CLINICAL PRACTICE GUIDELINES

An ESMO Product

Early and locally advanced non-small-cell lung cancer (NSCLC)

ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

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Screening

Screening method	Recommendation	LoE, GoR
Screening with LDCT (low-dose computed topography)	Reduces lung cancer-related mortality in high-risk subjects (heavy smokers [≥ 30 pack-years or ≤ 15 years since cessation] aged 55–74 years) • Questions remain about the definition of the at-risk population, screening intervals, age at end of screening, method of CT, cost-effectiveness and rate of false-positive diagnoses • A new, non-invasive LDCT protocol shows promise in reducing the false positive detection rate	I, A
	May be offered to well-informed heavy smokers aged 55–74 years within a dedicated programme in experienced CT centres	I, A
Other screening methods, such as chest X-ray, sputum analysis or biomarkers	Not recommended for clinical use	I, C

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Diagnosis and pathology/molecular biology

Work-up for diagnosis and staging

Parameter	Mandatory	Optional
General	Medical history* Physical examination* Assessing comorbidity Performance status	
Imaging	X-ray thorax CT thorax* PET-CT thorax* MRI brain†	Bone scintigraphy Contrast-enhanced CT brain
Laboratory	Blood cell counts Renal function Liver enzymes Bone parameters	
Cardio-pulmonary function	FVC, FEV_1, DLCO ECG If indicated: CPET	Ejection fraction, CAG
Tissue procurement	Bronchoscopy‡,§ EBUS/EUS mediastinal nodes* CT-guided biopsy	Mediastinoscopy

*Tests needed for clinical staging

†Screening for brain metastases by MRI might be useful in patients considered for curative therapy

‡Depending on site and size of tumour with biopsy/aspiration/brush/washing

§Bronchoscopy is usually sufficient to diagnose NSCLC, though may not allow a detailed sub-classification

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Diagnosis and pathology/molecular biology

Summary of recommendations

Recommendation	LoE, GoR
In clinical stages I-III, 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	III, A
The pathological classification NOS should be used only in cases where it is impossible to obtain enough tissue for further classification	V, A
The WHO classification of adenocarcinoma subtypes should be used	III, A
FDG-PET may contribute to the selection of patients for anatomical sublobar resections as low SUV_{max} values of peripheral tumours indicate lack of mediastinal metastases	III, A
The diagnostic approach to non-calcified pulmonary nodules should be based on existing standard guidelines	III, A

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Staging and risk assessment

Stage grouping UICC TNM 8

Stage	T - Primary Tumour	N - Regional Lymph Nodes	M - Distant Metastasis
Occult carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA1	T1a(mi) 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 T2a–b T3	N1 N1 N0	M0
Stage IIIA	T1a–c T2a–b T3 T4 T4	N2 N2 N1 N0 N1	M0
Stage IIIB	T1a–c T2a–b T3 T4	N3 N3 N2 N2	M0
Stage IIIC	T3 T4	N3 N3	M0

Brierley JD et al (eds). TNM Classification of Malignant Tumours, 8th edition: John Wiley & Sons, Inc., Oxford, 2016. Reprinted with permission from John Wiley & Sons, Inc.

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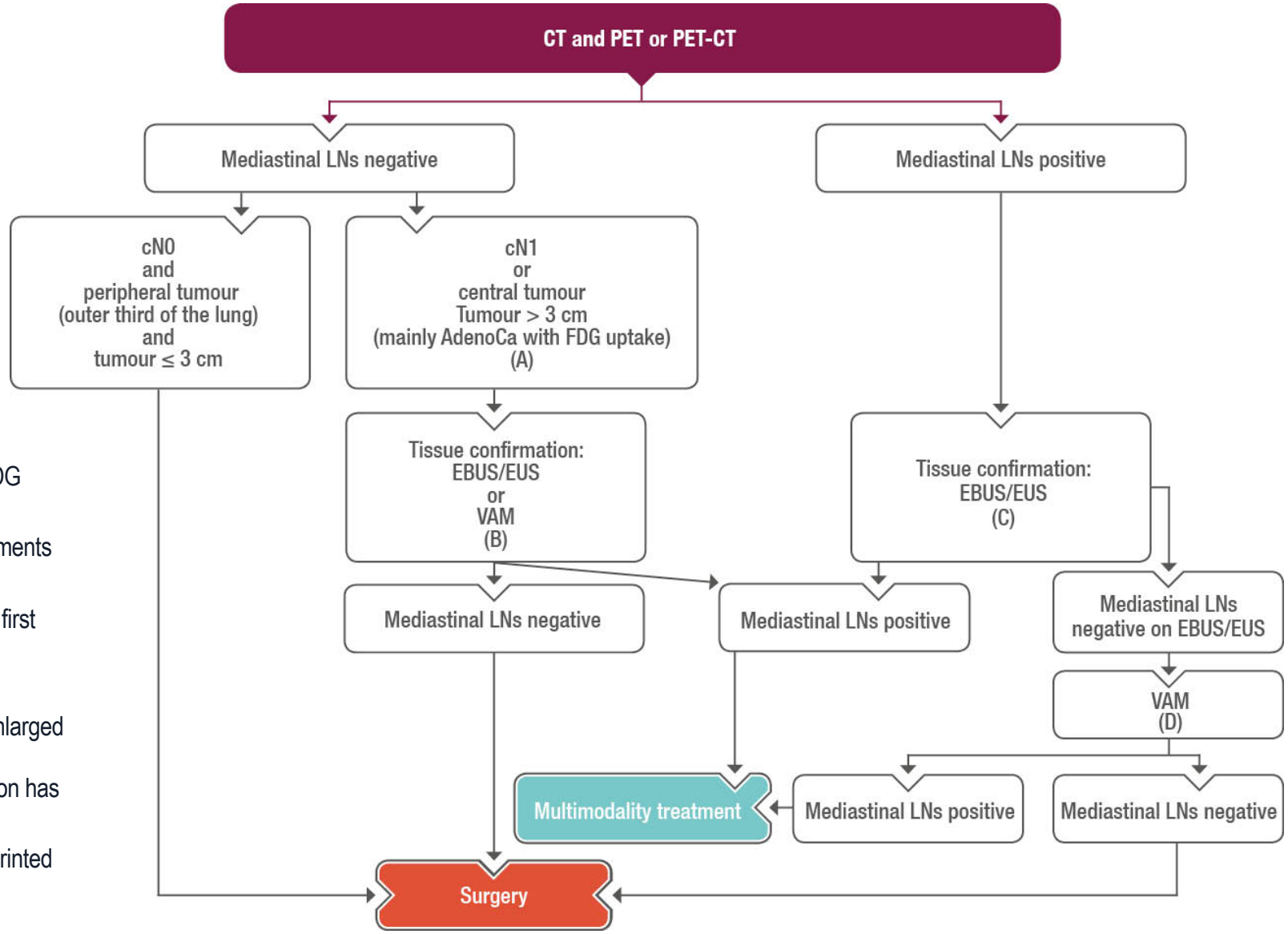
Staging and risk assessment

Locoregional LN staging in patients with non-metastatic NSCLC



(A) In tumours > 3 cm (mainly in adenocarcinoma with high FDG uptake) invasive staging should be considered

(B) Depending on local expertise to adhere to minimal requirements for staging

(C) Endoscopic techniques are minimally invasive and are the first choice if local expertise with EBUS/EUS needle aspiration is available

(D) Due to its higher NPV, in the case of PET-positive or CT-enlarged mediastinal LNs, VAM with nodal dissection or biopsy remain indicated when endoscopic staging is negative. Nodal dissection has an increased accuracy over biopsy

De Leyn P et al. Eur J Cardiothorac Surg 2014;3:787–98. Reprinted with permission.

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Staging and risk assessment

Locoregional staging

Summary of recommendations	LoE, GoR
The size of the invasive component should be used to assign T category	III, A
Subsolid lesions need dedicated radiological expertise for evaluation	V, A
Two primaries should be separately evaluated, staged and treated	III, A
Endosonography is recommended for abnormal mediastinal/hilar LNs	I, A
Needle aspiration under EBUS and/or EUS is preferred for pathological confirmation	I, A
Mediastinoscopy is indicated if EBUS and/or EUS negative	I, A
Screening brain MRI might be useful in patients considered for curative therapy	III, B

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Staging and risk assessment

Staging for locally advanced (stage III) NSCLC

Summary of recommendations	LoE, GoR
Contrast-enhanced chest and upper abdomen CT followed by PET or combined PET-CT with high resolution CT in patients planned for definitive treatment • Within 4 weeks before treatment	I, A III, B
Pathological confirmation is needed for single PET-positive distant lesions	V, B
Pathological staging of the mediastinum is advised in operable N2 patients	III, C
Brain imaging for initial staging should be carried out in patients planned for curative treatment	III, B
Contrast-enhanced brain MRI is the preferred method for brain staging	III, A

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Staging and risk assessment

Pre-treatment risk assessment

Summary of recommendations	LoE, GoR
In non-metastatic NSCLC, the cardiopulmonary fitness of the patient determines the choice of treatment	III, A
Risk-specific models can estimate the risk of postoperative morbidity/mortality	III, B
Assessment of cardiac and pulmonary function is necessary to estimate the risk of operative morbidity	III, A
Recalibrated RCRI is recommended	III, A
No further investigations needed if FEV_1 and DLCO > 80% of predicted values and no major comorbidities • For others, include exercise testing and split lung function	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 after resection	III, B

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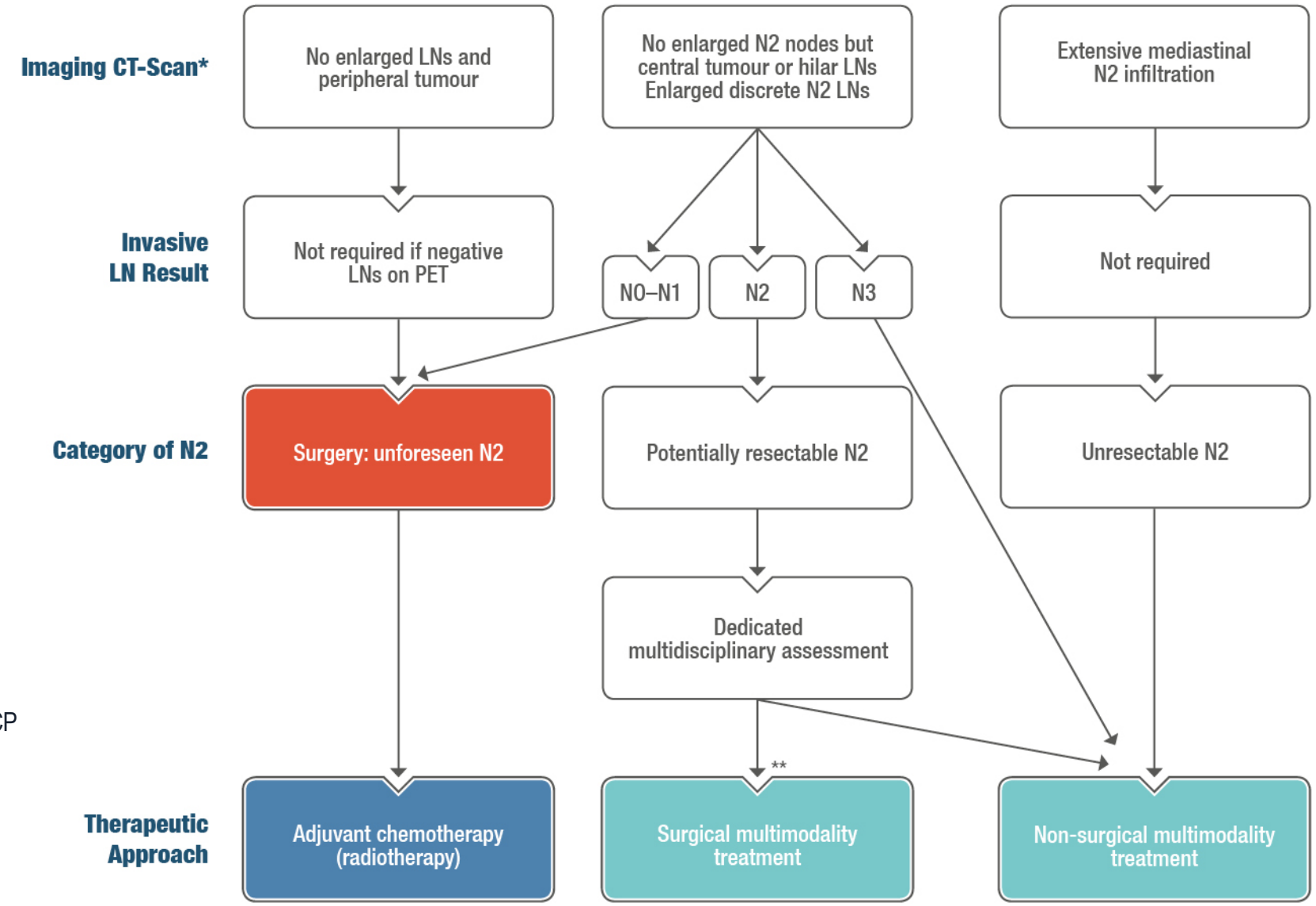
Staging and risk assessment

Treatment recommendations for patients with locoregional NSCLC, based on imaging, invasive LN staging tests and multidisciplinary assessment



*Category description according to CT imaging as in ACCP staging document (Silvestri GA et al. Chest 2013;143(5 Suppl):e211S–50S)

**Refer to slide 'Treatment: Locally advanced NSCLC (stage III) – Resectable'

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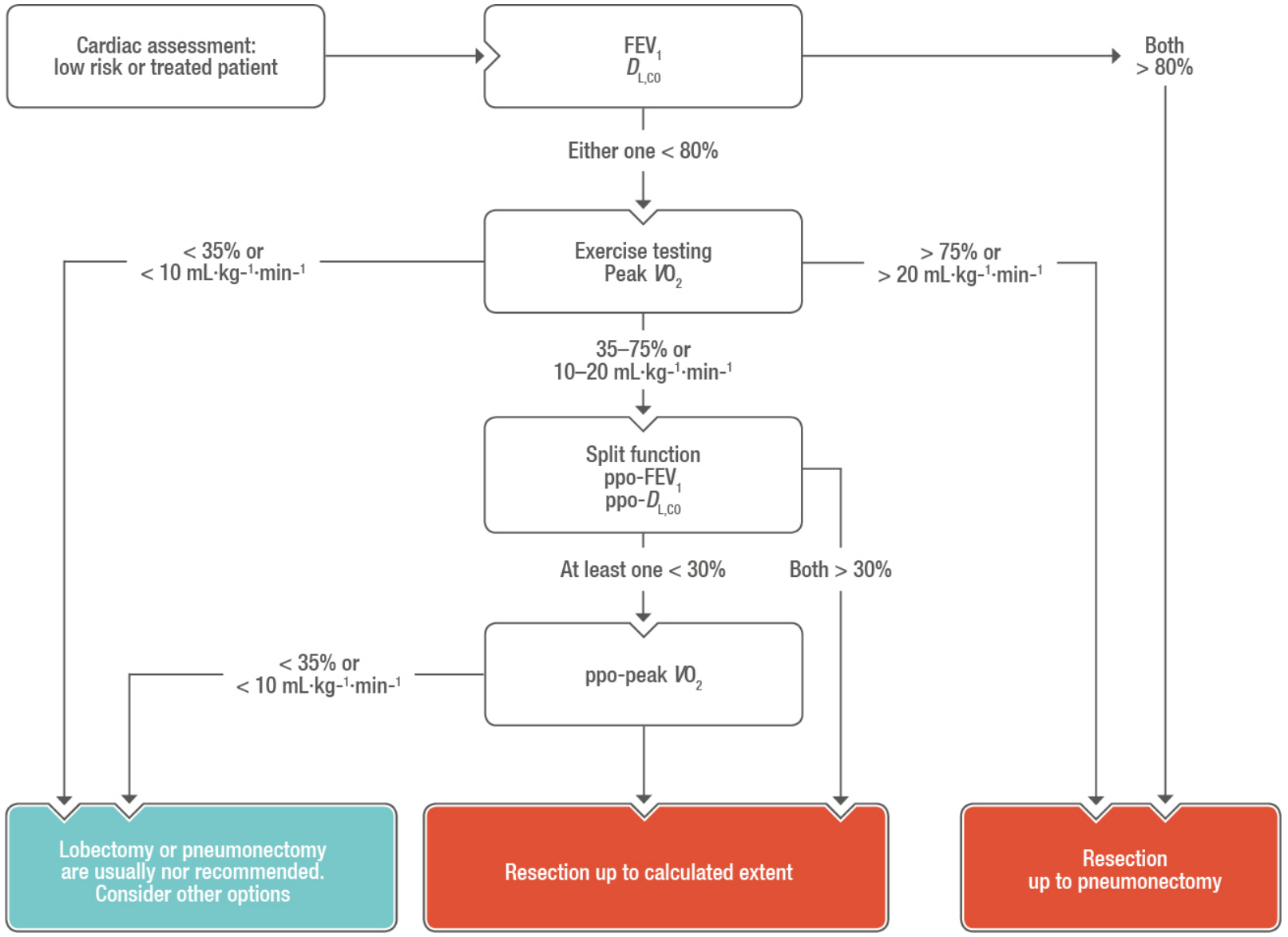
Staging and risk assessment

Preoperative respiratory evaluation



Brunelli A et al. Eur Respir J 2009;34:17–41.

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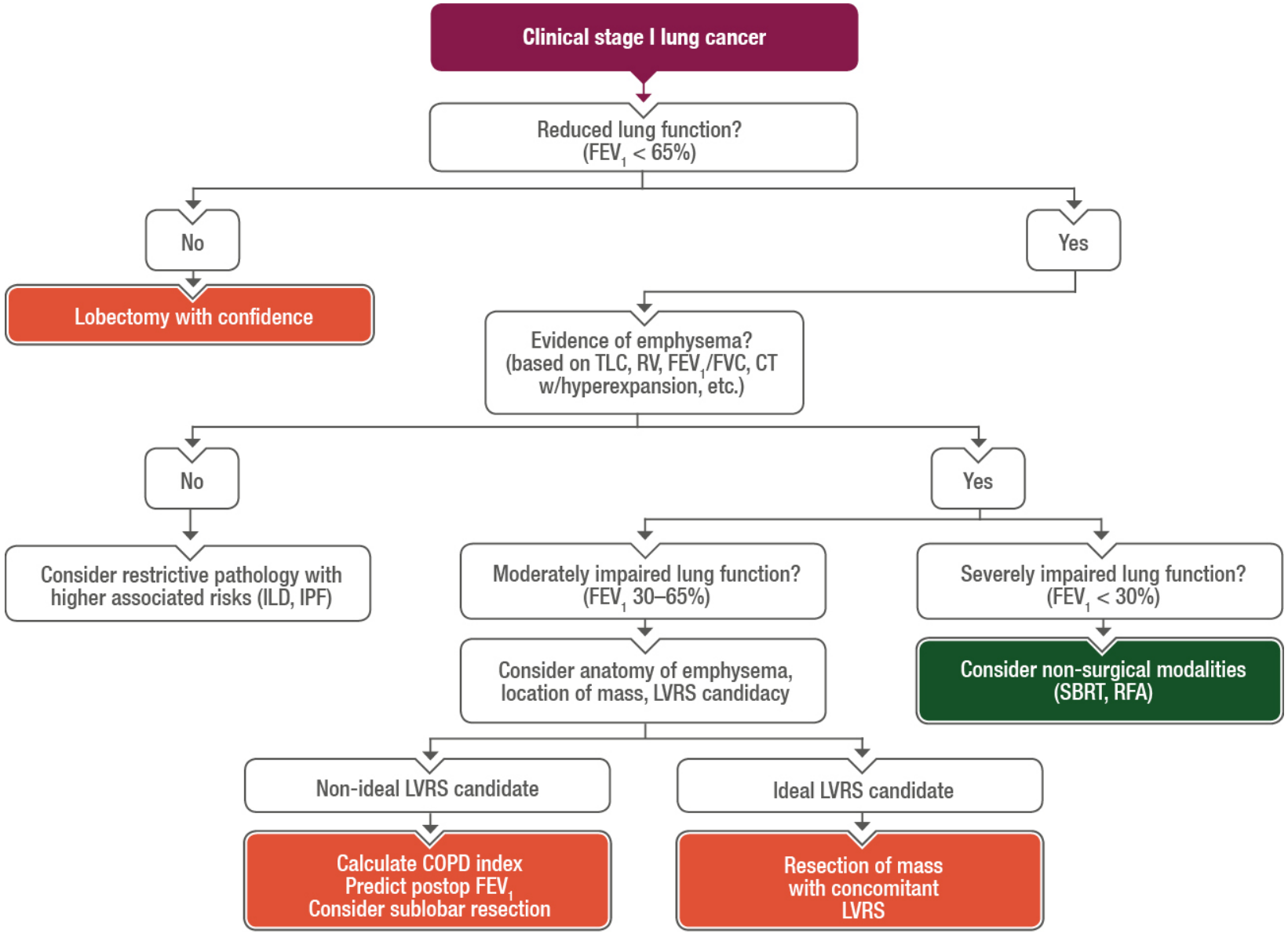
Staging and risk assessment

Patients with clinical stage I lung cancer and limited pulmonary function due to emphysema



Yacoub WN et al. Semin Thorac Cardiovasc Surg 2010;22:38–43.

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Staging and risk assessment

Recalibrated thoracic revised cardiac risk index

	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

Adapted from Brunelli A et al. Ann Thorac Surg 2010;90:199–203

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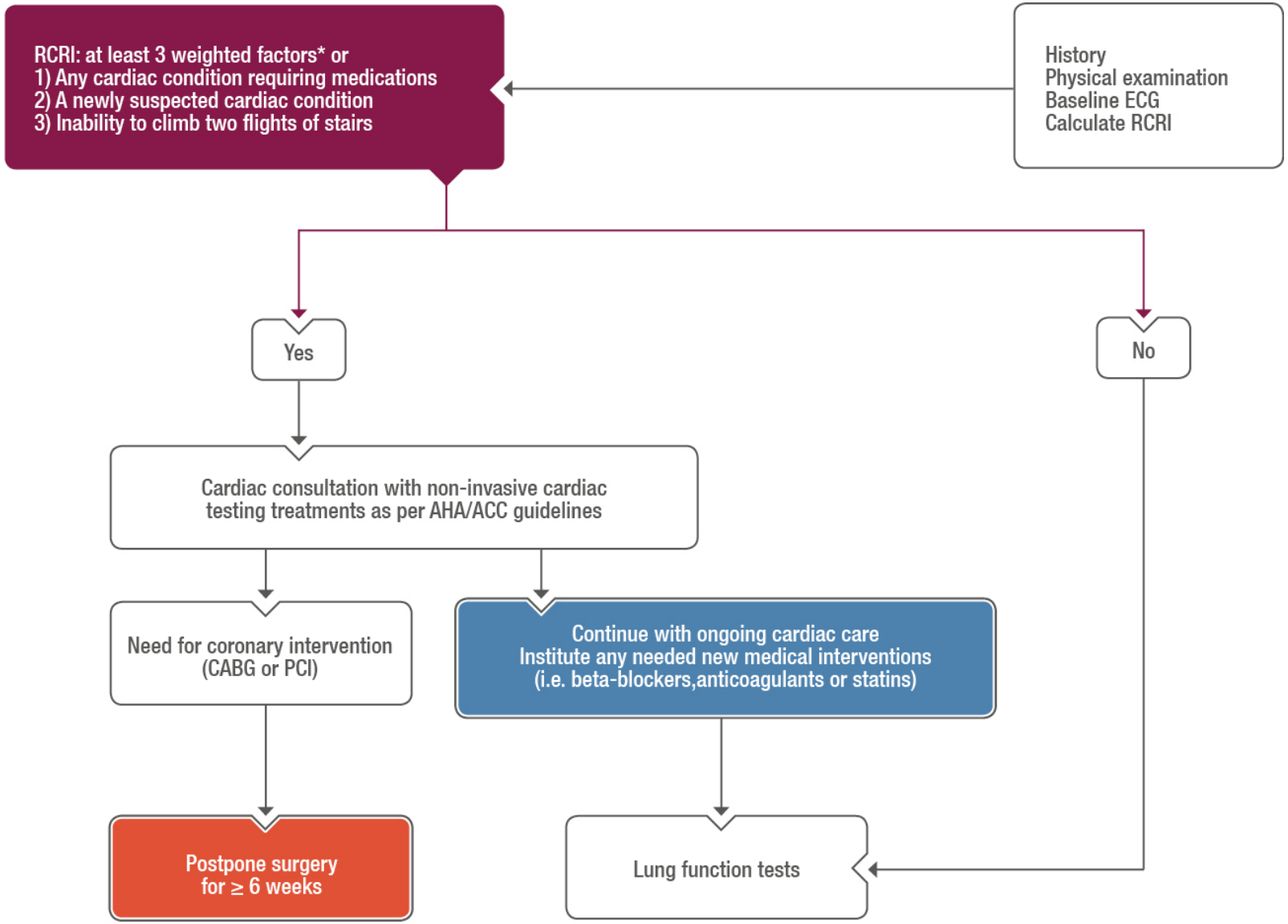
Staging and risk assessment

Preoperative cardiac evaluation



*Original RCRI weighted factors: high-risk surgery (including lobectomy or pneumonectomy); ischaemic heart disease (prior myocardial infarction, angina pectoris); heart failure; insulin-dependent diabetes; previous stroke or TIA; creatinine > 2 mg/dL

Brunelli A et al. Eur Respir J 2009;34:17–41. Reprinted with permission from the European Respiratory Society.

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Treatment

Early NSCLC (stages I and II)
– Surgery

Summary of recommendations	LoE, GoR
Surgery is the preferred treatment for stages I and II • Recommended for patients with only a non-centrally located resectable tumour on both CT and PET images • Anatomical resection is preferred over wedge resection	III, A I, A
Segmentectomy acceptable for pure GGO lesions or adenocarcinomas *in situ* or with minimal invasion	III, B
Lobectomy is the standard surgical treatment of tumours ≥ 2 cm with solid appearance on CT	II, B
LN dissection conform to IASLC specifications for staging	III, A
Thoracotomy or VATS access can be carried out as appropriate according to surgeon expertise	III, A
VATS is the preferred choice in stage I	V, C
Complete resection is recommended whenever possible in patients with multifocal disease • All patients with multifocal lung cancer should be discussed by an MDT	III, B

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Treatment

Early NSCLC (stages I and II)
– Systemic therapy

Summary of recommendations		LoE, GoR
Adjuvant ChT	Should be offered in resected stage II and III patients	I, A
	Should be discussed in resected stage IB patients with primary tumour > 4 cm	II, B
	Pre-existing comorbidity, time from surgery and postoperative recovery should be evaluated by an MDT	V, A
	A two-drug combination with cisplatin is preferable (cisplatin/vinorelbine is the most frequently studied regimen)	I, A
Targeted agents should not be used in the adjuvant setting		II, A
Adjuvant ChT after surgery is preferred over neoadjuvant before surgery		II, C
(Neo)adjuvant anti-PD(L)-1 checkpoint inhibitors are under evaluation in combination with standard of care		

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Treatment

Early NSCLC (stages I and II) – Radiotherapy

Summary of recommendations		LoE, GoR
Primary radiotherapy	SABR/SBRT in stage I is the treatment of choice at a biologically equivalent tumour dose of ≥ 100 Gy to the encompassing isodose	III, A
	SABR is associated with low toxicity in peripheral lung tumour in elderly and COPD patients	III, A
	Salvage surgery may be offered to patients with complications post-SABR	V, B
	For medically inoperable patients with tumours > 5 cm and/or moderately central location, radical RT using more conventional or accelerated schedules is recommended	III, A
Radiofrequency ablation	Patients with stage I NSCLC with strong contraindications for surgery and/or SABR may be treated with RFA	V, C
Postoperative radiotherapy	PORT is not recommended in completely resected cases	I, A
	PORT should be discussed if R1 resection (positive resection margin, chest wall)	IV, B
	Adjuvant ChT should be considered in stage IB with R1 resection and stage II and III with primary tumour > 4 cm	V, A
	RT should follow ChT when both are given in the adjuvant setting	V, C

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Treatment

Locally advanced NSCLC (stage III)
– Systemic therapy

Summary of recommendations	LoE, GoR
Platinum-based ChT (preferably cisplatin) is recommended when given with a curative intent	I,A
Perioperative treatment with cisplatin-based combinations are the treatment of choice; 3-4 cycles are recommended	I,A
• Cisplatin minimum total cumulative dose of 300mg/m^2	II,B
(Neo)adjuvant anti-PD-(L)1 checkpoint inhibitors are under evaluation in combination with standard of care; checkpoint inhibitors are under evaluation also as consolidation after CRT	

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Treatment

Locally advanced NSCLC (stage III) – Resectable

Summary of recommendations	LoE, GoR
Adjuvant ChT should follow after surgery for N2 disease documented only intra-operatively	I, A
PORT after complete resection may be an option after individual risk assessment	V, C
In case of single station N2 disease by preoperative pathological analysis, resection followed by ChT, induction ChT followed by surgery or CRT followed by surgery are options	IV, C
After preoperative ChT alone, PORT may be an option according to the locoregional relapse risks	IV, C
Concurrent definitive CRT is preferred in multistation N2/N3	I, A
Multimodality treatment strategy decisions should be evaluated by experienced MDT	IV, C
Concurrent CRT induction followed by definitive surgery • Treatment of choice is potentially resectable superior sulcus tumours • May be used for potentially resectable T3 or T4 central tumours in highly selected cases at experienced centres • Surgery should be carried out within 4 weeks from RT	III, A III, B III, B
There is no role for prophylactic cranial RT in stage III	II, A

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Treatment

Locally advanced NSCLC (stage III) – Unresectable

Summary of recommendations	LoE, GoR
Concurrent CRT is the treatment of choice for unresectable stage IIIA and IIIB • If not possible, ChT followed by definitive RT is a valid alternative • Cisplatin-based ChT is optimal for combination with RT in stage III • For CRT in stage III, 2–4 cycles of concomitant ChT should be delivered	I, A
For concurrent CRT, 60–66 Gy in 30–33 daily fractions is recommended • The maximum treatment time should not exceed 7 weeks	I, A III, B
'Biological intensification' is not standard practice in concurrent CRT schedules	III, B
In sequential approaches, RT over a short treatment time is recommended	I, A
There is no role for prophylactic cranial RT in stage III	II, A

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Treatment

Personalised Medicine/Immunotherapy

Summary of recommendations	LoE, GoR
There is no role for targeted agents in stage III outside clinical trials	I, A
Immunotherapy is under evaluation in early stages as (neo)adjuvant therapy and as consolidation after CRT; data should be awaited before any clinical use	I, A

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Follow-up

Long-term implications and survivorship

Summary of recommendations	LoE, GoR
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 history, physical examination and contrast-enhanced chest CT at least at 12 and 24 months, thereafter every 12 months is recommended	III, B
Frequency of follow-up visits: • 6-monthly CT scans for 3 years is recommended for patients suitable for salvage treatment • Individually adapted for those not suitable for salvage treatment	III, B V, B
FDG–PET is recommended when recurrence after SABR is suspected based on spiral chest CT	III, B
Patients suitable for salvage therapy should undergo a biopsy, whenever possible	III, B
Patients should be offered smoking cessation with behaviour techniques and pharmacotherapy	I, A

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Disclaimer and how to obtain more information

This slide set provides you with the most important content of the full ESMO Clinical Practice Guidelines (CPGs) on the management of early-stage, locally advanced non-small-cell lung cancer (NSCLC). Key content includes diagnostic criteria, staging of disease, treatment plans and follow-up.

The ESMO CPGs are intended to provide you with a set of recommendations for the best standards of care, using evidence-based medicine. Implementation of ESMO CPGs facilitates knowledge uptake and helps you to deliver an appropriate quality of focused care to your patients.

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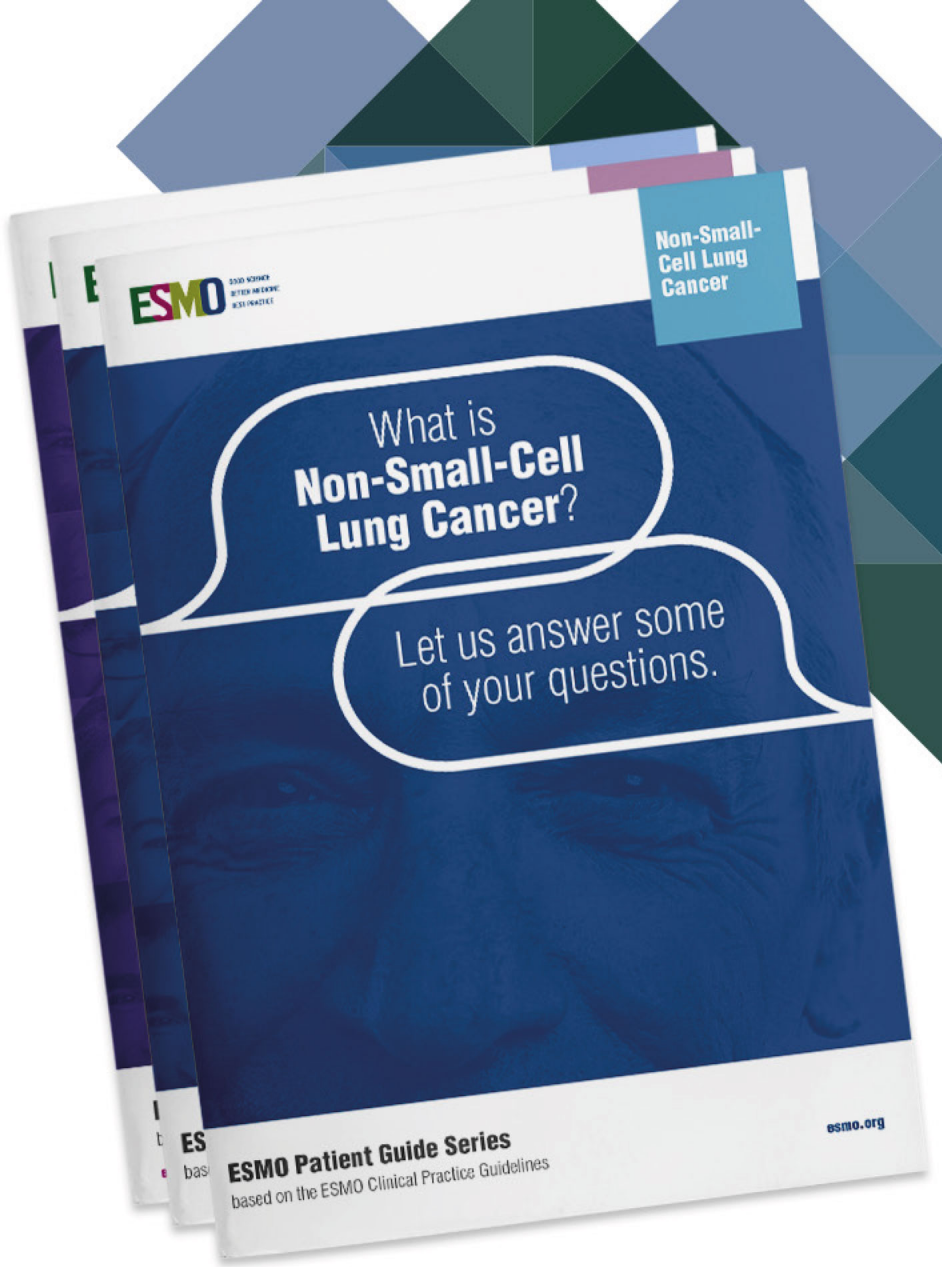

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