Prevention, Diagnosis, Therapy, and Follow-up of Lung Cancer

Interdisciplinary Guideline of the German Respiratory Society and the German Cancer Society*

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- German Society of Pathology,
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* Abridged Version.

1 Methodological Introduction

This abridged version is based on an interdisciplinary guideline which corresponds to development stage 3 (S3) of guidelines according to the classification of the Association of the Scientific Medical Societies in Germany (AWMF). The guideline development process is characterized by the combination of formal evidence-search, formal consensus, logic (algorithms), decision and outcome analysis, and interdisciplinary development with the cooperation of 15 German and Austrian medical societies. **Table 1** shows the relationship between levels of evidence, consensus, and resulting recommendation grades of the recommendations of this guideline. The recommendation grades A – D are added to the recommendations in the abridged version. For the evidence levels, see the full version [1].

For the preparation of this guideline the 6th edition of the TNM classification and staging system of UICC (International Union Against Cancer) was used which was valid until Dec 31, 2009. The changes in the classification and staging system carried out in the 7th edition, valid from Jan 01, 2010, are presented in chapter 5 (Diagnosis) of the full version of the guideline. The changes in the 7th edition of the UICC classification [4] result in an amendment in chapter 6 (Treatment of non-small cell lung carcinoma) and in the algorithm for the treatment of non-small cell lung cancer in stage IIIB (**Fig. 7**), where subgroup T4N0/1M0 no longer belongs to stage IIIB – as in the 6th edition –, but to stage IIIA. The recommendations for the therapeutic approach in subgroup T4N0/1M0 are not affected by the change in classification.

In this abridged version the recommendations of the guideline are summarized. The full version of the guideline has been published in printed form (Pneumologie 2010; 64, Supplement 2: S23 – S155) and electronic form (http://dx.doi.org/10.1055/s-0029-1243837). The electronic version includes the bibliography and appendices (occupational history form, evidence tables, addendum and guideline report).

2 Epidemiological Aspects of Lung Cancer

In all patients with lung cancer potential risk factors are to be investigated (smoking, occupational risk factors). A detailed history of potential occupational exposures is mandatory (**D**).

3 Prevention of Lung Cancer

Any exposure to tobacco smoke and secondhand smoking should be avoided (**A**).

In all patients with lung cancer the smoking status should be established and documented (**A**).

All smoking patients with lung cancer should be motivated to quit smoking. They should be offered participation in a qualified smoking-cessation program (**A**).

The implementation of workplace protection provisions and regulations, as required by law, together with continuous scientific review and risk assessment of hazardous substances, minimizes the risks from carcinogenic pollutants in the workplace (**A**).

To minimize the risk of lung cancer from exposure to radon gas the exposure to radon gas in homes must be consequently reduced through adequate technical measures (**A**).

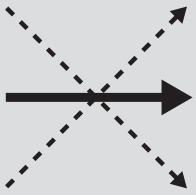
During the indication for medical application of ionizing radiation it is mandatory to weigh the benefits of its use against the potential risks of radiation exposure (**A**).

The lung cancer risk from air pollutants can be most effectively reduced by reducing the emission of diesel exhaust particles (**A**).

A diet that is rich in fruits, fresh vegetables, and tomatoes reduced the risk of lung cancer in several clinical trials and is therefore recommended (**C**).

Primary or secondary prevention by medication cannot be recommended outside of clinical studies (**A**).

Table 1 Relationship between levels of evidence and grades of recommendation (modified according to Oxford Center for Evidence-based Medicine 2001 [2] and AWMF [3]).

Evidence Level	Evidence Therapy	Diagnosis	Consensus Modifying criteria for recommendation	Grade of recommendation	
1a	Systematic Review (SR) of Randomized Controlled Clinical Trials (RCTs)	SR of Level 1 diagnostic studies	– Ethical aspects – Patient preferences – Clinical relevance, integrated outcome – Clinically significant deviation from study situation	A	Strong recommendation
1b	Individual RCT (with narrow confidence interval)	Validating cohort study with good reference standards			
1c	All or none	Absolute specifity for ruling in or absolute sensitivity for ruling out the diagnosis			
2a	SR of cohort studies	SR of Level > 2 diagnostic studies		B	Moderate recommendation
2b	Individual cohort study, low quality RCT	Exploratory cohort study with good reference standards			
2c	"Outcomes" Research				
3a	SR of case-control studies	SR of non-consecutive studies			
3b	Individual case-control study	Non-consecutive study			
4	Case-series, poor quality cohort and case-control studies	Case-control study, poor or non-independent reference standard	– Studies: consistency, effectiveness – Benefits, risks, side effects – Applicability	C	Weak recommendation
5	Expert opinion without critical appraisal, or based on physiology etc.	Expert opinion without critical appraisal, or based on physiology etc.		D	Missing or inconsistent studies, recommendation based on expert opinion

4 Early Detection of Lung Cancer

No clinical benefit of screening chest radiographs for the early detection of asymptomatic lung cancer, even in high-risk persons (e.g. smokers, asbestos exposure) has been established. Thus screening for lung cancer by chest radiographs in asymptomatic persons is not recommended (**A**).

No clinical benefit of screening CT scans for the early detection of asymptomatic lung cancer has been established up to now. Thus screening for lung cancer by CT scans in asymptomatic persons is not recommended either (**B**).

All asymptomatic persons insisting on CT scans for lung cancer screening should be given the opportunity to be included in a prospective, well designed, controlled, randomized clinical trial (**D**).

Based upon the clinical evidence available screening for lung cancer by sputum cytologic evaluation is not recommended (**A**).

Because of its invasive nature bronchoscopy is not suitable for the early diagnosis of lung cancer in asymptomatic risk collectives (**D**).

Screening for lung cancer with serum tumor markers is not recommended (**A**).

5 Diagnosis of Lung Cancer

Initial evaluation

In patients with suspected or known lung cancer a careful clinical evaluation including history and physical examination is strongly recommended (**A**).

It is strongly recommended that a patient with known lung cancer and a paraneoplastic syndrome is not precluded from potentially curative therapy on the basis of these symptoms alone (**A**).

Diagnosis

Chest X-ray examination (p.a. and lateral projections) is strongly recommended as initial radiological procedure (**A**).

In patients suspected of having lung cancer who are eligible for treatment a CT scan of the chest is strongly recommended, since the potential benefits outweigh the relatively low risk of a radiation-induced damage (**A**).

Bronchoscopy represents the most important method of confirmation of diagnosis. Before bronchoscopy, a CT scan of the chest is strongly recommended, since knowledge of the anatomical changes increases the diagnostic yield of the investigation (**A**). Diagnostic yield of bronchoscopy depends on the size of the tumor and of its location.

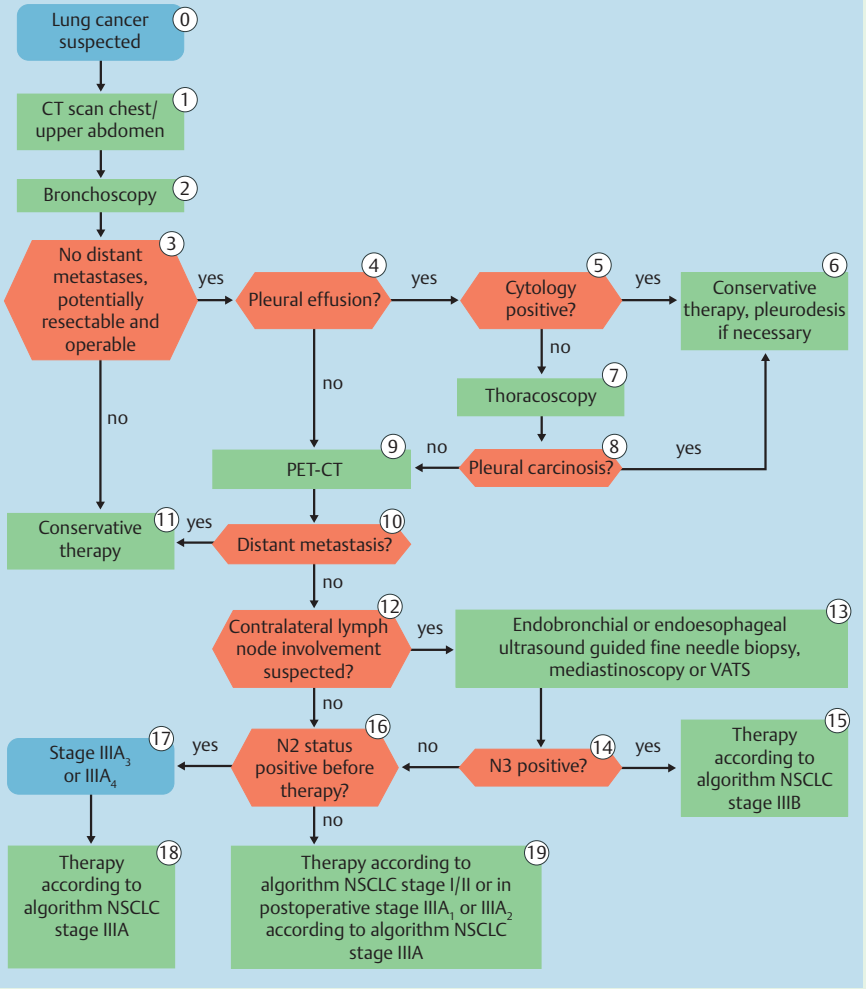


Fig. 1 Diagnostic algorithm for non-small cell lung cancer. In clinical stage IB – IIIB and curative treatment intention a study on brain metastases by cranial MRI is to be performed also under negative clinical examination findings.
Stages $IIIA_{1-4}$ correspond to the subclassification of Robinson [5, 6]: $IIIA_1$ mediastinal lymph node metastases in the postoperative histological examination in one lymph node level. $IIIA_2$ intraoperative finding of a lymph node involvement in one level. $IIIA_3$ involvement of one or more positions identified preoperatively by mediastinoscopy, needle biopsy, or PET. $IIIA_4$ „bulky disease“ (mediastinal lymph nodes > 2 – 3 cm with extracapsular invasion, lymph node involvement of multiple N2 positions, groups of multiple, positive small, 1 – 2 cm, lymph nodes) or fixed lymph nodes.

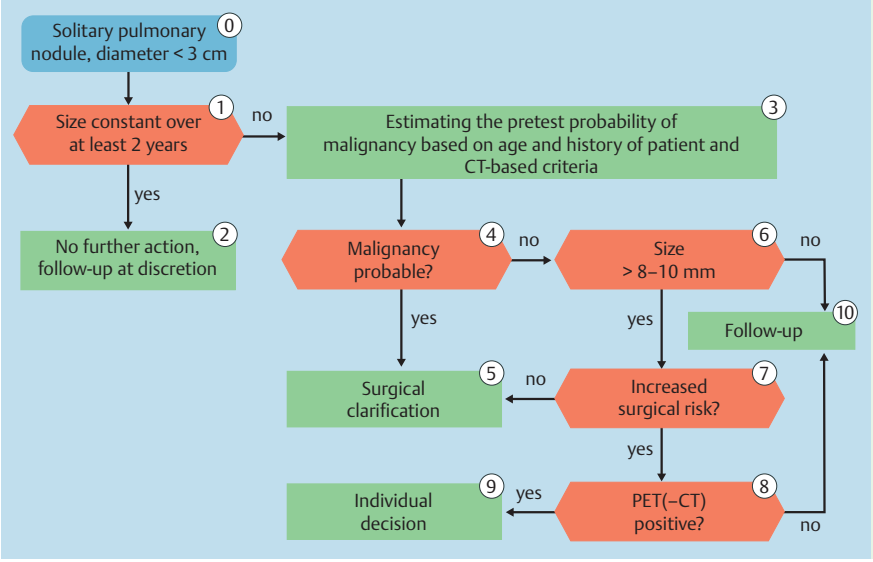


Fig. 2 Algorithm for diagnosis of the solitary pulmonary nodule.

In a patient with a central lesion bronchoscopy including various methods of tissue sampling is strongly recommended as primary method of confirmation of diagnosis (**A**).

In a patient with a peripheral lesion ≥ 2 cm in size transthoracic needle aspiration (TTNA) or bronchoscopy including various methods of tissue sampling under radiological guidance, such as fluoroscopy, is recommended (**B**).

In a patient with a peripheral lesion < 2 cm in size TTNA or bronchoscopy using modern navigation methods such as radial probe ultrasound or electromagnetic techniques are recommended (**B**).

The diagnosis of non-small cell lung cancer (NSCLC) made on the basis of cytology (by bronchoscopy, needle aspiration technique or sputum) can be accepted with a high degree of certainty for therapeutic management (**A**). If clinical presentation or clinical course is not consistent with that of small-cell lung cancer, a biopsy procedure for histological/immunohistochemical evaluation is recommended (**B**).

If in a case of a central tumor established methods to confirm a diagnosis such as bronchoscopy or TTNA cannot be conducted, sputum cytology is strongly recommended to certify the diagnosis (**A**).

In case of a pleura-based tumor, ultrasound- or CT-guided transthoracic needle aspiration (TTNA) is recommended (**B**). If the tumor is not pleura-based, CT-guided TTNA is strongly recommended in case of a negative bronchoscopy finding (**A**).

Due to missing data no recommendation can be made, whether in case of a peripheral tumor < 2 cm in size a bronchoscopy may be performed, in order to exclude endobronchial tumor growth or to assess endobronchial status before a planned surgical resection (**D**).

In case of suspected lung cancer, a surgical biopsy is recommended only, if less invasive methods of tissue sampling were non-diagnostic or could not be performed (**B**).

For the assessment of pleural effusion a transthoracic ultrasound (TTUS) is strongly recommended because of its higher sensitivity as compared to chest X-ray (**A**). In case of pleural effusion, a thoracentesis is strongly recommended to diagnose the cause of the pleural effusion (**A**).

In case of a negative cytologic finding after at most two thoracenteses, a thoracoscopy is recommended, if establishing the cause of the pleural effusion is believed to be clinically important (**B**).

Staging of lung cancer

Diagnosis of primary tumor (T-status)

In patients with suspected or known lung cancer who are eligible for treatment a CT scan of the chest with contrast including the upper abdomen (liver and adrenal glands) is strongly recommended as the most important method to assess the extent of the primary tumor (**A**). In addition, a differentiation between T1 and T2 tumors is also feasible.

Since CT assessment of mediastinal infiltration or infiltration of the chest wall may not be sufficient, additional methods such as thoracic ultrasound or MRI is recommended (**B**). Surgical exploration such as VATS can also be performed, provided there is no contraindication for resection (**C**).

In case of an extensive mediastinal infiltration (= T4 tumor) as assessed by CT scan, a further invasive confirmation may be waived (**B**).

In case of a superior sulcus tumor or tumor of the lung apex, a MRI is strongly recommended for assessment of tumor extension such as plexus involvement (**A**).

Lymph nodes (N-status)

In case of mediastinal lymph node enlargement (> 1 cm in short axis) in CT scan and in the absence of evidence for metastasis, the evaluation of mediastinal lymph node status is strongly recommended before treatment of the primary tumor (**A**).

In clinical stage IA with intention of curative treatment, a PET/CT scan can be performed for mediastinal and extrathoracic staging (**C**).

In clinical stage IB-IIIB with intention of curative treatment, a PET/CT scan is strongly recommended (**A**).

In case of a mediastinal lymph node change or enlargement (as assessed by CT, PET or PET/CT) and in the absence of evidence of metastasis (M0-status), a definitive evaluation of the lymph node status is strongly recommended before the intended curative treatment (**A**).

Depending on the experience of the investigator, endobronchial ultrasound with needle biopsy/aspiration (EBUS-TBNA), esophageal ultrasound with needle biopsy/aspiration (EUS-FNA), bronchoscopic needle aspiration (TBNA), transthoracic needle

biopsy/aspiration (TTNA) and surgical procedures such as mediastinoscopy or VATS are reasonable approaches. Transbronchial/transthoracic and endosonographic needle aspiration procedures are recommended to confirm, but not to exclude mediastinal lymph node metastasis (**B**).
In case of a mediastinal lymph node change or enlargement as assessed by imaging such as CT, PET or PET/CT and in case of a negative pathologic finding of a needle technique (EBUS, EUS, TBNA, TTNA), a mediastinoscopy, VATS or a suitable surgical technique are strongly recommended (**A**).

Distant metastases (M-staging)

In case of an abnormal clinical evaluation imaging for extrathoracic metastases is strongly recommended (**A**).
In clinical stage IB-IIIB and with intention for curative therapy imaging for extrathoracic metastases using head MRI and whole body FDG-PET is strongly recommended even in case of a negative clinical evaluation (**A**). If for medical reasons (e.g. diabetic metabolic state) a FDG-PET scan cannot be carried out, imaging for extrathoracic metastases using bone scan plus abdominal CT or bone scan plus abdominal ultrasound or whole body MRI is indicated.
In order to exclude cerebral metastasis, a MRI is strongly recommended (**A**). A cranial CT scan is only acceptable if there are contraindications to MRI (e.g. pacemaker) or claustrophobia (**A**).
In case of a suspected metastatic lesion as assessed by imaging, it is strongly recommended that a patient is not excluded from potentially curative treatment without pathologic confirmation of metastasis or overwhelming clinical or radiographic evidence of metastasis (**A**).

Small-cell lung cancer (SCLC)

In order to determine the tumor stage including detection of distant metastases, a FDG-PET scan is recommended, unless previously a M1 stage („extensive disease“) has been confirmed (**B**).

Neuroendocrine lung cancer

In well-differentiated neuroendocrine tumors a somatostatin receptor diagnosis may be performed to exclude somatostatin receptor-positive tumor manifestations (**C**).

Solitary pulmonary nodule

In every patient with a newly developed solitary pulmonary nodule (SPN; ≤ 3 cm in diameter), estimation of probability of malignancy, depending on age, diameter, morphology (e.g. spiculated border), location, smoking status, and extrathoracic malignancy is strongly recommended (**A**).
In every patient with a newly developed SPN a review with previous chest radiographs and CT scans is strongly recommended (**A**).
In case that a SPN is stable in size on CT imaging for at least 2 years, additional diagnostic evaluation is not recommended (**B**).
If **malignancy is suspected** in a patient with a SPN > 8 – 10 mm in diameter, evaluation by a surgical intervention as regular procedure is strongly recommended (**A**).
In a patient with a **malignancy suspected** SPN > 8 – 10 mm in diameter, and who is a candidate for curative surgery, transthoracic needle aspiration (TTNA) or bronchoscopy is not recommended as regular procedure for pathologic diagnosis (**B**).
In case of a **malignancy suspected** SPN > 8 – 10 mm in diameter in patients with increased risk for surgery, FDG-PET/CT scan is strongly recommended, if confirmation of diagnosis by invasive diagnostic methods is not possible (**A**).
In case of a SPN > 8 – 10 mm in diameter and low probability of malignancy or in case of a SPN < 8 – 10 mm in diameter, serial radiologic imaging tests are strongly recommended (**A**). CT- or low dose-CT scans are recommended as follow-up tests after 3 months, 6 months, 12 months, and 24 months (**B**).
In case of evidence of growth of SPN on imaging tests, a definitive pathologic evaluation is strongly recommended (**A**).

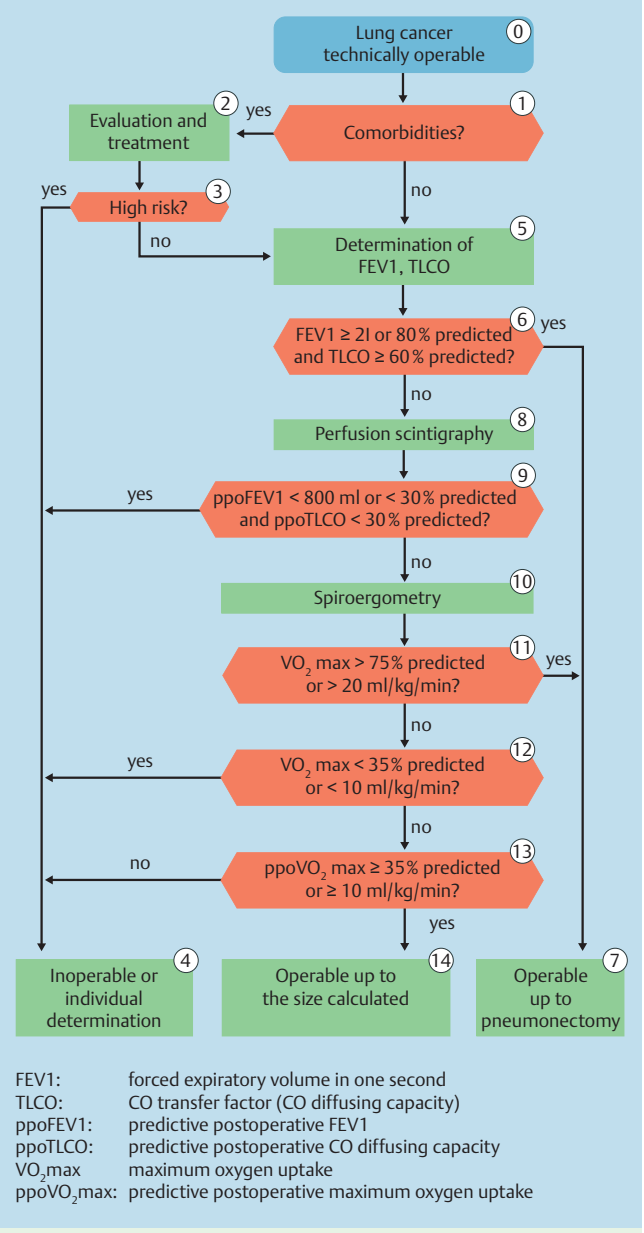


Fig. 3 Algorithm for the evaluation of operability for lung resections.

Pathology

A pathologic-anatomic assessment is strongly recommended for classification of lung tumor (typing), to determine tumor spread in resected tissue (p-staging), to assess the margins of resectate, to determine the grading, the grading of regression, prognosis-associated markers, and therapy-associated markers (**A**).

Assessment of Clinical and Functional Operability

In patients in advanced age (> 70 years) a particularly careful diagnostic evaluation and clinical assessment of comorbidities is recommended (**B**).

For the evaluation of lung function in critical cases and in a complex clinical situation, it is recommended that patients be assessed by an interdisciplinary team consisting of pneumologists, thoracic surgeons und radiation oncologists (**B**).

If in case of a planned lobectomy postbronchodilatory FEV1 is > 1.5 l und diffusing capacity (DLCO) > 60 % of predicted value, further lung function testing should not be performed. If in case of a planned pneumonectomy postbronchodilatory FEV1 is > 2.0 l and DLCO > 60 % of predicted value, further lung function testing is not recommended (**B**).

In patients, who according to FEV1- and DLCO-values are associated with increased perioperative and postoperative complications, a whole-body plethysmography, an arterial blood gas analysis at rest, a quantitative lung perfusion scan, and an exercise testing (spiroergometry) are recommended (**B**).

For assessment of increased risk of perioperative complications after lung resection a spiroergometry as standardised exercise test is recommended (**B**).

In case of a planned lung resection, recording of an ECG is strongly recommended (**A**). In case of a striking cardiac auscultation phenomenon or in case of clinical signs of myocardial failure, an echocardiography is recommended (**B**).

In the first 6 weeks after myocardial infarction, a lung resection is not recommended (**B**). In patients with myocardial infarction in the last 6 months before a planned lung resection, a cardiologic examination is recommended (**B**).

In case of a symptomatic stenosis or in case of a severe, but asymptomatic stenosis (> 70 %) of extracranial brain-supplying arteries, an interventional or surgical treatment of the stenosis is recommended before a planned lung resection (**B**).

6 Treatment of Non-Small Cell Lung Cancer (NSCLC)

Age and comorbidity

Higher age alone should not be the only reason to exclude patients from a treatment modality (chemotherapy, radiotherapy, surgery). Much more important is the spectrum of comorbidity (**C**).

Treatment of non-small cell lung cancer in stage I/II and T3N1M0 (IIIA)

Resection

In stage I/II radical resection is recommended, if adequate pulmonary function and lack of compromising contraindications are given (**A**).

In stage I/II with adequate cardiopulmonary function lobar resection is the recommended surgical approach (**A**).

If a lobar resection cannot be performed due to comorbidities or limitations of pulmonary function, a parenchyma-sparing resection or definitive radiotherapy is recommended. To define the appropriate approach, a multidisciplinary board, involving decision-makers with sufficient experience, is mandatory (**D**).

The primary goal of therapy is to be the radical resection with an appropriate tumor-free resection margin (**A**).

In all operated patients, a systematic lymph node dissection is necessary to provide an accurate staging and to potentially improve the prognosis (**C**).

Sleeve resection is recommended for patients with a tumor extent amenable to a parenchyma-sparing approach of resection (**D**).

For lung cancer with chest wall invasion a R0 situation is pivotal. In case of pleural invasion without rib involvement an extrapleural lysis may be approached; in case of deeper infiltration total chest wall resection is mandatory (**D**).

In spite of histologically documented R0 resection in chest wall infiltration, postoperative radiotherapy may be considered in individual cases (e. g. proximity of tumor location to the resection margin) (**D**).

In case of R1-resection, further surgery to achieve complete resection should be pursued. If further resection is not feasible, adequately dosed radiotherapy is recommended (60 Gy in 6 weeks): To define the appropriate approach a multidisciplinary board, involving decision-makers with sufficient experience, is mandatory (**D**).

In stage I, the VATS lobectomy shows no advantages in terms of morbidity and mortality in comparison to conventional open lobectomy. Thus it is currently not recommended to prefer VATS-lobectomy to conventional lobectomy (**B**).

Preoperative chemotherapy

In stage I randomized trials did not show an advantage of preoperative chemotherapy in terms of recurrence-free or overall survival. It is therefore not recommended beyond a clinical trial (**B**).

Accordingly this could not be shown for stage II disease – however, patient numbers with stage II disease in randomized trials were too low to approach statistically significant results. Thus, outside of a clinical trial preoperative chemotherapy is not recommended in stage II disease (**B**).

Postoperative chemotherapy

After R0-resection and systematic lymph node dissection patients in good general condition (ECOG 0/1) in stage II or $IIIA_1$/$IIIA_2$ (subclassification according to Robinson) are to receive adjuvant chemotherapy (**A**).

In stage IB, an individual treatment decision, considering comorbidity, age, and cardiopulmonary function is recommended (**D**).

After final wound healing adjuvant chemotherapy should begin within 60 days of resection (**D**).

The administration of 4 cycles of a cisplatin-based combination is recommended (**A**). Most of the positive studies employed vinorelbine as a combination partner.

Particularly in patients with significant comorbidity due to previous resection or preexisting disease it is recommended to conduct the adjuvant chemotherapy in an interdisciplinary environment with expertise in the multimodality treatment setting (**D**).

Postoperative radiotherapy and radio-/chemotherapy

In stage I, II adjuvant radiotherapy is not recommended after R0-resection (**B**).

In stage I, II adjuvant simultaneous chemoradiotherapy is not recommended after R0-resection (**B**).

Definitive radiotherapy in stage I/II, and T3N1 (IIIA)

In patients with stage I/II disease, inoperable due to limited pulmonary function or substantial comorbidity, definitive radiotherapy is recommended (**C**).

Inoperable patients with stage I/II should receive a total dose of > 60 Gy with conventional fractionation or treatment according

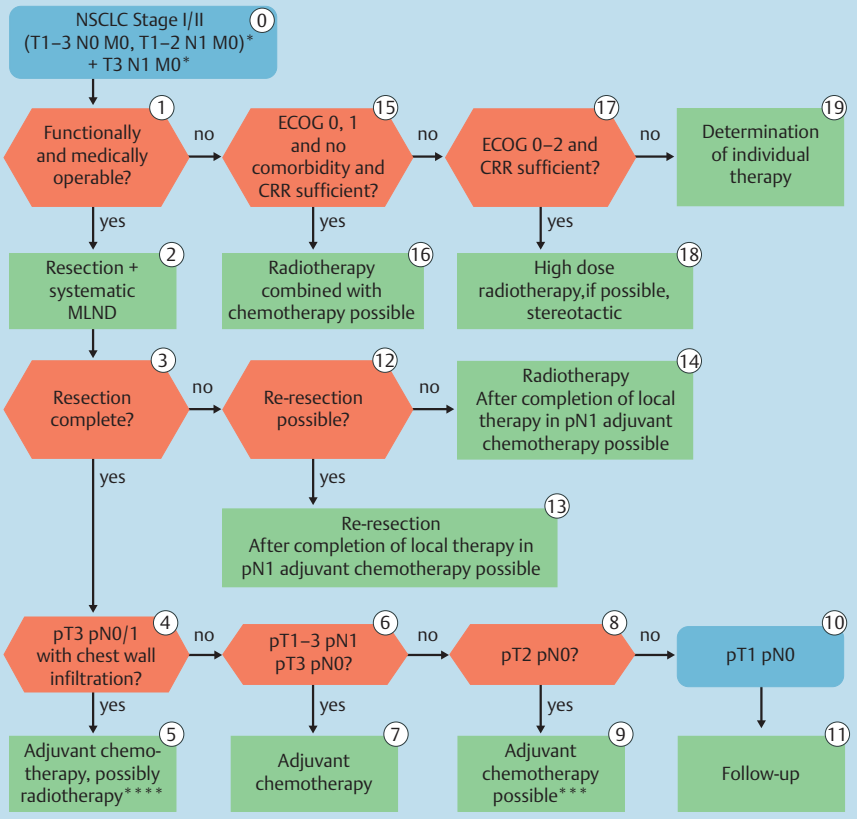


Fig. 4 Algorithm for the therapy of non-small cell lung cancer of stages I/II and T3N1M0.

MLND: Mediastinal Lymph Node Dissection; CRR: Cardiorespiratory Reserve.
Operability and resectability are assessed preoperatively by thoracic surgeon and pneumologist. Except for pT1 pN0 all patients will be presented after surgery or in inoperability to an interdisciplinary conference including at least pneumology, oncology, thoracic surgery, radiation oncology, and diagnostic radiology. The next steps (indication radiotherapy; indication chemotherapy) will be defined and documented.

* after a sensitive mediastinal staging according to diagnosis chapter.

** pN1 implies a high risk of systemic relapse; after R0 resection patients with pN1 (pT1–3) benefit most from adjuvant chemotherapy, therefore this can be recommended in an individual case also after completion of local therapy in previous R1/2 resection.

*** in exploratory subgroup analysis of adjuvant therapy studies pT2pN0 shows no consistent survival benefit with adjuvant therapy. A recommendation can be made in individual cases.

**** in cases of chest wall infiltration and histologically proven R0 resection the need of radiotherapy of the tumor bed may be discussed because of tumor location or vicinity of tumor to the resection margin.

to the CHART regimen (continous hyperfractionated accelerated radiotherapy treatment) (**B**).

An additional irradiation of the mediastinum in clinical stage I/II is not necessary (**D**).

In inoperable patients with stage T1 – 3N0 the indication for an adequately dosed stereotactic radiation therapy may be considered (**C**).

Pancoast tumor

In stage II-IIIB Pancoast tumors neoadjuvant chemoradiotherapy followed by resection is recommended. In case of contraindications against chemotherapy neoadjuvant radiotherapy alone should be followed by resection. Current data indicate that no postoperative chemotherapy or radiotherapy is recommended after R0-resection. To define the appropriate approach a multidisciplinary board, involving decision-makers with sufficient experience, is mandatory (**C**).

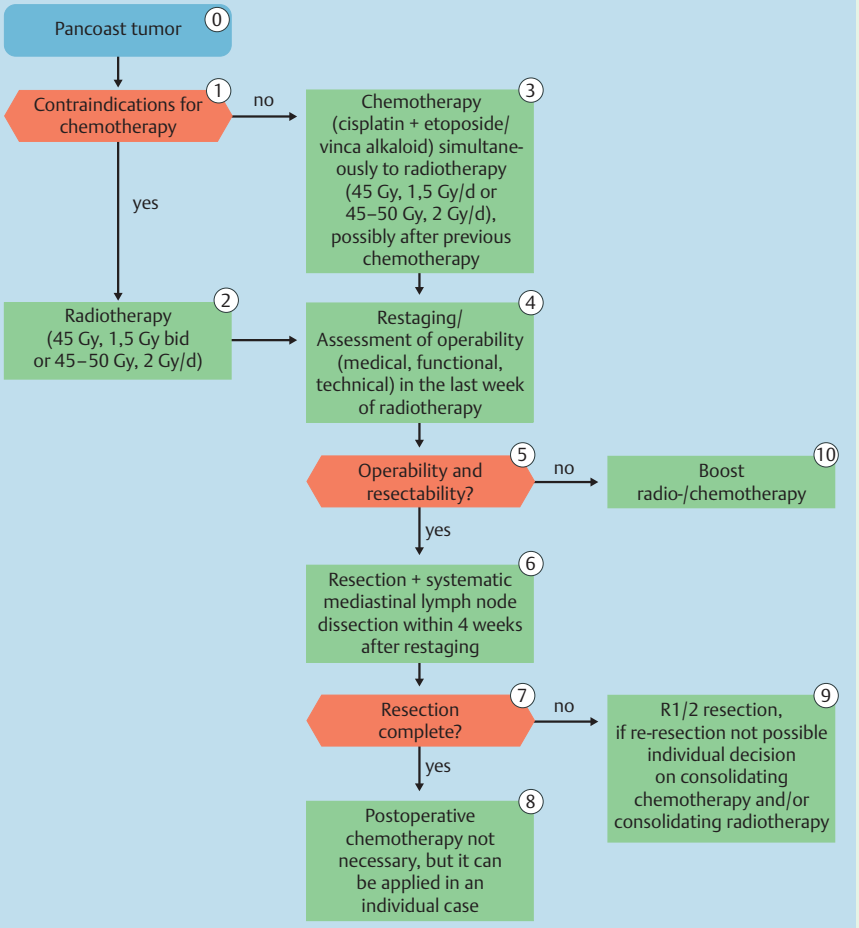
Patients with technical or functional inoperability should undergo definitive radio-/chemotherapy. To define the appropriate approach a multidisciplinary board, involving decision-makers with sufficient experience, is mandatory (**D**).

Treatment of non-small cell lung cancer in stage III (T1 – 3N2/T1 – 3N3/T4N0 – 3)

Heterogeneity of the subgroups in stage III – implications for patient selection

The TNM stages IIIA and IIIB used to differentiate between technically resectable – but prognostically unfavorable – tumor manifestations in stage IIIA and mostly technically inoperable disease extension in stage IIIB. Further developments in staging, surgical technique and multimodality approaches have shown the limitations of this classification for therapeutic decisions. An optimal choice of therapy requires an interdisciplinary discussion and treatment decision for each patient (at least involvement of respiratory medicine, oncology, thoracic surgery, radiation oncology and diagnostic radiology) (**D**).

The distinction of subgroups, particularly in stage IIIA-N2 according to the Robinson-classification, is of importance for prognosis and the choice of treatment (**B**).



Indications and therapy in centers.
In principle, such treatments from the beginning need interdisciplinary discussion and decision for reliable indication (conference with documentation and participation of at least pneumology, oncology, thoracic surgery, radiation oncology, and diagnostic radiology).

Fig. 5 Algorithm for the therapy of pancoast tumor.

Multimodality treatment including surgery in stage IIIA (N2) and in selected patients with stage IIIA (T4N0 – 1M0)[1]

Adjuvant chemotherapy in stage IIIA with incidental N2 status ($IIIA_1$/$IIIA_2$) is recommended after complete resection (R0) and systematic lymph node dissection (**A**).

After final wound healing adjuvant chemotherapy should start within 60 days of resection (**D**).

The administration of 4 cycles of a cisplatin-based combination is recommended (**A**). Most of the positive studies employed vinorelbine as a combination partner.

Particularly in patients with significant comorbidity, due to previous resection or pre-existing disease, it is recommended to conduct the adjuvant chemotherapy in an interdisciplinary environment with expertise in the multimodality treatment setting (**D**).

For patients with mediastinal lymph node involvement in stage $IIIA_1$ or $IIIA_2$ the indication for postoperative mediastinal radiotherapy should also be considered (**B**).

The irradiation should start no later than four weeks after completion of adjuvant chemotherapy and approach a target volume dose of 50 – 60 Gy (CT based three-dimensional treatment planning). Comorbidities have to be considered cautiously in the treatment planning (**B**).

Patients with stage $IIIA_3$ should preferentially be treated in the context of clinical trials to further define the therapeutic algorithm (**D**).

Outside of studies, patients in stage $IIIA_3$ with technically resectable tumor extent may be treated on an individual case based decision with an induction protocol (induction chemotherapy or chemo-/radiotherapy) followed by surgery (**B**).

These approaches should be confined to centers with advanced expertise in the field of multimodality treatment. An optimal choice of therapy requires an interdisciplinary discussion and treatment decision for each patient (at least involvement of respiratory medicine, oncology, thoracic surgery, radiation oncology and diagnostic radiology).

In the subgroup T4N0/1 an approach with primary surgery or the integration of surgery in the treatment approach should be considered in the following situations: carinal infiltration, resectable infiltration of the trachea, resectable lesions of the atrium, infiltration of the vena cava or the pulmonary artery, ipsilobar metastasis in tumor-bearing lobe (former T4 now T3) (**B**).

After surgery with R0-resection in patients of stage $IIIA_3$ who have received induction chemotherapy mediastinal radiotherapy should be considered; in those who have received induction chemo-/radiotherapy mediastinal radiotherapy is not mandatory (**B**).

[1] In the current 7th edition of the UICC classification T4N0-1M0 is assigned to stage IIIA and no longer – as in the sixth edition – to stage IIIB.

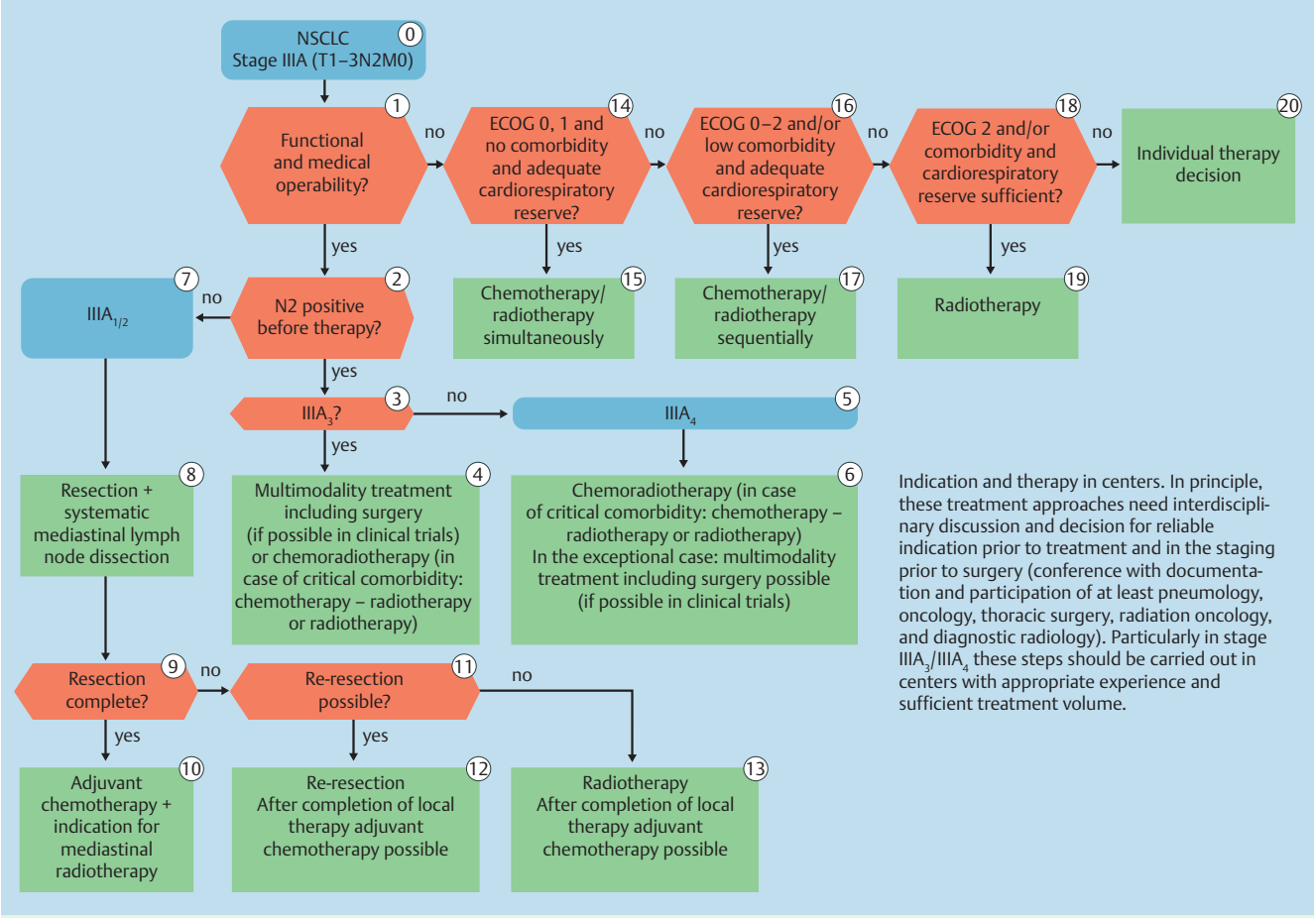


Fig. 6 Algorithm for the therapy of non-small cell lung cancer of stage IIIA (T1 – 3N2M0).

Patients with stage $IIIA_3$ – particularly with multiple N2 involvement – can be treated with a combination of radiotherapy and chemotherapy (definitive simultaneous chemo-/radiotherapy) as well (**A**).

Combination of chemotherapy and radiotherapy in stage III

Patients with stage $IIIA_3$ – particularly with multiple N2 involvement – can be treated with a combination of radiotherapy and chemotherapy (definitive simultaneous chemo-/radiotherapy) (**A**).

Patients with stage $IIIA_4$/IIIB should – if feasible due to tumor extent and comorbidity – receive a combination of radiotherapy and chemotherapy (**A**).

For selected patients with stage $IIIA_4$/IIIB a multimodality treatment approach, including surgery, might be pursued (**D**).

When compared directly – in appropriate patients – simultaneous radio-/chemotherapy is superior to the sequential approach. To select appropriate patients performance state and comorbidities have to be considered (**A**).

The sequence of chemotherapy followed by definitive radiotherapy improves median survival and 5-year survival rates in comparison to radiotherapy alone (**B**).

In terms of sequential or concurrent chemo-/radiotherapy cisplatin-based protocols should be employed (as combination partner in the simultaneous approach etoposide or vinca alkaloids should be selected) (**B**).

Typically two cycles of full-dosed cisplatin-containing combination chemotherapy (intertreatment interval 3 – 4 weeks) should be employed (**B**).

Given the high risk of systemic recurrence after definitive chemoradiotherapy, in individual cases a platinum-based combination chemotherapy might be pursued as consolidation treatment. This because of the historically promising data of the reference arm of a large multicenter randomized phase III trial (INT 0139) [7] (**D**).

Compared to concurrent chemo-/radiotherapy alone, the additional impact of consolidation chemotherapy has not been established in randomized trials. Of note, further consolidation with taxane-monochemotherapy after radio-/chemotherapy resulted in unacceptable toxicity and is not recommended (**A**).

Radiation therapy should typically approach a dose of 60 – 66 Gy with once-daily fractionation (**A**). The length of time depends on the single-fraction and extends typically over 6 – 7 weeks (**B**). An interruption of radiation therapy should be avoided (**C**).

Definitive radiotherapy in stage IIIA (N2)/IIIB (T4/N3)

In case of clinical stage III and contraindications against chemotherapy – beyond subgroups with very good prognosis after surgery alone – sole definitive radiotherapy is indicated (**B**). Patients with good performance status will benefit from more than one daily fraction (**A**).

Radiation therapy should typically approach a dose of 60 – 66 Gy with once-daily fractionation (**A**). The length of time depends on

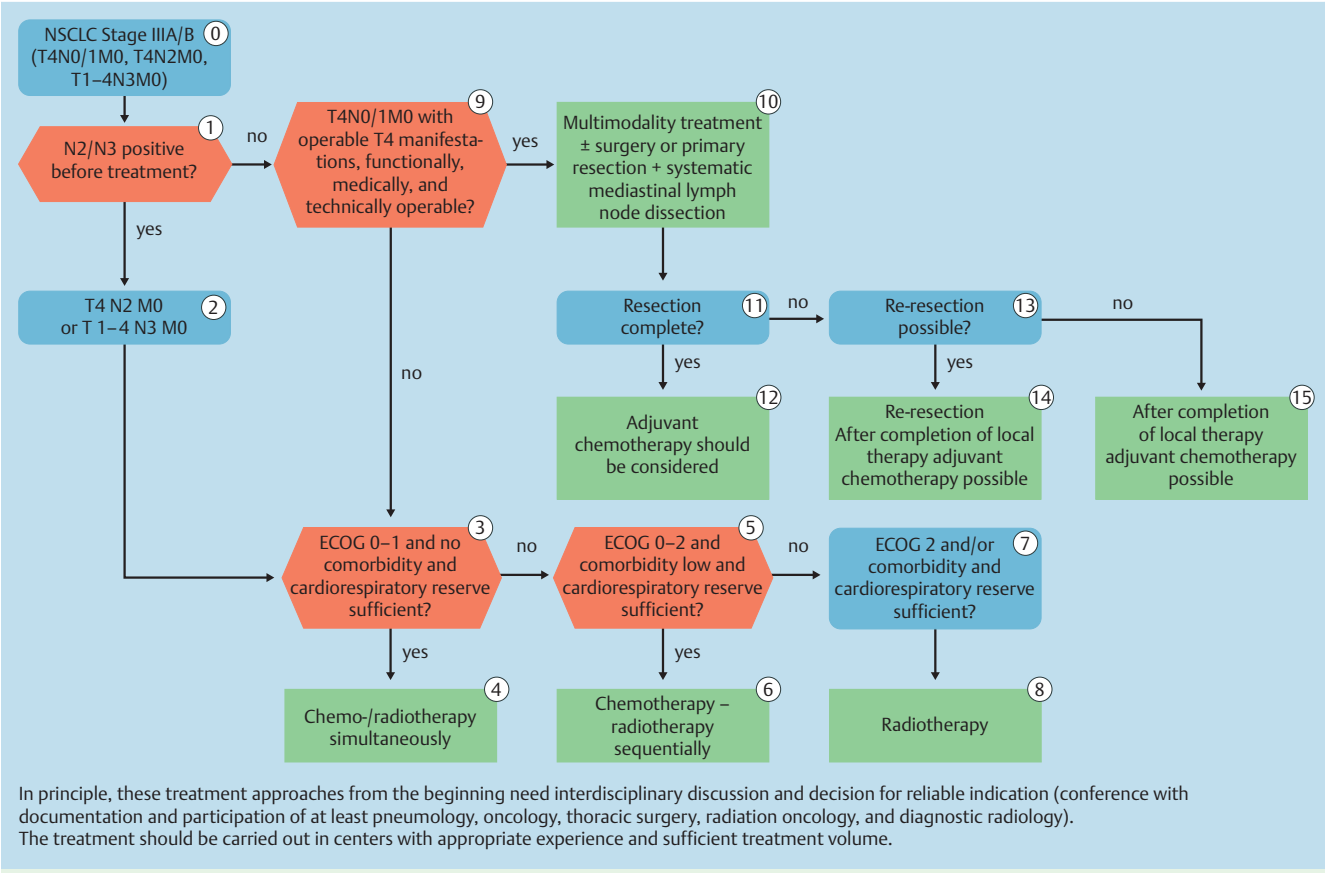


Fig. 7 Algorithm for the therapy of non-small lung cancer of stage IIIA/B (T4N0 – 1M0, T4N2M0, T1 – 4N3M0). In the current 7th edition of the UICC classification T4N0 – 1M0 is assigned to stage IIIA and no longer – as in the 6th edition – to stage IIIB.

the single-fraction and extends typically over 6 – 7 weeks (**B**). An interruption of radiation therapy should be avoided (**C**).
Palliative thoracic radiotherapy is indicated in patients not suitable for definitive radiotherapy and persisting symptoms (**A**).
According to the condition and the request of the patient shortened fractionation can be employed (**A**).

Treatment of non-small cell lung cancer in stage IV/IIIB (without indication for definitive radiotherapy)

The lifespan of patients with stage IIIB/IV is limited (median 8 – 12 months). Right from the beginning, a stable and reliable context of care should be provided, including an approach of interdisciplinary care (**D**).
In addition to medical treatment, aspects of education and information, facilitation of coping strategies, options for rehabilitation, psychosocial support, and social counselling should be addressed (**D**).
In stage IIIB/IV it should first be figured out whether a disease manifestation requires prompt intervention. This then should be done quickly and before the initiation of systemic therapy. Access to these technologies and procedures has to be ensured in time (**D**).
After presentation in an interdisciplinary center (pneumology, radiooncology, thoracic surgery, oncology, diagnostic radiology, nutrition counseling and therapy, psychological counseling and care, social service, palliative care, when needed tumor orthopedics and neurosurgery) quick decision making and provision of therapeutic measures should be provided (interdisciplinary tumor conference; documentation of the therapy setting) (**D**).

System therapy (first-line)

In patients with stage IIIB/IV and good general condition (ECOG 0,1) cisplatin-based combination chemotherapy is recommended to improve survival, disease control, and quality of life (**A**).
In case of relevant comorbidity (heart failure, renal insufficiency) carboplatin instead of cisplatin may be employed. Alternatively, a platinum-free combination with two „third-generation"-drugs can be employed (**B**).
In the first-line setting chemotherapy should continue up to 4 (-6) cycles. Currently there are no data that in terms of survival support a first-line maintenance chemotherapy (**B**).
Patients in poor general condition (ECOG 2) and those with contraindications against a platinum-based combination chemotherapy can receive a monotherapy with a „third-generation" – drug (eg vinorelbine, gemcitabine) in stage IIIB/IV (**A**).
For patients with stage IIIB/IV (ECOG 0,1) with non-squamous cell carcinoma, the treatment with bevacizumab in addition to platinum-based combination chemotherapy has improved response rate, median survival time and median progression-free survival significantly. In selected patients with stage IIIB/IV non-squamous cell carcinoma and good performance status (ECOG 0,1) – taking into account the contraindications – bevacizumab can be employed in first-line treatment in addition to platinum-based combination chemotherapy (**B**). Further characterization of patient subgroups that benefit most is warranted (**D**).

In patients aged > 70 years toxicity and lethality with bevacizumab might be significant. This should strongly be considered in older patients supposed to receive bevacizumab (**B**).
Even with ongoing treatment regular assessments should be performed to detect and treat symtoms compromising quality of life early (**B**).
With ongoing treatment regular assessments should be performed at 6-week intervals. After completion of therapy the control intervals are usually 6 – 12 weeks (**D**).
For patients with stage IIIB/IV, the treatment with cetuximab in addition to platinum-based combination chemotherapy has provided a statistically significant improvement in response rate and median survival. In patients with stage IIIB/IV cetuximab in addition to platinum-based combination chemotherapy can be used in first-line treatment (**B**). Further characterization of patient subgroups that benefit most is warranted (**D**). At the time of publication of the guideline cetuximab has not yet been approved for the treatment of non-small cell lung cancer.
In patients with activating mutations of the EGF receptor (especially del. 19; exon 21 L858R) gefitinib, in terms of response rate and progression-free survival, is significantly superior as compared to first-line chemotherapy (**B**). Gefitinib is approved in all lines of treatment of patients with a positive mutation status of EGFR. In the pivotal study the analysis of the mutation status was performed in patients with adenocarcinoma and minimal consumption of nicotine (94 % never-smokers).

System therapy (second-line and beyond)

For patients in good general condition with a disease progression after primary chemotherapy, the initiation of a second-line therapy is recommended until toxicities progress or occur (**A**). Despite low response rates, a survival prolongation and improvement of tumor-induced symptoms can be achieved. In Phase III studies have been assessed with appropriate evidence: docetaxel, pemetrexed, topotecan, vinflunine, gefitinib and erlotinib. For treatment, however, only docetaxel, pemetrexed (non-squamous carcinoma) and erlotinib have been approved.
Gefitinib has been approved in tumors with activating mutations of the EGF receptor (especially del. 19, exon 21 L858R) in all lines of therapy, even in second-line treatment (**B**). In the pivotal study the analysis of the mutation status was performed on patients with adenocarcinoma and minimal consumption of nicotine (94 % never-smokers).
In patients who keep progressing after a second-line therapy, a third-line should be performed (**B**).
In patients with long-term course of the disease and appropriate clinical situation even after „third-line“ – treatment another antitumor therapy might be instituted in case of disease progression to control symptoms (**D**).

Treatment of synchronous solitary metastases (brain, adrenal gland) involving resection of the primary tumor

In case of a definitely proven sole metastasis in the brain or adrenal gland and in the presence of a completely resectable lung cancer without evidence of mediastinal lymph node metastases (cT1 – 4, cN0 – 1) it is recommended to pursue, on an individual case based decision, cerebral metastasectomy followed by whole brain radiation or adrenalectomy and then resection of the lung tumor combined with pre-/postoperative chemotherapy (**C**)

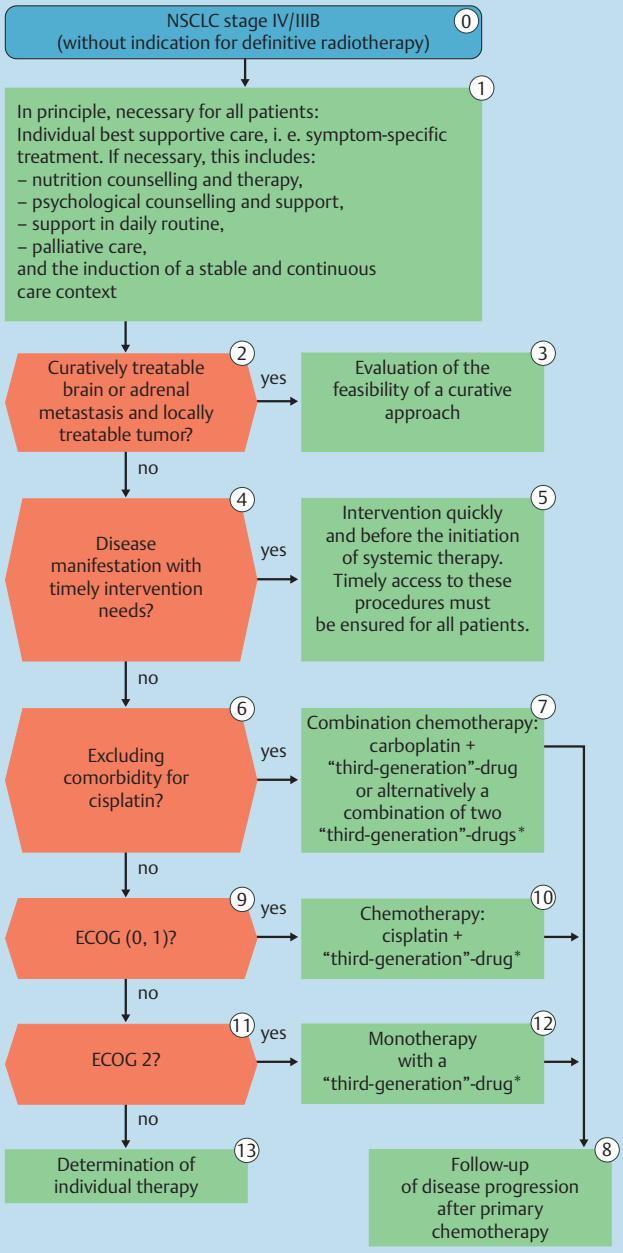
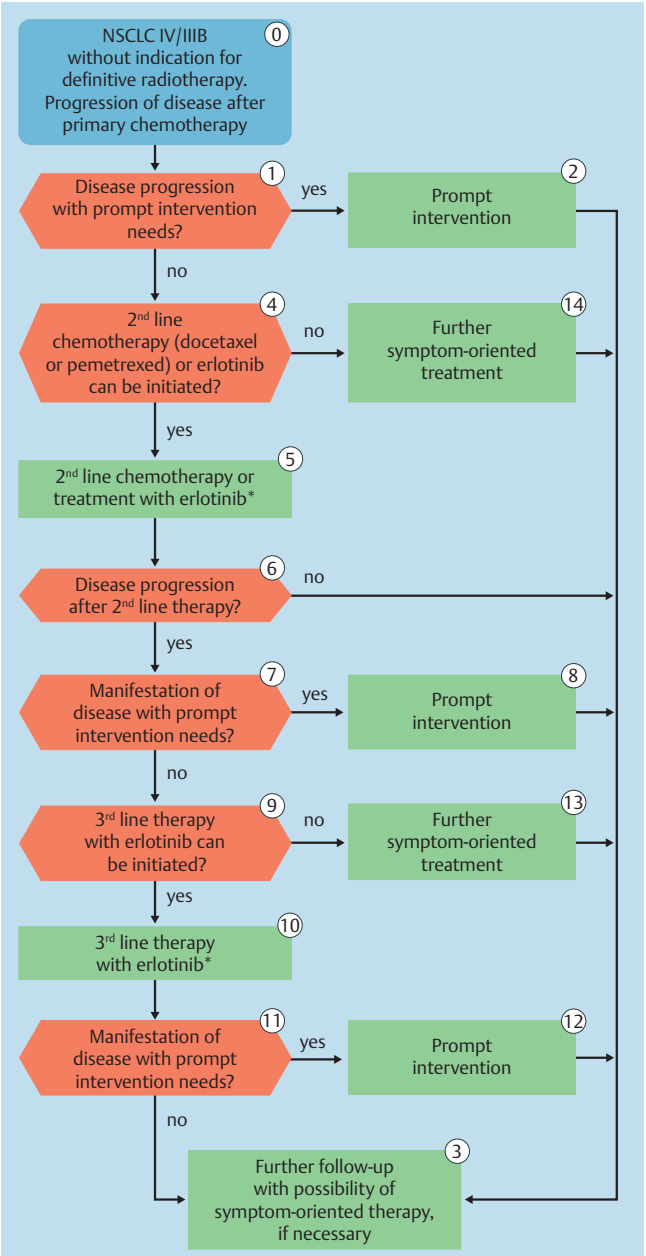


Fig. 8 Algorithm for the treatment of non-small cell lung cancer in stage IV/IIIB (without indication for definitive radiotherapy).

Brain metastases

In patients with a singular brain metastasis, a Karnofsky index > 70 and little or no extracerebral disease activity stereotactic radiosurgery is indicated as a local measure combined with whole brain radiotherapy (WBRT) (**A**).
After stereotactic irradiation of a singular brain metastasis and relevant extracerebral disease activity WBRT may be postponed as a component of salvage treatment in case of cerebral symptoms (**B**).



* In case of a proven activating EGFR mutation (particularly del 19, EXON 19; L858R, EXON 21) treatment should be initiated with gefitinib which compared to combination chemotherapy is associated with an improvement in response rate, progression-free survival, and quality of life. In the pivotal study the analysis of the mutation status was performed in patients with adenocarcinoma and minimal consumption of nicotine (94% never-smokers).

Fig. 9 Algorithm for the treatment of non-small cell lung cancer in stage IV/IIIB (without indication for definitive radiotherapy) with disease progression after primary chemotherapy.

In case of 2 – 4 brain metastases, Karnofsky index ≥ 70 and low or no extracerebral disease activity, stereotactic radiosurgery or neurosurgery followed by WBRT are recommended (**B**). In individual cases, the WBRT may be postponed for the case of occurrence of a cerebral relapse.

In patients with more than 3 – 4 brain metastases or in patients with a Karnofsky index < 70 or high extracerebral disease activity, WBRT is indicated as a palliative treatment approach (**A**).

Skeletal metastases

In patients with painful bone metastases, the indication for radiation therapy is to be checked (**A**).

For pain relief in bone metastases a 8 Gy single fraction is equally effective as a fractionated radiation therapy (4 × 5 Gy or 10 × 3 Gy) (**A**).

To control bone metastases, a fractionated radiotherapy is superior as compared to a single fraction, considering the necessity for further treatment, the occurrence of fractures, duration of symptom control, and metastatic myelocompression (**A**).

In the presence of bone metastases and expected long-term course of disease, the administration of bisphosphonates is recommended in addition to radiation therapy (**B**).

In bone metastases with an elevated fracture risk prophylactic surgery should be discussed interdisciplinary (**A**).

In patients with metastatic myelocompression and threatening spinal cord injury immediate initiation of radiation therapy (in addition to steroids) is recommended (**A**).

In patients with metastatic myelocompression and neurological symptoms the indication of a neurosurgical or orthopedic intervention, followed by radiation therapy, has to be assessed rapidly and therapeutic steps have to be performed immediately (**A**). In case of neurological symptoms or impending or already occurred paraplegia treatment has to start within 24 h (**A**).

Palliative surgery

In general, palliative pulmonary resections and chest wall surgery are based on individual case based decisions; general recommendations cannot be stated (**D**).

7 Treatment of Small Cell Lung Cancer (SCLC)

The tumor spread should be classified according to TNM characteristics and the current staging system of UICC (**C**). ECOG performance status, gender, and LDH (**A**) are of particular prognostic importance.

Treatment of small cell lung cancer in stage T1 – 2N0 – 1M0 (very limited disease)

Despite the rather negative Phase III experience, the long-term survival data of primary surgery seen in Phase II studies are very favorable. Therefore, primary surgery in patients with T1 – 2N0 – 1 SCLC without mediastinal lymph node involvement is a justified approach (**B**). Since the benefit of the operation has not been proven by a prospective randomized study, a pneumonectomy should be avoided in the light of postoperative function and quality of life. In addition, a mediastinal lymph node involvement has to be ruled out by the preoperative staging involving FDG-PET/CT.

Postoperatively adjuvant chemotherapy has to be added. Therapy of first choice is cisplatin/etoposide for 4 cycles. In the case of contraindications to cisplatin, the use of alternative protocols is preferable in any case to an abstention from adjuvant chemotherapy (**A**).

After surgical resection in all subgroups, in addition to adjuvant chemotherapy, prophylactic cranial irradiation is recommended. A frequently used approach is the administration of 30 Gy in 15 fractions (**B**).

In the case of N1 involvement an individual decision for mediastinal radiotherapy should be taken depending on the lymph node localization and the surgical assessment of radicality (**D**).

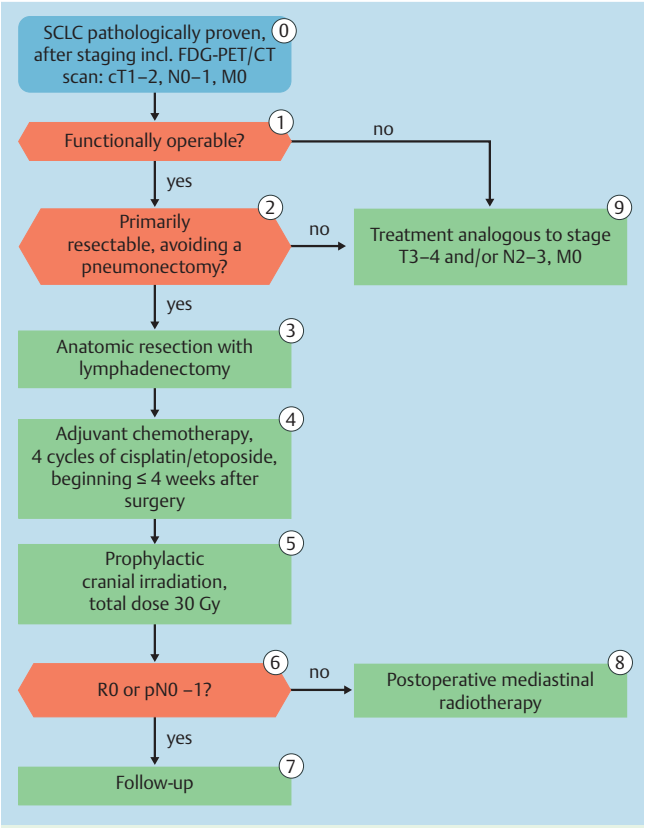


Fig. 10 Algorithm for the therapy of preoperative pathologically proven small cell lung cancer in stage cT1 – 2, N0 – 1, M0.

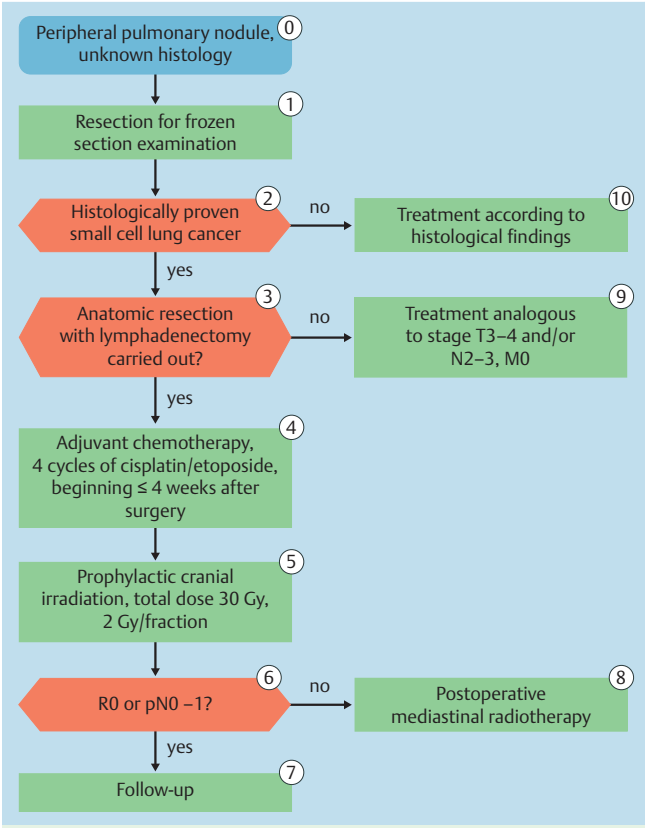


Fig. 11 Algorithm for the treatment of preoperative pathologically not confirmed small cell lung cancer in stage cT1 – 2, N0 – 1, M0.

In the case of N2 involvement mediastinal radiotherapy is recommended. This should be done at a dose of 50 – 60 Gy in conventional fractionation (**B**).

In the case of R1/2 resection an additional mediastinal radiotherapy is recommended as well (**D**).

In the case of already proven small cell lung cancer at a very early stage, preoperative chemotherapy seems to be comparable in efficacy to a postoperative approach. Patients can therefore be operated on first and then get chemotherapy, as well as receive initial chemotherapy and then surgery (**C**).

A primary definitive chemoradiotherapy is a treatment alternative; stage related effectiveness data or comparisons to the operating procedures, however, are not available. Therefore this treatment option is less proven than a surgical procedure (**C**).

Summary and rating

Patients with clinical stage T1 – 2N0 – 1, after exclusion of mediastinal lymph node metastases, should have a primary resection with adjuvant chemotherapy or neoadjuvant chemotherapy followed by surgery. All patients should receive, if possible, 4 cycles cisplatin/etoposide as chemotherapy. Postoperative mediastinal radiotherapy is to be discussed in the case of N1 involvement, it is recommended in the case of N2 involvement. Prophylactic cranial irradiation should be performed on all patients.

The resection of a pulmonary lesion with subsequent detection of a small cell lung cancer leads to an identical therapeutic approach.

Ultimately, it is unclear whether the excellent results of the operation reflect the high level of patient selection or the success of surgical therapy approach. Therefore, an alternative therapy is the carrying out of chemoradiotherapy analogous to that for patients with more advanced but localized disease. Due to the absence of TNM-related long-term survival data from patients receiving definitive chemoradiotherapy, the importance of this concept is currently being assessed but not yet proven. Such comparative studies should be pursued.

Treatment of small cell lung cancer in the tumor stages T3 – 4 and/or N2 – 3, M0 (limited disease)

First choice combination chemotherapy is cisplatin and etoposide (PE). The therapy should be performed over a period of at least four cycles. Carboplatin containing protocols are not sufficiently tested and should be used only in the case of clear contraindications against cisplatin containing schemes. Anthracycline containing regimens should be avoided (**A**).

Patients with primary tumor propagation capable of radiotherapy and without distant metastases should receive an irradiation of the primary tumor region (**A**).

In tumor stages T3 – 4 N0 – 1 and T1 – 4N2 – 3M0 (limited disease) radiotherapy should be applied simultaneously to chemotherapy with cisplatin and etoposide, if possible (**A**).

Patients treated with concurrent chemoradiotherapy should stop smoking (**B**).

Patients with tumor propagation capable of radiotherapy should receive an early simultaneous chemo-radiotherapy, if possible (**B**).

Patients with tumor propagation capable of radiotherapy should receive either an early hyperfractionated accelerated radiotherapy with a dose of 45 Gy or a conventionally fractionated early radiotherapy with a higher dose of 50 – 60 Gy (**B**).

In all patients with complete remission after chemo-radiotherapy, a prophylactic cranial irradiation should be carried out. Pre-

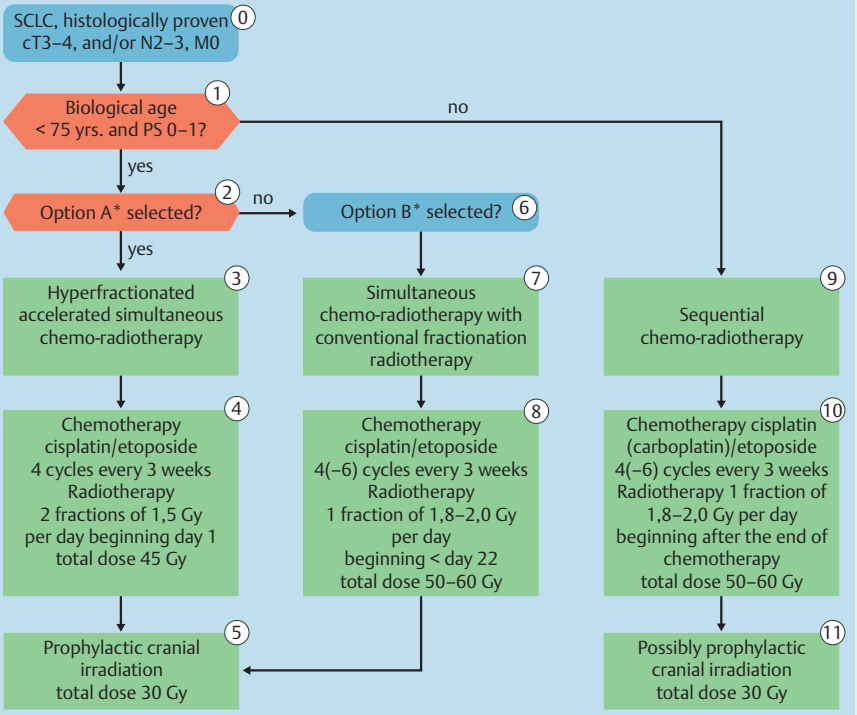


Fig. 12 Algorithm for the treatment of small cell lung cancer in stage T3 – 4 and/or N2 – 3, M0 (limited disease).

ferably a dose up to 30 Gy should be used in single daily doses from 1.8 to 2.0 Gy (**A**).

Neoadjuvant therapy is not a standard treatment in stage III. If a complete response of mediastinal lymph node involvement is achieved by neoadjuvant therapy, an anatomic resection can be discussed. The negative lymph node status should be histologically confirmed, a pneumonectomy is to be avoided (**C**).

An improvement of prognosis by intensified therapy has not yet been proven. Neither increasing the dose up to high dose chemotherapy nor shortening therapy intervals with or without the use of growth factors had a significant impact on prognosis. Dose intensification should therefore not be applied outside of studies (**A**).

Summary and rating

Patients with small cell lung cancer and tumor propagation capable of radiotherapy should receive combined chemoradiotherapy.

The chemotherapy protocol should consist of cisplatin/etoposide extending over 4 (– 6) cycles at 3-week intervals. The dose per cycle should not fall below cisplatin 80 mg/m² i.v., and etoposide 300 mg/m², divided into 3-day single doses.

The most favorable 5-year survival rates have been observed with concurrent hyperfractionated accelerated radiotherapy with a dose of 45 Gy, administered in two fractions of 1.5 Gy per day over a period of 15 days beginning with the first cycle of chemotherapy.

An alternative treatment strategy is the simultaneous conventional fractionated radiotherapy parallel to two cycles of PE as early as possible in the course of treatment. Here the aim should be a higher dose of 50 – 60 Gy with daily fractions of 1.8 to 2.0 Gy. The start of irradiation should take place no later than the beginning of the second chemotherapy cycle. The equivalence of concurrent conventionally fractionated irradiation with higher dose compared to hyperfractionated accelerated radiotherapy has so far not been established in a prospective study.

The consecutive implementation of chemotherapy followed by radiotherapy is appropriate for patients of advanced age or limited general condition or the presence of comorbidities.

All patients with remission after induction therapy should receive a cranial irradiation (30 Gy total dose in fractions of 1.8 to 2.0 Gy).

Treatment of small cell lung cancer in stage M1 (extensive disease)

Patients with small cell lung cancer and distant metastases are to receive primary chemotherapy (**A**). The most common combination consists of the drugs platinum and etoposide. Carboplatin is preferred because of better tolerability as compared to cisplatin (**B**).

Treatment alternatives are anthracycline containing therapy regimens as ACO (CAV) or ACE. Combinations of comparable efficacy are cis- or carboplatin plus topoisomerase I inhibitors (topotecan and irinotecan), paclitaxel or gemcitabine (**B**).

Multidrug protocols seem to be primarily an alternative to the standard platinum/etoposide protocol for selected patients in good general condition (**B**).

Dose-increased therapies are without benefit in patients with distant metastases and should not be used (**B**).

A convincing advantage of dose-intensified therapy has not yet been demonstrated. The treatment interval should not be extended beyond three weeks, if possible (**B**).

Primary monotherapy with carboplatin or oral etoposide or the application of a less intensive combination treatment with etoposide and vinca alkaloids lead to a reduction of response rate and a significant shortening of survival or tend to cause shorter survival times. The deterioration of response rates cause a worsening of symptom control and therefore a worsening of essential

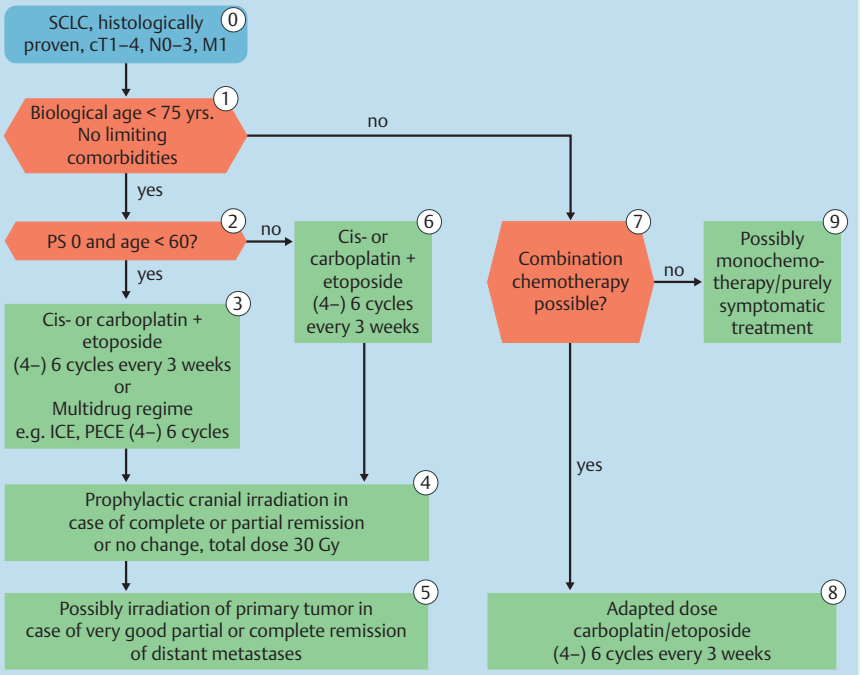


Fig. 13 Algorithm for the treatment of small cell lung cancer in the stage of distant metastasis M1 (extensive disease).
PS: ECOG/WHO Performance Status.
ICE: Ifosfamide, Carboplatin, Etoposide.
PECE: Cisplatin, Etoposide, Cyclophosphamide, Epirubicin.

parameters of quality of life. The administration of single agents or less intensive combinations should therefore be omitted as a rule (**A**).

Patients with brain metastases should be irradiated early in the course of therapy. In the case of symptomatic brain metastasis, the whole brain radiotherapy should start immediately after diagnosis, in the case of asymptomatic brain metastasis an early start of irradiation is desirable (**A**). When using a standard platinum/etoposide protocol, the irradiation can be applied parallel to chemotherapy.

Patients who respond to first line chemotherapy are to receive prophylactic cranial irradiation (**A**).

In the case of very good remission of distant metastases irradiation of the primary tumor is indicated as well (**B**).

Summary and rating

Patients with tumor spread not permitting irradiation should receive primarily a systemic chemotherapy, as a rule in 6 cycles at 3-week intervals. A shorter treatment duration appears to be justified when the patient obviously does not profit from a further continuation of treatment. Standard treatment protocols are cisplatin/etoposide and carboplatin/etoposide. The doses per cycle should not be lower than 80 mg/m^2 for cisplatin and AUC 5 for carboplatin. Etoposide should be used on three consecutive days in a cumulative total dose of at least 300 mg/m^2 (**A**).

Therapeutic alternatives are anthracycline containing regimens such as ACO or ACE. Combinations of cis- or carboplatin plus topoisomerase I inhibitors (topotecan and irinotecan), paclitaxel or gemcitabine have shown comparable efficacy (**B**).

Patients with remission are to receive an additional cranial irradiation after chemotherapy (**A**). In the case of very good remission of distant metastases an irradiation of the primary tumor is indicated as well (**B**).

Patients with brain metastases should receive a cranial irradiation early in the course of treatment (**A**). The other radiotherapeutic indications depend on the symptoms.

Treatment of older patients

In patients aged 70 years or more the selection of chemotherapy protocols has to be based on the existing comorbidities of the patients. In particular, cisplatin should only be given to selected patients in good general condition. Similarly, in the administration of anthracycline regimens, the specific cardiac and hepatic risk factors have to be observed. In cases where treatment is possible the combination of carboplatin/etoposide is the best tested regimen for elderly patients, and thus the therapy of first choice (**B**).

Decisive criterion for selecting the use of radiation therapy in elderly patients seems to be the general condition of patients rather than their calendar age.

At an age of 70 – 75 years a concurrent chemoradiotherapy is also possible in the case of very good general condition with results that are comparable to those of younger patients. At this age, therefore, a simultaneous procedure should be considered (**B**).

For patients of over 75 years of age there are no data concerning simultaneous chemo-radiotherapy. Because of the increased toxicity a simultaneous approach should be avoided in these patients. Here a consolidating irradiation of the primary tumor may be considered in the case of good general condition and lack of comorbidities (**C**).

The indications for prophylactic cranial irradiation are similar to those of the younger patient group (**C**). Cerebro-vascular risks of the patient should be given adequate attention.

Maintenance therapy

Overall, the value of a maintenance chemotherapy despite a positive meta-analysis has not been proven and therefore its routine use is not recommended (**A**).

Biological substances

Maintenance treatment with biological agents cannot be recommended at present (**A**).

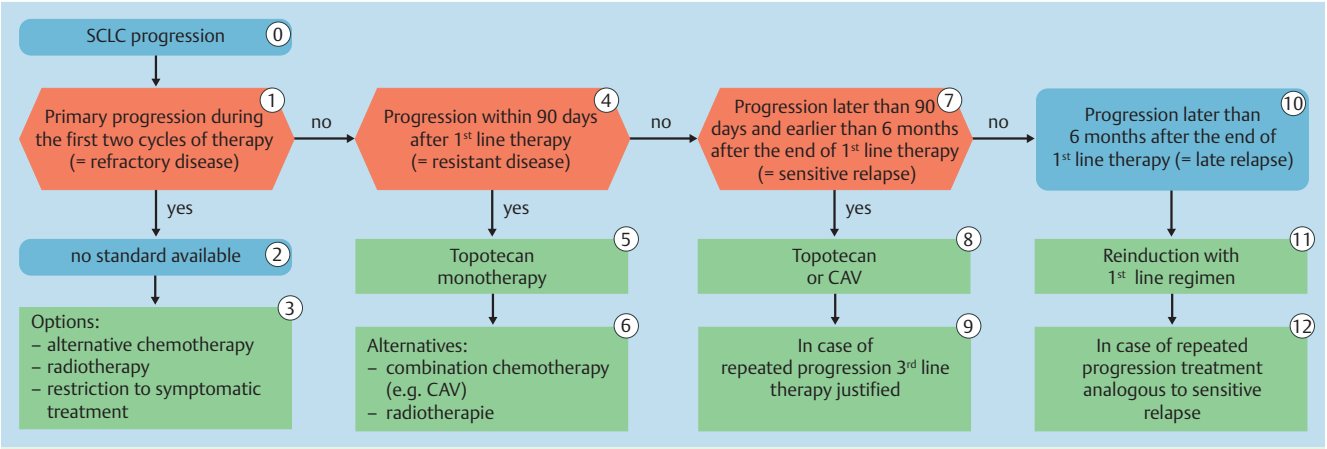


Fig. 14 Algorithm for the relapse treatment of small cell lung cancer.

Relapse therapy

Refractory disease (no response to first-line therapy, disease during the first two treatment cycles primarily progressive):
In patients of good general condition a second combination chemotherapy may be applied (**B**).
In patients of poor general condition, a restriction to symptom oriented measures is justified, since evidence of the effectiveness of a second combination chemotherapy in refractory disease has not been shown convincingly.
In locally refractory disease the possibility of palliative radiotherapy of the primary tumor should always be explored.
Resistant disease (remission or no change in the first-line chemotherapy, however, progressive disease within 90 days after the last dose chemotherapy):
For patients with resistant disease, a topotecan monotherapy has been proven as best choice by study results (**A**).
Possible treatment approaches are also a platinum-regimen after anthracycline treatment, and vice versa, and the use of paclitaxel- or irinotecan-containing protocols (**B**).
Sensitive relapse (remission or no change in the first-line, progressive disease later than 90 days and earlier than six months after the last chemotherapy):
With a sensitive relapse in each case, the application of a new chemotherapy is indicated. The efficacy of a topotecan monotherapy has been proven by a Phase III trial. A similar effect has been shown for combination chemotherapy with CAV (ACO) (**A**).
In non-platinum pretreatment, the administration of a platinum-containing therapy is useful. As an alternative, in particular paclitaxel and irinotecan containing regimens should be considered. These are available for patients with a sensitive relapse maybe even in third-line therapy (**B**).
Late relapse (remission or no change under the first-line therapy, disease progressive later than 6 months after the last chemotherapy):
The re-administration of the treatment protocol used primarily represents the treatment of first choice. This therapy should be used especially after a treatment free interval of more than 6 months (**B**).

Summary and rating

For refractory disease, the efficacy of second-line chemotherapy has not been proven or supported by studies. In clinical practice, an attempt seems justified in the case of good general condition and at the patient's request.

In resistant relapse the superiority of oral topotecan as compared to best supportive care has been proven. The administration of topotecan in this group is therefore the first therapy option.
In a sensitive relapse the superiority of topotecan as compared to best supportive care has also been shown. Here, the combination therapy with ACO is equally effective. After an anthracycline pretreatment a second-line platinum-based therapy should be applied.
In late relapse a reinduction therapy is the treatment of first choice.
Paclitaxel and irinotecan containing protocols are effective in the relapse situation, their use can be considered in primary refractory disease or in the third line of treatment.

New substances

As the evidence of prognosis improvement is pending, a use of newer drugs is justified only in clinical trials (**B**).

8 Treatment of Lung Cancer with Interventional Procedures

Malignant pleural effusion[2]

Appropriate examinations (bronchoscopy/CT scan of the chest) should ensure that the expansion of the lungs is not limited by a bronchial obstruction (**C**). Lung expansion should be evaluated by thoracentesis or small lumen chest tube (**C**).
In patients with lung cancer and recurrent, symptomatic, malignant pleural effusion, the thoracoscopic poudrage with talc (5 – 10g) represents the optimal procedure (**A**). It can be performed under general anesthesia or local anesthesia (**B**).
The talc used should be adjusted to particle size > 10 microns (**B**).
Treatment with talc slurry or a tetracycline derivative (doxycycline 500 mg) via chest tube causes fewer complications, however it is less effective. A pleurodesis with local cytostatics is not recommended (**B**).
In the case of a trapped lung, long-term chest drainage or a pleuroperitoneal shunt may be used (**C**).

[2] Definition: A pleural effusion is called malignant if malignant cells or tissues are detected in it.

Hemoptysis

In hemoptysis a bronchoscopy is indicated to identify the source of bleeding and to induce hemostasis by means of local measures (**B**).

Bronchial artery embolization is an effective and safe method for the treatment of massive or moderate, recurrent hemoptysis. In case of rebleeding it should be repeated (**B**).

Superior vena cava syndrome

The method of choice for palliation of superior vena cava syndrome is the percutaneous intravascular stent implantation, which allows a rapid and safe palliation. In therapy-naïve small cell lung cancer primarily a chemo- and/or radiotherapy is indicated, whereas stent implantation is reserved for patients with refractory or recurrent superior vena cava syndrome (**B**).

Tracheobronchial tumor obstruction

The palliative, endoscopic methods for the treatment of tracheobronchial tumor obstruction should be accessible to all cancer patients, even if the department performing the primary treatment does not offer these methods on location (**C**).

Mechanical methods, removal

The mechanical methods of removing exophytic tumor components with the edge of the rigid bronchoscope, with forceps or balloon catheters have an immediate impact, but can only be recommended for an emergency situation, if no other procedures are available (**C**). Balloon dilatation with the flexible bronchoscope is possible (**C**).

Laser therapy

In central tumor extension, especially with exophytic tumor tissue in trachea and main bronchi, the application of the laser provides immediate relief of symptoms (**C**).

Working with the rigid bronchoscope is recommended, particularly for large tumors in the trachea (**C**).

Combination with stenting and/or brachytherapy stabilizes the positive effect (**B**).

In some cases, small mucosal tumors can be eradicated, provided they are confined to the intraluminal surface. This procedure should only be considered for inoperable patients (**C**).

Electrical methods

Endobronchial electrical methods, especially the argon plasma coagulator (APC), are an inexpensive alternative to the ND-YAG laser for desobliteration of the central airways. Quality of life is improved (**C**).

For hemostasis APC is superior to all other local procedures (**C**).

In some cases, small tumors of the mucosa can be eradicated. This should only be considered for inoperable patients (**D**).

Cryotherapy

The endobronchial cryotherapy with rigid or flexible probe is gentle and safe with an effectiveness comparable to laser and APC. However, the effect is delayed. For tumor resection in patients not acutely threatened it can be recommended (**C**).

Cryotherapy can be tried for the curing of small mucosal tumors. Because of the high recurrence rate, this should only be considered for inoperable patients (**C**).

Photodynamic therapy

Photodynamic therapy (PDT) for symptom control in palliative treatment is only slightly superior to conventional laser. The quality of life is affected disproportionately because of skin sensitization. With the currently available sensitizers PDT can hardly be recommended for palliation, this may change if new sensitizers are approved (**C**).

For eradication of early tumors under 1 cm in diameter, which are limited to the mucosa, the PDT is the most effective method. A previous investigation by endobronchial ultrasound should be performed to rule out a deeper invasion (**C**).

In cancer lengths between 1 cm and 2 cm without deep invasion a combination with brachytherapy should take place (**C**).

Currently, these methods can be recommended only in studies. At first, surgery, even with bronchoplastic operations remains standard. A PDT can be justified in inoperable patients (**D**).

In individual cases, local operability can be achieved by PDT (**D**).

Bronchial and tracheal stents

The implantation of bronchial, tracheal and tracheobronchial stents is suitable for palliative treatment of symptomatic central airway stenosis. The therapeutic effect is immediate. Stent implantation can and should be combined with other methods (e.g. laser therapy, brachytherapy) and should in principle not be used as the last available method. After tumor regression stents can be removed in principle. Stent implantation should be offered or be accessible at a given indication in the context of interventional care for each patient (**C**).

Endobronchial brachytherapy

In patients without previous radiotherapy, the use of brachytherapy with palliative intention is appropriate in the individual cases for centrally stenosing tumors. If no radiotherapeutic preload is present, brachytherapy should be combined with percutaneous radiotherapy (**B**). In a tumor with stenosis of the central airways and radiotherapeutic preload endoluminal brachytherapy may be appropriate in certain cases (**C**). Brachytherapy as a boost for percutaneous radiotherapy in treatment approaches with curative intention is controversial and should only be carried out within studies (**D**).

9 Psycho-oncological Care of Patients with Lung Cancer

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Psycho-oncological treatment needs to be integrated in the overall concept of cancer therapy to reduce physical and psychosocial consequences of illness and treatment, to facilitate the disease process, as well as to improve the quality of life and to increase treatment compliance. Relatives of the cancer patient should be involved in the treatment (**D**).

All patients and their relatives should be informed early on by medical doctors about psycho-oncological help offered at the hospital (**D**).

Psycho-oncological interventions are to be based on the patients' individual needs and should be offered as early as possible. Validated screening instruments should be used in addition to the clinical impression to assess patients' needs. In the case of supra-threshold scores further diagnostic evaluation should be conducted, potentially including appropriate treatment by a qualified psycho-oncologist (**D**).

To ensure continuous psycho-oncological care after discharge from the hospital, the patients are to be informed on outpatient and aftercare services (such as psychosocial counselling, support groups, psychotherapy, governmental support etc.). A close linkage of inpatient and outpatient psychosocial care providers is desirable (**D**).
The health-related quality of life of patients should be regularly assessed in the course of the disease by the treating physician. This may, the disease situation of the patient permitting, include appropriate standardized questionnaires reflecting patient-assessed quality of life (**D**).

10 Supportive Treatment of Patients with Lung Cancer

Antiemetic prophylaxis and treatment

It is recommended to use antiemetic prophylaxis in patients who receive a low, moderate or highly emetogenic chemotherapy. This prophylaxis should be chosen according to the emetogenic potential of the chemotherapy and the risk factors of the patient (**A**).
For chemotherapy with minimal emetogenic risk no routine antiemetic prophylaxis is recommended (**D**).
Metoclopramide is only used in patients who experience nausea/vomiting, despite standard antiemetic prophylaxis.
For patients receiving local radiotherapy of a lung carcinoma no routine antiemetic prophylaxis is recommended (**C**).
In radiotherapy with a low emetogenic risk (craniospinal axis, fields including lower thoracic fields) an antiemetic prophylaxis with a 5-HT3-receptor antagonist may be given during the whole course of radiation or only in case of vomiting (**B**).
During chemoradiotherapy antiemetic prophylaxis should be given according to the emetogenic risk of the chemotherapy (**D**).

Treatment of anemia

Erythropoetin may be used in anemic patients to lower the need for transfusions of packed red cells during chemotherapy (**B**).
During treatment with erythropoetins a target hemoglobin of no more than 12.0 g/dl is indicated (**A**).
A high grade of caution is recommended in patients with a high thromboembolic risk.
When erythropoetin is used to treat anemia of patients with lung cancer, patients should be informed that a negative influence on life expectancy cannot be excluded (**B**).
Currently, outside of clinical trials, erythropoetin should not be used to treat tumor related anemia in patients with NSCLC who do not receive chemotherapy (**B**).

Treatment with growth factors of granulopoiesis

Primary prophylaxis with granulopoietic growth factors is recommended in patients receiving chemotherapy with a risk of febrile neutropenia greater than 20%, or with a risk of 10–20% depending on patient related risk factors (**A**).
Granulopoietic growth factors should not be given routinely in patients with neutropenia without fever or in addition to antibiotics in febrile neutropenia. These growth factors are to be considered, if there is a high risk for infection related complications, e.g. age above 65 years, pneumonia or sepsis (**C**).
During radiochemotherapy prophylactic administration of G-CSF is not recommended (**D**).

Table 2 Emetogenic risk in anticancer drugs used against lung cancer (according to Kris et al. 2006 [8]).

High risk (vomiting without antiemetic prophylaxis > 90%)	– Cisplatin
Moderate risk (vomiting without antiemetic prophylaxis 30–90%)	– Carboplatin – Cyclophosphamide – Doxorubicin – Epirubicin – Ifosfamide – Irinotecan – Paclitaxel
Low risk (vomiting without antiemetic prophylaxis 10–30%)	– Docetaxel – Etoposide – Gemcitabine – Pemetrexed – Topotecan
Minimal risk (vomiting without antiemetic prophylaxis < 10%)	– Bevacizumab – Vincristine – Vinorelbine

Table 3 Prophylactic antiemetic therapy in patients receiving chemotherapy according to ASCO- and MASCC-guidelines (Kris et al. 2006 [8]; MASCC 2006 [9]).

Emetogenic risk of chemotherapy	Prophylactic antiemetic therapy
high (> 90%)	5-HT3 receptor antagonist on day 1* dexamethasone on day 1 – 3§ aprepitant on day 1 – 3
moderate (30 – 90%)	5-HT3 receptor antagonist on day 1* dexamethasone on day 1 – 3 (plus aprepitant on day 1 – 3 in case of combination of anthracycline/ cyclophosphamide and risk factors)
low (10 – 30%)	dexamethasone on day 1
minimal (< 10%)	no routine antiemetic prophylaxis

* 5-HT3 receptor antagonists are equally effective and safe in comparable doses.
§ 5-HT3 receptor antagonists (in combination with dexamethasone) yield no additional effect against delayed nausea/vomiting.

Antibiotic prophylaxis during chemotherapy

During the first cycle of chemotherapy antibiotic prophylaxis can be given to reduce the risk of a febrile neutropenia (**B**).
The advantages and disadvantages of a prophylactic antibiotic administration should be carefully considered.

Prophylaxis and treatment of skin side effects of irradiation

During radiotherapy additional intensive physical irritations of the skin should be avoided (**D**).

Treatment of electrolyte disturbances

Syndrome of inadequate secretion of antidiuretic hormone (SIADH)

For causal treatment of SIADH in the context of lung cancer a rapid tumor directed treatment is recommended (chemotherapy, irradiation or tumor resection) (**B**).
For the initial symptomatic treatment fluid restriction and a cautious administration of saline is recommended (**D**).

Hypercalcemia

For patients with lung cancer and hypercalcemia fluid administration and aminobisphosphonates are the first choice (**A**).

Complementary medicine

Patients with a current or recent diagnosis of lung cancer should be asked about the use of complementary medicine. Patients then should have the opportunity to discuss these complementary measures with their doctor in a manner which considers their needs and which provides them with expert advise (**B**).
Use of substances without proven efficacy outside of clinical trials is not recommended (**D**).
If patients want to take herbal substances it should be excluded that there are possible pharmakodynamic or pharmakokinetic interactions with conventional agents taken at the same time (**A**).
During chemo- or radiotherapy nutritional agents with antioxidative properties should not be used in quantities which are much higher than the reference values given by national expert organizations for nutrition (**B**).
Patients with a current or recent diagnosis of lung cancer should receive expert advise during and after active treatment about optimal nutrition (**B**).
If possible, the use of other measures than drugs should be evaluated to reduce symptoms due to lung cancer or lung cancer treatment (**B**).

11 Palliative Care in Lung Cancer

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Dyspnea

For palliation of dyspnea oral or parenteral administration of opioids is recommended (**A**).
Administration of opioids by inhalation is not recommended (**C**).
Only in case of hypoxemia nasal administration of oxygen improves dyspnea (**B**).
Sedatives may help to reduce anxiety and distress (**D**).
Non-pharmacologic measures such as breathing techniques, physiotherapy or psychotherapy are important in relieving dyspnea in patients with lung cancer (**B**).

Malignant pericardial effusion

Due to a lack of randomized studies no single one of the various options for treatment of pericardial effusion can be preferentially recommended. In case of pericardial tamponade urgent drainage is necessary (**B**).

Pain

Treatment of pain is to be administered according to the WHO guidelines on cancer pain therapy (**A**).
Radiotherapy is the preferred treatment of localized bone pain (**A**), in case of multiple painful bone metastases treatment with systemic radioisotopes should be considered (**B**).

Anorexia/cachexia/dysphagia

Early assessment of patients with anorexia and weight loss is important to recognize treatable causes („secondary anorexia/cachexia“) as soon as possible (**D**).
Treatment of primary cachexia/anorexia syndrome with special nutritional supplements or enteral or parenteral alimentation is not helpful. Currently no evidence based drug therapy is available for treatment of cachexia/anorexia.
Stenosis by compression of tumor should be managed by local therapies (operation, radiation, interventional endoscopy).
If local therapy is not possible then feeding by means of a gastrostomy or by parenteral nutrition if gastrostomy is not possible should be initiated

Cough

In case of dry cough levodropropizine or dihydrocodeine can be used (**B**).

Terminal hemoptysis

For palliation of hemoptysis in the terminal patient opioids can be used (**D**).
In this very terminal situation invasive measures are not recommended (**D**).

Nausea and vomiting

Treatment of nausea/vomiting in advanced lung cancer depends on the underlying cause (**B**).
Symptomatic treatment may include administration of metoclopramide and/or dexamethasone (**C**).

Brain metastases

(regarding radiation see chap. „Treatment of NSCLC“ and „Treatment of SCLC“)
Patients with lung cancer and symptoms due to brain metastases are to receive dexamethasone (**A**).
For patients without seizures no anticonvulsive prophylaxis is recommended (**A**).
Decisions regarding the type of local treatment depend on several factors such as extent and activity of systemic disease, performance status and number of cerebral metastases (**A**).
In case of bad performance status and no response to corticosteroids mere treatment of symptoms (i.e. no tumor-directed therapy) should be considered (**C**).
More intensive treatment including stereotactic radiotherapy or surgery followed by whole brain radiotherapy may be recommended in patients with isolated brain metastasis and good performance status (KPS of 70 or higher) (**B**).

Spinal cord compression

Patients with suspected spinal cord compression are to recieve MRI (**A**).
In case of spinal cord compression a bolus of dexamethasone followed by continuous treatment is recommended (**A**).
Advantages and disadvantages of primary surgery should be weighed against radiotherapy alone according to individual factors. After surgery radiotherapy is recommended for consolidation (**A**).

Lambert-Eaton myasthenic syndrome (LEMS)

In addition to antitumor-directed treatment 3,4-diaminopyridine may improve muscle strength in patients with LEMS (**A**). In the acute phase immunglobulines may decrease symptoms (**B**).

Care during terminal phase

During terminal phase treatments without direct symptom improvement should be avoided, this is also applicable for parenteral fluid administration (**D**).
For dealing with distressing death rattle anticholinergics are useful.

Table 4 Indications for diagnostic procedures in follow-up of patients with lung cancer.

Diagnostic procedures	Indication
Bronchoscopy	High risk of local relapse (e. g. sleeve resection)
PET-CT scan	Exclusion of metastatic disease before further thoracic surgery
MRI	Brain and skeletal metastases
Chest radiography	Tumor kinetics
CT scan of the chest	Tumor kinetics and local tumor spread
Abdominal ultrasonography	Hepatic and adrenal metastases, paraaortic lymph node metastases
Abdominal CT scan	Abdominal metastases
Lung function testing, CO diffusing capacity	Lung function impairment, pneumonitis
Laboratory tests	At the physician's discretion

For palliative sedation midazolam, levomepromazine or phenobarbital are recommended (**D**).
Communication with patient and family members is of utmost importance (**D**).

12 Rehabilitation

Lung cancer patients benefit from single measures of rehabilitation (such as nursing interventions) with regard to quality of life (including psychological wellbeing) or dyspnea and such measures can therefore be recommended in the context of outpatient and inpatient rehabilitation (**B**). During anti-cancer-treatment (including high dose chemotherapy) aerobic endurance interval training (including lactate measurements and the analysis of heart rate variability) improves bone marrow regeneration and can also be recommended to regain physical performance more easily and more quickly. It is probable that comparable programs of cancer rehabilitation are also effective for lung cancer patients (**B**). Inpatient rehabilitation procedures can be recommended for the improvement of the quality of life and aerobic endurance capacity after primary treatment, if certain conditions of quality assurance are being met, such as standards implemented by the German Federal Agency for Rehabilitation (BAR) [10]. These standards focus on all elements of the infrastructure, the processes and the outcomes of rehabilitation. They also mandate experience in the rehabilitation of lung cancer patients that can be documented. The duration of rehabilitation should be flexible and adaptable to the individual patient need and should fulfill the requirements of health and pension insurance companies (**C**). These requirements are being set to avoid pension insurance payments or nursing interventions by rehabilitation. Outpatient rehabilitation measures can be implemented, if the institutions administering them can meet requirements comparable to rehab clinics. All institutions should have pneumological competence and offer special educational programmes for lung cancer patients. Primary care physicians should participate in the finding of the rehabilitation clinic (**D**). Patients after surgery and other significant treatments such as radio-chemotherapy and with extensive functional deficits should receive rehabilitation according to their individual context factors (occupation, profession, home situation, hobby activities) (**D**).

13 Follow-up

After completion of therapy, a structured, individual follow-up program should be provided for every patient. In this follow-up program all responsible persons should be involved. The focus should be the symptoms of the patients and psycho-oncology and social counselling should be integrated (**D**).
Patients with lung cancer should be sustainably motivated to quit smoking. To support patients in this effort, they should receive effective assistance for smoking cessation (**B**).
Posttherapeutic complications should be diagnosed and adequately treated in patients with curative treatment. The initial clinical presentation is recommended 4 – 6 weeks after completion of treatment, including a lung function test and the CO-diffusion capacity (DLCO) (**C**).
After curative treatment, surveillance should occur every 3 months during the first 2 years, every 6 months from year 3 through year 5 and annually 5 years after treatment. These intervals begin with the first presentation 4 – 6 weeks after completion of therapy. The visits include a detailed medical history, physical examination, and appropriate imaging procedures (**C**).
A general screening for brain metastases is not recommended, in high-risk patients, however, it is at the physician's discretion (**D**).
After palliative treatment, response, side effects, and symptoms should be evaluated one month after completion of treatment on the basis of medical history, physical examination, and chest x-ray. Clinical symptoms could lead to more imaging procedures. Clinical visits should be planned every 3 months. In patients with the option for further treatment the follow-up intervals can be reduced to 6 – 8 weeks. Appropriate imaging procedures should be used to detect a potential progress of the disease in time (**D**).

Conflict of interest

The Steering Committee has received from each author a completed form "Declaration of possible conflicts of interest", in which all relations to institutions of the pharmaceutical industry and medical device manufacturers had to be indicated. The Steering Committee reviewed the information and has not identified any conflicts of interest that could affect the professional independence of the authors with regard to the creation of the guideline.

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