



Evolution of thymic malignancy management in Japan

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Abstract: Although surgery for the thymus began as early as 1940 in Japan, resection of a thymic epithelial tumor continued to be challenging for clinical practitioners until the 1970's. Thereafter, introduction of the Masaoka clinicopathological staging system, development of extended thymectomy procedure, advancements in understanding of the pathological and biological characteristics of these tumors, and establishment of The Japanese Association for Research on the Thymus (JART) led to significant progress in clinical practice for treating affected patients. Presently, surgical resection procedures for thymic epithelia tumors are safely performed for more than 2,000 patients each year in Japan, approximately 40% of which are achieved using video-assisted thoracoscopic surgery (VATS). JART and Japanese clinicians are currently involved in global collaboration research activities with the International Thymic Malignancy Interest Group (ITMIG) and International Association for the Study of Lung Cancer (IASLC).

Keywords: The Japanese Association for Research on the Thymus (JART); Japanese Association for Chest Surgery (JACS); the Japanese Association for Thoracic Surgery (JATS); the Japan Lung Cancer Society (JLCS); database of thymic epithelia tumors

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Japanese physicians began clinical practice and research activities for thymic diseases as early as 1940, and have since produced important achievements in this field that have influenced medical professionals throughout the world. This study provides a brief summary of the evolution in management of thymic malignancy in Japan.

The first thymectomy procedure for a myasthenia gravis (MG) patient in Japan was performed by Tashiro in Nagoya in 1940, which was only 1 year after a report of thymoma resection performed in a patient with MG presented by Blalock. In contrast, the first thymectomy case in Japan was not associated with a thymoma (1). In 1948, Tsuda of Okayama University performed the first reported resection of a thymic tumor in Japan, which was a dermoid cyst and not a malignant tumor (2).

The first report of surgery for a thymoma came from Tohoku University. In 1953, Kasai *et al.* reported a series of

21 cases of mediastinal tumors treated at their institution, including one patient with a malignant thymoma who died during the operation (3). Later in 1955, Urabe of Kanazawa University reported their experience with surgery for two patients with malignant thymomas and also reviewed 93 cases of mediastinal tumors reported in Japanese literature, which included 2 benign and 3 malignant thymomas (4). Thus, surgery for thymoma in Japan actually began in the 1950's.

Surgery for mediastinal tumors was the focus of discussion at the annual conference of the Japan Surgical Society (JSS) in 1962, with reports and investigations presented by Hatano of Tokyo University (5), Takeda of Osaka University (6), and Kasai of Tohoku University (7). Hatano reported a review of 3,780 mediastinal tumors presented in international literature, which revealed 401 thymic tumors, while 69 thymomas (8 benign, 55 malignant,

6 unknown) were found in a search of Japanese studies. In addition, 12 surgical approaches including thoracotomy, median sternotomy, hemi-clam shell incision, and those in various combinations were demonstrated. That review also revealed difficulties with differential diagnosis of mediastinal tumors from aortic aneurysms, pleural tumors, and pulmonary disease. Takeda reported radiological findings of mediastinal tumors, and showed the significance of extrapleural sign in anterior mediastinal tumor cases and also demonstrated the usefulness of venography. Finally, Kasai reported a review of their experience with 66 mediastinal tumors, including 9 thymomas, of which 3 were benign and the remaining 6 were malignant. Among the 6 malignant thymomas, surgical treatment was performed for four cases, but complete resection was not achieved in any. While a partial resection was performed in one and exploratory thoracotomy in three cases. From this meeting, the thymus and thymomas gained the interest of a large number of Japanese surgeons.

Later, Takeda presented another report of experience with 33 thymic tumor cases, including 13 thymomas, 2 thymic cysts, 1 seminoma-like tumor, 2 lymphosarcoma, and 15 teratodermoid tumors in 1964 (8). That series included an interesting experience with a thymic tumor that showed diminished size after steroid administration. Based on current knowledge, those observations can be explained by a significant reduction in the lymphoid component of a WHO pathological type B1 or B2 thymoma from steroid administration. Watanabe at Keio University presented a series of 67 cases of thymoma in 1965 (9). MG, hematopoietic disease, and Sjögren's syndrome were associated in ten, six and one patient, respectively, and the pathological characteristics of a thymoma in association with MG revealed the significance of perivascular space. Thus, Japanese clinicians made important progress in the 1960's, though surgery for thymic tumors was still challenging and experience was limited.

Thereafter, outstanding achievements were attained in the field of pathology. Shimozato at National Cancer Center in Tokyo identified squamous cell carcinoma of the thymus and reported experiences with eight cases in 1977 (10). Later, the same group described comprehensive issues regarding the pathology of thymic epithelial tumors, which were helpful for both clinical and basic researchers (11).

Masaoka at Osaka University proposed a clinico-pathological staging system for thymoma in 1981 (12), which was based on staging systems presented independently by Bergh and Wilkins. Masaoka combined their systems,

which had three categories defined by invasion to adjacent organs, pleural dissemination, and metastasis, and reclassified them into five groups. It was rather surprising that the Masaoka staging system, which was created from experience with only 91 cases, had been the global standard for more than 30 years. In addition, Masaoka *et al.* also found thymic tissue distributed in the anterior mediastinum outside of the thymus (13), which led to establishment of an extended thymectomy procedure for MG (14). An extended thymectomy through a median sternotomy remained a common surgical procedure performed for MG as well as resection of a thymoma irrespective of its association with MG, though video-assisted thoracoscopic surgery (VATS) had become prevalent over the last 20 years.

As experiences in clinical practice accumulated throughout the 1990's, significant progress was seen in research of cases affected by thymic epithelial tumors. Involvement of the great vessels was shown to be associated with tumor recurrence and poor prognosis by Okumura at Osaka University (15), and based on that along with other reports, preoperative induction therapy for highly invasive thymic epithelial tumors became commonly adopted in the 2000's in Japan. During 1990's, controversy arose regarding the clinical significance of the pathological classification presented by Müller-Hermelink at Würzburg University, which was later adopted by the WHO. Several studies conducted by Japanese institutions independently confirmed the significance of the WHO pathological classification system regarding prognostic factors (16-18).

The Japanese Association for Thoracic Surgery (JATS) had been conducting scientific surveys of thoracic surgery cases since 1986, when the number of operations for thymic epithelial tumors in Japan was only 506 (19). Thereafter, according to steady advancements in understanding of oncological and pathological factors of thymic epithelial tumors, clinical practice including surgical treatment for thymic epithelial tumors gradually expanded in the 1990's, with the number of operations for thymic epithelial tumors increased to 2,104 cases in 2014, a 4.2-fold increased over a 29-year period (19).

Following the introduction of VATS in the 1990's, a VATS approach for thymic diseases was started by several institutions in Japan, as reported by Ando *et al.* (20). In the 2000's, several Japanese surgeons produced methods for sternal elevation (21-23), which might have prompted the indication of VATS for thymectomy. Presently, a VATS procedure is used in 40% of cases of thymoma resection in Japan. Yoshino *et al.* at Kyushu University reported the first

robotic-assisted thoracoscopic resection of a thymoma using the da Vinci system in 2001 (24). More recently, Suda *et al.* reported a single-port thymectomy procedure with the da Vinci system through a subxiphoid incision (25).

The Japanese Association for Research on the Thymus (JART), which was established by Masaoka and colleagues in 1982, participated in development of the ITMIG and IASLC global retrospective database project to establish a novel staging system using the TNM classification. Nearly one-third of approximately 9,000 cases collected by this global project were enrolled from the JART database. Following establishment of the novel TNM staging system, JART performed their own database studies and presented several new findings, including the significance of chest wall invasion by Masaoka stage III thymoma and number of pleural disseminations in Masaoka stage IVa disease (26,27), which suggested the necessity of future modifications of the UICC TNM staging system.

Several academic societies, including JSS, JATS, JART, Japanese Association for Chest Surgery (JACS), and Japan Lung Cancer Society (JLCS), have promoted clinical practice and research activities in regard to thymic malignancies for more than 60 years, from which universally accepted achievements have been presented. In addition to progress in surgical treatment procedures for thymic epithelial tumors, basic scientific research regarding the mechanism of tumor immunology as well as analysis of the genome are currently being pursued. In the near future, immune check-point inhibitors against the PD-1/PD-L1 pathway are expected to contribute to management of highly advanced tumors, especially unresectable thymic carcinomas. Furthermore, Japanese physicians and researchers are now actively participating in a variety of global collaborative studies to contribute to further progress in understanding and effective treatment of thymic disease.

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References

1. Fujii Y. Surgery of the thymus in Japan. *Gen Thorac Cardiovasc Surg* 2009;57:121-6.
2. Tsuda S, Sato K. Mediastinal dermoid cyst. *Geka* 1949;11:314.
3. Kasai M. Surgery for mediastinal tumors: experience in 21 cases. *Rinsho Geka* 1953;8:569-76.
4. Urabe M. Surgery of the mediastinum. In: Yanagi S, Tsuzuki s, Fukuda T. editors. *Nihon geka zensho*. Vol. 17. Tokyo: Kanehara, 1955:409-36.
5. Hatano S. Mediastinal tumor with special reference to thymoma and thymus-related tumors. *Nihon Gekagakkai Zasshi* 1962;63:198-205.
6. Takeda Y. Diagnosis of mediastinal tumors: application of venography. *Nihon Gekagakkai Zasshi* 1962;63:206-22.
7. Kasai M. Treatment of mediastinal tumors. *Nihon Gekagakkai Zasshi* 1962;63:223-35.
8. Takeda Y. Surgery of the thymus. *Nihon Kyobu Gekagakkai Zasshi* 1964;12:442-4.
9. Watanabe H. Thymoma — on its histopathological findings. *Saishin Igaku* 1965;20:2727-48.
10. Shimamoto Y, Kameya T, Nagai K, et al. Squamous cell

- carcinoma of the thymus. An analysis of eight cases. *Am J Surg Pathol* 1977;1:109-21.
11. Shimosato Y, Mukai K. Tumors of the mediastinum. In: Rosai J. editor. Atlas of tumor pathology. Third series. Fascicle 21, Washington, DC: Armed Forces Institute of Pathology, 1997.
 12. Masaoka A, Monden Y, Nakahara K, et al. Follow-up study of thymomas with special reference to their clinical stages. *Cancer* 1981;48:2485-92.
 13. Masaoka A, Nagaoka Y, Kotake Y, et al. Distribution of thymic tissue at the anterior mediastinum. Current procedures in thymectomy. *J Thorac Cardiovasc Surg* 1975;70:747-54.
 14. Masaoka A, Monden Y. Comparison of the results of transsternal simple, transcervical simple, and extended thymectomy. *Ann N Y Acad Sci* 1981;377:755-65.
 15. Okumura M, Miyoshi S, Takeuchi Y, et al. Results of surgical treatment of thymomas with special reference to the involved organs. *J Thorac Cardiovasc Surg* 1999;117:605-13.
 16. Okumura M, Ohta M, Tateyama H, et al. The World Health Organization histologic classification system reflects the oncologic behavior of thymoma: a clinical study of 273 patients. *Cancer* 2002;94:624-32.
 17. Nakagawa K, Asamura H, Matsuno Y, et al. Thymoma: a clinicopathologic study based on the new World Health Organization classification. *J Thorac Cardiovasc Surg* 2003;126:1134-40.
 18. Kondo K, Yoshizawa K, Tsuyuguchi M, et al. WHO histologic classification is a prognostic indicator in thymoma. *Ann Thorac Surg* 2004;77:1183-8.
 19. Committee for Scientific Affairs, The Japanese Association for Thoracic Surgery, Masuda M, et al. Thoracic and cardiovascular surgery in Japan during 2014: annual report by the Japanese association for thoracic surgery. *Gen Thorac Cardiovasc Surg* 2016;64:665-97.
 20. Ando A, Azuma T, Aoe M, et al. Thoracoscopic extended thymectomy in conjunction with a collar incision of the neck for cases of myasthenia gravis. *Kyobu Geka* 1996;49:95-8.
 21. Kido T, Hazama K, Inoue Y, et al. Resection of anterior mediastinal masses through an infrasternal approach. *Ann Thorac Surg* 1999;67:263-5.
 22. Takeo S, Sakada T, Yano T. Video-assisted extended thymectomy in patients with thymoma by lifting the sternum. *Ann Thorac Surg* 2001;71:1721-3.
 23. Ohta M, Hirabayashi H, Okumura M, et al. Thoracoscopic thymectomy using anterior chest wall lifting method. *Ann Thorac Surg* 2003;76:1310-1.
 24. Yoshino I, Hashizume M, Shimada M, et al. Thoracoscopic thymomectomy with the da Vinci computer-enhanced surgical system. *J Thorac Cardiovasc Surg* 2001;122:783-5.
 25. Suda T, Kaneda S, Hachimaru A, et al. Thymectomy via a subxiphoid approach: single-port and robot-assisted. *J Thorac Dis* 2016;8:S265-71.
 26. Yamada Y, Yoshino I, Nakajima J, et al. Surgical outcomes of patients with stage III thymoma in the Japanese nationwide database. *Ann Thorac Surg* 2015;100:961-7.
 27. Okuda K, Yano M, Yoshino I, et al. Thymoma patients with pleural dissemination: nationwide retrospective study of 136 cases in Japan. *Ann Thorac Surg* 2014;97:1743-8.

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