

Review

Clinical needs and pathology's answers in neuroendocrine neoplasms of the lung

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Summary

Lung neuroendocrine neoplasms (NENs) make up a variegated ensemble of malignancies encompassing typical carcinoid (TC) and atypical carcinoid (AC). These are low to intermediate grade neuroendocrine tumors (NETs), and large cell neuroendocrine carcinoma (LCNEC) and small cell lung carcinoma (SCLC), which are full-fledged high-grade neuroendocrine carcinomas (NECs) showing similar clinical outcomes. Through a peer interaction between oncologist and pathologist, we herein constructed a practical approach based on questioning and answering regarding 8 practical issues aimed to provide shared solutions for clinical decision-making. These issues were itemized as sequential steps guided by clinical reasoning and concerned differential diagnosis, combined subtypes, primary and metastatic tumors, small diagnostic material, predictive biomarkers, tumor staging and, lastly, standardizing terminology. This study takes advantage of the close interaction between oncologists and pathologists as a tool to better delineate the decision-making on lung NENs.

Key words: neuroendocrine neoplasms, lung, pathology, oncology, diagnosis

Introduction

Lung neuroendocrine neoplasms (NENs) account for about 20% of pulmonary malignancies and comprise neuroendocrine tumors (NETs) and neuroendocrine carcinomas (NECs)¹, according to the current diagnostic criteria of 2021 World Health Organization (WHO) classification on thoracic tumors (Tab. I). NETs as a whole are considered relatively well-differ-

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entiated neoplasms and include low-grade typical carcinoid (TC)/G1-NET and intermediate-grade atypical carcinoid (AC)/G2-NET, whereas NECs are high-grade carcinomas composed of either small (small cell lung carcinoma, SCLC) or large cells (large cell neuroendocrine carcinoma, LCNEC)^{1, 2}. Such a distinction is not only clinically compelling – all the current guidelines and clinical trials always require the sharp separation of NETs and NECs³⁻¹⁰ – but also finds confirmation on molecular grounds, as NETs and NECs are currently perceived as distinct and separate malignancies with their own specific alterations and no appreciable pathogenetic link or continuum among them¹. Lung NENs make up a clinico-pathologic spectrum endowed by increasing biological aggressiveness where the traditional four-tier pathology approach (*i.e.*, TC, AC, LCNEC, SCLC) conforms to a three-tier clinical outcome (*i.e.*, low-, intermediate- and high-grade for TC, AC and NEC, respectively) and to a two-tier molecular interpretation with no pathogenetic continuum (*i.e.*, NETs vs NECs)^{1, 2, 11-15}. Representative images of the above subtypes are depicted in Figure 1 A-G and Figure 2 A-E.

In this review article, a group of clinicians and pathologists experienced in lung NENs has explored 8 practical issues they considered important in the clinicopathologic handling of these patients by using a multidisciplinary approach and then summarizing their expert opinion on those topics.

Methods

An outlook of papers on the issues of clinical needs, pathology implications and molecular facts on lung NENs (not a systematic review) was carried out upon generating 8 key questions (Tab. II), which regard molecular alterations, diagnosis, prognosis, classification, treatment options and clinical facts in light of the 2021 WHO classification and the most updated international guidelines^{1, 3-10}. Only full-papers were considered along with smaller studies or single case reports, whenever appropriate, and the source was the English literature from PubMed/Medline until February 2025. The list of issues was reflecting the experience of oncologists and pathologists dealing with lung NENs with no intention to define diagnostic or therapeutical guidelines, but rather provide a subjective yet reasonable choice of practical issues useful in better characterizing these neoplasms. Methodologically, these 8 items were sequentially addressed, with the oncologist standpoints at first and the pathologist interpretations subsequently, with final shared comments at the end of each paragraph. As this is a review article on published literature data, no approval by Internal Review Board or Ethics Committee notification was needed.

Table I. Facts about neuroendocrine neoplasms of the lung: criteria according to the 2021 World Health Organization classification on lung tumors.

	Typical carcinoid/ NET G1 [†]	Atypical carcinoid/ NET G2 [†]	Carcinoid tumor/ NET with elevated mitotic counts and/or Ki-67 proliferation index [*]	Large cell neuroendocrine carcinoma (LCNEC)	Small cell lung carcinoma (SCLC)
Defining criteria					
Neuroendocrine morphology	Yes	Yes	Yes	Yes	Yes [§]
Mitoses per 2 mm²	0-1	2-10	>10	>10 (median: 70)	>10 (median: 80)
Necrosis	No	Focal, if any	Focal	Frequent	Frequent
Differentiation level	Well-differentiated	Well-differentiated	Well-differentiated	Poorly differentiated	Poorly differentiated
Neoplasm grade	Low	Intermediate	Intermediate	High	High
Ki-67 labeling index	Up to 5%	Up to 30%	> 30%	40-80%	50-100%
Combined with NSCC component	Very rare	Very rare	Not reported, but possible	Up to 25% of resected LCNEC	Up to 25% of resected SCLC
Cytology or biopsy samples					
Primary	Carcinoid tumor/ NET NOS	Carcinoid tumor/ NET NOS	Carcinoid with elevated proliferation	NSCC, possible LCNEC	SCLC
Metastasis	Metastatic carcinoid NOS	Metastatic carcinoid NOS	Carcinoid with elevated proliferation	NSCC, possible LCNEC	SCLC

NSCC, non-small cell carcinoma; NOS, not otherwise specified. [†]: Diagnostic criteria for typical and atypical carcinoid are applicable just to lung resection specimens. ^{*}: provisional category included in the 2021 WHO classification (see text for more details). [§]: neuroendocrine morphology is less evident in biopsy/cytology samples, where diagnostic judgment mainly relies on the recognition of small-sized cells.

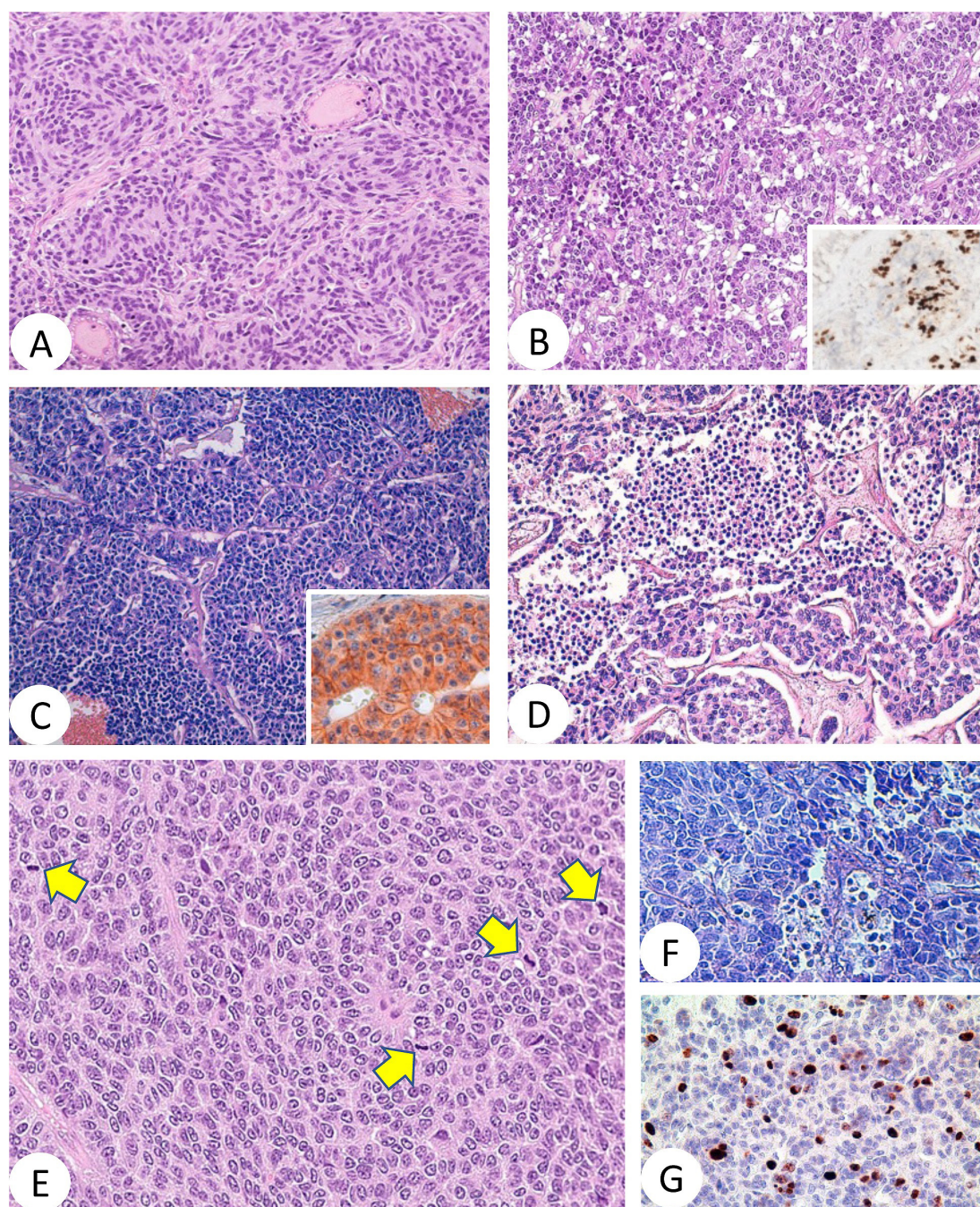


Figure 1. Histologic features of pulmonary neuroendocrine tumors. A spindle cell-shaped typical carcinoid (TC) features elongated tumor cells disposed in intertwining fascicles mimicking a mesenchymal neoplasm, with no necrosis or recognizable mitotic figures (A). Another TC example shows polygonal cells organized in trabecular and lobular structures of epithelial appearance, again with no necrosis or recognizable mitotic figures (B). INSM1 immunohistochemistry is shown to decorate tumor cell nuclei (B, inset). A case of atypical carcinoid (AC) presents with a solid histologic appearance, but superimposable cytologic characteristics (C), along with immunohistochemical membrane reactivity for somatostatin receptor type 2A (C, inset). Punctate necrosis is a histologic hallmark, which is diagnostic of AC (D). The new category of carcinoid tumor with elevated mitotic count and/or Ki-67 proliferation index exhibits increased mitotic activity (highlighted by yellow arrows) (E), punctate necrosis (F) and increased Ki-67 labeling index (G). Pictures taken at 20X or 40X magnification.

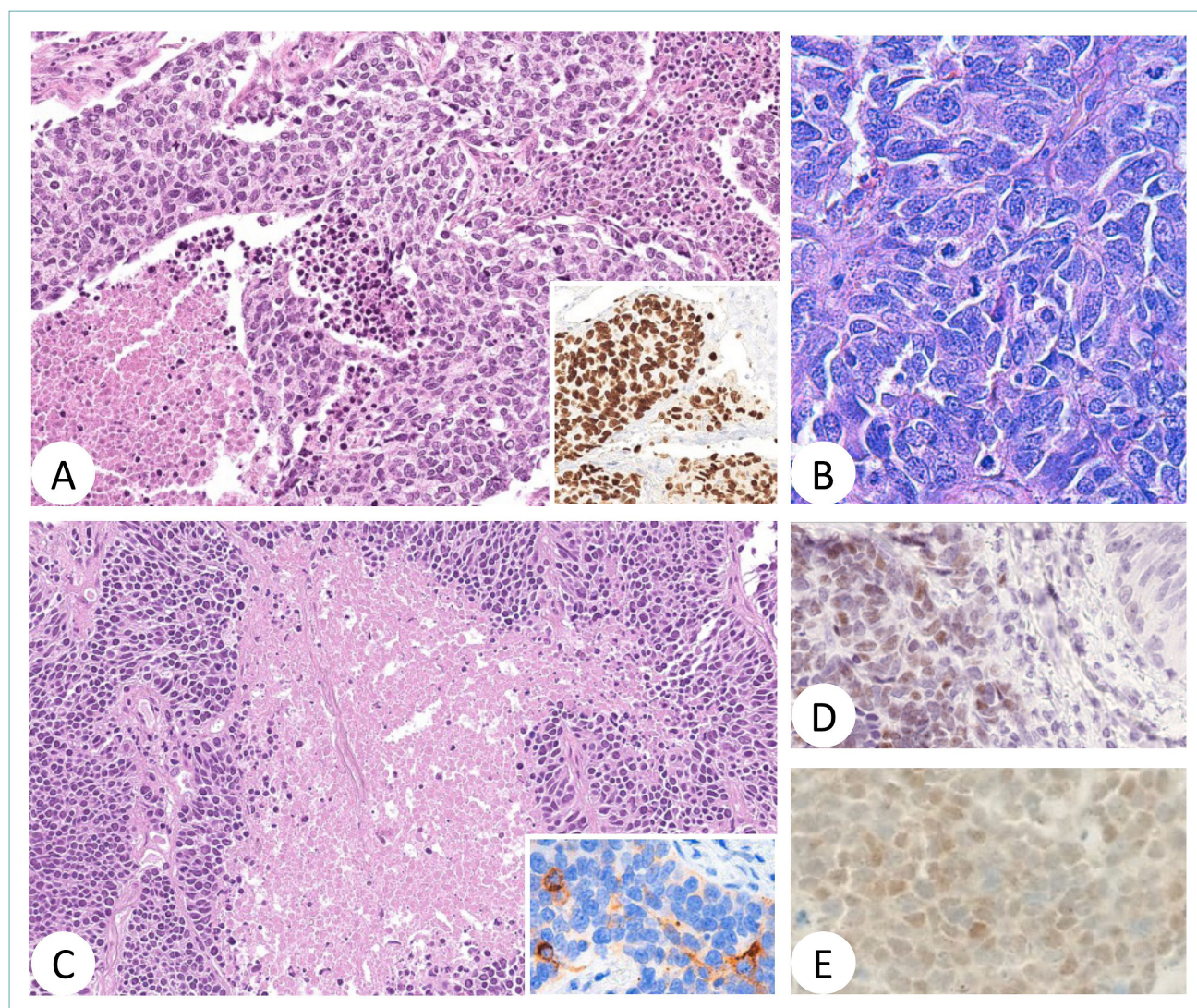


Figure 2. Histologic features of pulmonary neuroendocrine carcinomas. A large cell neuroendocrine carcinoma (LCNEC) is composed by organoid aggregates of tumor cells with peripheral palisading and abundant necrosis (A), with common TTF1 expression (A, inset). Tumor cells present with coarse nuclear chromatin and plentiful mitoses (B). Small cell lung carcinoma (SCLC) is characterized by small-sized tumor cells with extensive geographic-type necrosis (C) and faint immunohistochemical decoration for chromogranin A (C, inset). This case presents with variable immunoreactivity for the ASCL1 gene product (D). For comparison, another morphologically similar SCLC case expressed POU2F3 rather than ASCL1 (E). Pictures taken at 20X or 40X magnification.

Results

1. DISTINGUISHING AMONG HIGH-GRADE NECS AND CONVENTIONAL NSCCS/NON-NECS IN LOCAL/LOCALLY ADVANCED AND METASTATIC DISEASE

Oncologist. Distinguishing high-grade NECs from conventional non-small cell carcinomas (NSCCs), non-NECs, is a crucial step in the therapeutic management of

patients (https://www.iss.it/documents/20126/8403839/LG%20149_Polmone_agg2021)^{6, 16}. First of all, while surgery is the only curative intent for NSCCs/non-NECs, SCLCs or LCNECs are rarely treated with upfront surgery, inasmuch as just the uncommon very early stages (T1-2, N0/N1, M0, I-IIA stages) without evidence of mediastinal involvement are amenable of surgical resection. In contrast, treatment options for NSCCs/non-NECs include a broad range of systemic therapies¹⁷⁻²⁹

Table II. Interpretation items dealing with lung neuroendocrine (NE) neoplasms upon questioning by the oncologist and answering by the pathologist

1) Distinguishing among high-grade NECs and conventional NSCCs/non-NECs	
Oncologist.	There are different systemic therapy options (and related clinical trials) to treat NECs and NSCCs. There is uncertainty about the treatment of NSCCs with NE differentiation (NSCCs-NED).
Pathologist.	The rule is that NE markers should be used only if there is NE morphology.
2) Distinguishing among high-grade NECs (biopsy setting)	
Oncologist.	There are different systemic therapy options (and related clinical trials) to treat small cell lung carcinoma (SCLC) and large cell NE carcinoma (LCNEC). However, diagnosis on biopsy may be demanding and combined tumors could be missed in small diagnostic material.
Pathologist.	It is possible to distinguish SCLC and LCNEC in most cases, provided that core biopsies with larger amounts of tissue are available. Some uncertainty, however, may persist while assessing cell size and cytological features reliably: in these instances, the noncommittal term NEC NOS can be used. While combined tumors are not infrequent and could be missed in small samples as a function of random sampling, clinical correlations (e.g., nonsmokers) and molecular investigation may prove useful for the relevant diagnosis.
3) Distinguishing between pure and combined (3.1) or primary and metastatic (3.2) NECs	
Oncologist.	There are different biologic features and sensitivity to chemo/radiotherapy between pure and combined NECs, as well as between pulmonary and extrapulmonary sites (urologic, head-neck, gynecologic), thereby realizing biologically, behaviorally and therapeutically different contexts.
Pathologist.	About 25-30% of NECs with either small or large cells are combined with any other histologic subtype, which may be readily recognized upon morphology and appropriate immunomarkers, especially in surgical specimens. Distinguishing pulmonary vs extrapulmonary NECs may prove difficult if not impossible using morphology or immunohistochemistry. Molecular assessment may be helpful, despite doubts about its reproducibility or large-scale applicability.
4) Distinguishing among well-differentiated NETs	
Oncologist.	Different clinical behavior, PET scan appearance and therapeutic approaches exist between typical (TC) and atypical (AC) carcinoids, thus necessitating punctual diagnosis and coherence of terminology in all diagnostic settings. Uncovering primary or metastatic lung NETs is clinically warranted.
Pathologist.	Classification of carcinoids differs according to the diagnostic context making precise comparison between biopsies and resection specimens or between primary and metastatic sites a demanding task. Separation requires mitotic count per 2 mm ² and necrosis assessment, which can be reliably carried out just in resection specimens of primary tumors. Uncovering primary or metastatic lung NETs is feasible by means of immunohistochemical markers (e.g., TTF1 or OTP).
5) Distinguishing between ACs and LCNECs: is Ki-67 proliferation index the solution?	
Oncologist.	Straddling ACs and NECs, could the Ki-67 proliferation index be the solution? It may help if low, but not high.
Pathologist.	Ki-67 proliferation marker has prognostic and diagnostic implications in lung NENs, because it reliably distinguishes NET from NEC in every context, identifies carcinoids with elevated proliferation rates and roughly correlates with carcinoid classification as desirable but not essential diagnostic tool. It is recommended to report the value of Ki-67 on diagnoses.
6) Are there other treatment-related biomarkers?	
Oncologist.	There are many biomarkers (SSTR, OTP, CD44, ASCL1, MGMT score, NTRK, ALK, TMB, MMR, p53, RB...) that can aid in stratification of lung NETs/NECs (to treat patients better) by offering further strategies of treatment. Even characterization for hormone production (e.g., ACTH for Cushing syndrome) may be clinically warranted.
Pathologist.	Many studies have used these biomarkers to stratify diversely behaving patient subsets, especially in the setting of NETs but even NECs. Molecular testing is not routinely used in NETs/NECs, but it is up to clinical judgment and patients' demography/clinical presentation (e.g., lack of smoking history or increased likelihood of diverse mutations). Therefore, local feasibility of these assays should be discussed thoroughly with the pathologist, who should perform them on demand for justified clinical reasons.
7) Staging procedure	
Oncologist.	Information on state of margins, lymph node status (number of metastatic lymph node/number of total lymph nodes), presence of other neoplastic nodules and association with DIPNECH are clinically warranted, because one can best treat patient within a NEN-dedicated multidisciplinary team.
Pathologist.	pTNM-R classification according to UICC/AJCC scheme (currently the 8 th edition, but the 9 th is coming soon) is the required standard for staging all resection specimens, also for distinguishing multiple synchronous NETs (e.g., in the setting of DIPNECH) from intrapulmonary metastases. Future TNM classification should better address the issue of NET staging.
8) Standardized reporting	
Oncologist.	State of the art for clinical decision-making in the setting of lung NENs needs to develop shared language and clinical information integrated with pathology data, because specialists gravitating around these neoplasms are plentiful but the patient always is unique and at the center by definition.
Pathologist.	It is of the upmost relevance to standardize the pathology report by introducing essential or core and desirable or non-core criteria. Current schemes already exist, which could be further implemented in the near future by keeping in mind that pathology classification must be clinically oriented and clinically useful.

NEN, neuroendocrine neoplasm; NEC, neuroendocrine carcinoma; NSCC, non-small cell carcinoma; NE, neuroendocrine; NED, neuroendocrine differentiation; SCLC, small cell lung carcinoma; LCNEC, large cell neuroendocrine carcinoma; NET, neuroendocrine tumor; PET, positron emission tomography; TC, typical carcinoid; AC, atypical carcinoid; SSTR, somatostatin receptor; OTP, orthopedia homeobox; CD44, CD44 molecule (IN Blood Group); ASCL1, achaete-scute family BHLH transcription factor 1; MGMT, O-6-methylguanine-DNA methyltransferase; NTRK, neurotrophic receptor tyrosine kinase; ALK, ALK receptor tyrosine kinase; TMB, tumor mutation burden; MMR, DNA mismatch repair; RB: retinoblastoma; ACTH, adrenocorticotrophic hormone.

depending on the stage and the mutational patterns of disease, with neoadjuvant or adjuvant intents and may be further enhanced by the integration of local therapies³⁰⁻³³. While etoposide and platinum salts remain the agents of choice for NECs as a whole, with no targeted therapies being approved for these tumors³⁴, other agents are preferred for conventional NSCCs/non-NECs³⁵. Therefore, distinguishing between NECs and conventional NSCCs/non-NECs is a crucial and essential step before exploring their mutational profile. In conventional NSCCs/non-NECs, the analysis of *EGFR*, *ALK*, *KRAS*, *ROS1*, *BRAF*, *NTRK1/2/3*, *MET* exon 14 skipping mutation, *RET*, *ERBB2-HER2* and PD-L1 status is recommended to identify patients eligible for targeted therapies or immunotherapy. In some European countries, such as France, NGS and theranostic immunohistochemistry (including PD-L1 status) are recommended for RB1-proficient LCNECs on the basis of the Institute National du Cancer's (INCA) guidelines (see <http://www.e-cancer.fr/Patients-et-proches/Se-faire-soigner/Traitements/Therapies-ciblees-et-immunotherapie-specifique/Immunotherapie-mode-d-action>)³⁶. Accordingly, LCNECs with retained RB1 expression are treated like other conventional NSCCs/non-NECs unless they harbor targetable fusions or mutations, while the RB1-negative ones are treated just like SCLCs. However, the prognostic role of RB-1 still remains debated³⁷. Additionally, while single-agent anti-PD-1 or PD-L1 therapies have shown significant effectiveness in NSCCs/non-NECs, especially in those with high PD-L1 expression, this is not the case for SCLCs, where these therapies have limited efficacy when used alone and are recommended only in combination with a platinum-etoposide regimen³⁸. As far as local treatments are concerned, while prophylactic cranial irradiation (PCI) is recommended for limited-stage SCLCs, no PCI is established for conventional NSCCs/non-NECs. Lastly, a distinction between conventional NSCCs/non-NECs and NECs is clinically of the utmost importance especially for patient enrollment in clinical trials. In fact, neoplasms identified as NECs or suspected to be NE due to expression of NE biomarkers are excluded from trials focusing on conventional NSCCs/non-NECs.

Pathologist. The rule to approach lung cancer diagnosis always dictates subtyping according to three main differentiation lines, namely glandular for adenocarcinoma, keratinizing for squamous cell carcinoma and NE for NENs by combining morphology and appropriate panels of biomarkers^{1, 39-41}. The diagnosis of lung NENs is a stepwise process, where at first NE morphology needs to be recognized (organoid aggregates, ribbons, trabeculae, rosettes, stromal features such as high vascular density) and then subtyped according to cytologic (chromatin, nucleoli, cell size) and

immunophenotypic features^{1, 14}. As recommended by the 2021 WHO classification¹, if a NE morphology is missing, NE biomarkers (synaptophysin, chromogranin A and INSM1) should not be performed, because the clinical relevance to NE differentiation in otherwise conventional adenocarcinomas or squamous carcinoma is limited and such an immunoprofile is not required⁴². Therefore, the primacy of NE morphology over confirmatory immune markers has been reaffirmed as a guiding criterion for NEC definition by the current guidelines¹.

Shared solution. Use NE markers as appropriate and limit the use of NSCC-NED in practice, because it is confounding with no established clinical counterpart of treatment thus far.

2. DISTINGUISHING AMONG HIGH-GRADE NECs (BIOPSY SETTING)

Oncologist. As SCLCs and LCNECs are rarely treated by surgery, they are generally assessed through biopsy samples for the purpose of planning the therapeutic strategies^{43, 44}. In the metastatic setting, SCLCs and LCNECs differ in terms of systemic treatments and availability of clinical trials. There are 1248 registered studies for SCLCs compared to just five for LCNECs (see <https://clinicaltrials.gov>), highlighting the need for an accurate differential diagnosis. In this regard, LCNECs are no longer included in trials alongside SCLCs due to their differences in prognostic and predictive factor expression⁴⁴. Trials apart, according to the American Society of Clinical Oncology (ASCO) guidelines, platinum-etoposide regimen is deemed to be the most appropriate therapy for SCLCs and LCNECs, but the utility of NSCC regimens has been suggested in some LCNECs^{36, 45-47}. George et al., identifying two distinct subcategories of LCNECs according to different genomic profiles (SCLC-like or type II LCNEC and NSCC-like or type I LCNEC), suggested a better response to SCLC-regimens for SCLC-like LCNECs and a better response to NSCC-regimens for NSCC-like LCNECs⁴⁸. Conversely, Wang et al. reported no differences in terms of objective response rates, progression-free survival, and overall survival among LCNEC patients treated with SCLC- vs NSCC-regimens⁴⁹. However, when dividing LCNECs into the two molecular clusters⁴⁸, a better overall survival for patients with type II LCNEC (resembling SCLC) treated with SCLC regimens was reported as compared to other subcategories (37.7 vs. 10.5 months, $p = 0.039$). Since NEC patients are typically managed on the basis of small amounts of diagnostic material (e.g., cytology and biopsy samples), a reliable differential diagnosis is advocated through a strategic handling of lung tissue and appropriate immunohistochemistry adjuncts (e.g., RB1)³⁶ for the best

clinical decision-making.

Pathologist. Distinction between SCLC and LCNEC is accomplished by using a constellation of cytohistologic criteria (cell size and chromatin pattern) and immunohistochemistry details (Tab. I). SCLC is reliably diagnosed in resection, biopsy or cytology samples, whereas LCNEC may prove difficult to be recognized in small-sized material, where the term “NSCC with LCNEC features” is preferred, provided NE morphology and NE biomarkers are concurrently present¹. This task is demanding in smeared cytology samples⁵⁰, but the increasing use of cellblock preparations enables to readily appreciate the diagnostic criteria based on NE morphology and biomarkers⁵¹. Separation of SCLC and LCNEC, however, may be poorly reproducible owing to the subjective interpretation of cell size and cytological features, also considering the continuum between small and large cells⁵²⁻⁵⁵. As many as 10-15% of SCLC show larger cells with evident nucleoli and coarser chromatin, which are likely to correspond to the molecularly defined subtypes with low NE differentiation⁵⁶. In difficult instances, cytohistologic correlations are recommended, because cytology is considered the key tool to render an ultimate diagnosis of SCLC⁵⁷ or, alternatively, if some uncertainty should still persist, the noncommittal term high-grade NEC, not otherwise specified (NOS), is suggested by the 2021 WHO classification¹. Combined tumors are not infrequent in NECs^{1, 58, 59} and they can be missed in biopsy or cytology (see below, chapter 3.1). More recently, artificial intelligence algorithms have been proposed to improve separation among SCLC and LCNEC, but these tools are not routinely used at present^{10, 60, 61}. As RB1 expression is largely lost in SCLC but variably retained in LCNEC⁴⁸, the use of this simple immunostaining has been suggested in those RB1-proficient LCNEC, which could somewhat benefit from NSCC therapy protocols, whereas RB1-negative LCNEC would most benefit from drugs dedicated to SCLC³⁶.

Shared solution. Try to distinguish SCLC and LCNEC as much as possible, by maximizing all available diagnostic material (e.g., by using core biopsies offering larger amounts of tissue), because such a distinction is clinically warranted for decision making.

3. DISTINGUISHING BETWEEN PURE AND COMBINED (3.1) OR PRIMARY AND METASTATIC (3.2) NECs

3.1 Between pure NECs and combined (NECs composed by neuroendocrine and non-neuroendocrine components) lung carcinomas

Oncologist. International guidelines for cancer management underscore the relevance of distinguishing high-grade NECs of the lung, whether pure or com-

bined, for effective therapeutic purposes (see also: https://www.iss.it/documents/20126/8403839/LG%20149_Polmone_agg2021). Firstly, combined and pure NECs present with different clinical patterns: combined NECs, especially LCNEC, mostly show peripheral locations^{1, 62, 63}, whereas pure NECs, particularly SCLCs, are more commonly central^{64, 65}, necessitating tailored locoregional approaches. Secondly, localized disease occurs in as many as 70% of combined NECs compared to 40% of pure NECs, with a mere 5% of pure NECs diagnosed in stage I-II. This disparity of clinico-pathologic presentation leads to markedly different resection rates: 45% of combined NECs vs just 3% of pure SCLCs, thus resulting in significantly variable clinical outcomes. Lastly, combined NECs have lower response rates to chemo-radiotherapy as compared to pure SCLCs, but show a greater sensitivity to NSCC regimens^{36, 66}. Consequently, all these differences result in 2.5 times higher survival rates for patients with combined NECs than those with pure forms of SCLCs⁶⁷.

Pathologist. While most NECs, regardless of their subtyping, are histologically pure, up to 30%, whether SCLC or LCNEC, may combine with any other tumor type. Although a 10% threshold is required to define a combined SCLC with LCNEC due to the continuum between small and large cells and the purported greater biological aggressiveness of SCLC components, there is, however, no limitation regarding the percentage of NSCC or even sarcoma that may be recognized to classify the corresponding combined tumors^{1, 58, 59, 68}. Combined SCLCs are usually central lesions affecting major bronchi, whereas combined LCNECs prevail in peripheral location, thus reflecting possibly different pathogenesis mechanisms^{1, 13, 59}. Morphology and appropriate immunohistochemistry biomarkers are used to uncover such a type of tumors whose terminology remains a traditional one in the lung, while mixed neuroendocrine and nonneuroendocrine neoplasm (MINEN), as currently applied to the gastroenteropancreatic (GEP) tract⁶⁹, is discouraged. It is relevant to mention in the pathology report the various components of combined tumors for patient management and correct interpretation of metastatic deposits. In these instances, the finding of molecular traits common to NSCCs, such as *EGFR* mutation or *ALK* translocation, in otherwise classifiable NECs, especially if featuring SCLC, along with clinical correlations (e.g., nonsmokers), open up an avenue for *de novo* (in untreated patients) or transdifferentiated (in treated patients) SCLC developing from preexisting lung adenocarcinoma⁷⁰⁻⁷².

Shared solution. Up to one-fourth of NECs are combined with NSCC components, whose recognition is

clinically warranted due to different treatments and outcomes. Do not use the term MINEN in the lung. In small diagnostic material, combined NECs may be guessed by molecular profiling (e.g., *EGFR* mutations or *ALK* translocation).

3.2 Between primary and metastatic NECs

Oncologist. In case of suspected NEC of the lung, it is important for clinicians to distinguish between a primary lung neoplasm and a metastasis from other sites. In cases of suspected metastatic lung involvement from an unknown extra-pulmonary NEC, further radiologic and/or endoscopic examinations are necessary. For instance, if a lung metastasis from a small-cell NEC of the esophagus is suspected and the radiologic imaging is not conclusive, endoscopic evaluation with biopsy becomes mandatory⁷³. Similarly, if a small-cell NEC from the urinary bladder is suspected, a cystoscopy with a transurethral resection of the bladder may be indicated^{74, 75}. In all cases of unknown high-grade NEC primary, a ¹⁸Fluorodeoxyglucose (FDG) Positron Emission Tomography (PET)/Computed Tomography (CT) scan is recommended to identify any possible site of origin, regardless of the organ. While the staging differs among extrapulmonary NECs, it is noteworthy that, even in case of metastatic disease, the systemic approach is nonetheless quite similar and typically involves a combination of platinum-based polychemotherapy with or without immunotherapy^{5, 76} and, regardless of the completion of staging procedures, treatment should begin as soon as the diagnosis is confirmed. Due to rapid progression of the disease, many patients are unable to receive even first-line treatment⁷⁷. Of course, various clinical trials are tailored to the specific site of origin, as extrapulmonary NECs may have different prognostic, mutational and survival features⁷⁸⁻⁸¹.

3.2 Pathologist. The identification of metastatic NECs to the lung, whether SCLC or LCNEC, in pure or combined forms, may be challenging outside the proper clinical context and the personal history of patient⁸² and morphology and immunohistochemistry may fail to a large extent in this task (for example, TTF1 is consistently positive in most pulmonary and extrapulmonary NECs)⁸³. Intra-intertumor heterogeneity has been described in both SCLC⁸⁴ and LCNEC⁴⁸ with different transcriptomic subsets governed by master regulators of neuroendocrine differentiation. Moreover, a branched evolution with a shift to ancestral clones has been proposed in SCLCs underlying tumor relapse upon therapy⁸⁵. Such molecular characterization seems to reflect intrinsic functional subtypes rather than specific traits of the organ of origin, which cannot reliably be used for differentiating primary or metastat-

ic NECs at the level of the individual patient's cancer⁸⁶⁻⁹¹. The switch among transcriptomic subtypes, with evolution of NE^{high} to NE^{low} histotypes via *MYC* amplification or overexpression in experimental mouse models⁹², which in turn would cause a pro-tumorigenic microenvironment of therapy-resistant, stem cell-like non-NE cells to arise with feeding/trophic effects on metastatizing NE tumor cells⁹³, has weaker evidence in humans^{85, 94, 95}. While some molecular differences exist between pulmonary and extrapulmonary NECs^{88, 89}, many of the agreed-upon organ-specific transcription factors successfully used to create classification algorithms for unknown-primary NETs, such as OTP, TTF1, CDX2, PAX8, WT1 or ISLET-1, largely fail in NECs, due to either illegitimate transcription or alternative functions compared to other cancer models^{83, 96}. For example, *NKX2.1/TTF1* gene expression (a marker of type II pneumocyte and club cells commonly observed in pulmonary adenocarcinoma)⁹⁷ is documentable in as many as 80-90% of NE^{high} SCLCs according to the *ASCL1/TTF-1/NFIB* axis activation that potentially contributes to tumor development and metastatizing behavior⁹⁸. Furthermore, *NKX2.1/TTF1* gene product is also expressed in many extrapulmonary NECs, making this marker particularly unreliable in recognizing a primary or metastatic tumor⁸³. An intestinal origin of NECs, however, could be envisaged by the preferential *NKX2-5* expression (a gene involved in heart formation and development) observed in organoid models of digestive NEC compared to *ASCL1* and *POU2F3* expression that are more frequent in the lung⁹⁹ or by the fifth molecular subtype of NECs (beyond the classical *ASCL1*, *NeuroD1*, *POU2F3* and *YAP1* subtypes according to the Rudin and Gazdar's scheme⁸⁴) dependent on *HNF4-alpha* transcriptional regulator (a key gene involved in the development of the liver, kidney, and intestine), which is hallmarked by RB1^{WT}, GEP-like signature, NE^{high} phenotype and LCNEC appearance¹⁰⁰. Lastly, while undifferentiated NSCC may express NE markers, such as *SMARCA4*-¹⁰¹ or *SMARCB1*-^{102, 103} deficient undifferentiated tumors or *NUTM1*-rearranged carcinoma¹⁰⁴, as many as 10-20% conventional NECs, both primary and metastatic, driven by *YAP1* or *POU2F3*^{84, 90, 101, 105, 106}, lack NE differentiation and their recognition may be demanding in a diagnostic setting^{88, 107, 108}. A recent study by Zhang et al. compared by NGS 99 GEP NECs from the bile duct, colorectum, duodenum, esophagus, stomach, pancreas and unknown primary with 57 lung NEC of either small and large cells. It was found that *TP53/KRAS/CTNNB1* mutation and *TERT/IL7R* amplification prevailed in the former, whereas *GRIN2A/PTPRD/RB1* mutation and *NKX2.1/PIK3CA* amplification prevailed in the latter¹⁰⁹. These data sug-

gest that NGS analysis may assist in the appropriate clinicopathologic context in the differential diagnosis between pulmonary and extrapulmonary NECs.

Shared solution. Clinical history and presentation are useful to identify metastatic NECs to the lung, in that most site-specific immunohistochemistry biomarkers are largely shared by pulmonary and extra-pulmonary NECs and molecular characterization may be unpracticable in real life.

4. DISTINGUISHING AMONG WELL-DIFFERENTIATED NETs

Oncologist. After the first histologic description of pulmonary carcinoids in the 1930s¹¹⁰, diagnostic criteria for TC and AC were definitively established in the 1999 WHO classification of lung tumors¹¹¹ and subsequently maintained in the 2015¹¹² and 2021¹ WHO editions. As knowledge on lung carcinoids has continued to increase in the meantime, with distinct tumor properties and epidemiologic traits being uncovered (albeit ACs are by far the least frequent one)¹¹³, the current outlook on a two-tier clinical and prognostic stratification of carcinoid patients has been definitively accepted. Therefore, the pathological diagnosis of NETs and their distinction from NECs has become an absolute precondition for the oncologist in every diagnostic context, in virtue of major differences in clinical outcomes, functional imaging and therapeutic approaches^{7, 114}.

From a clinical perspective, compared to TCs, ACs are associated with a higher risk of nodal involvement, metastasis, larger size, peripheral location, local recurrence and worse prognosis¹¹⁵. With the replacement of conventional functional imaging based on ¹¹¹In- or ⁹⁹Tc-labelled radiotracers with ⁶⁸Gallium (⁶⁸Ga-) DOTA-peptide imaging, in addition to ¹⁸FDG-PET/CT scan, different functional patterns have been highlighted between ACs and TCs¹¹⁶. In a recent analysis by Jiang et al., TCs seem to show a greater distribution of somatostatin receptors (SSTRs), and higher ⁶⁸Ga-DOTA-peptide PET/CT positivity, compared to ACs, with SUVmax 36.5±21.6 vs 9±5.6 ($p < 0.002$). In turn, ACs seem to show a higher FDG uptake and thus a greater biologic aggressiveness in comparison with TCs (SUVmax 6.0±3.4 vs 3.7±2.6, $p = 0.05$)¹¹⁷. Furthermore, as many as 11-22% of lung carcinoids are associated with multiple endocrine neoplasia type 1 (MEN-1) syndrome, which shows a higher prevalence of ACs over TCs^{118, 119}. All these traits imply different management strategies and reflect different outcomes^{120, 121}.

Recognition of metastatic NETs to the lung represents another crucial issue. Since the lung may be reached by extra-pulmonary NETs^{122, 123}, identifying the organ of origin is essential when well-differentiated NETs

are detected in the absence of a primary site (CUP, carcinoma of unknown primary). In case of suspected GEP-NETs, ⁶⁸Ga-DOTA-peptide PET/CT may effectively trace them for diagnosis and staging purposes, whereas NETs arising in hollow organs may be uncovered by endoscopy. For instance, in low-grade G2 GEP-NET, a further ¹⁸FDG-PET/CT scan may be unnecessary, while in the event of ACs, this procedure is mandatory especially when ⁶⁸Ga-DOTA-peptide PET/CT scan is negative^{3, 124, 125}. In the choice of systemic treatment, identifying the primary is a key event according to international guidelines and nation-wide approvals. Beyond somatostatin analogues (SSA), the approved treatments for metastatic lung NETs include everolimus and chemotherapy¹²⁵. For all the other G1-G2 GEP-NETs, approved treatments include everolimus¹²⁶, chemotherapy¹²⁷, sunitinib (only for pancreatic NET)¹²⁸, peptide receptor radionuclide therapy (PRRT)¹²⁹ and, in some countries, surufatinib¹³⁰. Lastly, during follow-up and systemic treatment, knowing the origin of NETs helps guide imaging according to the natural history of disease. For instance, ileal NETs are mostly linked with liver and peritoneal metastases (67% when considering liver alone, peritoneum alone, and both)¹³¹ and, rarely, with bone metastases (1.2%)¹³². Conversely, lung NETs, beyond metastasizing to the liver, commonly spread, either synchronously or metachronously, to the lung, bone and brain, thus requiring different imaging approaches to accurately identify metastases at these sites¹³³.

Pathologist. Diagnosis of NET is carried out by the criteria outlined in Table I, namely mitotic count per 2 mm² and necrosis assessment as essential core criteria and Ki-67 labeling index (the product of the gene *MKI67* mapping to 10q26.2 chromosome)^{15, 134} as a nonessential (desirable) adjunct information¹ (henceforth, simply Ki-67). The resulting terminology will be TC/NET G1 and AC/NET G2 on resection and carcinoid tumor NOS and metastatic carcinoid NOS in biopsy/cytology samples of primary and secondary tumors, respectively^{1, 15, 135, 136}. Comparison between biopsy samples and resection specimens may be unreliable as far as mitoses and necrosis identification is concerned¹³⁷⁻¹³⁹. Of note, however, Reuling et al. have recently observed that overall size > 4 mm² of rigid or flexible bronchoscopy biopsies rather than their number accurately predicted AC histology, while Ki-67 (threshold around 5%) showed good concordance but not discriminative power for definitive diagnosis¹⁴⁰. All these considerations may nonetheless have a minor clinical impact, once a NEC diagnosis has been excluded, because in most instances TCs and ACs are resectable and the final risk attribution¹ is left to the subsequent examination of the surgical specimen

(see below for the category “carcinoid tumors with elevated proliferation”).

Regarding primary vs metastatic NETs, suffice it to say that, while pan-NE do not significantly contribute to this separation, specific panels of nuclear transcription factors are helpful to unveil the pulmonary or extra-pulmonary origin of NETs. In this regard, a combination of CDX2/Islet-1/PAX8 uncovers GEP NETs, of estrogen and progesterone receptors and TRPS1¹⁴¹ breast NETs/NECs, and of TTF1 and OTP the pulmonary origin of NETs. TTF1 is found especially in peripheral and often spindle-cell carcinoids in the setting of diffuse idiopathic pulmonary NE cell hyperplasia (DIPNECH)¹⁴², while OTP is a sensitive and purportedly specific marker of lung NET origin in cytologic and surgical specimens¹⁴³ (its specificity will hold until proven otherwise). Using a 40% OTP staining threshold in primary lung NENs, Viswanathan et al. have recently observed not only that 73% of TCs and 30% of ACs were positively stained for this marker (all NECs were instead negative), but also that this marker could operate discrimination among carcinoids¹⁴³, thus with potential diagnostic applications to bronchial biopsies^{139,144,145}. Immunohistochemistry for GATA binding protein 3 (GATA3) gene product (a transcription factor relatively unspecific that is expressed in many tumor types)¹⁴⁶ and estrogen/progesterone receptors have rarely been documented in single observations of lung NETs^{147,148}, thereby advising extreme caution to avoid the diagnostic trap of missing an unsuspected metastasis of breast NEN to the lung (Pelosi, personal unpublished observations). Notably, GATA3 is also expressed by paragangliomas/pheochromocytomas¹⁴⁹, thus making it important to verify keratin expression, which is usually lacking in these tumors.

Shared solution. The correct splitting of NETs into TCs and ACs helps better stratify patients for outcomes and treatments, but is practicable only on resection specimens. However, the noncommittal terms of carcinoid tumor/NOS and metastatic tumor NOS are nonetheless adequate to assist clinical decision making, provided that mitoses, necrosis and, hopefully, Ki-67 index are contextually specified in the pathology report. Uncovering primary or metastatic lung NETs is feasible and clinically warranted by means of immunohistochemical markers, but diagnostic traps should be carefully avoided. Different terminologies have to be adopted according to the different NET origin, if known, with metastatic carcinoid NOS being used for lung primaries and metastatic NETG1 to G3 GEP for gastroenteropancreatic derivation.

5. DISTINGUISHING BETWEEN ACs AND LCNECs: MAY THE KI-67 PROLIFERATION INDEX BE THE SOLUTION?

Oncologist. Since carcinoid-like LCNECs and highly proliferating carcinoids are on record among lung NENs and staging, imaging and therapeutic options may be different, distinguishing between carcinoids with elevated proliferation rates and LCNEC is becoming crucial to define the best therapeutic options^{1, 47}. This distinction, however, becomes less critical when comparing metastatic highly proliferating lung carcinoids with LCNECs showing lower proliferative indexes. In this scenario, the patient's performance status, tumor burden and the biologic behavior of disease guide the choice of systemic therapy more than the initial diagnosis. This is particularly true since histologic diagnosis may be based on a biopsy that does not necessarily represent the entire tumor. In this regard, possible treatments include alkylating agents or platinum-based chemotherapy for either instance¹⁵⁰⁻¹⁵⁶. Even if systemic therapies for lung carcinoids encompass everolimus and, in some trials or countries, PRRT and surufatinib¹⁵⁷, in cases with high tumor burden, aggressive biologic behavior and when tumor shrinkage is needed to improve symptoms, SCLC-like regimens may be more effective, regardless of histology. In these cases, more than apodictically distinguishing between high proliferative lung carcinoid and LCNEC, it becomes most important to pay attention to the tumor proliferation index, alongside clinical information (patient's performance status, tumor burden, medical history and functional imaging results)¹³⁸.

Pathologist. Although Ki-67 has been extensively studied over the years across the spectrum of lung NENs in virtue of its strong prognostic power^{134, 158, 159}, the 2021 WHO classification admits for this marker a nonessential, desirable or non-core role with two practical uses^{1, 160}: one for distinguishing NETs from NECs in biopsy or cytology samples, especially when occurring severe crush artifacts^{15, 134, 138, 160, 161}, the other for contributing to define primary or stage IV carcinoid tumors/NETs with elevated mitotic counts (> 10 mitoses per 2 mm^2) and/or Ki-67 proliferation index ($\geq 30\%$)^{1, 12, 47, 160, 162}. These tumors are currently classified as LCNECs in the pathology report, with the comment that morphology, expression of NE markers, retinoblastoma and wild-type pattern of p53, low tumor mutation burden, recurrently mutated genes (*MEN1*, *ARID1A*, *ARID1B*, *KDM5C*), lack of *RB1* and *TP53* inactivation and intermediate survival rates are more consistent with carcinoids than conventional LCNECs^{1, 12, 101, 162-164}. The identification of this provisional tumor entity dates back to previous genomic studies in which the term LCNEC-carcinoid like was introduced⁴⁷, characterized by recurrent *MEN1* mutation and borderline Ki-67 values with well differentiated NETs^{12, 101, 162}. This entity is homologous to NET G3 of

the GEP tract¹⁶³, although additional clinicopathologic and molecular investigations are needed to establish its proper position in the classification¹. Recently, attention has been drawn to lung carcinoids that are transcriptomically similar to NECs^{135, 165, 166}, termed by some authors as supra-carcinoids¹⁶⁷. Moreover, *TP53* or *RB1* alterations have been described in these proliferating carcinoids^{165, 168-170}, thereby expanding their spectrum of biological complexity. Conversely, the diagnosis of TC and AC is unpermitted by Ki-67 in any diagnostic context because of the imperfect biological correlation with mitotic count and necrosis^{1, 15, 135, 136}. However, different cut-off values ranging from 1.3 to 11.7%^{157, 171-178} have been reported to separate TCs from ACs with progression-free survival information, thus leading to an increasing interest even in biopsies^{137-139, 144}. In the metastatic setting of NETs or low proliferating LCNECs, where different therapies (e.g., SSA, temozolomide - capecitabine duet, PRRT) are an option¹³⁵, a stepwise approach based on Ki-67 and tumor differentiation could help in decision making^{15, 135, 158, 179, 180}. Furthermore, Ki-67 may be desirable in diagnoses of carcinoid tumors/NETs NOS or metastatic carcinoids NOS to improve clinical decision making, especially in association with other markers (OTP, retinoblastoma, CD44, SSTR2A, ASCL1, p53)^{138, 139, 144, 145, 172}, inasmuch as TC and AC separation is unfeasible. Of note, purported limitations of quantification are not specific to Ki-67, because even mitotic count and necrosis are culprits of interobserver inconsistency^{15, 181}. Phosphohistone H3 (PHH3) immunohistochemistry (a surrogate marker of mitotic figures) has been proposed to ameliorate mitotic count in terms of scoring times, mitosis detection and reproducibility of results^{182, 183}, although it does not improve diagnosis and provides a similar prognostic value to the current morphologic criteria¹⁸¹.

Shared solution. Ki-67 should always be included in pathology reports of lung NETs, since it helps in several ways: differential diagnosis between NETs and NECs; identification of highly proliferating carcinoids (especially in metastases); and clinical decision-making process as a whole. Defining Ki-67 index in NECs, especially SCLC, is currently of no clinical help.

6. ARE THERE OTHER TREATMENT-RELATED BIOMARKERS?

Oncologist. Over the years, various prognostic and predictive factors have been proposed for optimal lung NEN management. In metastatic TCs and ACs, after confirmation of SSTR expression, SSA have been approved as a first-line treatment¹²⁵. From this perspective, knowledge of clinical features has perfected the use of somatostatin receptors imaging (SRI) with an advancement in imaging techniques and radiotracers.

Since 2010, the best functional imaging for studying NETs was OctreoScan (In-111 pentetreotide), which however is currently considered obsolete, with up to 75% of discrepancy in lung NETs detection between OctreoScan and the newer generation SRI techniques¹⁸⁴. When SRI are not available or outdated, detecting SSTR distribution through alternative methods becomes crucial for indicating systemic treatments with SSA and PRRT¹⁸⁵.

Regarding other predictive targets, Kunz et al. have recently demonstrated the role of methylguanine methyltransferase (MGMT) assessment by promoter methylation and/or immunohistochemistry in the treatment of low-to-intermediate GEP NETs with temozolomide-based chemotherapy¹²⁷. In this study, MGMT deficiency was associated with a better response to temozolomide/capecitabine treated GEP NETs, which could become a possibility even for advanced lung carcinoid¹⁵⁶.

Lastly, specific gene alterations variably reported have been documented in tumor series or single case reports across the spectrum of lung NENs, which opened up an avenue for targeted treatments with some dramatic responses, such as *NTRK2-3*¹⁸⁶ and *EGFR*¹⁸⁷ mutations in LCNECs or *ALK* translocation in ACs and LCNECs¹⁸⁸. Recently, Zhang et al. described *ETV6-NTRK2* translocation in an AC patient who experienced complete response with entrectinib after several systemic efforts¹⁸⁹. Also, identifying carcinoid patients with high risk of progression¹⁹⁰ who could benefit from adjuvant treatment with chemotherapy or radiotherapy on the mediastinum as recommended by ESMO European Guidelines¹²⁵ is another clinical need. Lastly, detecting ACTH expression to predict potential endocrinologic paraneoplastic syndromes can help differentiate true Cushing syndrome from cushingoid changes due to concurrent steroid therapy¹⁹¹. This is particularly important for patients with brain metastases who may be heavily treated with steroids.

Pathologist. Most pathology laboratories are endowed by a vast armamentarium of immunohistochemical and molecular predictive assays¹⁹², which can help in clinical decision making. For instance, SSTR2 and SSTR5 immunohistochemistry may replace the functional imaging in lung TCs and ACs¹⁹³, with a 69% correlation rate with *in vivo* OctreoScan determination^{194, 195}. In particular, given the varying affinities that different peptides (DOTA-NOC, DOTA-TOC, DOTA-TATE)¹²⁴ may show for SSTR2, SSTR3, and SSTR5, the immunohistochemical confirmation of SSTR expression can assist in managing patients¹⁹⁵. Regarding MGMT scoring, Vatrano et al. demonstrated with different experimental approaches not only that a decreased activity in a large series of lung

carcinoids correlated with traits of aggressiveness, namely AC histology, larger size and higher T-N stage, but also that this assay provided the rationale for using alkylating agents in the same tumors ¹⁹⁶.

Next generation sequencing or other molecular techniques applied to the spectrum of lung NENs as a whole ¹⁹⁷ may assist the pathologist in discovering actionable or prognostic gene alterations within specific study protocols or under clinical guidance for decision-making. These include *NTRK2-3* ¹⁸⁶, *EGFR* ¹⁸⁷, *MEN1* ^{165, 166, 198} or *RB1/TP53* ¹⁹⁹ mutations, *DLL3* ²⁰⁰⁻²⁰², *EZH2* ²⁰³ or c-MYC ²⁰⁴ overexpression, *ETV6-NTRK2* ¹⁸⁹ or *ALK* translocation ¹⁸⁸, and microsatellite instability/mismatch repair deficiency ²⁰⁵, as well as tumor mutation burden assessment for IO ²⁰⁶ or trans-differentiation mechanism identification in *de novo* or treated NECs ^{70, 71}. Tumor mutation burden by NGS analysis is low in lung carcinoids and high in lung NECs, being correlated with Wnt, Hippo or Hedgehog signal activation ²⁰⁷, while *TP53* mutations is related with higher stromal PD-L1 expression ²⁰⁸. Recently, Werr et al., in a large collaborative study on pulmonary NETs ¹⁹⁰, have suggested that high *TERT* mRNA expression, leading to enhanced telomerase activity, identified clinically aggressive carcinoids, either TC or AC, with fatal outcome, thereby confirming our previous observations on *TERT* amplification (a surrogate for mRNA overexpression), which was shared by NETs and NECs and adversely affected survival ^{165, 209}. Of note, *TERT* can also be assessed by immunohistochemistry, thus potentially supporting its introduction in the clinical management of lung cancer ²¹⁰. Particularly interesting and easy to uncover by means of immunohistochemistry is the small subset (6%) of SCLC patients showing proficient *RB1* expression and *RB1*^{WT} status, who bear variable prognosis ¹⁹⁹ but showed immune-enriched profile with increased response to checkpoint inhibitor blockage (nivolumab and ipilimumab) in the CheckMate 032 trial ²¹¹.

Potential biomarkers for prognostic stratification in lung carcinoids (Ki-67, OTP, retinoblastoma, CD44, SSTR2A, Ki-67, ASCL1, p53) can be readily performed by immunohistochemistry even in biopsy samples, thereby helping the oncologist to widen the decision-making options ^{138, 139, 144, 145, 172}. Lastly, characterizing lung carcinoids for ACTH expression may be clinically warranted, inasmuch as these tumors are not so rare, do not always show overt Cushing syndrome and *per se* do not represent a clinically aggressive subtype ²¹².

Shared solution. Molecular testing is not routinely mandatory in NETs/NECs and in NSCC/non-NEC, but it is up to the clinical judgment and the patients' demography/clinical presentation, such as the lack

of smoking history or increased likelihood of driver mutations. In this regard, the opportunity of molecular testing should be taken into account in those cases, including transformed NECs and *de novo* NECs/NETs with driver alterations. Therefore, local feasibility of these assays should be discussed thoroughly with the pathologist, who should make them available on demand for justified clinical reasons.

7. STAGING PROCEDURE

Oncologist. According to the NCCN guidelines on NSCCs and NECs ^{6, 16} and the ESMO guidelines for the management of lung carcinoids and SCLC ^{5, 125}, the TNM staging scheme overlaps the AJCC/UICC system in use for lung NSCCs/non-NECs as refined in the 9th edition TNM classification of lung cancer ²¹³. Beyond prognostic significance, there are several therapeutic implications related to the different stages, especially in SCLC patients, in whom the classification of limited disease (*i.e.*, cancer confined to the thorax in a single radiation field) or extensive disease (*i.e.*, any T, any N, M1a/b/c) is clinically used ²¹⁴. From a clinical perspective, in case of non-metastatic disease, the pivotal data an oncologist must consider, beyond histologic characterization and proliferation index, include the state of margins (R1 or R2 if microscopic and macroscopic residual disease, respectively) and the number and location of lymph node metastases relative to the total number of removed lymph nodes ^{215, 216}. In the event of R1 or R2, a multidisciplinary evaluation is mandatory for determining the best course of action, in other words whether new surgery or, alternatively, radiotherapy with or without a systemic therapy should be planned (*e.g.*, in N2 ACs) ¹²⁵. This evaluation is crucial not only for immediate therapeutic decisions, but also a follow-up perspective. Given the lack of universally shared guidelines for follow-up timing and imaging, these specific details are critical for the NEN-dedicated multidisciplinary team to make informed decisions on a case-by-case basis. Moreover, in the setting of multifocal TCs and DIPNECH, underlying genetic syndromes should be ruled out ²¹⁷.

Pathologist. Lung NENs are staged according to the pathologic classification of TNM scheme (pTNM) by the UICC and AJCC ²¹³, including lung NENs. These proposals will account for residual tumor after resection (complete, uncertain or incomplete) ²¹⁸, stage grouping ²¹⁹, N descriptors ²²⁰, M descriptors ²²¹ and spread through air spaces ²²², in order to better meet the emerging needs of lung cancer patients. As the TNM system could not perfectly intercept the unique biologic properties of lung carcinoids, integrated staging/histology-based classification ^{223, 224}, combined stages ²²⁵ or prognostic scores ²²⁶ have been

proposed, but they still need confirmation. Bronchial, vascular and parenchymal resection should always be indicated in all lung NENs, including carcinoids ⁴, measuring the distance from tumor edges (especially in conservative resections) to guarantee radical excision (R0). Concomitant NE cell hyperplasia (NECH, *i.e.*, limited to the bronchial epithelium) in pathologic/syndromic DIPNECH (generalized NECH with tumorlets and obliterative bronchiolitis) ¹ should be recorded for staging purposes, especially in the event of multifocal/bilateral carcinoid nodules ^{142, 227, 228}.

Shared solution. Although TNM staging systems provide valuable prognostic and predictive information in lung cancer as a whole, it is more suited for NECs, while it should be perfected for NETs where an excess of low malignancy tumors is found. As long as new staging modalities will be made available, pathologic TNM and margin status should always be included in diagnostic reports.

8. STANDARDIZED REPORTING

Oncologist. Standardizing the pathologic report is crucial for NEN-dedicated oncologists, thoracic surgeons and other members of the multidisciplinary team to ensure comprehensive patient management. To achieve adequate disease description and proper evaluation of all therapeutic options, requirements on reporting must be shared with the pathologist within the team of lung NEN experts. In April 2024, a consensus meeting of experts in endocrinology, oncology and endocrine pathology was held in Rome under the aegis of the Working Group of Endocrine Pathology (GIPE) of the Italian Society of Anatomic Pathology and Cytology (SIAPEC-IAP) to preliminarily discuss how to construct a standardized pathology report for endocrine and neuroendocrine neoplasms, including lung NENs, aiming to identify diagnostic criteria projected into clinical decision making (Pelosi et al., manuscript in preparation).

Pathologist. In search of a shared standardized language, the 2021 WHO Classification on lung tumors offered practical solutions by devising essential (or core) and desirable (or non-core) criteria for both NETs and NECs ¹. While a detailed analysis on the subject is beyond the scope of this review article, suffice it to say that the College of American Pathologists (CAP), the International Collaboration on Cancer Reporting (ICCR), the European Society of Medical Oncology (ESMO) and the European Neuroendocrine Tumor Society (ENETS) have repeatedly stated the need for standardized pathology reports, also proposing templates for examining specimens of primary lung NENs, including carcinoids and NECs. These templates are based on dedicated checklists that are

useful for the sake of clarity, completeness of information and scientific soundness ²¹⁵.

In lung NETs, essential or core criteria comprise histologic subtyping into low grade TC/NET G1 and intermediate grade AC/NET G2 on resection and carcinoid tumor NOS/metastatic carcinoid on scarce diagnostic material of primary and metastasis, respectively, always reporting the values of defining criteria (mitoses per 2 mm² and necrosis and, desirably, Ki-67) (Tab. I). Immunohistochemistry for NE markers should be added to corroborate the pathology reporting. Pathologic TNM staging is also recommended after resection, with a comment on multiple NETs: pT factor is decided according to the highest lesion with “m” suffix for multicentricity (in the event of DIPNECH ^{142, 228, 229}) or pT3/pT4/pM1a factors are chosen for intrapulmonary seeding, with single pN and pM factors for all lesions collectively considered ²¹⁸. Although molecular testing is not routinely used in NETs/NECs and in NSCCs/non-NECs ^{1, 4, 6}, it is left to the clinical judgment and the patients’ demography/clinical presentation, such as the lack of smoking history, increased likelihood of driver mutations or transdifferentiation of NECs (*de novo* or after therapy).

In NECs, essential or core criteria comprise subtyping into SCLC and LCNEC, in pure or combined subtypes (Tab. I). SCLC is diagnosed in any type of material; LCNEC only in surgical specimens, but is termed “NSCC possible LCNEC” in biopsy/cytology samples. NECs are staged according to the same TNM-R system as conventional lung cancer, whereas limited-extensive disease for SCLC is used in a clinical context. DIPNECH is unlikely to occur in NECs ²²⁹. A panel of immunohistochemical markers desirably improves differential diagnosis towards histologic mimickers or combined subtypes ²³⁰ and, additionally, Ki-67 avoids misdiagnosing NETs for NECs (usually 50 to 100% in SCLC and 40 to 80% in LCNEC) ^{1, 161}.

Shared solution. Standardizing the pathology report should become the gold standard and priority for clinical decision making for lung NEN patients. Adoption of shared checklists could improve consistency, comparability and cross-study evaluation. The world of predictive markers is rapidly expanding with data essential for the clinical practice.

Conclusions

This lung NEN review article was conducted by peer questioning and answering between oncologists and pathologists, which reflects their engagement in the clinical decision-making on the one hand and the diagnostic effort on the other. In particular, we aimed

to present some practical and sequential steps that we adopt in clinical reasoning on both NETs and NECs, in order to elicit a critical and objective idea in the reader, who is hopefully capable of improving her/his own awareness and management skills. Our knowledge on lung NENs has moved from a generic tumor-centered vision to the current outlook focusing on the individual patient's cancer, where modern classifications are largely integrated with pathogenetic mechanisms to guide therapeutic choices¹. In this scenario, standardizing pathology reports and shared languages of lung NENs matter for consistency/quality, efficacy/time saving, improved decision-making and compliance/regulations.

The dramatic clinical presentation of lung NECs makes their distinction from NSCCs a clinical need. As this context is often mediated by small biopsies or cytology samples, distinguishing SCLC from LCNEC, as well as primaries from metastases, remains an essential one in light of non-overlapping therapeutic treatments. Moving on to the rarer NETs, the starting point, in our opinion, is the correct distinction between TCs and ACs or the use of a noncommittal terminology depending on the different diagnostic context (resection specimens and biopsy/cytology samples, respectively). The burden by the clinician will be to make appropriate material available by arranging all pre-operative or pre-therapeutic investigations and drive molecular testing requests (if any), while the burden by the pathologist will be to strategically manage all tumor tissues for diagnostic and predictive/prognostic purposes²³¹.

Clinical management or accrual into specific study protocols rely on a standardized tumor nosology, which encourages diagnostic consistency, cross-study evaluation and determining the clinico-pathologic characteristics of the individual patient. In this regard, templates for a minimum pathology data set have been made available from international organizations, with essential or core and desirable or non-core criteria to promote a common language²³². A Delphi consensus approach has been used for a minimum data set collection in GEP NENs²³³, and similar efforts should be implemented even in thoracic NENs for consistency^{1, 163, 233}. Recently, the special interest group on lung LCNEC of the British Thoracic Oncology Group (BTOG-LCNEC-SIG), which reunites oncologists, nurses, respiratory physicians, and pathologists in the UK, has been established to set care standards and improve outcomes for these patients²³⁴. The aims are to facilitate a UK consensus on the definition/diagnosis of LCNEC, develop a UK clinical consensus around clinical management, transfer results to the international community and define clinical trial eligibility as a new

setting for treatment progress²³⁴. In fact, our understanding of lung NENs has significantly grown over time in terms of biologic, pathologic, clinical, imaging, oncologic and molecular characterization, especially for life-threatening NECs¹³, many of which are presently given full consideration in daily practice for the treatment of the individual patient²³⁵. Combined, integrated, and deepened clinical and molecular analyses^{48, 70, 100, 167, 235} along with artificial intelligence tools^{61, 181} probably represent the future in lung NEN management and the basis for the next WHO classification.

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CONFLICT OF INTEREST STATEMENT

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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This is a review article on already existing literature data, for which no approval by Internal Review Board or Ethical Committee notification was needed.

AUTHORS CONTRIBUTION

Giuseppe Pelosi and Alice Laffi: conceptualization, data curation, literature investigation, methodology, supervision, validation, writing up of the original draft, critical revision and finalization of the manuscript; Mauro Papotti, Sylvie Lantuejoul, Jean-Yves Scoazec, Antonino Bruno, Fabrizio Bianchi, Barbara Bassani: data curation, methodology, validation, critical revision and finalization of the manuscript; Maria Gemelli, Riccardo Ricotta, Sergio Harari, Eleonora Duregon, Riccardo Papa, Angelica Sonzogni, Silvia Uccella, Carlo Carnaghi, Alexia Francesca Bertuzzi: validation, critical revision and finalization of the manuscript.

ABBREVIATION LIST

AC, atypical carcinoid; ACTH, adrenocorticotrophic hormone; AJCC: American Joint Committee on Cancer; ALK, anaplastic lymphoma receptor tyrosine kinase; ARID1A, AT-rich interaction domain 1A; ARID1B, AT-

rich interaction domain 1B; ASCL1, achaete-scute family BHLH transcription factor 1; ASCO, American Society of Medical Oncology; CAP, College of American Pathologists; CD44, CD44 Molecule (IN Blood Group); CD56/NCAM, neural cell adhesion molecule 1; CDX2, caudal type homeobox 2; CUP, carcinoma of unknown primary; DIPNECH, diffuse idiopathic pulmonary neuroendocrine cell hyperplasia; DLL3, delta like canonical notch ligand 3; DOTA, 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid; DOTA-NOC, DOTA-Nal3-octreotide; DOTA-TATE, DOTA-Tyr3-Octreotate; DOTA-TOC, DOTA-Phe-Tyr3-octreotide; EGFR, epidermal growth factor receptor; ERBB2-HER2, Erb-B2 receptor tyrosine kinase 2-HER2; ENETS, European Neuroendocrine Tumor Society; ESMO, European Society of Medical Oncology; ETV6, ETS variant transcription factor 6; EZH2, enhancer of zeste 2 polycomb repressive complex 2 Subunit; FDG, fluorodeoxyglucose; GATA3, GATA binding protein 3; G1-G2-G3, indicate low-, intermediate- and high-grade neoplasms, respectively; GEP, gastroenteropancreatic; GIPE: Italian Group of Endocrine Pathology; HNF4-alpha, hepatocyte nuclear factor 4 alpha; IASLC, International Association for the Study of Lung Cancer; ICCR, International Collaboration on Cancer Reporting; INCA, Institut National du Cancer (France); INSM1, INSM transcriptional repressor 1; IO, Immunology; Islet1/Isl1, ISL LIM homeobox 1; KDM5C, lysine demethylase 5C; Ki-67, the product of MKI67 gene marker of proliferation Ki-67; KRAS, KRAS proto-oncogene, GTPase; LCC, large cell carcinoma; LCNEC, large cell neuroendocrine carcinoma; MEN1, Menin 1; METexon14, MET proto-oncogene, receptor tyrosine kinase, exon 14 skipping mutation; MINEN, mixed neuroendocrine non-neuroendocrine neoplasm; MYC, MYC proto-oncogene, BHLH transcription factor; NE, neuroendocrine; NCCN, National Comprehensive Cancer Network; NEC, neuroendocrine carcinoma; NECH: neuroendocrine cell hyperplasia; NED, neuroendocrine differentiation; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumor; NeuroD1, neuronal differentiation 1; NOS, not otherwise specified; NSCC, non-small cell carcinoma; NGS, next generation sequencing; NKX2-5, NK2 homeobox 5; NTRK1-2-3, neurotrophic receptor tyrosine kinase 1-2-3; NUT, NUT midline carcinoma family member 1; OTP, orthopedia homeobox; p53, the product of the gene TP53; PAX8, paired box 8; PCI, prophylactic cranial irradiation; PD-1 (PDCD1), Programmed Cell Death 1; PD-L1 (CD274), Programmed Cell Death 1 Ligand 1; PHH3: phosphohistone H3; POU2F3, POU class 2 homeobox 3; PET, positron emission tomography; PRRT, peptide receptor radionuclide therapy; RB1, RB Transcriptional Corepressor

1; RET, Ret Proto-Oncogene; ROS1, ROS Proto-Oncogene 1, Receptor Tyrosine Kinase; SCLC, small cell lung carcinoma; SMARCA4, SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily A, member 4; SMARCB1, SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily B, member 1; SRI, somatostatin receptor imaging; SSA, somatostatin analogue; SSTR, somatostatin receptor; SUV, standardized uptake value; TC, typical carcinoid; TN, triple negative; TNM: tumor-node-metastasis staging system; TP53, tumor protein P53; TRPS1, transcriptional repressor GATA binding 1 of the trichorhinophalangeal syndrome types 1-3; TTF1/NKX2-1, thyroid transcription factor 1/NK2 homeobox 1; UICC, Union for International Cancer Control; WHO, World Health Organization; WT1, WT1 transcription factor; YAP1, Yes1 associated transcriptional regulator.

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