Editorial

Thymomectomy in early stage thymomas—case closed?

Marlies Keijzers, Jos G. Maessen

Department of Cardiothoracic Surgery, Maastricht University Medical Center, Maastricht, The Netherlands

Correspondence to: Dr. Marlies Keijzers, MD, PhD. Department of Cardiothoracic Surgery, Maastricht University Medical Center, P. Debyelaan 25, 6229 HX Maastricht, The Netherlands. Email: mkeijzers@gmail.com.

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Thymic epithelial tumors (TET) are rare tumors with an annual incidence ranging from 1.3 to 3.2 per million (1). Histologically TETs can be divided in thymomas and thymic carcinomas. A third of all patients with a thymoma will also be affected by an autoimmune disease, of which myasthenia gravis (MG) is most commonly found (2). Thymomas should be considered malignant because of their potential invasiveness. Incomplete surgical resection is one of the predictors of recurrence after resection of a thymoma. Therefore, it has been suggested that a total thymectomy should be the gold standard in all thymoma patients for oncological reasons and possibly to prevent the development of MG (post-thymectomy MG). However, some consider a resection of the thymoma alone (thymomectomy) sufficient in non-MG non-invasive thymomas. The reason for this is that some data suggested that a thymomectomy results in lower morbidity with the same early oncological outcome (3).

In this issue of the *Journal of Thoracic Disease* (*JTD*) Gu and colleagues report the outcome of the evaluation of tumor resection with or without total thymectomy for early stage thymomas (Masaoka-Koga stage I and II) using the Chinese Alliance for Research in Thymomas (ChART) retrospective database (4). The ChART retrospectively collected clinical data of 18 tertiary referral centers in China. Gu and colleagues analyzed 1,047 patients with early stage thymoma without pretreatment. A thymectomy was performed in 796 patients and a thymomectomy in 251 patients. Follow-up data with a median of 38 months was available for 78.4% of patients. Ten-year overall survival was similar between the thymectomy and thymomectomy group (91.6% *vs.* 89.4%). Patients who underwent thymomectomy underwent significant more adjuvant therapy (28.5% *vs.* 37.7%, P=0.007).

The overall recurrence rate was also similar in both groups (3.1% after thymectomy and 5.4% after thymomectomy). However, a stratified analysis showed a significant increased risk (2.9% after thymectomy *vs.* 14.5% after thymomectomy, P=0.001) of tumor recurrence in patients with Masaoka-Koga stage II thymomas undergoing thymomectomy. These high recurrence rates are worrisome after a follow-up of only 38 months since thymomas are known for their indolent nature and can give recurrences even after a follow-up of 10 years. One might conclude that a thymomectomy is acceptable in Masaoka-Koga stage I thymomas. However, differentiating between Masaoka-Koga stage I or II on pre-operative imaging and during surgery is almost impossible. Therefore, in our opinion, a total thymectomy should be performed in patients with a clinically stage I thymoma as well.

Another large study addressing the thymectomy *vs.* thymomectomy discussion was a retrospective analysis of the Japanese Association for Research on the Thymus (JART), where 1,286 patients were analyzed. (5) The 5-year overall survival was similar between both groups (96.9% after thymectomy *vs.* 97.3% after thymomectomy). Nevertheless, there was a trend towards more local recurrences in the thymomectomy group (2.2% *vs.* 0.4%, P=0.0613). Postoperative complications were seen more frequently after a thymectomy. However, these were non-life threatening with a 30 days mortality rate of 0%. This trend towards more local recurrences confirms our opinion to perform a total thymectomy in all thymoma patients.

Post-thymectomy MG is a phenomenon that is not clearly understood with a wide variety of incidence (0.9% to 20%) reported in the literature (6,7). Post-thymectomy MG has been reported in patients with tumor recurrence (8). However, it can also occur in patients without a tumor

recurrence (9). Whether the extent of the thymectomy influences the incidence of post-thymectomy MG remains under debate.

Gu and colleagues did not find any difference regarding the frequency of post-thymectomy MG. This is in line with results reported in two retrospective studies including smaller cohorts of thymoma patients (3,10). The analysis of 299 thymoma patients by Yamada *et al.* showed that serum anti-acetylcholine receptor antibodies (AChR-Ab) positivity, type B1/B2/B3 thymoma histology and incomplete resection were risk factors for the development of post-thymectomy MG (11). Nakajima *et al.* found that patients with post-thymectomy MG all showed high titers of AChR-Ab at the onset of MG (12). Although there were no differences seen in the frequency of post-thymectomy MG, these findings should be investigated in prospective trials.

As the authors acknowledge, the study suffers from limitations due to the retrospective design. First, the data were collected from many different institutions over a long period of time. Second, there was no uniform standard for the selection of the surgical approach, probably resulting in allocation-bias, an unavoidable but important drawback of non-randomized studies: the surgeon chose the approach according to his or her preference or specific baseline characteristics. If patients were receiving adjuvant therapy, this decision was based on the physicians' subjective evaluation as well. Propensity-matched analysis could have been performed to overcome the allocation-bias partially. Third, follow-up information was available in 78.4%, and although it is known that thymomas can reoccur after several years the median follow-up was only 38 months. Therefore, the study results should be interpreted with some caution.

Taken together, Gu and colleagues should be congratulated on the accomplishment of this study. These results offer important knowledge and they are doing tremendous work by collecting their data in the retrospective database and by building a prospective database. Only by the collaboration of the regional thymic groups and International Thymic Malignancy Interest Group our knowledge about the management of this orphan disease will improve. However, this case is not closed yet; we should yet be careful drawing firm conclusions. Analyses from prospective data with longer follow-up are needed. For the time being, in non-MG patients a total thymectomy should be recommended for early stage thymomas.

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Footnote

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