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CLINICAL PRACTICE GUIDELINES

Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

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Incidence and epidemiology

Lung cancer is the leading cause of cancer mortality worldwide with 1.8 million newly diagnosed cases, or 13% of all cancers diagnosed, in 2012 [1]. The worldwide numbers are still rising despite an ongoing small decline in the Western world. Global statistics estimate that 15% of lung cancers in men and 53% in women are not attributable to smoking, overall accounting for 25% [2].

Screening for lung cancer

Lung cancer symptoms occur late in the disease, so the majority of patients with lung cancer present with advanced disease. Unfortunately for those patients, the disease will not be curable with currently available therapies. Therefore, early detection might be a valuable approach to detect the disease at an earlier, asymptomatic and potentially curable stage. Screening evaluated in relatively small trials failed to show benefit if periodical chest X-ray and/or sputum cytology were used; screening by these techniques is therefore not recommended.

The much larger National Lung Cancer Screening Trial (NLST) comparing low-dose computed tomography (LDCT) to chest X-ray in over 53 000 current or former heavy smokers ($\geq$ 30 pack-years or $\leq$ 15 years since smoking cessation), aged between 55 and 74 years, showed a 20% reduction in lung cancer-related death and an overall all-cause mortality reduction of 6.7% [3]. LDCT screening thus reduces lung cancer-related mortality. However, this positive outcome generates new questions on the rate of overdiagnosis of indolent cancers, such as lepidic adenocarcinomas (previously named bronchioloalveolar carcinoma) [4, 5], although a pathology review according to the recent classification [6] made this unlikely, as it categorised 97% of the detected cancers as invasive [7].

How screening for lung cancer should become part of standard evidence-based practice therefore needs to be analysed further. Nevertheless, for part of the Western world this positive trial has resulted in guidelines for screening within high-risk groups [8, 9]. Implementation in other health care systems has not yet happened as confirmation of the results in a comparable trial in a different geographical area is crucial. Mature data of the NELSON study [10] are expected in 2017 and may result in confirmation. The NELSON study developed a non-invasive protocol based on volume measurement and growth rate resulting in a 10-fold reduction of the false-positive rate compared to the NLST, maintaining the same lung cancer detection rate [11].

An important question is how to translate the findings of both NLST and NELSON into advice on 'who to screen' (high-risk group), 'how often' (intervals between rounds), and 'for how long' (until which age). It is difficult to come to conclusions on how to perform screening for the detection of incidence cases as a screening study initially mainly deals with prevalence cases and the trial runs during a limited period of time. Questions such as, 'what is the optimal time between screening rounds?', and 'for how long should this be continued?', are difficult to answer, because the characteristics of tumours detected during the prevalence screening might differ from tumours detected during incidence screening [12]. Furthermore, findings detected during

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earlier screening rounds provide further possibilities for risk stratifications and may lead to guidance on the length of screening [13].

Recommendations:

- Screening with LDCT reduces lung cancer-related mortality [I, A]. It is not yet ready for large-scale implementation, mainly because the lung cancer mortality reduction rate lacks definite proof of a second study result, and partly because of remaining questions regarding definition of the at-risk population, timing, interval and method of computed tomography (CT, especially 2D versus 3D evaluation), how to handle (false-) positive findings and especially cost-effectiveness, notably in relation to smoking cessation [I, A].
- LDCT screening can be carried out outside a clinical trial provided it is offered within a dedicated programme with quality control, in a centre with experience in CT screening, a large volume of thoracic oncology activity and multidisciplinary management of suspicious findings [I, B]. Candidates are current or former heavy smokers ($\geq$ 30 pack-years or $\leq$ 15 years since smoking cessation) aged 55–74 years, who are well informed about potential benefits and risks. Individuals offered LDCT screening should be referred to a smoking cessation programme.
- LDCT screening should not be offered on an *ad hoc* individual basis, but patients requesting screening should be referred to a dedicated programme, as recommended above [V, B].
- Other screening methods, such as chest X-ray, sputum analysis or biomarkers are not recommended for clinical use [I, C].

Diagnosis and pathology/molecular biology

Diagnosis

The most common diagnostic test for lung cancer is fibreoptic bronchoscopy, often extended with evaluation of regional lymph nodes by endobronchial ultrasound (EBUS) and/or endoscopic ultrasound (EUS). In most cases this will be sufficient to diagnose non-small-cell lung cancer (NSCLC), although quite often the amount of obtained material is not sufficient to sub-classify the tumour in more detail.

For earlier stages of NSCLC, the need for a detailed pretreatment pathological diagnosis is not yet clear. In contrast to stage IV [14], the consequences of the upfront diagnosis for selecting the most effective therapy of stages I–III NSCLC are assumed to be less relevant.

For molecular analysis, the sample obtained through EBUS-guided aspirations of lymph nodes is often sufficient [15]. Commonly used tests are summarised in Table 1.

Table 1. Work-up for diagnosis and staging

	Mandatory	Optional
General	Medical history[a] Physical examination[a] Assessing comorbidity PS	
Imaging	X-ray thorax CT thorax[a] PET-CT thorax[a] MRI brain[b]	Bone scintigraphy Contrast enhanced-CT brain
Laboratory	Blood cell counts Renal function Liver enzymes Bone parameters	
Cardio-pulmonary function	FVC, FEV1, DLCO ECG If indicated: CPET	Ejection fraction, CAG
Tissue procurement	Bronchoscopy[b,c] EBUS/EUS mediastinal nodes[a] CT-guided biopsy	Mediastinoscopy

[a]Tests needed for clinical staging.
[b]See text.
[c]Depending on site and size of tumour with biopsy/aspiration/brush/washing.
CAG, coronary angiography; CPET, cardio pulmonary exercise testing; CT, computed tomography; DLCO, diffusing capacity of the lungs for carbon monoxide; EBUS, endoscopic bronchial ultrasound; ECG, electrocardiogram; EUS, endoscopic ultrasound; FEV1, forced expiratory volume in 1 second; FVC, forced expiratory vital capacity; MRI, magnetic resonance imaging; PET-CT, positron emission tomography computed tomography; PS, performance status.

Pathology

As pathologists will not necessarily be aware of the disease stage at the time of pathological diagnosis, a thorough comprehensive diagnosis is always recommended whenever possible.

The recent World Health Organization (WHO) classification, with its further sub-classification of (surgically resected) adenocarcinoma, shows differences in metastatic pattern, recurrence and survival between different histological subtypes [16]. This becomes even more relevant as different histological subtypes differ with regards to metastatic pattern, recurrence and survival. The beneficial effects of adjuvant chemotherapy (ChT) post-resection may differ depending upon this adenocarcinoma sub-classification [17–19]; prospective trials are needed to evaluate whether these retrospective findings have clinical consequences.

The pathological classification at diagnosis may influence initial treatment decisions such as the initial surgical approach. In a large surgical series ($n = 2268$) of resected adenocarcinoma of $\leq$ 3 cm in diameter, the categories adenocarcinoma *in situ* (AIS), minimally invasive adenocarcinoma (MIA) and lepidic predominant (Lep) were found to have no metastasis in N1 or N2 lymph nodes ($n = 329$), whereas the other categories with predominance of acinar, papillary, micropapillary or solid growth patterns had N1 or N2 involvement in 22.9% of patients (445 of 1939). Until now, these features are only detectable in full extent in resected material; further refining of preoperative work-up might make this applicable for prospective use [20]. Future work may determine if the extent of surgery could be limited to a segmentectomy in the AIS and MIA subtypes, and a lobectomy could be

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performed with lymph node dissection for the invasive types. Such decisions could be based on intra-operative frozen section examination, which has a high concordance rate with final pathology [21], but is far from being a validated standard practice due to several technical and logistical problems [22–24].

Preoperative diagnostic work-up may identify patients at higher risk for presence of regional lymph node metastases. By measuring primary tumour low maximum standardised uptake values (SUV_{max}) of fluorodeoxyglucose-positron emission tomography (FDG-PET) (< 3.0), it was possible to detect those cases with low probability of mediastinal lymph node metastases, and to select the suitable candidates for a sublobar resection [25]; however, this needs to be confirmed in comparable studies before it can be concluded that a low SUV_{max} value of a peripheral tumour is useful for selection of patients for a sublobar resection.

If bronchoscopy or transthoracic needle biopsy results in large ($\geq 0.7\ mm^2$) and multiple (≥ 2) biopsies, the concordance with the final tumour classification after resection is ~70% overall.

For the acinar type, concordance was low, whereas the others were more favourable, but still relatively low at ~70% [26]. These types of study require further validation. Based on these observations, and for other reasons, the idea of 'minimal amounts of tissue to come to a diagnosis' of cancer needs to be re-evaluated, and probably changed to 'as much tissue as possible' to allow better diagnosis and classification as early as possible in the trajectory to therapeutic decisions. In general, the rate of NOS (not otherwise specified) after the complete diagnostic work-up should be <10%.

Recommendations:

- In patients with clinical stages I–III lesions, a pretreatment pathological diagnosis is recommended prior to any curative treatment.
- Bronchoscopy is the recommended test to obtain a pathological diagnosis of centrally located tumours in stages I–III with biopsy of any visible lesion [III, A].
- The pathological classification NOS should be used only in cases where it is impossible to obtain enough tissue for further classification, or when steps to further classify the tumour are inconclusive [V, A].
- An exception to the requirement for a pretreatment diagnosis can be made if an experienced multidisciplinary group decides that the risks of obtaining pathology may be unacceptable in a patient in whom the likelihood of malignancy is high based on clinical and imaging findings [III, B].
- A pretreatment pathological diagnosis is strongly recommended for all patients before stereotactic ablative radiotherapy (SABR), unless a multidisciplinary tumour board is of the opinion that the risk-benefit ratio of the procedure is unacceptable. In such a situation, the predicted likelihood of malignancy should preferably be at least 85%, based upon accepted criteria [III, B] [25].
- The descriptive element of the recent WHO classification of adenocarcinoma subtypes should be used to describe bronchoscopic and CT-guided biopsies whenever possible [III, A].
- The revised adenocarcinoma classification may identify patient subtypes for whom an anatomical sublobar resection, rather than lobectomy, would be sufficient [III, A].
- FDG-PET may contribute for the selection of patients for anatomical sublobar resections as low SUV_{max} values of peripheral tumours indicate lack of mediastinal metastases [III, A]. This diagnosis may be made intra-operatively by video-assisted thoracoscopic biopsy and frozen section analysis.
- In isolated cases a diagnostic anatomical sublobar resection may be acceptable.

The solitary pulmonary nodule

Solitary pulmonary nodules are a common problem and are usually a diagnostic challenge. Depending on presence or lack of benign characteristics, such as calcification or no changes during at least 2 years, a diagnostic algorithm can be used to qualify the lesion as more or less likely to be malignant. However, it is important to note that validated diagnostic algorithms are not available in many populations. Guidelines developed by the British Thoracic Society (BTS) and the Fleischner Society were published recently [27, 28], but like many previous guidelines, have focussed on Western populations. For other areas, such as Asia, with a high prevalence of granulomatous disease and other infectious causes of pulmonary nodules, the recent Asian consensus guidelines are likely more appropriate. The latter recommend a lesser reliance on positron emission tomography (PET) scans in Asian populations, and greater use of non-surgical biopsy over surgical diagnosis or surveillance [29].

In general, it is important for clinicians to be aware of the emphasis they would place on a 'non-malignant' result from a percutaneous biopsy. If the clinical and radiological evidence would favour a surgical biopsy in any case, then the merits of non-invasive methods should be discussed with the patient.

Recent data from the NELSON study on incidental nodules might be applied to the solitary nodule and incorporated in guidelines [12]. Diagnostic procedures, as described in the previous section, will be of help in case further evaluation is needed.

Recommendations:

- The diagnostic approach to non-calcified pulmonary nodules should be based on existing standard guidelines [III, A], although new evidence on nodule management is emerging.
- Likelihood of malignancy based upon risk calculation methods used in CT screening studies should be used only to guide the clinical assessment of pulmonary nodules detected in the wider population [V, C].

Staging and risk assessment

During the 16th World Congress of Lung Cancer, the Union for International Cancer Control (UICC) presented the revised tumour, node and metastasis (TNM) classification of malignant tumours (UICC TNM 8), published in December 2016 [30] and effective since January 2017 (Table 2).

Recommendation:

- In non-metastatic NSCLC, detailed locoregional staging according to the 8th TNM staging system and the cardiopulmonary fitness of the patient determine the choice of treatment [III, A].

Locoregional staging

For locoregional staging, algorithms shown in Figures 1 and 2 are still applicable.

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Table 2. Staging and stage grouping UICC TNM 8 [30]

Occult carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA1	T1a(mi)	N0	M0
	T1a	N0	M0
Stage IA2	T1b	N0	M0
Stage IA3	T1c	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T2b	N0	M0
Stage IIB	T1a–c	N1	M0
	T2a–b	N1	M0
	T3	N0	M0
Stage IIIA	T1a–c	N2	M0
	T2a–b	N2	M0
	T3	N1	M0
	T4	N0	M0
	T4	N1	M0
Stage IIIB	T1a–c	N3	M0
	T2a–b	N3	M0
	T3	N2	M0
	T4	N2	M0
Stage IIIC	T3	N3	M0
	T4	N3	M0

UICC, Union for International Cancer Control; TNM, tumour, node and metastasis.
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The two most striking changes in UICC TNM 8 are the further subdividing and detailing of both T and M stage, although the consequences for therapeutic approach are not yet obvious in all situations.

The T stage was divided further by splitting T1 into three subgroups based on size (T1a $\leq$ 1 cm, T1b $>$ 1 cm to $\leq$ 2 cm, T1c $>$ 2 cm to $\leq$ 3 cm), this is continued into T2 (T2a $>$ 3 cm to $\leq$ 4 cm, T2b $>$ 4 cm to $\leq$ 5 cm), T3 ($>$ 5 cm to $\leq$ 7 cm) and T4 ($>$ 7 cm). The T2 category was further enriched by adding the previous T3 classifiers, atelectasis/pneumonitis and/or involvement of main bronchus, irrespective of distance to main carina. Invasion of the diaphragm was found to have a similar prognosis as other T4 tumours and has therefore been added to this category [31].

In addition to a further refinement of T stage overall, a number of questions that were—despite the major improvements—left unanswered in the UICC TNM 7 classification, have now been addressed, and should therefore be incorporated in a new guideline.

How to code and measure T and what size should be used? The new pathology classification for adenocarcinoma [6, 16] proposed that AIS be classified as Tis (AIS) and that MIA be coded as $T1_{mi}$. For part-solid tumours the size of the invasive component should be used to assign the T category for clinical staging; however, the whole size of the tumour should also be recorded. Pathological staging might be challenging in the situation of lepidic growth, and therefore, interaction with radiology might be needed to score the invasive (solid) component. The display is best with wide (lung) window settings, particularly in the case of subsolid lesions. For measuring the solid component of tumours, expert opinion favours lung or intermediate window settings [32].

CT follow-up studies have shown that incidental non-calcified non-solid lung lesions do not need shorter repeat CT examinations than 1–2 years and are definitely less aggressive than solid or part-solid lesions and often even indolent.

The use of the staging system for tumours with additional nodules has been left unchanged, although the approach to score same lobe nodules as T3, different ipsilateral lobe as T4 and contralateral as M1a should be restricted to the same histological (sub)type and, as such, be considered as intrapulmonary metastases [33]. In other situations, with more than one pulmonary site of disease, such as second primary tumours, these should be staged differently. To conclude if two foci are indeed two different primaries is difficult; criteria are presented but often it will be impossible to come to a definitive conclusion and the role of a multidisciplinary tumour board is important [34]. When the conclusion is the presence of two primaries, each tumour should be given a separate T, N and M category [35].

A specific problem is the tumour with a specific growth pattern, such as ground glass or lepidic, and the pneumonic type. The International Association for the Study of Lung Cancer (IASLC) proposes to determine the T of multifocal ground glass/lepidic tumours by the highest T-lesion, with either the number of tumours or *m* in parentheses to denote the multifocal nature, and that a single N and M category be used for all these lesions collectively. In daily practice, simply using *m* is to be preferred over trying to estimate the number of groundglass opacity (GGO) areas. For the pneumonic type, it is suggested to use size (or T3) if in one lobe, T4 if involving a different ipsilateral lobe, and M1a if contralateral; in that situation, the T stage will be based on the highest category in the most involved lung. For N and M, a single category should be used for all pulmonary areas of involvement [36]. Especially in the case where more than one lesion is present, and/or differences in growth pattern are observed [34–36], accurate staging is vital to avoid erroneous interpretations leading to a false stage, resulting in undertreatment.

For patients with abnormal mediastinal and/or hilar lymph nodes at CT and/or PET, endosonography is recommended over surgical staging [I, A]. If malignant nodal involvement is not found by this modality, subsequent surgical staging is recommended [I, B]. For peripheral tumours without mediastinal involvement on CT or PET-CT, mediastinal staging is advised in case of no uptake of FDG by the primary tumour and/or a tumour size $\geq$ 3 cm [II, C] [37].

The proposed new staging suggests leaving the N categories unchanged, but to record for future testing the sub-classification of single (N1a, N2a) or multiple (N1b, N2b) affected nodes. For the situation of so-called skip metastases, the N2a group is further divided into N2a1 (no N1) and N2a2 (with N1) [38]. Incorporation of specific consequences related to the new pathology classification [6, 16] and, through that, recognising specific categories with a much higher incidence of mediastinal metastases, even if the tumour size is $<$ 3 cm [20], remains to be confirmed.

A specific problem is whether it is necessary to evaluate the possible existence of brain metastases by brain magnetic resonance imaging (MRI). There is some controversy between existing guidelines: The National Comprehensive Cancer Network

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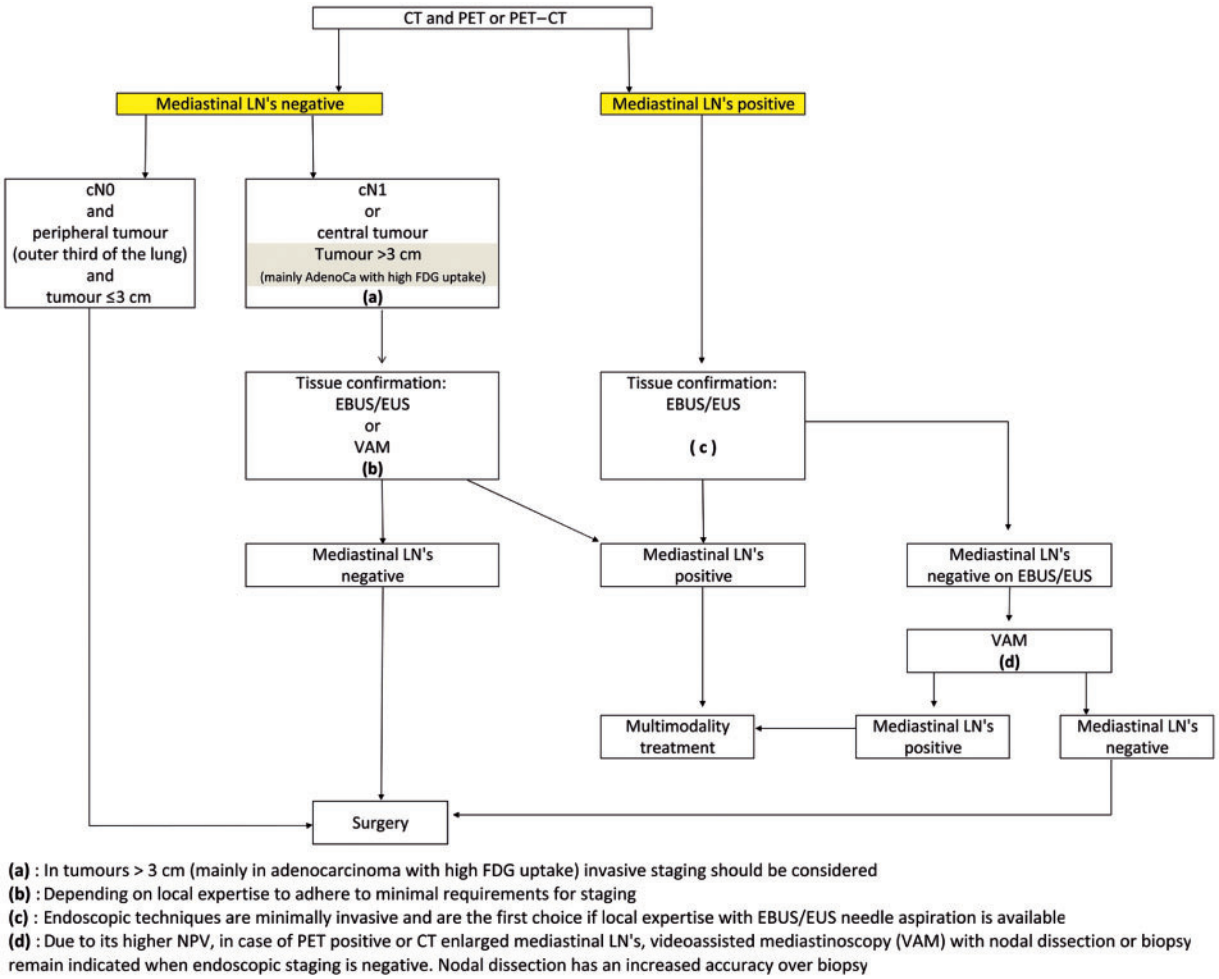


Figure 1. Suggested algorithm for locoregional lymph node staging in patients with non-metastatic NSCLC.
CT, computed tomography; EBUS, endoscopic bronchial ultrasound; EUS, endoscopic ultrasound; FDG, fluorodeoxyglucose; LN, lymph node; NPV, negative predictive value; NSCLC, non-small-cell lung cancer; PET, positron emission tomography; VAM, video-assisted mediastinoscopy. Reprinted from [137] with permission.

(NCCN) advises this for all patients except for those with stage IA [39], the BTS and the National Institute for Health and Care Excellence (NICE) for all patients considered for curative therapy [40, 41], whereas the American College of Chest Physicians (ACCP) restricts it to stage III/IV and symptomatic patients [42].

Whether this is cost-effective is unclear as the detection rate of brain metastases is very low [43].

Recommendations:

- For part-solid tumours, the size of the invasive component should be used to assign the T category for clinical staging [III, A].
- Subsolid lesions need dedicated radiological expertise for evaluating the lung lesion composition [V, A].
- If two lung lesions fulfil the criteria for two primaries these should be evaluated and treated accordingly [III, A].
- For patients with abnormal mediastinal and/or hilar lymph nodes at CT and/or PET, endosonography is recommended over surgical staging [I, A].
- The preferred first technique for pathological confirmation of suspect nodes is needle aspiration under EBUS and/or EUS guidance [I, A].
- If EBUS and/or EUS does not reveal nodal involvement in a situation of high clinical suspicion, mediastinoscopy is indicated [I, A].
- Mediastinoscopy is the test with the highest negative predictive value to rule out mediastinal lymph node disease [I, A].
- Screening for brain metastases by MRI might be useful in patients considered for curative therapy [III, B].

Pretreatment risk assessment

Any locoregional therapy must consider the pre-therapy situation of the patient but, even more importantly, their predicted post-treatment status. Most patients are older than 65 years of age and may have age- and life-style-related comorbidity. A therapeutic intervention for lung cancer will reduce the pulmonary and vascular reserve capacity, either acutely following resection, or more gradually following radiotherapy (RT). This functional loss needs to be estimated pre-therapy to determine whether an individual patient is able to cope with it and to maintain an acceptable quality of life.

For surgical candidates, algorithms for pretreatment evaluation have been developed and are used widely (Figure 3) [41, 44]. The

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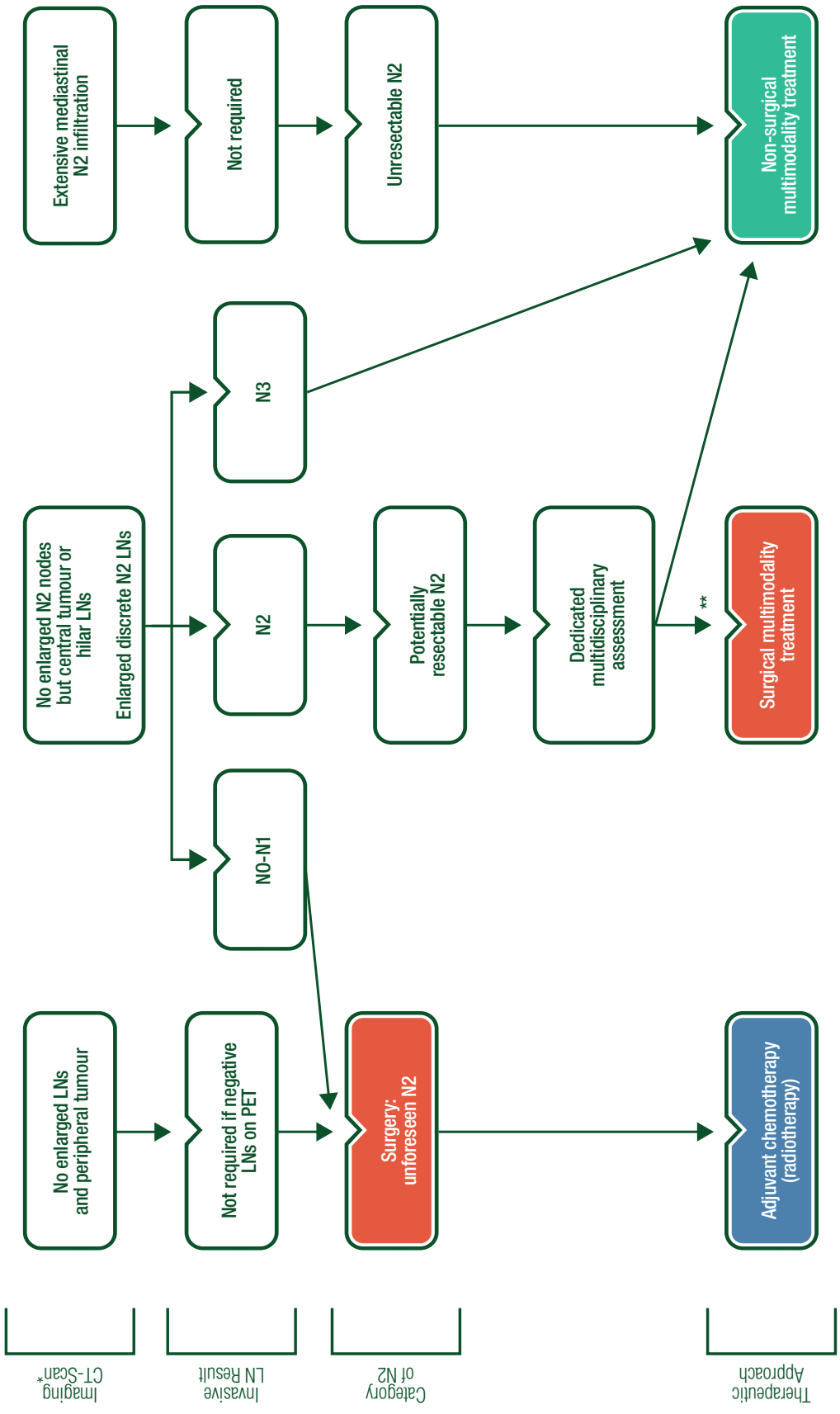


Figure 2. Treatment recommendations for patients with locoregional NSCLC, based on imaging, invasive lymph node staging tests and multidisciplinary assessment.
*Category description according to CT imaging as in ACCP staging document [42].
**See text for factors involved in the choice between non-surgical and surgical multimodality treatment.
ACCP, American College of Chest Physicians; CT, computed tomography; LN, lymph node; NSCLC, non-small-cell lung cancer; PET, positron-emission tomography.

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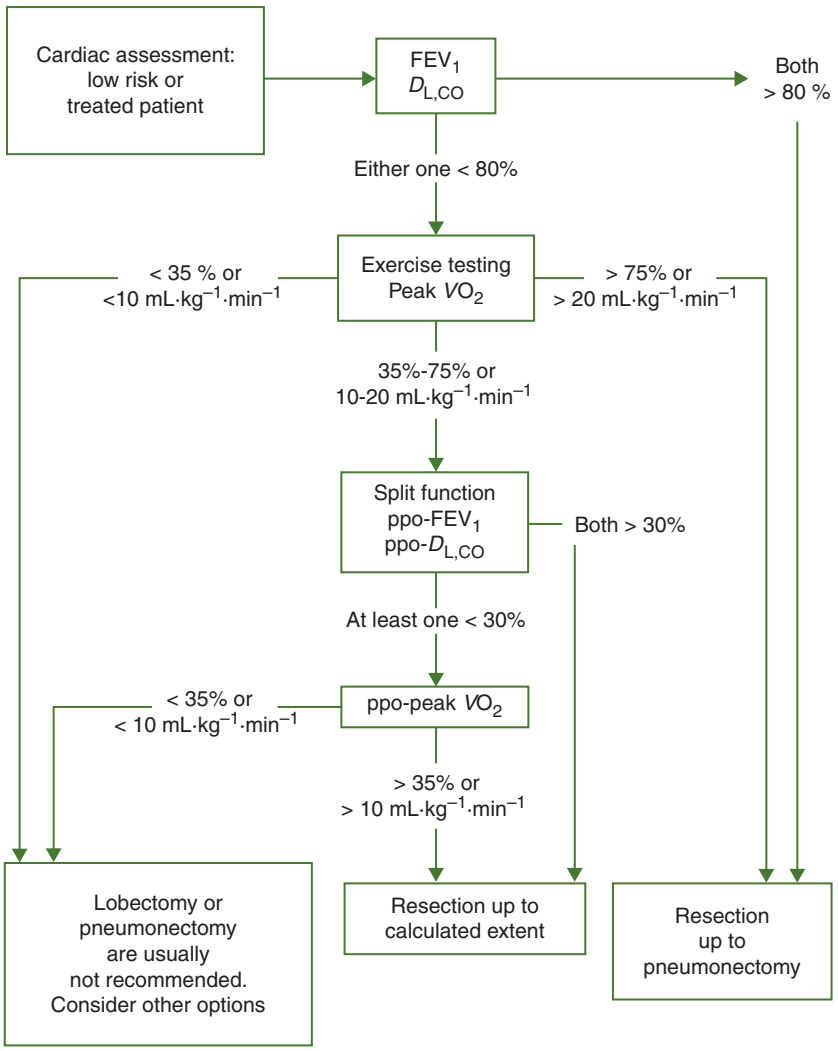


Figure 3. Preoperative respiratory evaluation.
DLCO, diffusing capacity of the lungs for carbon monoxide; FEV1, forced expiratory volume in 1 second; ppo, predicted postoperative; VO_2, oxygen consumption.
Reprinted from [50], with permission from the European Respiratory Society.

relative risk of postoperative morbidity and mortality can be predicted from preoperative forced expiratory volume in the first second (FEV_1) and diffusing capacity of the lung for carbon monoxide (DLCO). Patients with lower values might benefit from a more extensive assessment through pulmonary exercise testing. When maximal oxygen consumption (VO_2max) is < 10 mL/kg/min, patients are potentially at high risk for serious postoperative complications [III, A]. Surgical resection is usually acceptable if the predicted postoperative FEV_1 and DLCO values are $> 40\%$. This can be estimated from the number of bronchopulmonary segments to be resected taking into account the regional distribution of ventilation and perfusion. The problematic area is where no real guidelines exist, or the standard is not directly applicable, as resection of poorly functioning parts of the lung might improve the situation instead of making it worse (Figure 4) [45].

The risk of in-hospital death can be estimated by a scoring system such as Thoracoscore [46]; however, it was designed for a general population and its value for use in cancer patients is limited.

Evaluation of the cardiac risk assessment for lung resections by the recalibrated thoracic revised cardiac risk index (RCRI) is recommended (Table 3) [47], as it has been validated in this setting [48]. Schematic description of the steps to be taken for evaluating these aspects is given in Figure 5 (the figure is based on the original RCRI rather than the recalibrated RCRI).

Evaluating all these pros and cons should be done within a multidisciplinary team and in consultation with the patient. Concentration of expertise will certainly improve decision-making and be of benefit for treatment outcomes [49].

Unfortunately, the predicted tolerance for high-dose RT is less well defined and it is, in general, impossible to accurately determine the related acute and long-term risks [50]. Based on the known adverse effects of RT on vasculature and cardiac function, the dose to the heart should be minimised during RT planning [51–53].

In general, it is necessary to evaluate and optimise any comorbidities before planned surgery [41]; furthermore, trying to

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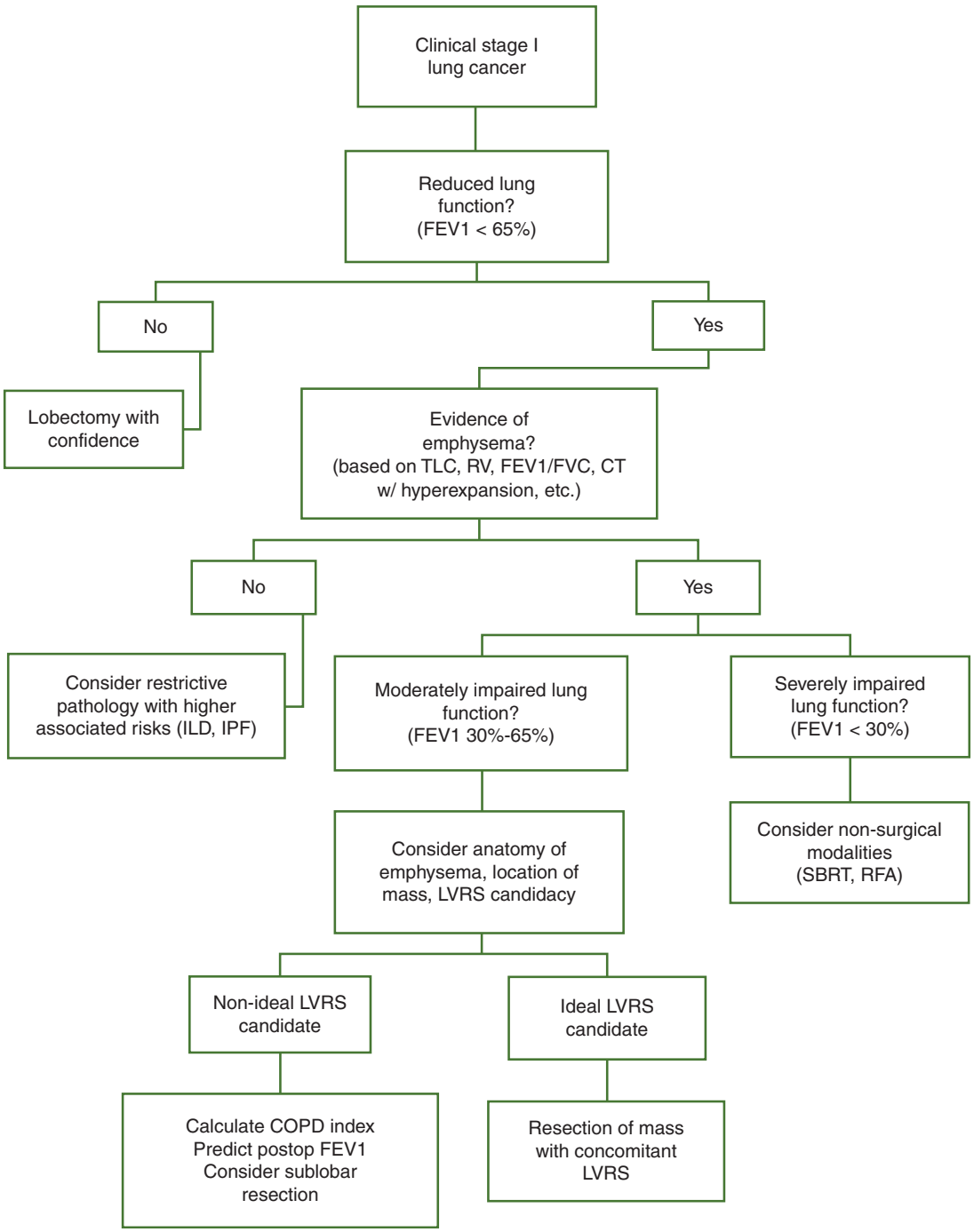


Figure 4. Algorithm for patients with clinical stage I lung cancer and limited pulmonary function due to emphysema.
CT, computed tomography; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume 1; FVC, forced vital capacity; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; LVRS, lung volume reduction surgery; RFA, radiofrequency ablation; RV, reserve volume; SBRT, stereotactic body radiotherapy; TLC, total lung capacity.
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optimise a patient's condition prior to surgery is beneficial, especially for those with a poor preoperative condition [54].

Recommendations:

- In non-metastatic NSCLC, the cardiopulmonary fitness of the patient will determine the choice of treatment [III, A].
- The risk of postoperative morbidity and mortality can be estimated using risk-specific models, although none have been validated in a cancer population [III, B].
- Before considering surgical resection, precise assessment of cardiac and pulmonary function is necessary to estimate risk of operative morbidity [III, A].

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Table 3. Recalibrated thoracic revised cardiac risk index (adapted from [47])

	Points
Weighted factors	
Ischaemic heart disease	1.5
History of cerebrovascular disease	1.5
Serum creatinine > 2 mg/dL	1
Pneumonectomy planned	1.5
Class groupings	
A	0
B	1–1.5
C	2–2.5
D	> 2.5

Ischaemic heart disease: history of myocardial infarction, history of positive exercise test, current complaint of chest pain (myocardial ischaemia), nitrate therapy, ECG with pathological Q waves. Cerebrovascular disease: transient ischaemic attack, stroke.
ECG, electrocardiogram.

- For cardiac assessment, use of recalibrated RCRI is recommended [III, A].
- Formal lung function testing should be undertaken to estimate postoperative lung function. For patients with FEV1 and DLCO values > 80% of their predicted pulmonary function tests and no other major comorbidities, no further investigations are advised before surgical resection [III, A]. For others, exercise testing and split lung function are recommended. In these patients, VO_2max can be used to measure exercise capacity and predict postoperative complications [III, A].
- Comorbidities should be evaluated and optimised before surgery [III, A].
- In patients with limited pulmonary function due to emphysema, a lung volume reduction effect may be observed by resection of the lung cancer within emphysematous lung tissue [III, B].

Treatment of early stages (stages I and II)

Surgery

The cornerstone of treatment of potentially resectable lung cancer is surgical removal of the tumour [55]. For those who are not willing to accept the risks, or are at very high risk, curative RT should be offered, either SABR or hypofractionated high-dose RT.

Based on the Lung Cancer Study Group (LCSG) 821 trial, lobectomy is the current treatment of choice for T1 tumours as the local recurrence rate after a more limited resection (segmentectomy or wedge resection) was found to be higher [56]. This study should be viewed within the context that staging and surgical methods have progressed significantly since its publication more than two decades ago. Whether the conclusions are still applicable for smaller lesions (T1a) seems uncertain, research based on large databases suggest a (limited) practice change [57]. In squamous cell carcinoma, lobectomy is superior to segmentectomy or wedge resection. For adenocarcinoma, wedge resection was inferior to lobectomy, whereas segmentectomy resulted in equivalent outcomes [57]. The same outcome of segmentectomy and lobectomy was reported in patients with radiologically pure solid cT1a adenocarcinomas [58]. As discussed in the section on diagnosis and pathology, the different types of adenocarcinoma have evolved in differences in metastatic pattern, recurrence and survival, and based on this, one might expect that a limited resection will be adequate in the least invasive subtypes [20, 21]. Currently two phase III studies (CALGB 140503, and JCOG0802/WJOG4607L) are recruiting [59] and waiting to mature after accrual had been reached [60], respectively.

Whether surgery should be done through standard open thoracotomy, or a video-assisted thoracoscopic surgery (VATS) procedure, is probably less important from oncological perspective [61], since comparative margin clearance and nodal dissection can be achieved. A point of concern might be the extent of lymph node staging [62]. For patients, the major benefit is the reduced postoperative morbidity and mortality, resulting in improved quality of life and making VATS the more attractive approach [63].

The management of lymph nodes during surgery is mainly dictated by the staging requirements for guaranteed 'R0 resection' status. This implies surgical evaluation of a minimum of six nodes/stations, three of which should be mediastinal, including the sub-carinal station, with no metastases found in most cranial resected nodes [64]. While in stage I cases, overall survival (OS), local recurrence rate and distant metastasis do not appear to be influenced by the method of lymph node assessment, systematic nodal dissection is recommended in stages II and IIIA [65]. Intraoperative nodal management may be influenced by the extent of preoperative lymph node mapping, particularly prior negative mediastinoscopy.

Patients presenting with multiple primaries should be assessed with curative intent. Complete resection is recommended, but combinations of resection and SABR have been found to be effective as well [66, 67].

Recommendations:

- Surgery should be offered to all patients with stage I and II NSCLC as the preferred treatment to all who are willing to accept procedure-related risks [III, A].
- For patients with a non-centrally located resectable tumour and absence of nodal metastasis on both CT and PET images, surgical resection is recommended [I, A].
- Anatomical resection is preferred over wedge resection [I, A].
- Anatomical segmentectomy is generally considered acceptable for pure GGO lesions or adenocarcinomas in situ or with minimal invasion [III, B].
- Lobectomy is still considered the standard surgical treatment of tumours ≥ 2 cm in size that have a solid appearance on CT [II, B].
- Lymph node dissection should conform to IASLC specifications for staging [III, A].
- Either open thoracotomy or VATS access can be carried out as appropriate to the expertise of the surgeon [III, A].
- VATS should be the approach of choice in stage I tumours [V, C].
- For patients with multifocal lung cancer, complete resection is recommended whenever possible. All patients with multifocal lung cancer should be discussed in a multidisciplinary tumour board [III, B].

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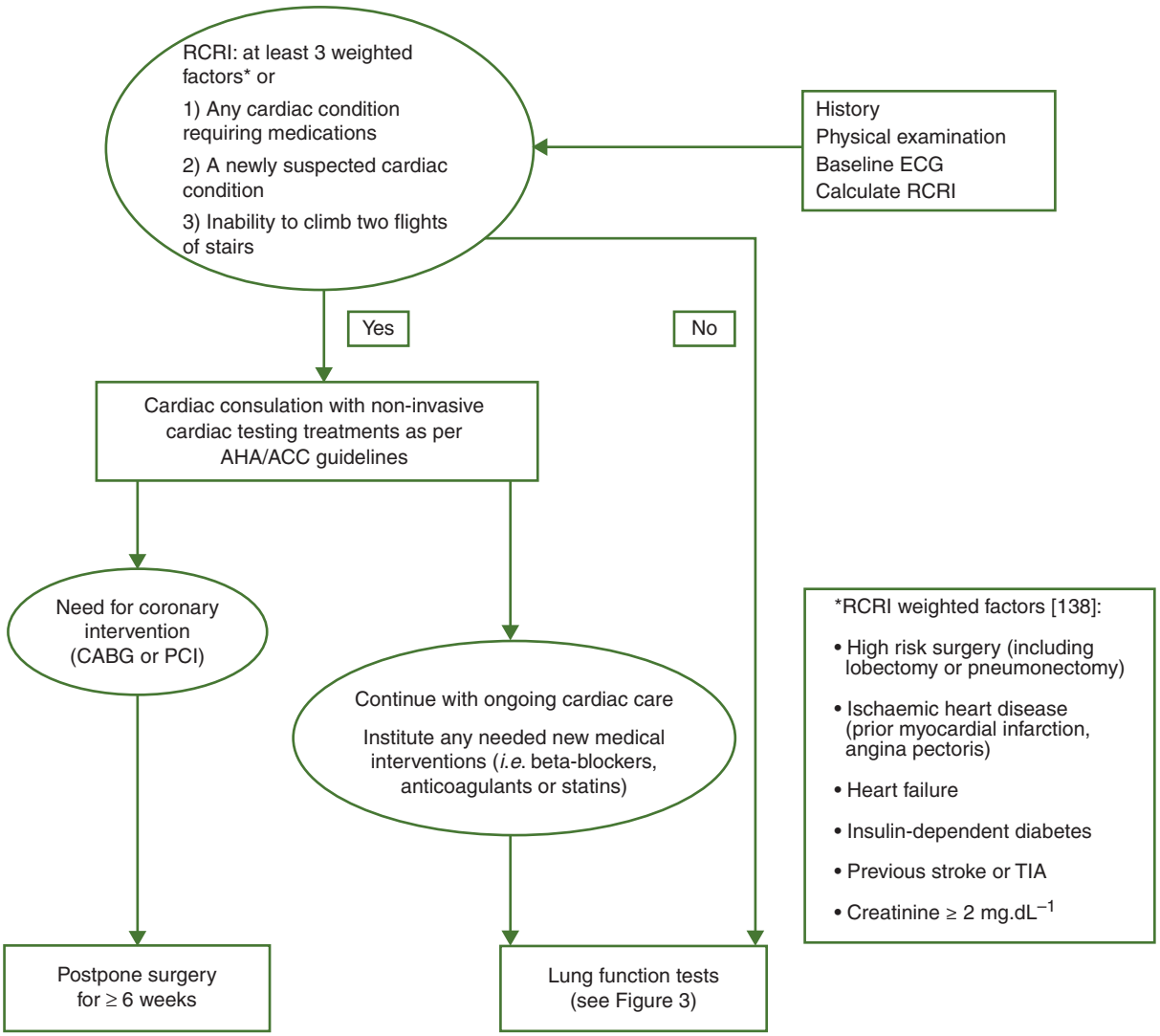


Figure 5. Preoperative cardiac evaluation.
AHA/ACC, American Heart Association/American College of Cardiology; CABG, coronary artery bypass grafting; ECG, electrocardiogram; PCI, percutaneous coronary intervention; RCRI, revised cardiac risk index; TIA, transient ischaemic attack.
Reprinted from [50], with permission from the European Respiratory Society.

Systemic therapy

In a period of about two decades, it has become clear that adjuvant ChT is of benefit for patients with N1 and N2 disease (stage II and III), resulting overall in 4%–5% absolute survival improvement at 5 years [68]. These results were obtained by administering cisplatin-based doublets, delivering at least 300 mg/m^2 of cisplatin in three to four cycles. Although for the accompanying drug, most data are available for the efficacy of vinorelbine, this does by no means exclude newer agents, with at least comparable efficacy, such as docetaxel, gemcitabine or pemetrexed. However, adding bevacizumab was not beneficial [69, 70]. Patient selection criteria for these studies, such as proper recovery from surgery and the absence of major comorbidities, are essential. Although in most studies the interval between surgery and the start of ChT was restricted to 6 weeks, a recent analysis of the National Cancer Database showed a comparable outcome in patients treated after a longer interval post-resection [71].

Its value in lower stages is less clear. For stage IA, postoperative ChT resulted in a worse outcome. In stage IB, a small overall benefit was found [68], a subgroup analysis indicated it was mainly due to the outcome in patients with tumours > 4 cm [72, 73].

Neoadjuvant ChT has not been evaluated as extensively as postoperative. However, comparing outcomes of both modalities did not reveal a major difference in OS [74, 75]. Its use might be beneficial as downstaging might be achieved [76], potentially resulting in a less extensive resection.

Predictive molecular markers have not been evaluated in prospective studies. For cases with mutation in epidermal growth factor receptor (*EGFR*) there is limited evidence coming from a meta-analysis [77], two major trials are currently recruiting to answer this important question [78, 79]. Until these outcomes become available, targeted agents should not be used in the adjuvant setting. Adjuvant immunotherapy trials using anti-PD-1 and anti PD-L1 checkpoint inhibitors in stage I-III adjuvant setting (trials NCT NCT02504372 and NCT02273375) are ongoing. A neoadjuvant trial using anti-CTLA4 and anti-PD-1 in stage I-III neoadjuvant setting has been also recently initiated (NCT02998528).

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Recommendations:

- Adjuvant ChT should be offered to patients with resected stage II and III NSCLC [I, A] and can be considered in patients with resected stage IB disease and a primary tumour > 4 cm [II, B]. Pre-existing comorbidity, time from surgery and postoperative recovery need to be taken into account in this decision taken in a multidisciplinary tumour board [V, A].
- For adjuvant ChT, a two-drug combination with cisplatin is preferable [I, A]. In randomised studies, the attempted cumulative cisplatin dose was up to 300 mg/m^2, delivered in three to four cycles. The most frequently studied regimen is cisplatin–vinorelbine.
- At the present time, the choice of adjuvant therapy should not be guided by molecular analyses, e.g. ERCC1 mutation testing [IV, B].
- In the current state of knowledge, targeted agents should not be used in the adjuvant setting [II, A].
- In view of the equivalence of neoadjuvant and adjuvant ChT for OS, the consistent results and broad evidence base support adjuvant ChT as the timing of choice [II, C].
- (Neo)adjuvant anti-PD(L)-1 checkpoint inhibitors are currently being evaluated in addition to current standard of care.

Primary radiotherapy

For patients with comorbidities or other reasons for inoperability, presenting with a peripherally located stage I NSCLC, or any patient refusing surgery, stereotactic radiotherapy [SABR or stereotactic body radiotherapy (SBRT)] is the preferred treatment, with local control rates of ~90% at 5 years [80, 81].

Current SABR practice generally utilises small planning margins based on 4-dimensional CT (4DCT), multiple radiation beams or arcs, all of which reduce the risk of normal organ toxicity [82]. Acute treatment-related toxicity is uncommon, as deterioration in quality of life [83]; however, the risk of high-grade and fatal toxicity is high in patients with pre-existing interstitial lung fibrosis and careful evaluation of the risks and benefits of the procedure by an expert tumour board is advised [84, 85].

Late toxicities reported in phase II trials include rib fractures [86], dyspnoea and ventricular tachycardia [80, 87].

In elderly patients, the introduction of SABR led to an improvement in population-based survivals of patients with peripherally located stage I, as well as a reduction of the number of untreated patients [88]. When SABR is unavailable, radical RT using hypofractionated schedules is preferred to the use of conventionally fractionated RT [89, 90].

Despite the available data on outcomes of SABR in patients with peripheral stage I tumours who are fit to undergo surgery [91, 92], there is currently no evidence to routinely recommend SABR for patients who are at low risk for surgical complications. Three randomised clinical trials in this population failed to complete accrual, and results from four new trials will be forthcoming in the coming decade [93]. A pooled analysis of two of the closed trials, the STARS and ROSEL studies, revealed comparable recurrence-free survival at 3 years [94]. Given the differences in early toxicity and quality of life between surgery and SABR, as well as the growing emphasis on patient reported endpoints when evaluating new treatments [95], more attention should be given towards developing tools for shared decision-making, as it may assist operable patients and their clinicians to define a management plan that is consistent with a patient's preferences and values [96, 97].

With the introduction of SABR for operable stage I tumours, a new problem arises when recurrence of these tumours is detected during follow-up. In those with proven recurrence (or a high suspicion), the possibility of salvage surgery should be considered [98–105].

The IASLC has defined 'central tumours' as tumours located within 2 cm in all directions of any mediastinal critical structure, including the bronchial tree, oesophagus, heart, brachial plexus, major vessels, spinal cord, phrenic nerve and recurrent laryngeal nerve [106]. For tumours located in the hilar region, SABR using 'risk-adapted' fractionation schemes can achieve high local control rates with limited toxicity [107]. However, care should be taken to distinguish moderately central tumours from so-called 'ultracentral' lesions, a term used to describe a planning target volume that overlaps the trachea or main bronchi [108]. SABR is not appropriate for ultracentral tumours, as increased toxicity has already been reported for this subgroup, after conventional and hypofractionated RT schemes. Data from a completed prospective Radiation Therapy Oncology Group (RTOG) study of SABR for moderately central tumour are expected in the near future, and until such time, a radical RT scheme using hypofractionated schedules can be considered an acceptable standard of care [89, 90].

Whether incorporating the new pathology classification [16], and the possible pretherapy detection of less invasive types [25, 26], would change recommendations for subgroups remains to be seen.

Recommendations:

- The non-surgical treatment of choice for stage I NSCLC is SABR. The dose should be to a biologically equivalent tumour dose of ≥ 100 Gy, prescribed to the encompassing isodose [III, A].
- SABR for early-stage peripheral lung tumours is associated with low toxicity in patients with chronic obstructive pulmonary disease (COPD) and the elderly [III, A].
- Salvage surgery, if feasible, may be offered to patients having complications post-SABR [V, B].
- Salvage surgery, if feasible, may be offered, using the same indications as for primary surgery in progressive disease after SABR, but surgery may be more difficult with higher operative risk [V, B].
- For medically inoperable patients with tumours with a size > 5 cm and/or moderately central location, radical RT using more conventional or accelerated schedules is recommended [III, A].

Radiofrequency ablation

Fortunately, not many patients have contraindications for both surgery and SABR [85]. For these patients radiofrequency ablation (RFA) might be a reasonable alternative although the level of evidence comes from observational studies only [109].

Recommendation:

- Stage I NSCLC patients with strong contraindications for surgery and/or SABR may be treated with RFA [V, C].

Postoperative radiotherapy

In a meta-analysis of rather old studies postoperative radiotherapy (PORT) was found to be detrimental if given to patients with N0 and N1 disease [110]. The case for unexpected N2 disease

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discovered at surgery is less clear, and currently evaluated in a large clinical trial, applying 54 Gy in 27–30 fractions [111]. The use of PORT after an R1 resection appears reasonable, but it is not supported by high-quality evidence.

Recommendations:

- PORT in completely resected early-stage NSCLC is not recommended [I, A].
- In case of R1 resection (positive resection margin, chest wall), PORT should be considered [IV, B].
- Even if such patients were not included in randomised, clinical trials (RCTs), adjuvant ChT should be considered in patients with R1 resection of stage IB disease and a primary tumour > 4 cm, stage II and III [V, A].
- In case both ChT and RT are administered post-surgery, RT should be administered after ChT [V, C].

Treatment of locally advanced stage (stage III)

Adequate staging through PET-CT imaging is indicated to rule out extracranial metastasis. Evaluation of the brain by MRI is indicated.

Platinum-based ChT is an essential part of the treatment of locally advanced NSCLC (LA-NSCLC) as it improves survival in tumours considered resectable, as well in unresectable tumours.

Recommendations:

- All patients planned for definitive stage III NSCLC treatment should undergo a diagnostic contrast-enhanced CT scan of the chest and upper abdomen followed by a PET or a combined PET-CT with a CT technique with adequately high resolution for initial staging purposes [I, A] in order to rule out detectable extrathoracic, extracranial metastasis, and to assess potential mediastinal lymph node involvement, ideally within 4 weeks before the start of treatment [III, B]. Single PET-positive distant lesions need pathological confirmation [V, B].
- For patients with operable N2 disease, pathological staging of the mediastinum is advised [III, C].
- All patients planned for curative stage III NSCLC treatment should receive brain imaging for initial staging [III, B]. Contrast-enhanced brain MRI is the preferred method for staging of the brain in stage III disease [III, A]. If it is not possible to perform MRI, dedicated contrast-enhanced brain CT scan is advised [III, B].

Resectable LA-NSCLC

Resectable in this situation usually refers to the following situations:

- single station N2 disease where other nodal stations have been biopsied and proved to be benign. Postoperative ChT should then be advised [112];
- T4N0 tumours where nodal disease had been excluded by invasive methods when a R0 resection is considered to be feasible;
- after induction therapy, when there has been nodal downstaging and a pneumonectomy can be avoided.

All such cases should be evaluated within an experienced multidisciplinary team.

The treatment of resectable LA-NSCLC remains a matter of debate. There is only one trial comparing the two locoregional modalities head-to-head, surgery and RT (60 Gy), in patients with at least a minimal tumour response [113], no difference in survival was found. In the Lung Intergroup Trial 0139, the induction regimen of chemoradiotherapy (CRT) (45 Gy), was followed by surgery or definitive RT to a dose of 61 Gy [114]. No significant difference in OS was found, but disease-free survival was significantly better in the trimodality arm. An explanation for this difference is the higher early toxic death rate in the surgery arm, apparently due to the higher number of early postoperative deaths in the group of patients undergoing right-sided pneumonectomy. Excluding pneumonectomy for an unplanned subgroup analysis of matched surgical patients treated by lobectomy, the surgical patients had a better survival. Two more recent studies confirmed the outcomes with regard to disease-free survival and OS after induction therapy followed by surgery. The SAKK study failed to show benefit by adding relatively low doses of RT (45 Gy) to ChT [115], whereas the ESPATUE trial confirmed that CRT (45 Gy) followed by surgery, is as good as CRT with definitive RT (65–71 Gy) given as a boost in the last week of CRT [116].

As these studies showed no clear benefit for one of the local therapies over the other, the choice of local treatment modality can vary across countries and centres.

Recommendations:

- If, despite adequate mediastinal staging procedures, N2 disease is only documented intra-operatively, surgery should be followed by adjuvant ChT [I, A]. In case of complete resection, addition of PORT is not routinely recommended, but may be an option following individual risk assessment [V, C].
- If single station N2 disease can be demonstrated by preoperative pathological nodal analysis, resection followed by adjuvant ChT, induction ChT followed by surgery or induction CRT followed by surgery are options. If induction ChT alone is given preoperatively, PORT is not standard treatment, but may be an option based on critical evaluation of locoregional relapse risks [IV, C].
- In multistation N2 or N3, concurrent definitive CRT is preferred [I, A]. An experienced multidisciplinary team is of paramount importance in any complex multimodality treatment strategy decision, including the role of surgery in these cases [IV, C].
- In potentially resectable superior sulcus tumours, concurrent CRT induction followed by definitive surgery is the treatment of choice [III, A]. The same strategy may be applied for potentially resectable T3 or T4 central tumours in highly selected cases and experienced centres [III, B]. In both situations, surgery should be carried out within 4 weeks after the end of RT [III, B].

Systemic therapy

Which ChT is optimal has not been investigated extensively. In fact, information coming from studies in stage IV has hardly been applied in this situation, probably the only exception being the PROCLAIM study, evaluating the use of pemetrexed-cisplatin versus standard cisplatin-etoposide, but failing to show any improvement except for less haematological toxicity [117]. Consolidation ChT after CRT failed to improve progression-free survival (PFS) [118]. There is no beneficial role for induction ChT before CRT [119], although in many centres for practical

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reasons, related to planning of RT, one cycle will be given prior to concurrent CRT. Adjuvant immunotherapy trials, using anti-PD-1 and anti-PD-L1 checkpoint inhibitors in stage I-III adjuvant setting, as well as the combination of anti-CTLA4 and anti-PD-1 in stage I-III neoadjuvant setting, are ongoing. A consolidation trial using an anti-PD-L1 drug in consolidation after CRT will deliver results very soon (NCT NCT02125461).

Recommendations:

- For curative-intent management, patients should be able to undergo platinum-based ChT (preferably cisplatin) [I, A].
- (Neo)adjuvant anti PD(L)-1 checkpoint inhibitors are currently being evaluated in addition to current standard of care. Checkpoints are also being evaluated after CRT as consolidation therapy.

Unresectable LA-NSCLC

Unresectable in this situation refers to the situation that—even after induction therapy—a complete resection (R0) would not be possible, based on evaluation within a multidisciplinary team, including an experienced thoracic surgeon.

Sequential CRT (induction ChT followed by RT), usually given at a dose of 60–66 Gy in 30–33 fractions over 6–7 weeks, was compared to concurrent CRT at comparable doses in several phase III trials and in a meta-analysis [120].

Concurrent CRT is considered the preferred treatment for patients who are fit, as it leads to higher 5-year survival rates, albeit at the cost of a higher rate of reversible oesophagitis. In recent phase III trials delivering concurrent CRT to doses between 60 and 66 Gy, the incidence of grade 3 or higher oesophagitis ranged from 7% to 21%, with corresponding rates of grade 3 or higher radiation pneumonitis ranging from 2.5% to 7% [51, 118]. Another area of concern is the early mortality rate of 10% following concurrent CRT. Tumour volume and pulmonary function were found to be risk factors associated with mortality in the first 180-day post-treatment in a multi-institutional analysis of 1245 patients [121]. The use of radiation doses in excess of 66 Gy is not recommended outside trials, as delivery of 74 Gy with concurrent CRT led to a poorer survival [51].

For elderly and/or less fit patients with clinically relevant comorbidities, the sequential approach is a reasonable choice [50]. An individual patient data meta-analysis of trials conducted prior to 2006 found that accelerated RT schedules which are delivered in a shorter overall treatment time led to an absolute benefit of 2.5% in 5-year OS [89]. Based on this, accelerated RT schedules delivering once-daily fractions of 2.6–3 Gy, to a total dose of up to 60–66 Gy, are recommended in patients who receive either sequential CRT or RT alone for stage III NSCLC.

Recommendations:

- Concurrent CRT is the treatment of choice in patients evaluated as unresectable in stage IIIA and IIIB [I, A]. If concurrent CRT is not possible—for any reason—sequential ChT followed by definitive RT represents a valid and effective alternative [I, A].
- There is no role for prophylactic cranial irradiation in stage III NSCLC [II, A].
- In the absence of contraindications, the optimal ChT to be combined with radiation in stage III NSCLC should be based on cisplatin. There are no firm conclusions supporting single-agent carboplatin as a radiation sensitiser [I, A].
- Most comparative studies of concurrent CRT versus sequential administration were using cisplatin + etoposide or cisplatin + vinca alkaloid (typically: cisplatin + vinorelbine), or cisplatin + pemetrexed if non-squamous histology. There are no comparative phase III trials using the paclitaxel/carboplatin regimen. When delivered perioperatively cisplatin-based combinations are considered the treatment of choice, in the absence of contraindications [I, A].
- In the stage III disease CRT strategy, two to four cycles of concomitant ChT should be delivered [I, A]. There is no evidence for further induction or consolidation ChT. In the perioperative setting, three to four cycles of cisplatin-based ChT are recommended [I, A], aiming at a total cumulative dose of at least 300 mg/m^2 of cisplatin [II, B].
- 60–66 Gy in 30–33 daily fractions is recommended for concurrent CRT [I, A]. Maximum overall treatment time should not exceed 7 weeks [III, B]. 'Biological intensification', such as treatment acceleration, is not standard practice in concurrent CRT schedules [III, B].
- In sequential approaches, RT delivered in a short overall treatment time is recommended [I, A].

Personalised medicine

Although proven to be beneficial in stage IV patients with driving mutations, such as in *EGFR* or translocation of anaplastic lymphoma kinase (*ALK*), the role of targeted agents in stage I, II and III has not been evaluated properly. From the meta-analysis [77], no conclusion can be drawn for adjuvant use of targeted therapy in *EGFR* mutated stage I-III NSCLC. The only study in which more staging details are given included only 36 patients with stage III; however, details on outcome of those patients were not given [122].

Recommendations:

- There is currently no role for targeted agents in stage III NSCLC outside clinical trials [I, A].
- Immunotherapy is being studied in early NSCLC as (neo)adjuvant therapy and as consolidation after CRT; data should be awaited before any clinical use [I, A].

Follow-up, long-term implications and survivorship

NSCLC patients treated with radical intent are at risk of developing new cancer related problems, with potentially considerable consequences and different dynamics over time:

- treatment-related complications, treatment of existing comorbidities;
- detection of treatable relapse;
- detection of second primaries.

In the early phase after lung cancer resection, readmission for complications is not rare; 12.8% of patients listed in a large Surveillance, Epidemiology, and End Results (SEER) programme database were readmitted within 30 days after discharge shortly

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Table 4. Summary of recommendations

Incidence/epidemiology

- Screening with LDCT reduces lung cancer-related mortality [I, A]. It is not yet ready for large-scale implementation, mainly because the lung cancer mortality reduction rate lacks definite proof of a second study result, and partly because of remaining questions regarding definition of the at-risk population, timing, interval and method of CT (especially 2D versus 3D evaluation), how to handle (false-) positive findings and especially cost-effectiveness, notably in relation to smoking cessation [I, A].
- LDCT screening can be carried out outside a clinical trial provided it is offered within a dedicated programme with quality control, in a centre with experience in CT screening, a large volume of thoracic oncology activity and multidisciplinary management of suspicious findings [I, B]. Candidates are current or former heavy smokers ($\geq$ 30 pack-years or $\leq$ 15 years since smoking cessation) aged 55–74 years, who are well informed about potential benefits and risks. Individuals offered LDCT screening should be referred to a smoking cessation programme.
- LDCT screening should not be offered on an ad hoc individual basis, but patients requesting screening should be referred to a dedicated programme, as recommended above [V, B].
- Other screening methods, such as chest X-ray, sputum analysis or biomarkers are not recommended for clinical use [I, C].

Diagnosis

- In patients with clinical stages I–III lesions, a pretreatment pathological diagnosis is recommended prior to any curative treatment.
- Bronchoscopy is the recommended test to obtain a pathological diagnosis of centrally located tumours in stages I–III with biopsy of any visible lesion [III, A].
- The pathological classification NOS should be used only in cases where it is impossible to obtain enough tissue for further classification, or when steps to further classify the tumour are inconclusive [V, A].
- An exception to the requirement for a pretreatment diagnosis can be made if an experienced multidisciplinary group decides that the risks of obtaining pathology may be unacceptable in a patient in whom the likelihood of malignancy is high based on clinical and imaging findings [III, B].
- A pretreatment pathological diagnosis is strongly recommended for all patients before SABR, unless a multidisciplinary tumour board is of the opinion that the risk-benefit ratio of the procedure is unacceptable. In such a situation, the predicted likelihood of malignancy should preferably be at least 85%, based upon accepted criteria [III, B] [25].
- The descriptive element of the recent WHO classification of adenocarcinoma subtypes should be used to describe bronchoscopic and CT-guided biopsies whenever possible [III, A].
- The revised adenocarcinoma classification may identify patient subtypes for whom an anatomical sublobar resection, rather than lobectomy, would be sufficient [III, A].
- FDG-PET may contribute for the selection of patients for anatomical sublobar resections as low SUV_{max} values of peripheral tumours indicate lack of mediastinal metastases [III, A]. This diagnosis may be made intra-operatively by video-assisted thoracoscopic biopsy and frozen section analysis.
- In isolated cases a diagnostic anatomical sublobar resection may be acceptable.

Solitary pulmonary nodule

- The diagnostic approach to non-calcified pulmonary nodules should be based on existing standard guidelines [III, A], although new evidence on nodule management is emerging.
- Likelihood of malignancy based upon risk calculation methods used in CT screening studies should be used only to guide the clinical assessment of pulmonary nodules detected in the wider population [V, C].

Staging and risk assessment

- In non-metastatic NSCLC, detailed locoregional staging according to the 8th TNM staging system and the cardiopulmonary fitness of the patient determine the choice of treatment [III, A].

Locoregional staging

- For part-solid tumours, the size of the invasive component should be used to assign the T category for clinical staging [III, A]
- Subsolid lesions need dedicated radiological expertise for evaluating the lung lesion composition [V, A].
- If two lung lesions fulfil the criteria for two primaries these should be evaluated and treated accordingly [III, A].
- For patients with abnormal mediastinal and/or hilar lymph nodes at CT and/or PET imaging, endosonography is recommended over surgical staging [I, A].
- The preferred first technique for pathological confirmation of suspect nodes is needle aspiration under EBUS and/or EUS guidance [I, A].
- If EBUS and/or EUS does not reveal nodal involvement in a situation of high clinical suspicion, mediastinoscopy is indicated [I, A].
- Mediastinoscopy is the test with the highest negative predictive value to rule out mediastinal lymph node disease [I, A].
- Screening for brain metastases by MRI might be useful in patients considered for curative therapy [III, B].

Pretreatment risk assessment

- In non-metastatic NSCLC, the cardiopulmonary fitness of the patient will determine the choice of treatment [III, A].
- The risk of postoperative morbidity and mortality can be estimated using risk-specific models, although none have been validated in a cancer population [III, B].
- Before considering surgical resection, precise assessment of cardiac and pulmonary function is necessary to estimate risk of operative morbidity [III, A].
- For cardiac assessment, use of recalibrated RCRI is recommended [III, A].
- Formal lung function testing should be undertaken to estimate postoperative lung function. For patients with FEV1 and DLCO values > 80% of their predicted pulmonary function tests and no other major comorbidities, no further investigations are advised before surgical resection [III, A]. For others, exercise testing and split lung function are recommended. In these patients, VO_2max can be used to measure exercise capacity and predict postoperative complications [III, A].
- Comorbidities should be evaluated and optimised before surgery [III, A].
- In patients with limited pulmonary function due to emphysema, a lung volume reduction effect may be observed by resection of the lung cancer within emphysematous lung tissue [III, B].

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Table 4. Continued

Treatment of early stages (stages I and II)

Surgery

- Surgery should be offered to all patients with stage I and II NSCLC as the preferred treatment to all who are willing to accept procedure-related risks [III, A].
- For patients with a non-centrally located resectable tumour and absence of nodal metastasis on both CT and PET images, surgical resection is recommended [I, A].
- Anatomical resection is preferred over wedge resection [I, A].
- Anatomical segmentectomy is generally considered acceptable for pure GGO lesions or adenocarcinomas *in situ* or with minimal invasion [III, B].
- Lobectomy is still considered the standard surgical treatment of tumours $\geq$ 2 cm in size that have a solid appearance on CT [II, B].
- Lymph node dissection should conform to IASLC specifications for staging [III, A].
- Either open thoracotomy or VATS access can be carried out as appropriate to the expertise of the surgeon [III, A].
- VATS should be the approach of choice in stage I tumours [V, C].
- For patients with multifocal lung cancer, complete resection is recommended whenever possible. All patients with multifocal lung cancer should be discussed in a multidisciplinary tumour board [III, B].

Systemic therapy

- Adjuvant ChT should be offered to patients with resected stage II and III NSCLC [I, A] and can be considered in patients with resected stage IB disease and a primary tumour > 4 cm [II, B]. Pre-existing comorbidity, time from surgery and postoperative recovery need to be taken into account in this decision taken in a multidisciplinary tumour board [V, A].
- For adjuvant ChT, a two-drug combination with cisplatin is preferable [I, A]. In randomised studies, the attempted cumulative cisplatin dose was up to 300 mg/m^2, delivered in three to four cycles. The most frequently studied regimen is cisplatin–vinorelbine.
- At the present time, the choice of adjuvant therapy should not be guided by molecular analyses, e.g. *ERCC1* mutation testing [IV, B].
- In the current state of knowledge, targeted agents should not be used in the adjuvant setting [II, A].
- In view of the equivalence of neoadjuvant and adjuvant ChT for OS, the consistent results and broad evidence base support adjuvant ChT as the timing of choice [II, C].
- (Neo)adjuvant anti-PD(L)-1 checkpoint inhibitors are currently being evaluated in addition to current standard of care.

Primary radiotherapy

- The non-surgical treatment of choice for stage I NSCLC is SABR. The dose should be to a biologically equivalent tumour dose of $\geq$ 100 Gy, prescribed to the encompassing isodose [III, A].
- SABR for early-stage peripheral lung tumours is associated with low toxicity in patients with COPD and the elderly [III, A].
- Salvage surgery, if feasible, may be offered to patients having complications post-SABR [V, B].
- Salvage surgery, if feasible, may be offered, using the same indications as for primary surgery in progressive disease after SABR, but surgery may be more difficult with higher operative risk [V, B].
- For medically inoperable patients with tumours with a size > 5 cm and/or moderately central location, radical RT using more conventional or accelerated schedules is recommended [III, A].

Radiofrequency ablation

- Stage I NSCLC patients with strong contraindications for surgery and/or SABR may be treated with RFA [V, C].

Postoperative radiotherapy

- PORT in completely resected early-stage NSCLC is not recommended [I, A].
- In case of R1 resection (positive resection margin, chest wall), PORT should be considered [IV, B].
- Even if such patients were not included in RCTs, adjuvant ChT should be considered in patients with R1 resection of stage IB disease and a primary tumour > 4 cm, stage II and III [V, A].
- In case both ChT and RT are administered post-surgery, RT should be administered after ChT [V, C].

Treatment of locally advanced stage (stage III)

- All patients planned for definitive stage III NSCLC treatment should undergo a diagnostic contrast-enhanced CT scan of the chest and upper abdomen followed by a PET or a combined PET-CT with a CT technique with adequately high resolution for initial staging purposes [I, A] in order to rule out detectable extrathoracic, extracranial metastasis, and to assess potential mediastinal lymph node involvement, ideally within 4 weeks before the start of treatment [III, B]. Single PET-positive distant lesions need pathological confirmation [V, B].
- For patients with operable N2 disease, pathological staging of the mediastinum is advised [III, C].
- All patients planned for curative stage III NSCLC treatment should receive brain imaging for initial staging [III, B]. Contrast-enhanced brain MRI is the preferred method for staging of the brain in stage III disease [III, A]. If it is not possible to perform MRI, dedicated contrast-enhanced brain CT scan is advised [III, B].

Resectable LA-NSCLC

- If, despite adequate mediastinal staging procedures, N2 disease is only documented intra-operatively, surgery should be followed by adjuvant ChT [I, A]. In case of complete resection, addition of PORT is not routinely recommended, but may be an option following individual risk assessment [V, C].
- If single station N2 disease can be demonstrated by preoperative pathological nodal analysis, resection followed by adjuvant ChT, induction ChT followed by surgery or induction CRT followed by surgery are options. If induction ChT alone is given preoperatively, PORT is not standard treatment, but may be an option based on critical evaluation of locoregional relapse risks [IV, C].
- In multistation N2 or N3, concurrent definitive CRT is preferred [I, A]. An experienced multidisciplinary team is of paramount importance in any complex multimodality treatment strategy decision, including the role of surgery in these cases [IV, C].
- In potentially resectable superior sulcus tumours, concurrent CRT induction followed by definitive surgery is the treatment of choice [III, A]. The same strategy may be applied for potentially resectable T3 or T4 central tumours in highly selected cases and experienced centres [III, B]. In both situations, surgery should be carried out within 4 weeks after the end of RT [III, B].

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Table 4. Continued

Systemic therapy

- For curative-intent management, patients should be able to undergo platinum-based ChT (preferably cisplatin) [I, A].
- (Neo)adjuvant anti PD(L)-1 checkpoint inhibitors are currently being evaluated in addition to current standard of care.
- Checkpoints are also being evaluated after CRT as consolidation therapy.

Unresectable LA-NSCLC

- Concurrent CRT is the treatment of choice in patients evaluated as unresectable in stage IIIA and IIIB [I, A]. If concurrent CRT is not possible—for any reason—sequential ChT followed by definitive RT represents a valid and effective alternative [I, A].
- There is no role for prophylactic cranial irradiation in stage III NSCLC [II, A].
- In the absence of contraindications, the optimal ChT to be combined with radiation in stage III NSCLC should be based on cisplatin. There are no firm conclusions supporting single-agent carboplatin as a radiation sensitiser [I, A].
- Most comparative studies of concurrent CRT versus sequential administration were using cisplatin + etoposide or cisplatin + vinca alkaloid (typically: cisplatin + vinorelbine), or cisplatin + pemetrexed if non-squamous histology. There are no comparative phase III trials using the paclitaxel/carboplatin regimen. When delivered perioperatively cisplatin-based combinations are considered the treatment of choice, in the absence of contraindications [I, A].
- In the stage III disease CRT strategy, two to four cycles of concomitant ChT should be delivered [I, A]. There is no evidence for further induction or consolidation ChT. In the perioperative setting, three to four cycles of cisplatin-based ChT are recommended [I, A], aiming at a total cumulative dose of at least 300 mg/m^2 of cisplatin [II, B].
- 60–66 Gy in 30–33 daily fractions is recommended for concurrent CRT [I, A]. Maximum overall treatment time should not exceed 7 weeks [III, B]. 'Biological intensification', such as treatment acceleration, is not standard practice in concurrent CRT schedules [III, B].
- In sequential approaches, RT delivered in a short overall treatment time is recommended [I, A].

Personalised medicine

- There is currently no role for targeted agents in stage III NSCLC outside clinical trials [I, A].
- Immunotherapy is being studied in early NSCLC as (neo)adjuvant therapy and as consolidation after CRT; data should be awaited before any clinical use [I, A].

Follow-up, long-term implications and survivorship

- NSCLC patients treated with radical intent should be followed for treatment-related complications, detection of treatable relapse or occurrence of second primary lung cancer [III, A].
- Surveillance every 6 months for 2 years with a visit including history, physical examination and—preferably contrast-enhanced—volume chest CT scan at least at 12 and 24 months is recommended, and thereafter an annual visit including history, physical examination and chest CT scan in order to detect second primary tumours [III, B].
- For individual patients, follow-up with six-monthly CT scans for 3 years is recommended for patients who are suitable for salvage treatment (e.g. surgery, local ablative therapy) [III, B]. The frequency of the follow-up visits can be tailored to the individual patient for those not suitable for salvage treatment [V, B].
- The selective use of FDG–PET is recommended when recurrence after SABR is suspected based on serial spiral chest CT [III, B].
- Due to a high number of false-positive findings on PET, patients suitable for salvage therapy should undergo a biopsy, whenever possible [III, B].
- NSCLC patients should be offered smoking cessation, as this leads to superior treatment outcomes. Combining behaviour techniques with pharmacotherapy is the preferred approach [I, A].

2D, 2 dimensional; 3D, 3 dimensional; ChT, chemotherapy; COPD, chronic obstructive pulmonary disease; CRT, chemoradiotherapy; CT, computed tomography; DLCO, diffusing capacity of the lungs for carbon monoxide; EBUS, endobronchial ultrasound; EUS, endoscopic ultrasound; FDG–PET, fluorodeoxyglucose positron emission tomography; FEV1, forced expiratory volume in 1 second; GGO, ground glass opacity; IASLC, International Association for the Study of Lung Cancer; LA-NSCLC, locally advanced NSCLC; LDCT, low-dose CT; MRI, magnetic resonance imaging; NSCLC, non-small-cell lung cancer; NOS, not otherwise specified; OS, overall survival; PET, positron emission tomography; PORT, postoperative radiotherapy; RCRI, revised cardiac risk index; RCT, randomised controlled trial; RFA, radiofrequency ablation; RT, radiotherapy; SABR, stereotactic ablative radiotherapy; SUV_{max}, maximum standardised uptake value; TNM, tumour, node and metastasis; VATS, video-assisted thoracoscopic surgery; VO_2max, maximal oxygen consumption; WHO, World Health Organization.

after the resection; reasons were respiratory insufficiency, pneumonia, pneumothorax and cardiac complications. Patient factors associated with readmission were resection type, age, prior induction CRT and preoperative comorbidities, including congestive heart failure and COPD. The 90-day mortality in those readmitted at 30 days is 6-fold that of those not readmitted. This emphasises the need for adequate care and more intense early follow-up in patients at risk of developing postoperative problems [123]. Overall, the 90-day mortality is nearly double the 30-day mortality, with a considerable difference between low and high-volume hospitals [124]. Overall, these patients have a significant excess conditional mortality with an—increasing over time—relative contribution of cardiovascular and respiratory co-morbidity [125].

In a large group of resected patients, standardised follow-up revealed that during the first 4 years after surgery, the risk of recurrence ranged from 6% to 10% per person per year, but decreased thereafter to 2% [126]. Within this period a pattern can be recognised, during the first and second year recurrence is mainly local and rare thereafter, whereas at the end of the second year until the end of the fourth year, recurrence is dominated by distant metastases decreasing over time [127]. After 5 years, these are virtually absent. The risk of developing a second primary lung cancer exhibits a more uniform pattern over time, ranging from 1% to 6% per person per year and did not diminish over time [126, 128]. This is not restricted to cancers developing in smokers but was observed at a comparable magnitude in non-smokers [129].

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Table 5. Table of levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System[a])

Levels of evidence	
I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, expert opinions
Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events and costs, ...), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

[a]By permission of the Infectious Diseases Society of America [139].

Surveillance after treatment with curative intent is only useful if detection of a recurrence, locally or distant, or detection of a metachronous primary will result in potentially life-prolonging or preferable curative therapy. Curative therapy after a local recurrence is often not possible, resulting only in 5-year survival rates of ∼15% [130, 131].

For second primaries, the outcome is better with 5-year survival rates ranging from 25% to 60% [132, 133].

This illustrates that detection of local recurrence or a metachronous primary may lead to therapy resulting in long-term disease-free survival. Therefore, regular screening for both is likely to be worthwhile.

There are no prospective trials evaluating what will be the most optimal follow-up after surgery. As most local relapses will be seen during the first two years after treatment, a follow-up visit every 6 months is recommended during that period, and annually thereafter. A new finding detected through history, physical examination and/or imaging (preferably CT) usually needs to be discussed in an experienced multidisciplinary team taking into account that a new finding could be a treatment complication, a metastasis or a new primary.

For patients initially treated with SABR, the late local recurrences can be observed for up to 5 years post-treatment, and the incidence of second primary lung tumours appears to be similar to that post-surgery [81, 134]. As it may be sometimes difficult to distinguish post-SABR recurrences from focal fibrosis, high-risk radiological features have been identified [135] and the use of such a scheme has recently been independently validated [136].

Patients who have undergone ChT and RT for stage III NSCLC, are at high risk of developing progressive disease, either locally or at metastatic sites. Establishing locoregional disease progression is often a diagnostic challenge, but this is important in patients who may be fit for salvage treatments [98–105].

Smoking cessation is crucial in all lung cancer patients treated with curative intent, and patients should be offered support to achieve this goal.

Recommendations:

- NSCLC patients treated with radical intent should be followed for treatment-related complications, detection of treatable relapse or occurrence of second primary lung cancer [III, A].
- Surveillance every 6 months for 2 years with a visit including history, physical examination and—preferably contrast-enhanced—volume chest CT scan at least at 12 and 24 months is recommended, and thereafter an annual visit including history, physical examination and chest CT scan in order to detect second primary tumours [III, B].
- For individual patients, follow-up with six-monthly CT scans for 3 years is recommended for patients who are suitable for salvage treatment (e.g. surgery, local ablative therapy) [III, B]. The frequency of the follow-up visits can be tailored to the individual patient for those not suitable for salvage treatment [V, B].
- The selective use of FDG–PET is recommended when recurrence after SABR is suspected based on serial spiral chest CT scan [III, B].
- Due to a high number of false-positive findings on PET, patients suitable for salvage therapy should undergo a biopsy, whenever possible [III, B].
- NSCLC patients should be offered smoking cessation, as this leads to superior treatment outcomes. Combining behaviour techniques with pharmacotherapy is the preferred approach [I, A].

Methodology

These Clinical Practice Guidelines were developed in accordance with the ESMO standard operating procedures for Clinical Practice Guidelines development http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology. The relevant literature has been selected by the expert authors. A summary of recommendations is shown in Table 4. Levels of evidence and grades of recommendation have been applied using the system shown in Table 5. Statements without grading were considered justified standard clinical practice by the experts and the ESMO Faculty.

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This manuscript has been subjected to an anonymous peer review process.

Disclosure

PEP has reported advisory boards for Bristol-Myers Squibb, Boehringer Ingelheim, Novartis, AstraZeneca, Janssen Pharmaceuticals, Merck Sharp & Dohme and Roche; received honoraria from Roche and travel grants from Merck Sharp & Dohme, Boehringer Ingelheim, Pfizer and Celgene; KMK has reported lecture honoraria and/or consultancy fees from AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly, Merck KGaA, Merck Sharpe & Dohme, Novartis, Pfizer, Roche and Roche Diagnostics; SS has reported advisory boards for Lilly Oncology and research sponsored by Varian Medical Systems; JV has reported advisory boards, consulting and honoraria from Merck Sharp & Dohme, Boehringer, Eli Lilly, AstraZeneca and Novartis; MO, DW, CE and SP have reported no conflicts of interest.

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