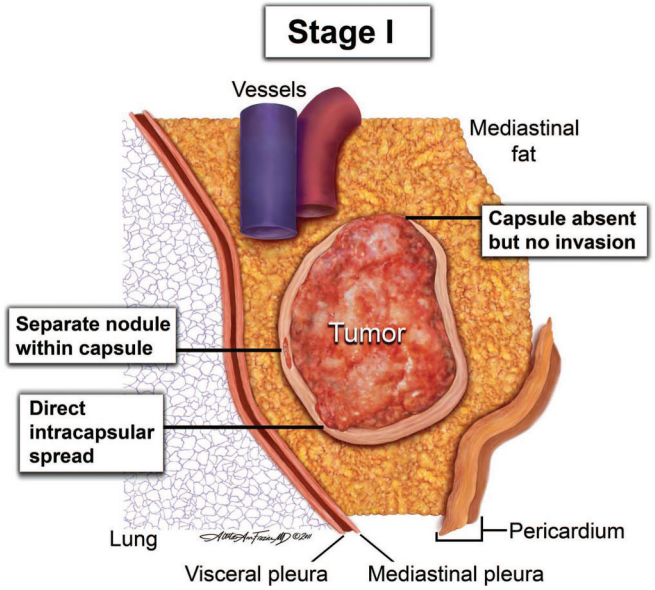

FIGURE 1. Penetrations within the fibrous capsule of a thymoma are classified as noninvasive, although they do (partially) invade the capsule. Absence of a capsule by itself does not constitute invasion.

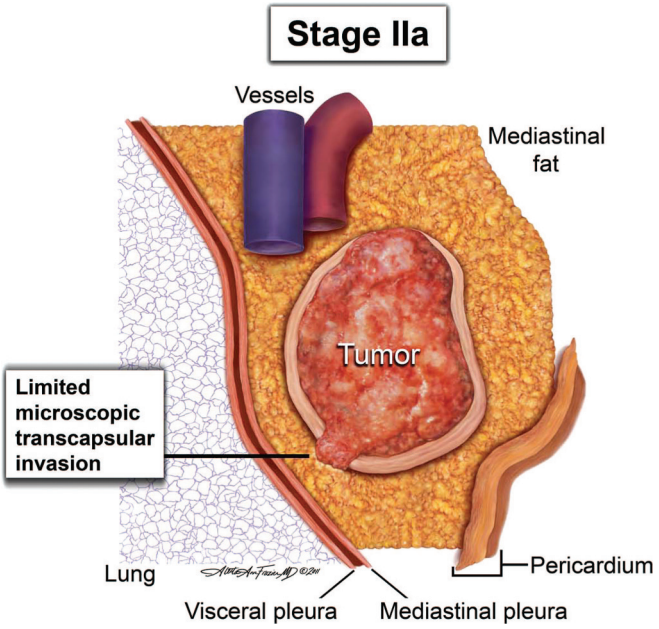

FIGURE 2. Schematic diagram of transcapsular invasion included in stage IIa.

should be classified as stage IIa, minimally invasive (Figure 2).[16] The tumor should be classified in this manner if extension beyond the capsule is demonstrated, whether this invades perithymic fat or normal thymus outside of an encapsulated thymoma. Conversely, a simple interface of the tumor with the adjacent tissue in areas devoid of a complete capsule should not be designated as invasion (should be classified as stage I).

We propose that only microscopically confirmed invasion into adjacent structures be counted; if invasion is suspected but demonstrated microscopically not to be present, then the initial suspicion should not count in the stage classification. It should be noted in prospective data collection, however, so that further clarification of how best to address this issue can be accomplished. The original Masaoka staging system did not require microscopic confirmation of suspected involvement.[1,18] However, the ITMIG consensus is to be consistent with how other malignancies are classified and not deviate by allowing a gross impression to carry more weight

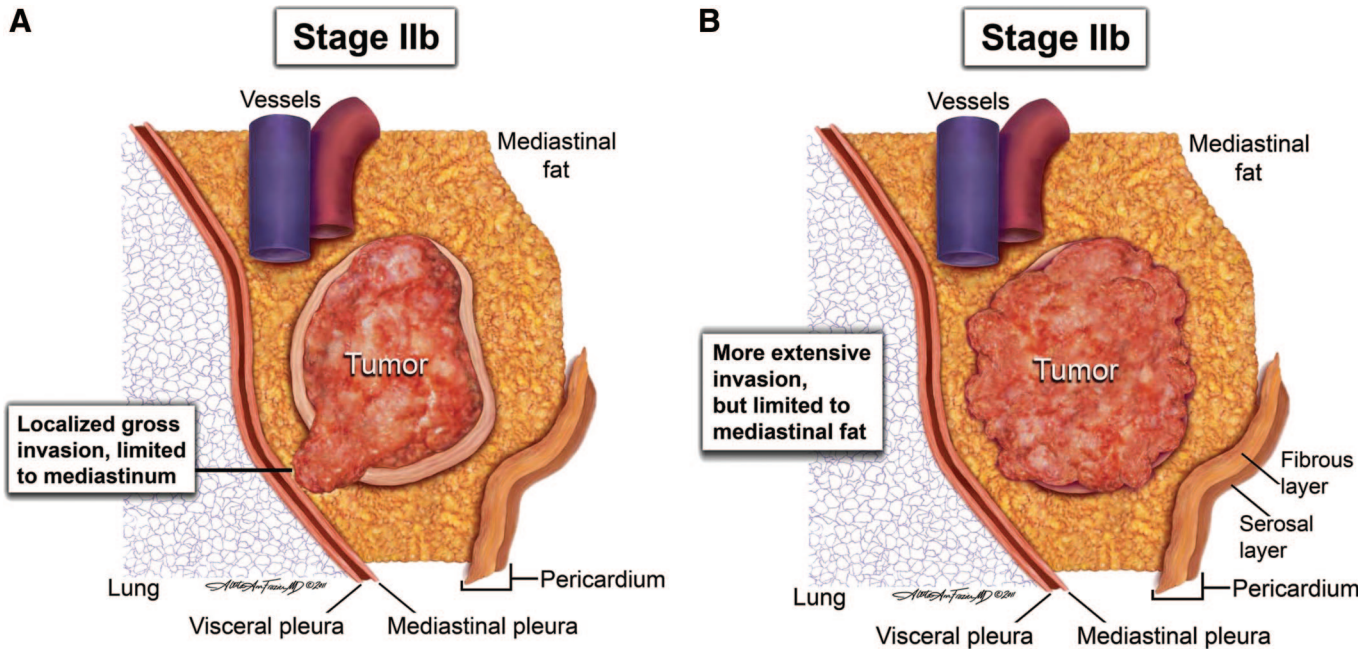

FIGURE 3. *A* and *B*, Types of invasion included in stage IIb. This may range from (*A*) a single area of localized invasion to (*B*) more extensive involvement of the mediastinal fat without pleural or pericardial involvement.

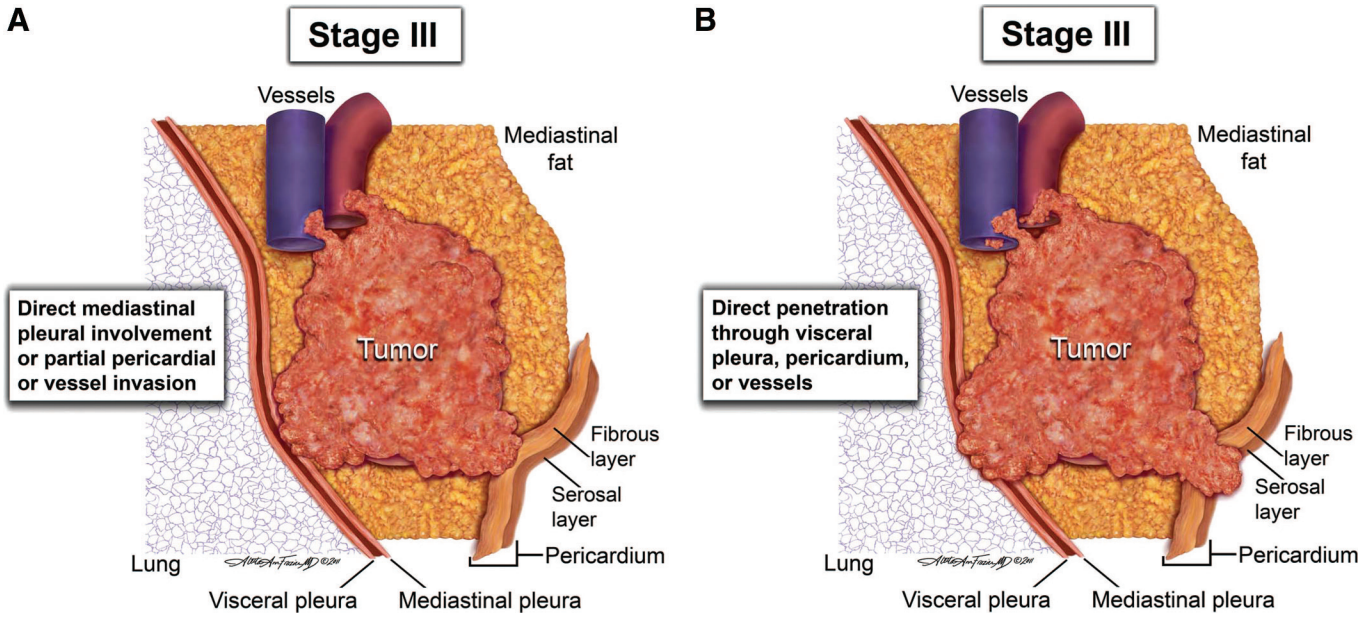

FIGURE 4. *A* and *B*, Types of invasion included in stage III. *A*, Schematic diagram of involvement of the mediastinal pleura or partial involvement of the pericardium, or vessels. *B*, Penetration through the pericardium, the visceral pleura, or into the phrenic nerve.

than what is seen microscopically. Furthermore, it creates a more logical progression in the Masaoka-Koga system, with stage IIa being minimally invasive (microscopically confirmed) and IIb grossly invasive (microscopically confirmed).

Masaoka-Koga stage IIb tumors are grossly invasive into surrounding thymic or mediastinal fatty tissue (which is microscopically confirmed, Figure 3*A*,*B*). We propose that this should include tumors with extension up to the mediastinal pleura or pericardium without involvement thereof. We recognize that this may be difficult to distinguish. Whenever the tumor extends close to the mediastinal pleura or pericardium without invasion, the distance from the tumor to the pleura or pericardium should be noted. Details of the process that should be used to assess this is addressed in another article.[16]

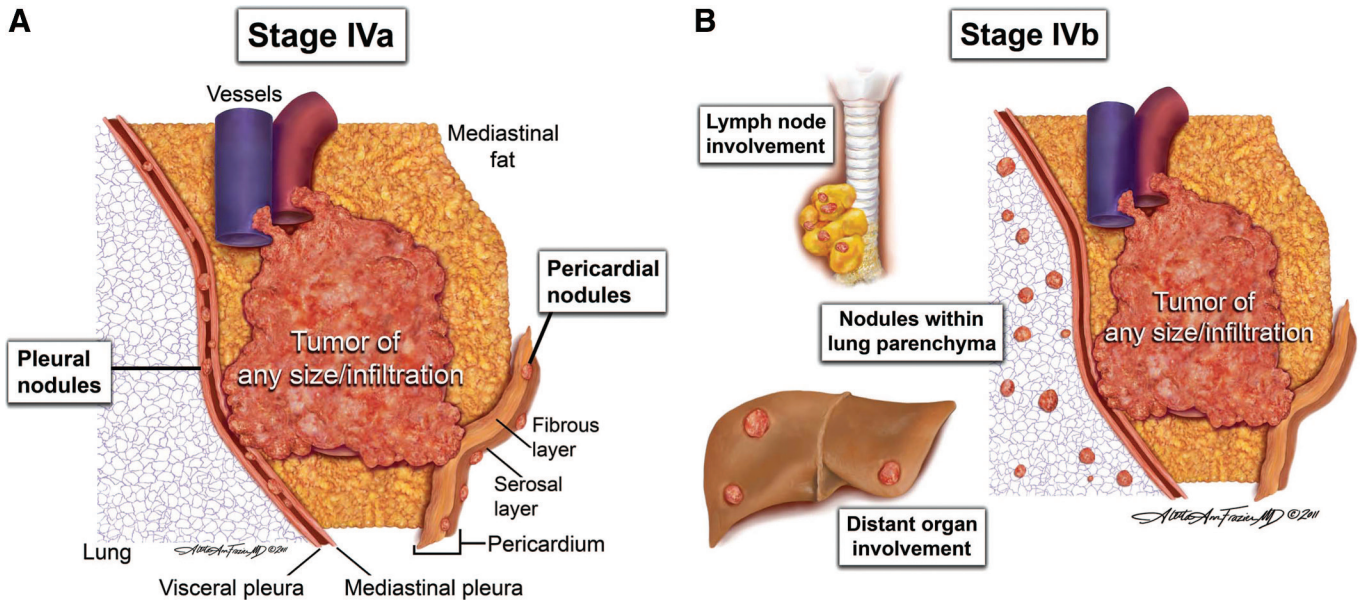

FIGURE 5. *A* and *B*, Separate foci of tumor included in stage IV. *A*, Separate nodule on the pleural or pericardial surfaces classified as IVa. *B*, Involvement of nodal sites, extrathoracic sites, or parenchymal lung nodules.

The decision to draw the line differentiating stage IIb and III at the level of any involvement of the mediastinal pleura or pericardium is primarily because this seems to be most consistent with the existing Masaoka-Koga classification (stage III: "macroscopic invasion into …pericardium"). Furthermore, no invasion is probably just as easy (or difficult) to define as partial invasion or penetration of mediastinal pleura or pericardium. Finally, in the past, the mere identification of the mediastinal pleura in particular has been inconsistent, and any attempt to pay attention more consistently to this structure represents a step forward.[16] Prospective study of this issue is needed to arrive at a delineation of stages that is less arbitrary and is supported by data.

If there is suspicion of tumor involvement grossly into the mediastinal pleura or pericardium, but microscopically this is not the case, the tumor should be noted as adherent, but classified as stage I, IIa, or IIb as indicated by the microscopic findings. This should be described as "tumor adherent to but not invading" the mediastinal pleura or pericardium in the pathology report. A clear definition of adherence is difficult to articulate; we propose this should mean that the tumor appears to be grossly so close to the pleura or pericardium that resection is deemed necessary. Distinguishing between simple adherence without invasion and microscopic invasion of the mediastinal pleura or pericardium represents a deviation from how the Masaoka or Koga classification systems seem to have been originally defined.[1,18] Nevertheless, consistency with the classification of other malignancies demands this interpretation, and therefore, this represents the consensus of the ITMIG members. Prospective evaluation of this issue is needed.

Stage III

The pericardium is mentioned somewhat ambiguously in the Masaoka-Koga classification in both stage IIb and III. We propose that any involvement (either partial or penetrating) of the mediastinal pleura or pericardium should be classified as stage III, and that prospective data be collected on these nuances. A note should be made in the pathology report if there is invasion only into the fibrous layer of the pericardium or if there is penetration into the serosal layer or onto the serosal pericardial surface. The mediastinal pleura is a much less substantial structure. We propose that a discontinuous elastin layer with adjacent tumor be classified as evidence of mediastinal pleural involvement (Figure 4*A,B*).

Tumor invading across the pleural space to involve the visceral pleura is also designated as stage III. The pathology report should note if the visceral pleura is disrupted (using elastin stains if necessary). Tumor invasion into the lung parenchyma or invasion into the innominate vein or other vascular structures warrants a stage III designation (either partial invasion or penetration, microscopically confirmed). We propose that tumor invasion into the phrenic or vagus nerves should be counted as stage III, although this is not specified in the Masaoka-Koga classification. Which organs are involved and the extent of involvement (invasion into or through) should be recorded for future study.

Stage III should be assigned according to the principle that microscopic findings are the final determinant rather than a gross impression that is not borne out microscopically. Therefore, adherence alone of such structures as the lung, phrenic nerve, or pericardium should not count if lack of involvement is demonstrated microscopically. Microscopic invasion into the mediastinal pleura, pericardium, phrenic nerve, etc. is required to classify the tumor as stage III, even if there are adhesions of these structures to the tumor of thymus. Only direct invasion of the primary tumor should be counted with respect to intrapericardial structures; involvement of the exterior surface of the aorta, superior vena cava,

or pulmonary artery by a separate and distinct tumor implant should be classified as stage IVa.

Stage IVa

Pleural or pericardial tumor nodules that are separate from the primary tumor are classified as stage IVa. These separate tumor nodules may be located on the visceral or parietal pleural or the pericardial or epicardial surfaces (Figure 5*A*). Direct extension of a thymic malignancy to the pericardial or pleural surface without separate nodules is classified as stage III.

Stage IVb

Involvement of nodes close to the thymus is stage IVb. This includes nodes in the anterior mediastinum, the paratracheal, and subcarinal regions and nodes along the superior poles of the thymus gland. Nodes elsewhere in the mediastinum or within the chest should also be included in this stage classification as well. Extrathoracic nodes (with the exception of neck nodes next to the thymus) should be thought of as distant metastases (but would not change the stage classification); this is consistent with the definition used for other tumors (e.g., lung cancer).

Pulmonary nodules that are in the lung, with a rim of normal lung between the nodule and the pleural surface are regarded as distant metastases. Involvement of extrathoracic tissues (excluding the cervical perithymic areas) should be classified as distant metastases (Figure 5*B*).

We propose using the terms pulmonary and extrathoracic metastases rather than hematogenous metastases. The former term describes an anatomic location which is factual, whereas the latter implies a mechanism of spread that is purely speculative. There are no data to prove the presumed mechanisms, and an increasing body of data from other tumors suggests that the process of metastatic spread is complex, involving factors related to adhesion, migration, implantation, angiogenesis, etc. and not simply the presence of tumor cells in the bloodstream.

DISCUSSION

Many of the definitions proposed in this document are arbitrary, and we accept that alternative definitions may be equally or more valid. Prospective study is needed to resolve these issues. This calls for a database with sufficient detail to study these nuances. It also requires consistent data, which mandates consensus around a starting point. The definitions proposed here represent exactly such a consensus; they are inherently somewhat arbitrary and largely not validated and are subject to change in the future once sufficient data are available.

The proposed definitions have focused primarily on pathologic staging, because that is the focus of the Masaoka-Koga system. We recognize the need for better definition of preoperative clinical stage characteristics, but this article only addresses the need for consistent interpretation of an existing stage classification system. Definition of clinical staging characteristics must be addressed separately.

The definitions adopted by ITMIG in this document arguably represent some minor deviations from the previously published Masaoka-Koga system. The previous publications did not define precisely what constituted mediastinal pleural or pericardial involvement, and one can argue where the dividing line should be drawn. In fact, such a debate has occurred during the process of creation of this document, and the proposed definitions represent the final consensus on what was felt to be a reasonable (but arbitrary) consistent starting point. Perhaps, the most clear deviation from the previously published wording of the Masaoka and Koga stage classifications is the requirement that macroscopic suspicion of involvement be confirmed microscopically (for pathologic stage). This position is taken in virtually every other tumor type, and it seems wise not to adhere to a different standard for thymic malignancies.

ITMIG proposes that the Masaoka-Koga stage classification be applied to thymoma and thymic carcinoma (including thymic carcinoid tumors and other less common types of thymic malignancy). In the absence of data, it seems better to maintain consistency and simplicity. Because nodal involvement is much more common in thymic carcinoma than thymoma, this may prove to be problematic. However, adding significant complexity by having two different definitions should be based on compelling data that this is worthwhile.

CONCLUSION

ITMIG has chosen to use the Masaoka-Koga stage classification system, consistent with what has been adopted most broadly. Nevertheless, many nuances have never been clearly defined and are often interpreted differently. These nuances are defined in this document to achieve more consistent application of the Masaoka-Koga stage classification system. These definitions will be used in ITMIG projects and studies, and we hope that these will be voluntarily adopted worldwide, so that collaboration is facilitated. At the same time, prospective data collection will allow future evaluation of the appropriateness of the definitions as proposed in this document.

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