## appendix 2

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# 2nd ESMO Consensus Conference in Lung Cancer: locally advanced stage III non-small-cell lung cancer

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To complement the existing treatment guidelines for all tumour types, ESMO organises consensus conferences to focus on specific issues in each type of tumour. The 2nd ESMO Consensus Conference on Lung Cancer was held on 11–12 May 2013 in Lugano. A total of 35 experts met to address several questions on non-small-cell lung cancer (NSCLC) in each of four areas: pathology and molecular biomarkers, first-line/second and further lines of treatment in advanced disease, early-stage disease and locally advanced disease. For each question, recommendations were made including reference to the grade of recommendation and level of evidence. This consensus paper focuses on locally advanced disease.

**Key words:** non-small-cell lung cancer, locally advanced, stage III, recommendations, ESMO

## methods

A detailed literature review was done by the writing group for this manuscript and was extended after sending out the preliminary paper to all other Panel Members (see Appendix). All available meta-analysis, randomized phase III trials and phase II trials considered by the panel as of key importance were put forward for the scoring of the guidelines. The scores for level of evidence and grade of recommendation were proposed and fully consented within the writing committee that met at the Consensus Conference in Lugano. In an initial summary discussion meeting at the Consensus Conference, these scores were already presented to the full Consensus Panel and evaluated and amended whenever necessary. During the final writing process, these scores were further consented within the writing group together with the full consensus panel. Final given levels of evidence and grades of recommendation in this manuscript were consented without significant divergence between the different panel members if not otherwise openly specified in the text (Table 1). Statements without grading were considered standard clinical practice by the experts. The methods both for the conference and the writing process for this topic were as those for the other three manuscripts produced from this conference [2–4]. To minimise

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potential bias from the Consensus Panel and writing group, the full multidisciplinary manuscript input came from medical oncologists, radiation oncologists, thoracic surgeons, pulmonologists and also from pathologists and molecular pathologists.

This manuscript covers locally advanced disease defined as stage III disease determined at initial staging, as well as stage III disease found as pathological stage III following upfront surgical resection treatment. Table 2 shows the different patient subsets of stage III non-small-cell lung cancer (NSCLC). The Robinson Classification that includes subsets of patients that are found only to be pathologically within stage III disease (IIIA1 and IIIA2) is mentioned here and later in the text for historical reasons (see also Table 2). Some centres still classify patients within stage IIIA(N2) based on these criteria although, generally, this classification has lost some of its importance in guiding treatment algorithms for individual treatment decisions.

**Table 1.** 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 with demonstrated heterogeneity |
| III | Prospective cohort studies |
| IV | Retrospective cohort studies or case–control studies |
| V | Studies without control group, case reports, experts 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, 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 [1].

## introduction

### heterogeneity in disease

*Locally advanced NSCLC in this manuscript is defined as stage III NSCLC patients according to the most recent (7th) edition of the International Association for the Study of Lung Cancer (IASLC)/ Union for International Cancer Control (UICC) TNM staging classification.* Stage III NSCLC represents a heterogeneous group of patients even in the most recent version of the IASLC/UICC TNM staging system (7th edition) [5]. The treatment of such patients may be a challenge because of their local presentation, especially in the case of an advanced primary tumour (T4 situation) with local infiltration of vital mediastinal organs or involvement of locoregional mediastinal lymph nodes (N2 or N3 nodes) and the risk of metastatic recurrence (see Table 2) [5]. Consequently, the IIIA subset is still to be differentiated from the IIIB subset of NSCLC. Definitive cure rates as well as long-term prognosis differ significantly between these two sub-stages (see Table 2) [5].

Furthermore, most randomised studies were carried out in the pre-positron emission tomography (PET) scan era. The high rate of undiagnosed distant metastases in these patients has most probably diluted any real effect of local control on the overall outcome. Thus, the current stage III NSCLC population has changed as well as the related treatment [6, 7]. These changes also contribute to the difficulty of interpreting results. Improved outcomes of stage III patients in current studies compared with previous trials may result from stage migration, because of the increased use of PET and magnetic resonance imaging (MRI) of the brain. There have been improvements in surgery (lung-sparing techniques, minimally invasive surgery, pre- and post-operative care), radiotherapy (e.g. image guidance, adaptive and respiratory movement techniques) and adjuvant or neoadjuvant chemotherapy has become a standard of care in operable stage III patients [8, 9]. Adjuvant chemotherapy is

**Table 2.** Patient subsets and sub-stages included into stage III non-small-cell lung cancer

| IASLC/UICC 7 | Definition | TNM subsets | Description | Robinson classification |
|---|---|---|---|---|
| IIIA | Incidental N2 (unforeseen N2) | T1–3 N2 | N2 found at surgery | |
| | | | Microscopic N2 (final pathology) | IIIA1 |
| | | | Microscopic/macroscopic N2 (frozen section) | IIIA2 |
| IIIA | Potentially resectable N2 | T1–3 N2 | Minimal N2/single station at staging | IIIA3 |
| IIIA | Potentially resectable N2 | T1–3 N2 | Pancoast tumour subsets, T3-4 N1, T3 N2 selective | – |
| | But: risk of incomplete resection | | centrally located IIIA(N2) | IIIA3 |
| IIIA | Unresectable N2 | T1–3 N2 | Bulky and/or multilevel N2 at staging | IIIA4 |
| IIIA | Potentially resectable T4 | T4 N0–1 | Pulmonary artery, carina, spine, trachea, vena cava, right | – |
| | But: risk of incomplete resection | | atrium | |
| IIIB | Unresectable T4 | T4 N0–1 | Oesophagus, heart, aorta, pulmonary veins | – |
| | | T4 N2 | | |
| IIIB | Unresectable N3 | T1–4 N3 | N3 nodes at staging | |

defined as post-operative chemotherapy that is aimed at the treatment of micrometastases to improve cure rates after curative complete resection of the tumour at surgery. Neoadjuvant chemotherapy is defined as preoperative chemotherapy given to patients that are planned for a curative resection at surgery (again for improving cure rates by the early treatment of micrometastases). The technical advances of radiotherapy allow for better integration with chemotherapy or surgery [10].

## heterogeneity in tumour histopathology

There are data showing that squamous cell carcinoma patients with stage III disease tend to have a somewhat better overall survival (OS) prognosis when treated with more aggressive combined-modality protocols. They also show a trend for more local and locoregional relapse in comparison with adenocarcinoma and large cell carcinoma patients who tend to develop more systemic relapses (especially an exceptionally high cumulative rate of brain relapse) [11, 12]. However, up to now, this has not led to different management strategies for these different entities.

## heterogeneity in tumour location and extension

Large central infiltrating primary tumours without lymph node metastasis (T4N0) have a significantly lower tendency to develop systemic metastatic spread than small tumours with extensive mediastinal nodal involvement (e.g. T1N3) [13]. These two entities are characteristic of the remaining wide spectrum in morphological presentation of patients among the current stage III disease groups. These morphological differences may potentially represent underlying differences in individual tumour biology, but the exact cellular mechanisms for this heterogeneity are still to be determined. The number of involved lymph node stations and the location of the nodes also influence the tumour prognosis [14].

## heterogeneity in individual patient risk profile

Long-term smokers (still representing the majority of lung cancer patients) typically harbour significant smoking-induced comorbidities such as reduced pulmonary function due to chronic obstructive pulmonary disease, significant cardiac problems related to coronary heart disease and vascular problems due to smoking-induced arteriosclerosis (peripheral and cerebral extension) [15]. Thus, this general profile of cardio-pulmonary higher risk patients may significantly hamper curative-intent and radical treatment strategies.

## inter-institution diversity (technical availability/local expertise/experience)

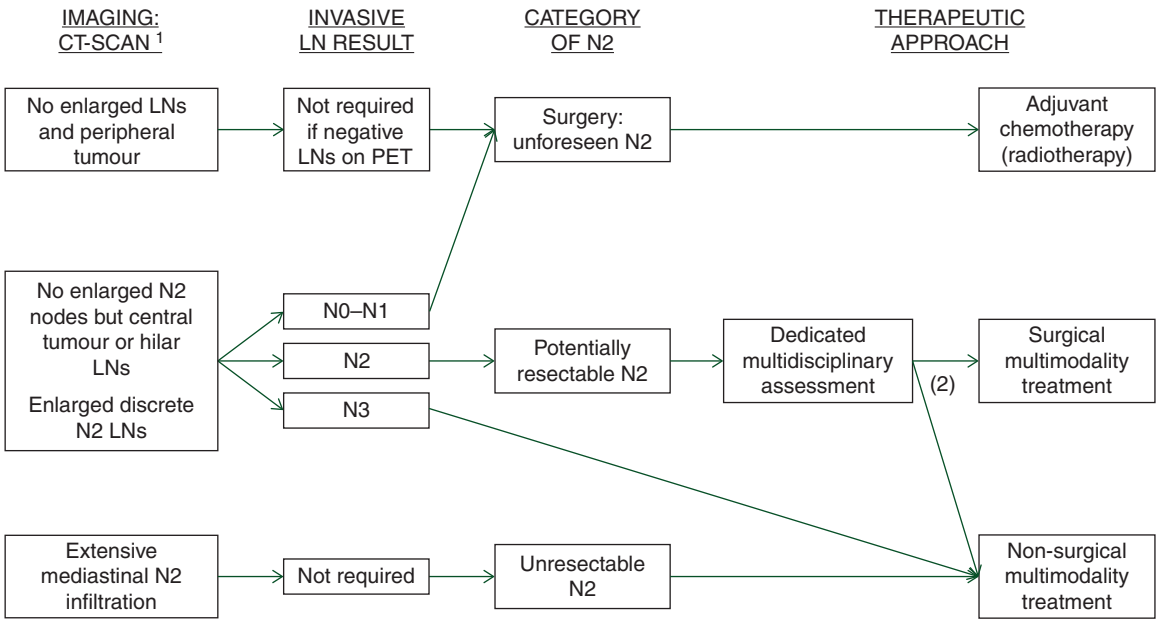
Stage III disease curative-intent strategies require considerable expertise of the staff at the treatment centre. Thoracic surgery for stage III disease may imply extensive operations including sleeve resections and resection of locally invaded mediastinal organs (e.g. trachea, vena cava, vertebra, pericardium, parts of the right atrium) [16]. Expertise in radiation oncology is needed to be able to evaluate toxicity/efficacy ratio, specify target volumes and determine organs at risk and doses that can safely be delivered. Expert staff are also needed to proceed with appropriate treatment including proper quality assurance, bearing in mind that treatment is a multi-modality strategy [10].

*in consideration of the guidelines, an individualised decision must be made within a multidisciplinary team.* With this background of individual risk profiles and different morphological tumour presentation on one hand, and different treatment strategies on the other, the patient with stage III disease should be discussed by a multidisciplinary team including pulmonologists, thoracic/medical oncologists, radiation oncologists and thoracic surgeons [17]. Closely integrated radiologists and nuclear medicine physicians for clinical imaging of the tumours, and pathologists for primary diagnosis and local extension at the time of surgery (frozen sections) must be available at the individual institution.

*due to the complexity of most stage III disease presentations that require multidisciplinary treatment, management should be carried out in high-volume centres.* High procedure volume is strongly associated with improved survival after lung cancer surgery [18]. For other multi-modality treatment strategies (induction chemotherapy followed by surgery, definitive chemoradiotherapy), it is at least possible that high procedure volume may play a comparably important role. Concerning radiotherapy, it has been shown that, within clinical trials where quality assurance of radiotherapy has been implemented, protocol deviations of radiotherapy delivery were associated with increased risks of treatment failure and overall mortality [19]. Another example is Pancoast tumour resection (sulcus superior tumours) after combined chemoradiotherapy; this should preferably be carried out in centres with specific expertise in the management of Pancoast tumours [20].

*results interpretation limited by conduct of trials in highly selected patient sub-populations.* While randomised phase III clinical trials in stage IV disease and early disease stages I and II can frequently recruit between 400 and 2000 patients, there are significantly fewer randomised, controlled trials completed in stage III disease [8, 9]. The majority of randomised trials defining the standards of care in stage III disease enrolled between 80 and 500 patients [21–24]. This reflects a significant selection bias of patients for inclusion into these randomised trials [in terms of age, performance status (PS) and stage], questioning the generalisation of these trial results to each individual patient presenting with a stage III NSCLC. If we consider trials that compared sequential versus concomitant chemotherapy and radiotherapy, they included few patients older than 70 years of age (only 16%) [25], whereas the median age for diagnosis of lung cancer is currently ~72 years of age.

The gold standard end point in clinical trials is OS. However, a recent study, based on a re-analysis of randomised trials having evaluated radiotherapy and chemotherapy contribution in locally advanced and operable NSCLC patients, investigated a possible correlation between OS and surrogate end points. It seems to show that disease-free survival can be a valid surrogate end point for OS in studies of adjuvant chemotherapy, and progression-free survival (PFS) could be a valid surrogate for OS in trials evaluating chemotherapy and radiotherapy in locally advanced lung cancers [26]. With lung cancer patients at high risk for comorbidity-related events,




[1] Category discription according to CT imaging as in ACCP staging document (Chest 143 Suppl 5:211S-250S, 2013), see text for more details.
[2] See text for factors involved in the choice between non-surgical and surfical multimodality treatment.

**Figure 1.** Suggested algorithm for treatment in patients with logoregional non-small-cell lung cancer, based on imaging, invasive lymph node staging tests and multidisciplinary assessment. Reproduced from [17], by permission of Oxford University Press, on behalf of ESMO.

some investigators also think that cancer-specific survival (rarely determined, not yet included in published clinical trials results) may be a further important surrogate end point for OS in these stage III disease populations with multiple competing underlying risks [27].

### additional staging systems for stage IIIA NSCLC

Surgical resection remains an important part of the multidisciplinary management at least for selected stage IIIA(N2) patients. Thus, some centres (although overall in decreasing numbers) still stratify patients according to the 'Robinson Classification of N2-disease' (see also Table 2) [28]. This classification—besides the routine TNM staging—may further mirror some of the heterogeneities of stage III disease. With definitive chemoradiotherapy now being increasingly carried out at several thoracic institutions, this classification has lost some of its former clinical importance to guide treatment algorithms, but is mentioned here for historical reasons.

The ESMO 2013 Clinical Practice Guidelines [17] presented a more practical scheme, integrating CT-scan findings, the application of invasive staging, the categories of N2 disease and the ensuing treatment strategy (Figure 1). This approach is further detailed in the 'incidental IIIA(N2) (unforeseen N2)' and 'potentially resectable IIIA(N2) disease' sections of this document.

## how do we sub-stage stage III NSCLC for decision making?

*Recommendation 1: In the rare cases when stage III disease patients undergo primary surgical resection, there is a proposed definition of a surgically complete resection. In the majority of patients where stage III disease is confirmed by initial staging investigations, it is still of importance to classify them at baseline as resectable (1), potentially resectable with an increased risk for incomplete resection (2) or unresectable (3).*

In the rare cases where patients are initially taken to surgery and are resected and found to have stage III NSCLC, complete resection is pathologically defined by the confirmation of negative surgical margins in the resected specimen, including the highest mediastinal node negativity at the time of resecting surgery and/or mediastinal lymph node dissection [29]. Difficulty in assessing extra-capsular lymph node extension upfront has a comparable impact on positive resection margins [14, 30, 31]. The majority of patients in stage III, however, will be found to have stage defining extension (e.g. T, N) in the initial imaging and invasive staging investigations. Since the possibility of complete resection is an outcome parameter with major impact on the overall prognosis of the patient, the multidisciplinary panel including radiologists, pulmonologists and thoracic surgeons should classify the patient upfront as either clearly potentially resectable (1), potentially resectable as part of an intermediate group (2) or definitely unresectable (3). In the intermediate group, resection is deemed to have an underlying increased risk of an incomplete resection. Here, typically tumours of the superior sulcus (Pancoast) and specific centrally located tumours (T3/T4 involvement) can be identified [13, 32]. Evaluating and predicting these parameters upfront is key for adequate planning of the definitive local treatment without treatment interruptions (either surgery, a neoadjuvant chemotherapy or

chemoradiotherapy approach, as defined by an initial combination chemotherapy given before any definitive local therapy such as surgery or primary definitive radiation/chemoradiotherapy), because of its complexity and the risk that a wrong decision may result in an unsuccessful outcome. This could lead to palliative treatment (e.g. an incomplete resection after preoperative concurrent chemotherapy and radiotherapy to a dose of 45 Gy).

## what is the optimal diagnostic work-up for stage III NSCLC patients?

### positron emission tomography–computed tomography

*Recommendation 2.1: All patients planned for definitive stage III NSCLC treatment should undergo a diagnostic high-resolution CT followed by a PET or a combined positron emission tomography–computed tomography (PET-CT) with a CT technique with adequately high resolution for initial staging purposes [I, A] in order to rule out detectable extra-thoracic extra-cranial 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].*

Several randomised trials have investigated the diagnostic impact of whole body PET-CT for initial staging of stage III NSCLC patients [33–37]. This investigation may rule out extracerebral metastases before decision making for any local treatment with a curative intent. Mediastinal lymph node staging may be initiated by this method [34]. Further pathological confirmation of suspected lymph node stations should follow using endoscopic bronchial ultrasound (EBUS), endoscopic ultrasound (EUS), cervical mediastinoscopy or video-assisted thoracoscopy (VATS) investigations including video-assisted mediastinoscopy (VAMS) or video-assisted mediastinal lymphadenectomy [38–41]. Single PET-positive distant lesions need pathological confirmation before accepting stage IV clinical staging status for any patient [6]. The quality of the local CT component in this setting is critical. Only the most modern generation of PET-CT scanners have high-resolution CT scanners embedded into the investigation. A high-enough-resolution CT scan for initial imaging evaluation of the primary tumour and the mediastinal organs should not be skipped for a less diagnostically accurate conventional CT scan.

### (minimally) invasive mediastinal staging (1) (transbronchial needle aspiration /EBUS/EUS/ mediastinoscopy)

*Recommendation 2.2: PET-positive mediastinal findings should be pathologically assessed [I, A]. Invasive mediastinal staging may still be indicated despite PET negativity in case of suspicious lesions (primary tumour of >3 cm large axis, central tumours, cN1, CT-enlarged lymph nodes with small axis >1 cm) [III, B].*

*Endoscopic methods should be preferred as the initial interventional procedure whenever feasible [I, A]. In case of negative endoscopic findings, and high suspicion of mediastinal node involvement, surgical staging is indicated [I, A].*

PET-positive mediastinal findings should always be confirmed cytologically or histologically, preferably at first by minimally invasive mediastinal staging. Methods available include transbronchial needle aspiration, guided by EBUS or oesophageal EUS [35, 38–41]. PET-CT has a high negative predictive value but its positive predictive value is not so widely accepted [37, 38]. Therefore, if significant impact on the overall treatment strategy is assumed, which is the case with most stage III NSCLC, PET-positive mediastinal findings should be pathologically assessed. If mediastinal nodes are PET-negative but suspicion of tumour involvement remains (criteria: primary tumour of $\geq$3 cm large axis, central tumours, cN1, CT-enlarged lymph nodes with their small axis $\geq$1 cm), there may still be an indication for minimally invasive mediastinal staging investigations in the form outlined above [37, 38].

Following PET-CT investigations, endoscopic methods represent the easiest interventional procedure [37]. If the results of these diagnostic procedures are negative despite a high suspicion of mediastinal node involvement, surgical staging of the mediastinum is clearly indicated [35]. If surgical staging of the mediastinum is indicated, VAMS is the preferred technique for upper mediastinal lymph nodes and VATS is preferred for aortopulmonary lymph nodes [35].

### brain MRI/brain CT

*Recommendation 2.3: 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]. Alternatively, dedicated contrast-enhanced brain CT can be carried out [III, B].*

Patients with locally invading T4 tumours and N2 or N3 mediastinal nodal involvement have an underlying high risk of primary brain metastases [42, 43]. Therefore, if curative definitive treatments are planned for these patients, initial staging of the brain with adequate imaging methods should generally be carried out [44]. The method of choice is contrast-enhanced brain MRI. Contrast-enhanced brain CT can be carried out as a valid alternative in case of contraindications to MRI or unavailability. Some studies have shown an adequate positive predictive value for this method but its quality may vary from centre to centre and needs further critical evaluation [45].

## what are the most relevant comorbidities assessed in the clinical work-up of stage III NSCLC patients?

*Recommendation 3.1: Cardio-pulmonary functions are relevant for multidisciplinary treatment decisions including surgery [II, A] or radiotherapy [III, C].*

Patients for whom a surgical intervention is planned must be functionally assessed for surgery. This includes adequate cardio-

pulmonary function testing. Guidelines for these evaluations have been published by the European Respiratory Society (ERS) [15]. Cardiac function may be investigated by electrocardiogram (ECG), echocardiography, stress ECG, stress echocardiography or even coronary angiography including left ventricular catheterisation, in selected cases [15]. Pulmonary function testing includes spirometry and diffusion capacity of the lung for carbon monoxide, split function studies (especially perfusion scintigraphy) and exercise tests (in particular, peak oxygen consumption) [15]. With a specific lung resection planned at surgery, lung function parameters can be predicted for the post-operative setting following assumed lobectomy as well as pneumonectomy [15]. These parameters have been standardised and are important in evaluating patients fit for radical (curative) surgical treatment. The ERS consensus group has also made some proposals for patients planned for curative radiotherapy and chemoradiotherapy approaches [15]. Unfortunately, currently post-radiotherapy lung function cannot be readily predicted taking into account the planned treatment volumes. There is indeed a lack of data on the influence, if any, of pulmonary function tests on radiation-induced lung toxicity, the interplay between pre-existing comorbidities and systemic treatments and possible adverse effects [10]. More prospective data are warranted on the toxicity and outcome of chemoradiotherapy. Many studies, mostly retrospective, have addressed the relationship between dose and volume to organs at risk, such as normal lung, heart, oesophagus and spinal cord, in predicting the probability of radiation-induced damage. Some of these studies have included patient factors [46, 47]. In conformal radiotherapy, dose volume histograms (DVH) to the tumour and nodal volume, as well as organs at risk, contribute to determining the optimal treatment plan for each individual patient. Dose constraints have thereby been defined according to DVH parameters and several normal tissue complication probability models in the clinic, and are also being used in prospective studies [47, 48]. No robust data are, however, currently available linking DVH data to heart toxicity.

*Recommendation 3.2: Comorbidities are of paramount importance since the potential risk of toxicity/morbidity/mortality has to be balanced with the potential benefit of any aggressive curative-intent treatment strategy [III, A].*

The comorbidity profile of the patients has to be critically analysed before any curative-intent treatment decision in stage III disease [49, 50]. This includes definitive surgery on one hand, but also definitive chemoradiotherapy on the other. Significant toxicities during aggressive treatment can be observed following a history of recent vascular events of the patient, such as myocardial infarction or stroke (e.g. within the last 6 months before treatment). Further significant comorbidities are represented by renal insufficiency or necessary haemodialysis that may create difficulties at the time of chemotherapy or surgery. Heart failure and cardiac rhythm disorders must be critically acknowledged—as well as diabetes mellitus, which must be treated adequately before any local treatment. Frequently used scores include the Charlson Comorbidity Index (CCI) in either the full or an abridged, simplified version [50, 51]. However, the ERS recommends the use of the full version of the CCI for better comparability of the datasets. Evaluation of comorbidities is included in a comprehensive geriatric assessment for elderly patients [49]. Insufficient prospective evidence has been generated to reliably disqualify a patient from radical treatment based on one of these scores, and further prospective studies are urgently needed.

*Recommendation 3.3: For curative-intent management, patients should be able to undergo platinum-based chemotherapy (preferably cisplatin) [I, A].*

Both for (neo-)adjuvant chemotherapy coupled with complete resection in stage IIIA disease as well as for concurrent or sequential chemoradiotherapy protocols in stage III disease, the patients should be able to undergo platinum-based chemotherapy [8, 9, 24]. Concurrent chemoradiotherapy is defined as simultaneous (same-day) administration of an active chemotherapy in parallel to ongoing thoracic radiotherapy fractions. Sequential chemoradiotherapy is defined as giving upfront combination chemotherapy for several cycles followed by a block of fractionated radiotherapy only (for 5–7 weeks). The clearest evidence exists for cisplatin-based doublets (cisplatin and etoposide or cisplatin and vinorelbine or other vinca alkaloids). This has been sufficiently demonstrated by the Lung Adjuvant Cisplatin Evaluation (LACE) meta-analysis [8]. Cisplatin can be easily administered to the majority of patients excluding only those few with significant renal failure or heart failure [52, 53].

## what are the optimal multi-modality combinations for the different stage III disease sub-stages?

### incidental IIIA(N2) (unforeseen N2)

*Recommendation 4.1: If, despite adequate mediastinal staging procedures, N2 disease is only documented intra-operatively, surgery should be followed by adjuvant chemotherapy [I, A]. In case of complete resection, addition of post-operative radiotherapy is not routinely recommended, but may be an option following individual risk assessment [V, C].*

Patients that were classified as having stage I or stage II disease in the staging investigations but are found to have an incidental intra-operative N2 diagnosis [old classification: microscopic N2-involvement (final pathology) Robinson IIIA1 and microscopic/macroscopic N2-involvement (frozen section) IIIA2] have a relatively good prognosis and must be considered for adjuvant chemotherapy (Table 2, Figure 1) [8] . Adjuvant chemotherapy is defined as chemotherapy, given after the complete resection of a resectable tumour, to reduce relapse based on micrometastases. These patients typically cannot be identified upfront and pre-operatively as having stage III disease. There is an ongoing discussion about adjuvant post-operative radiotherapy for these patients and, therefore, an ongoing European trial (LungART) is evaluating this strategy [54]. Retrospective analysis from randomised trials and from a SEER database analyses suggest a potential benefit of adjuvant radiotherapy in N2 disease [55–57]. Even though it is unclear whether modern adjuvant post-operative radiotherapy may have an impact on the outcome of such patients, if the individual assessment of locoregional risks shows a high probability of local failure, post-operative radiotherapy may be a

valid option. It should then be delivered after adjuvant chemotherapy, as concurrent post-operative chemoradiotherapy is not routinely recommended [58]. Patients who have been incompletely resected with an R1 (microscopic) or R2 (macroscopic) resection specimen result should be discussed individually in the multidisciplinary panel. Post-operative thoracic radiotherapy or even, in rare cases, concurrent chemoradiotherapy protocols may be an option for some of these patients but no clear guideline currently exists since the number of these patients is extremely small. For decision making, it is probably best to weigh the risks of locoregional relapse against the risk of systemic relapse in the individual patient. With better and more critical selection for stage III disease patients to undergo surgical measures the percentage of incomplete resections can be kept sufficiently low.

## potentially resectable IIIA(N2) disease

*preoperative diagnosis of IIIA(N2)*

> *Recommendation 4.2.1: Possible strategies include several options: induction chemotherapy followed by surgery, induction chemoradiotherapy followed by surgery, or concurrent definitive chemoradiotherapy [I, A]. No recommendation can yet be made; however, an experienced multidisciplinary team is of paramount importance in any complex multi-modality treatment strategy decision. If induction chemotherapy alone is given preoperatively, post-operative radiotherapy is not standard treatment but may be an option based on critical evaluation of locoregional relapse risks [IV, C].*

In patients with preoperatively confirmed IIIA(N2) disease based on the staging investigations carried out, different multimodality treatment strategies can be envisaged, including induction chemotherapy followed by surgery [22, 59–64], induction chemoradiotherapy followed by surgery, or definitive chemoradiotherapy protocols [24, 65–74] (Table 2, Figure 1). Only full-dose, definitive concurrent chemoradiotherapy versus induction concurrent chemotherapy and radiotherapy followed by surgery has been investigated in a prospective randomised North American Intergroup trial, in which patients had to have histo- or cytologically proven N2 disease and for whom definitive chemoradiotherapy was to be considered the standard approach (comparator arm of this study) [23]. Patient selection for this multicentre randomised trial included patients that were evaluated to be potentially resectable with stage IIIA(N2) disease. No difference in OS by intent to treat analysis but a better PFS for patients with surgery was observed [23]. It is the general perception that both treatment strategies remain possible options in this situation based on the final results of this clinical trial. However, toxicity of surgery in the local treatment centre setting remains a significant issue. In the Intergroup study, 54 of the 155 resections were pneumonectomies; 14 patients treated with pneumonectomy died within 30 days after surgery. An observed 26% mortality rate in the right-sided pneumonectomy patients is significantly higher than what is generally considered acceptable for this procedure and, also, has not been seen and reported by experienced thoracic centres in Europe, North America and Asia. A recent analysis, systematic review and meta-analysis of perioperative mortality after neoadjuvant therapy and pneumonectomy for NSCLC revealed an overall 30-day mortality of 7% among the 27 published studies included in the review which is significantly less reported toxicity than in the multicentre North American study—predominantly after pneumonectomy [75–78].

Other centres have carried out large trials with induction chemotherapy followed by surgery, or by definitive chemoradiotherapy without surgery, with more or less comparable OS data [21, 22, 24, 60–65].

The EORTC study also required upfront cytological or histopathological proof of N2 disease in a group of patients defined as unresectable per protocol [22]. Patients received three cycles of induction chemotherapy treatment—18 different chemotherapy protocols were included—and those who showed any response (complete, partial or minor) to induction were randomised either to surgical resection or definitive radiotherapy. Patients included into this trial were most likely in advanced IIIA(N2) disease as only 50% of the patients could be randomised following induction [22]. No difference was noted between the two randomisation arms in either OS data of both arms or PFS results. The patient population of this study is probably not directly comparable with the one included into the Intergroup trial, which makes combined analysis of these two trials very difficult. The selection procedure of the EORTC study with upfront induction chemotherapy was probably responsible for the upfront more advanced stage IIIA(N2) population. Another criticism of this study is that the comparator arm was radiotherapy alone and not concurrent chemoradiotherapy. This, furthermore, makes the final impact of its outcome difficult to bring into perspective with the more standard concurrent chemoradiotherapy strategies for these patients in the present day.

A recent study by the Swiss Group (SAKK) was presented at ASCO in 2013 [79] and at ESMO in 2014 [80]. The study included patients with cytologically or histologically proven IIIA (N2) disease and randomised to induction chemotherapy followed by surgery versus induction chemotherapy followed by radiotherapy and then definitive surgery. Both the primary end point of the trial (OS) as well as the secondary end point (PFS) showed no significant differences between the arms. It is noteworthy that the employed induction chemotherapy protocol was cisplatin and docetaxel. Since a high percentage of patients could be taken to surgery following induction chemotherapy alone, the patient selection of this study included more potentially resectable IIIA(N2) disease patients and the induction chemotherapy turned out to be quite effective in inducing downsizing and downstaging.

Based on these different trials results, it is the general perception that, in these complex treatment situations, the overall expertise of the multi-modality team at the treatment centre is probably of more importance for the overall outcome of the patient than the exact schedule and permutation of the multimodality treatment protocol [17]. It should be outlined that such treatment should preferably be decided upfront, in the presence of an experienced thoracic surgeon, respecting the delay of ~4 weeks between the end of radiotherapy and surgery and the fact that any split in the radiotherapy application has to be avoided, if possible.

*potentially operable IIIA(N2) disease and selected IIIB disease—but at high risk of incomplete resection*

*Recommendation 4.2.2: In potentially resectable superior sulcus tumours, concurrent chemoradiotherapy 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 radiotherapy [III, B].*

For potentially resectable superior sulcus tumours, concurrent chemoradiotherapy induction followed by surgery has become the standard of care [81] (Table 2, Figure 1). As randomised trials are difficult to perform because of rarity of these tumours, this recommendation is based on a multicentre prospective phase II Southwest Oncology Group (SWOG) trial in North America, which demonstrated an excellent complete resection rate and markedly improved 5-year survival rates [81]. A comparable strategy using concurrent chemoradiotherapy to downsize the primary tumour and down-stage centrally located tumours may be applied to certain T3 N2 or T4 N0-1 tumours [28, 29, 66–69]. Several groups have reported excellent complete response and long-term survival rates following such induction therapy in these IIIA and selected IIIB subset [28, 29, 66–69]. Recently, a German Group presented a pilot phase II trial and a randomised phase III trial looking at surgery versus definitive chemoradiotherapy boost following complex induction chemotherapy and concurrent chemoradiotherapy (ESPATÜ) [66, 82]. No benefit in OS and PFS for surgical resection was noted in this trial but both study arms showed excellent long-term survival results. The patient subsets of this study included one-third potentially resectable IIIA(N2) disease patients and one-third centrally located T4N0-1, both groups with underlying risks for incomplete resection. The best results for the patients in this study were noted in the T4N0–1 subset [now stage IIIA (IASLC/UICC 7th edition)].

### unresectable IIIA (N2) disease and IIIB disease patients

*Recommendation 4.3: Concurrent chemoradiotherapy is the treatment of choice in patients evaluated as unresectable in stage IIIA and IIIB [I, A]. If concurrent chemoradiotherapy is not possible—for any reason - sequential approaches of induction chemotherapy followed by definitive radiotherapy represent a valid and effective alternative [I, A].*

This group includes both unresectable IIIA(N2) disease based on bulky and multiple mediastinal nodal involvement and IIIB disease based on unresectable T4 involvement or any N3-disease in the mediastinal nodes (Table 2, Figure 1). For these patient groups, definitive radiotherapy and chemotherapy combinations remain the treatments of choice. Concurrent chemoradiotherapy generally gives significantly better OS results than sequential chemotherapy and radiotherapy protocols in unresectable IIIA and IIIB disease [21–24, 83–86]. This is based on several phase III trials and a meta-analysis based on individual patient data [25]. There was a significant benefit of concomitant chemoradiotherapy on OS with an absolute benefit of 4.5% at 5 years [hazard ration (HR) 0.84; $P = 0.004$]. These trials were carried out with presently outdated staging methods and mostly 2D radiotherapy techniques.

Patients who are considered to be unfit for concurrent chemotherapy and radiotherapy can be treated with induction chemotherapy and high-dose radiotherapy with curative intent [87–90]. Accelerated radiotherapy may be beneficial in this situation [91–93] as it has shown superior results [90, 92]. Also, the results of an individual-patient-data-based meta-analysis for non-concurrent chemoradiotherapy further support this individualised strategy [92].

Few groups have piloted surgery after combined-modality approaches in N3-disease patients—mostly chemoradiotherapy. There is old phase II data from SWOG and from the West German Cancer Centre Group and from several other investigations looking at this subset [65, 67–69]. In the ESPATÜ trial presented at ASCO 2014, one-third of the patient group included patients with T1–3N3 disease with N3 proven and found at staging mediastinoscopy [82]. Long-term survival was also noted in both arms of this patient subset. The other groups having explored surgical resection for selected N3 patients after induction chemoradiotherapy also noted promising results, but this could be related to patient selection and no final evaluation of this treatment strategy can currently be given [65–69, 82]. Concurrent chemoradiotherapy remains the treatment of choice for these patient groups outside specific expertise generated by the treatment group or well-designed clinical trials.

### prophylactic cranial irradiation

*Recommendation 4.4: There is currently no role for prophylactic cranial irradiation in stage III NSCLC [II, A].*

Relapse pattern in stage III NSCLC patients has shown a high cumulative risk of developing brain metastases [42, 43]. Several trials have explored prophylactic cranial irradiation (PCI) within the multi-modality strategy. A significant impact on brain relapse as first site of failure and on overall-brain relapse rate has clearly been demonstrated [42]. However, a recent large Radiation Therapy Oncology Group (RTOG) phase III trial addressing the issue of PCI in stage III disease patients treated with multi-modality therapy was not able to demonstrate a significant impact on OS by PCI versus observation [94]. This trial closed prematurely because of poor accrual; although it was underpowered, it showed that PCI could decrease the rate of brain metastases. Other trials are open to accrual.

## what is the optimal chemotherapy to be given to stage III disease patients?

### cisplatin or carboplatin in combination with radiotherapy

*Recommendation 5.1: In the absence of contraindications, the optimal chemotherapy 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].*

For fit patients with inoperable stage III NSCLC, cisplatin-based chemotherapy given concurrently to radiation therapy is recommended [24]. According to level I evidence-based medicine,

cisplatin may be combined with etoposide, vinorelbine or other vinca alkaloids [24, 25]. However, in some patients, based on specific comorbidities, other treatment modalities may alternatively be considered: single-agent cisplatin or carboplatin-based chemoradiotherapy, sequential chemotherapy and radiotherapy or even radiotherapy alone. These alternatives can be proposed to patients with higher risks of infection, general or pulmonary complications. There are already randomised clinical trials showing the efficacy of single-agent cisplatin delivered concomitantly with radiotherapy [85, 95, 96]. On the contrary, single-agent carboplatin has failed to improve survival when given concurrently with radiotherapy in two prospective randomised trials [96, 97]. Recently, an Asian randomised clinical trial comparing radiotherapy alone with combination of daily single-agent carboplatin and radiotherapy in elderly patients >70 years of age has shown that combined chemoradiotherapy could improve outcome in a selected group [98]. However, relatively significant haematological toxicity was reported. As these data focus on elderly Asian populations, some experts think that further safety data should be collected in Caucasian patients before implementing this approach as a routine schedule, only for high-risk patients with significant comorbidities. The major criticism against this trial however, is that even in elderly patients, standard treatment should be a platinum-based doublet given concurrent to radiotherapy. Age alone is not an argument against a curatively intended protocol.

Several North American studies have used the weekly carboplatin and paclitaxel regimen concomitantly with radiotherapy with conflicting results. Despite this regimen having served as a standard comparator regimen in large clinical trials in North America and also in some parts of Europe and Asia, it is not accepted by all physicians in these regions [83, 99, 100]. Moreover, such a combination remains an accepted and valid option for patients who cannot receive cisplatin-based chemotherapy because of existing significant comorbidities. If low-dose weekly chemotherapy schedules are used in the concurrent treatment phase, it is highly recommended to use a full-dose platin doublet given either before or after the radiotherapy application.

### chemotherapy combination

*Recommendation 5.2: Most comparative studies of concurrent chemoradiotherapy versus sequential administration were using cisplatin + etoposide or cisplatin + vinca alkaloid (typically: cisplatin + vinorelbine). 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].*

Several randomised trials comparing concurrent and sequential chemoradiotherapy were included in the individual-patient-data-based meta-analysis [21, 24–26]. The North American trial using cisplatin and vinblastine is interpreted as a study demonstrating the superiority of the concurrent strategy [24]. The small Czech randomised study compared the more modern cisplatin and vinorelbine doublet and showed a benefit for the concurrent strategy [85]. The West Japan Lung Cancer Group study (although strongly supporting concurrent chemoradiotherapy) was based on a mitomycin C combination, now rarely used because of potential lung toxicity described in earlier observations [21, 76]. In the Japanese study, split-dose radiation was used—a strategy that would not be supported by modern radiation biology considerations [101]. The French trial used cisplatin and etoposide and favoured the concurrent administration with manageable toxicity [84]. The survival benefit induced by a platinum-based concomitant strategy has been emphasised in an individual-patient-data-based meta-analysis [25, 86]. Even if carboplatin–paclitaxel-based chemoradiotherapy is frequently used, especially in North America, it should be underlined that no carboplatin–paclitaxel-based regimen was evaluated in any of the individual-patient-data meta-analyses [25]. There is one underpowered randomised phase II study that compared a carboplatin and paclitaxel combination directly to a cisplatin-based combination, for which the results favoured the cisplatin–etoposide combination in terms of survival [87]. This leads to the consensus that cisplatin-based doublets should be preferred in stage III disease multi-modality protocols when treatment has a curative intent.

### number of chemotherapy cycles

*Recommendation 5.3.1: In the stage III disease chemoradiotherapy strategy, two to four cycles of concomitant chemotherapy should be delivered [I, A]. There is no evidence for further induction or consolidation chemotherapy. In the perioperative setting, three to four cycles of cisplatin-based chemotherapy are recommended [I, A], aiming at a total cumulative dose of at least 300 mg/m2 of cisplatin in the adjuvant setting [II, B].*

The majority of randomised clinical trials in stage III NSCLC patients treated by concurrent chemoradiotherapy used two to four cycles of cisplatin-based combination chemotherapy [25]. Based on adjuvant chemotherapy in stage II and stage III disease, four cycles of cisplatin-based combination chemotherapy are defined as the standard of care [8]. In the LACE adjuvant meta-analysis, one of the main prognostic factors was the delivery of a cumulative cisplatin dose >300 mg/m$^2$ [8].

*Recommendation 5.3.2: Regarding stage III disease chemoradiotherapy, two to four cycles of concomitant chemotherapy should be delivered [I, A].*

There is no evidence for extended induction or consolidation beyond these three to four cycles [99, 100].

In operable patients, in the large randomised phase III Intergroup trial 0139, the comparative arm used four cycles of cisplatin and etoposide given together with thoracic radiotherapy at a dose of 61 Gy. This serves as a landmark study in operable stage III(N2) disease [23]. In this study, two cycles were given as consolidation following the definitive chemoradiotherapy protocol (in 75% of patients).

## what is the optimal radiation regimen given to stage III NSCLC patients?

### dose and fractionation in concurrent chemoradiotherapy

*Recommendation 6.1.1: 60–66 Gy in 30–33 daily fractions is recommended for concurrent chemoradiotherapy [I, A].*

*Maximum overall treatment time should not exceed seven weeks [III, B]. 'Biological intensification', such as treatment acceleration, is not standard practice in concurrent chemoradiotherapy schedules [III, B].*

The majority of clinical concurrent chemoradiotherapy regimens in stage III NSCLC have used 60–66 Gy cumulative radiotherapy doses in conventional daily fractions of 1.8–2.0 Gy [24, 84–86]. A detailed look at the relationship of overall treatment duration and outcome in these studies has confirmed that prolonged treatment time is a critical issue in this setting, as it is in other tumour types [92]. The RTOG 0617 study has confirmed that radiation dose escalation (with conventional 2 Gy per fraction regimen leading to a prolonged treatment time exceeding seven weeks) and concurrent CT is not the way forward. In this phase $2 \times 2$ factorial design phase III randomised, controlled trial, patients with stage III NSCLC were randomised to receive high-dose (74 Gy in 37 fractions) or standard-dose (60 Gy in 30 fractions) radiotherapy concurrently with weekly paclitaxel/carboplatin with or without cetuximab [83]. In a planned interim analysis after 90 events, the high-dose arms were closed for futility. At a median follow-up time of 22.9 months, survival of 419 eligible patients was significantly inferior with high-dose compared with standard-dose radiotherapy; median OS was 28.7 months [95% confidence interval (CI) 24.1–36.9] for patients who received standard-dose radiotherapy and 20.3 months (17.7–25.0 months) for those who received high-dose radiotherapy (HR 1.38, 95% CI 1.09–1.76; $P = 0.004$). However, treatment intensification should not be abandoned in stage III NSCLC. This is an area of active research, facilitated by the rapid development of advanced radiotherapy techniques.

### dose and fractionation in sequential chemoradiotherapy

*Recommendation 6.1.2: Promising outcome is achieved with accelerated radiotherapy [I, A]. A potential radiation schedule could be the delivery of 66 Gy in 24 fractions [II, C].*

Accelerated radiotherapy has resulted in improved 5-year survival rates compared with so-called conventional radiation schedules, i.e. 2 Gy per day five times per week [53, 90, 92]. The CHART regimen serves as a good example that was investigated in a large phase III trial in a few stage II disease and mostly stage III disease patients and resulted in a significant survival benefit when compared with conventionally fractionated treatment application [53]. Even today, this treatment protocol is selectively used in several European centres, especially in the UK where it was initially piloted. Apart from multiple fractions per day schedules, an accelerated high-dose regimen was investigated in one phase II study and one phase III study of 66 Gy in 24 daily fractions [90]. These specific schedules represent valuable alternatives in patients where concurrent chemoradiotherapy protocols may not be possible because of comorbidity profile issues and expected toxicities.

### radiation doses in the preoperative setting

*Recommendation 6.1.3: Standard preoperative radiation doses within chemoradiotherapy protocols should be between 40 and 50 Gy in conventional fractionation or 40–45 Gy in accelerated fractionation (bid application) [I, B].*

The majority of clinical trials that have given preoperative chemoradiotherapy have used 40–50 Gy cumulative doses in conventional fractionation of 1.8–2.0 Gy per day. Several groups have also employed accelerated hyper-fractionation given as 1.5 Gy twice daily up to 40–45 Gy. These regimens have been used within larger phase II and randomised multicentre phase III studies. Furthermore, some investigators have piloted higher radiation doses up to 60–63 Gy in conventional fractionation, but this has only been done within the phase II setting. As increased preoperative toxicities (also described in the literature) may result from these treatment intensifications (e.g. radiation pneumonitis, acute respiratory distress syndrome), it is advisable to give these higher doses only in the setting of prospective controlled clinical trials. Higher preoperative radiation doses may result in higher pathological complete remission rates and may potentially optimise preoperative downsizing and down staging but these advantages must be carefully weighed against the potentially higher resulting toxicities.

### elective mediastinal nodal irradiation

*Recommendation 6.2: Elective mediastinal nodal irradiation—prophylactic irradiation of non-involved mediastinal nodes—is not recommended [I, B].*

Prophylactic irradiation of non-involved mediastinal nodes is no longer recommended when using modern diagnostic and chemoradiotherapy strategies, neither in sequential nor in concurrent chemoradiotherapy [102]. Microscopic disease at this level is assumed to be treated by systemic chemotherapy combined with radiation. However, selective nodal irradiation can only be recommended when at least a fluorodeoxyglucose (FDG)–PET-CT scan is available and shows signs of locoregional extension. Adequate mediastinal staging is, therefore, also recommended in non-surgical patients targeted for treatment with curative intent [91].

### radiotherapy technique

*Recommendation 6.3: Quality assurance and dose constraints are required as a prerequisite [I, A].*

It is recommended that high-dose radiotherapy is prepared and executed according to standards such as those of the European Organisation for Research and Treatment of Cancer (EORTC) [10]. More and more centres use respiration-correlated CT scans (or '4D CT'), so as to take into consideration tumour movement in thoracic oncology [103, 104]. Respiratory gating and tumour movement adaptations, as well as intensity-modulated radiotherapy, are important points for further improvement of targeting radiation delivery to the primary tumour and involved nodes [103, 104]. However, these treatment modalities are not yet used at all treatment centres.

## what is the optimal surgical management in resectable stage III NSCLC patients?

### type and extent of surgery

*Recommendation 7.1: The optimal surgical management aims at complete resection—preserving as much non-involved parenchyma as possible, preferably carried out by lobectomy/*

*sleeve resection [I, A]. Complete resection necessarily includes systematic mediastinal nodal exploration. In selected patients, pneumonectomy must be carried out, but should be adequately selected and the procedure restricted to experienced centres [III, B].*

Curative surgery in stage III disease will preferably include surgical techniques such as lobectomies, bi-lobectomies and sleeve resections, to spare lung tissue as much as possible [77]. Nevertheless, in recent years, it has become clear that in selected patients, complete resection will require a pneumonectomy or, in some cases, a sleeve pneumonectomy, which can be safely conducted in experienced high-volume centres [75, 77, 78].

### post-operative mortality related to surgical intervention

*Recommendation 7.2: Based on reported series, post-lobectomy and pneumonectomy mortality rates should not exceed 2%–3% and 3%–5%, respectively [IV, B].*

Post-operative mortality resulting from stage III disease surgical resections should be evaluated in every thoracic centre. Modern published series show that surgical 30-day mortality ranges between 2%–3% for lobectomy and 3%–8% for pneumonectomy [77, 78]. Importantly, it has been recognised that there is a significant relationship between volume and outcome in surgery of lung cancer, supporting the notion that these procedures should be restricted to experienced centres [78].

## do patient characteristics contribute to treatment decisions in stage III NSCLC?

### age

*Recommendation 8.1: Age itself has not been shown to influence outcome following surgery plus adjuvant chemotherapy or definitive concurrent chemoradiotherapy [I, A]. However, data are limited for the elderly population and, in particular, in patients above 75 years of age.*

Age alone is not a good parameter to predict outcome in stage III disease after surgery and adjuvant chemotherapy. Due to the small numbers, an exploratory analysis of the randomised trial from the National Cancer Institute of Canada in patients over 80 years failed to demonstrate a benefit of adjuvant chemotherapy [105]. On the other hand, the LACE meta-analysis did not show a negative impact of age on the outcome of adjuvant chemotherapy [8]. Furthermore, the outcome of elderly patients was not inferior in the chemoradiotherapy trials by the Cancer and Leukemia Group B and the RTOG [24]. A recent analysis of data from the SEER database showed that treatment of elderly patients with stage IIIA (N2) NSCLC is highly variable in North America and varies not only with specific patient and tumour characteristics but also with regional income level [106]. However, the number of elderly patients in all randomised adjuvant and chemoradiotherapy trials is still too small to allow for robust conclusions. Until more evidence is generated, comorbidity issues should predominate over age alone with respect to decision making.

### performance status

*Recommendation 8.2 Reduced PS is a significant negative prognostic factor with regard to OS results following a treatment strategy of surgery plus adjuvant therapy. Treatment planning must be therefore be individualised [III, B].*

While data on age are still controversial, increasingly PS is accepted as a significant negative prognostic factor in stage III disease. This has been demonstrated in the context of patients treated by surgery plus adjuvant chemotherapy and also in definitive chemoradiotherapy protocols [8, 26, 100]. When treatment decisions are to be made for patients with PS Eastern Cooperative Oncology Group 2, an individual risk/benefit analysis is particularly important. Medical history (e.g. infections) resulting in reduced PS should be analysed, and every attempt to treat a reversible condition and, thereafter, potentially improve the general condition and PS must be considered.

## is there a place for targeted agents in the treatment of stage III NSCLC?

*Recommendation 9: There is currently no role for targeted agents in stage III NSCLC outside clinical trials [I, A].*

The large randomised SWOG trial in North America demonstrated an inferior OS in a patient group receiving an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (gefitinib) as consolidation therapy compared with placebo after chemoradiotherapy and consolidation docetaxel [107]. The reasons for this detrimental effect are still to be explored, looking at potential specific toxicities following chemoradiotherapy and/or docetaxel or underlying tumour-related adaptive biological mechanisms. Gefitinib was also evaluated as adjuvant treatment in the post-operative setting for stage IB–II–IIIA disease patients in a phase III underpowered trial, with disappointing results [108]. However, this study did not select the recruited patient population on the basis of EGFR mutations. Therefore, any interpretation for the subset of EGFR mutated patients should be considered with caution. A third randomised trial has recently been presented—the North American four-arm randomised trial using cetuximab in addition to concurrent chemoradiotherapy that was also unable to demonstrate any benefit from the addition of the targeted agent [83]. Outside well-designed and closely monitored clinical trials in target-based selected populations, there is currently no role for targeted agents in stage III NSCLC.

## what is the optimum follow-up after radical therapy for stage III NSCLC patients?

### after radical therapy

*Recommendation 10.1: Thoracic and upper abdominal CT scan (including adrenals) should be carried out every 6 months for 2 years, and yearly thereafter [III, C] for 3 years. No routine PET-CT is recommended. It might be considered only in the case of abnormalities detected by CT scan [III, C].*

No evidence from randomised trials is available to define optimal follow-up in treated stage III NSCLC patients. PET-CT—although of considerable value in initial staging for stage III disease patients—has no routine role for the follow-up of stage III NSCLC patients after surgical-based multi-modality treatment [109]. A large French randomised trial has been carried out to investigate follow-up in surgically (completely) resected patients with stage I–III and results are awaited [110]. Currently, experts can only extrapolate recommendations for follow-up strategies, either based on evidence from follow-up policies in large published clinical trials, individual physician choices or on consented local (Cancer Centre) policies. In selected cases, ambiguous abnormalities detected on CT scans may be individually further investigated with PET-CT follow-up, but final cytological or histological confirmation (e.g. bronchoscopy, EBUS/EUS) is usually recommended to confirm a suspicion of relapse.

### brain imaging methods

*Recommendation 10.2: Patients with stage III disease following multi-modality treatment have a high risk of brain relapse. Selected patients with a high risk of brain relapse may be followed up with brain imaging methods aiming at early detection and treatment of single-site relapses with curative intent [V, C].*

Long-term survival patterns in stage III NSCLC trials have pointed to the very high cumulative risk of developing brain metastases after multi-modality treatment [42, 43]. Adenocarcinoma patients, in particular, may represent a specific subgroup with an increased risk profile. Availability of modern radiation techniques for oligometastatic brain lesions in recent years (e.g. stereotactic brain radiotherapy) may argue in favour of an individualised follow-up using brain MRI to detect these oligometastatic brain failures, which are now amenable to local treatment.

### smoking cessation

*Recommendation 10.3: Patients treated for stage III disease should be strongly encouraged to quit smoking and/or participate in smoking cessation programmes [I, A].*

Long-term survival analysis, relapse patterns and competing risk analysis of stage III NSCLC patients including the risk of developing second lung cancers and smoking-related events (comorbidity events) are strong arguments to implement smoking cessation programmes as part of any curatively intended management of early and locally advanced NSCLC patients including stage III disease [66, 111, 112].

## note

Levels of evidence and grades of recommendation have been applied using the system shown in Table 1. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty.

## conflict of interest

Stahel has reported Consultancy/honoraria: Abbott, Amgen, Astellas, Boehringer Ingelheim, Daiichi-Sankyo, GlaxoSmithKline, Genentech, Eli Lilly, Roche. Felip has reported Consultancy/honoraria: Lilly, GlaxoSmithKline, Pfizer, Roche, Boehringer Ingelheim. Peters has reported Consultancy/honoraria: Roche, Eli Lilly, AstraZeneca, Pfizer, Boehringer Ingelheim, Bristol-Myers Squibb, Merck Serono, Daiichi-Sankyo, Tesaro. Kerr has reported Speakers' bureau: Abbott Diagnostics, Roche, AstraZeneca, Eli Lilly, Pfizer. Besse has reported Research grants: Pfizer, Roche, Boehringer Ingelheim, AstraZeneca. Vansteenkiste has reported that he is the Eli-Lilly Chair in Respiratory Oncology at the Leuven University (research funding) and is the AstraZeneca Chair in Personalised Lung Cancer Care at the Leuven University (research funding). Eberhardt has reported Advisory board: GSK, GlaxoSmithKline Amgen, Novartis, Merck, Teva, Roche, AstraZeneca, Lilly, Boehringer Ingelheim, Pfizer, Bristol-Myers Squibb; Speakers' bureau: Roche, AstraZeneca, Lilly, Boehringer Ingelheim, Pfizer, GlaxoSmithKline, Amgen, Novartis, Hexal, Merck; Research grants: Eli Lilly. Edelman has reported Advisory board and/or research funding: Genentech, Boehringer Ingelheim, Lilly, Endocyte. Baas has reported Research grants: Pfizer. Reck has reported Advisory board: Hoffmann-La Roche, Lilly, Pfizer, AstraZeneca, Bristol-Myers Squibb, Daiichi-Sankyo; Speakers' honoraria: Hoffmann-La Roche, Lilly, Pfizer, Bristol-Myers Squibb, AstraZeneca, Daiichi-Sankyo. Paz-Ares has reported Scientific advisor /Speakers' bureau: Lilly, Roche, Pfizer, Merck, Boehringer Ingelheim, Desi pharma, Celgene. Meldgaard has reported Speakers' bureau: Roche. Nicolson has reported Speakers' bureau: Roche, Lilly, Boehringer Ingelheim, Pfizer, Otsuka; Research grants: Roche, Lilly, Boehringer Ingelheim, Pfizer, Novartis. Senan has reported Research grants and honoraria: Varian Medical Systems; member of phase III trial management group conducted by Lilly Oncology. Faivre-Finn has reported Research grants AstraZeneca, Eli Lilly. Rocco has reported Speakers' bureau/grants: Covidien. Lim has reported Research support: ScreenCell and PointHope; previously Speakers' bureau for Roche and Imedex and Advisory board for Strategen, Abbott Molecular and GlaxoSmithKline; patent pending with Clearbridge BioMedics; stock in Pfizer. Westeel has reported Consultancy/honoraria: Lilly, Roche, Boehringer Ingelheim and AstraZeneca (for lectures); Advisory role: Lilly, Roche and AstraZeneca; currently conducting research sponsored by Merck Serono. Mok has reported Speaker's bureau and Honoraria from: AstraZeneca, Roche, Eli Lilly, Merck Serono, Eisai, Bristol-Myers Squibb, BeiGene, AVEO, Pfizer, Taiho, Boehringer Ingelheim, GlaxoSmithKline Biologicals, Clovis Oncology; Research funding from AstraZeneca. Bubendorf has reported Speakers' honoraria: Pfizer, Roche and Abbott Molecular, Inc.; research supported by and stock held in Roche. Novello, Marchetti, Syrigos, Smit, Adjei, Van Schil, Douillard, Weder, De Ruysscher, Le Pechoux, De Leyn, Veronesi and Dooms have declared no potential conflicts of interest. Crinò and O'Byrne have not reported any potential conflicts of interest.

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## appendix

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