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REVIEW ARTICLE

Nordic 2023 guidelines for the diagnosis and treatment of lung neuroendocrine neoplasms

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ABSTRACT

Lung neuroendocrine neoplasms (NEN) are a heterogeneous population of neoplasms with different pathology, clinical behavior, and prognosis compared to the more common lung cancers. The diagnostic work-up and treatment of patients with lung- NEN has undergone major recent advances and new methods are currently being introduced into the clinic. These Nordic guidelines summarize and update the Nordic Neuroendocrine Tumor Group's current view on how to diagnose and treat lung NEN-patients and are meant to be useful in the daily practice for clinicians handling these patients. This review reflects our view of the current state of the art of diagnosis and treatment of patients with lung-NEN. Small cell lung carcinoma (SCLC) is not included in these guidelines.

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Introduction

The guidelines summarize the current view of the Nordic Neuroendocrine Tumor Group, NNTG, on how to diagnose and treat patients with lung neuroendocrine neoplasms (lung-NEN). The diagnostic work-up and treatment of patients with NEN have improved during the recent years. The evidence behind NEN treatment has improved significantly due to controlled randomized trials for gastroenteropancreatic NEN (GEP-NEN). Recently, improvements have also been attained in lung-NEN.

The classification of lung-NEN differs from the general NEN classification. According to the 2021 WHO classification of lung tumors [1,2], the neuroendocrine tumors of the lung are separated into two major categories–well-differentiated tumors (lung-NET) and poorly differentiated carcinomas (lung-NEC). Lung-NET is further divided into typical carcinoid (TC) and atypical carcinoid (AC). Lung-NEC comprises large-cell neuroendocrine carcinoma (LCNEC) and small-cell lung carcinoma (SCLC) (Table 1).

Lung-NEN accounts for approximately 20% of lung primary tumors, with SCLC accounting for 13–15%, LCNEC approximately 3%, and carcinoids 2% (with a typical to a typical ratio of 6:1 to 10:1). The incidence of lung-NET ranges from 1.4–7.8/100,000 [4–6].

These guidelines do not address SCLC.

Classification and pathology

The prototype lung-NEN are well-circumscribed tumors, either associated with central bronchi or the peripheral lung parenchyma and bronchioles. They exhibit solid, insular and trabecular architecture, often with rosette formations, suggestive of neuroendocrine differentiation and consist of cells with small round uniform nuclei with granular chromatin and eosinophilic cytoplasm. In the WHO classification, mitotic index is used to denote proliferation index. Currently, Ki-67 is not a part of the diagnostic criteria in lung-NEN. However, it is encouraged to assess Ki-67 as a part of the diagnostic

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Table 1. Lung-NEN versus GEP-NEN WHO terminology and criteria.

Lung-NEN (WHO 2021)			GEP-NEN (WHO 2019)		
Terminology		Criteria: Mitotic counts/2mm^2	Terminology	Criteria: Mitotic counts/2mm^2	Criteria: Ki67 index
Differentiated					
TC	Lung-NET	<2	GEP-NETG1	<2	<3%
AC	Lung-NET	2–10 (or necrosis)	GEP-NETG2	2–20	3–20%
–	–	–	GEP-NETG3	>20	>20%
Poorly differentiated					
SCLC and LCNEC	Lung-NEC	>10	NEC (small cell or large cell)	>20	>20%
Combined neoplasms					
Combined NEC and NSCLC			MINEN		

NEN: Neuroendocrine neoplasm; *NET*: Neuroendocrine tumor; NEC: Neuroendocrine carcinoma; *GEP*: Gastroenteropancreatic; *TC*: Typical carcinoid; *AC*: Atypical carcinoid; *SCLC*: Small cell lung cancer; *LCNEC*: Large cell neuroendocrine lung cancer; *NSCLC*: non-small cell lung cancer; *MINEN*: Mixed neuroendocrine non-neuroendocrine neoplasm. The table is modified from [3].

routine [2]. TC have a low mitotic count (<2 mitosis/2 mm^2) and lack necrosis. Conversely, in AC a higher mitotic count (2-10 mitosis/2 mm^2) and/or foci of necrosis can be detected [1,2]. Notably, the distinction between TC and AC can only be made in lung resection specimens, as a small biopsy might lack representative foci of necrosis and mitotic hotspots. The current classification does not entirely adhere to the proposed common framework of neuroendocrine neoplasms [7]: At present, there is no entity denoting the well differentiated, high-grade neoplasm, corresponding to the GEP-NET G3. It may be anticipated that the subgroup of differentiated AC with high proliferative Ki67-index (>20%) may in due course be classified as lung-NET G3.

Immunohistochemistry should include neuroendocrine markers, i.e., synaptophysin and chromogranin A (CgA), and Ki-67 proliferation index. A positive TTF-1 staining strongly suggests a bronchopulmonary tumor origin. However, TTF-1 is negative/non-informative in a significant fraction of lung carcinoids. A hormone panel is usually negative. The expression of somatostatin receptors (SSTR) is variable and largely mirrors the imaging results on DOTA-somatostatin analogue PET. The Ki-67 index is primarily used as a predictive parameter in lung-NEN and to guide the systemic treatment. Importantly, as TC and AC cannot be distinguished on biopsy specimens, the Ki-67 proliferation index here represents an important diagnostic indicator of the aggressiveness of the tumor. Genetically, Lung-NEN commonly harbor acquired mutations in chromatin remodeling genes, including regulators of histone methylation, acetylation and the SWI/SNF complex. Mutations in MEN1, ARID1A and EIF1AX represent the most commonly occurring mutations [8]. Conversely, mutations characteristic of SCLC is uncommon, i.e., aberrations in TP53, RB1, EP300, CREBBP and the NOTCH family genes [9]. The inhibitory NOTCH ligand, delta-like ligand 3 (DLL-3), is expressed on the surface of the majority of LCNEC. LCNEC are more heterogeneous and exhibit genetic aberrations both from the SCLC and non-small cell lung cancer (NSCLC) spectra. Recent studies on the molecular profiling suggest that there are subgroups of LCNEC that have more resemblance with SCLC (having TP53/RB1 co-alterations) whereas others may present with NSCLC-like features such as KRAS, STK11 and KEAP1 mutations. For this reason, a pathological work-up as in NSCLC (e.g., including EGFR, ALK, KRAS and PD-L1) may be considered in select cases of LCNEC [6].

Lung-NEC usually grow in larger solid irregular sheaths with prominent areas of necrosis and abundant mitosis (above 10 per 2 mm^2) and high proliferation index, usually above 30%. The LCNEC display larger pleomorphic atypical nuclei with prominent nucleoli. Notably, the expression of synaptophysin and chromogranin A may be weak or absent and may prompt use of a more sensitive, but less specific indicators of neuroendocrine differentiation such as CD56 and INSM1. Moreover, TTF-1 is generally not informative of tissue origin in high-grade NEN, as it can be expressed in NEC derived from any organ. Reflex comprehensive upfront mutational testing is currently not indicated in LCNEC.

In addition to the above tumors, the 2021 WHO classification of lung tumors define diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) as a rare premalignant lesion. It is characterized by multifocal, generalized, often bilateral neuroendocrine cell hyperplasia. This linear and micronodular hyperplasia is typically associated with bronchioles that can be seen with fibrosis and chronic inflammation, "constructive bronchiolitis", which might explain clinical obstructive symptoms at presentation. Tumorlets are small, less than 5 mm groups of neuroendocrine cells that extend beyond the airway mucosa and are morphologically similar to TC. The clinical significance is unknown. When micronodular tumor aggregates exceed 5 mm in diameter, they are classified as carcinoid/lung-NET.

Key points for classification and pathology

- Pathological work-up for lung-NET includes morphology with differentiation, mitotic count, and presence of necrosis.
- Immunohistochemistry for CgA, synaptophysin, and Ki-67 should be performed.

Lung-NET: Typical and atypical carcinoids

Presentation

Patients with lung-NET often present with respiratory symptoms, like coughing, wheezing, and recurrent pneumonia. A strong association with smoking, as seen in lung-NEC, has not been established for TC and AC. Distant metastases occur in <5% of patients with TC and in approximately 20-

30% of patients with AC. Metastases to regional lymph nodes, liver, skeleton, and brain are most common. Lung-NET is usually sporadic, however, less than 5% are associated with multiple neuroendocrine neoplasia type I (MEN-1). Screening of younger (<40 years) patients for primary hyperparathyroidism and optionally MEN1 gene mutation analysis should be considered. TC are generally small at presentation, most often with localized disease, while AC at the time of diagnosis usually is larger and more frequently harbor N1/N2 metastases [10]. Carcinoid syndrome and Cushing syndrome due to ectopic ACTH production in patients with lung-NET are extremely rare.

Radiological and nuclear medicine imaging

Tumor staging according to TNM is based on intravenously (IV) contrast-enhanced chest-CT and CT or magnetic resonance imaging (MRI) of the abdomen. This is performed in combination with somatostatin receptor imaging (SRI). PET is usually performed as a PET/CT [11] and ^{68}Ga-DOTATOC versus -TATE have comparable diagnostic accuracy. ^{64}Cu-DOTATATE may have advantages over ^{68}Ga-DOTATOC in the detection of lesions, but the patient-based sensitivity is the same. Contrast-enhanced MRI of the liver, especially with a hepatocyte-specific contrast medium and including diffusion-weighted imaging (DWI), is preferable to contrast-enhanced CT because of the considerably higher sensitivity for detection of liver metastases on MRI [12]. The use of ^{18}F-fluoro-deoxy-glucose (FDG)-PET/CT in lung-NEN has been debated. However, recently FDG-PET/CT was found to be positive in 81-93% of TC and 86-96% of AC [13,14]. For patients in whom peptide receptor radionuclide therapy (PRRT) is considered, FDG-PET/CT may add value for the identification of possible mismatched lesions (FDG positive, SRI negative).

Biochemical markers

At diagnosis, measuring CgA could be considered in all patients while PTH, calcium, and glucose measurements are recommended when there is a suspicion of MEN-1 syndrome [15–17]. CgA is elevated in most patients with NET, but is not specific and can also be elevated in healthy subjects and in patients with, e.g., kidney failure. However, several studies demonstrate a close correlation between plasma CgA and tumor burden. Furthermore, the plasma CgA concentration at baseline is an important predictor of patient outcome [18,19]. Several guidelines recommend a combination of imaging and plasma CgA measurement for monitoring, during both treatment and follow-up of NET patients. Yet, with CT as a reference, the sensitivity of plasma CgA to detect progression was only 36% in a recent prospective study of GEP-NET patients [20]. Further, the clinical utility in diagnosis and management was low in a recent study in lung-NET [21] and CgA seems to be less useful than previously believed. In patients with carcinoid syndrome, 5-hydroxyindoleacetic acid (5-HIAA) should be measured even in the absence of liver metastases [22],. In a recent retrospective study, carcinoid heart disease (fibrosis of right-sided heart valves) was not detected in lung-NET patients in the absence of liver metastases. N-terminal pro-brain natriuretic peptide (NT-pro-BNP) should therefore not be measured routinely.

Ectopic Cushing syndrome is rare among lung-NET patients. Serum cortisol, 24h urine-free cortisol, and adrenocorticotropic hormone (ACTH) should be measured on a clinical indication. Secretion of growth hormone (GHRH), IGF-1 and ectopic insulin is even less frequent, and should similarly only be measured when clinically indicated [23].

Key points for imaging and biochemistry

- Clinical work-up should include chest/abdominal CT.
- SRI (^{68}Ga-DOTATOC/TATE PET/CT or ^{68}Cu-DOTATATE PET/CT) should be performed to establish somatostatin receptor status.
- If PRRT is considered, dual imaging with FDG PET/CT and SRI should be performed, as discordant lesions may be a contraindication.
- CgA seems to be less useful, while PTH, ionized calcium, blood glucose, and other specific markers such as 5-HIAA and ACTH only when clinically indicated.

Treatment of localized and locoregional disease

Surgery

Surgery is the only curable treatment for lung-NET. For localized NET, surgical resection is the treatment of choice, and all patients should be evaluated for surgery. The "gold standard" is anatomical resection (lobectomy or segmentectomy) and systematic lymph node dissection. In early stages (I and II), a minimally invasive approach such as Video Assisted Thoracoscopic Surgery (VATS) is recommended [10,24–27]. For smaller (<-2 cm) peripheral TC, it has been proposed that a wedge resection may be sufficient. But in a recent study, it was concluded that anatomical resection achieves superior overall survival compared to wedge resection [28]. A lobectomy has traditionally been recommended for localized NET. For medically unfit patients with compromised lung function, that cannot tolerate a lobectomy, a segmentectomy is recommended over a wedge resection, due to a higher risk of local recurrence. However, a recent randomized controlled trial showed superior overall survival for segmentectomy vs. lobectomy for NSCLC $\leq$ 2 cm, indicating segmentectomy as a viable option for carcinoids $\leq$ 2 cm [29]. In centrally located NET, a parenchyma sparing strategy involving bronchial sleeve resection (whereby no pulmonary tissue is resected), bronchial- and/or vascular sleeve lobectomy is recommended over pneumonectomy [30].

Surgical resection should be considered in lung-NET patients with N2 disease. In patients medically unfit for a bronchial sleeve resection, an endomucosal resection may be considered, with careful follow-up including bronchoscopy [31]. Repeated endomucosal resections may be indicated in inoperable patients with recurrent atelectasis. It is recommended to follow an enhanced recovery after surgery (ERAS) protocol to ensure optimal surgical outcomes [32]. Stereotactic body radiation therapy (SBRT) may be

considered in physiologically inoperable patients with peripherally located tumors [33].

Endobronchial stent and, e.g., laser-, argon-, or cryotherapy may be used in the palliative setting. Currently, there are no data to support the use of adjuvant treatment after radical resection of lung-NET.

Key points for treatment of locoregional disease

- Anatomical resection is recommended. For carcinoids $\leq$2 cm a segmentectomy is preferred.
- Resection should be considered in N2 disease.
- For central tumors,bronchial sleeve resection is preferred over pneumonectomy.
- A minimal invasive approach (VATS) is recommended.
- Otherwise, surgical principles as in NSCLC including lymph node dissection.
- Adjuvant treatment is not recommended.

Treatment of advanced disease

Somatostatin analogues

Lung-NET often expresses SSTR. Therefore, the two long-acting somatostatin analogs (SSA) of octreotide and lanreotide have been used in the treatment. The well-documented effect of SSA in GEP-NET has been adapted for lung-Net al. Though a randomized phase III trial was stopped early for insufficient recruitment. Available evidence for the use of SSA in lung NETs only derives from small phase II studies or retrospective analyses. There are a few dedicated prospective studies supporting the use of SSA, e.g., pasereotide and octreotide LAR, in lung-NET patients [34,35] and despite the low level of evidence, SSA is widely recommended as first-line treatment in slow growing well-differentiated lung-NET (Ki-67 $<$ 10%). To determine whether the lack of SSTR expression should exclude the use of SSA is debatable. In the rare instance of a functioning lung-NET, SSA treatment prevents excess secretion of serotonin that causes carcinoid syndrome and carcinoid heart disease. SSA may also be useful in very rare lung-NET patients with hypercalcemia, acromegaly, and ectopic Cushing syndrome.

Protein kinase inhibitors

Treatment of progressive lung-NET with the mTOR inhibitor everolimus is associated with a median progression-free survival time (PFS) of approximately 9 months. The addition of octreotide or pasereotide to everolimus probably contributes to its positive effect on symptom and disease control [34,36]. Currently, there are no published studies on the use of the tyrosine kinase inhibitor sunitinib in TC or AC.

Peptide receptor radionuclide therapy (PRRT)

PRRT is primarily indicated in non-resectable and metastatic lung-NET with high tumor SSTR expression on SRI PET/CT. The treatment is usually administered as 4 cycles of ^{177}Lu-DOTATATE with 8–14 weeks intervals. Data with more personalized and dosimetry-based treatments are emerging and we are awaiting results. The published data on the efficacy of PRRT in lung-NET are mainly of retrospective nature, and indicate similar results to those of PRRT in GEP-NET, with better results in TC than AC [37,38].

PRRT is applied as second- or third-line therapy. Salvage therapy with PRRT is feasible in patients who progress after previous successful PRRT. Most patients tolerate additional cycles of ^{177}Lu-DOTA-SSA well, although the treatment effect is usually less than for the initial PRRT [39].

Key points for PRRT

- PRRT is indicated in non-resectable and metastatic lung-NET with high tumor SSTR expression on SRI PET/CT.
- PRRT is applied as second or third-line therapy.

Chemotherapy and immune checkpoint inhibitors

Chemotherapy in metastatic disease may be considered in selected patients with lung carcinoids. Data on temozolomide-based therapy are emerging, and retrospective studies have demonstrated the clinically relevant efficacy of temozolomide + capecitabin [40]. Streptozotocin + 5-FU has exhibited a low to moderate activity in lung-NET and may be considered for fit patients after failure of prior treatment lines under careful consideration of the benefit-harm ratio. Otherwise, chemotherapy should be restricted to patients with fast-growing tumors, usually atypical carcinoids with high proliferation, e.g., Ki-67 $>$ 50%. In these rare patients, the treatment approach can be like that for LCNEC. At present, there are no controlled trials indicating a clinical benefit from the treatment of lung-NET with immune checkpoint inhibitors. The use of chemotherapy and/or immune checkpoint inhibitors should therefore preferably be offered in the setting of a clinical trial.

Key points for treatment of advanced disease

- First-line treatment in advanced and metastatic BP NET (Ki67 $<$ 10%) is SSA.
- Second-line treatment is PRRT or everolimus (Ki67 $<$ 20%).
- Temozolomide-based chemotherapy or streptozotocin/5-FU may be considered in selected patients with advanced tumors.
- For aggressive tumors with high Ki-67 $>$ 50% treatment should be like that of LCNEC.

Follow-up

Based on retrospective studies, we recommend that radically operated patients should generally be followed for at least 10 years, due to the risk of recurrence. TC has a very indolent behavior with $<$7% recurrence risk, whereas it seems to be higher in AC with a higher proliferation index [13,41,42]. We recommend a contrast-enhanced CT of the chest and CT/MRI of the abdomen yearly in TC and every six months in AC with Ki-67 index $>$10%. After 5 years we recommend scanning of the patient every second year. Bronchoscopy is only considered in cases with increased risk for local recurrence

[41]. Patients with locally advanced disease in good performance status should be followed with a contrast-enhanced CT of the chest and CT/MRI of the abdomen every 6 months. The follow-up should be individualized, always considering the type of surgery, previous and ongoing non-surgical treatment, the tumor's aggressiveness and tumor burden, as well as the patient's age and comorbidity, to provide the most appropriate surveillance.

Large-cell neuroendocrine carcinoma (LCNEC)

Characteristics

LCNEC is related to smoking and patients are likely to be male and older.

Compared to other lung cancers, the resection rate of LCNEC is higher than for SCLC, however, the prognosis for resected LCNEC is generally worse than that of NSCLC [3,43].

The clinical course and treatment are for many, but not all LCNEC patients, stage-by-stage comparable to that of SCLC. The 5-year survival rate is 10-15% in patients with disseminated disease, and up to 50% among surgically resected patients [10,43,44]. For inoperable patients receiving chemotherapy, the expected median survival is about 1 year.

Very rarely, carcinoid-like types, characterized by MEN-1 mutations and low mutational burden, are found [45].

Treatment of localized and locoregional disease

Surgery is the treatment of choice and follows the same principles as in NSCLC [10]. Hence, in contrast to lung-NET, most LCNEC patients with N2 disease are considered unresectable. The role of adjuvant treatment is not yet fully defined. Data from small prospective and larger retrospective studies suggest that adjuvant SCLC-like chemotherapy may reduce the relapse rate [43,44]. In the absence of prospective randomized trials, the optimal radiotherapy schedules or chemoradiotherapy in the treatment of the locally advanced stage of LCNEC has yet to be definitively established. The use of concomitant chemo-radiotherapy in stage III corresponds to the treatment of SCLC: Cis- or carboplatin plus etoposide concomitant with either hyper-fractionated accelerated thoracic radiotherapy or conventionally fractionated radiotherapy regimes may be considered [45].

The incidence of brain metastases in LCNEC is lower than in SCLC but may be higher than in NSCLC, and perhaps as high as 40% at two years [44,46]. Prophylactic cranial irradiation is not yet recommended but should be investigated as a means of improving outcomes.

Treatment of advanced and relapsed disease

The mainstay of systemic treatment is platin-based chemotherapy. Due to the heterogeneity of the disease, conflicting results have emerged on whether to use NSCLC-like chemotherapy or SCLC-like regimens. In summary, SCLC-like regimes have produced the most robust data, even though NSCLC-like chemotherapy may also be an option [47–49]. An often-used palliative systemic treatment is 4-6 courses of carbo- or cisplatin plus etoposide. Etoposide may be substituted by irinotecan. Preliminary data suggest that the two major molecular subtypes and occurrence of wild-type RB1 gene or RB1 protein expression might have a predictive value for chemotherapy response and choice of treatment, but this observation needs to be validated in randomized prospective clinical trials.

Due to the lack of robust prospective trials second-line treatment modalities may vary. They may include re-induction of platin-etoposide and, e.g., topotecan, docetaxel, paclitaxel, gemcitabine or temozolomide ± capecitabine [43]. There are not sufficient data to recommend the use of PRRT. Second-line treatment and PRRT should preferably be offered in the setting of a clinical trial.

Sequencing-based molecular profiling may identify patients that will benefit from novel targeted therapies. At least one alteration potentially targetable by investigational agents was present in two-thirds of LCNEC. EGFR mutations are rare but may be seen more frequently in peripheral tumors and in tumors with combined histology. ALK, ROS1, BRAF, RET, FGFR1 or ERBB2 alterations are sometimes detected, as are mutations influencing the PI3K/AKT/mTOR pathway [47–51]. Response to immune checkpoint inhibitors has been reported only casuistically [52,53]. Studies of immunotherapy in clinical trials are warranted. Furthermore, DLL-3 has recently been identified as a compelling therapeutic target and is currently under clinical investigation, both with antibody-drug conjugates and T-cell-engaging antibodies.

Follow-up and supportive care

The follow-up of patients with LCNEC should mimic the strategy for SCLC, including close monitoring with contrast-enhanced CT of the chest and abdomen, blood samples and clinical assessment. Use of routine brain MR surveillance may rest on institutional practice. Smoking cessation should be encouraged.

Key points for LCNEC

- LCNEC is a highly aggressive disease with an overall poor prognosis.
- Generally, adhere to SCLC treatment. However, NSCLC-like LCNEC may be considered for NSCLC-therapy.
- Additional pathology in NSCLC-like LCNEC is recommended to identify potential druggable oncodrivers.
- DLL-3 targed therapies are under investigation in LCNEC.

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