Author’s response to reviews

Title: Recurrence after thymoma resection according to the extent of the resection

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Author’s response to reviews: see over
Reviewer’s report
Title: Recurrence after thymoma resection according to the extent of the resection
Version: 2 Date: 30 November 2013
Reviewer: MarcoLucchi
Reviewer’s report:
This article by Mi Kyung Bae et al is a excellent and well written paper on the role of the extent of the resection in thymoma without myasthenia gravis. It would like to address the role of a complete or extended thymectomy versus a limited thymectomy in case of early stage thymoma without MG.
This is one of the biggest single institution experience and the follow-up is as long as necessary to draw some conclusions. Obviously there are some limitations related to the fact that is a retrospective study, done in a long time period, with a selection bias related to the choice of the single surgeon. However these are the limits of all the studies concerning the treatment of rare diseases, performed in a long period, and retrospectively analyzed. However the authors rightly emphasized these limitations and did not state any definitive conclusion. In this sense the description of the results is clear as well as the conclusions are reasonable.
In any case the results achieved by the authors must be diffused to the international readers and I would like to congratulate the authors for their hard work and contribution.
Level of interest: An article of outstanding merit and interest in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:
I disclose that I have no conflict of interest

#1.Response to Reviewer 1

→ Thanks for your warm comments and suggestions on our manuscript. Henceforth, we’ll also make every effort to conduct thymoma studies.
Review: “Recurrence after thymoma resection according to the extend of resection”

Summary:
In their study “recurrence after thymoma resection according to the extend of resection” the authors investigate the relationship between the extend of resection and the likelihood of tumor recurrence. The aim of the study is, to find out whether an extended thymectomy is correlated with a prolonged overall-survival. In a period of 26 years a total of 491 patients with resected thymoma were included in the study. Follow-up data were collected in order to count the number of local recurrence or metastases. The collected data were analysed in a retrospective study. The results showed no difference in the outcome concerning the recurrence rate between two compared groups (limited thymectomy vs. extended thymectomy).

Review:
# The question posed by the authors not new and therefore several studies about this topic have been published before, e.g. latest publication in november 2013 (Kazuo Nakagawa et al. “Does the Mode of Surgical Resection Affect the Prognosis/Recurrence in Patients WithThymoma?”). This study presents nearly the same methods and same results).

→ We formerly presented our manuscript in the session of oral presentation of the annual meeting at the 3rd International Thymic Malignancy Interest Group (ITMIG) held in Fukuoka, Japan between November 25 and 26, 2012. At the time, our manuscript was recognized as a novel attempt. This is because the ITMIG recommends a complete thymectomy for patients without myasthenia gravis (MG) and extended thymectomy for those with MG. Thus, less than a complete thymectomy is currently considered inappropriate except for the fact that it may be attempted in a clinical trial setting. In other words, many surgeons perform limited thymectomy in patients with thymoma without MG in an actual clinical setting. Moreover, there are no sufficient evidences demonstrating the recommendation of ITMIG. Furthermore, there are many medical institutions where a complete thymectomy is routinely performed for all patients with thymoma. We have therefore received many questions and opinions regarding our surgical policy when we presented our paper at the aforementioned academic meeting. Of course, there were not many published studies in this series at the time [1]. To our knowledge, however, as the minimally invasive surgery has been increasingly performed, there has been an increased interest in a limited thymectomy that is a relatively easier surgical modality. Presumably, this might have led to the increased publication about a limited thymectomy in patients with early stage thymoma [2, 3]. From this context, it has been of interest whether a limited thymectomy would be appropriate for the surgical management of thymoma in recent years. But this deserves further long-term follow-up as well as prospective studies. A limited resection has not caused a poor prognosis, which is beyond the scope of the standard treatment modalities such as the ITMIG recommendation. We are therefore confident that our methods are novel attempts.
# The range of the follow-up period is very widespread (1 to 255 month). One month of follow-up is definitely not sufficient, there has to be at least a period of 6 months.

→ We surgically treated our clinical series of patients between January 1986 and December 2011. Then, patient follow-up was completed until August of 2012. In addition, there was one patient who had been followed up during a 1-month period. The corresponding patient died of respiratory failure due to the aggravation of postoperative symptoms of MG. We assume that it would not be valid to censor the patient during a 1-month follow-up period without excluding such patient.

# In those patients who did not show up for follow-up examination the data were “collected” via phonecalls (which is not reliable!).

→ We totally agree with you regarding this matter. Also in our previous manuscript [4], we received the same comments from the journal reviewer. At the time, the reviewer asked us to disclose the actual number of such patients. We specified a total of nine patients for whom the data was collected by a phone call, as clarified in the current manuscript.

Please understand that it is actually difficult to collect the objective data after a regular follow-up was completed after surgery in patients with thymoma, showing a favorable prognosis, because their long-term survival is relatively longer. To put this in another way, we may encounter some cases in which we cannot obtain objective data in patients where more than ten years have elapsed since the surgery.

# Question about the reliability? It is not possible to compare data when no CT-scans or even an simple physical examination can be performed. These patients had to be excluded from the statistical analysis!

→ From the same context, as we have stated earlier, patients with thymoma show a relatively longer survival. Currently, there are no criteria for the optimal period of CT scan in such patients. According to the ITMIG recommendation, however, a computed tomography (CT) scan of the thorax should be performed during a minimum period of five years since the surgical resection. Otherwise, it should also be performed at a regular follow-up, accompanied by a chest radiography, until 11 years since the surgery. Thereafter, it is recommended that a chest radiography be performed alone [5]. That is, there are no criteria for performing a CT scan after 11 years have elapsed since the surgery. It is also recommended, however, that a diagnosis of recurrence be made based on clinical suspicion rather than CT findings because there is a long interval between the CT examinations [5].

Also, please understand that this is applicable to thymoma rather than other malignancies. In more detail, we at our medical institution perform a follow-up of patients who were surgically treated for lung cancer based on a rigorous, consistent policy. We are not confident, however, if it would be reliable to perform a CT scan solely for the purpose of conducting clinical studies in patients with thymoma where more than ten years have elapsed since the surgery.
The adjuvant treatment after surgery is explained very poor “...however, because this strategy was not standardized for the entire study period, the strategy for adjuvant therapy was patient-specific according to each surgeon’s preference...”. It is not clear, what the surgeon’s preference was. With no clear and defined adjuvant therapy regimen it is hard to understand how groups can be compared. In my opinion it is not possible to state that the investigated effects (tumor recurrence) are absent or present just because of the extent of surgery. The effects of any adjuvant therapy can not be defined. In order to compare two groups patients need at least a standardized adjuvant therapy and/or a standardized type of resection (which is difficult in extended resections, of course).

As you have pointed out, we stated that this strategy was not standardized for the entire study period the strategy for adjuvant therapy was patient-specific according to each surgeon’s preference. Even at the present, there are no established criteria for performing adjuvant therapies in patients with stage II cancer in particular. That is, there is a variability in the postoperative adjuvant modality between the surgeons in such patients. For example, some surgeons perform radiotherapy, but others never perform adjuvant therapies. As described here, there is a variability in the treatment strategy for the use of postoperative adjuvant therapies between the medical institutions and between the surgeons, even from a worldwide perspective. It is therefore imperative that the international data be collected as currently initiated by the ITMIG. This should also be accompanied by the establishment of consistent treatment strategy.

“extended... [or] ... limited thymectomy, depending on the stage and size of the thymoma as well as the clinical judgment of the surgeon. This policy has been supported by the results of a report previously published by our institution, which found that there was no difference in survival between extended thymectomy and limitedthymectomy (thymomectomy)”. What is the bias?? Were these results defined willingly or unwillingly supporting the statement of the previous study from the same institution?

We should have revised our treatment policy into the use of extended thymectomy in all the patients with thymoma if we had observed shorter survival in those undergoing limited thymomectomy as compared with those undergoing extended thymectomy when we prepared our previous manuscript [6]. To put this in another way, no surgeons would have performed thymomectomy thereafter. At the time, however, there was no significant difference in the survival between the thymomectomy group and the extended thymectomy group. Thus, based on our previous manuscript, we have been confident that there is no significant difference in the prognosis between the two surgical modalities. This is a rationale that we have continually performed a limited thymectomy at our medical institution.

26 years is a very long period of time (1986-2011, leading to different types of resection, technical or diagnostic changes and different treatment (medication). On the one hand, 26 years are positive for the large number of patients that could be included in the study. But on the other hand it has to be secured, that the long period of time doesn’t affect the composite of the sample (meaning the ongoing development of new techniques in diagnostics, therapy and treatment that could have influenced the study results). That is always a big problem in a
We totally agree with you. We also admit that 26 years is such a long period that it may cause variability and bias; this is one of the limitations of the current study. But please understand that it is also a limitation of all the studies in this series; it is unavoidable not only because such studies have examined rare diseases for long periods of time under the retrospective design. This explains why most of the studies in this series have been conducted for long periods of time under the retrospective design in a single-institution setting. Therefore, it is often difficult to compare the results between the medical institutions because there are differences in the treatment outcomes and definitions. To resolve this, the ITMIG has been formed and the international database has been established. Thus, considerable efforts have been made to prepare the reliable, consistent guidelines. So, please understand that there are some unavoidable limitations of the studies about thymoma. This will be resolved, however, when the abovementioned global efforts are realized.

# The authors do not always give a reason why they use a certain method:
# e.g. the choice of the statistical test they used

We did not have an in-depth knowledge about detailed statistical methods. We have therefore consulted a statistician before conducting the current study. We therefore prepared the valid study protocol according to the judgment of the statistician. We still do not know the exact matching and the relevant details. This is the reason why the statistician helped us a lot in preparing the current manuscript and then was listed as a co-author of the current manuscript.

# stage and size of the tumor were connected within the analysis. This is - according to other studies - not allowed (see: Stroebel P et al. Tumor recurrence and survival in patients treated for thymomas and thymic squamous cell carcinomas: a retrospective analysis. J ClinOncol 2004 (22):1501-1509.

We're sorry, but we cannot understand what you mean by the involvement of the size and stage of the tumor in the statistical analysis. It would be greatly appreciated if you clarify this.

# Despite the large number of patients, both groups compared were very heterogeneous and therefore hard to compare. A smaller but more homogeneous group would be more valuable.

We totally agree with you regarding this matter. It would be more acceptable to analyze patients with Stage I/II cancer. We are grateful for your comments.

# The two investigated groups are surgically not defined very well. It is not clearly pointed out which anatomical structures were resected and which left behind. e.g. “leaving residual thymic tissue” for the limited thymectomy. What kind of tissue was left behind? And how much? And where?

We used the same definitions as those used by Onuki et al. [1] That is, the following figures (b) and (c) illustrate the limited thymectomy group. Therefore, we added the statement on page 7.
In summary the paper has to be rejected in its present form. The clinical question is already answered and presents nothing new. The article has profound weaknesses in statistics and structure (e.g. follow-up, type of extended resection, remaining tissue, defined adjuvant therapy).

Thanks for your great concerns on our manuscript. We totally agree on your comments that there are major limitations as well as a bias in our study. But we regret to say that we could not revise our manuscript considering your comments although we’re fully aware of our problems. We sincerely hope that you consider that we have encountered such limitations and we cannot resolve them at the moment. In addition, please also consider that we have consulted a statistician in an effort to minimize the limitations of our study through a meticulous review of the study protocol.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests.

<Reference>