Classification and Imaging Findings of Lung Neoplasms

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Introduction

Lung cancer is one of the most important avoidable causes of death in the developed and developing world. Early in the disease, the relative lack of symptoms frequently results in delayed diagnosis, with more than 80% of patients found to have advanced disease at the time of diagnosis.[1] The mortality rate from lung cancer has risen proportionally to the smoking rate in men and women in the 20th century.[2] It became the leading cause of cancer-related death around the 1950s in men and has risen dramatically in women starting the 1960s, eventually surpassing deaths from breast cancer in women around 1987.[2,3] In the last decades, the classification of lung cancer has significantly improved as a result of efforts toward understanding the morphologic and molecular features of these tumors. The end goal of improved classification is to provide precision in diagnosis and guide toward the optimal treatment for each patient.

Lung cancer has been historically categorized into 2 main histologic groups: non−small-cell lung cancer (NSCLC, 85% of all lung cancers) and small-cell lung cancer (SCLC, 15% of all lung cancers).[4] Despite its neuroendocrine origin, carcinoid tumors have a much better prognosis, and they deserve to be classified separately from SCLC. NSCLCs were mainly subcategorized into squamous cell carcinoma (SCC), adenocarcinoma, and large cell carcinoma (LCC). Until 2008, the combination of simple histopathologic differentiation (NSCLCs vs SCLC) along with clinical staging

was enough to make treatment decisions, as there were no therapeutic implications of classifying NSCLC tumors further. However, a large study of patients with lung cancer in Japan demonstrated a significant better survival of adenocarcinoma compared to other subtypes of NSCLCs.[5] Additionally, Scagliotti et al published the first prospective trial that showed a significant survival difference based on histologic typing (adenocarcinoma vs SCC) in advanced NSCLC.[6] The more recent molecular-target treatments, particularly in adenocarcinoma, such as epidermal growth factor receptors (EGFR) and anaplastic lymphoma kinase (ALK) inhibitors that resulted in improved response compared to standard chemotherapy.[7]

Those facts, along with the accumulating evidence on lung cancer genetics and molecular targets, suggest that lung cancer is a heterogeneous group of diseases even within the same histological subtype.[4] The correlation of radiological findings with molecular targets has been rising, which increases the importance of diagnostic imaging in the management of lung neoplasms. The goal of this study is to review the classification of lung neoplasms correlating to imaging findings and molecular targets.

The 2015 WHO Classification

The WHO histopathologic classification of lung neoplasms was recently updated in 2015. Compared to previous versions, there was a significant improvement diagnostic precision by relying not only on light microscopy, but also on immunohistochemical (IHC) analysis.[8] The importance of differentiating adenocarcinoma from SCC, instead of labeling them all under the NSCLC umbrella as the 2004 WHO classification, was also emphasized in the 2015 WHO classification as it has significant consequences for treatment choice. Given the advances in our understanding of selected targets for therapy, the 2015 WHO classification also recommends molecular testing on many lung neoplasms, particularly in adenocarcinomas, which may help personalize treatment strategies.[8]

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Table 1 Summary of the Five Categories of Lung Neoplasms and Main Histologic Types*

Epithelial Tumors	Mesenchymal Tumors
Adenocarcinoma	Pulmonary hamartoma
Squamous cell carcinoma	Chondroma
Small cell carcinoma	PEComatous tumors
Carcinoid tumors (typical and atypical)	Lymphohistiocytic tumors
Large cell carcinoma	Extranodal MALT lymphoma
Adenosquamous carcinoma	Diffuse large cell lymphoma
Sarcomatoid carcinomas	Tumors of ectopic origin
Other and unclassified carcinomas	Germ cell tumors (teratomas)
Salivary gland-type tumors	Intrapulmonary thymoma
Papillomas	Melanoma
Adenomas	Metastatic tumors

MALT, mucosa-associated lymphoid tissue.

*Histologic types are not restricted to those above. For the more comprehensible classification, please refer to the original 2015 WHO Classification table. Adapted from Travis et al. The 2015 World Health Organization Classification of Lung Tumors.[8]

A total of 5 main categories of lung tumors are described in the 2015 classification: epithelial tumors, mesenchymal tumors, lymphohistiocytic tumors, tumors of ectopic origin, and metastatic tumors (Table 1). Each category is composed of many histological types (eg, epithelial tumors—adenocarcinoma, SCC, SCLC), which can be further classified into histological subtypes (eg, adenocarcinoma—lepidic adenocarcinoma, acinar adenocarcinoma, papillary adenocarcinoma).[8] The most common histologic types of lung cancer encountered in clinical practice are discussed below.

Adenocarcinoma

Demographics

Adenocarcinoma is the most common histologic type of lung cancer, accounting for approximately 40% of all cases.[9] The prevalence of adenocarcinoma in women is at least 2 times higher than SCC (45%-54% vs 11%-21% of SCC), whereas in men, the distribution of adenocarcinoma and SCC is roughly equal (38% vs 33% of SCC).[10,11] Part of the explanation for this consistent difference in the distribution of histologic types between men and women is attributed to different sex-related susceptibilities to molecular aberrations caused by smoking and other carcinogens.[12] EGFR mutations, for example, are associated with adenocarcinoma and more frequently found in women.[13]

Although cigarette smoking is more commonly associated with SCC and SCLC, it also represents a significant risk factor for adenocarcinoma.[9] The incidence of adenocarcinoma is increasing in smokers, which has been associated with deeper inhalation of cigarettes with lower levels of tar and nicotine, allowing a more peripheral distribution of the smoke in the lungs.[9,14,15] Although adenocarcinoma is more common in never smokers (compared to other histologic types), it is also associated with smoking. Adenocarcinoma is the most common histologic type seen in never smokers (62% adenocarcinoma vs 18% of SCC).[16,17] This is thought to be related to the environmental factors (eg, pollution, second-hand smoking) and many already identified hormonal and genetic factors, although no unique susceptibility gene has been designated to explain the higher prevalence of adenocarcinoma in never smokers.[9,16,18]

Histopathology

Lung adenocarcinoma is an epithelial neoplasm with glandular differentiation or mucin production. However, adenocarcinoma comprises a spectrum of radiologic and morphologic features explained by the different histologic patterns and degrees of differentiation of this neoplasia. The spectrum of adenocarcinoma has been categorized into 3 main groups of lesions by the 2011 IASLC/ATS/ERS and 2015 WHO classification of lung adenocarcinoma: preinvasive, minimally invasive, and invasive adenocarcinoma.[8,19] Also, another key change in the 2011 review was the discontinuation of the term "bronchioloalveolar carcinoma" (BAC), which was used to describe well-differentiated adenocarcinoma associated with better outcomes.[19,20] Now the term BAC was replaced by adenocarcinoma in situ (AIS) and minimally invasive carcinoma (MIA), both with a near 100% chance of disease-specific survival upon resection.[19]

The preinvasive group is represented by 2 benign lesions—atypical adenomatous hyperplasia (AAH) and AIS. Since the 2011 IASLC/ATS/ERS review, AIS is recognized as a second preinvasive lesion along with AAH, as both patterns are associated with a 100% disease-specific survival upon complete resection.[19] A summary of the histopathologic and imaging characteristics of both lesions is shown in Table 2. AAH is a small (usually ≤5 mm) proliferation of mildly to moderately atypical nonmucinous cells (pneumocytes II or club cells) within alveolar walls and respiratory bronchioles. AIS is a small adenocarcinoma (≤3 cm) with restricted bronchoalveolar growth with no invasion, which may be described as "lepidic growth." The word "lepidic," derived from the Greek word for "skin" or "membrane," describes tumoral growth that lines alveolar walls, instead of filling its contents.[21] Both lesions usually present as a small pure ground-glass nodule (GGN) nodule on CT, so the differentiation of AAH and AIS is only possible after histologic evaluation.

MIAs are mostly mucinous adenocarcinomas (≤3 cm) with a predominantly bronchoalveolar growth with a limited invasion of the myofibroblastic stroma of ≤5 mm in its greatest dimension.[8,19] If the tumor invades lymphatics, blood vessels, air spaces, or pleura, the neoplasia should be labeled as an invasive adenocarcinoma.[8] Observational studies show that complete resection of MIA is associated with a near 100% disease-specific survival.[19] As opposed to AAH (nonmucinous only), AIS and MIA can sometimes be classified as mucinous if mucin-producing cells are noted within the tumor, in which case different clinical and radiologic features are observed. Tumors greater than 3 cm with either no invasion (AIS pattern) or ≤5 mm invasion (MIA pattern) should be classified as "lepidic adenocarcinoma, suspected AIS or MIA."[8]

Table 2 Summary of Histologic and Imaging Findings of the Adenocarcinoma Spectrum

	Preinvasive		Minimally Invasive	Invasive Adenocarcinoma
	AAH	AIS	MIA	
Growth pattern	Pure lepidic		Predominantly lepidic	Invasive with mixture of histologic subtypes, or lepidic growth >3cm
Size	≤5 mm	≤3 cm	≤3 cm	>3 cm or less (if invasive as below)
Invasion	Absent	Absent	Myofibroblastic invasion ≤5 mm	Myofibroblastic invasion >5 mm lymphatic, blood, pleura, or airspace
Disease survival	~100%		~100%	Depending on clinical staging, histologic type, and genetics
Imaging	Mostly pure GGN		Part-solid or pure GGN	Solid nodule (↑ acinar, solid) Subsolid, pure GGN (↑ lepidic) Multifocal consolidation (↑ mucinous)

AAH, atypical adenomatous hyperplasia; AIS, adenocarcinoma in situ; GGN, ground-glass nodule; MIA, minimally invasive adenocarcinoma; ↑, more often associated with.

Invasive adenocarcinoma comprises the large group of neoplasms that presents one or more of the following characteristics: size >3 cm, deep stromal invasion (>5 mm), invasion of surrounding tissue (vessel, lymphatics, air space or pleura), or the presence of tumor necrosis.[8] They are composed of a heterogeneous mixture of several histologic subtypes (eg, lepidic, acinar, papillary), thus quantifying the "predominant" subtype is vital to adenocarcinoma characterization, which has shown some correlation to prognosis.[22,23]

Imaging Features

Overall, the imaging spectrum of lung adenocarcinoma has a good correlation to histologic findings (Fig. 1). Attempting to differentiate invasive from noninvasive lesions is one of the primary roles of imaging. AAH always present as a GGN due to its pure lepidic growth, usually measuring <5 mm, although larger nodules of up to 10 mm have been described (Fig. 2).[24] AIS often presents as a small GGN and most measure between 5 and 20 mm. MIA is frequently described as a part-solid nodule with a solid component of less than 5 mm, in which the solid part often corresponds to its invasive component.[25] However, the solid component can often be larger than 5 mm due to factors other than invasive neoplasia, such as fibrosis, mucus, or collapse that can also cause a solid appearance.[26] Even AIS may eventually become a part-solid nodule in the presence of alveolar collapse, fibrosis, etc. Although mucinous AIS and MIA are rare, they may also present as solid nodules.[27]

Invasive adenocarcinoma usually appears as a solid or part-solid nodule, and less frequently as a pure GGN, which corresponds to their heterogeneous mix of histologic
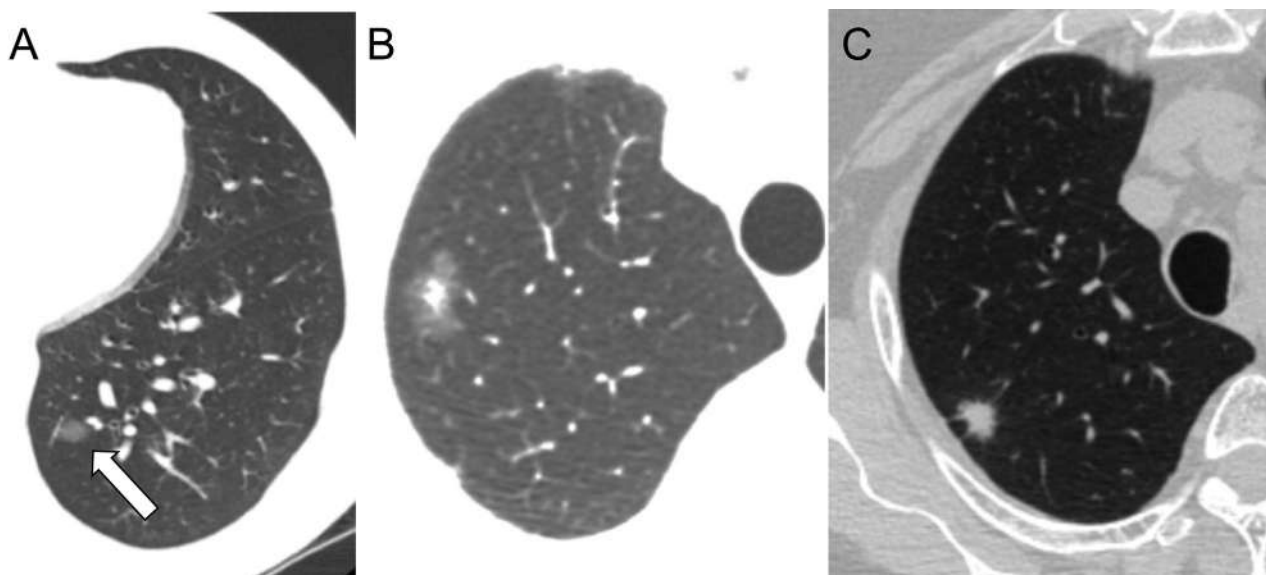

Figure 1 The radiological spectrum of lung adenocarcinoma. (A) Axial CT shows pure ground-glass nodule measuring 7 mm nodule in the left lower lobe (arrow), diagnosed as adenocarcinoma in situ. (B) Axial CT depicts a part-solid right upper lobe nodule measuring 12 mm with a 4 mm solid component. Final diagnosis was minimally invasive adenocarcinoma. (C) Axial CT shows a solid pulmonary nodule of 1.1 cm with spiculated margins in the periphery of the right superior lobe. Patient was later diagnosed with invasive adenocarcinoma.
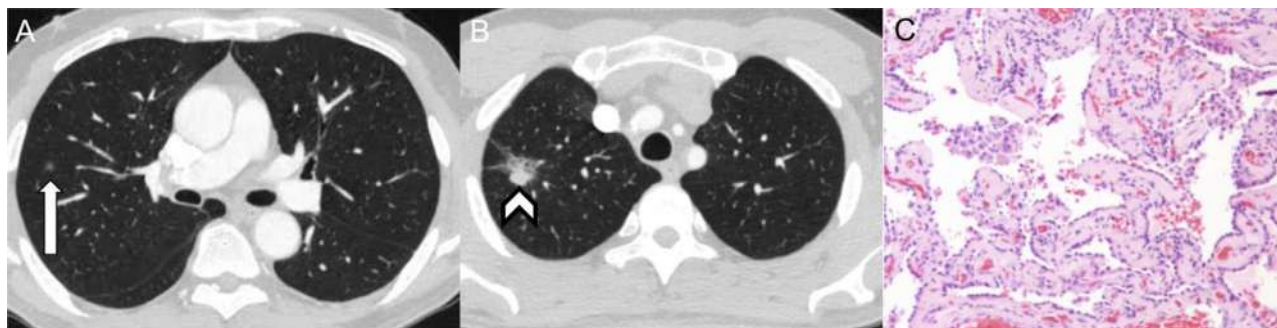
Figure 2 A 67-year-old man with atypical adenomatous hyperplasia and synchronous invasive adenocarcinoma. (A) Axial CT depicts a small pure ground-glass nodule (arrow) measuring 4 mm in the anterior segment of the right upper lobe. (B) Axial CT shows a subsolid nodule with spiculated margins (arrowhead) in the apical segment of the right upper lobe measuring 2.0 cm with a solid component of 1.0 cm. CT-guided transcutaneous lung biopsy revealed a poorly differentiated adenocarcinoma and the patient underwent a right upper lobectomy. (C) Microscopy of the small ground-glass nodule revealed a lesion with less than 5 mm showing proliferation of mild to moderately atypical low columnar cells lining alveoli, compatible with atypical adenomatous hyperplasia.

Figure 3 A 76-year-old male undergoing imaging staging of a renal cell carcinoma. (A) Chest radiography depicts a large round mass in the upper part of the left hemithorax. (B) Axial postcontrast CT exhibits a large pulmonary mass with heterogeneous contrast enhancement and extensive hypoattenuating areas corresponding to necrosis. (C) CT-guided transthoracic needle biopsy revealed solid sheets of large polygonal malignant cells with prominent nucleoli, eosinophilic cytoplasm, and positive TTF-1 staining.

patterns. Invasive mucinous adenocarcinoma often presents as multifocal and multilobar consolidations.[28,29] While lepidic predominant adenocarcinomas tend to appear as pure GGN or part-solid nodules with a high proportion of GGN, acinar and solid patterns are usually associated with solid nodules or masses (Fig. 3).[30] Invasive adenocarcinoma may also present tumor cavitation mainly due to intratumoral bronchiectasis, whereas cavitation of SCC is usually attributed to tumor necrosis.[31]

Therefore, there is a significant overlap between imaging features of AAH, AIS, MIA, and invasive adenocarcinoma. Thus, the risk of invasive adenocarcinoma should not be diminished despite the possibly "benign" characteristics of a nodule (Fig. 4). For instance, recent studies have shown that the prevalence of invasive adenocarcinoma in persistent pure GGNs is about 25%-40%.[32-35] However, there are some clues that may support one histologic diagnosis over another. Pure GGNs with larger diameters (>10 mm) favor the diagnosis of invasive adenocarcinoma,[33,35] although no specific threshold by itself is indicative of referral for biopsy in such cases.[36] However, numerous reports have demonstrated that

pure GGNs ≥6 mm can be safely followed every 1-2 years for 5 years with no change in mortality.[37] Persistent part-solid nodule with a solid component >5 mm is associated with a higher likelihood of invasive disease, thus further diagnostic evaluation is recommended.[37]

SCC
Demographics

SCC accounts for approximately 20% of cases of lung cancer.[9] It was the most frequent histologic type of lung cancer, peaking in the United States in the mid—1980s (affecting 17 per 100,000 person-years), but has now declined to around 11 per 100,000 person—years between 2006 and 2010, while adenocarcinoma incidence rose in the same period.[38] Although all major types of lung cancer are significantly associated with smoking, SCC and SCLC have the strongest overall association with it.[39] The risk of cancer declines with smoking cessation, more rapidly for SCC than adenocarcinoma, which
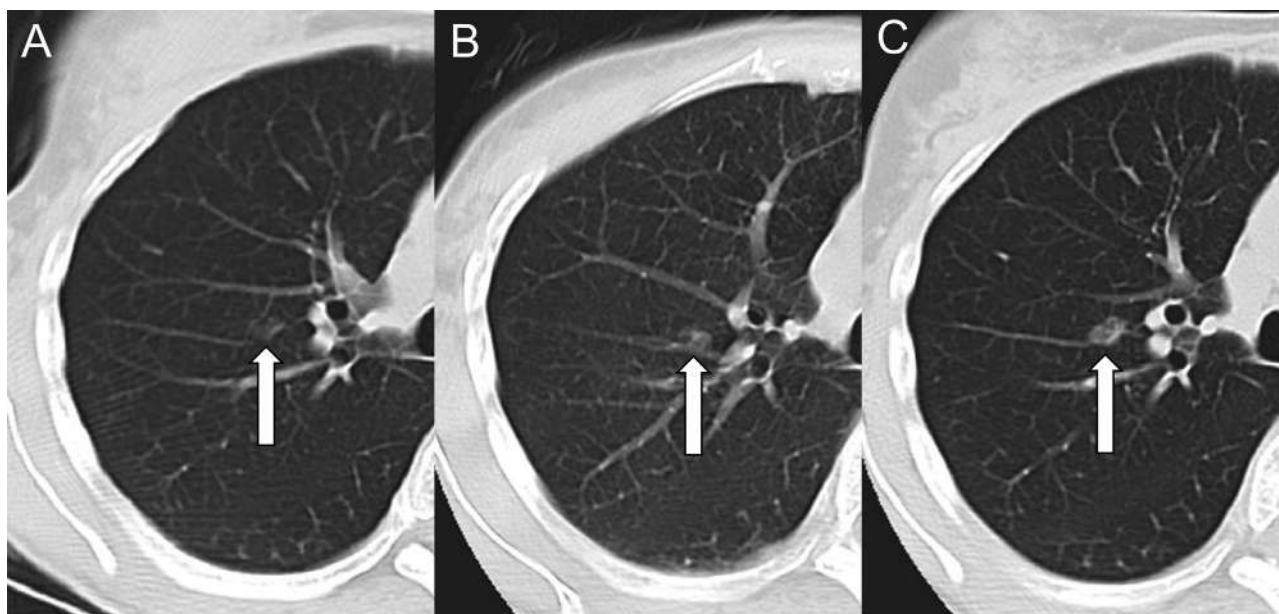
Figure 4 Imaging follow-up of a small ground-glass nodule. (A) Axial CT scan depicts a small pure ground-glass nodule measuring 10 mm nodule centrally located in the right upper lobe. (B) Imaging follow-up in 12 months showed persistence of the nodule and mild increase in attenuation. (C) In the second year of follow-up, the nodule increased in size (13 mm) and attenuation. Patient underwent right upper lobectomy and histopathologic analysis revealed an invasive adenocarcinoma with predominantly lepidic pattern.

is one of the contributing factors to the recent change in the relative frequency of each histologic type.[39] SCC has historically prevailed in males and most often presents in the older population (>60 years).[40,41]

Histopathology

SCC arises from epithelial cells and is morphologically characterized by the proliferation of atypical and often pleomorphic squamous cells. Formerly, SCC was defined by the presence of morphologic features of squamous cell differentiation, such as keratinization or intercellular bridges between adjacent cells on light microscopic study.[4] Thus, many poorly differentiated tumors without these characteristics that expressed squamous cell markers were previously categorized in other histologic groups (eg, LCCs). However, the 2015 WHO classification redefined the SCC subtypes as keratinizing, nonkeratinizing, and basaloid carcinoma. With the addition of IHC analysis, poorly differentiated carcinomas that do not present microscopic features of keratinization or intercellular bridges are now classified as nonkeratinizing SCC when exhibiting defining SCC markers such as p40, CK5/6, and p63.[4,8] Albeit there is no clear prognostic relevance in categorizing SCC in these subtypes, the growing scientific data on molecular profiling may eventually lead to new targeted treatments.[42]

Imaging Features

More than two-thirds of SCC present as nodules or masses centrally located within the lung, involving lobar or segmental bronchi.[43] SCC is the histologic group that most commonly

shows cavitation; among all cases of cancerous cavitation in one series, SCC represented 82% of the sample.[44] The walls of these malignant cavities typically have irregular and thick margins.[44] Despite these classically described features, one-third of SCC present in the periphery of the parenchyma as a solid nodule or mass, usually with irregular margins, pleural indentation, and no calcification.[45] Secondary changes of peripheral lung and bronchi, such as obstructive pneumonia and atelectasis, are also frequently encountered because of the proximal location of these tumors (Fig. 5).[43]

Small Cell Lung Carcinoma

Demographics

SCLC is the third most common histologic type of lung cancer, accounting for approximately 15% of all lung cancer.[46] SCLC is strongly associated with heavy smoking, given that nearly all patients are current or former smokers, and it is rarely diagnosed in never smokers (less than 3% of all SCLC).[47] The median age at diagnosis is about 70 years.[48] Fortunately, the proportion of SCLC has gradually decreased in the last 30 years in the United States, especially among men.[46] There was a historical male predominance (2:1) in SCLC probably because of the higher smoking rates among men, which have gradually decreased over the years until 2002 when the male-to-female ratio equalized.[46] Other risk factors include exposure to substances such as polyaromatic hydrocarbons, halogenated ethers, radon, and arsenic.[49] SCLC is an aggressive and rapidly progressive tumor and as such around 60%-70% of patients first

Figure 5 Evaluation of a centrally located lung mass. (A) Axial CT reveals an infiltrative mass in the left upper lobe (arrow) with secondary atelectasis (arrowhead). (B) Gross specimen sample after left upper lobe lobectomy. (C) Histopathology revealed islands of large polygonal malignant cells containing keratin pearls and intercellular bridges compatible with keratinizing SCC.

diagnosed with SCLC have extensive disease with dismal prognosis.[48,50]

Histopathology

SCLC is pathologically, molecularly, and biologically very different from other lung cancers.[51] This neoplasia is part of the group of neuroendocrine tumors, along with large-cell neuroendocrine carcinoma (LCNEC) and carcinoid tumors.[8] The histologic hallmarks of SCLC are the presence of dense sheets of small cells with scant cytoplasm, ill-defined borders, nuclear molding, finely granular chromatin, and high mitotic index. Also, Ki-67 proliferation index is highly elevated on IHC.

Imaging Findings

Over 90% of SCLCs are located within the central aspect of the chest as they arise from the basal epithelium in a lobar or main bronchi.[52] SCLCs commonly manifest as large central mass with mediastinal or hilar lymphadenopathy (80%-90% of cases), as they rapidly metastasize to regional lymph nodes.[53,54] Occasionally, SCLCs can present as coalescent mediastinal lymphadenopathy without visualization of the primary tumor (Fig. 6).[53] Due to its central location, these tumors often compress the main bronchi, causing atelectasis or postobstructive pneumonia, and confine mediastinal structures such as the heart and the main vessels (eg, superior vena cava syndrome).[48,53,54] Pleural involvement is seen in up to 40% of patients, most commonly presenting as pleural effusion or pleural nodules with or without effusion.[55]

Contrast-enhanced CT allows for better visualization of the lesion and mediastinal or vascular involvement of the tumor. Thoracic MRI may also be used for the assessment of tumor extension to the mediastinum.[54] SCLC can also manifest in unusual manners (<10% of cases), such as a peripheral well-defined nodule or mass, an airspace opacity, or even as lymphangitic carcinomatosis.[48] Intratumoral calcifications can also be seen in approximately 20% of patients.[56]

Carcinoid Tumors
Demographics

Carcinoid tumors have been regarded as indolent tumors with favorable long-term survival after surgical resection, despite a higher mortality rate reported for atypical carcinoid.[57,58] They

Figure 6 A 55-year-old female presenting with anorexia. (A) Chest radiography reveals enlargement of the mediastinum. (B) Contrast-enhanced CT depicts lymph node enlargement in the subcarinal (arrowhead) and right hilar stations (arrow) and no visible parenchymal lesion. (C) Mediastinoscopy with lymph node sampling revealed round small blue cells with minimal cytoplasm, nuclear molding, and finely dispersed chromatin, compatible with small-cell lung carcinoma.
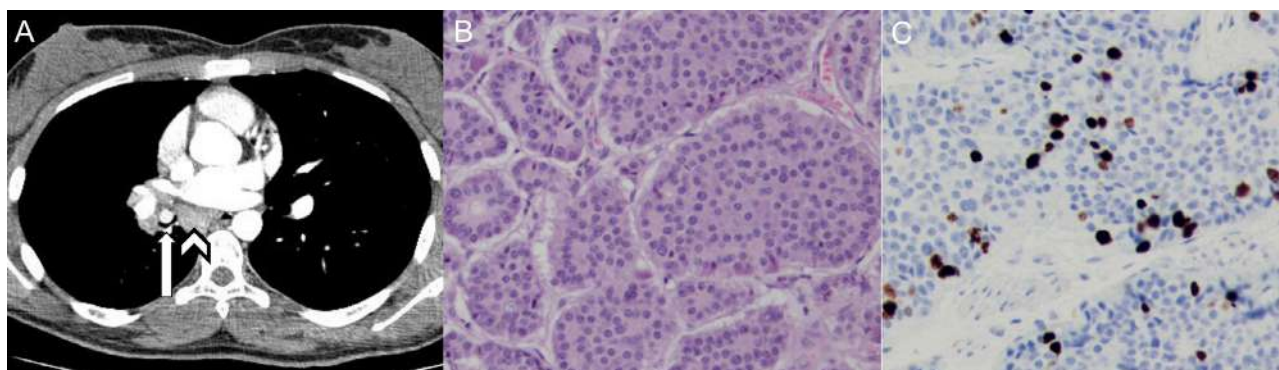
Figure 7 Evaluation of an endobronchial nodule. (A) Postcontrast axial CT shows a small endobronchial nodule with marked contrast enhancement in the right main bronchus (arrow) and subcarinal lymph node enlargement (arrowhead). (B) Histopathology revealed uniform tumor cells with a polygonal shape, round to oval nuclei with salt and pepper chromatin, inconspicuous nucleoli in an organoid and pseudoglandular pattern. Mitotic count was 5 per 2 mm^2. (C) Ki-67 staining revealed an 8% proliferative index, compatible with the diagnosis of atypical carcinoid tumor.

may arise in virtually any site in the body, but the lungs are one of the most common sites (25% of all carcinoid tumors).[59,60] The incidence of lung carcinoid is increasing over the years, probably due to better imaging techniques and increased surveillance to detect more asymptomatic tumors.[59,61] However, they still account for only 1% of all lung malignancies in adults.[62]

Previous reports have suggested an apparent predilection for females and whites, but these differences disappear in more age-adjusted incidence analysis.[58] The average age at diagnosis is around 50 years for typical carcinoid and 60 years for atypical.[57,63] Although smoking does not appear to have a causal relation to carcinoid compared to other lung cancer, it does increase the odds of developing this condition, especially the atypical subtype.[64]

Histopathology

Lung carcinoid is part of a spectrum of neuroendocrine tumors. If SCLC and LCNEC are high-grade and aggressive tumors, typical carcinoid is the low-grade and indolent tumor at the other end of the spectrum.[8] The biological behavior of atypical carcinoid lies in between those 2 groups. Both carcinoid tumors can appear as nests of uniform, polygonal cells with finely dispersed chromatin, and inconspicuous nucleoli. It is the mitotic rate and presence of necrosis that distinguishes between typical (<2 mitosis per 2 mm^2; no necrosis), atypical tumors (2-10 mitosis per 2 mm^2 or necrosis), and high-grade SCLC and LCNEC (>10 mitosis per 2 mm^2, median of 80/2 mm^2, frequent necrosis).[8] Ki-67 proliferative index is especially useful in biopsy samples where assessing mitotic count and necrosis may be difficult.[8,65]

Imaging Findings

Most carcinoid tumors are centrally located and arise from the lobar bronchi or mainstem bronchi (Fig. 7).[60] They are typically located close to the bifurcation area of the mainstem bronchi.[66] About 20%-30% occur distal to segmental bronchi and are socalled peripheral carcinoids.[48,66] Therefore, carcinoids usually

manifest on CT as an oval hilar or perihilar lesion often associated with an endobronchial component.[66,67] Imaging findings of typical and atypical are similar, except that atypical carcinoids are usually larger (mean diameter 3.6 vs 2.3 cm), more likely to occur in the periphery, and more likely to metastasize.[48]

Distal atelectasis or consolidations can also be seen due to airway obstruction. Because carcinoids are highly vascularized tumors, they frequently show marked and homogeneous enhancement on contrast-enhanced CT, which may also help to distinguish the tumor from adjacent atelectasis or consolidation.[66,67] Lymphadenopathy may be seen either due to hyperplasia from chronic distal infections or metastasis, the latter being more frequently encountered in atypical lesions.[67] Also, punctuate or diffuse calcifications can be seen in up to 30% of tumors.[68]

LCC

Demographics

LCC currently accounts for up to 2%-3% of all cases of lung cancer.[9,38,40] The incidence of LCC has started to decline over the years, probably because of the new criteria for the classification of poorly differentiated tumors and more routine use of IHC.[8] Many undifferentiated tumors were moved from the category of LCC to become a subtype of other histologic patterns according to the expression of specific IHC markers (eg, LCNEC is now classified as a neuroendocrine tumor). LCC has a male predominance, mean age at diagnosis of 60 years, and is strongly associated with smoking.[39,40,69]

Histopathology

LCC is a poorly differentiated neoplasm that lacks any clear squamous, glandular, and neuroendocrine differentiation by microscopy and IHC.[8] LCC is characterized by sheets of round to polygonal cells with prominent nucleoli and pale cytoplasm. Since 2015 WHO classification, poorly differentiated carcinomas are only classified as LCC if they lack defining

IHC markers, such as TTF-1 (adenomatous differentiation), p40 (squamous cell), or chromogranin (neuroendocrine).[8] Therefore, LCC should not be confused with LCNEC, as the latter expresses chromogranin and synaptophysin. LCC is a diagnosis of exclusion and cannot be accurately diagnosed on small biopsies or lymph node metastasis.

Imaging Features

LCC is typically described as a large peripheral mass (usually >4 cm) with lobulated or spiculated margins that often exhibit focal necrosis and cavitation.[44,70-72] However, many of the descriptive studies currently available were conducted when many undifferentiated tumors were categorized as subtypes of LCC. These studies are predominantly composed of cases of LCNEC, and therefore may not accurately represent the actual imaging findings of LCC. However, considering the aggressive behavior of these poorly differentiated tumors, it is very likely they mostly present as large masses with areas of necrosis and early metastasis, such as the LCNECs.

Genetics and Radiogenomics

With the current advances in lung cancer treatment, distinguishing adenocarcinoma from other histologic groups and testing the molecular profile of each tumor is crucial to guide tailored therapies for each patient.[8,73,74] Lung adenocarcinoma is the histologic group that more frequently expresses genetic mutations with already tested molecular-targeted therapy. The most frequently identified mutations in adenocarcinoma are the Kirsten rat sarcoma viral oncogene homolog (KRAS), EGFR, ALK, C-ros oncogene 1 (ROS-1), and BRAF. The genetic profile of adenocarcinoma often correlates to the histologic patterns: lepidic adenocarcinoma is often associated with EGFR mutation, whereas acinar, solid, and mucinous adenocarcinomas are more frequently KRAS mutated.[8] KRAS is also associated to approximately 40% of LCC cancers.[75]

Although KRAS mutations are the most prevalent adenocarcinoma mutation (around 30%) in the United States and Europe, there is no specific targeted therapy available for KRAS.[76] On the other hand, EGFR tyrosine-kinase inhibitors (TKIs) were the first molecular target in lung cancer.[73] Lung adenocarcinoma expressed EGFR mutations in around 20% of non-Asian patients and up to 50% of Asian patients.[77,78] Other individual targets of currently available molecular therapy are ALK, ROS-1, and BRAF, which may be present in up to 3%-5% of adenocarcinoma.[73,76] Last, SCLC rarely expresses any of the common adenocarcinoma mutations.[79] SCLC is characterized by nearly universal inactivation of 2 known tumors suppressor genes (TP53 and RB-1), for which no molecular targets are available.[80]

Radiogenomics refers to the relationship of the imaging features of a disease (eg, CT characteristics of a lung nodule) and its pattern of gene expression.[81] The field is rapidly growing in evidences, particularly in lung cancer, because of the development of genotype-directed therapy for NSCLC.[82,83] The correlation of gene expression and imaging can be performed either using quantitative computer-derived imaging features (eg, edge sharpness) or semantic terms (eg, lobulated margins). Gevaert et al demonstrated that both computer-derived features and semantic terms are associated with the expression of specific gene clusters.[82] For instance, the presence of air bronchogram was related to the overexpression of KRAS genes, which is a marker of poor prognosis in NSCLC.[82] EGFR mutations have been correlated to different CT findings in adenocarcinoma, such as a high ratio of ground-glass component of a part-solid nodule, bubblelike lucency, and pleural retraction.[84] A recent deep learning model using quantitative CT features has shown superior predictive performance (74% accuracy) for EGFR mutation in adenocarcinoma compared to a model using semantic features (62% accuracy).[85] Mutations on ALK, ROS-1, and other genes associated with lung cancer were also evaluated in several other studies in the literature.[86-88] However, there is no imaging finding or assessment that replaces molecular analysis.

Conclusion

Lung cancers encompass a heterogeneous group of neoplasms with different histologic, genetic, and imaging features. The 2015 WHO classification incorporates the advances in understanding the pathologic and molecular features of lung tumors. This improves diagnostic accuracy and ultimately works in synchrony with precision medicine in cancer care. Imaging will continue to have a crucial role in the diagnostic evaluation of lung lesions, aided by advances in radiogenomics and artificial intelligence, and continue contributing to the prediction of molecular expression in lung cancer.

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