

The Creation of the International Thymic Malignancies Interest Group as a Model for Rare Diseases

By Frank C. Detterbeck, MD

Overview: Similar to other orphan diseases, little progress has been made in the past decades in thymic malignancies. A determination to make a difference, despite the challenges facing a rare disease, led to the formation of the International Thymic Malignancies Interest Group (ITMIG) in 2010. This organization has brought together the majority of those focused on the management of thymic malignancies and has built a foundation for scientific collaboration, including con-

THYMOMA IS a relatively rare malignancy. The age-standardized incidence has been reported to be 2.5 and 2.8 per million in Denmark and Iceland, respectively.^{1,2} Studies in the United Kingdom and United States have reported incidence rates of 0.72 to 1.5 per million, but these series may have missed many smaller thymomas (i.e., those previously thought to be benign).^{3,4} A study of the Surveillance Epidemiology and End Results (SEER) database in the United States from 1973 to 2006 found a modest and consistent increase in incidence (Fig. 1).⁵ This was true for all subtypes and stages, suggesting that the increased incidence was unlikely to be an artifact (e.g., because of a higher prevalence of computed tomography imaging).

A recent comparative analysis of SEER data from 1988 to 2003 found that there was no improvement in survival during this period (Fig. 2).⁶ For each stage of disease, there was no consistent evidence of even a trend toward better survival in more recent years, despite potential advances in medicine and surgery.

Why has no progress in outcomes been seen over the past 2 decades? A major factor is certainly that the disease is relatively rare and physicians have largely worked independently. The treatment approach has been primarily empiric, based on individual judgment with little supporting data. In addition, most published studies are retrospective series spanning many decades during which many changes have occurred and provide only a vague idea of what can be learned from this experience (Fig. 3). Clinical trials have been rare, involving only limited numbers of patients in phase II studies. Also, as it is with any rare disease, research funding mechanisms and health care structures make it difficult to establish a scientific basis for approaching the disease. Thus funding is not available because there is no scientific basis to build on, and there is no scientific basis because there is no funding.⁷

In the case of thymoma, several other issues have hampered progress. First, a common misconception is that many thymomas are benign. The data do not support this, and this misnomer should be abandoned.⁸ However, this misconception together with the view that the thymus (in adults) is an involuted functionless organ contribute to a lack of interest in and focus on thymic malignancy. This is worsened by the fact that cardiac surgeons see the thymus every day as inconsequential tissue and frequently are willing to remove or debulk a thymic malignancy with little understanding of the disease process itself.

Another factor has been the inconsistency with which

sistent use of terms, an international database, and multidisciplinary engagement of clinicians and researchers from around the world. ITMIG has embarked on the development of novel approaches to research particularly suited to a rare condition. ITMIG has gained substantial recognition for the rapid progress that has been made and serves as a model for the advancement of knowledge in a rare disease.

terms have been interpreted. This makes published data almost impossible to compare. Yet for a rare disease, collaboration is absolutely essential. For example, published literature contains a variety of outcome measures; because of the nature of thymic malignancies, associated diseases and causes of death, these yield dramatically different outcome results (Fig. 4).⁹ These distinctions have rarely been appreciated, and no consistency in reporting results had emerged until the advent of the ITMIG.

The Development of ITMIG

ITMIG was inaugurated as a formal not-for-profit organization in May 2010. ITMIG is an academic organization, whose mission is 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.

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 having to search for prolonged periods before finding a physician who was truly knowledgeable about thymic malignancy. This group held two conferences in 2007 and 2008 to which physicians active in this disease were invited. In addition to stimulating discussion and some collaborative projects, it became clear that real progress in a rare disease such as thymic malignancy would require creating a scientific infrastructure to foster collaborative research. At a third meeting held in 2009 at the National Institutes of Health in Bethesda, Maryland, a provisional structure was created and tasked with the formal development of ITMIG.¹⁰

Many professional organizations have come forward to support the creation of ITMIG, including the American Association for Thoracic Surgery, the European Association of Cardiothoracic Surgeons, the European Society for Myasthenia Gravis, the European Society of Thoracic Surgeons,

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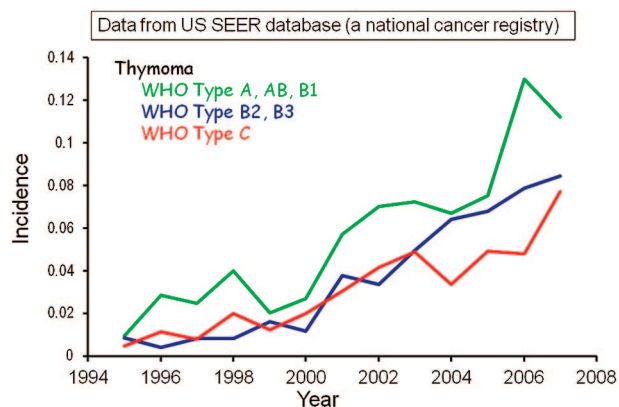


Fig. 1. Changing incidence of thymoma and thymic cancer. Data taken from the Surveillance Epidemiology and End Results (SEER) database.⁵

the Fleischner Society, the General Thoracic Surgical Club, the International Association for the Study of Lung Cancer (IASLC), the Japanese Association of Chest Surgeons, the Japanese Association for Research on the Thymus, the Japanese Association for Thoracic Surgery, the mediastinal workgroup of the European Society of Pathologists, the Myasthenia Gravis Foundation of America, the Society of Thoracic Radiologists, the Society of Thoracic Surgeons, and the Thoracic Oncology Network of the American College of Chest Physicians.

As of January 2012, ITMIG has nearly 400 members from all continents (except Antarctica). ITMIG is a multispecialty organization, involving thoracic surgeons, medical and radiation oncologists, pulmonologists, radiologists, pathologists, neurologists, and basic science researchers. Perhaps the most important early achievement of ITMIG has been the enthusiastic engagement of nearly all of those around the world who have been active in studying thymic malignancies. The ITMIG annual meetings in 2010 (in New York) and in 2011 (in Amsterdam) have been well attended with many submitted abstracts and posters.

ITMIG Projects and Accomplishments

A prerequisite for collaboration is the ability to speak the same language. Differences in the interpretation of terms were surprisingly wide in this field and largely unrecog-

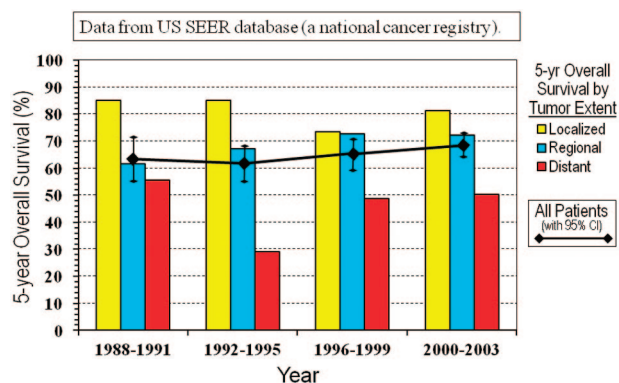


Fig. 2. Trends in 5-year survival for thymoma and thymic cancer by tumor extent. Data taken from the Surveillance Epidemiology and End Results (SEER) database.⁶

nized. The ITMIG community organized a broad process to clarify critical terms. Multiple workgroups were assembled, and core members drafted initial proposals, which were vetted with workgroup members. At a 2-day workshop at Yale University with broad international representation, these definitions were discussed and revised so that they would be aligned with one another. These were then further refined by the workgroups with input from the entire ITMIG membership. The final documents were approved by the ITMIG membership for use in all ongoing research and publications. The level of engagement and broad consensus in this process was in itself a major accomplishment of ITMIG. These definitions were published in a supplement to the *Journal of Thoracic Oncology* (JTO) in July 2011 and are openly available for download from the ITMIG or JTO websites (itmig.org and jto.org).

A fundamental aspect of cancer research is stage classification, but there is no formal classification system for thymic malignancies. ITMIG partnered with IASLC, which has extensive experience in developing the revision of the staging system for lung cancer, to develop an official thymic stage classification system for the next (eighth) edition of the stage classification of tumors in 2017. This project is conducted under the auspices of the Union for International Cancer Control and American Joint Committee on Cancer, the entities that determine the official classification systems for all tumors.

The histologic classification of thymic malignancies has also been a source of confusion and controversy. There is

KEY POINTS

- Progress in a rare disease cannot occur without global collaboration.
- The consistent use of terms across a field of study is necessary for collaboration.
- Details of how outcomes are reported for thymic malignancies are critically important when comparing results.
- The recognition of the limitations inherent in data from small patient cohorts is important to appropriately interpret available results.
- Compared with traditional approaches, innovative approaches to statistics and clinical science provide a research strategy better suited to a rare disease.

PubMed Literature Search: Thymoma

January 1989-December 2009 (n=1991 papers)

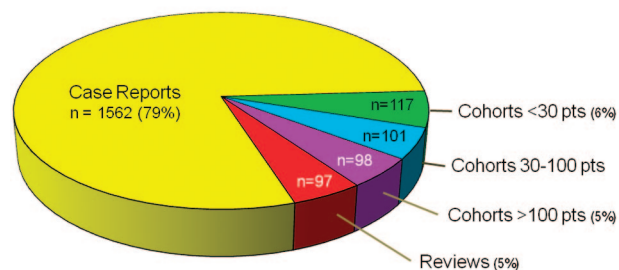


Fig. 3. Overview of published literature results from a PubMed search from 1989 to 2009 for thymoma, grouped by type of paper and size of patient cohort.

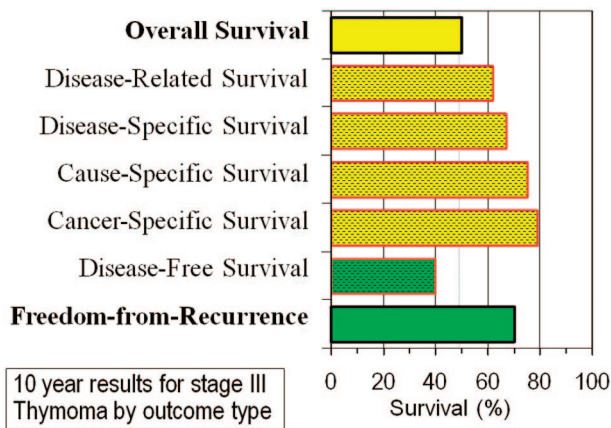


Fig. 4. Ten-year outcomes for different outcome measures in the same cohort of resected patients with stage III thymoma.⁹

variability in how the current World Health Organization classification system is interpreted and applied, and its prognostic value is inconsistent. ITMIG has conducted two international workshops to identify the sources of the difficulties and to develop a strategy for defining a better system.

Clinical science depends heavily on statistics to separate what we know from perceptions or beliefs. However, a rare disease presents many statistical challenges. The limited number of patients magnifies misperceptions caused by common practices about how clearly something has been demonstrated. ITMIG invested effort in developing an understanding of the limitations and techniques to minimize or at least evaluate the level of uncertainty (Fig. 5). As examples, confidence intervals around survival curves provide a clearer picture of the findings, and identification of prognostic factors may carry a risk of false-positive or false-negative findings that should be acknowledged. A description of such issues has also been published in the JTO supplement.¹¹

A sophisticated, detailed international ITMIG database has been built on the HUBzero platform, thus benefiting from the engineering expertise of Purdue University, over a million users of this platform for multiple major initiatives, and more than a decade of research and experience in developing platforms for international collaboration involving multiple disparate types of data and analyses. Furthermore, the developers of this platform are focused on providing tools to facilitate research rather than on promoting a commercial product. The database is linked to a virtual tissue bank that is actively accruing samples.

Strategy for the Future

Making progress in a rare disease is more challenging than in a common condition. Merely trying to duplicate the measures taken in common will leave thymic malignancies still far behind other areas, despite facilitating some degree of progress. Therefore a specific focus of ITMIG is to seek out novel and innovative approaches that allow ITMIG to leapfrog ahead. Each annual meeting has several lectures chosen specifically to promote insight and thinking in areas that are not widely known but may have implications for thymic malignancies. Innovative strategies and research approaches are being explored as well.

A search for a novel strategy that would maximize the rate of progress led ITMIG to a collaborative project at Simon

Cancer Center at Indiana University and the Purdue Department of Engineering. This project, known as Cancer Care Engineering (CCE), applies techniques of complex modeling to cancer research. Developing an adaptive model allows new insights to be quickly assessed in a virtual manner and allows for more strategic planning of how to prioritize and how best to attempt to validate early findings. Such an approach has been successful in other types of cancer, and the people involved in the CCE project had independently come to the idea that the adaptation of this approach would be particularly useful in a rare disease—coincident with ITMIG's initiative to find novel approaches that would maximize progress. The initial accomplishments of ITMIG provide a good foundation on which to build this effort; it is now time to begin actual development of this approach.

The traditional clinical research approach relies on providing clear proof of one approach over another through the use of randomized clinical trials. Although this is part of the scope of ITMIG's research plans, this strategy is also associated with major challenges, especially in a rare disease. ITMIG therefore is also including other approaches, particularly the use of Bayesian statistics. These do not seek to prove superiority or exclude expectations based on prior data (i.e., "biases") as with the traditional frequentist approach. Instead, the Bayesian approach makes use of prior knowledge and quantifies the possibility that one treatment is or is not better. Bayesian analyses have the advantage in a rare disease of being applicable no matter how many patients are available for inclusion and of refining predictions based on each observation as it happens, instead of blinding for years until the data are mature.

Traditional research approaches also play a role, where applicable, in the ITMIG approach. However, in a rare disease this requires global collaboration. It is hard enough negotiating the regulatory hurdles for a multi-institutional study in one country much less meeting expectations across many countries. ITMIG has partnered with the International Rare Diseases Initiative, which is a collaboration between relevant organizations in the United States, the United Kingdom, and Europe, to manage such issues.

A problem that is magnified for a rare disease is funding for the infrastructure necessary to perform collaborative

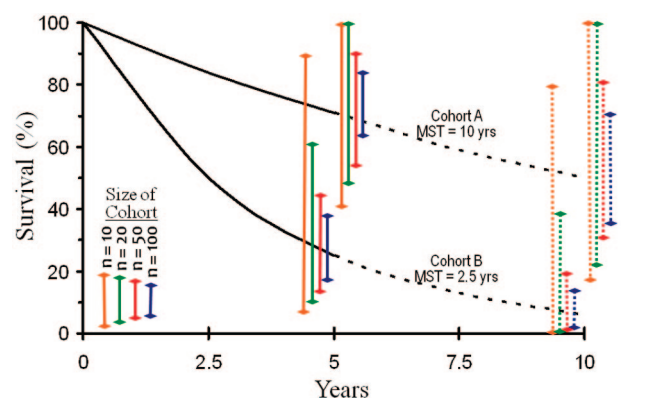


Fig. 5. Precision in estimating. The vertical bars are 95% confidence intervals for a 5-year study, based on a standard model of exponentially decreasing survival, a constant rate of accrual, and no loss to follow-up.⁹

Abbreviation: MST, median survival time.

work and to accomplish the work itself. Traditional mechanisms such as research grants are difficult to qualify for—projects without a large clinical effect or with limited data existing have a low chance of competing for funding. Industry generally sees the market niche as small with little return on investment. ITMIG has struggled with these issues but has managed to stay afloat. The work performed by the ITMIG members, of course, is purely donated time by physicians, researchers, and other health care professionals who feel that the opportunity to move forward is simply something they have to support. Several industry sponsors have donated unrestricted gifts in what represents primarily an altruistic gesture. Many related professional organizations have not only officially endorsed ITMIG but also have been willing to provide start-up money. The bulk of funding, however, comes from patients and their families and friends, most notably from the Foundation for Thymic Cancer Research.

However, one advantage for a rare disease is that a relatively small amount of funding can have a substantial effect precisely because it is a rare disease. This limits the

size and cost of the infrastructure needed and promotes willingness on a broad front for people to volunteer a manageable amount of time. Maintaining such willingness broadly and consistently remains a challenge. ITMIG members are engaged and committed, in part because it is easier to have a feeling of ownership in a smaller group and because the effort seems to produce real progress.

Conclusion

Thymic malignancies and other mediastinal tumors represent rare diseases, in which there has been little progress over many decades. For a rare disease, it is clear that progress is only possible if international collaboration can be achieved. ITMIG represents an organization that is devoted to making progress in the management of rare diseases through international collaboration. ITMIG has built an infrastructure, has engaged a broad multidisciplinary group of people in a global initiative, and sought novel approaches to maximize the progress that can be made in improving outcomes for patients with these orphan diseases.

Author's Disclosures of Potential Conflicts of Interest

Author	Employment or Leadership Positions	Consultant or Advisory Role	Stock Ownership	Honoraria	Research Funding	Expert Testimony	Other Remuneration
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