CONTINUING MEDICAL EDUCATION

Lung Cancer: Current Diagnosis and Treatment

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SUMMARY

Background: Much progress has been made in the treatment of lung cancer in the last ten years (adjuvant chemotherapy, targeted therapy, individualized therapy). Nonetheless, lung cancer is still the leading cause of death due to cancer and thus remains a major medical, scientific, and social problem.

Method: This review is based on national and international recommendations and selected articles from the literature.

Results: Cigarette smoking is the major pathogenic factor for lung cancer. Lung cancer can be divided into two major types that differ in their biological behavior, small cell lung cancer and non-small cell lung cancer. Whenever possible, the diagnosis should be confirmed by biopsy, the extent of disease should be documented in detail (international TNM classification/staging), and the patient's functional level should be assessed with a view toward treatment planning. Surgery for non-small cell lung cancer with curative intent is possible up to stage IIIA, while stage IIIB is the domain of radiotherapy. Surgery for small cell lung cancer with curative intent is possible for rare cases in early stages (T1N0 and T2N0, i.e., stage IA and IB). As long as small cell lung cancer is restricted to one side of the chest, simultaneous radiation therapy and chemotherapy are indicated. If a malignant pleural effusion or distant metastases are present, both lung cancers are treated palliatively with platinum-based chemotherapy.

Key words: lung cancer, diagnosis, treatment, targeted therapy, cigarette smoking

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Lung cancer is by far the most common malignant tumor originating in the lung. The four major histological types of lung cancer are:

- squamous cell carcinoma (30% to 40% of lung cancers)
- adenocarcinoma (25% to 30%)
- non-small cell lung carcinoma (less than 10%), and
- small cell lung carcinoma (15% to 20%).

These four types are subdivided into numerous subtypes (1). A notable subtype is bronchoalveolar carcinoma (synonym: alveolar cell carcinoma), a rare subtype of adenocarcinoma, that lines the alveoli as it grows. Lung cancers can be classified according to a variety of criteria. Histologically a distinction is made between small cell lung carcinoma (15% to 20%) and non-small cell lung carcinoma, because of differences in their biological behavior and the implications of these differences for treatment and prognosis.

Because of the effectiveness of particular therapies, non-small cell lung carcinomas are divided into squamous cell carcinoma and non-squamous cell carcinoma, and they are characterized using techniques of molecular pathology. More than 30% of lung cancers have elements of a variety of histological types (1).

The learning goals for the reader are:

- To become familiar with the diagnostic workup for lung cancer
- To acquire an overview of the principles of stage-dependent treatment.

This article is based on an evaluation of national and international recommendations and on a selective literature review.

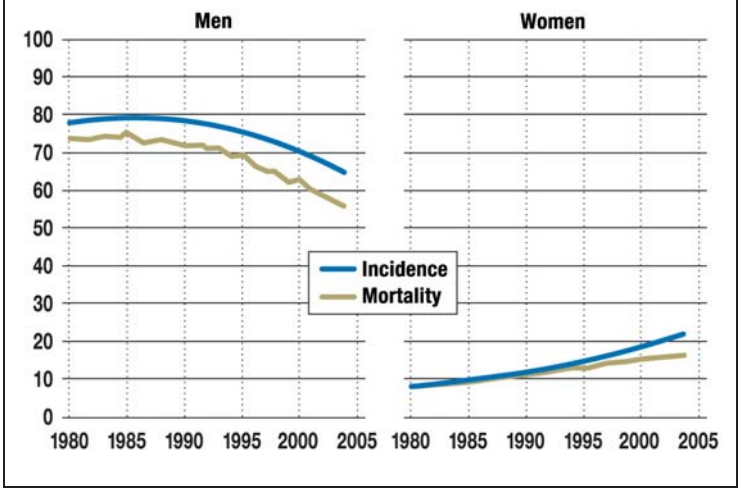
Epidemiology, etiology, and pathogenesis

Lung cancer is the third most frequently diagnosed cancer in Germany in both men and women (2). The

Basic histological classification

Because of differences in their biological behavior, the distinction between small cell lung cancer and non-small cell lung cancer is important.

GRAPHIC



Incidence and mortality

Course over time of age-adjusted incidence (blue) and mortality (green) from lung cancer (left: men; right: women) in Germany from 1980 to 2004 (cases and deaths per 100 000 population) (2). Reproduced by kind permission of the Robert Koch Institute

BOX

Symptoms and findings of lung cancer and frequency distribution of important symptoms*[1]

Symptoms and findings of endobronchial growth

Cough (8% to 75%), hemoptysis (6% to 35%), pain, wheezing (0% to 2%), poststenotic pneumonia, dyspnea (3% to 60%), stridor (0% to 2%)

Symptoms and findings of intrathoracic extension

Chest pain (20% to 49%), hoarseness, upper airway inflow obstruction, Horner's triad, pleural effusion, pericardial effusion, dysphagia, raised diaphragm

Systemic signs of cancer

Weight loss (0% to 68%), night sweats, fatigue, fever (0% to 20%)

Symptoms and findings of distant metastases

Bone pain (6% to 25%), headache, neurological or psychiatric abnormalities, paraplegia, hepatomegaly, pathological fractures

Symptoms of paraneoplastic syndromes

Cushing syndrome, syndrome of inappropriate ADH secretion, Lambert-Eaton syndrome, Perre-Marie-Bamberger syndrome, etc.

*[1] Frequency data from [11]; ADH, antidiuretic hormone

annual incidence in Germany is 65 per 100 000 for men and 21 per 100 000 for women. The peak incidence is between the ages of 75 and 80 years (2). At the same time, both in Germany and worldwide, lung cancer is the most frequent cause of death from cancer among men, and in Germany it is the third most frequent cause of death from cancer among women. In men the figures are steady or slightly reducing, but in women the rate is going up. Both incidence and mortality rates reflect cigarette consumption in a given population about 20 years ago (3) (*Figure*).

Exogenous noxae have a decisive role in the development of lung cancer—in particular, cigarette smoke inhalation. About 90% of lung cancers may be ascribed to this cause (3). Once smoking has stopped, the risk of developing lung cancer reduces over time. Other relevant etiological factors are occuptional exposure to asbestos, polycyclic hydrocarbons (in soot and tar), chromates, arsenic, and nickel. Radon, a gaseous radioactive decay product of uranium, is naturally present as background radiation that varies in intensity from region to region and is also present in uranium mines. In both cases it can cause local clustering of cases of lung cancer (3). It is estimated that between 9% and 15% of lung carcinomas have causes other than cigarette smoking (3). The carcinogenesis of a lung cancer probably goes back years or even decades. During this period, the affected cells undergo numerous changes at the molecular level, which eventually lead to an invasively growing lung carcinoma.

Symptoms/clinical presentation

Most patients with lung cancer have symptoms at the time they are diagnosed. However, there are no specific early symtoms. The symptoms of lung cancer (*Box*) may be caused by endobronchial growth, intrathoracic extension, or distant metastases. In addition, systemic signs of cachexia and, occasionally, also symptoms of paraneoplastic syndrome may be encountered.

Diagnosis

The diagnostic workup for lung cancer must include histological confirmation of the diagnosis, evaluation of how far the tumor has spread (staging), and an analysis of the patient's functional status with a view to treatment possibilities. The scope of the workup must be always governed by the patient's overall situation and the prognosis that can be achieved. For example, one would not embark on complicated invasive diagnostic

Smoking as a cause of lung cancer

Cigarette smoking is by far the most important factor in the development of lung cancer.

Early symptoms

Lung cancer has no real early symptoms, so it is often only diagnosed when it has reached an advanced stage.

procedures for precise N-staging in a patient who already has extensive confirmed distant metastases. In non-small cell lung cancer in particular, important aspects of therapy depend on accurate staging and on accurate evaluation of the patient's functional status. The sections on evaluating the extent of disease and evaluating functional status therefore relate to non-small cell lung cancer.

Histological confirmation

For treatment, the most important thing is to distinguish between small cell and non-small cell lung cancer. Distinguishing between various subtypes of non-small cell cung cancer is also becoming increasingly important because of variations in the licensing and effectiveness of particular chemotherapeutics and targeted therapies. For this reason, histological confirmation is carried out in all cases if possible. In situations in which it is impossible to obtain a biopsy specimen by reasonable means, an unambiguous cytology result is adequate. Bronchoscopy allows confirmation of the primary tumor with a sensitivity of 0.88 for central tumors and 0.78 for peripheral tumors (4), and can provide information for T-staging and cytology samples for N-staging. In addition, transthoracic puncture, guided by ultrasound, fluoroscopy, or computed tomography (CT) may be needed. Only exceptionally is endobronchial or esophageal ultrasonography necessary in addition to confirm the diagnosis, but they can be useful for mediastinal lymph node staging. So far as possible without running excessive risks, histological confirmation from a lung specimen is preferable to confirmation on the basis of a metastatic sample.

Evaluating the extent of disease

For small cell and non-small cell lung cancer, the international staging system is used (*Tables 1 and 2*) (5, 6). In small cell lung cancer a further distinction is made between "limited disease" (i.e., disease limited to one hemithorax) and "extensive disease" (extension beyond one hemithorax) (7).

T-descriptor: The most significant examination for T-descriptor assessment is contrast-enhanced CT. In a few situations, magnetic resonance imaging (MRI) can deliver more detailed information about invasion of thoracic structures (8). In patients with a Pancoast tumor, MRI is absolutely essential in order to assess invasion of the vascular and neural structures of the brachial plexus and for operative planning.

N-descriptor: Contrast-enhanced chest CT has a sensitivity between 51% and 64% and a specificity between 74% and 86% in staging mediastinal lymph nodes (8), which makes it inadequate as a sole procedure for evaluating the mediastinum in a patient without distant metastases. The most accurate non-invasive procedure for mediastinal N-staging is positron emission tomography (PET) or PET-CT; however, with a sensitivity of 74% and a specificity of 85% (8), it is by no means perfect. If an enlarged lymph node is present (>1 cm), the sensitivity of PET/PET-CT rises to 100%, with a specificity of 78% (9). If curative therapy is intended, PET-positive mediastinal lymph nodes are biopsied for definitive analysis. Available methods for this, depending on the localization of the target lymph node, are mediastinoscopy (including video-assisted mediastinal lymphadenectomy), endobronchial and esophageal ultrasonography, and transbronchial needle aspiration (TBNA) (10). PET and PET-CT allow exact identification of the target node for biopsy confirmation for lymph node staging.

M-descriptor: In general, distant metastases speak against treatment with curative intent. The most frequent locations of distant metastases are brain, liver, skeleton, lungs, and adrenals.

Suitable imaging procedures for detecting distant metastases are:

- Contrast-enhanced cranial CT or MRI
- Bone scintigraphy
- Ultrasonography
- CT or MRI of the liver and adrenals
- PET, PET-CT.

The patient history, clinical findings, and lab results can provide important clues to whether there are any distant metastases and point the way to the next diagnostic steps (e1). Especially in patients with N2 or N3 tumors at diagnosis, there must be a raised expectation of asymptomatic distant metastases.

In general, the only reason not to aim at potentially curative therapy is when distant metastases have been confirmed by biopsy or may be regarded as definite on the basis of clinical or radiological findings.

PET and PET-CT in the staging of non-small cell lung cancer: PET/PET-CT imaging is of central importance in tumor staging. Ruling out distant metastases by a negative finding saves further diagnostic procedures, while the detection of structures suggestive of metastasis can guide the next step and move the diagnostic process rapidly forward. In patients in

Diagnosis

The diagnostic workup of lung cancer includes histological confirmation, staging (diagnosis of extent of disease), and characterization of the patient's functional status.

Staging

Staging of the extent of disease follows the internationally accepted staging classification.

TABLE 1

TNM classification of lung cancer in the 6th edition (5, 6) and proposal for the 7th edition (25)

	6th edition		Proposal for the 7th edition	
T	TX	Primary tumor cannot be assessed, or evidence of malignant cells in sputum or bronchial lavage fluid but no visualization of tumor on imaging or bronchoscopy	TX	Primary tumor cannot be assessed, or evidence of malignant cells in sputum or bronchial lavage fluid but no visualization of tumor on imaging or bronchoscopy
	T0	No evidence of primary tumor	T0	No evidence of primary tumor
	Tis	Carcinoma in situ	Tis	Carcinoma in situ
	T1	Tumor ≤ 3 cm greatest diameter, surrounded by lung tissue or visceral pleura, no bronchoscopic evidence of invasion proximal to the lobar bronchus (i.e., main bronchi are free)*[1]	T1	Tumor ≤ 3 cm greatest diameter, surrounded by lung tissue or visceral pleura, no bronchoscopic evidence of infiltration proximal to the lobar bronchus (i.e., main bronchi are free)*[1]
			T1a	Tumor ≤ 2 cm greatest diameter
			T1b	Tumor > 2 but ≤ 3 cm greatest diameter
	T2	Tumor > 3 cm or tumor with one of the following features: – invasion of the main bronchus, ≥ 2 cm distal to the carina – invasion of the visceral pleura – associated atelectasis or obstructive pneumonia extending as far as the hilus but not involving the whole lung	T2	Tumor > 3 but ≤ 7 cm with one of the following features: – invasion of the main bronchus, ≥ 2 cm distal to the carina – invasion of the visceral pleura Associated atelectasis or obstructive pneumonia extending as far as the hilus but not involving the whole lung
			T2a	Tumor > 3 but ≤ 5 cm greatest diameter
			T2b	Tumor > 5 but ≤ 7 cm greatest diameter
	T3	Tumor of any size with direct invasion of one of the following structures: – chest wall (including tumors of the superior sulcus) – diaphragm – phrenic nerve – mediastinal pleura – parietal pericardium or tumor in the main bronchus < 2 cm distal to the carina, without involvement of the carina and without associated atelectasis or obstructive pneumonia of the whole lung	T3	Tumor > 7 cm or any tumor with direct invasion of one of the following structures: – chest wall (including tumors of the superior sulcus) – diaphragm – phrenic nerve – mediastinal pleura – parietal pericardium or tumor in the main bronchus < 2 cm distal to the carina, without involvement of the carina and without associated atelectasis or obstructive pneumonia of the whole lung or satellite tumor nodule(s) in the same lobe
	T4	Tumor of any size invading one of the following structures: – mediastinum – heart – great vessels – trachea – recurrent laryngeal nerve – esophagus – vertebral body – carina or separate tumor nodule(s) in the same lobe or tumor with malignant pleural*[2] or pericardial effusion	T4	Tumor of any size invading one of the following structures: – mediastinum – heart – great vessels – trachea – recurrent laryngeal nerve – esophagus – vertebral body – carina – or separate tumor nodule(s) in another ipsilateral lobe
N	NX	Regional lymph nodes could not be evaluated	NX	Regional lymph nodes could not be evaluated
	N0	No regional lymph node metastases	N0	No regional lymph node metastases
	N1	Metastasis/metastases in the ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary lymph nodes, including involvement by direct extension of the primary tumor	N1	Metastasis/metastases in the ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary lymph nodes, including involvement by direct extension of the primary tumor
	N2	Metastasis/metastases in the ipsilateral mediastinal and/or subcarinal lymph nodes	N2	Metastasis/metastases in the ipsilateral mediastinal and/or subcarinal lymph nodes
	N3	Metastasis/metastases in the contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene or supraclavicular lymph nodes	N3	Metastasis/metastases in the contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene or supraclavicular lymph nodes
M	MX	Distant metastases could not be evaluated	MX	Distant metastases could not be evaluated
	M0	No distant metastases	M0	No distant metastases
	M1	Distant metastases, including separate tumor nodules in another pulmonary lobe	M1	Distant metastases
			M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural*[2] nodes or malignant pleural (or pericardial) effusion
			M1b	Distant metastases

*[1] A superficially extending tumor with invasion limited to the bronchial wall is always classified as T1.

*[2] In patients with lung cancer, pleural and pericardial effusions are usually due to the tumor. In a few patients, however, if multiple cytological examinations are negative for the presence of tumor cells, the effusion is not hemorrhagic and is not an exudate. If these factors are present, and if the clinical evaluation also indicates that the effusion is not caused by the lung cancer, the effusion should not be taken into account as a staging criterion.

clinical stages IB to IIIB, in whom curative therapy should be attempted, PET/PET-CT scanning (if available) should be carried out for mediastinal N-staging and for M-staging; in stage IA this examination should be considered (8).

Evaluating functional status

The initial evaluation of lung function is governed by the risk carried by the planned treatment and the quality of life that it would achieve. In addition, cardiovascular co-morbidities and any severe impairment of liver or renal function are taken into account. Detailed recommendations exist for the assessment of functional operability (12). A patient with a forced expiratory volume (FEV_1) of more than 80% of the norm (FEV_1 > 80% of norm) (or >2.0 L) and a diffusion capacity of more than 80% of the norm may be referred without further evaluation for chest surgery up to and including pneumonectomy. If either of these values is below 80% of the norm, further evaluation with spiroergometry is required. If this shows a maximum oxygen consumption above 75% of the norm or if the value is greater than 20 mL/min/kg, the patient is a suitable candidate for surgery up to and including pneumonectomy.

If the maximum oxygen consumption is below 40% of the norm or less than 10 mL/min/kg, functional inoperability must be assumed. If the maximum oxygen consumption is between these limits, postoperative FEV_1 values are estimated on the basis of quantitative ventilation/perfusion scintigraphy of the lung. If these values are above 40% of the norm, the operative procedure envisaged can be carried out; if they are below 40% of the norm, the patient must be regarded as inoperable. If one of the values is above and one below 40% of the norm, the decision is guided by the maximum oxygen consumption calculated for the postoperative status, and in this case 35% of the norm or 10 mL/min/kg is taken as the threshold for operability.

Special aspects of the diagnostic workup of small cell lung cancer

In addition to history, clinical exam, and routine laboratory tests, the diagnostic workup of small cell lung cancer should include CT of the chest and abdomen (at least liver and adrenals), bone scintigraphy, and contrast-enhanced cranial CT or cranial MRI. PET is not recommended for regular staging (7). PET/PET-CT has the potential to determine tumor stage more accurately in some patients, and to prevent unnecessary treatment if distant metastases are discovered or, conversely, to allow radiochemotherapy if distant metastases are ruled out. Future guidelines may therefore give PET/PET-CT a larger role in small cell lung cancer.

Treatment

Local therapy modalities are surgery and radiotherapy. For systemic therapy, conventional chemotherapy and increasingly also targeted therapies (i.e. interventions that affect tumor-specific structures at the molecular level) are employed. Chemotherapy is polychemotherapy—so long as the patient's condition permits.

Treatment for lung cancer is often multimodal. Radiotherapy and chemotherapy can be administered simultaneously as radiochemotherapy. Chemotherapy, radiotherapy, and radiochemotherapy may precede surgery (neoadjuvant therapy) or may follow it (adjuvant therapy).

If a lung tumor with mixed histology contains a combination of small cell lung cancer and non-small cell lung cancer, it should be treated as small cell lung cancer.

The German S3 guidelines on lung cancer are in preparation. The guidelines of the American College of Chest Physicians (ACCP) dating from 2007 are based on a systematic analysis of the published data. In these guidelines, the quality of the evidence on which a recommendation is based is graded as high (A), intermediate (B), or low or very low (C). The outline of therapy given below, where it relies on central statements of the ACCP Guidelines, reproduces their grading of the evidence (A–C) (13).

Treatment of non-small cell lung cancer

Stages I and II: In 25% to 30% of cases of non-small cell lung cancer, the diagnosis is made at this early stage (14). For patients without contraindications for surgery, resection is the treatment of choice (A). The oncosurgical procedure includes among other things lobectomy, bilobectomy (removal of two adjacent pulmonary lobes), and pneumonectomy with systematic mediastinal lymphadenectomy. After complete resection, platinum-based adjuvant chemotherapy is recommended for stage II tumors (A), but not generally for stage I tumors except in clinical trials. Adjuvant radiotherapy is not recommended after complete resection. In patients with stage I or II tumors who cannot

Basic diagnostic procedures

Basic diagnostic procedures include CT of the chest and upper abdominal organs, bronchoscopy, and usually bone scintigraphy. Further diagnostic procedures are added as required.

Distant metastases

Specific abnormalities in the clinical history and examination (see Box) and in laboratory results (blood profile, GOT, AP, and calcium should be determined) indicate the presence of distant metastases.

TABLE 2

Staging of lung cancer according to TNM findings *(see Table 1)*[*1]

	6th edition				Proposal for the 7th edition			
		T	N	M		T	N	M
Occult carcinoma		X	0	0		X	0	0
0		is	0	0		is	0	0
I	IA	1	0	0	IA	1a, b	0	0
	IB	2	0	0	IB	2a	0	0
II	IIA	1	1	0	IIA	1a, b	1	0
						2a	1	0
						2b	0	0
	IIB	2	1	0	IIB	2b	1	0
		3	0	0		3	0	0
III	IIIA	1–3	2	0	IIIA	1,2	2	0
		3	1	0		3	1,2	0
						4	1,0	0
	IIIB	4	0–2	0	IIIB	4	2	0
		Any	3	0		Any	3	0
IV		Any	Any	1	IV	Any	Any	1a, b

[*1] according to the 6th edition (5, 6) and proposal for the 7th edition (25)

undergo surgery, radiotherapy with curative intent is indicated (B) (14).

Stage IIIA: 15% to 20% of non-small cell lung cancers are diagnosed at this stage (1). This stage corresponds to T3N1M0 status. These tumors are often—except in the presence of contraindications—operated on like stage I and II non-small cell lung cancer. The operation is followed by adjuvant chemotherapy (15). Stage IIIA also includes tumors with N2 status (10% of all non-small cell lung cancers) and those on the borderline between operability and nonoperability (stage IIIB). This is a very heterogenous group, ranging from cases in which N2 lymph nodes were unexpectedly found in the histological analysis of the operative specimen, to N2 lymph nodes unexpectedly found intraoperatively, and single or multiple lymph nodes known about preoperatively, to "bulky disease" in the mediastinum. In cases where an N2 situation is discovered intraoperatively, the operation should be carried out as planned together with systematic lymphadenectomy of the involved nodes (C). When an N2 situation is discovered intra- or postoperatively and the patient's general condition is good, adjuvant platinum-based chemotherapy should be given (A) and radiotherapy should be considered (C). When the N2 status is confirmed preoperatively and lymph node involvement is not extensive (no bulky disease), treatment is tailored individually on an interdisciplinary basis (C). For these patients, as for those with bulky N2 disease, platinum-based radiochemotherapy is recommended (B), and in patients whose general condition is good both parts of the therapy should be carried out simultaneously.

Stage IIIB: About 10% to 15% of patients with non-small cell lung cancer have stage IIIB disease at the time of diagnosis (16). This stage is the domain of

Functional status

In addition to determining co-morbidities, the functional part of the diagnostic workup must establish whether adequate lung function would be expected to remain after any planned curative treatment.

Non-small cell lung cancer Stages I to II

In these stages treatment is given with curative intent. Stages I and II are the domain of surgical treatment.

radiochemotherapy. Patients whose disease is staged as IIIB on the ground of malignant pericardial or pleural effusion (which for the next classification in the future have been proposed to belong to stage IV) can only be treated palliatively, like patients in stage IV. For patients whose disease is staged as IIIB because of satellite disease in the same lobe and who do not have N2 status, operative treatment should be considered (C).

In all other cases, in which the IIIB staging is principally on the basis of N3 status (no pericardial or pleural effusion), a platinum-based radiochemotherapy regimen is the method of choice (A), and in patients in good general condition simultaneous therapy should be preferred to sequential therapy. In the case of patients in poor general condition or who have experienced more than 10% weight loss, the decision must be taken whether to carry out radiochemotherapy sequentially (C). In all other cases, if tumor symptoms are present, palliative radiotherapy can be carried out.

Stage IV: In 40% to 50% of patients, those in whom non-small cell lung cancer is diagnosed when it has reached stage IV, only palliative treatment can be offered (17). The success of chemotherapy depends on appropriate selection of the patients. General condition as assessed using the Karnofsky index/ECOG performance status, age, and co-morbidities are decisive factors.

A milestone in the palliative therapy of non-small cell lung cancer occurred when the effectiveness of platinum-based chemotherapy was demonstrated in comparison to supportive therapy (median survival 6.5 vs. 3.6 months) (18). The combination of platinum with a modern combination partner (a taxane, gemcitabine, vinorelbine) leads to survival times of around 10 months. The chemotherapy not only lengthens life, but in most patients also improves symptoms. For patients in good general condition, combination therapy with two substances (usually platinum-based) is recommended (A). At the age of 70 to 80 years, monotherapy is preferred (A) (unless there are no relevant co-morbidities [B]). After the age of 80, treatment decisions are taken on an individual basis (C).

Recent times have seen increasing individualization of the treatment of non-small cell lung cancer. In bevacizumab (a monoclonal antibody against vascular endothelial growth factor, VEGF), for the first time a licensed targeted therapy is available for first-line treatment of non-squamous non-small cell lung cancer in combination with chemotherapy. The chemotherapeutic pemetrexed is licensed for first-line treatment of non-squamous non-small cell lung cancer. Both these substances have increased overall survival in patients with stage IIIB/IV non-squamous non-small cell lung cancer to over 12 months (19, 20).

Other factors such as the expression of endothelial growth factor (EGF) receptors or other structures associated with carcinogenesis, and the expression of chemotherapy-resistant factors such as ERCC-1, can also play a role in guiding treatment.

In second and later lines of treatment, the chemotherapeutic docetaxel (e2) and the tyrosine kinase inhibitor erlotinib (e3) are licensed for all non-small cell lung cancers. Pemetrexed is also licensed for second-line therapy for non-squamous cell lung cancer (e4), and the receptor tyrosine kinase inhibitor gefitinib (e5) is licensed for all lines of treatment of non-small cell lung cancer with activating mutations in the EGF receptor. Maintenance or consolidative therapy (e6) is at present not recommended in advanced lung cancer. Recently studies have been published showing that patients in good general condition (ECOG 0 or 1) after four to six cycles of a platinum-based combination treatment have a survival advantage from receiving maintenance/consolidative therapy (with chemotherapy or targeted therapy). Pemetrexed is licensed for non-squamous cell cancers for maintanance therapy (e7). A final evaluation and recommendation on this subject is awaited.

Treatment of small cell lung cancer

Stages I–III: In these stages a combination of platinum-based chemotherapy and radiotherapy is indicated (A). If the patient's general condition allows and the patient has limited disease, radiochemotherapy should be carried out simultaneously and the irradiation should be accelerated and hyperfractionated (7).

Patients with a malignant pericardial or pleural effusion are treated as for stage IV disease. In stage I (T1N0, T2N0, stages IA and IB), operative treatment followed by adjuvant chemotherapy may be considered (C).

Stage IV: In most patients (60% to 70%) the disease is at this stage when it is diagnosed (7). Palliative chemotherapy takes the form of four to six cycles of platinum-based chemotherapy (B). Etoposide and irinotecan are recommended combination partners, although irinotecan is not licensed for this indication. If complete extrathoracic remission is achieved,

Non-small cell lung cancer
Stage III

In stage IIIA, management depends on N status. Stage IIIB is the domain of radiochemotherapy.

Non-small cell lung cancer
Stage IV

In 40% to 50% of patients, the diagnosis is made in stage IV. Only palliative therapy can be offered to these patients.

TABLE 3

Prognosis of non-small cell lung cancer*[1]

	Clinical stage		Pathological stage	
	5-year survival	Median survival	5-year survival	Median survival
IA	50%	60 months	73%	119 months
IB	40%	37 months	54%	70 months
IIA	24%	38 months	48%	54 months
IIB	25%	18 months	38%	33 months
IIIA	18%	14 months	25%	23 months
IIIB	8%	10 months	19%	16 months
IV	2%	6 months	21%	18 months

*[1] The cases on which this prognosis classification is based were collected as part of the development of a proposal for a new staging and classification system, but were grouped together into stages according to the current 6th edition of this system for an analysis of prognosis (25). Both clinical stage (evaluated preperatively) and pathological stage (evaluated postoperatively on the basis of the surgical specimen) are shown

consolidative or remission-promoting thoracic radiotherapy may be considered (C).

Recurrent or refractory disease: Disease that recurs earlier than 3 months after completion of initial treatment is regarded as refractory. Irrespective of the time of recurrence, a further course of chemotherapy should be offered if the patient's general condition allows (B) (7). If there is a good response to the first treatment protocol with a relatively long disease-free interval, the first protocol may be repeated. Topotecan is licensed for second-line use, or else an anthracycline-based protocol may be employed (e8, e9).

Prophylactic cranial irradiation: All patients who have achieved complete remission, or have undergone curative resection in stage I, should be offered prophylactic cranial irradiation (PCI) (B, C) (7). There is now reason to believe that a broad group of patients, including those with only partial remission, benefit from PCI (21).

Undesired drug effects during chemotherapy

All chemotherapeutic substances used to treat lung cancer are frequently or very frequently associated with bone marrow depression. This toxicity can require the use of growth factors, transfusion of red or white blood cell concentrate, dose adjustments, and even the interruption of therapy. Because of nausea and vomiting, adequate antiemetic premedication should be provided when any of the chemotherapeutics under discussion are given, especially the platinum-based combinations. In addition, with some substances nephrotoxicity (e.g., cisplatin), neurotoxicity (e.g., of taxanes), or cardiotoxicity (e.g., vinorelbine, taxanes) must be taken into account. Hair loss after chemotherapy is usually reversible. Cisplatin therapy must be accompanied by fluid and electrolyte administration. Treatment with taxanes must be preceded by prophylactic measures against allergic reactions. Treatment with pemetrexed must be accompanied by folic acid and vitamin B_{12} replacement.

Other treatment options

In palliative situations, radiotherapy and in special cases also surgery are used to treat local tumor-related problems. Examples are irraditation to alleviate pain caused by tumor (radiotherapy for pain), radiotherapy or surgical treatment of brain metastases, and palliative resection of infected tumors. Existing or imminent bronchial obstruction can be treated by interventional endoscopy, transcutaneous irradiation, or afterloading intraluminal brachytherapy. Pleurodesis and pericardiodesis are also available for palliative intervention.

Prognosis

The 5-year survival rate in lung cancer is around 15% and is closely dependent on stage. *Table 3* gives the prognosis for the various stages of non-small cell lung cancer with appropriate treatment. For small cell lung cancer, the prognosis of which is measured in weeks to months if untreated, the median survival with treatment is 16 to 22 months for limited disease and about 10 months for extensive disease (7).

Early diagnosis—screening

At the present time, screening for lung cancer is not recommended (22–24). In studies with regular "low-dose" CT, lung cancers were diagnosed in early stages and thus with a better prognosis. Whether "low-dose" CT can also reduce the disease-related mortality—as is required for a screening program—is currently being investigated in large studies.

If lung cancer is suspected in a patient, especially one at high risk of developing lung cancer, chest CT and bronchoscopy should be carried out.

Small cell lung cancer
Stages I to III

In stages I to III a combination of platinum-based chemotherapy and radiotherapy is indicated, if the patient's general condition allows and if there is no malignant effusion.

Small cell lung cancer
Stage IV

In stage IV small cell lung cancer, palliative platinum-based chemotherapy is indicated, if the patient's general condition allows.

Prevention

All measures that reduce cigarette smoking reduce the incidence of lung cancer (3).

Conflict of interest statement
Professor Hammerschmidt has received lecture fees and travel expenses from Roche and lecture fees from GlaxoSmithKline. Professor Wirtz declares that no conflict of interest exists according to the guidelines of the International Committee of Medical Journal Editors.

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Prognosis

The 5-year survival in lung cancer is around 15% and is strongly dependent on disease stage.

Screening

At present, screening examinations for lung cancer are not recommended.

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For e-references please refer to:
www.aerzteblatt-international.de/ref4909

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Please answer the following questions to participate in our certified Continuing Medical Education program. Only one answer is possible per question. Please select the answer that is most appropriate.

Where these questions relate to TNM classification and staging, the 6th edition (4, 5) is used.

Question 1

Why is the distinction between small cell lung cancer and non-small cell lung cancer important?

a) Because it distinguishes lung cancers due to cigarette smoking from those that arise independently of this noxa.
b) Because it distinguishes lung cancers due to occupational noxae from those that arise independently of such noxae.
c) Because it allows lung cancers to be distinguished on the basis of their biological properties.
d) Because it distinguishes lung cancers with early symptoms from those without early symptoms.
e) Because it distinguishes lung cancers of ectodermal from those of endodermal origin.

Question 2

In the course of the carcinogenesis of lung cancer, changes in cell biology occur. What, according to the current state of knowledge, is required for malignant transformation to take place?

a) Spontaneous mutation of the EGF receptor, leading to constant activation of receptor tyrosine kinase
b) Spontaneous mutation of the EGF receptor, leading to constantly reduced responsiveness of receptor tyrosine kinase
c) Simultaneous malignant transformation of several cells
d) Several cumulative changes in cell biology
e) Influence of two separate noxae over a long period

Question 3

What initial test(s) should be carried out in a patient at high risk of lung cancer who is suspected of having lung cancer?

a) Mediastinoscopy
b) Transbronchial needle aspiration
c) Endobronchial ultrasonography
d) PET or PET-CT
e) Thoracic CT and bronchoscopy

Question 4

What is the place of PET/PET-CT in the diagnostic workup of lung cancer?

a) PET/PET-CT is chiefly used for research purposes in lung cancer.
b) PET/PET-CT is used when available for patients with non-small cell lung cancer for whom curative therapy is being considered.
c) In most cases of non-small cell lung cancer, PET/PET-CT replaces biopsy confirmation.
d) In all cases of non-small cell lung cancer, PET/PET-CT replaces biopsy confirmation of suspected distant metastases.
e) PET/PET-CT is mainly used in small cell lung cancer, less often in non-small cell lung cancer.

Question 5

In a patient with non-small cell lung cancer for whom curative operative therapy is to be attempted if possible, a PET-positive lymph node is discovered. What should be the next step?

a) Start palliative radiotherapy
b) Curative resection
c) Histological/cytological confirmation
d) CT
e) PET-CT

Question 6

A patient has a non-small cell lung tumor in the right upper lobe, diameter 2.5 cm. There is no contact with the pleura, no endobronchial tumor growth, and no distant metastasis. The surgical specimen from upper lobe resection with systematic mediastinal lymphadenectomy shows involvement only of intrapulmonary lymph nodes.

In what stage is this tumor according to the 6th edition of the staging and classification system?

a) Stage IA
b) Stage IB
c) Stage IIA
d) Stage IIB
e) Stage IIIA

Question 7

In a 65-year-old patient in good general condition and with unrestricted functional status, a non-small cell lung cancer 5 cm in diameter is discovered in the left lower lobe. The tumor is in contact with the visceral pleura; the main bronchi appear free on endoscopy; cytological analysis of a left-side pleural effusion shows malignancy; CT shows markedly enlarged lymph nodes on both sides of the trachea; PET shows no signs of distant metastases.

What is the correct procedure?

a) Start palliative irradiation
b) Start palliative chemotherapy
c) Start radiochemotherapy
d) Start neoadjuvant chemotherapy followed by curative surgery if the response is good
e) Perform resection with curative intent followed by adjuvant chemotherapy

Question 8

Which procedure is central to the evaluation of the T descriptor in the diagnosis of disease extent?

a) Contrast-enhanced CT
b) PET
c) Magnetic resonance imaging
d) Endobronchial ultrasonography
e) Chest X-ray

Question 9

In which age group is the incidence of lung cancer highest?

a) 45–50 years
b) 55–60 years
c) 65–70 years
d) 75–80 years
e) 85–90 years

Question 10

Which treatment for stage I–III small cell lung cancer, if there is no malignant effusion or distant metastasis, is supported by high-grade evidence, so long as the patient's general condition allows it?

a) Platinum-based chemotherapy and radiotherapy
b) Chest radiotherapy alone
c) Chemotherapy alone
d) Chemotherapy with a receptor kinase inhibitor
e) Surgery followed by adjuvant chemotherapy

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The solutions to the following questions will be published in issue 5/2010.

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For issue 1–2/2010 plan to offer the topic „Drug Resistant Tuberculosis".

Solutions to the CME questionnaire in issue 41/2009: Suckfüll M: Perspectives on the Pathophysiology and Treatment of Sudden Idiopathic Sensorineural Hearing Loss::
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CONTINUING MEDICAL EDUCATION

Lung Cancer—Current Diagnosis and Treatment

Stefan Hammerschmidt, Hubert Wirtz

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