Lung Cancer

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Lung cancer is the most widespread neoplasm in the world and the first cause of cancer death for males; its incidence is globally increasing in the female population. The mortality rate is increasing in Asia and Africa and decreasing in Western countries, possibly due to the advancement of more precise and more readily available diagnostic tools and the development of new therapeutic strategies.

A complete surgical resection is associated with improved survival, but only about 25–60% of patients are eligible for intervention at the time of diagnosis. The most important prognostic factor in lung cancer is cancer stage at diagnosis. The TNM (Tumor, Nodes, Metastasis) system that evaluates the cancer's anatomical extension is the most widely used and internationally accepted tumor staging system. Since its first publication by Pierre Denoix in 1943, it has been constantly updated. In 2017, the International Association for the Study of Lung Cancer (IASLC) issued the 8th edition of the "TNM classification of malignant tumors," based on a larger sample size from several reference centers.

Traditionally, the TNM applied only to Non-Small Cell Lung Cancer (NSCLC) that accounts for 85% of lung cancer cases and would not be applicable to microcytomas or Small Cell Lung Cancer (SCLC). Indeed, for SCLC only "local" and "extended" disease are distinguished, often leaving systemic chemotherapy as the only viable option. However, since the 7th edition it can be used to evaluate SCLC as well.

Imaging plays a key role in the management of lung cancer and is highly reliable, thanks to the constant development of new diagnostic techniques, with PET and PET-CT being worth particular mention.

The clinical staging of neoplasms through imaging (cT, cN, cM) should not be confused with the definitive histological or pathological staging occurring after surgical resection or biopsy (pT, pN, pM). When surgically resected, a description of

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the resection margins (R1: cancer cells present microscopically at the resection margin; R0: disease-free margins) should also be included. The correlation between clinical and pathological staging is around 35–55% and is expected to increase in the future. The current TNM is summarized in Tables 5.1, 5.2, and 5.3 (adapted from the 8th Edition Lung Cancer TNM Staging Summary) (Fig. 5.1).

Table 5.1 T staging, 8th TNM edition

T—primary tumor *(greatest diameter guides size assessment)*		
TX		Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0		No evidence of primary tumor
Tis		Carcinoma in situ
T1		≤3 cm Surrounded by lung or visceral pleura Without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)
	T1mi	Minimally invasive (≤5 mm) adenocarcinoma
	T1a	≤1 cm
	T1b	Between 1 and 2 cm
	T1c	Between 2 and ≤3 cm
T2		>3 cm but ≤5 cm Or tumor with any of the following features: – Involves main bronchus regardless of distance to the carina, but without involving it – Invades visceral pleura – Associated with atelectasis or obstructive pneumonitis that extends to the hilar region, either in part or the entire lung
	T2a	>3 cm but ≤4 cm
	T2b	>4 cm but ≤5 cm
T3		>5 cm but ≤7 cm Or invading any of the following: – chest wall (including superior sulcus tumors) – phrenic nerve – parietal pericardium Or associated separate tumor nodule(s) in the same lobe as the primary
T4		>7 cm Or invading any of the following: – diaphragm – mediastinum – heart – great vessels – trachea – recurrent laryngeal nerve – esophagus – vertebral body – carina Separate tumor nodule(s) in a different ipsilateral lobe to that of the primary

Modified from: Goldstraw P, Chansky K, Crowley J, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the stage grouping in the forthcoming (8th) edition of the TNM classification of lung cancer. J Thorac Oncol. 2016;11:39–51, with permission from Elsevier

Table 5.2 N staging, 8th TNM edition

N—regional lymph nodes *(also counts when involvement by direct contact occurs)*		
NX		Regional lymph nodes not assessable
N0		No metastasis to regional lymph nodes
N1		Metastasis in following *ipsilateral* lymph nodes: – peribronchial – hilar – intrapulmonary
	N1a	Involvement of one N1 station nodes
	N1b	Involvement of multiple N1 stations nodes
N2		Metastasis in the following *ipsilateral* lymph nodes: – mediastinal – subcarinal
	N2a1	Involvement of a single N2 station nodes without N1 involvement
	N2a2	Involvement of a single N2 station nodes with N1 involvement
	N2b	Involvement of multiple N2 stations nodes
N3		Metastasis in the following *ipsilateral*: – scalene – supraclavicular OR following *contralateral* lymph nodes: – mediastinal – hilar – scalene – supraclavicular

Modified from: Goldstraw P, Chansky K, Crowley J, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the stage grouping in the forthcoming (8th) edition of the TNM classification of lung cancer. J Thorac Oncol. 2016;11:39–51, with permission from Elsevier

Table 5.3 M staging, 8th TNM edition

M—distant metastasis		
M0		No distant metastasis
M1		Distant metastasis
	M1a	Separate tumor nodule(s) in contralateral lobe Pleural or pericardial nodules Malignant pleural or pericardial effusion
	M1b	Single extrathoracic in single organ (or single non-regional lymph node)
	M1c	Multiple extrathoracic metastases in ≥1 organ

Modified from: Goldstraw P, Chansky K, Crowley J, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the stage grouping in the forthcoming (8th) edition of the TNM classification of lung cancer. J Thorac Oncol. 2016;11:39–51, with permission from Elsevier

Staging

Subsets of certain T, N, and M categories can be grouped into different stages of the disease, as these share similar treatment options and prognosis. In Table 5.4 and 5.5, we list a simplified and a more detailed version.

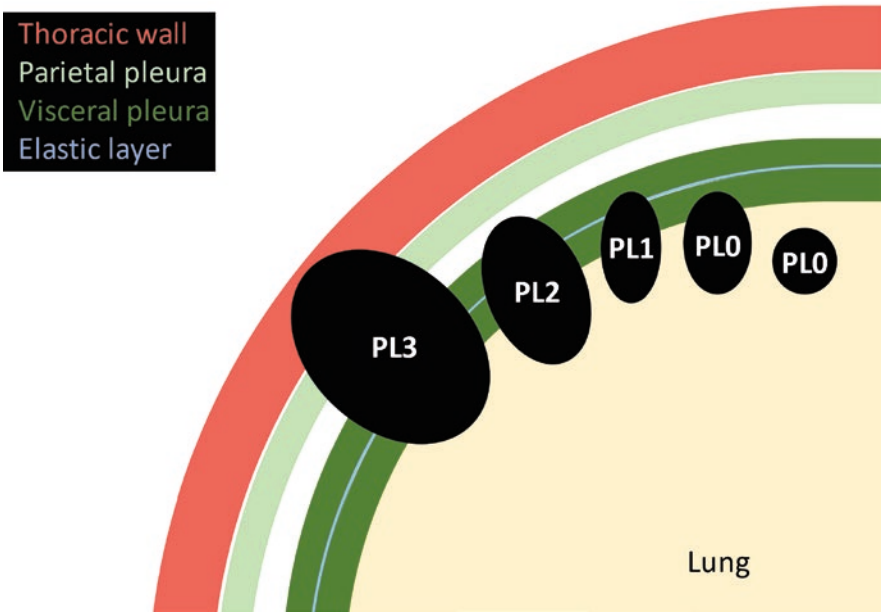


Fig. 5.1 *PL0*, tumor within the subpleural lung parenchyma OR invading superficially into the pleural connective tissue; *PL1*, tumor invades beyond the elastic layer; *PL2*, tumor invading the pleural pseudocavity; *PL3*, tumor invading any component of the parietal pleura. PL1 & PL2 = T2 and PL3 = T3

Table 5.4 Simplified TNM staging

	N0	N1	N2	N3
T1	IA	IIB	IIIA	IIIB
T2a	IB	IIB	IIIA	IIIB
T2b	IIA	IIB	IIIA	IIIB
T3	IIB	IIIA	IIIB	IIIC
T4	IIIA	IIIA	IIIB	IIIC
M1a	IVA	IVA	IVA	IVA
M1b	IVA	IVA	IVA	IVA
M1c	IVB	IVB	IVB	IVB

Modified from: Detterbeck, Frank C, et al. The eighth edition lung cancer stage classification. Chest. 2017;151.1:193–203, with permission from Elsevier

Table 5.5 Detailed TNM staging

Stage	T	N	M
Occult carcinoma	TX	N0	M0
0	Tis		
IA1	T1mi or T1a		
IA2	T1b		
IA3	T1c		
IB	T2a		
IIA	T2b		
IIB	Any T1 or T2	N1	
	T3	N0	
IIIA	Any T1 or T2	N2	
	T3 or T4	N1	
	T4	N0	
IIIB	Any T1 or T2	N3	
	T3 or T4	N2	
IIIC	T3 or T4	N3	
IVA	Any T	Any N	M1a or M1b
IVB	Any T	Any N	M1c

Modified from: Goldstraw P, Chansky K, Crowley J, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the stage grouping in the forthcoming (8th) edition of the TNM classification of lung cancer. J Thorac Oncol. 2016;11:39–51, with permission from Elsevier

Table 5.6 Lung adenocarcinoma classification IASLC/ATS/ERS 2011

Pre-invasive lesions: • Atypical adenomatous hyperplasia AAH (<5 mm) • Adenocarcinoma in situ AIS (<3 cm, no invasion)
Minimally invasive adenocarcinoma MIA (<3 cm, invasion <5 mm)
Invasive adenocarcinoma (>3 cm, invasion >5 mm)

Invasive Pulmonary Adenocarcinoma

Pulmonary adenocarcinoma is the most common variant among lung tumors, accounting for more than 50% of all histotypes. It belongs to the category of Non-Small Cell Lung Cancer (NSCLC), is found more frequently in women and non-smokers and develops predominantly in the lung periphery. A new classification for adenocarcinoma (IASLC/ATS/ERS, 2011, Table 5.6) has recently been proposed (and been confirmed in the latest TNM) and includes, in addition to invasive adenocarcinoma, pre-invasive forms such as atypical adenomatous hyperplasia, adenocarcinoma in situ (previously "bronchioalveolar carcinoma"), and minimally invasive adenocarcinoma.

In *Atypical Adenomatous Hyperplasia (AAH)*, atypical type II pneumocytes or Clara cells start proliferating locally along the alveolar wall and respiratory bronchioles. Radiologically, this usually appears as a small non-solid nodule (up to 5 mm) that can remain stable for years.

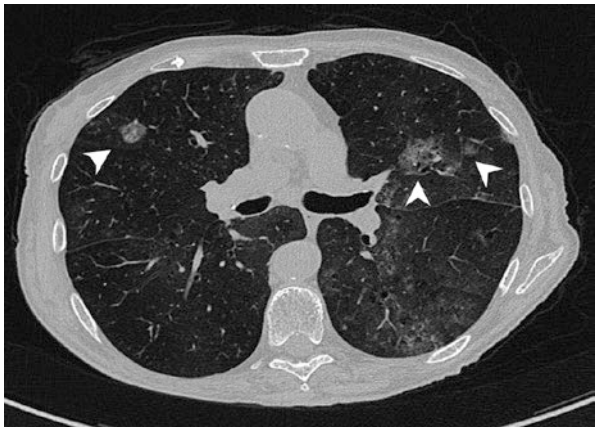


Fig. 5.2 Invasive pulmonary adenocarcinoma: multiple mixed parenchymal nodules (*arrowheads*)

In situ adenocarcinoma (ISA), existing as a mucinous or a non-mucinous variant, is formed by neoplastic cells that tend to spread along pre-existing anatomical structures, preserving an intact alveolar architecture without stromal or vascular invasion, a process known as lepidic growth. Radiologically, it appears as a localized, non-infiltrating lesion of up to 3 cm in size, generally non-solid and only rarely mixed.

Minimally invasive adenocarcinoma (MIA) has a predominantly lepidic growth, the overall size is <3 cm with an invasive component smaller than 5 mm. On CT scans, it appears mixed, prevalently non-solid with small solid elements (<5 mm).

Invasive adenocarcinoma includes several histologic patterns such as lepidic, acinar, papillary, micropapillary, and solid; however, the mixed variants are very common. Radiologically, it may occur as a single pulmonary nodule, a segmental or lobar parenchymal consolidation area, or predominantly interstitial diffuse lung disease. In the latter case, multiple more-or-less defined parenchymal solid or mixed nodules in a bronchocentric distribution pattern are the most frequent CT finding, and are often associated with a halo sign; multiple areas of parenchymal consolidation with air bronchograms is another possible presentation (Figs. 5.2 and 5.3).

Based solely on a CT scan, it can be very difficult to distinguish a primary pulmonary adenocarcinoma from diffuse alveolar metastases; in such cases, other key diagnostic criteria need to be evaluated, such as concurrent extrapulmonary tumors and/or mediastinal or thoracic lymphadenopathies located in sites that are not typical of primary pulmonary neoplasms.

Primary Syn- and Metachronous Lung Tumors

A non-negligible percentage (~8%) of newly diagnosed lung tumors arises in patients with a history of cancer, be it thoracic or extrathoracic.

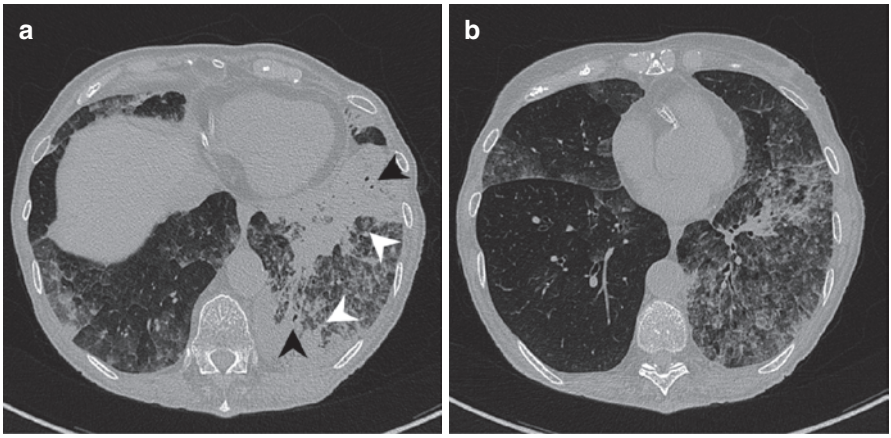


Fig. 5.3 Invasive pulmonary adenocarcinoma: (**a**) Parenchymal consolidations (*white arrowheads*) in a lobar/segmental distribution with air bronchograms (*black arrowheads*), (**b**) Diffuse interstitial involvement of the left lower lobe

Table 5.7 Martini and Melamed criteria for the definition of second primary lung cancer

Synchronous MPLC	Metachronous MPLC
A. Physically distinct and separate tumors	A. Histologically different
B. Histotype:	B. Histologically the same, if:
1. Different	1. Tumor-free interval between the neoplasms ≥2 years
2. Same but in different segment, lobe, or lung if: (a) Origin from carcinoma in situ (b) No evidence of carcinoma in common lymphatics (c) No extrapulmonary metastases at the time of diagnosis	2. Origin from carcinoma in situ 3. Second tumor in different lobe or lung but: (a) No evidence of carcinoma in common lymphatics (b) No extrapulmonary metastases at the time of diagnosis

Multiple Primary Lung Cancer (MPLC) cases are increasing in number, both because of improvements in diagnostic techniques and increased survival of oncologic patients.

Multiple primary lung tumors can be both synchronous and metachronous and because of their similar histologic characteristics it can be particularly difficult to distinguish them from metastases. This difficulty is further enhanced within areas of previous radiotherapy that alters tissue morphology.

The distinction between primary, synchronous, metachronous lung cancer, and intrapulmonary metastases is currently based on well-defined clinical and pathological criteria (Tables 5.7, 5.8, and 5.9).

New molecular and genomic analyses can aid in clearly differentiating between these; this is especially important for the correct choice of treatment that may be surgical as a first line in a second primary lung cancer.

Table 5.8 Modified criteria by Antakli et al. for the definition of second primary lung cancer

A. Different histological conditions
B. Same histological conditions with two or more of the following: 1. Anatomically distinct 2. Associated pre-malignant lesion 3. No systemic metastases 4. No mediastinal spread 5. Different DNA ploidy

Table 5.9 Modified criteria by Shen et al. for the definition of second primary lung cancer

A. Same histology, anatomically separated: 1. Cancers in different lobes 2. No N2, 3 involvement 3. No systemic metastases
B. Same histology, temporally separated: 1. Time interval between appearance of cancers ≥4 years 2. No systemic metastases from any tumor
C. Different histology: 1. Different histotype 2. Different molecular genetic characteristics 3. Arising separately from foci of carcinoma in situ

Lung Lymphoma

Lung lymphoma describes the involvement of the pulmonary parenchyma by a lymphoma. This can occur through two main mechanisms:

Secondary pulmonary lymphoma: the most common form, found in about 4% of patients with Non-Hodgkin Lymphoma (NHL). It is caused by hematogenous spread of the disease (both Hodgkin and Non-Hodgkin Lymphoma) or direct invasion of the pulmonary parenchyma from contiguous hilar or mediastinal lymph nodes. This disease is, thus, the progression of a known hematologic disorder arising from the mediastinum or other extrathoracic locations.

Primary pulmonary lymphoma: rarely encountered, it represents only 3–4% of extranodal lymphomas and 0.5–1% of all lung tumors. Lesions are found within the pulmonary parenchyma without extrapulmonary manifestations. Primary lung lymphomas include three main classes: low- and high-grade B-cell lung lymphoma and lymphomatoid granulomatosis.

Pulmonary lymphomas may appear as multiple bilateral, sometimes bronchocentric, nodules, diffuse opacities with a reticulonodular pattern, or parenchymal consolidation areas that may contain cavities or air bronchograms (Fig. 5.4). Pleural thickening and pleural effusion can be associated with such findings.

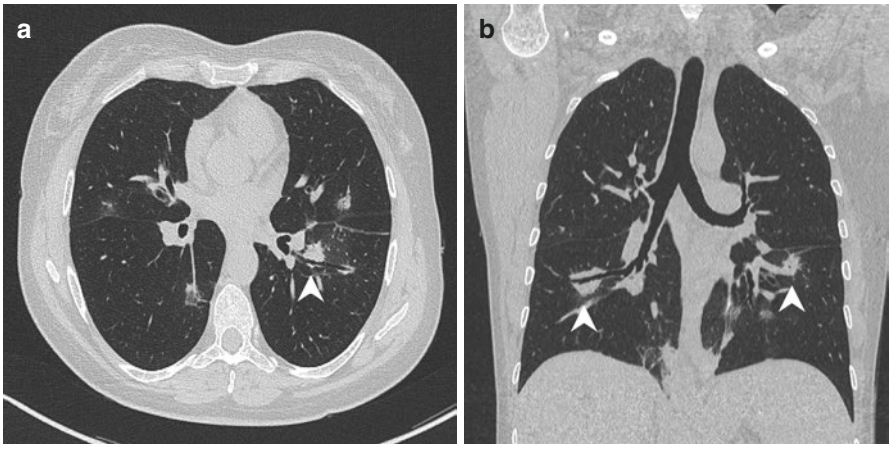


Fig. 5.4 Pulmonary lymphoma: bilateral parenchymal nodules, some of which bronchocentric (*arrowheads*)

Kaposi's Sarcoma

Kaposi's sarcoma is a mesenchymal tumor of medium to low aggressiveness that involves the vascular and lymphatic system. In about a third of Kaposi's sarcoma patients, there is lung involvement with nodular and interstitial pattern. On CT scans, ill-defined "flame-shaped" nodules are seen bilaterally. They are neither calcific, nor cavitary, often bronchocentric, and found in a symmetrical fashion in the parahilar and basal regions; surrounding semisolid irregular areas, thickening of the interlobular septa, pleural effusion, and lymphadenopathy may occur.

Metastases

A very high percentage (84–98%) of multiple lung lesions are metastatic in origin. Pulmonary metastases are very common and result from hematogenous or lymphatic dissemination from lung, breast, gastrointestinal, soft tissues, bone, and genitourinary neoplasms.

Hematogenous metastases are solid nodules, roughly rounded, of varying size, and more commonly found in the lung periphery. Peculiar characteristics can be related to specific primary cancer histotypes:

- Miliary: numerous tiny nodules spread over the entire lung fields are more common in melanoma, medullary thyroid cancer, and renal cancer (Fig. 5.5).
- Large (up to more than 10 cm): typical of sarcoma, colorectal and renal cancer, and melanoma (Fig. 5.6).
- Cavitated: more common in squamous cell carcinoma of the head and neck, cervix and bladder, gastric adenocarcinoma, and sarcoma (Fig. 5.7).

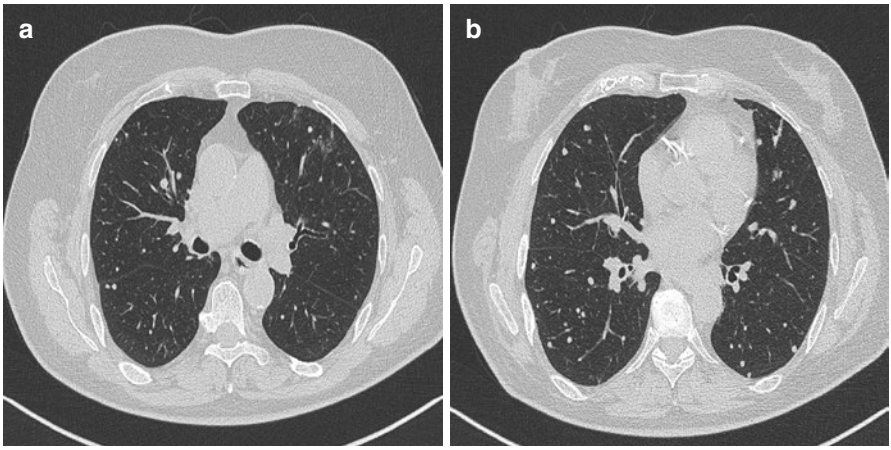
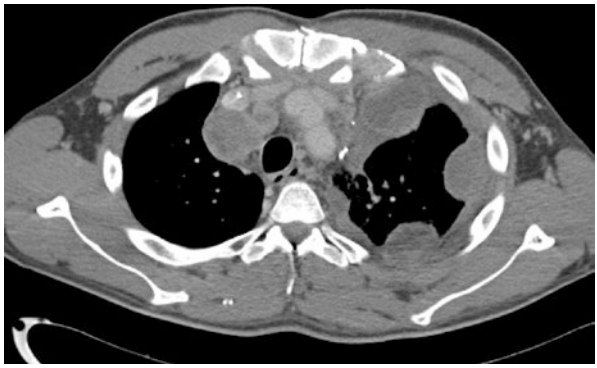


Fig. 5.5 Metastases secondary to medullary thyroid cancer

Fig. 5.6 Metastases secondary to sarcoma



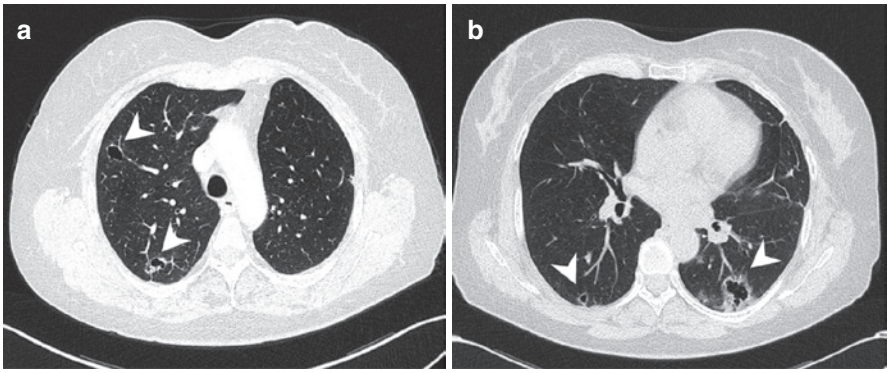


Fig. 5.7 Cavitated metastases secondary to cervical cancer (*arrowheads*)

- Calcific: typical of osteosarcoma, chondrosarcoma, papillary thyroid cancer and mucinous cancers of the gastrointestinal tract, breast, and ovaries; intranodular calcifications may be the result of chemotherapy (Fig. 5.8).
- Lepidic growth: uncommon, can be attributed to the spread of pulmonary adenocarcinoma and gastrointestinal adenocarcinomas. They present as areas of consolidation resembling pneumonia, sometimes with air bronchograms; they can also appear as semisolid nodules with a peripheral halo.
- Hemorrhagic: with peripheral "halo sign," most commonly found in highly vascularized tumors, such as choriocarcinomas, angiosarcomas, and melanomas (Fig. 5.9).

Lymphogenous metastases present with a diffuse interstitial infiltration with reticulonodular pattern, as seen in carcinomatous lymphangitis. A micronodular, irregular thickening of both the interlobular septa and peribronchovascular interstitium occurs and is sometimes associated with pleural carcinomatosis and spread

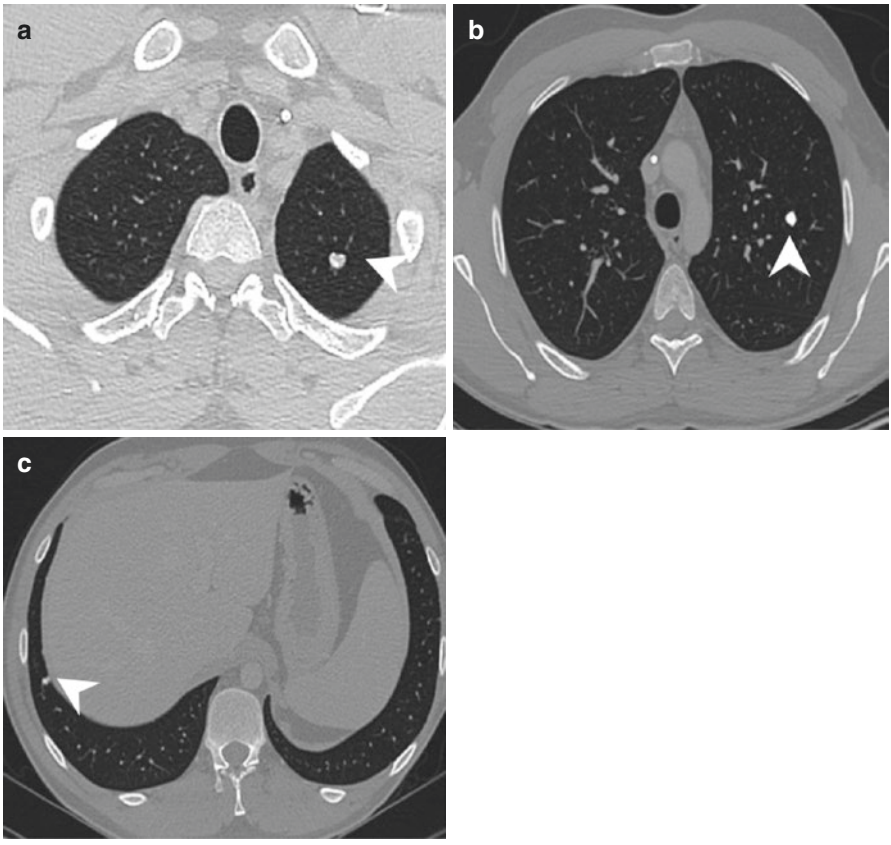


Fig. 5.8 Calcified metastases secondary to mucinous tumor (*arrowheads*)

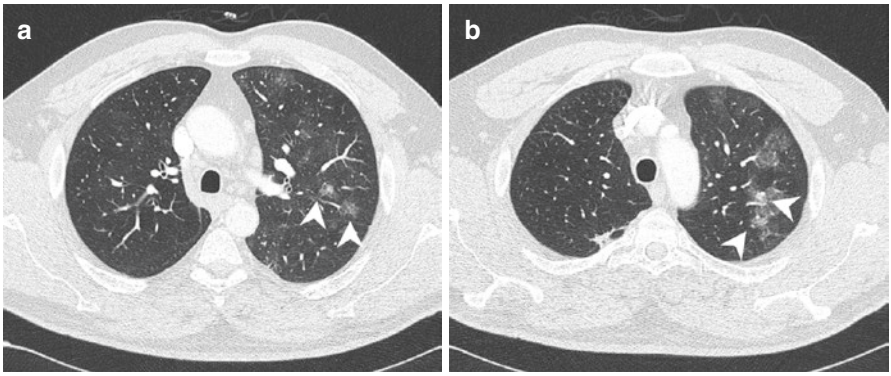


Fig. 5.9 Hemorrhagic metastases secondary to melanoma (*arrowheads*)

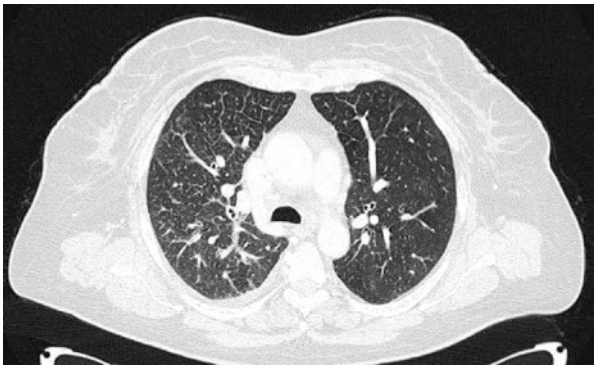


Fig. 5.10 Carcinomatous lymphangitis secondary to breast cancer

along the fissures. This is most commonly observed in adenocarcinomas of the stomach, breast, and pancreas (Fig. 5.10).

Resectable and Unresectable Disease

Evaluating the resectability of a lung cancer is a complex analytical process; the criteria to be used are still heavily debated. Imaging has a central role and only rarely histology is necessary to evaluate the extent of disease.

The new TNM may be helpful in both prognostic stratification and evaluating the resectability of a lung cancer. In general, stages I and II are always resectable while stage IV is by definition inoperable (Table 5.10). Stages IIIA and IIIB describe a "locally advanced" disease without distant metastases. In these cases, an evaluation of the patient's individual characteristics is necessary to decide the best therapeutic strategy.

Table 5.10 Stage and resectability

Stage	Resectable?
Ia	Yes
Ib	
IIa	
IIb	
IIIa	Selected patients
IIIb	No
IV	

Types of Resection

Surgery is planned based on the tumor characteristics and patient compliance.

Minimal resections such as **segmentectomy** or **wedge resection** are an option for stage I lung cancer. While wedge resection provides better postoperative compliance with a lower incidence of respiratory failure in patients with reduced pulmonary function, segmentectomy shows better results in terms of lower locoregional recurrence rates. These improved outcomes may be due to a complete removal of the lymphatic vessels that drain the tumor, not performed during wedge resections.

Most lung tumors are treated with **lobectomy**, which results in better oncological outcomes than the previously listed methods; when not sufficient for complete eradication of the neoplasm, **pneumonectomy** is performed.

Pneumonectomy is generally indicated when neoplastic tissue infiltrates the major or minor fissure, resulting in involvement of both upper and lower lobes. In addition, the infiltration of hilar structures, such as the main pulmonary artery, upper and lower pulmonary veins, and/or the main bronchus, makes a pneumonectomy mandatory. A special exception is the infiltration of the main bronchus only; here, a lobectomy can be performed after a sleeve resection with bronchoplasty. Likewise, a focal involvement of the main pulmonary artery can be treated with resection and angioplasty. Before pneumonectomies, an evaluation of the patient's fitness for surgery is needed, especially in cases of heart failure and low pulmonary reserve.

Resectability Considering the Extension of the Primitive Tumor

Mediastinal Involvement

Despite being T4 (stage III, locally advanced disease), a focal involvement of the mediastinal pleura and/or fat does not preclude surgical resection. However, whenever the removal of a large proportion of mediastinal fatty tissue is to be expected, this should be considered as a condition of non-resectability because of the high rate of locoregional recurrence.

On CT scans, mediastinal involvement is defined as:

- contact margins of >3 cm between tumor and mediastinum
- tumor extends into mediastinal adipose tissue
- pericardial and pleural thickening

Unfortunately, CT scans has low accuracy in diagnosing minimal mediastinal infiltrations. When this is suspected, inducing a pneumothorax and scanning at maximum inhalation and exhalation have been reported to increase sensitivity. Infiltration of vital structures (heart, great vessels, esophagus, vertebrae, or trachea) is generally a contraindication to surgery. Imaging criteria for infiltration are contact around >90° of the aorta, no adipose tissue between tumor and mediastinal structures, presence of mass effect. Some authors reported that CT and MRI scans are equally valid in evaluating mediastinal infiltration; however, both methods offer low accuracy since infiltration and contiguity are often being hard to distinguish.

There are some exceptions in case of infiltration of vital structures where surgery can still be a therapeutic option: when the carina is infiltrated, it is sometimes possible to resect the distal 3–4 cm of the trachea with pneumonectomy and sleeve resection with bronchoplasty (with termino-terminal anastomosis between the contralateral main bronchus and the trachea). Furthermore, a small portion of the left atrium can be resected if infiltrated. If the disease extends to the intrapericardial segment of the pulmonary arteries, it can be resectable if the portions not involved are long enough for clamping (Fig. 5.15). When only the tunica adventitia of the aorta is involved, it is possible to perform an accurate adventitial dissection. The infiltration of the upper vena cava can be treated by using grafts. Finally, a focal infiltration of a vertebral body can be removed "en-bloc."

Chest Wall Involvement

Stoelben and Ludwig have shown that the invasion of the chest wall is rare, affecting 5% of patients that underwent resection of lung cancer; in T3N0M0 patients treated with surgery the survival is good, even when the tumor size was above 7 cm (T4 according to 8th TNM, which the study predates). Therefore, the invasion of the chest wall generally does not preclude resection.

Several authors have demonstrated a marked improvement in survival when patients with invasion of the thoracic wall underwent surgery with negative resection margins, even when N2. On CT scans, the only certain criterion for diagnosing chest wall infiltration is the direct visualization of extension outside of the rib cage, with or without rib or vertebral erosion. Inducing a pneumothorax can help visualizing a parietal invasion, similarly to mediastinal invasions. With Pancoast's tumors, MRI has better sensitivity than CT in evaluating surrounding structures. When an infiltration of the upper fissure is suspected, many consider radio- and chemotherapy before submitting the patient to surgery.

Infiltration of the Diaphragm

Patients with diaphragm infiltration, in good general health and no lymph node involvement, should be resectable with "en bloc" removal of the diaphragm, as suggested by many authors.

Rocco et al. have reported that in cases of diaphragmatic infiltration removal with wide resection margins, followed by the placement of a diaphragmatic artificial prosthesis, can be an excellent strategy; the authors reported a five-year survival of 20%.

Resection Considering Lymph Node Involvement

Patients with ipsilateral mediastinal metastases (N2) are considered resectable with the exception of a "bulky" involvement. However, there is no clear definition of "bulky" disease. In the literature, the most frequently used expressions are: dominant lymph node with a short axis >25 mm (according to other authors >30 mm); lymph nodes with extracapsular extension of neoplastic tissue; two or more N2 lymph nodes involved (Fig. 5.11).

Patients with "bulky" N2 nodal disease undergo neoadjuvant chemotherapy and only if the lymph node masses regress properly can surgery be considered; otherwise, the treatment of choice will be radiotherapy.

Patients with contralateral mediastinal and hilar, scalene or supraclavicular lymphadenopathies (N3) are placed in stage IIIB and are therefore considered inoperable (Figs. 5.12, 5.13, 5.14, 5.15, and 5.16).

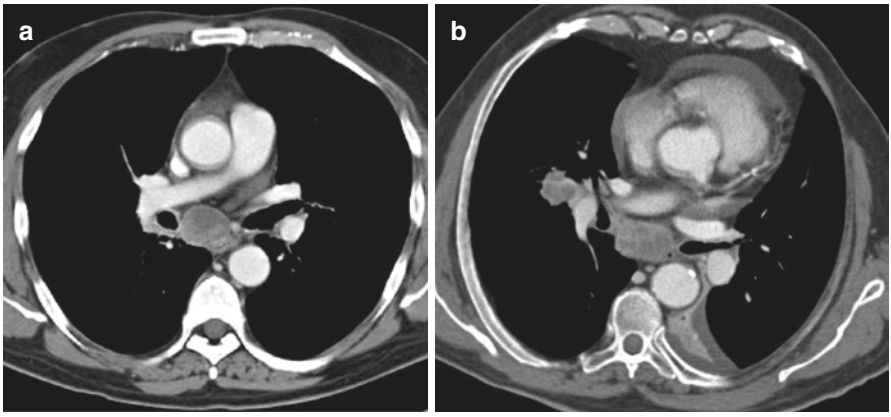


Fig. 5.11 "Bulky" N2: (**a**) Subcarinal lymph node >25 mm. (**b**) Subcarinal and ipsilateral hilar lymph node >25 mm

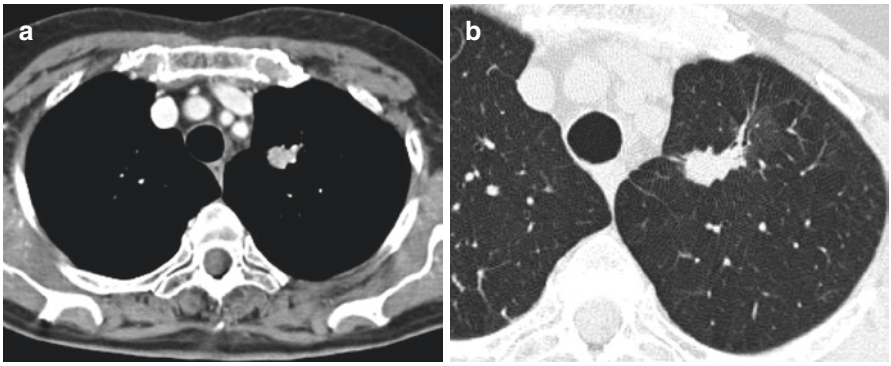


Fig. 5.12 T1b: T 2–3 cm

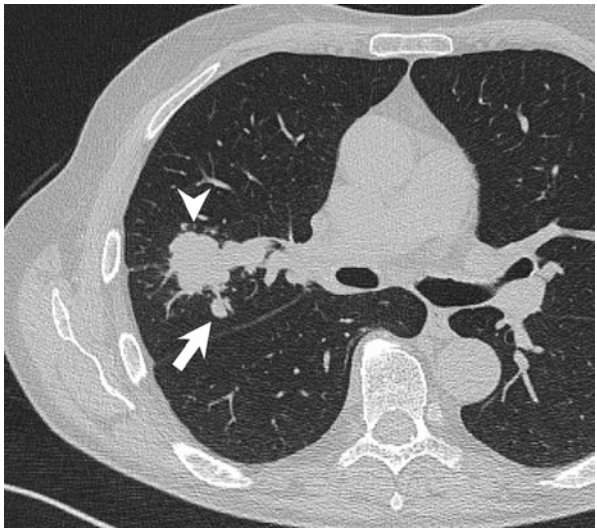


Fig. 5.13 T3: satellite nodule in the same lobe (*arrow*) as the primary tumor (*arrowhead*)

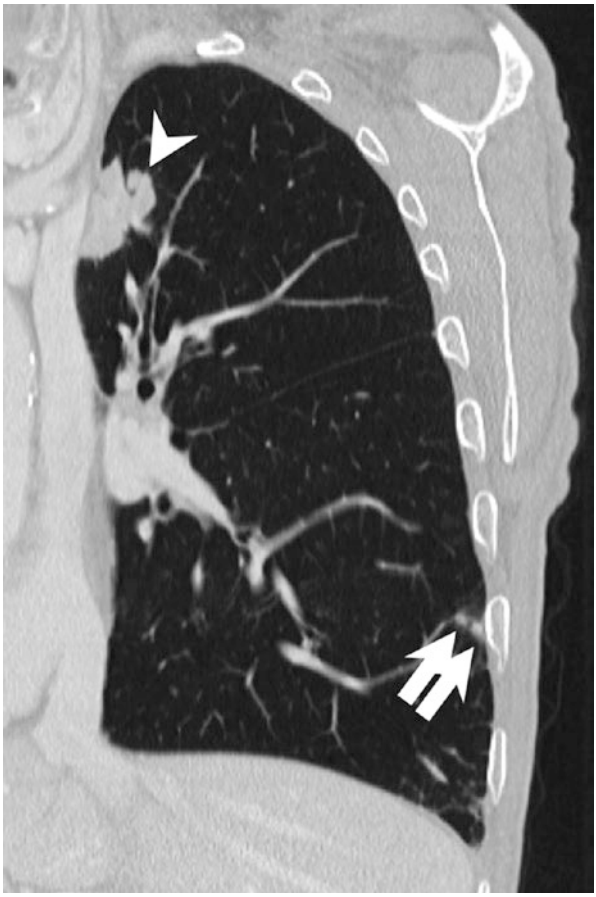


Fig. 5.14 T4: ipsilateral satellite nodules in a different lobe (*arrows*) as the primary tumor (*arrowhead*)

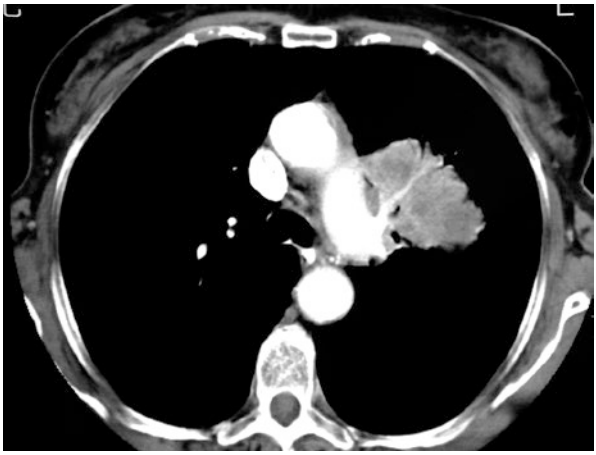


Fig. 5.15 T4: pulmonary artery infiltration

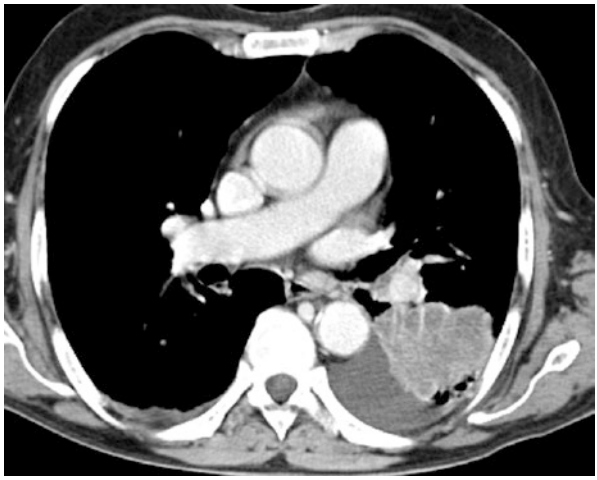


Fig. 5.16 M1a: neoplastic effusion

Suggested Readings

Lim W, et al. The 8th lung cancer TNM classification and clinical staging system: review of the changes and clinical implications. Quant Imaging Med Surg. 2018;8(7):709–18.

Robinson LA, et al. Treatment of non-small cell lung cancer-stage IIIA: ACCP evidence-based clinical practice guidelines (2nd edition). Chest. 2007;132(3 Suppl):243S.

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Quint LE. Lung cancer: assessing resectability. Cancer Imaging. 2003;4:15–8.

Zugazagoitia J, et al. The new IASLC/ATS/ERS lung adenocarcinoma classification from a clinical perspective: current concepts and future prospects. J Thorac Dis. 2014;6(Suppl 5):S526–36.