The genotypic-phenotypic approach redefines the prognostic evaluation of lung neuroendocrine neoplasms

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Abstract

Lung neuroendocrine neoplasms are heterogeneous in terms of morphological features and clinical behavior. The four-tired WHO classification scheme, together with TNM stage, are currently the most effective prognostic indicators and, to date, they define the clinical management and therapeutic strategies in these neoplasms. However, in the last decade novel information on the phenotypical characteristics and molecular background of these tumors resulted in the proposal of novel biomarkers indicative of biological or clinical behavior. Although most of them are strongly histotype-dependent, some others have been proposed to be significantly associated to tumor characteristics also within individual tumor groups, and are therefore potential additional and complementary tools, with special reference to the carcinoid patients group whose prognostic prediction is still very uneffective. Indeed, these candidate biomarkers are still to be integrated in a multimodal approach and are in the vast majority of cases not validated in independent or prospective series and have been analyzed, with special reference to the molecular ones, on relatively small case series. Once the characterization of these tumors will be further refined, the clinical impact of these information will be strongly determined by their potentiality to be integrated with the current classification, and the tight collaboration between those who are active in this subject (diagnostic pathologists, molecular pathologists/biologists, clinicians) is necessary for a validation in the clinical practice.

Keywords carcinoid; lung; molecular genetics; neuroendocrine neoplasms; prognosis; proliferation

Introduction

In the last decade novel information on the phenotypical characteristics and molecular background of lung neuroendocrine neoplasms resulted in the proposal of novel biomarkers indicative of biological or clinical behavior. However, most of them are strongly histotype-dependent, and only few are significantly associated to tumor characteristics also within individual tumor groups, and are therefore potential additional and complementary tools, with special reference to the carcinoid patients group whose prognostic prediction is still very ineffective (Figure 1).

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State of the art and current guidelines

Morphological classification and its clinical impact: lung neuroendocrine neoplasms encompass an extremely heterogeneous group of tumors whose spectrum of either morphological or clinical characteristics varies from well-differentiated indolent to poorly differentiated and highly fatal diseases.

Currently, the correct application of the diagnostic criteria coded by the most recent WHO classification is the standard for the definition of the four main types of lung neuroendocrine neoplasms, which includes in increasing degree of aggressiveness, typical carcinoid, atypical carcinoid, large cell neuroendocrine carcinoma and small cell carcinoma.[1] Accurate mitotic count, and the assessment of the presence of necrosis are required for the histological diagnosis of the different histotypes in the routine practice. In fact, typical carcinoid has fewer than two mitoses/2 mm^2 and absence of necrosis, and atypical carcinoid has 2–10 mitoses/2 mm^2 and/or foci of punctate necrosis. Small cell and large cell neuroendocrine carcinomas have more than 10 mitoses/2 mm^2 (usually greater than 50/2 mm^2) and extensive geographic necrosis. Growth pattern (organoid vs diffuse) and cell size (small vs large) together with secondary features such as nuclear characteristics (i.e. presence of nucleoli in large cell neuroendocrine carcinoma or molded/finely granular nuclei in small cell carcinoma) are used to better classify poorly differentiated forms, whereas they do not serve to distinguish typical and atypical carcinoids. Indeed, these criteria are almost identical since nearly 20 years, thus proving their reliability with special reference to surgical samples. In fact, this classification scheme is by far the most relevant prognostic indicator in the entire spectrum of lung neuroendocrine neoplasms as well as in the group of carcinoids only, followed by TNM staging that incorporated pulmonary carcinoids in the 7th edition.[2] Histological variants of carcinoids (spindle cell, oncocytic, and melanocytic) may impact on differential diagnosis, but do not have clinical relevance.

Grading of neuroendocrine lung tumors is intrinsically present in the current classification scheme which poses each histological type into three groups: typical carcinoids are low-grade malignant, atypical carcinoids are intermediate-grade malignant, and small cell and large cell neuroendocrine carcinomas are high-grade malignant neoplasms. However, establishing a grading system in lung neuroendocrine neoplasms independent of histology could be clinically useful, and some proposals have been made recently adding proliferation index to pure morphological features (see below). Nonetheless, none of these proposals is currently indicated as mandatory by WHO nor is used in the clinical practice to specifically determine clinical management or therapeutic strategies.

As to concern carcinoid histotypes, in the case of localized disease surgery is the treatment of choice with the aim of removing the tumor and preserving as much lung tissue as possible. There is no consensus on adjuvant therapy in lung carcinoids and there is only a weak recommendation that patients with atypical carcinoids with positive lymph nodes, especially if there is a high proliferative index, should be considered

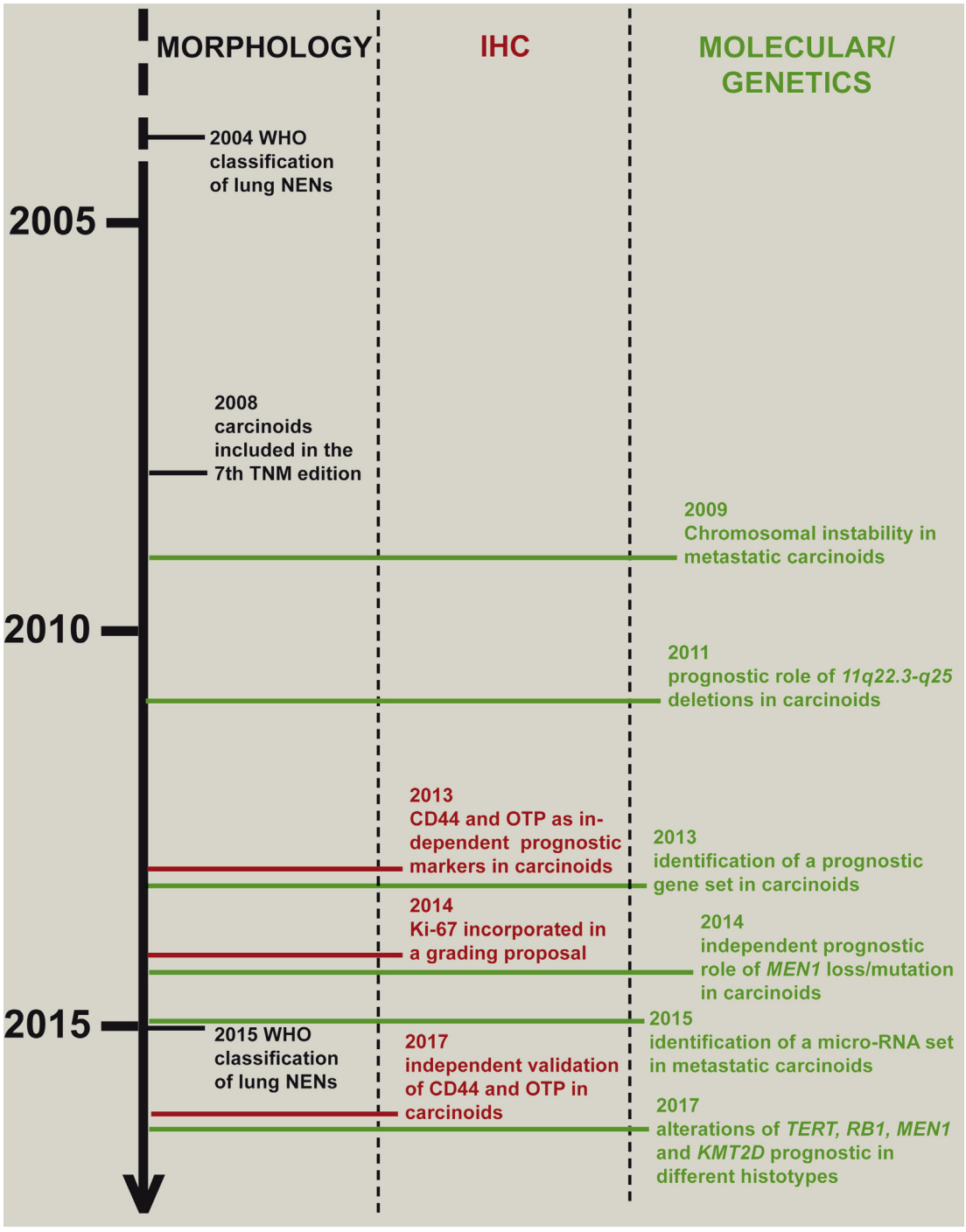

Figure 1 Timeline of most promising – histotype-independent – prognostic biomarkers discovered in the lung carcinoid group.

for adjuvant therapy, but this possibility has to be discussed on an individual patient basis in the context of multidisciplinary tumor board meeting.[3] In advanced carcinoid cases, the medical management must incorporate a multidisciplinary approach but the prognostic heterogeneity and absence of curative therapeutic options at the metastatic stage make quality of life a core issue, and each therapeutic strategy ("cold" or "hot" somatostatin analogs, mTOR inhibitors or chemotherapy) is selected independently from pathological parameters including histotype. A role for surgery in a curative intent is also considered for large cell neuroendocrine carcinoma, being adjuvant treatment associated with reduced risk of progression even in early stages although on a retrospective data collection base[4] and with no tools for clinical or pathological prognostic sub-grouping. In small cell carcinoma, which usually presents at advanced disease stage, a multimodal approach, including chemotherapy plus

