Letter to the Editor

# Recent topics of lung neuroendocrine tumors

**Yoshinobu Ichiki[1,2], Hiroki Matsumiya[2], Masataka Mori[2], Masatoshi Kanayama[2], Yusuke Nabe[2], Akihiro Taira[2], Shinji Shinohara[2], Hidenori Goto[1], Taiji Kuwata[2], Masaru Takenaka[2], Soichi Oka[2], Yasuhiro Chikaishi[2], Takashi Fukuyama[3], Naoko Imanishi[2], Kazue Yoneda[2], Koji Kuroda[2], Noritada Kobayashi[3], Kozo Nakanishi[1], Fumihiro Tanaka[2]**

[1]Department of General Thoracic Surgery, National Hospital Organization, Saitama Hospital, Wako, Japan; [2]Second Department of Surgery, University of Occupational and Environmental Health, School of Medicine, Kitakyushu, Japan; [3]Division of Biomedical Research, Kitasato University Medical Center, Kitamoto, Japan

*Correspondence to:* Yoshinobu Ichiki, MD, PhD. Department of General Thoracic Surgery, National Hospital Organization Saitama Hospital, 2-1 Suwa, Wako, Saitama, 351-0102, Japan. Email: y-ichiki@med.uoeh-u.ac.jp.

*Response to:* Simbolo M, Di Noia V, D'Argento E, *et al.* Exploring the molecular and biological background of lung neuroendocrine tumours. J Thorac Dis 2019;11:S1194-8.

Submitted Jun 04, 2019. Accepted for publication Aug 02, 2019.
doi: 10.21037/jtd.2019.08.40
**View this article at:** http://dx.doi.org/10.21037/jtd.2019.08.40

Pulmonary neuroendocrine tumors (NET), a subtype of lung cancer, comprises typical carcinoids (TCs), atypical carcinoids (ACs), large cell neuroendocrine carcinoma (LCNEC), and small cell lung carcinoma (SCLC). TCs and ACs are low-to-intermediate malignant tumors, on the other hand LCNEC and SCLC are high-grade carcinomas (1).

We reported that programmed cell death-ligand 1 (PD-L1) expression of 105 pulmonary NETs was not a significant prognostic factor. Our molecular expression analysis of SCLC showed that neuroendocrine markers such as chromogranin-A (CGA) and synaptophysin (SYN) had tendency of poor prognosis, even if there was no significant difference. Though neuroendocrine markers have a possibility to become one of the prognostic factors affecting criteria of adjuvant chemotherapy or postoperative follow-up intervals in patients with SCLC, further analysis is needed for a definitive conclusion (2). Simbolo *et al.* introduced several reports on the molecular and biological background of pulmonary NET as a comment on our study (3). Interestingly, there are different molecular subgroups (described as SCLC-like, NSCLC-like and carcinoid-like) in LCNEC (4). The SCLC-like cases had co-alteration of TP53 and RB1 genes, while the NSCLC-like group harbored mutation in TP53 gene with concurrent mutation in KRAS and/or STK11 genes. The carcinoid group had mutations only in MEN1 gene. Owing to the recent developments in molecular analysis, it is necessary to change the limitations of past dogmas according to the upcoming evidence.

Kim *et al.* revealed that PD-L1 expression of SCLC and LCNEC was low (5). Frequency of infiltrative immune cells and PD-L1 expression on immune cells were associated with a higher mutation burden of cancer cells. Though phosphatase and tensin homolog (PTEN) mutation was related with infiltrative T-cell decrease infiltration and less effect of immune checkpoint inhibitor therapy in malignant melanoma (6), PTEN loss was found in 18 of 189 patients (9.5%) and was not correlated with PD-L1 expression (5).

Hermans *et al.* reported that PD-L1 expression was detected in 16% of 98 stage IV LCNEC. PD-L1 expression was independent of molecular subtypes like TP53, RB1, STK11 and KEAP1 but was associated with CD8 expression. LCNEC patients with PD-L1 and/or CD8 expression had better over all survival (7).

Spread through air spaces (STAS) is a new invasive pattern of adenocarcinoma and squamous cell carcinoma of the lung with poor prognosis. Rania *et al.* reported that STAS detection ratio was 26% of 487 pulmonary NETs (TCs: 16%, ACs: 37%, LCNECs: 43%, SCLCs: 46%) (8). STAS existence had relation with not only distant metastasis but also higher cumulative incidence of recurrence (CIR) and lung cancer-specific cumulative incidence of death (LC-CID) in the overall cohort and the AC, SCLC, and LCNEC cohorts except for TC cohort (due to few recurrences and deaths). STAS had a close relation to higher CIR and LC-

CID, independent of histologic subtype in multivariate analysis stratified by stage. STAS had a relation with early, distant metastasis and worse LC-CID in pulmonary NETs patients. STAS was independently a worse prognostic factor in LCNEC or SCLC patients.

Further development in molecular and biological profiling based on immunohistochemical staining and molecular analysis using tumor specimens might enable us to get better diagnostic definition and treatment strategy of pulmonary NETs. It is important that a large prospective study of pulmonary NETs is performed to connect to the novel treatment.

## Acknowledgments

*Funding:* Ichiki acknowledges support from Grant support: JSPS KAKENHI (19K09294).

## Footnote

*Conflicts of Interest:* 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. Travis WD. Advances in neuroendocrine lung tumors. Ann Oncol 2010;21 Suppl 7:vii65-71.
2. Ichiki Y, Matsumiya H, Mori M, et al. Predictive factors of postoperative survival among patients with pulmonary neuroendocrine tumor. J Thorac Dis 2018;10:6912-20.
3. Simbolo M, Di Noia V, D'Argento E, et al. Exploring the molecular and biological background of lung neuroendocrine tumours. J Thorac Dis 2019;11:S1194-8.
4. Rekhtman N, Pietanza MC, Hellmann MD, et al. Next-Generation Sequencing of Pulmonary Large Cell Neuroendocrine Carcinoma Reveals Small Cell Carcinoma-like and Non-Small Cell Carcinoma-like Subsets. Clin Cancer Res 2016;22:3618-29.
5. Kim HS, Lee JH, Nam SJ, et al. Association of PD-L1 Expression with Tumor-Infiltrating Immune Cells and Mutation Burden in High-Grade Neuroendocrine Carcinoma of the Lung. J Thorac Oncol 2018;13:636-48.
6. Peng W, Chen JQ, Liu C, et al. Loss of PTEN Promotes Resistance to T Cell-Mediated Immunotherapy. Cancer Discov 2016;6:202-16.
7. Hermans BCM, Derks JL, Thunnissen E, et al. Prevalence and prognostic value of PD-L1 expression in molecular subtypes of metastatic large cell neuroendocrine carcinoma (LCNEC). Lung Cancer 2019;130:179-86.
8. Aly RG, Rekhtman N, Li X, et al. Spread Through Air Spaces (STAS) Is Prognostic in Atypical Carcinoid, Large Cell Neuroendocrine Carcinoma, and Small Cell Carcinoma of the Lung. J Thorac Oncol 2019;14:1583-93.

**Cite this article as:** Ichiki Y, Matsumiya H, Mori M, Kanayama M, Nabe Y, Taira A, Shinohara S, Goto H, Kuwata T, Takenaka M, Oka S, Chikaishi Y, Fukuyama T, Imanishi N, Yoneda K, Kuroda K, Kobayashi N, Nakanishi K, Tanaka F. Recent topics of lung neuroendocrine tumors. J Thorac Dis 2019;11(8):E133-E134. doi: 10.21037/jtd.2019.08.40