Principles of Cancer Staging

12

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Background

Worldwide, approximately 1.3 million persons will be diagnosed with lung cancer each year (WHO 2008). Of these, not more than 15% will survive for 5 years or longer. Although cessation of smoking is the most effective approach to solve this problem, it is not expected that in the near future, the incidence of lung cancer will diminish. Smoking cessation programs may be offered in the Western world; the real threat lies in the less-developed nations and countries with booming economies like China.

For those patients presenting with lung cancer, various treatment modalities are available. The methods available and used most are surgery, radiation therapy, and chemotherapy. Although each method can lead to cure, the toxicity profile varies considerably. Currently, a combination of two or three modalities is proposed to patients.

Lung cancer can be roughly divided into three groups: non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), and a remaining group that is not smoking related. The incidence of NSCLC is 75%, and for SCLC, it is 15%. NSCLC can be subdivided into adenocarcinoma, squamous cell carcinoma, large cell carcinoma, or not otherwise specified (NOS). The growth pattern of these various types is slightly different, and also the response to treatment varies.

In order to make advances in the treatment of cancer and to communicate optimally between different centers, there is a need for a standard nomenclature. Patients with lung cancer vary in a number of factors with respect to biological behavior, comorbidity, age and performance, and extent of disease. Staging is one of the methods to group patients who have a more or less similar prognosis. Correct description of the other factors of the patient and his or her disease and a proper (randomized) study execution will allow scientists to value reported findings and to select the best treatment for each patient. Stage grouping can thus be seen as one of the approaches to narrow down the optimal treatment approaches for a typical patient.

The first attempt to stage patients was made in the 1940s in France. Later, Mountain based the first TNM staging system on the data of 2,155 patients of the MD Anderson hospital in Texas. This initiative was subsequently adopted by both the AJCC (American Joint Committee on Cancer) and UICC (Union Internationale Contre le Cancer-International Union for Cancer Control) and resulted in a uniform classification in 1987. Since then, the TNM system was updated on a regular basis, incorporating data of more patients. Initially, only a minority of patients from the Middle and Far East and Europe were included. In the last decade, a great effort has been undertaken by the International Association on the Study of Lung Cancer (IASLC) to update and expand the database of the TNM system. This effort resulted in the seventh edition of the stage classification and is based on data from >20 countries contributing to a total of 67,725 patients with NSCLC and 13,290 patients with SCLC (Fig. 12.1).

Clinical Staging

Clinical staging is the process of determining the extent of the disease by using limited invasive procedures and anatomical landmarks, excluding aspects of the biological behavior of the disease or patient characteristics. It comprises of a tumor or T status, a lymph node or N status, and the presence of metastases or M status. After finalizing the required examinations, the clinical staging will be noted as a cTxNxMx. It must be noted that clinical staging is not as accurate as the final pathological staging, which is indicated as a pTxNxMx. In addition, an interim staging after induction chemo- and radiotherapy will be indicated by yTxNxMx.

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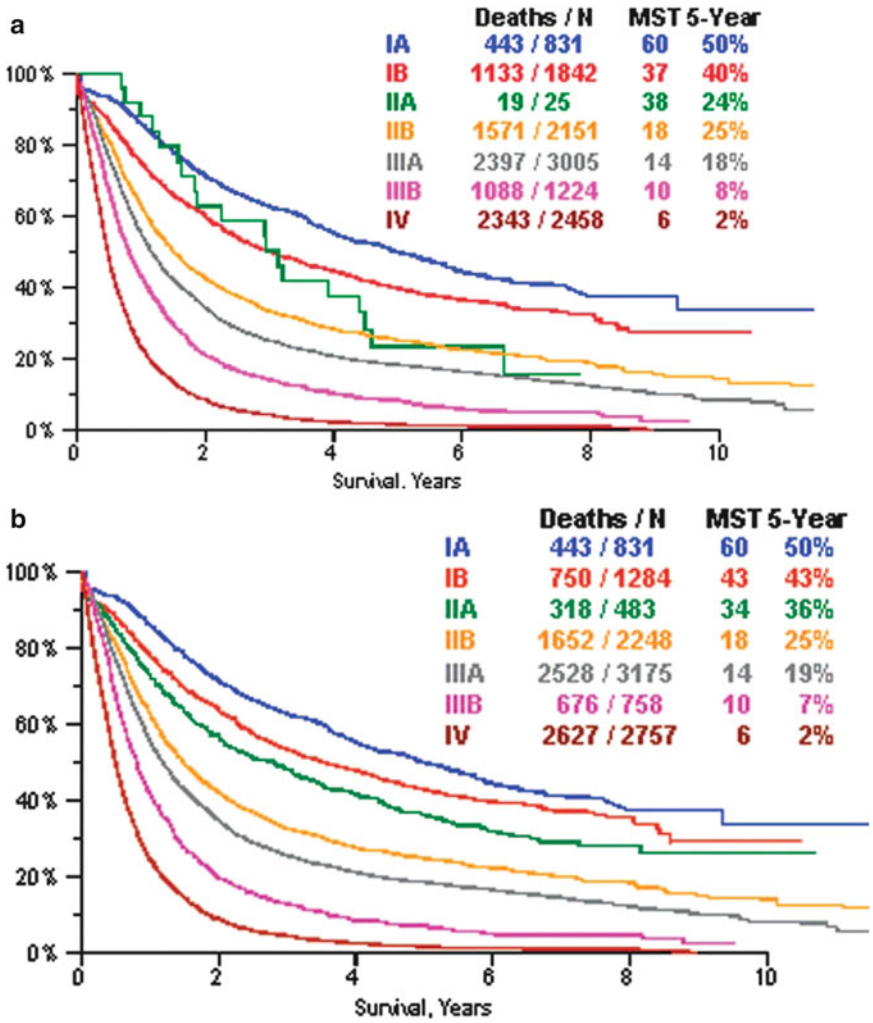

Fig. 12.1 Survival curves according to the seventh IASLC staging system. In *panel A*, the survival figures for the different clinical stages are presented. In *panel B*, the same survival curves are presented but now for the pathological staging. There is a clear difference between the number of stages IB and IIA between the clinical and pathological stages, indicating that imaging techniques in these two groups are often difficult (From The IASLC Lung Cancer Staging Project: Proposals for the Revision of the TNM Stage Groupings in the Forthcoming (Seventh) Edition of the TNM Classification of Malignant Tumours. Peter Goldstraw, FRCS,* John Crowley, Ph.D.,† Kari Chansky, MS,† Dorothy J. Giroux, M.Sc.,†Patti A. Groome, Ph.D.,‡ Ramon Rami-Porta, M.D.,§ Pieter E. Postmus, Ph.D., Valerie Rusch, M.D., and Leslie Sobin, M.D.,# on behalf of the International Association for the Study of Lung Cancer International Staging Committee and Participating Institutions. Reprinted with permission from Wolters Kluwer)

Clinical staging consists of the following procedures: physical examination, radiological examination, nuclear medicine examination, endoscopic investigations, and limited surgical interventions.

Physical Examination

The first step in staging is to examine the patient and find signs or symptoms that indicate local or distant dissemination of the disease. Findings during the physical examination will also be of help to plan the next steps. This will avoid examinations that will not contribute to the staging process and finally shorten the time between presentation and start of treatment. Signs of collateral blood flow and elevated central venous pressure will urge the physician to order vascular contrast examinations, sometimes combined with placement of an expandable vascular stent. The appearance of enlarged lymph nodes in the supraclavicular region will indicate at least an N3 status. Signs of Horners' syndrome (unilateral ptosis, myosis, enophthalmus, and reduced sweating) or pain in one shoulder or arm indicates involvement of the cervical plexus by invasion of the tumor. A low position of the diaphragm or reversed movement during respiration is indicative of severe COPD or involvement of the phrenic nerve. Diminished breath sounds and dullness at percussion are indicators of pleural effusion, atelectases, or consolidation of a part of the lung. The appearance of lymph nodes in the axilla or subcutaneous metastases will upstage the patient to stage IV disease when malignant cells are found at fine-needle biopsy. Additional CT or PET scans can be omitted in these cases.

Clinical signs of cyanosis, weight loss, paraneoplastic syndromes, comorbidities, low-performance status, medication use, and the psychological condition of the patient are important factors in the process of final treatment planning.

Radiological Examinations

Information obtained from a standard *chest X-ray* (PA and lateral view) will be the first step in imaging studies. Localization of the primary disease and presence of atelectases or pleural effusion will help to decide on the next investigation. Although less frequently used nowadays, *fluoroscopy* can be of help to identify superimposed lesions, pleural lesions, a reversed movement of the diaphragm, or stenosis of one of the central airways by movement of the mediastinum during forced inspiration.

Computed tomography is the examination of choice to determine the anatomical landmarks of the tumor and to obtain information about any possible mediastinal lymph node involvement. The extent of the primary tumor can be determined, and the size of the tumor can be measured. Not always a clear discrimination can be made between actual growth into surrounding tissues, as is shown in Fig. 12.2. The appearance of post-obstructive pneumonia or atelectasis can also negatively influence the measurement. Sometimes a PET scan (see below) can be of help. For discrimination of the lymph nodes in the hilar and mediastinal region, contrast-enhanced scans are a requisite. The currently available CT scans are fast and have a high resolution that allows multiplane viewing. Coronal and sagittal images can be constructed in addition to the axial recordings and help to determine whether the primary tumor is invading the mediastinum or other vital structures (Fig. 12.3).

In the following figures, examples of different stages with the plotted anatomical/radiological landmarks are presented.

Positron emission tomography is considered a standard examination for the staging of the early stages of NSCLC. Using fluorodeoxyglucose (FDG), the scan can identify metabolic processes in the body. This tool can discriminate

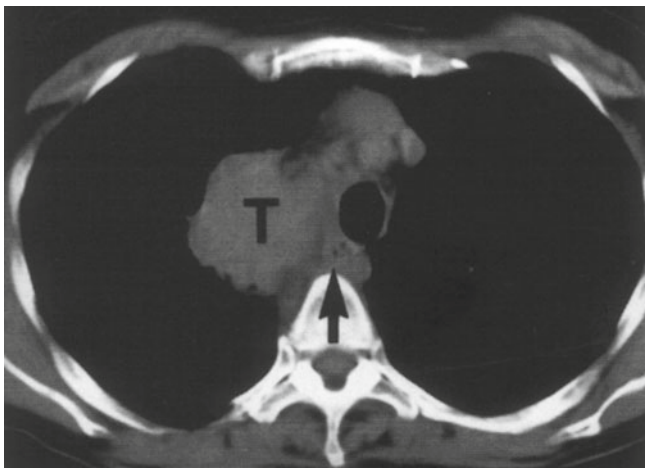

Fig. 12.2 Axial CT image of a patient with NSCLC. The tumor is located adjacent to the mediastinum. Although there is an indication that the more ventral part of the tumor (T) is probably growing into the mediastinum, the more dorsal part might be separate. The arrow indicates the location of the esophagus. This tumor is graded as minimally a T3 based on the CT image alone. Additional EUS and EBUS examination can be used to better visualize the local situation

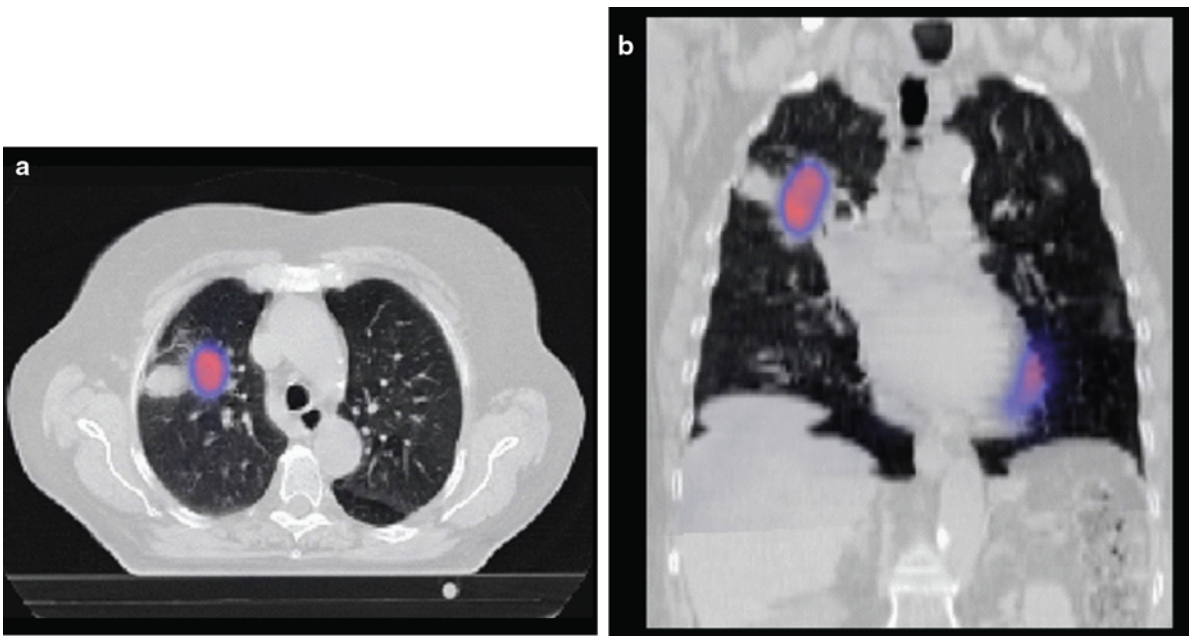

Fig. 12.3 Combination of PET and CT scans using fusion techniques. The CT and PET are made on the same time and corrected for anatomical variation in position of the patient. The axial and coronal images show a tumor-avid lesion in the anterolateral part of the *right upper* lobe (RUL). The CT scan shows a PET negative extension that is due to post obstruction atelectasis. Some physiologic activity of the myocardium is visible

Table 12.1 Causes of false-positive and false-negative PET

False positive	False negative
Talc pleurodesis (up to 4 months after procedure)	Hyperglycemia
Sarcoidosis	Tumor is not FDG avid
Rheumatoid arthritis	Too long interval after FDG injection
Wegeners' granulomatosis	Small size (<8 mm)
Chronic lymphatic disorders	Carcinoid tumors
Infectious (pneumonia, abscess, fungal, mycobacterial)	Ground-glass appearance of tumor (previously known as bronchioloalveolar cell carcinoma)
Radiation pneumonitis/esophagitis	
Invasive procedures	
Benign tumors (Warthin's' tumor, colonic polyps, adrenal adenomas)	

Table 12.2 Accuracy of combined PET-CT scanning for lung cancer. In the older studies, the CT scan was performed separately from the PET scan resulting in less accurate matching

PET-CT scan	Year	Number of patients	Accuracy (%)	Reference
T-stage	2003	50	88	Lardinois
	2004	129	64	Cerfolio
	2005	36	97	Halpern
	2007	50	86	De Wever
N-stage	2003	50	81	Lardinois
	2004	129	78	Cerfolio
	2005	36	78	Halpern
	2007	50	84	De Wever

between processes that have a high, low, or absent metabolic activity. When the primary tumor is FDG avid, the sensitivity to detect malignant lymph nodes or distant metastases is very high. The PET scan cannot be interpreted reliably when the primary tumor is not FDG positive or in case of a concurrent infection or other causes (Table 12.1). Concurrent infections occur often in patients with central obstruction by the tumor or due to COPD. Sarcoidosis is one of the well-known diseases that have a high FDG uptake and can mimic a tumor or positive lymph nodes. Therefore, it is important to obtain proof of one of the involved lymph nodes or lesions found in distant sites. The PET scan is not informative on the presence of ingrowth into other structures like the mediastinum when the primary tumor is centrally located. The modern scans combine CT and PET and allow projecting both images on top of each other (Fig. 12.3 and Table 12.2), enabling the physicians to decide on the further diagnostic steps (Fig. 12.4). The combination of CT scan lymph node size and PET activity improves the sensitivity and specificity.

Endoscopic Investigations

These investigations are described in other chapters of this book. Standard procedures like bronchoscopic examination with or without fluoroscopy are the basis for the diagnosis and appreciation of endobronchial extension.

In the current work-up of the mediastinum in patients with NSCLC, the indication for mediastinoscopy has declined because of the reliability and safety of the endobronchial techniques. Endobronchial ultrasound (EBUS) and endoesophageal ultrasound techniques (EUS) are now readily available, and most cancer centers and university clinics now have experienced staff. Mediastinoscopy can therefore be reserved for special cases or for the evaluation of the mediastinum after induction therapy.

Surgical Staging

Surgical procedures in the staging process can be subdivided into *mediastinoscopy*, *thoracoscopy*, *and exploratory thoracotomy*. In the case of mediastinoscopy, it has already been discussed that the indication has been reduced since the introduction of EBUS and EUS. Even for the lymph node stations in the aortopulmonary window, the need for a parasternal mediastinoscopy has been reduced. Cervical and para-mediastinal mediastinoscopy are merely indicated when the endobronchial ultrasound examination was not representative or available or when a larger tumor specimen is required. The need for more histology specimen is now indicated in the case of studies or when first line treatment with targeted biologicals is planned.

A thoracoscopic examination has limited indications in the primary staging process. In the case of a presentation with pleural lesions and effusion, at least two separate pleural fluid specimens must be examined at the cytology department. When returned negative or in case of a dry tap, a thoracoscopy can be indicated to prevent a futile thoracotomy. In some cases, a thoracoscopy can be indicated because of the need for histology or as part of specific study requirements. In some countries, pulmonologists perform medical thoracoscopies for inspection of the pleural cavity, to evacuate the fluid, to take pleural biopsies, or even to perform a pleurodesis. In other cases, a video-assisted thoracoscopy (VATS) is performed in the operating room with optimal sedation of the patient. This examination is typically performed by the thoracic surgeon or in specialized centers by the pulmonologist.

In selected cases, a thoracotomy is performed for means of both staging and resection. These cases are cases in which no diagnosis could be obtained by other means or when the tumor lies adjacent to the mediastinum and ingrowth is considered unlikely. These indications are becoming less frequent as a result of the implementation of EUS and transthoracic fine-needle aspiration.

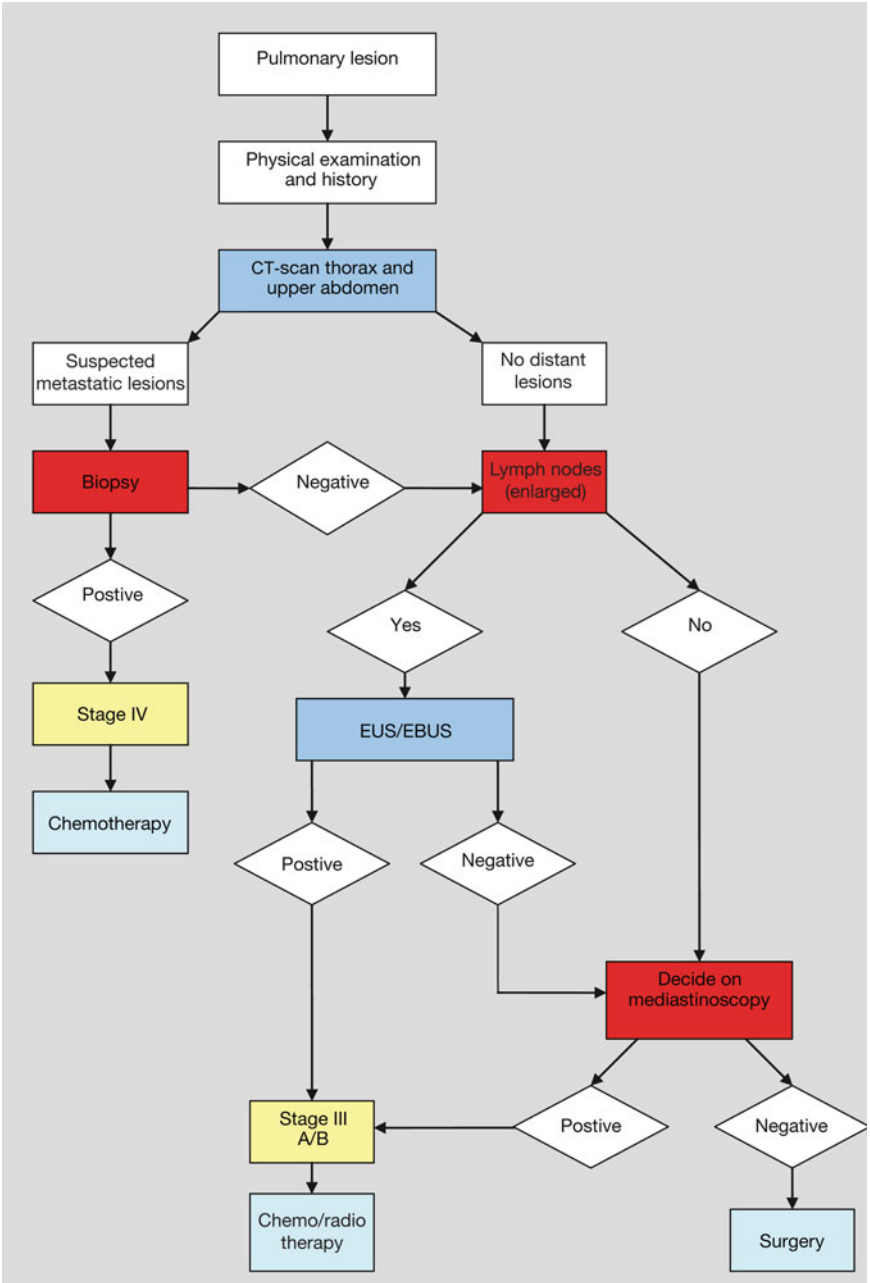

Fig. 12.4 Decision-making tree of patients presenting with a pulmonary lesion with a high level of suspicion for lung cancer

TNM Classification

Staging is considered to be one of the backbones in designing an optimal treatment in lung cancer. With proper staging, it is possible to select the best treatment and to compare studies from different centers.

In the last few years, the TNM classification has undergone significant changes. Based on a worldwide initiative of the IASLC (International Association on the Study of Lung Cancer), 19 countries included data on 67,725 patients with NSCLC in the period of 1990–2000. This effort resulted in the seventh international staging system and is now widely used since January 1, 2009. The suggestions made included additional cutoffs for tumor size, with tumors >7 cm moving from T2 to T3, to reassign the category given to additional pulmonary nodules in some locations, and finally reclassifying malignant pleural effusion as an M descriptor. This has resulted in the new staging and grouping system, as shown in Tables 12.3 and 12.4.

Recommendations

The principles of staging have undergone important changes over the last few years. Besides the introduction of the PET-CT scan, the more recent availability of endoscopic

Table 12.3 Staging of primary tumor, lymph nodes, and metastases according to the seventh edition of the IASLC staging system (adapted from the seveth IASLC staging system)

Tx	Tumor cells detected in sputum or bronchial washings: primary tumor cannot be assessed by radiology or bronchoscopic examination
T0	No evidence of the primary tumor
Tis	Carcinoma in situ
T1	Greatest size ≤3 cm, beyond main bronchus, not invading visceral pleura
	Superficial growing tumor which is of any size but limited to the bronchial wall and may extend into the main bronchus
T1a	Tumor ≤2 cm greatest diameter
T1b	Tumor >2 cm but ≤3 cm
T2	Tumor > 3 cm but ≤ 7 cm or tumors with any of the following aspects: invasion of the visceral pleura, located in the main bronchus but ≥2 cm of the main carina, associated with atelectasis or obstructive pneumonia which extends the lobe but does not involve the whole lung
T2a	Tumor >3 cm but ≤5 cm
T2b	Tumor >5 cm but ≤7 cm
T3	Tumor >7 cm or involvement of chest wall (including sulcus superior tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium, within 2 cm of the main carina (but no involvement of the carina), atelectasis or obstructive pneumonia of the whole lung, separate tumor nodules in the same lobe
T4	Tumor of any size that invades the major organs, involvement of the main carina, vertebral bodies, recurrent laryngeal nerve, tumor nodule(s) in a different lobe
Nx	Regional lymph nodes cannot be assessed
N0	No involvement of regional lymph nodes
N1	Metastases in the ipsilateral peribronchial hilar lymph nodes or intrapulmonary lymph nodes. No differentiation is made between direct extension and metastases
N2	Metastases in the ipsilateral mediastinal lymph nodes and/or subcarinal lymph nodes
N3	Metastases in the contralateral mediastinal, contralateral hilar lymph nodes. Metastases in the ipsi- or contralateral supraclavicular or scalene lymph nodes
Mx	Distant metastases cannot be assessed
M0	No distant metastases
M1	Presence of distant metastases
M1a	Separate tumor nodule(s) in a contralateral lobe, tumor with pleural nodules or malignant pleural or pericardial effusion
M1b	Distant metastases

Table 12.4 Stage grouping according to the seventh edition of the IASLC staging system (adapted from the seventh IASLC staging system)

N status				
T status	N0	N1	N2	N3
T1a	IA	IIA	IIIA	IIIB
T1b	IA	IIA	IIIA	IIIB
T2a	IB	IIA	IIIA	IIIB
T2b	IIA	IIB	IIIA	IIIB
T3	IIB	IIIA	IIIA	IIIB
T4	IIIA	IIIA	IIIB	IIIB
M1a	IV	IV	IV	IV
M1b	IV	IV	IV	IV

techniques has improved the pretreatment diagnosis of mediastinal involvement in patients with NSCLC. Currently, the use of the seventh edition of the staging system by the IASLC is mandatory to optimally stage patients. The optimal treatment choice, however, does not solely depend on the stage but should also take into account patient characteristics like performance, comorbidity, and psychological status. For a general approach, the decision tree in Fig. 12.4 can be used.

Suggested Reading

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