The International Thymic Malignancy Interest Group

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Abstract

Thymic tumors are considered an orphan disease, and therefore treatment recommendations have been largely empiric, based on small, retrospective, often poorly characterized series of patients. The International Thymic Malignancy Interest Group (ITMIG) has organized individual efforts, making collation of individual experiences and global collaboration possible. This article summarizes the development of ITMIG and accomplishments achieved since its inception in 2010. A great deal of infrastructure has been built, paving the way for scientifically robust progress in the future. Guidelines such as the NCCN Clinical Practice Guidelines in Oncology are of significant clinical value despite being, of necessity, largely consensus-based. The ITMIG provides the foundation for development of more evidence-based guidelines in the future. (JNCCN 2013;11:589–593)

Thymic tumors are relatively rare, and fall under the rubric of an orphan disease. This makes it difficult to have solid foundation of evidence on which to base treatment recommendations. More importantly, it severely limits the ability to develop an evidence base on multiple levels: it is difficult to develop the ideas for prospective studies, even more difficult to find funding for them, and a challenge to accrue adequate numbers of patients. In fact, examination of SEER database results spanning several decades reveals that no significant progress has been achieved.¹

The treatment of thymic malignancies has been largely empiric. A review of published studies from 1989 through 2009 found that only 5% involved cohorts of greater than 100 patients, and even fewer were prospective. Development of treatment guidelines, therefore, is difficult, and relies on expert opinion. The first formal treatment guidelines for thymic malignancies were assembled by the Japanese Association for Research in Thymoma (JART) in 2009, and these are currently undergoing revision. The NCCN, a longstanding leader in the development and dissemination of clinical guidelines, also proposed guidelines for thymic malignancies in 2009,² which are updated annually, with the current version appearing elsewhere in this issue (to view the most recent version of these guidelines, visit NCCN.org). However, these proposed management strategies remain primarily empirically based, and underscore the need for an organized effort to provide a scientific basis for clinical care.

The Development of the International Thymic Malignancy Interest Group

Advancement of the knowledge pertaining to a rare disease such as thymic malignancies requires a collaborative, global effort. The need for this led to the development of the International Thymic Malignancy Interest Group (ITMIG). ITMIG was inaugurated as a formal not-for-profit organization in May of 2010. ITMIG is an academic organization with a mission to promote the advancement of science related to thymic malignancies and other mediastinal conditions to achieve better outcomes for patients. The goal of ITMIG is to develop an infrastructure that facilitates collaboration, and to create innovative approaches that maximize the progress that can be made.

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²Dr. Detterbeck disclosed that he receives honoraria as a lecturer on the IASLC stage classification system, supported by Lilly Oncology and as a member of a grant review panel for Pfizer Inc.

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The catalyst for the development of ITMIG came from the Foundation for Thymic Cancer Research, an organization formed by patients and family members who were frustrated about their need to search for prolonged periods before finding a physician who was truly knowledgeable about thymic malignancy. This group held 2 conferences in 2007 and 2008 to which physicians active in this disease were invited. These conferences stimulated an exchange of ideas and some limited collaborative projects, but it became clear that real progress would require the creation of a scientific infrastructure to foster collaborative research. At a third meeting, held in 2009 at the National Institutes of Health in Bethesda, a provisional structure was created, which led to the formal development of ITMIG in 2010.3

**ITMIG Accomplishments**

A key accomplishment of ITMIG has been to create a global community (approximately 30% each from Europe, North America, and Asia). Most people around the world who are active in thymic malignancies are collaborating with ITMIG (Figure 1). The membership has grown rapidly since ITMIG was formed, with more than 400 members currently. The membership has been engaged in the various ITMIG projects, and has been active in many ITMIG committees and workgroups. This community spans all continents (except Antarctica), and includes all specialties active in this space (thoracic surgery, radiation oncology, medical oncology, pathology, neurology, epidemiology, statistics, and basic science research).

At least as important as the reach of ITMIG is the culture that has been established. ITMIG has adopted an “open source” philosophy. Anyone interested and willing to contribute to the advancement of knowledge in thymic diseases is welcome to participate in any of the committees or workgroups. ITMIG has developed a culture of openness, sharing, and collaboration. The structure that ITMIG has developed to promote progress is designed to be a resource for individuals to use, with the idea that the collective work of many individuals moves things forward faster than a focus on control and oversight.

Several productive regional thymic interest groups also exist, most notably among which are JART and the thymic working group of the European Society of Thoracic Surgeons (ESTS).4-6 ITMIG fully supports these regional groups and seeks to help them grow, with the idea that strong regional groups are in line with the ITMIG goal of making progress. Nevertheless, it is important that all groups are also willing to cooperate to promote the research that requires a global effort.

An early ITMIG initiative was to establish a common language, which is fundamental to collaborative work. Because scientific efforts in thymic disease have for the most part been isolated in single institutions, the meaning of terms that are used and the outcomes reported are variable. This is akin to people who have been mostly isolated having evolved different dialects and colloquialisms that hamper effective communication. ITMIG assembled multiple workgroups, which proposed definitions and terms to be used consistently in thymic research moving forward. ITMIG held several workshops with broad international multispecialty participation to arrive at consensus definitions, which were then approved nearly unanimously by the ITMIG community. Most of these have been published together in a supplemental issue of the *Journal of Thoracic Oncology.*7-17

A matter of some debate has been the histologic classification of thymic malignancies. Issues related to the system defined by the WHO have led to some ambiguity and variability in its application.18,19 ITMIG has brought together the large majority of pathologists around the world who have been active in research on this disease, and developed proposed refinements that should lead to greater consistency. This should provide a basis for further progress, perhaps through development of a grouping of histologic types according to grades of biologic aggressiveness. Much work is ongoing.

No official stage classification system exists for thymic malignancies. Furthermore, although the system first proposed by Masaoka in 1981 has been used most widely, differences exist in its application.9 ITMIG has partnered with the International Association for the Study of Lung Cancer (IASLC) to develop a system for the next (8th) edition of the AJCC/UICC official stage classification manual. This work is ongoing but clearly represents an international effort that would not have been possible without the strength of ITMIG and IASLC.

ITMIG has constructed a Web-based retrospective and prospective database that includes
multiple tools to allow linkages and analysis using a sophisticated platform. This involved a great deal of technical and regulatory work to establish a versatile system that can be used effectively. The retrospective portion of the database includes more than 9000 cases from every continent, representing by far the largest thymic experience ever assembled. Population of the prospective database is ongoing. The extent to which the global thymic community has come together and actually contributed to this resource is impressive, providing proof of how well ITMIG has brought individuals from around the world together toward a common goal. A thymic tissue bank has also been established and is accruing cases. This is linked to the annotated clinical database.

**ITMIG Projects Under Development**

Histologic classification of thymic malignancies has been a controversial area. The current WHO classification system is used widely, but has areas of ambiguity that result in variability. ITMIG has engaged most pathologists active in this area and conducted 2 workshops to address the issues. The outcome of this work should contribute to producing a refined system for the next revision of the WHO classification that is more reproducible in the pathologist’s hands and more useful in the clinician’s hands for patient management.

The initial focus of ITMIG was on thymoma, which constitutes the largest group of mediastinal tumors. However, many mediastinal malignancies are even rarer and need an organized effort. ITMIG has launched work groups focused on thymic carcinoma and thymic carcinoids, and discussion of other mediastinal malignancies is underway.

Molecular characterization of tumors is providing new insights, and progress is being made in thymic malignancies. ITMIG has been building a thymic tissue bank to support this. Initial discussions are underway to study certain biomarkers and participate in the Cancer Genome Atlas project.

The large number of patients in the retrospective database, and the developing prospective database, provides a resource for simple retrospective comparisons of different therapeutic approaches that has not been possible before. Although this cannot provide clear proof that a particular approach is truly better, it does represent a step above the empirically derived approaches used to date. The ability to analyze this collective experience is a significant asset in developing prospective clinical trials or streamlining exploratory molecular analyses from tissue in the thymic tissue bank.

![Figure 1](image-url) World map of International Thymic Malignancy Interest Group members.
Adding science to clinical management requires clinical research. Several clinical trials are under development. Most notably is a large randomized trial designed to assess the role of adjuvant radiotherapy for resected stage III thymoma. One difficulty regarding a rare disease is that answering these clinical questions requires global collaboration, which requires an infrastructure. ITMIG has been actively working with several organizations around the world to accomplish this, aided by a group called the International Rare Cancers Initiative (IRCI). IRCI is focused on breaking down political and regulatory barriers so that conducting these international clinical trials is feasible. It now appears likely that ITMIG will be able to stitch together various organizations around the world and thus have the infrastructure and cooperation needed to make an international randomized clinical trial a reality.

Because of the challenges facing rare diseases, ITMIG has realized from its inception that it must use innovative approaches that optimize what can be learned from a smaller number of events. Bayesian statistics offer an ability to allow each observation to inform the knowledge base and quantify how likely or uncertain it is that a particular direction is leading to better outcomes. The infrastructure needed (ie, broad engagement, prospective data collection) is now in place to begin using this approach to make progress.

A challenge in rare diseases is providing knowledge and judgment to a broadly disseminated number of clinicians who will see these patients only sporadically. The Internet has made information more accessible, and contributed to a change in how people acquire the information they need. However, simple availability of facts regarding a rare disease is not enough. Furthermore, the methods that effectively impart factual knowledge to learners and those that impart judgment and problem-solving skills are different. ITMIG is embarking on a larger initiative to apply advances in the understanding of adult learning for different types of cognitive skills to develop a series of educational tools, accessible by Internet, that more optimally meet the needs of less experienced clinicians when encountering a rare disease.

Conclusions
The ITMIG has experienced dramatic growth since its inception in 2010. The ITMIG has been successful in engaging those active in thymic malignancies in an international collaborative community. Resources and infrastructure have been developed to allow collective work to be performed. Many initiatives are underway, in various stages of development, which provide a huge opportunity to make progress in ways that would have been utterly impossible before 2010. The goal, of course, is to improve treatment outcomes in these rare diseases. So far, treatment approaches have been primarily empirically based. The initiative of JART and NCCN in proposing guidelines is a useful guide for the many clinicians who encounter these rare malignancies only sporadically, yet they remain empirically based. The efforts of ITMIG should allow the development of guidelines that have a more solid evidence base.

References


