Pulmonary Neuroendocrine Tumors: From a Clinical, Genetic and Pathologic Perspective

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ABSTRACT

Neuroendocrine tumors may develop on the whole body with the majority being found in the gastrointestinal and pulmonary system. Pulmonary neuroendocrine tumors comprise 20% of all lung cancers and represent a spectrum of tumors with variable histopathological characteristics, genetic features and biological behaviors. The latest World Health Organization classification separated these tumors into 4 subgroups: typical carcinoid tumor, atypical carcinoid tumor, large-cell neuroendocrine carcinoma and small-cell lung carcinoma.

The clinical presentation depends on site, size, and growth pattern of the tumor but centrally localized tumors cause obstructive respiratory symptoms as coughing, hemoptysis, dyspnea, and chest pain, while peripheral tumors are usually asymptomatic with incidentally signs. Genetically large-cell neuroendocrine carcinomas and small cell carcinomas have higher mutation rates associated with tobacco-carcinogens. Typical and atypical carcinoids are respectively low, and intermediate grade tumors but they both have the capacity to develop metastases into regional or distant lymph nodes. Large-cell neuroendocrine carcinomas and small cell carcinomas are biologically aggressive tumors and have a poorer prognosis than other non-small cell carcinomas. The management of lung neuroendocrine tumors should be individualized by multidisciplinary teams including pulmonologists, surgeons, pathologists, medical and radiation oncologists, and radiologists.
Increased awareness and knowledge about the biology and genetic characteristics of these tumors with the support of controlled clinical trials of patients may accelerate the discovery of new markers for accurate diagnosis and therapy options.

**Keywords:** Pulmonary neuroendocrine tumors; Genetics; Clinicopathology; Treatment

**INTRODUCTION**

Pulmonary neuroendocrine tumors (NETs) have a broad clinicopathologic spectrum, and display variable morphological characteristics, and biological behaviors. They constitute 20% of all lung carcinomas, and their incidence rates have increased with the help of the development of imaging modalities within the last decades [1-3]. According to the most current classification of the World Health Organization (WHO), NETs have been categorized into 4 subtypes as typical carcinoid, atypical carcinoid, large-cell neuroendocrine carcinoma (LCNEC), and small cell carcinoma (SCC). This classification fundamentally is based on morphology namely number of mitoses, and necrosis [4].

Carcinoid tumors of the lung are malignant tumors arising from the mature cells of the pulmonary diffuse neuroendocrine system which display neuroendocrine morphology, and differentiation. Low and intermediate grade tumors are classified as typical and a typical carcinoid tumors, respectively. Diagnostic criteria which differentiate typical carcinoids from atypical ones were set forth in 1990 WHO classification, and in 2004, and 2015 WHO classifications only slight modifications were applied [1-7]. These tumors have not any causal relationship with LCNECs or SCCs or share a common genetic/epidemiological /clinical characteristics [7].

Large-cell neuroendocrine carcinoma was included in the 1999, and 2004 WHO classifications as a variant of large-cell carcinoma (LCC), while in the latest WHO classification it was described under the heading of “Neuroendocrine Tumors”. Although it shares some characteristics with small-cell carcinomas, it is a distinct entity with different clinical characteristics, histology, prognosis, and survival rates [4,6]. Combined LCNECs contain components of adenocarcinoma, squamous cell carcinoma, spindle cell carcinoma and/or giant cell carcinoma. If these components were combined with small-cell carcinoma, then they are classified as combined SCCs [4].

Small-cell carcinomas are among the most prominent malignancies in all fields of oncology with their characteristic clinical, and genetic features, its responsiveness to specific chemotherapies, and utmost reliable histopathological diagnosis [8]. Combined small-cell carcinoma contains as an additional component any one of the histological types of non-small cell lung carcinoma generally including adenocarcinoma, squamous cell carcinoma, LCC, LCNEC or less frequently spindle cell and giant cell carcinoma [4].
INCIDENCE, EPIDEMIOLOGY, ETIOLOGY

Carcinoid tumors are rare tumors and constitute 1-2% of all pulmonary carcinomas, and 20-25% of all types of carcinoid tumors. Its age-adjusted estimated incidence varies between 0.2-2 cases per 100,000 people. Though it is rarely seen, its annual prevalence in women, and men increased nearly 6% within the last 30 years [7,9-11]. This increase is said to be possibly related to the development of diagnostic methods, and widespread use of immunohistochemical methods [7]. Most of them are seen between 4. and 6. decades, and typical carcinoid at a median age of 45 years, while atypical carcinoid tends to appear one decade later. It is slightly more often seen in men relative to women, and in Caucasians rather than black race. Steuer et al. reported that median age of onset was 65 years for atypical carcinoids, while their study population consisted of 69% female patients, and 87% Caucasians [12].

Typical carcinoids is not related to cigarette smoking, while atypical carcinoids have been more frequently reported in smokers. Generally they are sporadic lesions, while 5% of them, mostly being typical carcinoids, accompany multiple endocrine neoplasia type 1. The ratio between typical and atypical carcinoid is 8-10/1, and atypical carcinoid tumor is the least seen tumor among all pulmonary NECs [7,9-14]. Their mechanisms of development, and progression are not clear, most of them are de novo cases [4,7]. Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNEH) and tumorlets are precursors of some types of pulmonary carcinoid tumors which develop in the presence of proliferated pulmonary neuroendocrine cells [14].

Large-cell neuroendocrine carcinomas are also rare tumors, and their incidence rates vary in different series, while it is seen in 2.1-3.5% of respected pulmonary cancer specimens. Since cytological diagnosis is very challenging, its incidence is thought to be higher than estimated [3,15,16]. It is mostly seen in men (nearly 85%) with a median age of 65.8 years, and 85-98% of the patients have a history of smoking [16-18]. Though its progenitor cell origin has not been fully characterized, based on animal experiments, it has been suggested that they develop from pluripotent epithelial Clara-like cell types which display neuroendocrine differentiation [4]. Miyoshi et al. performed molecular analyses, and demonstrated their SCC-like genomic profile, and displayed highly prevalent TP53, and RB1 gene mutations [19,20].

However small cell carcinomas constitute nearly 15% of lung carcinomas, based on USA data every year more than thirty thousand newly diagnosed cases are detected [8,21,22]. Its incidence peaked both among men and women at mid-1980s, and at the start of 1990s, and in the year 2010 its incidence rates decreased both in men (11.3/100,000), and women (6.7/100,000). Among types of lung cancer, SCC is most strongly correlated with smoking [4]. Small cell carcinomas characteristically carry a molecular signature associated with smoking. The most potent carcinogens which induce development of SCC are polycyclic aromatic hydrocarbons (benzopyren), and tobacco-specific nitrosamines called as nicotine-derived nitrosoaminoketone [4,8,21-24].
Most of the well-differentiated pulmonary NETs are centrally localized in main (10%) or lobar bronchi, while the remaining cases in peripheral zone of the lungs [9,10,13,25]. Atypical carcinoids tend to localize in peripheral zone [26]. Centrally localized tumors induce obstructive respiratory symptoms as coughing, hemoptysis, dyspnea, and chest pain, while peripheral tumors are asymptomatic with incidentally detected signs. More than 90% of the pulmonary NETs are nonfunctional, and rarely carcinoid syndrome due to production of peptide, Cushing syndrome, and acromegaly are seen [4,27]. More than 40% of the cases can be incidentally detected on chest X-ray [7]. Contrast-enhanced computed tomography is the gold standard diagnostic tool. Most often they are visualized as round or oval, slowly growing, hyper vascular tumors with smooth or lobular contours (Figure 1) [27]. Bronchoscopy is indicated in centrally located forms also for biopsy. Flexible bronchoscopy is preferred, however the clinician should be aware of the risk of bleeding. For patients with a high risk of bleeding, rigid bronchoscopy may be preferred. For peripheral lesions endoscopic transbronchial biopsy or more frequently transthoracic CT-guided biopsy is recommended. It should not be forgotten that in small biopsy specimens it is difficult to differentiate between typical, and atypical carcinoid tumors [28-30].

**Figure 1:** Typical carcinoid tumor showing round/oval, smooth and lobular contours in the perihiler area of the right middle lobe on thorax CT.
Contrary to typical, and atypical carcinoids large-cell neuroendocrine carcinomas are frequently peripheral tumors. In a study performed by Garci-Yuste et al. 2/3 of the cases have been reported as localized in the parenchyma of the peripheral pulmonary zone [31]. Therefore coughing, hemoptysis, postobstructive pneumonia are less frequently seen in most of these cases, mostly an asymptomatic nodule, chest pain, dyspnea, and nonspecific symptoms are observed [18]. Paraneoplastic syndromes are rarely detected [16]. Just like patients with SCCs they very frequently present with lymph nodes (60-80%), and distant metastases (40%). Conventional radiological examinations did not reveal any disease-specific sign, and frequently these peripheral tumors with irregular contours demonstrate expansive growth (Figure 2). Ten percent of these tumors may contain calcifications [3]. Despite their peripheral location rarely they are associated with pleural effusion [6]. Since neuroendocrine tumors frequently express somatostatin receptors, SSTR scanning has been recommended for preoperative staging, and postoperative follow-up. The studies on usefulness of FDG-PET imaging in neuroendocrine tumors have yielded debatable outcomes. [3,16]. IASLC recommends use of TNM staging which evaluates tumor size, lymph node involvement, and metastases in the prediction of the prognosis of neuroendocrine tumors [3]. Pulmonary NETs are staged based on AJCC/IASLC TNM staging system. For accurate staging conventional imaging modalities, scanning, PET, multiphase CT, and MRI should be used [7,9,32].

Figure 2: A case of LCNEC displaying a huge central and peripheral tumor with irregular contours localized in the left superior lobe on thorax CT.
Small-cell carcinoma typically leads to formation of a large hilar mass, and bulky mediastinal lymphadenopathy (Figure 3). Frequently the patients present with widespread symptoms of metastatic disease as weight loss, bone pain, neurologic symptoms, and debility [22]. Multiple number of neurologic, and paraneoplastic syndromes have been associated with SCCs. Among neurologic syndromes, most frequently, Lambert Eaton myasthenic syndrome, encephalomyelitis, and sensory neuropathy, among endocrine neoplastic syndromes hyponatremia of malignancies due to production of polypeptide hormones, inappropriate ADH secretion syndrome and Cushing syndrome are seen [21,22].

![Thorax CT of small cell carcinoma showing large hilar mass with bulky mediastinal lymphadenopathy in the middle of the right lung.](image)

**Figure 3:** Thorax CT of small cell carcinoma showing large hilar mass with bulky mediastinal lymphadenopathy in the middle of the right lung.

Small-cell carcinoma can be observed with radiological signs seen in all spectrum of lung cancers. However because of its faster doubling time it tends to present with larger hilar mass in advanced stage, when compared with other NSCLCs. Characteristic radiological images consist of a large hilar mass, and bulky mediastinal lymph nodes. The mass is frequently lobulated, and endobronchial. Rarely cavitation is seen, and involvement of hilar vessels, and vena cava is more frequently observed relative to NSCLC [4,8,21,22]. For staging TNM classification is used, in addition to previous classification based on sub typing as diffuse disease (presence of malignant pleural or pericardial effusion or hematogenous metastasis passing across the ipsilateral hemithorax), and
limited-stage disease (contained within the hemithorax) [24]. However use of TNM classification is more frequently recommended, because it also describes prognostic subtypes within the limited-stage disease [33]. For staging, CT for lung, liver, and adrenal gland, MRI or CT for the visualization of brain are recommended. Since SCCs have faster metabolic activities, staging based on PET/CT has a higher accuracy rate. Mediastinal staging is not recommended for patients with invasive disease who are not candidates for surgical resection. Staging should not only focus on affected areas manifesting symptoms. In 30% of the patients without bone pain or higher alkaline phosphatase levels, results of bone scanning have indicated the presence of SCCs [22].

**GENETIC FEATURES**

Among all pulmonary, and other tumors, pulmonary carcinoids have the least somatic mutation rates (0.4/million bases). TP53, and RB1 mutation, and inactivation is very rare (<5%) in typical carcinoids, while it is slightly more frequent in atypical carcinoids. The only important MEN1 somatic mutations are observed in 40% of the patients with sporadic carcinoids without relevant family history, and slightly more frequently in atypical carcinoids. This mutation is not observed in LCNECs, and SCCs. In 35% of the cases, mutations are found on polycomb complex 1 and 2, and in 25% of the cases, on ARID1A, SMARCC1, SMARCHC2, SMARCA4 which are associated with SWI/SNF complex gene pathway, and in 72% of them candidate driver mutations are detected. A genetic difference between typical, and atypical carcinoids suggesting their development from a common clonal proliferation has not been observed so far. Besides results of the molecular analyses strongly support the assertion that carcinoid tumors are not early-stage progenitors of LCNECs, and SCCs, instead they are distinct proliferations from both genetic, and phenotypic perspectives [4,34,35].

Large-cell neuroendocrine carcinomas have extremely higher mutation rates associated with tobacco-carcinogens as is the case with SCCs. In LCNECs most frequently mutations are detected on TP53 and RB1 genes. In addition activated mutations on KIT, EGFR, ERBB2, and FGFR1 genes, and increased number of copies on ERBB2, and SETBP1 genes have been reported [6,19,36]. Rekhtman et al. analyzed 241 cases of LCNEC using next generation sequencing method, and based on their genomic characteristics, TP53 (78%), RB1 (38%), STK11 (33%), KEAP1 (31%), and KRAS (22%) genes were found to be the most frequently mutated genes. In this study based on their genomic profiles, LCNECs were divided into 2 minor, and 2 major subgroups as follows: SCC-like (TP53+RB1 comutation/loss), NSCC-like (TP53+RB1 combined with NSCLC-type mutations STK-11, KRAS, and KEAP1) and carcinoid-like (MEN1 mutation). They reported multiple number of clinicopathologic differences between SCC-like, and NSCC-like types, and they concluded that biologically, LCNECs are heterogenous tumors [36].

High-grade neuroendocrine tumors of the lung carry characteristic tobacco-carcinogen associated molecular signature. Premature inactivation of TP53 leads to genomic instability, and loss of chromosome 3p, 4q, 5q, 13q, and 15q. Mutations inactivating Rb1 are more frequently
seen in SCCs, rather than LCNECs, and characterize SCCs [4,8,19]. In a substantial group of SCCs, PTEN mutations, and FGFR1 amplification are seen. While P53 mutations are not observed in typical carcinoids, it is observed in 25% atypical carcinoids, 59% of LCNECs, and 71% of SCCs [23]. Besides, genomic, and epigenomic changes as c-kit overexpression, telomerase activation, RASSF1 inactivation, and p14ARF loss have been reported in SCCs [4].

**HISTOPATHOLOGIC AND IMMUNOHISTOCHEMICAL CHARACTERISTICS**

Central carcinoid tumors are well-circumscribed, round-oval, sessile or pedunculated tumors. Endobronchial component is seen in 54% of atypical, and 31% of typical carcinoids. Average tumor diameter ranges between 0.5-9.5 cm, and atypical carcinoids are larger (generally >3 cm) tumors with higher infiltrative potential when compared with typical carcinoids [4,26,37]. According to the latest WHO classification typical carcinoids have been described as tumors larger than 0.5 cm with 2 mitoses/2 mm² without necrotic areas, while atypical tumors are larger than 0.5 cm containing 2-10 mitoses/2 mm² with or without necrotic foci [4]. These tumors demonstrate most frequently organoid, and trabecular patterns, and also rosette formation, papillary, pseudoglandular, and follicular growth patterns, and fine fibrovascular stroma reflecting neuroendocrine differentiation. Tumor cells are uniform, polygonal-shaped, and contain moderately abundant cytoplasm with fine granular nuclear chromatin (Figure 4) [1,4,7,9,37-39]. In peripheral tumors spindle cells are apparently more dominant. However, in some tumors, cells contain melanin, and accumulation of amyloid can be observed. Rarely metaplastic bone or cartilage may be seen.

Atypical carcinoids have coarser granular chromatin, and more conspicuous nucleoli [1,6,15,21]. Though nuclear pleomorphism, and nuclear membrane irregularities are more frequently seen in these tumors relative to typical carcinoids, these characteristics have not any sensitivity, and specificity, and hence they are devoid of prognostic significance [10]. In atypical carcinoids usually, focal areas of necrosis are seen, occasionally they may appear as large zones. During resections focal areas of necrosis should be carefully sought for accurate typing. The field of view (FOV) with the highest number of mitoses should be evaluated. Number of mitoses at 2 mm² should be counted, rather than 10 x magnification as indicated in the previous WHO classification, and at least 2-10 mitoses should be detected. Because of the availability of different microscope models, number of fields of view which constitute a 2 mm² area of the tumor under great magnification should be calculated. If 2 or 10 (or closer to upper or lower limits) mitoses are detected in an area of 2 mm² then number of mitoses seen at at least 3 different sets of 2 mm² areas should be counted, and their average should be calculated [4].
Figure 4: Typical carcinoid tumor composed of uniform, polygonal-shaped cells with fine granular nuclear chromatin, demonstrating organoid, and trabecular patterns on microscopic examination (H&E, 100).
Pulmonary carcinoids are stained positively with some neuroendocrine markers as chromogranin A, synaptophysin, and CD56. Eighty percent of the cases are pancytokeratin-positive, however they are typically HMW-CK-negative. Apart from scarce number of cases most of them are TTF-1 negative [4]. However using different TTF-1 clones varying rates of positivities have been obtained. For example Matoso et al. reported that SPT24 clone of TTF-1 could identify 60% of the cases with carcinoid but 8G7G3 clone identify only 17.4% [40]. Similarly La Rosa et al. demonstrated that when compared with 8G7G3/1 clone, SPT24 clone can most frequently identify peripheral carcinoids, and less differentiated neuroendocrine carcinomas [41]. In atypical carcinoids all of the neuroendocrine markers may not be positive, so using a panel of neuroendocrine markers has been recommended [10]. In 50% of typical, and atypical carcinoids estrogen receptor-positivity has been observed [10,42].

In the most recent WHO classification for typing of pulmonary NET, Ki67 is not a diagnostic criterion, while inclusion of Ki-67 proliferation index in pathology reports apart from mitosis, and necrosis is recommended [7]. Ki-67 proliferation index is especially used to differentiate low-intermediate grade NETs from poorly differentiated neuroendocrine carcinomas in samples of biopsy or cytology demonstrating crush artefacts [4,7,43-46]. Generally, Ki67 proliferation index is observed in less than 20% of carcinoid tumors (usually less than 5% of typical, and less than 20% of atypical carcinoids), 40-80% of LCNECs, and 50-100% of SCCs. Pelosi et al. recommended determination of Ki67 by examining warm points under 40x magnification or by counting at least 2000 cells at a FOV of 2 mm² [43]. In carcinoids threshold value changes between 2.5, and 30%, and typical, and atypical carcinoids with overlapping Ki67 values have been detected. The possible explanation of inability to differentiate effectively between biologically similar tumor variants using Ki67 proliferation index can be related to the presence of a weak correlation between Ki67 proliferation index, and number of mitoses [43,47,48]. Therefore for the discrimination between typical and atypical carcinoids, Ki67 proliferation index cannot be used because of unreliable results [7,43].

Large-cell neuroendocrine carcinomas form large mass lesions frequently on the periphery, and upper lobe of the lung. Their greatest diameters have been reported to vary between 0.9, and 12 cm, and they are necrotic tumors invading frequently pleura, and chest wall. In some cases bleeding can be seen, but cavitations are rarely observed [49]. Large-cell neuroendocrine carcinomas may show patterns, indicating neuroendocrine differentiation such as organoid, nested, and trabecular patterns, rosette formation, and peripheral palisading, multiple rosette-like structures, and solid nests forming a cribriform pattern (Figure 5). Tumor cells are larger than the size of three lymphocytes, and have polygonal configuration, moderately abundant cytoplasm, coarse granular chromatin, and prominent nucleoli. For the establishment of diagnosis more than 10 mitoses should be detected per 2 mm². Approximately 70-75, and rarely less than 30 mitoses are detected per 2 mm² FOV. Ki67 proliferation index ranges between 40, and 80%. Necrotic areas are observed as large zones, and infarcts, however punctate areas of necrosis may be also
observed [4,16,50,51]. Combined LCNECs contain components of adenocarcinoma, squamous cell carcinoma, spindle cell carcinoma and/or giant cell carcinoma. If these components can be very well discerned, then any amount of tumor material suffices for diagnosis. Each component should be indicated in the histology report [4].

For the diagnosis of LCNEC, neuroendocrine differentiation should be confirmed. Takei et al. recommended combined use of three neuroendocrine biomarkers including (NCAM)/CD56, chromogranin A, and synaptophysin [17]. Positivity rates of these biomarkers in LCNEC have been reported as 92-100% for NCAM/CD56, 80-85% for chromogranin A, and 50-60 % for synaptophysin. However for the establishment of diagnosis, more than 10 % of the cells should be stained positively without doubt. Apart from NSE, positively stained one neuroendocrine marker usually establish the diagnosis [4]. In lung cancer NCAM/CD56 is a biomarker with lower specificity, but maximum sensitivity for neuroendocrine differentiation [52]. Chromogranin A, and synaptophysin are the most reliable stains which differentiate LCNEC from other non-neuroendocrine tumors with diagnostic accuracy [53-55]. Neuroendocrine markers tend to be negative in poorly differentiated neuroendocrine tumors, and LCNECs where all of these three biomarkers do not positively stained are interpreted as poorly differentiated tumors with adverse prognosis. Nearly half of the cases demonstrate TTF-1 expression and seldom naps in a positivity has been reported [4,56,57].

Figure 5: Large cell neuroendocrine carcinoma composed of tumor cells with moderately abundant cytoplasm, coarse granular chromatin, and prominent nucleoli and showed organoid pattern, rosette formation, and peripheral palisading (H&E, X200).
Since majority of small-cell carcinomas are not amenable to surgical resection, limited number of information are available concerning their macros copy. More than half of the cases are observed as perihilar masses with intense lymph node involvement. Five percent of the cases present with solitary peripheral nodule. Tumor progresses all along the bronchial mucosa, and extrinsically compress bronchi leading to narrowing, and occlusion of the bronchial lumen [33]. It may contain large necrotic areas, however cavitation, and cystic degeneration are rarely seen [21]. Under light microscope, SCCs frequently show laminar diffuse growth pattern and composed of small-sized, round or spindle-shaped tumor cells with narrow cytoplasm and fine granular chromatin (Figure 6). Nuclear molding is frequent, and cell contours are rarely discerned. Less frequently structural patterns as nests, trabeculae, peripheral palisading, and rosette-like formations are seen [8,21,22,24]. Crush artefact leads to oozing or spreading of nuclear chromatin. Necrosis is frequent, and widespread. On necrotic areas, basophilic deposits of DNA stemming from necrotic cellular debris on vessel walls may be seen (Azzopardi effect). Pelosi et al. examined the characteristics which differentiates SCCs from carcinoid tumors in small biopsy samples, and reported that SCCs contain thick-walled vascular channels with glomeruloid configuration, while carcinoid tumors comprise of thin-walled dilated blood vessels [45].

![Figure 6](image-url): Microscopic examination of SCC showed diffuse growth pattern of small-sized, round or spindle-shaped tumor cells with narrow cytoplasm and fine granular chromatin (H&E, X200).
Relatively higher number of mitoses are seen in SCCs (min ≥ 10 mitoses /2 mm² and median, 80 mitoses/2 mm²). In the study by Pelosi et al. Ki67 index was found to range between 60, and 96% (mean ± SD, 81.2±13.4 %). It should not be forgotten that proliferation rate will decrease in biopsy materials obtained from SCCs after chemotherapy, and number of mitoses may drop to the level seen in carcinoid tumors [8].

As a practical rule in SCCs, tumor cell diameter equals to or smaller than the sum of nearly 2-3 lymphocytes. However in SCCs a spectrum of cellular morphology is seen, and large cells approaching to the size of large-cell carcinoma cells may be observed. In 1981 WHO classification, they were classified as intermediate subtype, however in the most recent WHO guidelines this closure has not found any acceptance. In their morphometric studies, Travis et al. suggested that, in SCCs a continuum in spectrum towards large cell is evident, and the investigators recommend that different ion between these entities should not be based only on cell size but also multiple number of morphologic criteria should be taken into account [8,58]. Another issue which was indicated in the studies by Travis , and Nicholson is that the size of the biopsy sample also effects the size of the tumor cell [8,21]. In larger specimens, especially in open lung biopsy, and resections, SCC cells appear to be larger than their normal size. The explanation of this phenomenon is that especially in large-sized well-fixed materials, crush artefacts are rarely seen, cytoplasm is better preserved, and cell contours are very well discerned.

Almost all cases of small-cell carcinomas display punctate, paranuclear or diffuse cytoplasmic staining with broad-spectrum cytokeratine-antibody mixtures as AE1/AE3 cocktail, CAM5.2, and MNF116. SCCs never stain with high-molecular weight cytokeratin cocktails [6]. In the diagnosis of small-cell carcinoma, for the confirmation of neuroendocrine differentiation a panel of neuroendocrine markers may be used. The least specific, but the most sensitive marker is NCAM/CD56. Though variable staining percentages have been reported in different series, one may say that in SCCs synaptophysin, and CD56 display diffuse, and strong, while chromogranin demonstrates focal, and weak staining [4]. Sands et al. reported that SCCs display more strong staining with CD56, rather than synaptophysin, and chromogranin, while for carcinoid tumors the opposite is more frequently observed [59]. Travis indicated that in less than 10% of the cases, all neuroendocrine markers may be negative, however if the tumor demonstrates diagnostic morphologic characteristics, then the diagnosis of SCC should be established [8].

Especially when less specific clones are used 90-95 % of SCCs are TTF-1-positive [4]. In different studies this rate generally varies between 70, and 90 percent. It should not be forgotten that in 44-80% of non-pulmonary small-cell carcinomas TTF-1 positivity may be detected [8]. Ki67 proliferation index is extremely high in SCCs ranging between 50-100% with a median value of 85 percent [4,8,43].
PROGNOSIS AND SURVIVAL

Although typical, and atypical carcinoids are respectively low, and intermediate grade tumors, they both have the capacity to develop metastases into regional or distant lymph nodes. Garcia-Yuste et al. performed a large-scale multicenter study, and observed lymph node metastases in 9, and 36% of the cases with typical, and atypical carcinoids, respectively [31]. Local recurrences were seen in 2% of typical, and 7% of atypical carcinoids, while distant metastases were observed in 4% of typical, and 26% of atypical carcinoids [60]. Median 5-year survival rates have been reported as 90% for typical, and 60% for atypical carcinoids [4]. Steuer et al. detected metastases in 20% of atypical carcinoids at the time of diagnosis, and reported 1-, and 3-year survival rates as 86 and 67%, respectively [12]. Daddi et al. found age, history of smoking, and lymph node involvement as statistically significant prognostic factors in multivariate analyses [61].

Beasley et al. demonstrated that cases manifesting 6-10 mitoses/2 mm² were more aggressive than those with 2-5 mitoses/2 mm², and indicated that cases with tumor size ≥ 3.5 cm had even more aggressive course [62]. Multiple number of studies have been performed on the prognostic significance of Ki67 in especially low-intermediate grade NETs. Pelosi et al. indicated that threshold values of Ki67 index ranging between 2.5, and 5.8% group typical and atypical carcinoids accurately and irrespective of their morphologic characteristics into different prognostic categories [43]. However further studies should be performed on prognostic value of Ki67, because of relevant controversial results, and lack of any consensus on this issue [4,47]. In carcinoid tumors TNM classification is important in prognosis, and for accurate pathologic staging of cases candidate for surgical resection, systematic nodal dissection is recommended [4].

Large-cell neuroendocrine carcinomas have been reported to be biologically aggressive as SCCs, and have a poorer prognosis than NSCCs with a 5-year median survival rates ranging between 13, and 57 percent. Even in early stages, tumor recurrences, and distant metastases rapidly develop despite complete resection [16,60,63]. Iyoda et al. reported 5-year median survival rate as 35.5%, and 5-year median disease-free survival rate as 27.4%, for all stages, and indicated that great majority of relapses develop within the first 2 years [64]. In their study because of limited number of cases available, specific prognostic, and predictive markers could not be identified, however LCNECs with CD56/kromogranin A/synaptophysin negativity were interpreted as tumors with poor prognosis [56].

Median survival in small-cell carcinomas is 12.7 months, while in metastatic disease 2-year survival rate is 10%, and in non-metastatic disease 5-year-survival rate is nearly 25 percent [6]. Advanced stage disease, poor performance status (3-4), weight loss, increased levels of biomarkers (ie. increased LDH levels) related to aggressive disease are poor prognostic factors. Young age, good performance status, normal creatinine and LDH levels, a single metastatic region have been associated with improved prognosis in various studies [22].
TREATMENT

In pulmonary typical and atypical carcinoids surgical resection is the only curative option and treatment alternative. In central tumors, bronchial sleeve resection or sleeve lobectomy, and lung-sparing surgery, and in peripheral tumors lobectomy or sleeve segmentectomy together with complete anatomic resection are recommended. In compliance with IASLC recommendations, lymph node dissection should be applied on 6 mediastinal lymph node regions including 3 subcarinal nodes so as to achieve R0 resection [7,32,65]. It has been also suggested that radical resection is possible for all regions, and also in metastatic disease with limited involvement surgical treatment directed at affected areas has been recommended.

Medical treatment includes somatostatin analogues, mTOR inhibitors, cytostatic chemotherapy, and radio-peptide receptor targeted treatment alternatives. Ten percent of typical, and atypical tumors are hormone-producing functional tumors, and for the symptomatic control of these tumors somatostatin analogues as octreotide, and lanreotide are gold standard treatment modalities [7,32,60]. As an inhibitor of mTOR pathway, everolimus is a target-directed, FDA approved therapeutic agent to be used in the treatment of progressive, non-functional, well-differentiated pulmonary NETs [7,9,32]. NCCN NET guidelines recommend systemic cytotoxic chemotherapy in patients with advanced metastatic disease without any chance of curative treatment. NCCN Small Cell Lung Cancer guidelines recommend cisplatin-etoposide regimen for stage II/III atypical carcinoids. However ENETS guidelines recommend systemic chemotherapy in following conditions: (1) atypical carcinoids with Ki67 values within ULN (15%) (2) rapidly progressive tumors within 3-6 months (3) cases with somatostatin-receptor negativity or cases unresponsive to other treatments [32].

Because of scarce number of cases, a standard treatment regimen is not available in LCNECs. Despite multimodal treatment approaches used in advanced stage carcinomas, 5-year mean survival rates are very low, and even in stage 1 patients higher postoperative recurrence rates are observed [3]. In stage 1, and 2 patients, surgery should be the primary treatment regimen. However even in stage 1 cases, surgery as monotherapy is said to be inadequate treatment. In early stages, in the absence of lymph node metastases, lobectomy or pneumonectomy is preferred for their potential favorable effect on survival [18]. Whereas, many cases are not amenable to surgical resection because of local or systemic dissemination. In a study by Veronesi et al. in surgically removed 144 stage 1 cases with LCNEC, the authors demonstrated that, though not statistically significant pre and postoperative chemotherapy ensured a favorable disease progression [66]. Neoadjuvant platinum-based regimen is preferred for the treatment of potentially resectable tumors. Rossi et al. demonstrated effectiveness of adjuvant therapy with cisplatin and etoposide [67]. In many studies, effectiveness of platinum, and chemotherapy regimens used for SCC has been reported [3,36,60]. In a recently published study by Derks et al. superiority of platinum-gemcitabine chemotherapy over platinum-pemetrexed, and platinum-etoposide treatment was
demonstrated [23]. In these extremely rare tumors, optimal multimodal treatments should be evaluated, and developed using multidisciplinary approach in multicenter prospective studies [18,63-67].

When compared with other pulmonary tumors SCCs are more sensitive to chemotherapy, and radiotherapy. In borderline success, combined chemotherapy and thoracic radiotherapy is the standard treatment approach, while platinum-etoposide combination is the most prevalently used regimen. In patients with widespread disease, and brain metastases, chemotherapy is instituted based on neurologic symptoms of the patient before, and after whole brain radiotherapy. According to the guideline published by National Comprehensive Cancer Network (NCCN) in the year 2012, in cases with borderline pulmonary cancer, if nodal involvement is not seen, then complete resection, chemotherapy, thoracic, and mediastinal radiotherapy, and prophylactic cranial chemotherapy are employed. According to assessments in NCCN Guidelines Version 2.2014 Small Cell Lung Cancer, cases other than stage 1 NCNN patients do not benefit from surgery [21,22].

CONCLUSION

Pulmonary neuroendocrine tumors (NETs) have a broad range of clinicopathologic spectrum, and show variable histopathological characteristics, and biological behaviors. Until now, they have been increasing in incidence. But as compared to NSCLCs, fewer researches have been done about neuroendocrine tumors of the lung. Recently new genetic aberrations for pulmonary NETs have been identified and they would be promising targets to develop useful diagnostic markers and also treatment options. Increased awareness, new markers for accurate diagnosis and controlled clinical trials of patients with lung NET are needed to deal with these tumors.

References


