Peer Review File

Reviewer A

The paper was well written as case series, and this study is interesting for all thoracic surgeons. But there are several problems and confusing, and the following questions and suggestions should help to further strengthen the report.

1.The WHO classification was revised in 2021, so it is inappropriate to cite 2015 as a reference. Thymic neuroendocrine neoplasms are classified as Neuroendocrine tumors (TC, ATC) and Neuroendocrine carcinomas (SC, LCNEC, etc.).
The article is listed as "review" but I think the citations are inadequate. As far as I can find, even if you give more than 20 reports, Moran and Suster 2000 (n=80), Gaur 2010(n=160), Song 2014(n=22), Ose 2018(n=30) etc. should be added.
And papers that are described only in Chinese are not suitable to be cited in international journals (Ref. 31,32). I suggest these ref. should be deleted.

Reply : Thank you for your valuable advice.
(1) We have updated the reference for WHO pathological classification in 2021.
  Changes in the text: Page 5, line16-21;

(2) We have reviewed the literatures you mentioned above and added them to the text. Meanwhile, we have streamlined and optimized the contents of Table 3.
  Changes in the text: Page 24-34, Table 3;

(3) According to literature search results, there are few reports from China, and there is insufficient medical evidence about thymic neuroendocrine tumors. The Chinese literatures (Ref. 31,32) cited in this paper are closely related to the surgical treatment and prognosis of thymic neuroendocrine tumors. They were published in The Chinese Journal of Pathology and can be retrieved in PubMed. They are of certain value for the treatment of thymic neuroendocrine tumors in Chinese people. Therefore, we hope to preserve these Chinese literatures.

2.Methods
2-1 Please add diagnostic criteria for pathological diagnosis in Methods.
Reply : Pathological diagnosis criteria was the 2021 WHO Classification of the thymus and mediastinum. We add this criteria in the"method"section.
Changes in the text: Page 7, line13-14;

2-2 Tumor marker test items should also be written in the methods section.
Reply : We added tumor marker test items in the "method" section. Tumor markers tested before surgery included embryonic antigen(CEA), CA19-9, CA125, CA153, squamous cell

carcinoma antigen(SCC), neuron specific enolase(NSE) and alpha fetoprotein(AFP). Tumor markers were normal in four patients, and only outliers were listed in Table 1.

Changes in the text: Page 7, line9-11;

2-3   The last sentence of "Surgical techniques" is unnecessary because it is a matter of course.

Reply : We have deleted this sentence as advised.

Changes in the text: Page 8, line 11.

3.Results

3-1   Since there are 5 results, I recommend that the results should be written in Patients number. It is confusing because "One patient" is the subject.

Reply : According to your suggestion, we used Patient number (case 1 to 5) in our writing of the results and discussion section.

Changes in the text: Page 10-15, the results and discussion section;

3-2 Please add TNM classification not only Masaoka stage.

Reply : We mentioned in the "methods" section that the 8th edition of TNM classification of thymic epithelial tumors was used for tumor staging and added TNM staging results of each patient in Table 1.

Changes in the text: Page 7, line 14-16; Page 19-21, Table 1;

3-3 Table 2: Is tumor invasion pathological diagnosis?

Reply : Yes, tumor invasion and stage result of each patient were pathologically confirmed.

Changes in the text: none.

4.Discussion

The author's opinion should be based on your own experience, but there are many inadequate conclusions to be drawn from the report of only 5 cases.

Please provide references.

・Discussion p13 line 9-18 ;Is this the author's opinion? There are many reports that complete resection is a prognostic factor for thymic NETs as well as thymic carcinomas. You need to cite such literature and then write what the surgical strategy should be.

Reply :   Discussion p13 line9-18 is mainly our point of view. In this section, we focus on the surgical strategy for neuroendocrine tumors of the thymus. Through literature review, we found that a large proportion of previous clinical studies did not report complete surgical procedures and outcomes. The contents of surgical classification, the recommended surgical resection scope, potential combined resection and reconstruction of surrounding organs are based on our usual clinical practice. This part also refers to the results of the literature, so we have added the reference in this part according to your suggestion.

Changes in the text: Page 13, line 9-21;

・Discussion p14 line5-8 ; Please provide references.

Reply： Through literature review, lymph node dissection is strongly recommended for accurate staging and improved prognosis, and we have added the reference. However, few clinical studies have specifically reported the details of lymph node dissection. At present, due to insufficient data on lymph node dissection of Th-NENs, and there is no consensus on the number and scope of lymph node dissection. In our daily clinical practice, lymph nodes around the phrenic nerve, innominate vein, superior vena cava, trachea and cervical root are recommended to be removed. we add the above sentences to this section.
Changes in the text: Page 14, line 5-9;

・Discussion p14 line10-11；What is your rationale for doing so?
Reply： In our clinical practice, median sternotomy is preferred for patients with tumor diameter greater than 5cm and obvious tumor invasion. Lateral thoracotomy is also an option for patients with tumors clearly located on one side of the thorax, or for patients with difficulty with a median thoracotomy approach. In recent years, video-assisted thoracoscopic (VATS) thymectomy via intercostal or subxiphoid incisions has been more and more widely used and is suitable for patients with tumors less than 5cm in diameter and no obvious tumor invasion. We modified this section and add the above sentences to this section.
Changes in the text: Page 14, line 17-21; Page 15, line 1-2;

・Discussion p14 line14-17；Please provide references.
Reply： we believe that tumor size is not the most important determining factor for minimally invasive surgery, and the extent and severity of tumor invasion have a greater impact on the choice of surgical approach. This is the experience of our center and we do not refer to literature, so we added "we believe that".
Changes in the text: Page 15, line 5.

・Discussion p15 line11-16；Please provide references.
Reply： We revised this section and added references.
Changes in the text: Page 15, line 11-21; Page 16, line 3-8;

5．Conclusions
It should be summarized and brief because it is too long. You include what should be described in Discussion part.
For example, database construction should also be discussed in Discussion.
Reply： We have streamlined the conclusion section. The deficiencies of existing clinical studies and recommendations for a multi-center database are included in the discussion section.
Changes in the text: Page 3, line 18-21; Page 4, line 1-3; Page 16, line 3-21; Page 17, line 1-4;

The paper deals with a relevant problem. Neuroendocrine tumours of the thymus are very rare diseases and the most knowledge is provided by small case series. The best therapeutic algorithm is still to be defined. Therefore, I regard the article worth being published, but clearly needs some improvement and language editing.

Surgery is regarded as the mainstay of therapy in any case where the tumor is technically resectable. Nevertheless, there is no data to confirm this. I would suggest to discuss that issue by comparing it with the existing long term outcome data of medical therapies (e.g. Anamaterou et al. 2021). I think a graphic visualization of the results (e.g. Kaplan-Meyer-curve) could ease the understanding.

Reply： Thank you for your valuable advice.

Despite the lack of definitive data, Gaur and Sullivan report on two large sample retrospective studies from the SEER database. Follow-up results showed that the 5-year survival rate after radical surgical resection was significantly better than that after medical treatment. Anamaterou reported 4 cases of Th-NENs (including 3 cases treated with surgery and 1 case treated with Octreotide) treated with everolimus after disease progression, with progress-free survival of 7-42 months. Case 1 in this study, who developed bilateral axillary lymph node metastases 116 months after extended thymectomy, was treated with Sandostatin LAR for 1 year and everolimus for maintenance therapy, and has survived for more than 134 months. These data suggest that everolimus may be a therapeutic approach for recurrent Th-NENs. We have added these findings to the discussion section.

Thank you for your valuable suggestions on graphic visualization of survival results. However, since there were only 5 patients in this study and most of the studies on Th-NENs did not provide the survival time of each case, we did not make a K-M curve, but directly displayed the survival time of each case in this study and listed the survival data of each study report.

Changes in the text: Page 16, line 9-15;

in CONCLUSIONS it should be mentioned what this paper adds to our current knowledge. Considering the existing data and the current ESMO guideline (Baudin et al 2021), please discuss when you regard radical resection the most important method to improve diagnosis and specify if there are cases with doubts about the appropriateness of surgical therapy. from a retrospective point of view, would you still advocate for surgery in the LCNEC cases (pat. 4 and 5)? Are there markers in your work and in the literature that may predict fatal outcomes? Did you apply the nomogram model of Tang et al?

Reply： Thank you for your valuable advice. We revised the discussion section and conclusion section.

For LCNEC type tumors, if the patient is at early stage and complete resection can be achieved, we believe that surgery is of great value and postoperative systemic therapy is also very important.

Both case 4 and case 5 in this group were relatively advanced LCNEC with poor prognosis, suggesting that the decision of whether such patients are suitable for surgery

should be made with great caution. If it is difficult to achieve complete resection, the surgical efficacy will be poor.

In our clinical work, tumor stage, grade of tumor differentiation, surgical resectability, and surgical margin are the most important prognostic factors. It is also an important factor in determining whether surgery can be performed. Tumor size alone is not the most important factor in determining surgery and prognosis. This is consistent with most literature reports. This idea is written in the discussion section, page 16 line 17-19.

The value of Tang's study lies in providing an easy-to-use and quantifiable clinical tool for the prognosis and surgical selection of thymic neuroendocrine tumors, thus providing a reference for surgical decision making. So we'll put the results of this study in the discussion section.

Changes in the text: Page 17, line 3-21; Page 18, line 1-4;

between the series of Cardillo, of Ahn and your reports there are enormous differences in 5y and 10y OS. Can you explain this?

Reply :

In Cardillo's study, the proportion of masaoka stage III-IV patients was 53% (10/19). All patients received expanded thymectomy and invasive organ resection, and the R0 excision rate was 80%. Local recurrence occurred in only 2 patients during follow-up and re-do surgery was performed. The larger surgical resection range may be the reason for the lower local recurrence rate and longer overall survival in this group.

In Ahn's study, the proportion of masaoka stage III-IV patients reached 67% (14/21). Although the R0 resection rate reached 80%, the author did not report the surgical method and resection scope. The high proportion of advanced tumors was an important reason for poor prognosis of this group of patients.

In our study, the proportion of patients with Masaoka stage III-IV was 60% (3/5). Although all patients received extended resection, the incidence of lymph nodes and distant metastasis was high, leading to poor prognosis, with a median OS of 49 months.

We believe that most of the studies on Th-NENs had small sample sizes and varied perioperative treatment modalities and surgical strategies, which may lead to significant differences in prognostic data.

Changes in the text: There are no changes in the text.

Please add information about Ki67/MIB-1 or mitotic count of the tumors
Which tumor markers did you use?

Reply : We added the immunohistochemical characteristics of 5 patients, as shown in Table 1. There was no Ki-67 data in case 5, but only immunohistochemical results of Syn and CgA.

Did you assess quality of life?

Reply : We didn't assess the patient's quality of life. In future studies, we will pay attention to follow-up patients' quality of life.

Minor revisions

page 3 line 7: two patients
Reply : We corrected the language error.
Changes in the text: Page 3, line 7;

page 6 line 6 and 13/19: literature
Reply : We corrected the language error.
Changes in the text: Page 6, line 6; Page 13, line 19;

14/11: "may is an the" is to be revised
Reply : We corrected the language error.
Changes in the text: Page 14, line 13;

table 2 headline: "outcome" instead of "prognosis" seems more reasonable
Reply : We have modified the above word.
Changes in the text: Page 21, Table 2;

Table 2, pat 4: the metastases were rather "detected on" than "occurred during" postoperative
CT
Reply : We have modified the above word.
Changes in the text: Page 22, Table 2;