Lung neuroendocrine tumors: A systematic literature review (Review)

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Abstract. Neuroendocrine tumors (NETs) can have multiple localizations in the human body however, most often, it appears in the in thorax at tracheobronchial tree and the thymus. NETs are a group of tumors with heterogenous malignancy that evolve from neuroendocrine cells, with the lung being the second target organ after the gastrointestinal tract. These rare tumors are usually asymptomatic and non-functional with little information regarding incidence in the specialty literature. The main purpose of this review, was the analysis of the available literature in all aspects while mainly focusing on molecular diagnosis data and secondly, by using this molecular landscape to establish a differentiation of lung neuroendocrine tumors (LNETs). By analyzing the literature, new data were revealed regarding histological evaluation, genetic aberrations, prognosis depending on the type of LNET and therapeutic options that derive from these. Efficient management of these tumors is essential in the handling of symptoms and increase in life expectancy, especially in patients with functional tumors. Histological differentiation of LNETs is important in establishing proper therapeutic options and prognosis. Combined types of LNETs remain a controversial topic of discussion regarding diagnosis and treatment, a topic on which further studies are required in order to improve diagnosis in this group of tumors with heterogenous malignancy.

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Contents

1. Introduction

Lung neuroendocrine tumors (LNETs) are a group of rare tumors with heterogenous malignancy originating

in amine precursor uptake and decarboxylation (APUD) neuroendocrine cells from Kulchitsky cells (argentaffin cells) (1). The first description of carcinoid tumors belongs to Siegfried Oberndorfer who considered these tumors to have a slow growth, being cancer-like tumors (2). Following this discovery, further research led to the discovery of Kulchitsky cells in the bronchial epithelium and establishing a relationship between them and different types of LNETs. In 1947, Hoffman introduced the term of pulmonary tumorlet, a term that describes a form of low-grade neuroendocrine carcinoma that is capable of metastasizing to the lymph nodes (3). These tumorlets are more often discovered in women and are considered preneoplastic lesions. Azzopardi introduced the term of oat cell carcinoma in 1959 after a study on 100 cases of pulmonary tumors (4).

Gould introduced the concepts regarding multidirectional differentiation of neuroendocrine cells that can evolve in mucus-producing cells, squamous cells and pulmonary carcinomas. In addition, in 1977, he introduced the terms neuroendocrine mass and endocrine carcinomas (5).

Arrigoni *et al* described atypical carcinoids (AC) as a histological presentation of bronchial carcinoid tumors (6). Eloesser, using a transbronchial approach, performed the first surgical resection of a bronchial carcinoid in 1939 (7). The neuroendocrine cells from which neuroendocrine tumors (NETs) derive are located in numerous places in the human body (8). The lung is the second organ, after the liver, in the localization of NETs, making up 25% of all NETs and 1-2% of all cancers (9).

Other authors considered that LNETs represent 20% of the total number of lung cancer cases (10). In addition to the single pulmonary localizations there have been cases described of two or more carcinoid tumors or tumorlets of the lung, gastrointestinal tract and pancreas. Other localizations such as the breast, ovary, testicle, endometrium, vulva, cervix, kidney, extrahepatic bile tract, thymus or nasal sinuses are rare (11).

In the thorax, NETs are found most often in the tracheobronchial tree, the lung or the thymus. Bronchial carcinoid tumors represent 10% of all carcinoid tumors and 4% of the total lung tumors (12). Large cell neuroendocrine carcinoma (LCNEC) is present in 3% of lung cancer cases and small cell lung cancer (SCLC) in approximately 15% of cases (13).

2. Materials and methods

The present study is a review of the literature published, to date, between 1981-2020 which was conducted on the studies identified in Pubmed after searching the following key words: 'neuroendocrine', 'lung tumors', 'pulmonary tumors', 'small cell tumors', 'large cell tumors'. Initially 103 studies were identified; after excluding papers which were not written in English as well as those in which a full text was not available, the remaining 78 studies were included in the present review.

3. Epidemiology

LNETs are relatively rare tumors. Information regarding their incidence and prevalence is limited in specialty literature. Of the LNETs, pulmonary carcinoids have an incidence of 0.2-2/100.000 cases both in the USA and the EU (14). Modlin *et al* have identified an increase of up to 6% per year in LNETs (15). Another study held in the USA between 2004 and 2014 has identified an annual increase in the incidence of LNETs of 7% (16). Furthermore, another study regarding the incidence of LNETs in the USA identified an increase from 1.09/100.000 cases in 1990 to 5.25/100.000 in 2004 (9). Most studies present a linear increase in the incidence of LNETs due to the increase in carcinoid tumors and not large cell neuroendocrine cancer or SCLC. Lung tumors consist of 75-80% NETs, 1-2% carcinoid tumors, 3% LCNEC and 15-20% SCLC (17,18).

Pulmonary carcinoids appear usually between the 4th and 6th decade of life, with a median age of 45 years. However, they are the most common primary pulmonary neoplasms in children and teenagers. Regarding risk factors, smoking is not a factor such as it is in SCLC and LCNEC (17). Typical carcinoid (TC) is 10 times more frequent than the atypical one that metastasizes in 50% of cases (19). There have been cases of double metachronous primary NETs (in the larynx and lung) reported in literature (7-9). In these cases, it is difficult to establish whether the tumors are metachronous or one of them is primary and the other is secondary. However, synchronous metastases in LNETs are present in 28% of cases (9).

4. Classification

LNETs consist of multiple grades of malignancy tumors, from low-grade to extremely aggressive tumors with a severe evolution and prognosis. In 2015, the World Health Organization (WHO) established that histological LNETs are classified as a common group and form a separate histopathological entity (20). In this entity, there are several neoplasia included such as TC, AC, large cell neuroendocrine cancer (LCNEC) and SCLC. The criteria on which this classification was established are: Histopathological aspect, Ki-67 index, mitotic rate and the presence of necrosis.

TC is a tumor with carcinoid histology, with <2 mitosis/2 mm^2 [10 high-power fields (HPF)], lack of necrosis and a size of 0.5 cm or greater. AC is a tumor with carcinoid morphology, with 2-10 mitosis/2 mm^2 (10 HPF) or necrosis (spotted). LCNEC is a tumor of neuroendocrine morphology (organoid clusters, palisades, trabecular cells) with a high mitotic rate of >11/2 mm^2 (10 HPF), with a median of 70/2 mm^2 and necrosis (often large areas). Non-small cell carcinomas have large cell size type characteristics with low nuclear to cytoplasm ratio, gross or fine chromatin, and frequent nucleoli. These tumors have fine nuclear chromatin and no nucleoli and qualify as non-small cell lung cancer (NSCLC) due to their large size and abundant nuclear cytoplasm. Immunohistochemistry positive results for neuroendocrine markers, other than neuron specific enolase (NSA), can qualify the tumor as LCNEC. Small cell lung carcinoma presents with small cells, scant cytoplasm and fine, granular chromatin, absent nucleoli and a high mitotic rate (>11/2 mm^2 10 HPF; and median of 80/2 mm^2 10 HPF) and frequently with large zones of necrosis (18).

As it can be observed form the WHO classification, one of the most important criteria, especially for LNET, is immunohistochemical examinations for neuroendocrine markers. In general, LNETs are positive for chromogranin

A, synaptophysin and CD56. However, in types of LNETs that have to be differentiated from NSCLC, thyroid transcription factor 1 (TTF1) marker must be considered for solid adenocarcinomas and p40 (IL12, subunit p40) for nonkeratinizing squamous cell cancer. However, there are numerous cases where differentiating between LNETs and SCLC is difficult, the behavior of LNETs being very variable. This led to a consensus of the experts from WHO and from the International Agency for Research on Cancer (IARC) in 2018, establishing the following categories of NETs (21): TC and G1, neuroendocrine carcinoma, well differentiated neuroendocrine carcinoma or low-grade carcinoma; G2, moderately differentiated neuroendocrine carcinoma, intermediate grade neuroendocrine carcinoma or AC; G3, poorly differentiated neuroendocrine carcinoma, high-grade neuroendocrine carcinoma (HG-LNEC), SCLC and LCNEC. From this consensus, it can be observed that G3 is also found in pancreatic NETs. Numerous studies have stated that G3 LNETs appear as poorly differentiated carcinomas, LCNEC or SCLC (8,17,22-24).

High-grade neuroendocrine tumors (HG-NETs) are difficult to diagnose and classify according to the new WHO classification. Due to this, some authors proposed a new approach in classifying HG-NETs using their molecular landscape into three categories (3). The first category, aggressive primary HG-NETs which account for 70-75% of SCLC as well as intermediate LCNEC are sometimes similar to non-small cell. The second category consists of secondary HG-NETs that account for 20-25% of LNETs and 6% of the total cases of lung cancer as well as a mix of neuroendocrine components with cell lines similar to NSCLC. The third category is that of indolent NETs that account for 5% of LNETs and 1% of all lung cancers. In this category there are both the TC and AC in women and young patients (3).

5. Precursor lesions

Travis *et al* considered that LNETs may develop from a preexistent precursor lesion, lung neuroendocrine cell hyperplasia (20). This phenomenon is most often presented in patients with chronic lung illnesses such as: bronchiectasis, obliterative bronchiolitis and interstitial lung disease (20). In 25% of cases of carcinoid tumors, the presence of neuroendocrine hyperplasia of the lung tissue surrounding the tumor can be found (25). Usually, a nodular proliferation of neuroendocrine cells under 0.5 cm is considered a tumorlet, with microscopical examination revealing no mitosis or necrosis, a low Ki67 index (19).

Another form of precursor lesion is diffuse idiopathic neuroendocrine cell hyperplasia (DIPNECH), with the presence of fibrosis and small nodular aggregates (neuroendocrine bodies) (20). Pathology examinations confirmed that DIPNECH appears most often in women and patients with obliterative bronchiolitis (23). There is no obvious connection between poorly differentiated LNETs and DIPNECH (26). Studies observed that almost 5% of cases of TC and AC are associated with multiple endocrine neoplasia type 1 (MEN-1) (25-27). Histopathological tests introduced the term of multidirectional differentiation for cases where mucus-producing cells or squamous cells are present in pulmonary carcinoids (28). This explains the mixed forms of LNETs.

6. Clinical features

Generally, their localization, type, dimensions and aggressiveness determine the clinical features of LNETs. The main clinical manifestations of carcinoid tumors are coughing, dyspnea, recurrent respiratory infections and hemoptysis (29). Peripheral LNETs are generally asymptomatic and are discovered accidentally. Considering the ectopic hormonal activity of the tumor, there are two categories: functioning secreting (hormone or hormone precursor) and non-functioning tumors (8). More than 90% of LNETs are non-functioning (30). In case of functioning LNETs, they secrete a series of ectopic hormones such as adrenocorticotropic hormone (ACTH), leading to Cushing syndrome in carcinoid tumors, or antidiuretic hormone (ADH), determining the syndrome of inappropriate antidiuretic hormone secretion (SIADH), or serotonin, leading to carcinoid syndrome (31). Some paraneoplastic syndromes are associated such as Lambert-Eaton syndrome (myasthenic syndrome) or cerebellar syndrome coexisting with limbic encephalitis and anti-neuronal nuclear antibody type 2 (anti-Ri) in LCNEC (32).

7. Tumor staging

When staging LNETs the recommendations from the 7th edition of the Union International Cancer Control/American Joint Committee on Cancer (UICC/AJCC) should be considered, with a TNM staging system for non-NET lung cancer, also for TC and AC. In addition to these types of tumors, TNM staging also applies for LCNC and SCLC, which are capable of metastasizing to lymph nodes and other organs (18,33).

8. Biological landscape of lung neuroendocrine tumors (LNETs)

LNETs occur from diffused localized neuroendocrine cells from the respiratory system. WHO morphological classification of LNETs in four categories is the result of epidemiologic, genetic, biological and clinical studies, leading to a differentiation of biological aggression and their capacity to genetically modify (34). Comparative studies of NET phenotypes from the resected tumor and nodal metastases reveal a genetic differentiation between them. This is more frequent in SCLC (34,35).

Immunologic markers used to differentiate NETs are chromogranin A, synaptophysin, CD56 and NSE. In order to discriminate between well-differentiated and poor differentiated NETs, Ki-67 antigen is more frequently used (34,36). A correlation between Ki-67 antigen, mitotic index and presence of tumors necrosis would lead to a more comprehensive and accurate diagnosis of LNETs (37). Based on immunohistochemistry, a new entity of NETs, highly proliferative carcinoids is described, with a 20% greater Ki-67 antigen index, and a smaller mitotic index, with 10 mitosis/mm^2.

Fabbri *et al* considered that using the Ki-67 labeling index is improved in the diagnosis of LNETs metastasis when compared with necrosis or neuroendocrine markers (38). NET specific markers based on location are: TTF1 in the lung, CDX2 in the intestines, ISL and PAX8 for the pancreas and rectum (39). Some studies have revealed that SCLC is positive

for TTF1 in over 90% of cases (38-40) while others suggested using CXCL-12 cytokines for LNETs, especially for AC (41,42).

In order to differentiate LNET subtypes, and especially for LCNEC, the mutation of tumoral protein P53 (TP53) and transcriptional receptor RB1 (RB1) have been observed. Using this, two subgroups of LCNEC have been identified: NSCLC-like and SCLC-like. These mutations however are not significant in cases of TC or AC (42). The loss of RB-1 is detected in 80-100% of cases of high grade differentiated NETs (43). A number of studies used neuroendocrine multigene transcript 'liquid biopsy' neuroendocrine neoplasm test (NETest) for LNETs in order to diagnose and monitor disease status. An increase of NETest levels is indicative of neuroendocrine neoplasia (44). A study on mice revealed that high-grade neuroendocrine carcinoma is generated by the loss of suppressor genes (TP-53 and RB-1) that appear in SCLC and LCNEC as weak as the suppression of phosphatase and tensin analog (PTEN) gene in SCLC (45).

Another useful tumor cell marker for differentiating between LCNEC and bronchial carcinoid is neuroectodermal stem cell marker (Nestin). It presents high levels, especially in LCNEC and is useful in predicting the prognosis (46). Stathmin-1 is associated with malignancy in NSCLC and is used in the differential diagnosis with high-grade LNETs. Stathmin-1 is a protein responsible for cancer cell survival, used in the signal transduction of malignant cells, and found at high levels in high-grade lung neuroendocrine tumors (HG-LNETs), being used for differential diagnosis between NSCLC and SCLC and LCNEC (47).

A large genetic and transcriptomic study identified two types of molecular subgroups for LCNEC: type I, LCNC with biallelic modifications of TP53 and STK11/KEAP 1 (37% of cases) and type II, LCNEC enriched for biallelic inactivation of TP53 and RB-1 (42% of cases). LCNEC with these two molecular subtypes allows for differentiating from other LNETs and especially with SCLC (48). TP53 mutation is present in 50% of cases of NSCLC and in over 70% of cases of SCLC (18). LCNEC can appear combined with adenocarcinoma or squamous cell carcinoma, while some types of SCLC can be combined with components of LCNEC (18). Programmed death-ligand 1 (PD-L1) was studied in LNETs and its presence was observed in 10.4% of cases of LCNEC and in 5.8% of cases of SCLC and was not identified in bronchial carcinoid (49). A previous study revealed that PDL-1 is active in HG-LNEC and is correlated with an increased rate of mutations (50). Inamura *et al* revealed that PD-L1 positivity is associated with low mortality in cases of HG-LNEC (51).

Genetic studies performed on LCNEC revealed that positive FOXp3 and tumor infiltrating lymphocyte (TiLS) represent favorable prognosis while CD4, CD8 and TiLS are an unfavorable prognosis factor. High presence of PD-L1 in LCNEC may constitute an argument in the use of anti-PD-L1 antibodies in the course of treatment (22,52).

After the classification conducted by WHO regarding LNETs in the four histological types, scientists observed that there is a general genetic profile behind it. Due to this, RB-1 and telomerase reverse transcriptase (TERT) modifications are common to all four types. However, MEN-1 and histone-lysine N methyl transferase 2d (KMT2d) mutations influence the prognosis in AC and SCLC (22).

RB-1 along with p107 and p130 have an important role in tumor genesis of SCLC. The loss of RB-1 offers an increased susceptibility to neuroendocrine lineages in the lung (13). A number of studies revealed that 16% of SCLC tumors and 10% of low-grade neuroendocrine subtypes lose their expression of neuroendocrine markers: ASCL1, NeuroD1 and NKx2-1. This loss of neuroendocrine expression results in major morphology modifications such as growth characteristics, with major clinical implications (53,54). Glucose transfer transporter 1 (GLUT-1) is a protein that helps in the process of glucose transport, found in increased levels in all types of neuroendocrine cancers, indicating an HG-LNET (10).

The predictive role of systemic inflammation markers in patients with LNETs has been evaluated: neutrophil-lymphocyte ratio (NLR), lactate dehydrogenase (LDH), advanced lung cancer inflammation index (ALI) and lung immune prognostic index (LIPI). The evaluation of these markers at the time of diagnosis could have a significant part in LNETs. A low ALI has an improved prognosis while a high NLR has a poor prognosis. High LIPI and LDH would also be associated with a poor prognosis (55).

The use of insulinoma associated protein 1 (INSM 1) in the diagnosis of SCLC has proven to be extremely useful. The cases of SCLC that were negative for neuroendocrine markers tested positive for INSM-1 in 75% of cases. This indicated a high specificity and sensitivity in detecting SCLC (56). Russo *et al* considered that in order to diagnose and monitor LNETs, the most important tool is the serum dosing of chromogranin A in association with urinary dosing of 5 hydroxyindoleacetic acid (5-HIAA). Using this they observed that a low level of 5-HIAA and an increased serum chromogranin A represent an indicator of poor clinical evolution (57).

In a comparative study in genic reorganization of neurotrophic tropomyosin receptor kinase (NTRK) and anaplastic lymphoma kinase (ALK), it was observed that NTRK is specific to malignant pleural mesothelioma while ALK as single arrangement was identified in intermediate-grade NETs (58-61). The pathway Kelch-like Ech-associated protein 1/nuclear factor erythroid 2-related factor 2 (KEAP1/NRF2) was investigated due to its implication in cancer cell survival and treatment resistance. Genetic unbalance of KEAP1/NRF2 by a KEAP1 hypermethylation system appears to be a frequent occurence in lung carcinoid tumors (62).

Delta-like 3 drosophila (DLL3) gene has a high expression in NETs, especially in LCNEC and SCLC (63). For an improved diagnosis, Brcic *et al* used anti DLL3 antibodies in order to detect the presence of the DLL3 gene (63). Another marker used in the diagnosis and prognosis of NETs is orthopedic homeobox protein, being identified in 50% of cases of TC and 20% of LCNEC cases (64). Another marker used is NK6 homeobox-1 (NKx6.1), being detected in low-grade NETs in both the lung and pancreas (64).

Detassis *et al* attempted the detection of miR375-3p in formalin-fixed paraffin-embedded (FFPE) samples, leading to a differentiation of LNETs from low-grade NETs but without being able to differentiate between NSCLC and SCLC (65).

9. Radiological diagnosis

More than 40% of LNET cases are discovered by accident during routine chest radiographies (66). The gold standard in imaging is thoracic computed tomography (CT) with

contrast and, for more sensitivity, single photon emission CT for somatostatin receptors using 99mTc-Tektrotyd tracer. This imaging technique is used in identifying primary LNETs as well as local and distant metastasis. 99mTc-Tektrotyd has a high affinity for somatostatin receptors, making it a markedly improved option in detecting well-differentiated NETs (67). However, for low-grade NETs, 68Ga-DOTANOC positron emission tomography (PET-CT) is markedly more sensitive. 18 fluorodeoxyglucose PET-CT is the most useful tool in discovering low grade NETs as well as intermediate grade NETs, with equal sensibility as both other PET-CTs (68). In general, somatostatin receptor PET is useful in identifying metastatic disease (69).

Bronchoscopy is extremely useful in diagnosing all forms of NETs, especially those that present with bronchial expression, being a safe method and also the most often used one for histopathological diagnosis.

10. Surgical treatment

The goal for treatment is complete anatomical resection and mediastinal lymphadenectomy, with lobectomy or sleeve resection being preferred. Interventional bronchoscopy such as endobronchial resection should be reserved for patients with high surgical risk or as preoperative preparations (69).

Regional therapy includes surgery for liver metastasis or other solid organs but in general is reserved for cases of AC (19). Local radiotherapies such as microwave ablation, stereotactic ablative radiotherapy, radiofrequency ablation are reserved for cases that have refused surgery (69). Adjuvant therapy is used after surgery for cases of AC and LCNEC with obvious benefits towards survival, with an association of radiotherapy and chemotherapy (70). Other authors have used programmed cell death protein 1 (PD-1) inhibitors in association with chemotherapy and radiotherapy for the treatment of LCNEC (71).

11. Advanced LNETs therapy

Standard treatment for advanced SCLC is chemotherapy using cisplatin and etoposide, usually as a continuous intravenous infusion (72). Peri and Fazio used everolimus as first line therapy for advanced and non-functional LNETs (73). For functional cases of LNETs, most patients receive somatostatin analog therapy (SSA) as the first line of treatment in carcinoid syndrome. Patients with Cushing syndrome require control of the ectopic cortisol secretion (73). Other therapeutic options are radionuclide therapy of the peptide receptors as well as external beam radiation, especially in patients with tumors positive for somatostatin receptors, as palliative treatment in metastatic disease (73).

12. Conclusions

In LNETs, histopathological diagnosis and the molecular landscape are extremely important, especially in HG-LNETs. LNETs have a series of common traits; however, they represent a heterogeneous group of tumors regarding aggressiveness, evolution and prognosis. They remain a subject of controversy regarding treatment and diagnosis of the LNET subtypes.

To this end, a multidisciplinary approach is necessary in establishing a correct diagnosis and multimodal treatment in order to obtain favorable results.

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Ethics approval and consent to participate

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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