Standard Outcome Measures for Thymic Malignancies

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Abstract: Thymic malignancies present particular issues due to the pace of disease progression, patterns of recurrence, and causes of death that make nuances of how outcomes are reported particularly important. The relatively limited number of patients also creates a challenge to glean as much as possible from the available experience, but risks over-interpretation and potentially misleading conclusions. Therefore the International Thymic Malignancy Interest Group has developed a set of standards for reporting of outcome measures of clinical studies, which have been adopted for collaborative projects undertaken by the organization. Widespread adoption of this baseline will enhance the ability to compare results from different series.

Key Words: Thymoma, Mediastinal disease, Thymic carcinoma, Statistics, Outcomes, Recurrence.

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Thymic malignancies are relatively uncommon, with an incidence of approximately 2.5 to 3.2 per 10^6 people,[1,2] and care is widely dispersed across many institutions. The literature consists almost exclusively of retrospective single institution series, which often extend over multiple decades of experience to have a reasonable number of patients. Comparing the results from one center to another is often difficult because of differences in the outcomes that are reported and the definitions used. Significant progress cannot be made unless a standard and uniform set of definitions and outcomes measures are adopted.

The International Thymic Malignancy Interest Group (ITMIG) is a collaborative effort of interested individuals around the world to develop an infrastructure that facilitates progress in this disease. One of the first steps in this process is the development of standard outcome measures and definitions. This article describes the measures adopted by the ITMIG membership that form the basis for ITMIG collaborative projects.

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METHODS

The process used in development of this document was designed to represent both underlying evidence and a broad consensus of ITMIG members. An initial workgroup consisting of surgeons, a medical oncologist, and a statistician (J.H., F.C.D., P.J.L., and Z.W.) was assembled to review measures that have been used in the existing literature This workgroup formulated preliminary recommendations, which were refined by an extended workgroup (Giuseppe Giaccone, Gregory Riely, Nicolas Girard, Meinoshin Okumura, Charles Thomas, Edith Marom, Andrea Bezjak, and Alexander Brunelli) and distributed to all ITMIG members for further discussion and input. The final recommendations, which are presented in this article, were approved and adopted by ITMIG members at the annual meeting in New York on May 6, 2010.

PROPOSED MEASURES

Stage Classification

No official stage classification for thymic malignancies has been defined by the Union Internationale Contre le Cancer and the American Joint Commission on Cancer. Various staging systems have been proposed,[3] including the Masaoka system,[4] the Koga modification of the Masaoka system,[5] the French Groupe d'Étude des Tumeurs Thymiques system,[6] and a T, N, and M system.[7] Most of centers and published reports use the Masaoka Stage Classification System, with studies since 1995 generally using the Koga modification (Table 1, Masaoka-Koga). The Masaoka-Koga stage classification system is recommended by ITMIG for current use.

The Koga modification differs from the original Masaoka system in that microscopic invasion into (but not through) the capsule is classified as a stage IIb by Masaoka but as stage I by Masaoka-Koga. This modification is supported by the fact that most pathologists do not consider partial invasion into the capsule to be significant, and survival data appear to bear this out.[5,8,9] Furthermore, this definition of the staging system is consistent with the definition of encapsulated and invasive thymoma adopted by ITMIG (Which way is up? A collaborative position paper on standards of handling and processing of thymic tissue by surgeons and pathologists, submitted). Another difference is that adherence to adjacent structures or microscopic invasion into but not through the mediastinal pleura or pericardium is classified as stage IIb by Masaoka-Koga but is not clearly defined in the original Masaoka definition.

TABLE 1. Masaoka-Koga Staging System

Stages	Definitions
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*.[5]

Despite widespread use, the Masaoka-Koga system has many ambiguities that have not been clearly defined. These issues are beyond the scope of this article and will be addressed in a separate publication by ITMIG. Furthermore, evaluation and statistical validation of the stage classification of thymic malignancies are being undertaken by ITMIG and the International Staging Committee of the International Association for the Study of Lung Cancer. This requires collection of data and details beyond the Masaoka-Koga stage and will include evaluation of alternative stage classification schemas. This will be addressed separately in a manual associated with the ITMIG database.

The focus of staging has been on pathologic stage (i.e., as defined after resection). However, the clinical stage (the assessment before treatment is initiated) is of much more clinical importance, especially because surgery is not always the first step in the treatment. Unfortunately, the correlation of tumor characteristics and the reliability of staging tests in defining clinical stage have not been well defined. This subject must be addressed prospectively in a more detailed manner in a future publication. Until such definitions are available, we suggest that authors estimate the stage according to the Masaoka-Koga system based on their best judgment. We strongly encourage authors to report not only the pathologic but also the clinical stage.

Survival

A standard outcome measure is overall survival. It is concrete and generally easy to verify and certainly should be reported in any clinical outcomes study of thymoma. For many cancer types, this is an adequate general measure of outcomes related to the cancer, because survival after a recurrence is generally short, and the majority of deaths are due to the original cancer. However, thymomas have a number of characteristics that make overall survival problematic for assessment of thymoma-related outcomes. Many patients die of other causes, especially in stage I and stage II tumors (Figures 1*A, B*). Patients may also live for many years despite a recurrence. Therefore, more specific measures are needed in addition to overall survival.

More specific measures generally involve either considering a specific cause of death or type of recurrence, or both. The issue of whether the cause of death is determined accurately or unduly attributed to cancer has been studied in general and found to be quite reliably assigned,[10–12] and it is highly likely to apply to thymoma as well. However, there are issues with what is considered a relevant cause of death in the existing literature on thymoma. Disease-free survival, recurrence-free survival, cancer-specific survival, progression-free survival, etc., each involve a different definition of a relevant outcome event as shown in Table 2. These differences are important in the case of thymoma, because the incidence of these events is high (Figure 1*A*). Furthermore, approximately 15 to 20% of patients with thymoma have or develop another type of cancer as well.[3,13,14] As an example, the estimated outcomes for a stage III thymoma using these different definitions is provided in Figure 2.

Actuarial outcome curves that depict a specific type of event (e.g., only local recurrence or a particular cause of death) are often misleading, usually yielding overly optimistic results.[15] This is because the actuarial method requires statistical independence of the specific event from others, which is generally not the case (e.g., the time to local recurrence and time to distant recurrence are likely to be correlated).[15] Depending on the degree to which outcome events are linked, an actuarial estimate of only one type of outcome (a flawed method) can easily underestimate the actual rate of this outcome by 30 to 50%.[15] Therefore, it is better to analyze death or failure in general, and then to compare proportional causes of death or failure to avoid this problem of "competing risks."[15] We propose, therefore, that whenever possible, the proportion of recurrence types and the proportion of causes of death be reported.

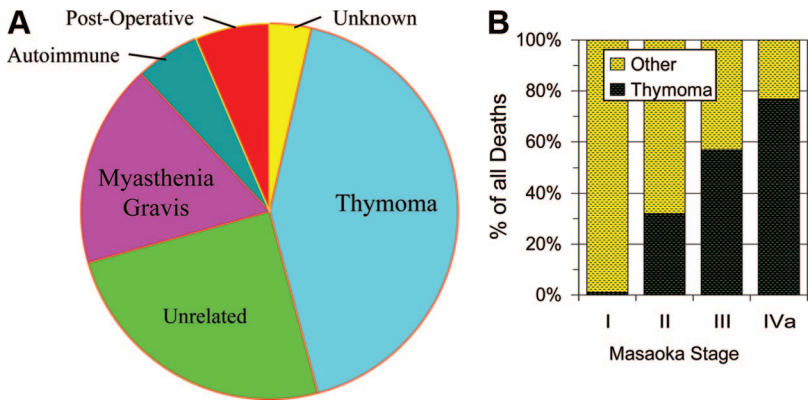

FIGURE 1. Overall cause (*A*) and stage-specific (*B*) cause of death after resection of patients with thymoma. Results are an average of studies from 1980 to 2009 of ≥100 patients reporting this data.[3]