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Foreword

Advances in pulmonary neuroendocrine tumor management

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The spectrum of neuroendocrine tumors (NETs) of the lung include on the one hand typical carcinoids and atypical carcinoids with a more indolent behavior and, on the other hand, the highly aggressive poorly differentiated large- and small-cell carcinomas. Pulmonary NETs account for approximately 25% of all malignant lung cancers, the vast majority being represented by small-cell lung carcinoma. Carcinoid tumors are much rarer and do not exceed 2% of all malignant lung tumors, most of them being typical carcinoids. Despite typical carcinoid tumors having been considered benign, it has become clear for many years that the fraction of these tumors metastasize not only to local lymph nodes in the mediastinum but also with the liver and bone. Therefore, these tumors, although considered to be benign, need to be followed up for very long periods of time, at least 10 years after operation, but late recurrences up to 15 years after the primary operation have been reported [1–4].

A classification system has developed by the WHO that combines architectural growth patterns of tumor cells with mitotic index and the presence of necrosis for the purpose of recognising the four different categories purposed in the spectrum of pure lung NETs [1]. In the future, a new classification system will emerge that will hopefully resemble the classification system that has been developed for gastrointestinal NETs. No established treatment for bronchial carcinoid tumors that is based on large randomized control trials has been established so far. However,

surgery is recommended as first-line treatment in all cases if possible, including exploration of the mediastinum lymph nodes. Local regional treatment of liver metastases includes radiofrequency ablation, radio- or chemo-embolization, whereas peptide receptor radionuclide therapy (PRRT) can be considered for patients with more widespread disease. The medical treatment has by tradition included biotherapy for the slow-growing tumors such as typical carcinoid tumors with somatostatin analogs and IFN- α as a basis. More recently, everolimus and sunitinib have been applied in smaller series. Atypical carcinoids with higher proliferation can be subjected to chemotherapy, including streptozotocin plus fluorouracil, the old treatment, but more recently temozolomide $\pm$ capecitabine. In the more extreme cases with mitotic index >10 , cisplatin plus etoposide can still be considered as standard of care but can also be replaced by temozolomide + capecitabine + bevacizumab [5,6]. In *in vitro* studies, a combination of EGF receptor inhibitors (erlotinib) in combination with everolimus exerts synergistic effect in inducing apoptosis in atypical carcinoid cell lines [7]. A problem might be that this is too toxic to be applied in patients. The *c-Met* oncogene is an alternative target for specific antiproliferative therapies and has been investigated in other tumor models and has also been looked at in small-cell lung carcinoma [8]. Very important steps forward for the new classification tumor biology-based system development of new markers for early recurrence as well as response to treatment are warranted. Such biomarkers are still lacking. However, molecular imaging seems very promising with new tracers that can be applied for localization, early detection of recurrence and also possible indicator of response. Such tracers are ^{68}Ga -DOTATATE/DOTATOC but FDG PET/CT also gives valuable information about the aggressiveness and proliferation of the tumor. We will hopefully see development of new biomarkers in the future. This book also includes a specific chapter on small-cell lung cancer as well as large-cell neuroendocrine carcinoma (Chapter 5), which are completely different types of NETs compared with the more indolent typical and atypical bronchial carcinoids.

Finally, a specific chapter on thymic carcinoids (Chapter 6) is included because this rather rare NET is gaining more and more attention and can present with florid clinical pictures, such as Cushing syndrome, particularly in patients with multiple endocrine neoplasia type 1. This tumor type is mostly aggressive with a tendency to metastasize early and worse prognosis. The treatment is not essentially different from the different subtypes of bronchial or lung NETs.

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