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Review

Grading lung neuroendocrine tumors: Controversies in search of a solution

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Summary. *Background*. Pathological grading of tumors is a way to measure biological aggressiveness. In lung neuroendocrine tumors (NET), grading is tautologically included into the current 2015 WHO histologic classification. Little is known, however, about alternative grading systems in lung NET.

Methods. Through an extensive search of the English literature on lung NET (updated to April 2016), the following key questions were addressed: a) current concepts of grading; b) clinicians' requests for grading; c) functional parameters for grading; d) Ki-67 labeling index (LI) for grading; e) towards an effective pathology grading system.

Results. There is some room for inconsistency in the histologic classification of lung NET, likely due to the varying attribution of defining criteria. Innovative diffusion-weighted imaging upon magnetic resonance or molecular analysis could help separate indolent from aggressive lung NET, thus integrating a grading approach other than histology. Troubles in the clinical handling of metastatic or individual tumors when relying on morphology alone support the development of a lung-specific grading system for the more accurate prediction of prognosis and planning therapy in individual patients. To integrate the 2015 WHO classification using innovative grading based on Ki-67 LI, mitotic count and necrosis, a new proposal is emerging where three categories of lung NET are identified, namely Lu-NET G1, Lu-NET G2 and Lu-NET G3, which would allow tumors with similar behavior and therapy to be better handled according to their own biological potential.

Conclusion. A new formulation of lung NET grading could have clinical relevance for the individual handling of patients.

Key words: Neuroendocrine, Tumor, Lung, Grading, Ki-67, Gene, Magnetic resonance

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Introduction

Pathologic tumor grading is an operational way to express the aggressiveness potential of human malignancies resulting in dismal prognosis and reduced survival (Edge et al., 2010; Sobin et al., 2010) or to quantify the risk of precursor lesions (dysplasia and in situ carcinoma) to give rise to or associate with invasive tumors (Holland et al., 1994; Leong et al., 2001; Breuer et al., 2005; Ishizumi et al., 2010; Yatabe et al., 2011; Basturk et al., 2015b; Bennett et al., 2015; Geetha et al., 2015; Travis et al., 2015a; Kuijpers et al., 2016a,b). Tools for grading are usually specific morphologic attributes, either quantitative or qualitative, which are deemed to accurately parallel the natural history of tumors, thereby predicting the ultimate behavior at the level of an individual patient's cancer (Holland et al., 1994; Breuer et al., 2005; Edge et al., 2010; Ishizumi et al., 2010; Sobin et al., 2010).

Traditionally, tumor grading has adopted histologic

and/or cytological traits (cell differentiation) to create two-tier to four-tier scales according to a steady increase in cell abnormalities, based on the premise that reduced resemblance of tumors with respect to the normal cell counterpart is associated with a higher propensity to grow and disseminate, responsible for relentlessly reduced survival (see http://www.cancer.gov/about-cancer/diagnosis-staging/prognosis/tumor-grade-fact-sheet and (Edge et al., 2010; Sobin et al., 2010). Currently, the relevance of tumor grading to planning patient treatment or staging is greater for certain types of cancer, such as tumors affecting soft tissue (Coindre et al., 2001; Sobin et al., 2010), bone (CDM et al., 2013), brain (Louis et al., 2016), breast (Lakhani et al., 2012), prostate (Kryvenko and Epstein, 2016) and kidney (Ha et al., 2016), in which there is a case mix of indolent to highly aggressive tumors. At variance are highly deadly cancers, such as lung (Barletta et al., 2010; Kadota et al., 2012a,b; Sigel et al., 2012; Warth et al., 2012, 2016; Westaway et al., 2013; Zhao et al., 2015; Travis et al., 2016a; Weichert et al., 2016), pancreas (Luttges et al., 2000; Basturk et al., 2015b; Sigel et al., 2015) or ovary (Ryu et al., 2009; Sica et al., 2010; Bodurka et al., 2012), which have much less effective grading models, and the relevant clinical context of application is still unclear.

Traditionally, grading systems have been featured on G1 to G3 scales by inversely linking cell differentiation to clinical behavior according to defining schemes, which depend on diverse institutions or tumor types (Sundquist et al., 1999; Coindre et al., 2001; Sobin et al., 2010; Kryvenko and Epstein, 2016). Briefly, G1 tumors indicate slow-growing lesions closely looking like the normal cell counterpart they have originated from or are differentiating towards. G3 tumors refer to fast-growing lesions composed of anaplastic cells with no definite signs of differentiation. G2 tumors comprise intermediate lesions in terms of morphology traits and clinical aggressiveness (Edge et al., 2010; Sobin et al., 2010). It is evident, however, that such cell differentiation-dependent grading systems may be disappointing due to the objective difficulty in ascertaining cell lineages for ultimate comparison (for instance, in tumors with uncertain cell derivation) or attributing reproducible morphologic traits to each defining category, thus resulting in some intra- and inter-observer inconsistency (Kaye et al., 2016; Kuijpers et al., 2016a,b; Kweldam et al., 2016; Priemer et al., 2016).

To overcome these drawbacks, many grading systems have adopted multiple criteria selected by multivariate analysis of several histological features, which are diversely scored independently of each parameter to obtain a final grade by adding all attributed scores (Thomas et al., 2009; Kryvenko and Epstein, 2016; Louis et al., 2016; Moch et al., 2016). In lung adenocarcinoma, for example, grading has been greatly strengthened by crossing tumor architecture (Sica et al., 2010) and different expression levels of mitotic count, at least for resection specimens representing stage I of disease (Kadota et al., 2012a).

As grade would mirror the capability of tumor cells to grow and spread (Edge et al., 2010; Sobin et al., 2010), it would be an intensive property of tumors independent of their extension (and hence stage), exactly as the temperature of a body is proportional to the amplitude of molecular vibrations but not to the quantity of thermal energy (Gibbs free enthalpy) (Rietman et al., 2016), which in turn depends on mass. In this scenario, high-grade tumors are expected to behave aggressively even if of small size or serendipitously confined to the origin organ, exactly as small-sized bodies have limited heat capacity but may have high temperature. Tumor grade is not necessarily a stable and unchangeable property of tumors but may worsen over time according to a linear progression scheme of molecular and morphologic changes or a sudden emergence of aggressive cell subsets (Breuer et al., 2005; Ishizumi et al., 2010; Yatabe et al., 2011), either spontaneously (de novo carcinogenesis) or triggered by therapy intervention for selective pressure on resistant clones (Breuer et al., 2005; Ishizumi et al., 2010; Sequist et al., 2011; Yatabe et al., 2011).

Most grading systems have been variably based on cancer development-related defining criteria, such as necrosis, cell proliferation (mitotic count, cell cycle-related antigens), cell differentiation (size, nuclear-cytoplasmic ratio, nuclear features, growth patterns), neo-angiogenesis or changes at the tumor-stroma interface (budding) (Luttges et al., 2000; Coindre et al., 2001; Ryu et al., 2009; Barletta et al., 2010; Sica et al., 2010; Sobin et al., 2010; Bodurka et al., 2012; Kadota et al., 2012a,b; Lakhani et al., 2012; Rindi et al., 2012; Sigel et al., 2012; Warth et al., 2012; Westaway et al., 2013; Pelosi et al., 2014b; Basturk et al., 2015b; Sigel et al., 2015; Zhao et al., 2015; Ha et al., 2016; Kryvenko and Epstein, 2016; Louis et al., 2016; Travis et al., 2016a; Warth et al., 2016; Weichert et al., 2016). It is clear that greater clinical aggressiveness of tumors results in a reduced likelihood of effectively stratifying patients in sub-categories by attaining grading criteria. As lung neuroendocrine tumors (NET) are behaviorally heterogeneous, ranging from quite indolent to very aggressive tumors (Rekhtman, 2010; Pelosi et al., 2014a-c; Travis et al., 2015a,b), a grading system is potentially useful to stratify these tumor patients at the level of individual patients' cancers (Rindi et al., 2014b).

This article is intended to address the issue of grading in lung NET by reviewing relevant information on pathology, innovative imaging, molecular profiling and the Ki-67 labeling index (Ki-67 LI) in light of current challenging requests by clinicians. As lung NET needs to be clinically stratified to plan treatments, the question is not whether to grade or not to grade these tumors but rather how best to grade them. The hope is that integrating traditional morphology with closer criteria to cancer biology will allow researchers to place an innovative terminology into context for the best handling of lung NET at the level of individual patients' cancers.

Materials and methods

A detailed bibliography search (not a systematic review) on grading in lung NET was performed until June 2016. The bibliography search was limited to English literature, with only full papers of peer-reviewed journals being on record. A practical key-question list of pathology, clinics, imaging and molecular issues relative to grading in lung NET was prepared, with several items included in the search: carcinoid, typical, atypical, small cell, large cell, LCNEC, SCLC, grading, mitoses, count, necrosis, Ki-67, prognosis, survival, molecular, aggressiveness, therapy, cancer development, biomarker, gene, sequencing, mutation, positron emission tomography, fluoro-deoxy-glucose, octreoscan, somatostatin receptor, imaging, magnetic resonance, and weighted diffusion.

Results

The paper aims to address the current state of the art for grading in lung NET, providing possible interpretation keys and mediating a final managerial proposal. In detail, a few key questions were herein addressed: a) current concepts of grading; b) clinicians' requests for grading; c) functional parameters for grading; d) Ki-67 labeling index for grading; e) towards an effective pathology grading system. The following presentation will address these key questions in light of recently published papers, with relevant key points summing up major interpretation issues included at the end of each item.

Current concepts of grading

Lung NET are currently catalogued according to diagnostic criteria based on morphology, which have been confirmed to have substantial validity in the last three WHO classifications (Travis et al., 1999, 2004, 2015b). They thus comprise four histological variants, namely typical carcinoid (TC), atypical carcinoid (AC), large-cell neuroendocrine carcinoma (LCNEC) and small-cell carcinoma (SCC), which have recently been pushed to enter a unique box of tumors showing NE morphology and differentiation along with pre-invasive lesions, such as diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) with a chance for the development of carcinoids (Travis et al., 2015b). In particular, LCNEC has been removed from the confusing and all-inclusive chapter of large-cell carcinoma in the 1999 and 2004 WHO classifications (Travis et al., 1999, 2004). SCC is no longer considered a separate tumor entity that is simply opposed to non-small-cell lung carcinoma (NSCLC) for clinical purposes (Travis et al., 2004), and the debated term of NSCLC with NE differentiation (NSCLC-ND) has been eliminated because of uncertain clinical value (Pelosi et al., 2003b; Howe et al., 2005; Ionescu et al., 2007; Segawa et al., 2009; Sterlacci et al., 2009; Petrovic et al., 2011; Gottschling et al., 2013; Derks et al., 2016a) (the current recommendation is not to perform immunohistochemistry (IHC) for NE markers if the relevant morphology is lacking, whatever material is dealt with) (Travis et al., 2013, 2015a, 2016b).

A large body of literature has been supporting the notion that the stratification of lung NET according to epidemiology (age, sex, smoking habits), molecular knowledge (association with MEN1 syndrome, *menin, RB1, TP53* mutations and other gene pathway alterations), clinics (occurrence of regional lymph node and distant metastases, association and type of para-neoplastic syndromes, response to different therapies) and behavior (survival) fits well with an operational three-tier prognostic arrangement paralleling a steady increase in tumor aggressiveness (Godwin and Brown, 1977; Asamura et al., 2006; Moran and Suster, 2007; Righi et al., 2007, 2010a,b, 2014; Moran et al., 2009; Rekhtman, 2010; Travis, 2010; Pelosi et al., 2014a-c, 2015c; Rindi et al., 2014b; Rossi et al., 2014; Travis, 2014; Caplin et al., 2015; Filosso et al., 2015b; Travis et al., 2015a). In this continuous spectrum, however, only TC and AC are behaviorally distinguishable from each other (Garcia-Yuste et al., 2000, 2007; Canizares et al., 2014; Garcia-Yuste and Matilla, 2014), while LCNEC and SCC often merge with overlap of survival curves when limiting to morphology (Garcia-Yuste et al., 2000; Jones et al., 2004; Travis, 2010, 2014; Rossi et al., 2014; Naidoo et al., 2016).

In the past, there had been attempts to introduce a concept of grading in the classification of NET (Capella et al., 1994, 1995; Wick, 2000; Cerilli et al., 2001; Moran and Suster, 2007; Moran et al., 2009; Pelosi et al., 2014a, 2015c; Rindi et al., 2014b), by variably intermingling the notion of cell differentiation (Capella et al., 1994, 1995; Wick, 2000; Cerilli et al., 2001; Axiotis, 2002; Huang et al., 2002), applying different thresholds to current defining criteria (Axiotis, 2002; Huang et al., 2002) or extending to them the taxonomy devised for gastroenteropancreatic (GEP) NE neoplasms (NEN) (Capella et al., 1994, 1995; Zahel et al., 2012). These proposals, however, failed to become widespread, likely due to historical reasons and a purported lack of undisputable clinical benefits compared to existing WHO classifications (Travis et al., 1999, 2004, 2015a). In particular and at variance with GEP NEN (Klimstra et al., 2010a,b, 2015; Yang et al., 2013; Klimstra, 2016), cell differentiation is not an accepted criterion for classifying lung (and even thymus) NET (Marx et al., 2015; Travis et al., 2015b), although TC and AC are as a whole *de facto* well-differentiated tumors in both anatomical sites as opposed to poorly differentiated LCNEC and SCC (Caplin et al., 2015) when using morphology and the relative amount of dense-core NE granules (highlighted by chromogranin A IHC) as judgment criteria (Klimstra et al., 2010a; Caplin et al., 2015; Travis et al., 2015b). However, SCC remains a mere histologic diagnosis in both the lung and the thymus, which lacks obvious NE morphology apart from

nuclear characteristics (size and chromatin texture) and does not require NE marker demonstration for ultimate diagnosis (although it is detectable in 90% or more of cases and strongly recommended by current guidelines) (Caplin et al., 2015; Marchevsky and Wick, 2015; Marx et al., 2015; Travis et al., 2015a). In turn, LCNEC requires NE morphology and clear-cut NE differentiation in 10% or more of the tumor cells at either site to distinguish them from conventional carcinomas (Rossi et al., 2014; Caplin et al., 2015; Marx et al., 2015; Travis et al., 2015a). Therefore, it is not surprising that some discrepancy may arise in AC (tautologically well differentiated) with respect to the irregular distribution of dense-core NE granules or borderline (around ten) mitosis counts (Caplin et al., 2015) or in SCC (tautologically poorly differentiated) because of the unexpected abundance of dense core granules (see Fig. 1 depicting an example of differentiation-discrepant lung SCC).

At variance with GEP NET (Rindi et al., 2006, 2012, 2014a), morphologic classification in the lung (and thymus) has been tautologically equated to grading (Marx et al., 2015; Travis et al., 2015b). Accordingly, TC and AC comprise low-grade and intermediate-grade malignant NE tumors with long-term and intermediate survival rates, respectively, LCNEC and SCC encompass full-blown high-grade NE carcinomas, both with dismal prognoses (Pelosi et al., 2014a,b, 2015c; Marx et al., 2015; Travis et al., 2015b).

The diagnosis of NET is a stepwise process (Franks

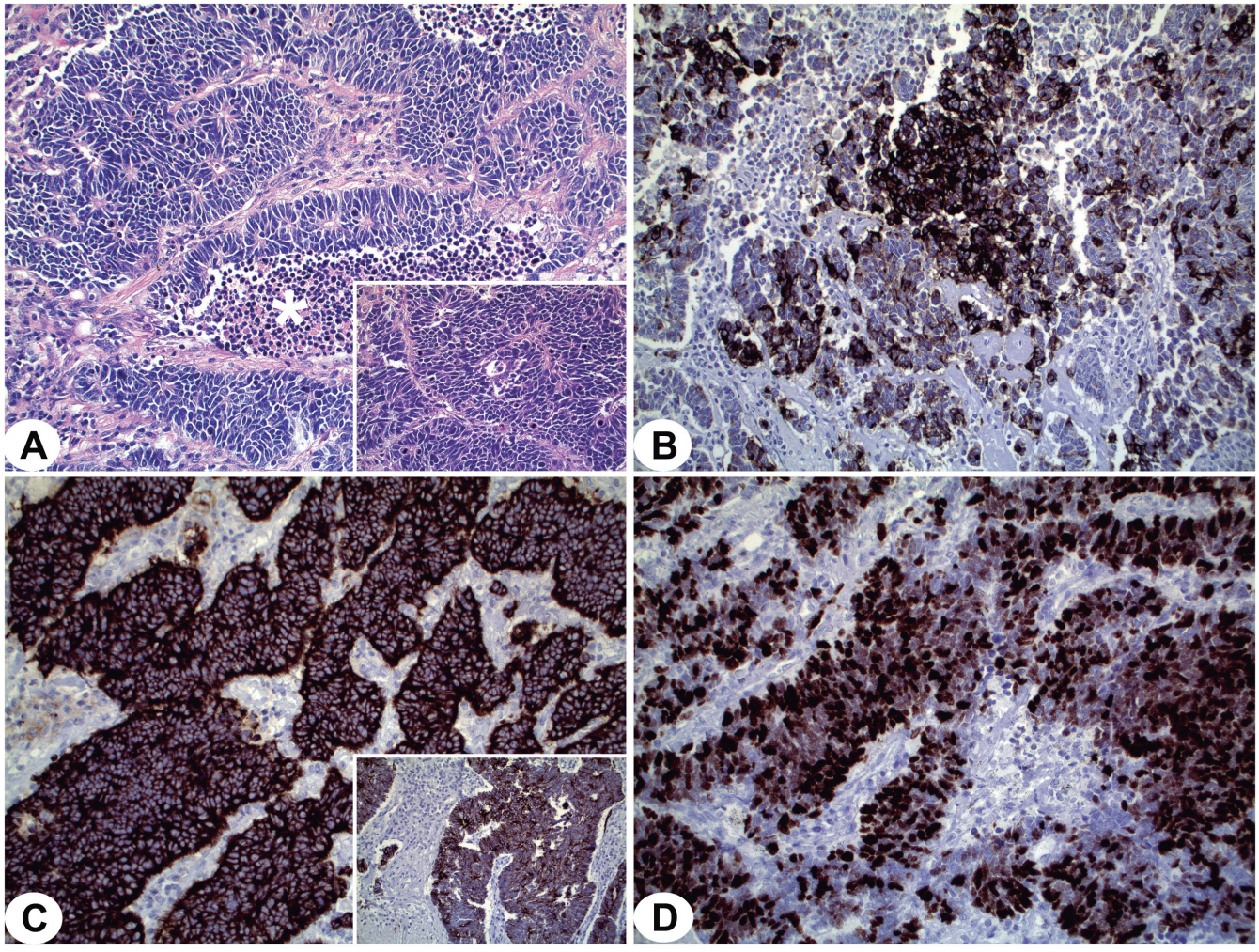

Fig. 1. A case of peripherally located small cell carcinoma featuring well retained neuroendocrine differentiation levels in the form of rosettes and trabecular architecture, along with nuclear molding (inset) and extensive necrosis (white asterisk) consistent with high-grade neuroendocrine tumors **(A)**. This tumor exhibited strong chromogranin A decoration witnessing high content of neuroendocrine secretion granules **(B)**, along with diffuse and intense synaptophysin accumulation **(C)**, focal cytokeratin pool AE1-AE3 reactivity (**C**, inset) and very high Ki-67 labeling index **(D)**, revealing common properties of high-grade tumors with well retained neuroendocrine differentiation.

and Galvin, 2008) where NE morphology, number of mitoses per 2 mm^2, occurrence and qualitative extent of tumor necrosis and cytological details are used to catalogue TC, AC, LCNEC and SCC (Table 1). The Ki-67 antigen labeling index (Ki-67 LI) is significantly ranked among these four categories of tumors (recently reviewed by Pelosi et al., 2014c), but it is currently not advisable to perform this technique using proliferation markers other than mitotic count to diagnose because of the partial overlap of Ki-67 LI values between biologically adjacent tumor variants (TC vs. AC; AC vs. LCNEC; LCNEC vs. SCC) (Pelosi et al., 2014c; Travis et al., 2015b). While IHC for NE markers is recommended,—even if not mandatory—for an ultimate diagnosis of lung NET (Caplin et al., 2015; Travis et al., 2015b), the exclusion of Ki-67 LI from classification is less understandable even if it has been ascribed to imperfect inter-observer reproducibility and sub-optimal correlation with defining criteria, namely mitotic count and necrosis (Pelosi et al., 2014a-c). However, the same difficulty (and hence overlap) holds true for morphology in borderline/gray-zone tumors where the subjective attribution of defining criteria may cause the same diagnostic misinterpretation (TC vs. AC; AC vs. LCNEC; LCNEC vs. SCC) (Travis et al., 2015b). This results in low diagnostic reproducibility of lung NET on surgical specimens considered as a whole (Travis et al., 1998a; Marchevsky et al., 2001; Iyoda et al., 2007; Righi et al., 2007; den Bakker et al., 2010; Ha et al., 2012; den Bakker and Thunnissen, 2013; Warth et al., 2013; Swarts et al., 2014b), apart from the distinction of the two spectrum extremes (i.e., TC from SCC) (Travis et al., 1998a). In biopsy samples, the challenging appreciation of solely morphologic details may even lead to the opposite conclusion, especially in the presence of crush artifacts (Pelosi et al., 2005).

Grading lung NET according to the same taxonomy as that used on GEP NEN is not likely to be successful because of the adopted cut-off thresholds and selection biases rather than the incoherence per se of Ki-67 LI and mitoses to construct a histology-independent grading system (Zahel et al., 2012). Interestingly, when looking at survival curves of lung NET, it appears that TC are behaviorally quite homogeneous tumors with flat curves approaching 100% life expectation at long-term follow-up, whereas SCC shows steep survival curves in the first two years with a negligible fraction of long-term survivors at the five-year follow-up (even if this fraction is higher on surgical series) (Filosso et al., 2002, 2015b; den Bakker et al., 2010; Travis, 2010, 2014; den Bakker and Thunnissen, 2013; Lou et al., 2013; Caplin et al., 2015; Kunz, 2015; Travis et al., 2015b; Yokouchi et al., 2015; Schmitt et al., 2016). This means that current diagnostic criteria are sufficient to extract the two behavioral ends, i.e. TC and SCC, from the box of lung NET. Major difficulties instead arise on AC and LCNEC where a non-negligible fraction of five-year survivors (up to 15–25% of patients according to different institutions) may be found, indicating that diagnostic criteria based solely on morphology do not reliably predict prognosis in these tumors (Travis et al., 1998b; Jones et al., 2004; Asamura et al., 2006; Righi et al., 2007, 2010a,b; Rindi et al., 2014b; Filosso et al., 2015a). A major interpretation issue could be that the current criteria for AC or LCNEC (Table 1) are too wide and/or unsuitable or not sufficiently exhaustive to identify a unique category of tumors (Swarts et al., 2013b; Toffalorio et al., 2014; Derks et al., 2016b). As a matter of fact, AC with six to ten mitoses are reported to have a significantly worse prognosis (Beasley et al., 2000), while the minimum of 11 mitoses per 2 mm^2 with no theoretic upper limit required for LCNEC is unlikely to identify a homogeneous tumor category with regard to clinical behavior, molecular alterations or response to therapy (Veronesi et al., 2006; Varlotto et al., 2011; Naidoo et al., 2016; Rekhtman et al., 2016). In fact, recent studies have confirmed that LCNEC are genetically and phenotypically heterogeneous in terms of clonal expansion and cell differentiation, with some of them looking like conventional NSCLC rather than SCC (Swarts et al., 2012; Seidel, 2013; Pelosi et al., 2015b; Rekhtman et al., 2016). To complicate this scenario, there are lung NET (as well as thymus or GEP NEN) that look like AC or G2 tumors, exceeding the allowed mitotic count, which tautologically would be classified as LCNEC in the lung and thymus and NE carcinoma (NEC) in the GEP tract according to current criteria (Sobin et al., 2010; Travis et al., 2015b). Genetically, these tumors are more akin to AC (Rekhtman et al., 2016) or different from GEP NEC (Tang et al., 2016),

Table 1. Diagnostic features for lung neuroendocrine tumors according to the 2015 WHO classification.

Variable	Typical carcinoid	Atypical carcinoid	Large-cell neuroendocrine carcinoma	Small-cell carcinoma
Neuroendocrine morphology	yes (organoid)	yes (organoid)	yes (organoid)	yes (nuclear features)
Cytological criteria	no	no	yes	yes
Mitoses/2 mm^2	1	2-10	≥11	≥11
Necrosis	no	punctate	extensive	extensive
Use of immunohistochemistry	recommended	recommended	defining	recommended
Combined variant	no	no	yes	yes
Chromogranin A and synaptophysin	positive	positive	positive 80-90%	positive 80-90%
Ki-67 labeling index	up to 5%	up to 25%	40-80%	50-100%

which are thought to derive from preexisting lower grade NE tumors (Moran and Suster, 2000; Pelosi et al., 2015a; Tang et al., 2016).

In this scenario, a not negligible bias is due to the low reproducibility of lung NET diagnoses with disturbing inter-observer variability (Travis et al., 1998a; Marchevsky et al., 2001; den Bakker et al., 2010; Ha et al., 2012; den Bakker and Thunnissen, 2013; Swarts et al., 2014b; Marchevsky and Wick, 2015), which allows tumors to move from one category to another. This impedes an effective cross-study evaluation and introduces inconsistency into the survival/grading analysis. It is surprising that functional parameters, such as Ki-67 LI and the quantification of necrosis, have not been challenged for grading or even classification, crediting only mitotic count, cell features and the qualitative description of necrosis (Marx et al., 2015; Travis et al., 2015b).

Key points

The grading of lung NET is inherently included in the current classification, which is in turn exclusively based on morphological criteria. Evidence is emerging, however, that morphology may be inadequate to reliably predict prognosis in challenging tumors at the boundaries of intermediate categories, such as AC and LCNEC, with a few of these tumors behaving differently from expected.

Clinicians' requests for grading

The therapy for lung NET depends on several factors, including histological diagnosis, radiology and nuclear medicine imaging, the occurrence of clinical symptoms (functioning vs. non-functioning), tumor burden, and clinical risks, especially in quickly progressing disease and tumor traits for personalized therapy (Gridelli et al., 2013; Caplin et al., 2015; Pusceddu et al., 2016). The current WHO classification (Travis et al., 2015a), however, with its quadripartite division into four histologic variants, is not completely consistent with the subsequent clinical management of lung NET patients. This holds particularly true for metastatic disease, where therapeutically challenging tumors, such as AC or LCNEC, are difficult to recognize, as diagnostic criteria have been based on surgical specimens (Travis et al., 2015a). Notably, the diagnosis of carcinoid with no further specification would only be permitted on small biopsy or cytology samples. Only a suspicion of LCNEC could be raised for biopsy specimens (cytology is deemed unsuitable) (Travis et al., 2011, 2013, 2015a; Caplin et al., 2015).

In the setting of metastatic disease, once poorly differentiated NE carcinoma has been reasonable excluded (Volante et al., 2011, 2015), it is unimportant whether TC or AC is encountered, because the treatment of either tumor type is mainly based on biological drugs (somatostatin analogues or m-TOR pathway inhibitors) and/or peptide receptor radionuclide therapy (PRRT) (Fazio et al., 2013; Chan and Kulke, 2014; Righi et al., 2014; Ferolla, 2015; Pelosi et al., 2015c; Yao et al., 2016), once the clinical balance on patients has been guided by means of imaging, symptoms, tumor burden, individual risks of evolving disease and the presence of actionable targets (Caplin et al., 2015; Pusceddu et al., 2016).

The treatment of clinically more aggressive metastatic NET, once SCC has been ruled out (this corresponding to life-threatening carcinoid or LCNEC), is again independent of histology and would include biological therapies, PRRT or alkylating-based chemotherapy, to avoid the administration of platinum/etoposide (Fazio et al., 2013; Yao et al., 2016). In other words, it is clinically relevant to separate highly aggressive NET, the behavior and therapy of which would merge with that of classical SCC, from lesions showing a wider and often inexplicable range of patient prognosis, biological potential and clinical response. The category of these NET with intermediate prognoses could be further dissected according to a managerial concept of grading independent of but integrated with more traditional histology. In this scenario, three main practical situations could be identified: a) a completely indolent-behaving tumor, which biologically corresponds to TC and, as such, could be treated with no particular clinical pressure; b) a low-to-moderate malignancy tumor corresponding to lower-aggressive AC or even some LCNEC, which are still manageable with reasonable timing according to biological treatments only; and c) a moderate to higher malignancy tumor corresponding to aggressive AC or LCNEC (the latter yet not so aggressive as true SCC, which could feature the recently described molecular entity of SCC-like LCNEC (Rekhtman et al., 2016)), which are managed better by biological treatments along with non-platinum-based chemotherapy.

This interpretation of heterogeneously behaving and variably responsive lung NET has clinical and molecular correlations (Ding et al., 2008; Swarts et al., 2012; Swarts et al., 2013a; Naidoo et al., 2016; Rekhtman et al., 2016). In the lung, this setting is similar to what has recently been suggested for the G3 category of GEP NEN, where the further separation into G3 NET (therapeutically and molecularly more akin to G2 NET) or G3 NEC (to treat with aggressive platinum-based chemotherapy) has been proposed on the basis of Ki-67 LI, mitotic count and tumor morphology (Bastrurk et al., 2013, 2014, 2015a; Sorbye et al., 2013; Velayoudom-Cephise et al., 2013; Basturk et al., 2014; Rindi et al., 2014a; Basturk et al., 2015a; Hijioka et al., 2015; Tang et al., 2016).

Once again, an integrated classification of lung NET that merges morphology (Travis et al., 2015b) with an effective grading system based on or including Ki-67 LI (Rindi et al., 2014b) would be a desirable and clinically

warranted goal.

Key points

The wide range of behaviorally intermediate tumors and some troubles in the multimodality therapy for AC and LCNEC, especially when dealing with metastatic lesions, with tumors merging with indolent TC and tumors bordering highly aggressive lesions not different from SCC, favors a lung-specific grading system that would help clinicians to better correlate tumor behavior with the choice of therapy options.

Functional parameters for grading

Even if grading derives from a pathological evaluation under microscope and should not be equated to prognostic scores, which however may play a role, functional imaging and molecular alterations of lung NET are worthwhile approaches to unravel malignancy potential by distinguishing indolent from aggressive tumors.

Imaging

While computed tomography (CT) identifies lung NET as a function of extent and hence is useful in tumor staging, positron emission tomography techniques (PET) parallel the level of metabolic recruitment of tumors by measuring either fluoro-deoxy-glucose (FDG) uptake (FDG-PET) or the number of somatostatin receptors by means of somatostatin receptor scintigraphy (Octreoscan™ and, more recently, 68Gallium PET). In recent years, these metabolic or functional images have been fused with morphological CT images for the improved localization of lesions (PET/CT). The likelihood of FDG uptake or 68Gallium binding is a function of biological properties of tumors in terms of the proliferative activity and/or content/bio-disponibility of somatostatin receptors (especially SSTR-2 and SSTR-5), which are closely associated, depending on cell differentiation and, hence, tumor grading. Accordingly, Octreoscan™ and 68Ga PET/CT underpin particularly low-grade lung NET, whereas the opposite holds true for 18F-FDG-PET/CT, which reveals high-grade tumors with different levels of diagnostic and prognostic accuracy based on specific biological properties. In this setting, TC revealed higher uptake values on 68Ga-DOTATATE-PET/CT (Kayani et al., 2009) or 68Ga-DOTA-peptide PET/CT, whereas 18F-FDG PET/CT was superior in discovering AC with a higher detection rate (Kayani et al., 2009; Venkitaraman et al., 2014; Lococo et al., 2015). Likewise, TC showed a higher maximal standard uptake value (SUVmax) on 68Ga-DOTATOC-PET/CT when compared to AC (Jindal et al., 2011; Venkitaraman et al., 2014); 18F-FDG uptake correlated significantly with Glut1, HIF-1α, VEGF and CD34 expression and tended to increase from low-grade to high-grade lung NET (Kaira et al., 2013), showing high specificity for the metastatic involvement of mediastinal lymph nodes in AC (94%) only (Pattenden et al., 2015). The combined use of these two different PET tracers (68Ga-DOTATOC and 18F-FDG) may help distinguish between TC and AC, thereby providing the best NET detection rate (Lococo and Treglia, 2014).

Among imaging techniques, lung magnetic resonance imaging (MRI) is gradually gaining relevance to clinical practice. The major limitation of lung MRI is due to technical troubles, such as low proton density, inhomogeneity of the magnetic field, and cardiac and respiratory motion artifacts (Koyama et al., 2013; Wang et al., 2014). It is, however, clinically useful in children with chronic lung diseases, such as cystic fibrosis, where repeated CT scans are dangerous due to the associated radiation burden (Ciet et al., 2016). MRI is also gaining wider acceptance for clinical grading (indolent versus aggressive tumors) through the use of diffusion-weighted imaging (DWI), inasmuch as it highlights different tumor types and intra-tumor heterogeneity that may correlate with biological behavior and hence tumor grading (Herneth et al., 2003). DWI is a non-invasive technique that is capable of probing the structure of biological tissues, thus aiding with tissue characterization. DWI exploits the random motion of water molecules (Brownian motion) in tissues, and the range of motion (diffusibility) of water molecules can be quantified by the apparent diffusion coefficient (ADC), where low ADC values indicate restricted diffusion. This molecular motion strictly depends on tissue structure, particularly on the presence of obstacles to water diffusibility such as membranes, tight junctions, fibers, macromolecules and cell organelles. High tumor cellular density, as can be observed in neoplasms, is therefore linked to reduced water diffusibility, which can be detected and quantified using DWI on MRI. Liu et al. (2015) demonstrated that ADC values for lung cancer were helpful in evaluating pathological grade and tumor cellular density, with a negative correlation between ADC values and tumor grade. Koyama et al. (2014) showed that DWI is more useful for the differentiation of SCLC from NSCLC than MR-STIR (short-tau inversion recovery sequence, a solely morphological sequence), with SCLC exhibiting significantly lower ADC values than NSCLC. Despite these studies, the correlation between ADC values and tumor cellularity is not always clear, and it can be influenced by varying technical or environmental factors (degree of necrosis and/or microstructural changes preceding necrosis) (Matoba et al., 2007; Uto et al., 2009).

To the best of our knowledge, there are no studies attempting to characterize different subgroups of lung NET in order to establish a relationship between imaging and histological grading. However, an inverse correlation between ADC values and Ki-67 LI or tumor cellularity is on record for pancreatic NET (Wang et al., 2011), supporting a theoretic application to lung NET. In the near future, a better mathematical fitting of a non-Gaussian diffusion model to the DWI signal decay, as

compared to mono-exponential analysis, could be expected for lung NET. Recently, Heusch et al. (Heusch et al., 2013) studied an NSCLC population comprised of two LCNEC, demonstrating that the simultaneous PET and non-Gaussian diffusion acquisition were feasible in these tumors with well-correlated SUV values.

Novel molecular imaging approaches to lung NET have been developed in recent years, taking advantage of hormones and products secreted by tumor cells, such as 18F-3,4-dihydrophenylalanine (DOPA), which can be used to trace amine precursor uptake in lung carcinoids (Jager et al., 2008). These newer agents, however, are more useful to stage the disease rather than to grade NET (Hicks, 2010).

Key points

Although there have been few systematic studies on the relationship between imaging and histologic grading in lung NET to date, PET scan and diffusion-weighted imaging upon MRI are emerging as promising techniques to unravel the level of biological recruitment of these tumors.

Molecular studies

A comprehensive study of the molecular landscape underlying the pathophysiology of lung NETs is required to improve grading and support therapy decisions. Genomics and systems biology approaches can shed light on the fundamental mechanisms that lead to pathology development, exploiting information at the cellular level to tackle the inherent heterogeneity of cancer disease, enhancing the concept of diagnosis and, consequently, of treatment, toward so-called precise medicine.

A systematic analysis of genomic alterations in very large data sets of lung cancer samples has allowed investigators to characterize sequence variants of the main histological subgroups, including NETs. While carcinoids did not present significant somatic copy number alterations, SCLC showed significantly amplified chromosomal regions at 1p (*MYCL1*), 2p (*MYCN*), 5p, 8p (*FGFR1*) and 19q (*CCNE1*) and deletions of 3p (*FHIT*) and 13q (*RB1*) (Seidel, 2013). LCNECs represent a very heterogeneous group, showing genomic alterations and expression profiling pertinent to other histologic subtypes, which have been deeply characterized in a recent study (Rekhtman et al., 2016). This analysis identified distinct LCNEC subtypes: SCLC-like, characterized by *TP53* and *RB1* co-mutation/loss and other SCLC-type alterations along with higher proliferative activity of SCLC-like tumors; NSCLC-like, characterized by the lack of co-altered *TP53* and *RB1* and the occurrence of NSCLC-typical mutations (*STK11, KRAS, KEAP1*) along with exclusive exocrine differentiation marker expression in NSCLC-like tumors; and carcinoid-like, characterized by less frequent genetic alterations and the presence of mutations in the *MEN1* gene (Rekhtman et al., 2016).

The occurrence of the *MEN1* mutation along with decreased expression was associated with poor prognosis in a specific study on carcinoids (Swarts et al., 2014a). The same holds true for low expression levels of *CD44* and *OTP* genes (Swarts et al., 2013a,b). Furthermore, the two genes *CEACAM1* and *GC* were identified as potential IHC markers that can be used to distinguish between typical and atypical carcinoids, because they are significantly upregulated in the latter subtype (Toffalorio et al., 2014).

More generally, a signature of 26 testis-specific and placental-specific genes has been identified, with ectopic expression in adult somatic tissues associated with the aggressiveness of tumors and characterized in lung cancer (Rousseaux et al., 2013). Indeed, it is a recurrent finding that transcriptional programs regulating developmental processes can be triggered unexpectedly, leading to cancer development and progression. Specifically, it was observed in a study involving 293 lung cancer patients, including lung NET, that tumors expressing at least 3 of these 26 genes had an aggressive phenotype, leading to quick relapse and/or metastasis and very low survival. Interestingly, the prognostic power of this 26-gene set was not dependent on clinical stage or histological subtype, and it proved to be very efficient for overall survival prediction among early-stage patients (Rousseaux et al., 2013), as well as for tumor grading. This aberrant activation of normally silent developmental genes was mainly associated with epigenetic deregulation, such as the demethylation of silenced promoters or other chromatin alterations.

Several epigenetic modifications have been correlated directly with grade in lung NET (Karpathakis et al., 2013). For example, *RASSF1* promoter methylation status may be used as a biomarker for grading (Pelosi et al., 2010), and the presence of the two histone markers H4KA16 and H4KM20 inversely correlates with grade and Ki67 LI (Li et al., 2011).

There are different opportunities for the regulation of gene expression. MicroRNA, a class of noncoding RNAs, exert this action at the post-transcriptional level. In a recent study (Mairinger et al., 2014), 12 microRNAs have been found to be differentially expressed across lung NET, eight showing a negative and four a positive correlation with grade. However, this analysis has been accomplished on 12 pulmonary NET patients, so, although it is very tempting to draw conclusions about lung NET biology along with the identification of effective biomarkers, further validation on a wider sample size is needed to confirm the reproducibility and feasibility of these results.

Key points

Several investigations about the molecular profiling of pulmonary NET have been reported so far, though this disease category has been less studied. A comprehensive molecular portrait of lung NET, integrating different

levels of evidence, could also improve grading procedures and lead to new and more specific therapeutic options derived from a reliable estimation of the cellular disease potential based on the characterization of its gene expression program.

Ki-67 labeling index for grading

The role of KI-67 LI in the grading of lung NET, expressed as the percentage of decorated tumor cells showing nuclear compartmentalization (usually counting 2000 tumor cells in areas of highest staining or hot spots) is still a debated matter (Pelosi et al., 2014c) at variance with its well-established use in GEP NEN (Pelosi et al., 1996; Rindi et al., 2006, 2012, 2014a; Klimstra et al., 2010a,b, 2015; Sobin et al., 2010; Klimstra, 2016). Critics have argued about inter-observer reproducibility (Travis et al., 1998a; Marchevsky et al., 2001; den Bakker et al., 2010; Ha et al., 2012; den Bakker and Thunnissen, 2013; Swarts et al., 2014b; Marchevsky and Wick, 2015), controversies related to manual or automated assessment (Walts et al., 2012; Warth et al., 2013), the overlap of adjacent tumor categories (TC vs. AC; AC vs. LCNEC; LCNEC vs. SCC) because of imperfect co-linearity with accepted diagnostic criteria (mitotic count and necrosis) (Pelosi et al., 2014a,b, 2015c), the unsuitability of cytology or biopsy samples for reliable quantification due to the wide spectrum of tumor differentiation or intra-tumor heterogeneity (Pelosi et al., 2014c; Pelosi et al., 2015c; Travis et al., 2015b) and the role of independent prognosticators (Greenberg et al., 1987; Costes et al., 1995; Granberg et al., 2000; Van Eeden et al., 2002; Pelosi et al., 2003a; Pelosi et al., 2003b; Igarashi et al., 2004; Das-Neves-Pereira et al., 2008; Rugge et al., 2008; Skov et al., 2010; Grimaldi et al., 2011; Walts et al., 2012; Zahel et al., 2012) (and hence tumor-grading forerunners) in multivariate analysis (Zahel et al., 2012; Rindi et al., 2014b). Incidentally, any reference to a grading system dealing with KI-67 LI in lung NET was not mentioned in the 2015 WHO classification, where the primacy of histology was again reaffirmed (Travis et al., 2015b).

Recent reproducibility studies in lung NET, however, have revealed less than 1.5% of variability for Ki-67 LI, with an out-performance over mitotic count with regard to inter-observer agreement (Walts et al., 2012; Warth et al., 2013). Many of the issues raised, however, are not different from those that accompanied the birth and development of an effective grading system in GEP NEN based on KI-67 LI and mitotic count (Rindi et al., 2006, 2012, 2014a; Klimstra et al., 2010a,b, 2015; Sobin et al., 2010; Klimstra, 2016), thus indicating that there could still be room for an integrated use of Ki-67 LI through a revised policy of tumor grading attribution in lung NET. Although Ki-67 LI has been ranked among diverse histologic variants in the 2015 WHO classification (TC: ≤5%; AC: up to 20%; LCNEC: 40-80%; SCC: 50-100%), the only current recommended use of this marker concerns the diagnostic separation of TC or AC on one hand and SCC on the other, especially in small biopsy or cytology samples, which is by far superior to necrosis, mitotic count and NE markers (Helpap and Kollermann, 2001; Lin et al., 2003; Aslan et al., 2005; Pelosi et al., 2005; Zheng et al., 2013; Travis et al., 2015b).

Many studies have addressed the prognostic role of Ki-67 LI in lung NET, especially TC and AC, sometimes with conflicting results in multivariate analysis (Greenberg et al., 1987; Costes et al., 1995; Granberg et al., 2000; Van Eeden et al., 2002; Pelosi et al., 2003a; Pelosi et al., 2003b; Igarashi et al., 2004; Das-Neves-Pereira et al., 2008; Rugge et al., 2008; Skov et al., 2010; Grimaldi et al., 2011; Walts et al., 2012; Zahel et al., 2012), whereas few have investigated the relevance of Ki-67 LI, alone or jointly with others, to construct a grading system (Zahel et al., 2012; Rindi et al., 2014b). Other works have correlated the distribution of Ki-67 LI with tumor grade according to the usual diagnostic categorization, thus reflecting well-known variations in tumor differentiation rather than introducing a true grading system based on this marker (Tsuta et al., 2011; Zheng et al., 2013). There is co-linearity but not a perfect relationship among Ki-67 LI, mitosis and necrosis. This co-linearity may become a resource to develop a synergistic grading system only if specific and independent cut-off thresholds are devised for each parameter in these tumors (Rindi et al., 2014b).

At variance with GEP NEN (Yang et al., 2011), comparative studies on the prevalence of Ki-67 LI, necrosis and mitosis in paired biopsies and surgical specimens of lung NET are still lacking. It is, however, clinically important to characterize tumor aggressiveness, especially in the context of metastatic disease, when considering the inconsistency of the current classification on biopsy samples (Pelosi et al., 2005; Travis et al., 2015b). We recently found that Ki-67 LI was accurate for biopsy samples as surgical specimens by stratifying tumors for histological subtypes, once hot-spot areas were identified in either type of material, whether 2000 cells, 2 mm^2-spanning tumor regions or the entire biopsy fragments were counted (Pelosi et al, manuscript in preparation). This investigation could be prodromal to the development of an effective grading system for lung NET biopsies based mainly on Ki-67 LI, inasmuch as it is superior to evaluations of mitosis and necrosis in this type of material (Pelosi et al., 2005).

Key points

There is no consensus on the use of Ki-67 LI as a diagnostic tool, prognosticator or grading maker in lung NET due to either histology-dependent-criteria for classification or methodological-biological reasons. However, Ki-67 LI is by far superior to any other indicator of tumor aggressiveness in lung NET biopsies, such as necrosis and mitotic count. As most lung NET are metastatic at the time of the initial diagnosis, there is

clinical urgency to maximize Ki-67 LI assessment for this type of material.

Towards a proposal of integrated pathology grading

The 2015 WHO terminology for lung NET are known worldwide, with extensive clinical experience related to diagnosis, molecular alterations, prognosis and therapy planning. In particular, TC, AC, LCNEC and SCLC are perceived as distinctive tumor entities so it would appear reductive to categorize TC as G1, AC as G2 and LCNEC and SCC as G3 tumors. Nonetheless, inconsistencies in diagnosis, therapy, and the prognostic/predictive value of classification at the level of individual tumors lead to the need for a global re-thinking of lung NET (Pelosi et al., 2014a,c). Furthermore, tumor grading in NET is so familiar to most clinicians that it should not be so hard or untimely to extend this concept to lung NET.

As there is always some potential inter-observer variation due to either subjective interpretation or heterogeneous intra-tumor distribution of defining criteria, a multi-parametric evaluation with different cut-off levels for each parameter could minimize these drawbacks (Hochwald et al., 2002; McCall et al., 2013; Rindi et al., 2014b). In this frame of mind, we have recently proposed an innovative grading system based on the study of 348 surgically resected lung NET belonging to all histologic variants (105 TC, 75 AC, 86 LCNEC and 82 SCC), which were investigated for Ki-67 LI, mitotic count and necrosis quantification (Rindi et al., 2014b). These parameters had been chosen because they reflected functionally generalized but differentially regulated mechanisms of growth and maintenance in tumor development (Pelosi et al., 2014b). The advantage of this approach would be that tumor aggressiveness could be deciphered from three different but converging angles, based on the premise that using more parameters would lead to a greater likelihood of compensating for inconsistencies among them. Interestingly, two of these three parameters are both defining criteria in the 2015 WHO classification on lung NET (Travis et al., 2015b) and valuable effectors of grading on GEP NEN (Rindi et al., 2006, 2012, 2014a; Sobin et al., 2010). Each parameter was tiered according to three expression levels, which were independent of each other at multivariate analysis (Table 2). Accordingly, G1 tumors were defined if at least two out of three parameters were at Level 1; G2 if at least two out of three parameters were at Level 2; and G3 if at least two out of three parameters were at Level 3. The resulting grading system outperformed each individual parameter in predicting overall patient survival, resulting in a G1 to G3 grading system showing minimal overlap of 95% confidence intervals among defining categories. Interestingly, all TC clustered into the G1 category, whilst a fraction of LCNEC and even SCC entered the G2 category in keeping with the clinical observation that a few of these patients pursue an unexpectedly less aggressive clinical course (Brock et al., 2005; Tsuchiya et al., 2005; Asamura et al., 2006, 2008; Abedallaa et al., 2012). As far as the challenging category of AC was concerned, it was split into all tumor grades to reflect the inherent behavioral heterogeneity of these tumors, some of which behave quite similarly to TC, whereas others fit with high-grade NET (Rindi et al., 2014a). As this grading system was set up on surgical specimens, a further evolution could be identifying adequate criteria for small biopsies, which may prove to be particularly effective in metastatic lung NET as happens on GEP-NET (Rindi et al., 2006, 2012; Klimstra et al., 2010a,b, 2015; Sobin et al., 2010; Klimstra, 2016).

This proposal could be stepwise integrated with the 2015 WHO classification according to the following procedure: Step 1, classify tumors according to WHO; Step 2, grade tumors separately by itemizing them into G1 to G3 categories; Step 3, integrate the grade assignment with traditional histology. Accordingly, it is possible to formulate a new terminology, namely Lu-NET G1, Lu-NET G2 and Lu-NET G3, which would be managerially oriented to handle lung NET tumors with similar histology that behave differently. Briefly, Lu-NET G1 would indicate low-grade malignant TC or AC;

Table 2. Grading system in lung neuroendocrine tumors based on a tripartite evaluation of parameters.

Cut-off levels	Variables		
	Mitoses (10 HPF or 2 mm^2)	Ki-67 labeling index (%)	Necrosis quantitation
Level 1	2	<4	absent
Level 2	>2-47	4-25	≤10%
Level 3	>47	≥25	>10%

Ki-67 labeling index indicates the percentage of immunoreactive tumor cells. For details on application of the grading see the text.

Table 3. Integrated classification on lung neuroendocrine tumors.

Category	Histology	Decision levels	Variables		
			Mitoses (10 HPF or 2 mm^2)	Ki-67 labeling index (%)	Necrosis quantitation
Lu-NET G1	TC, AC	2 at level 1	2	<4	absent
Lu-NET G2	AC, LCNEC, SCC	2 at level 2	>2 to 47	4-25	≤10%
Lu-NET G3	LCNEC, SCC, AC	2 at level 3	>47	≥25	>10%

Lu-NET G2, intermediate-grade malignant AC with a contribution of LCNEC or even SCC; Lu-NET G3, high-grade malignant SCLC and LCNEC and occasional AC patients (Table 3). This practical approach could avoid over-treating with platinum-etoposide AC and LCNEC/SCC patients destined to be better classified as Lu-NET G1 and Lu-NET G2, respectively, as well as under-treating AC patients categorized as belonging to Lu-NET G3 with somatostatin analogues. At variance with GEP NEN, cell differentiation would no longer be considered in lung NET because the same histologic variant could be diversely distributed across different risk categories for death or treatment. A further evolution of this grading system could be used to interpret the intra-tumor heterogeneity of Ki-67 LI in terms of asymmetry, kurtosis and cell entropy to unravel the behavioral properties of these tumors (Pelosi et al, manuscript in preparation).

Key points

A grading system based on Ki-67 LI, necrosis and mitotic count evaluation in surgical specimens of lung NET is clinically useful to tune the most appropriate therapy in individual tumor categories, especially for biopsy samples and metastatic disease where Ki-67 LI is by far superior to necrosis and mitotic count.

Conclusion

The basic question is not whether to grade or not to grade lung NET but rather how to grade these tumors for operational decisions in the management of individual cancer patients. Lung NET shows profound differences in terms of epidemiological, molecular, clinical, pathological and behavioral traits, which however converge into a three-tier prognostic spectrum encompassing tumors of low, intermediate and high malignancy. As conventional histology is not completely apt to reliably predict prognosis or decipher therapy options, especially in metastatic disease, a concept of grading is clinically justified for personalizing treatments. This tumor grading should be based on diverse parameters to account for either intra-tumor heterogeneity or subjective interpretation when assessing defining criteria. The goal is to integrate well-known histology with an innovative grading system to better re-classify lung NET for clinical purposes. Whether Ki-67 LI could play a role in grading biopsy samples should be a matter of further investigation.

Future perspective

Morphologic classification is destined to remain a backbone in the diagnosis, prognosis and clinical management of lung NET in virtue of its relationship with tumor behavior and clinical implications. It is, however, clinically warranted to implement this traditional approach with a biologically more adapted grading system based on proliferation parameters, such as Ki-67 LI, especially in the setting of metastatic disease where morphology may be more deceptive. Recent improvements in the therapy of lung NET will increase even more the clinical relevance of such grading systems in the management of these tumor patients.

Bullet points

- The current WHO classification is still the backbone for diagnosis, prognosis and clinical management of lung NET
- TC are low malignant, AC intermediate malignant and SCLC/LCNEC high malignant tumors, with some homologies with G1 and G2 NET and G3-NEC of the GEP tract, respectively
- Tumor grading is tautologically included in the current classification, but there is a growing awareness on the clinical utility of an integrated grading system to personalize treatments especially in the handling of metastatic lung NET
- Stepwise combination of grading and histology (Step 1: to classify tumors according to WHO; Step 2: to grade tumors separately by itemizing them into G1 to G3 categories; Step 3: to integrate the grade assignment with traditional histology according to Lu-NET G1, Lu-NET G2 and Lu-NET G3 terminology) could translate lung NET with similar histology into a more robust correlation with clinical behavior and treatment.

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This work is dedicated to the memory of Carlotta, an extraordinarily lively girl who untimely died of cancer in the prime of life.

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