Editorial

Thymic neuroendocrine neoplasms—what we know, what we don't know, and what to do about it

Matthias Lang[1], Thomas M. Pausch[1], Chrysanthi Anamaterou[2]

[1]Department of General, Visceral, and Transplantation Surgery, University Hospital Heidelberg, Heidelberg, Germany; [2]Department of Nuclear Medicine, University Hospital Heidelberg, Heidelberg, Germany

Correspondence to: Matthias Lang. Department of General, Visceral and Transplantation Surgery, University Hospital, Heidelberg, Germany. Email: matthias.lang@med.uni-heidelberg.de.

Comment on: Huang C, Sun YG, Wu QJ, *et al.* Surgical treatment of intermediate to high grade thymic neuroendocrine neoplasms: case series of five patients and literature review. Transl Cancer Res 2022;11:3535-47.

Keywords: Atypical thymic carcinoid; neuroendocrine tumor of thymus; thymic neuroendocrine carcinoma; thymic neuroendocrine neoplasia of the thymus; typical carcinoid of thymus

Submitted Nov 17, 2022. Accepted for publication Dec 05, 2022. Published online Jan 09, 2023
doi: 10.21037/tcr-22-2645
View this article at: https://dx.doi.org/10.21037/tcr-22-2645

Neuroendocrine neoplasms of the thymus (t-NEN, also referred to as thymic carcinoid) are exceedingly rare tumors. Huang *et al.* present the results of their single center retrospective analysis of histologically confirmed thymic neuroendocrine neoplasia (1). All patients have been treated at the Department of Thoracic Surgery, Beijing Hospital. Between 2008 and 2020 five patients were diagnosed with thymic neuroendocrine neoplasia and underwent surgical resection.

As expected in this disease, the cases were quite heterogeneous. Three atypical carcinoids (AC) and two large cell carcinoma (LCNEC) were included. The proliferation indices Ki-67 reported were 5%, 10%, 30% and 40% and lacking in one case of LCNEC. Masaoka-Koga staging varied from IIb to IVb and TNM staging from a T1aN0M0, stage I to a T4N2M1b, stage IVb. The tumor size was within the expected limits (45–84 mm). Two patients received neoadjuvant therapy and afterwards VATS, and median sternotomy, respectively. Three patients underwent extended thymectomy directly, each of them by different means: via VATS, median sternotomy, and in one case resection of anterior mediastinal tumor, sternal metastases, superior vena cava and partial right atrium via median sternotomy and cardiopulmonary bypass. He was one of 2 patients to receive adjuvant platinum based chemotherapy. In the other patient the neoadjuvant platinum based chemotherapy was continued after surgery. Both patients died as early as 4 and 8 months after surgery, respectively. Another patient was subject to adjuvant radiotherapy. The disease-free survival (DFS) ranged between 0 and 116 months, the overall survival (OS) between 4 and 134 months. The heterogeneity of the findings shows as well in the course of the diseases: Only one patient remained disease free at the last follow-up at 52 months. The others suffered relapses on quite different sites: bone metastases, metastases at axillary lymph nodes, and metastases in brain and lungs, respectively. The fifth patient died of concurrent metastatic ovarian cancer. The maintenance therapy consisted of somatostatin analogues for one year followed by everolimus in one patient, radiotherapy in another patient and platinum based chemotherapy in both LCNEC. In one case a watch and wait strategy was chosen.

In summary, there are 5 patients with completely different courses of disease. Thus, on first sight there is the sobering conclusion that the credibility of conclusions is limited due to the very small number of enrolled cases, as stated by the authors. Nonetheless, there is an urgent need for data in these very rare diseases. And in this context, any carefully analyzed case series as the work presented here adds valuable knowledge.

There are quite some publications that deal with t-NEN.

Large scale databases offer the best option to collect data on rare diseases. Therefore, the largest evaluation comes from the SEER database, which includes 160 patients and gives the most precise insight in this disease so far (2). On the other hand, the German Registry for Neuroendocrine Tumors (NET-Register) does not state t-NET as an own entity, but subsums them regrettably as "other manifestations" (3). The ESMO guidelines on lung and thymic carcinoids are characterized by the weak data situation. It advocates surgery in resectable t-NEN but is in general focused on lung NET (4).

Huang *et al*. integrated 22 sources referring to the surgical therapies. We would like to add two surgical papers to the discussion: Wang *et al.* in 2016 published 18 t-NEN cases in this journal (5). And in June 2022, Chen *et al.* reported their retrospective analysis of a remarkable 104 cases in a single center (6).

In Wang *et al.*, 14 of 18 resected t-NEN resulted in metastatic disease, with a median follow-up of 16 months (range, 10–112) and a 5-year overall survival of 67%. In Chen *et al.*, 41 patients out of 104 developed distant metastases. The median follow-up time was 70 months with a 5-year overall survival of 54%.

Some more publications are related to medical therapies of t-NEN, which we summarized recently (7). Everolimus, temozolomide and in high proliferative disease platinum based chemotherapies are the recommended options. By now there is still no definite data to prove the benefit of any therapy—including surgical therapy. Patients with thymectomy have a longer OS and DFS, but the vast majority presents metastatic disease in the further course of disease. Therefore, one may discuss whether the better OS is due to an early stage of disease that allows resection or to surgery on its own.

And there are interesting aspects from the pathologist's point of view regarding the molecular features of t-NET that may lead to a better understanding of the entity (8). The distinction of specific molecular clusters may help to adapt the therapeutic approach.

In conclusion, we feel it is time to summarize the current knowledge on t-NEN in a certain review. The authors state that "in the future, multi-center, large-sample clinical studies are urgently needed to explore better treatment modality". However, after the open-label randomized multi-center LUNA trial failed to enroll enough t-NEN (9), it is questionable whether this is a realistic goal.

New immunohistochemical and molecular features may help to distinguish t-NEN more precisely. We should work toward ensuring that thymic tumors are perceived as a distinct entity in neuroendocrine tumor registries. More of these registries should be established and—optimally—linked. And we would like to encourage all colleagues to publish their cases.

There is still a lot to do.

Acknowledgments

We thank Mrs. Sowmya Baumann (Plauen) for language editing.
Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Translational Cancer Research*. The article did not undergo external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2645/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Huang C, Sun YG, Wu QJ, et al. Surgical treatment of intermediate to high grade thymic neuroendocrine neoplasms: case series of five patients and literature review. Transl Cancer Res 2022;11:3535-47.
2. Gaur P, Leary C, Yao JC. Thymic neuroendocrine tumors: a SEER database analysis of 160 patients. Ann Surg 2010;251:1117-21.

3. Maasberg S, Pape UF, Fottner C, et al. Im Namen aller Teilnehmer am Deutschen NET-Registers. Neuroendocrine Neoplasia within the German NET Registry. Z Gastroenterol 2018;56:1237-46.
4. Baudin E, Caplin M, Garcia-Carbonero R, et al. Lung and thymic carcinoids: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up☆. Ann Oncol 2021;32:439-51. Erratum in: Ann Oncol 2021;32:1453-5.
5. Wang HB, Yang Y, Fan XW, et al. Thymic neuroendocrine tumors: An analysis of 18 cases and a literature review. Transl Cancer Res 2016;5:789-96.
6. Chen Y, Zhang J, Zhou M, et al. Real-world clinicopathological features and outcome of thymic neuroendocrine tumors: a retrospective single-institution analysis. Orphanet J Rare Dis 2022;17:215.
7. Lang M, Hackert T, Anamaterou C. Long-term effect of everolimus in recurrent thymic neuroendocrine neoplasia. Clin Endocrinol (Oxf) 2021;95:744-51.
8. Bohnenberger H, Ströbel P. Recent advances and conceptual changes in the classification of neuroendocrine tumors of the thymus. Virchows Arch 2021;478:129-35.
9. Ferolla P, Brizzi MP, Meyer T, et al. Efficacy and safety of long-acting pasireotide or everolimus alone or in combination in patients with advanced carcinoids of the lung and thymus (LUNA): an open-label, multicentre, randomised, phase 2 trial. Lancet Oncol 2017;18:1652-64.

Cite this article as: Lang M, Pausch TM, Anamaterou C. Thymic neuroendocrine neoplasms—what we know, what we don't know, and what to do about it. Transl Cancer Res 2023;12(1):1-3. doi: 10.21037/tcr-22-2645

