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SPECIAL ARTICLE

Multidisciplinary consensus statement on the clinical management of patients with stage III non-small cell lung cancer

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Abstract
Stage III non-small cell lung cancer (NSCLC) is a very heterogeneous disease that encompasses patients with resected, potentially resectable and unresectable tumours. To improve the prognostic capacity of the TNM classification, it has been agreed to divide stage III into sub-stages IIIA, IIIB and IIIC that have very different 5-year survival rates (36, 26 and 13%, respectively). Currently, it is considered that both staging and optimal treatment of stage III NSCLC requires the joint work of a multidisciplinary team of expert physicians within the tumour committee. To improve the care of patients with stage III NSCLC, different scientific societies involved in the diagnosis and treatment of this disease have agreed to issue a series of recommendations that can contribute to homogenise the management of this disease, and ultimately to improve patient care.

Keywords Lung cancer · Multimodal management · Staging · Multidisciplinary team · Induction therapy · Chemotherapy · Radiotherapy · Surgery

Introduction

In the 8th edition of the TNM classification proposed by the International Association for the Study of Lung Cancer (IASLC), accepted by the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC), stage III non-small cell lung cancer (NSCLC) encompasses patients who, in the absence of metastatic disease (M0), present N2 or N3 disease, a tumour with T4 characteristics or one classified as T3 N1 [2] (Table 1). It is, therefore, a very heterogeneous definition, which includes patients with resected, potentially resectable and unresectable tumours.

To improve the prognostic capacity of the 8th edition of the TNM classification compared to the previous one, certain modifications have been carried out, focusing mainly on: (a) defining the T category that has been regrouped based on the tumour diameter, with 1-cm increment in size between T1a, T1b, T1c, T2a and T2b; T3 for 5−7-cm tumours, and T4 for tumours larger than 7 cm. A tumour is considered T2 when there is main bronchial involvement that does not reach the main carina or partial/total atelectasis/pneumonitis, and T4 when there is invasion of the diaphragm [1, 2]; and (b) dividing stage III into sub-stages IIIA, IIIB and IIIC, since survival rates between stages are significantly different, with 5-year survival of 36, 26 and 13%, respectively [2, 3].

Staging and treatment of stage III NSCLC requires multidisciplinary management by expert physicians, and evaluation by cancer committees is essential. Given the heterogeneity of stage III NSCLC, the scientific societies involved in this work (*Grupo Español de Cáncer de Pulmón* [GECP], *Sociedad Española de Cirugía Torácica* [SECT], *Sociedad Española de Medicina Nuclear e Imagen Molecular* [SEMNIM]; *Sociedad Española de Oncología Médica* [SEOM]; *Sociedad Española de Oncología Radioterápica* [SEOR];

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Table 1 Stage IIIA in the 8th TNM classification of lung cancer

T	N	M
Stage IIIA		
T1a	N2	M0
T1b	N2	M0
T1c	N2	M0
T2a	N2	M0
T2b	N2	M0
T3	N1	M0
T4	N0	M0
T4	N1	M0
Stage IIIB		
T1a	N3	M0
T1b	N3	M0
T1c	N3	M0
T2a	N3	M0
T2b	N3	M0
T3	N2	M0
T4	N2	M0
Stage IIIC		
T3	N3	M0
T4	N3	M0

See the definition of the T, N and M descriptors in Goldstraw et al. [3]

Sociedad Española de Neumología y Cirugía Torácica [SEPAR] and *Sociedad Española de Radiología Médica* [SERAM]) have developed this consensus statement to homogenise its treatment and, ultimately, improve the care of patients with stage III NSCLC.

Staging of stage III NSCLC

Non-invasive staging

Correct clinical staging is essential to manage patients with lung cancer. The first steps in the study of a possible thoracic neoplasm are the clinical history and a chest X-ray [4]. Further examinations should then be carried out to determine the local and distant involvement of the neoplasm. Computed tomography (CT) with intravenous contrast is the preferred technique in the study of lung cancer [2, 5], and it should include the entire thorax and upper abdomen. It is not necessary to cover a larger area of the abdomen, since it does not significantly increase the accuracy of staging [6]. Positron-emission tomography (PET) with the glucose analogue ^{18}F-FDG and especially, PET/CT with ^{18}F-FDG, have revolutionised the staging of lung cancer.

T staging by CT will be indicated by the size of the main tumour, and this is one of the prognostic factors [2]. However, the degree of invasion of the mediastinal structures or the chest wall modifies the value of the T descriptor, as it impacts prognosis [7]. CT allows assessing the invasion of mediastinal vascular structures, although other techniques such as ultrasound or magnetic resonance imaging (MRI) have better results than CT when assessing the infiltration of the parietal pleura and the chest wall [1, 8]. In the preoperative assessment of Pancoast tumours, MRI plays a fundamental role, with better results than CT scans [9].

When assessing mediastinal lymph node involvement, PET/CT with ^{18}F-FDG also plays a key role, with better results than CT [10–14]. However, its sensitivity is diminished in lymph nodes that are smaller than 10 mm in its short axis [15].

Initially, the presence of metastasis will be ruled out by cytohistological confirmation of suspicious lesions and possible extrathoracic lymph nodes that can classify the tumour as N3. A fine-needle aspiration (FNA) or an ultrasound-guided core-needle biopsy (CNB) can also be used [16, 17].

The initial scans should include the organs with the greatest potential of lung cancer metastases. One of the major contributions of PET/CT with ^{18}F-FDG in the initial diagnosis of lung cancer is the detection of previously unknown metastases, with the consequent change in staging [18].

Brain MRI is indicated in patients with lung tumours who are going to be treated with curative intent, to screen for brain M1 [19]. Brain MRI is superior to CT [20] and to PET/CT [21].

Non-surgical intrathoracic invasive staging

In the case of already diagnosed intrathoracic tumours, stage III (N2 or N3) will be established without requiring pathological confirmation when there is an extensive mediastinal infiltration (bulky disease) [22].

In central tumours or those with enlarged hilar and mediastinal lymph nodes, the tumoral nature of the lymph nodes should be confirmed. An endobronchial ultrasound (EBUS)-guided puncture will be performed since the positive and negative predictive values (PPV and NPV, respectively) of CT or PET are insufficient. EBUS would provide access to enlarged paratracheal, posterior tracheal, subcarinal, hilar, interlobar and lobar lymph nodes; and/or an endoscopic ultrasound (EUS) with access to paratracheal, subcarinal, paraesophageal and pulmonary ligament lymph nodes. Both techniques have a sensitivity close to 90% and a specificity of 100% [17, 22–25]. However, if the result is negative, not assessable or not sufficiently reliable (NPV: < 90%), staging must be completed with surgical techniques [24, 26, 27].

Peripheral thoracic tumours without nodal disease require mediastinal invasive staging if not subsolid and with a diameter greater than 3 cm [28], since in these cases the possibility of finding occult N2 nodes exceeds 10% [22–24, 28] (Fig. 1).

Invasive surgical staging

Invasive surgical mediastinal staging should be performed when the result of non-surgical invasive techniques is negative or non-assessable. Despite the greater morbidity and mortality, these methods are the standard of excellence of mediastinal staging, having a higher NPV (Table 2).

Transcervical mediastinoscopy

In the transcervical mediastinoscopy, a biopsy should be performed at a minimum number of nodal stations (#4R, #4L and #7), as well as at stations #2R and #2L if they can be identified. Complications are scarce, with most being mild, and mortality is practically non-existent [29].

Extended cervical mediastinoscopy

Extended cervical mediastinoscopy is performed through the same incision of conventional mediastinoscopy and allows exploring the paraaortic and aortopulmonary window (#5 and #6) in the tumours of the left upper lobe, which are not accessible through conventional mediastinoscopy.

Left parasternal mediastinotomy

In the left parasternal mediastinotomy, stations #5 and #6 are explored through a second incision in the second left parasternal intercostal space.

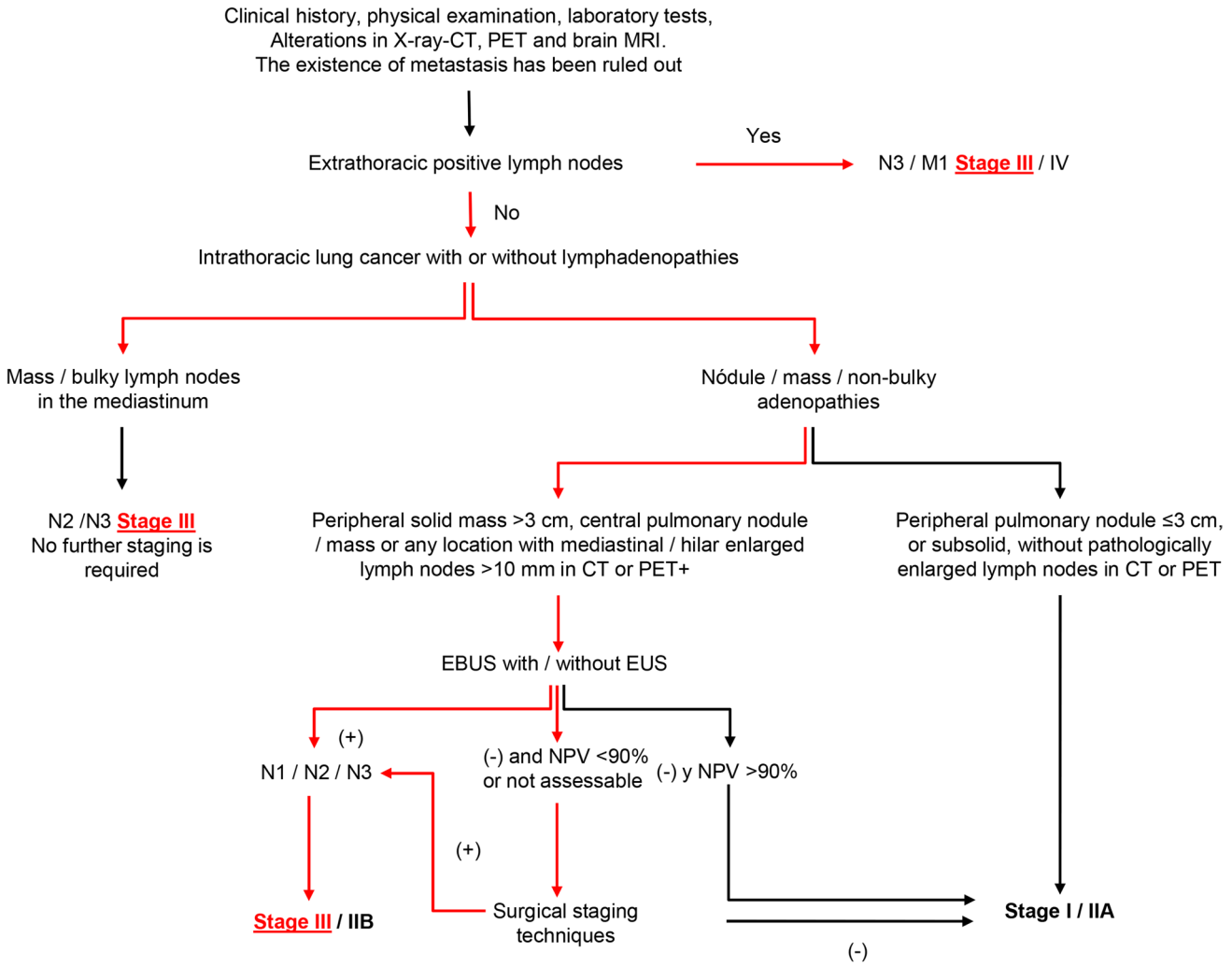

Fig. 1 Performance algorithm for the staging of NSCLC* [17]. *The pathways leading to the diagnosis of stage III are highlighted in red. *CT* computed tomography, *NSCLC* non-small cell lung cancer, *EBUS* endobronchial ultrasound, *EUS* endoscopic ultrasound, *PET* positron-emission tomography, *PET/CT with* ^{18}*F-FDG* PET/CT with 18F fluorodeoxyglucose, *NMR* nuclear magnetic resonance, *X-ray–CT* X-ray–computed tomography, *NPV* negative predictive value

Table 2 Main invasive surgical techniques for stage III NSCLC staging

Technique	Patients	Sensitivity (%)	Specificity (%)	NPV (%)	PPV (%)
Transcervical mediastinoscopy [130]	1362	86	100	> 94	100
Extended cervical mediastinoscopy [131]	221	67	100	94	100
Left parasternal mediastinotomy [132]	45	86	100	89	100
Videothoracoscopy [133]	55	100	100	100	100
VAMLA [134]	144	94	100	–	100
TEMLA [135]	698	96	100	99	100

NSCLC Non-small cell lung cancer, *TEMLA* transcervical-extended mediastinal lymphadenectomy, *VAMLA* video-assisted mediastinal lymphadenectomy, *NPV* negative predictive value, *PPV* positive predictive value

Mediastinum pleuroscopy

Mediastinum pleuroscopy is indicated when lymph node (N) and pleural (M) dissemination should be ruled out. Unlike all the other explorations, this technique should be performed with single-lung ventilation [30, 31].

Videothoracoscopy

The main advantage of videothoracoscopy is that it allows the exploration of the lower stations (#8, #9), but requires single-lung ventilation. It is also useful in the pre-operative staging of the T descriptor, as it can identify unresectable tumours that are not detected with imaging tests [32].

Video-assisted mediastinal lymphadenectomy (VAMLA)

The objective of VAMLA is the lymphadenectomy of those stations that can be accessed through mediastinoscopy (#4R, #4L, #7, #2R, #2L).

Transcervical-extended mediastinal lymphadenectomy (TEMLA)

TEMLA provides the opportunity for a much wider lymphadenectomy to the lower stations except for station #9. Morbidity and mortality are higher than in a conventional mediastinoscopy.

Methods of restaging after induction

Imaging studies

Although the usefulness of CT in restaging is uncertain, it has been observed that the response to neoadjuvant treatment by CT scan predicts a higher survival rate [33]. CT-based complete response has a high predictive value for complete pathological response, although it tends to underestimate it [34]. PET with ^{18}F-FDG offers good results when assessing the treatment response of the primary tumour and metastases, although it is less accurate in the assessment of the mediastinal response, with a false negative rate of 20% and a false positive rate of 25% [35]. As a prognostic factor, the degree of reduction of the standardized uptake value (SUV) in the primary tumour may be predictive of survival and of the pathological response to treatment [36–38].

Cytohistological confirmation studies

Re-evaluation usually starts with the same techniques used for initial staging.

Non-invasive or minimally invasive techniques

Bronchoscopy is reserved to confirm local tumour progression. Transbronchial needle aspiration (TBNA) achieves a correct diagnosis in 71% of patients and avoids other invasive procedures in 35% of cases [39]. The use of FNA by EBUS or EUS in restaging has a sensitivity lower than 80%, with an NPV lower than this value [40–42]. Using both EBUS and EUS combined does not improve these results [43, 44]. When the results of EBUS and/or EUS do not show malignancy, it is recommended to use a surgical technique to reduce the proportion of false negatives [26, 45].

Surgical techniques

The first mediastinoscopy can be reserved for restaging when N2 is initially confirmed by TBNA, EBUS or EUS during the initial staging.

Re-mediastinoscopy is technically more complex. It shows a sensitivity higher than 60% (range 60–74%), a specificity of 100%, an accuracy greater than 80% (range 80–92%), a PPV of 100% and a NPV of 73% (range 73–86%) [46–48].

There are no restaging cases using VAMLA. As for TEMLA, authors present a restaging series with a sensitivity

of 95%, an NPV of 97%, an accuracy of 98% and a specificity and PPV of 100% [49]. Finally, there is only one study that uses videothoracoscopy as a restaging method [50] with a sensitivity of 83%, a NPV of 64% and a specificity of 100%.

Pre-treatment functional assessment

Pre-operative functional assessment

Before surgery, it is necessary to check patient's heart function with patient's history and heart medication revision. It is also necessary to check if they have a thoracic revised cardiac risk index value that does not exceed 1.5 points [51]. The patient must be referred for a cardiology consultation if necessary.

To assess the risk derived from pulmonary resection, a pulmonary function study should be performed. This study should calculate the maximum expiratory volume in the first second of forced expiration (FEV1) and the diffusion capacity of the lung for carbon monoxide (DLCO) planned in the post-operative period (ppoFEV1 and ppoDLCO) [51–53]. When both indexes are greater than 60% of their theoretical values, the patient presents low risk and does not require further studies [51]. When the ppoFEV1 or the ppoDLCO is less than 30%, a cardiopulmonary exercise testing (CPET) will be indicated to quantify maximum oxygen consumption (VO_{2max}). If this is lower than 10 mL/kg/min (or less than 35% of its theoretical value), the surgical risk is high. If the value is between 10 and 20 mL/kg/min (between 35 and 75% of the theoretical value) the risk is intermediate, and if they are above the latter values the risk is low. When the ppoFEV1 or the ppoDLCO is less than 60% and both exceed 30%, a CPET may be indicated, or stair climb/shuttle walk test may be used before CPET (Fig. 2) [51].

Pre-radiotherapy functional assessment

Although there are no clearly defined FEV1 or DLCO limits for radiotherapy, the same criteria of surgical case series are used in most chemotherapy/radiotherapy clinical trials. Both the dosimetric parameters, the mean lung dose (MLD) and the percentage of healthy lung volume that receives at least 20 Gy (V20) are effective tools to assess the risk of pulmonary toxicity, although some studies support the importance of the clinical characteristics of patients in the estimation of lung damage secondary to radiation [54].

Multimodal management of stage III NSCLC

Incidental stage IIIA (N2)

The need for adjuvant treatment has been evidenced by the poor results of local control and overall survival (OS) after surgery in patients with stage IIIA NSCLC. Several randomised clinical trials and meta-analyses have shown a

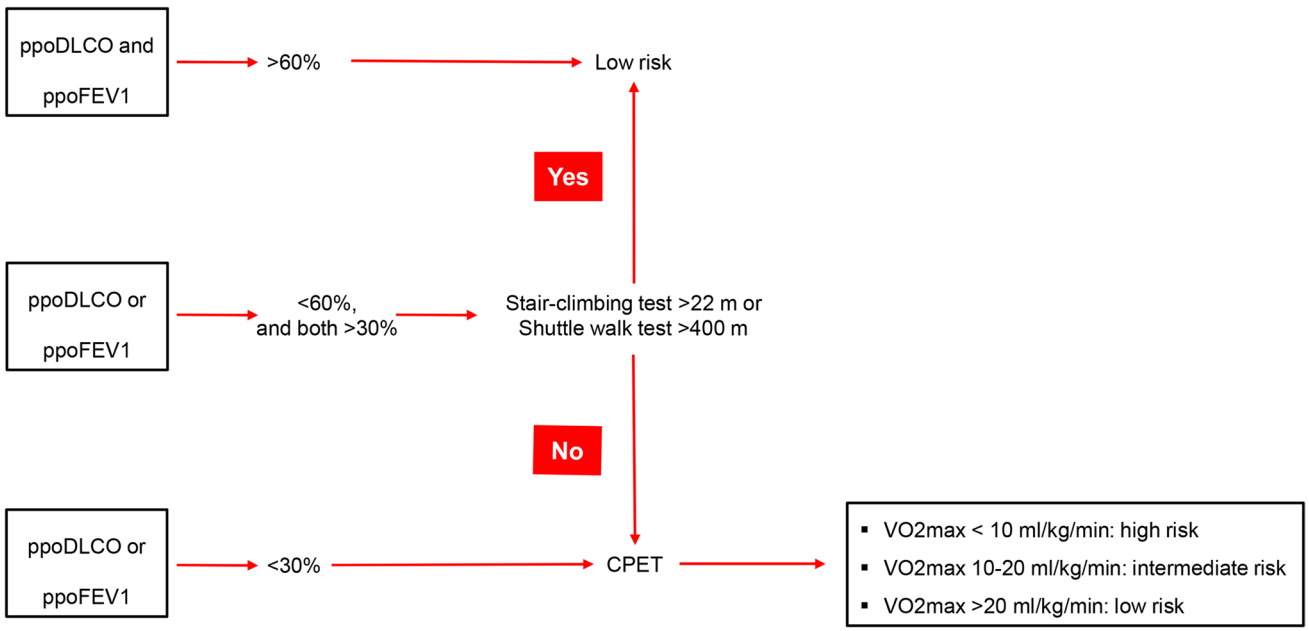

Fig. 2 Pre-operative functional assessment [51]. *DLCO* diffusing capacity of the lung for carbon monoxide, *ppoDLCO* planned post-operatively DLCO, *FEV1* forced expiratory volume in the first second, *ppoFEV1* planned post-operatively FEV1, *CPET* cardiopulmonary exercise test, VO_{2max} maximum oxygen consumption

5% increase in OS at 5 years when administering adjuvant platinum-based chemotherapy [55, 56].

The role of post-operative radiotherapy (PORT) remains controversial. A first meta-analysis conducted in 1998 showed a relative increase in the risk of death (21%), with a lower survival rate in patients receiving PORT [57]. However, a subsequent subgroup analysis established that this negative impact occurred in N0–N1 patients, although it was not clearly demonstrated in N2 patients. In several meta-analyses and subsequent retrospective studies, PORT in N2 patients reduced the risk of local relapse, without showing significant differences in OS [58–62]. However, since most of these studies were not performed with advanced radiotherapy techniques, the validity of their results could be questioned. It is, therefore, a priority to obtain information from randomised trials with modern techniques to establish its real impact on OS [63].

Regarding the sequence of treatments, it is recommended to administer sequential treatment starting with chemotherapy and to reserve concomitant treatment for patients with unresectable residual tumours, since adjuvant chemotherapy–radiotherapy has not shown an increase in OS and there was a greater toxicity.

Potentially resectable stage IIIA (N2)

The group of patients with stage IIIA N2 NSCLC is heterogeneous and their treatment should be discussed in a multidisciplinary committee. For this purpose, the individual characteristics of the patient, such as age, lung function, comorbidity and functional status, must be considered before and after the induction therapy (Fig. 3).

The main objectives of induction therapy are: (a) to eradicate subclinical metastases and mediastinal lymph node disease; (b) to improve local control of the disease; (c) to increase resectability; and (d) to reduce the magnitude of surgical resection.

The factors associated with a better prognosis in patients who undergo surgery are: confirmation of a complete response of the mediastinal (ypN0), achieving a complete resection and confirmation of a complete pathological response.

Induction chemotherapy

Several phase III studies have shown that platinum-based induction chemotherapy increases OS [64–71]. In stage IIIA (cN2) patients, induction chemotherapy increases OS compared to surgery alone [67, 69, 72, 73]. These results have been confirmed in a subsequent meta-analysis [41].

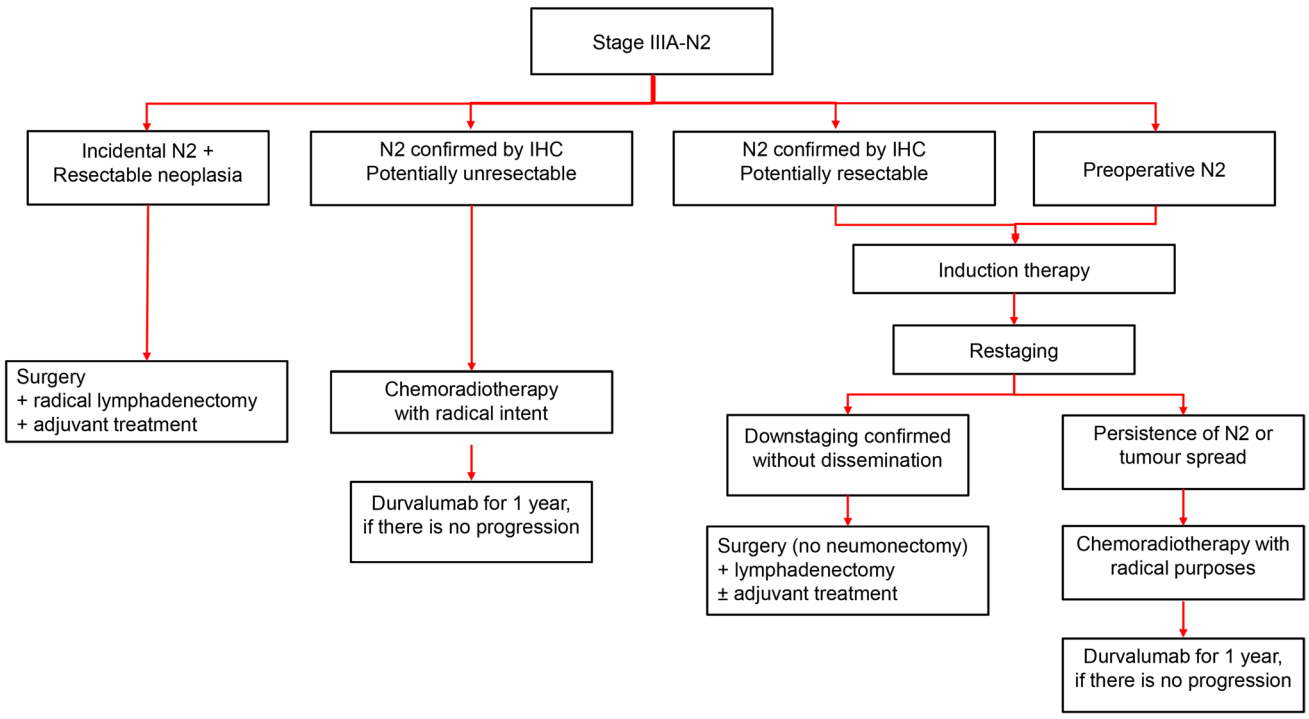

Fig. 3 Algorithm for the clinical management of patients with stage IIIA-N2 NSCLC. *NSCLC* Non-small cell lung cancer, *IHC* immunohistochemistry

Induction chemoradiotherapy

The trials that analyse the role of treatment with induction chemoradiotherapy followed by surgery failed to show a survival benefit except in certain subgroups of patients [74–76]. A clinical trial randomised patients with resectable N2 disease (75% a single station affected) to receive a concomitant chemoradiotherapy treatment (radiation dose of 45 Gy + cisplatin–etoposide) followed by surgery or radical radiotherapy (61 Gy). This trial showed a significant benefit in progression-free survival (PFS) in favour of trimodal treatment, without significant differences in OS [74]. The lack of benefit in the surgery arm may be a consequence of a higher early mortality, especially in patients who underwent a pneumonectomy. A study in patients with resectable stage III NSCLC showed a benefit for induction chemotherapy in terms of the pathological response, and also an improvement of the mediastinal stage, with no differences in survival rates [77].

A meta-analysis showed that the addition of radiotherapy to induction therapy does not increase survival [78], which raises questions about the need to add radiotherapy. It should be noted that several randomised studies have shown that mediastinal downstaging is associated with a better prognosis [79].

Surgical treatment after induction

Surgical resection after induction therapy is indicated when imaging tests rule out extrathoracic disease progression, functional assessment after induction therapy indicates that the patient can tolerate resection, restaging techniques confirm an improvement of the mediastinal status and the type of resection ensures a complete resection, but avoids a pneumonectomy [74, 75].

The goal of surgical treatment after induction therapy is to achieve surgery with complete resection (R0). The R0 criteria defined by the IASLC include: (a) tumour-free resection margins confirmed microscopically; (b) systematic mediastinal lymph node dissection; (c) no extracapsular invasion of affected nodes; and (d) the most distal node resected should be free of disease [80].

There is some consensus that a minimum of six lymph nodes from three N2 stations should be analysed (always including station 7) [81–83]. An adequate lymphadenectomy is considered a criterion for surgical quality [84, 85]. Surgical resection is not recommended if R0 surgery is not feasible, radical radiotherapy could be administered if not previously done [86].

Based on the results obtained in patients who underwent surgery after induction therapy and still had mediastinal lymph node involvement (ypN2), surgery can be an option despite the persistence of N2 involvement in very specific cases, such as initial disease confined to a station that is not enlarged (resectable stage IIIA-N2), with PET/CT with ^{18}F-FDG results showing minimal residual disease, with resection less than a pneumonectomy, and when R0 is feasible.

Adjuvant treatment with chemotherapy

Although adjuvant chemotherapy improves disease-free survival in R0 patients [87], no specific data support adjuvant chemotherapy after induction therapy and surgery in initial stage IIIA-N2 NSCLC. Therefore, administration of adjuvant chemotherapy should be tailored for each patient, according to the pathological response and the pathology findings.

Adjuvant treatment with radiation therapy

Adjuvant radiotherapy therapy to the mediastinum is not recommended in pN0 or pN1 stage. When there is multiple hilar involvement, in extracapsular invasion or in pN2 stage, adjuvant radiotherapy may be considered if it has not been administered during induction therapy [88].

Administration of adjuvant radiotherapy to the T is not recommended in patients with surgery R0 and in the case of R1 or R2 surgery, adjuvant radiotherapy if not administered previously [88].

Unresectable stages IIIA (N2), IIIB and IIIC

Determination of unresectability in patients with stage III NSCLC must be determined by a multidisciplinary committee.

Treatment with concomitant chemotherapy/radiotherapy

Concomitant chemotherapy/radiotherapy is the treatment of choice for patients with a good general condition (ECOG 0–1) and a weight loss of less than 5% in the previous 3 months [89]. This is a radical treatment that aims to cure the disease. A platinum-based chemotherapy regimen is recommended [90]. Gemcitabine regimens are not recommended because of higher pulmonary toxicity. The recommended radiotherapy dose is 60–66 Gy [91]. Concurrent chemoradiotherapy provides a median OS of 22–25 months and a 5-year OS of 20% [92], with a grade 3 toxicity or higher consisting of oesophagitis (7–21%) and pneumonitis (3–7%) [93].

Treatment with sequential chemoradiotherapy

In patients with ECOG > 1, weight loss greater than 5% and a large volume to be irradiated with an unacceptable risk of

pneumonitis, the recommendation is to administer induction chemotherapy followed by radical radiotherapy.

Systemic treatment of stage III NSCLC

Adjuvant chemotherapy after stage IIIA (N2) incidental disease

Patients with N2 disease documented during surgery are candidates for adjuvant chemotherapy (level of evidence: I, recommendation grade: A). The recommended regimen in patients without contraindications is cisplatin doublet chemotherapy, since it has shown to improve OS in complete resected patients. The recommended number of cycles is four (level of evidence: I, recommendation grade: A) [14]. Cisplatin–etoposide and cisplatin–vinorelbine are the platinum doublets with the greatest evidence, as shown in the LACE meta-analysis [56]. Carboplatin can be administered if there are contraindications for treatment with cisplatin.

Induction chemotherapy

Patients with potentially resectable IIIA-N2 disease can receive pre-operative treatment with chemotherapy, with or without radiotherapy, followed by surgery. The recommended induction chemotherapy regimen in patients without contraindications is to administer three to four cycles of a cisplatin doublet, based on complementary chemotherapy studies (level of evidence: II, recommendation grade: B).

Neoadjuvant chemotherapy has been shown to improve OS. In a meta-analysis of 15 randomised studies, a significant 5-year overall survival benefit of 5% was observed in patients at stage IB–IIIA (HR: 0.87; 95% CI 0.78–0.96; $p = 0.007$) [73].

Chemotherapy combined with radiotherapy

In patients with unresectable stage III NSCLC, the administration of chemotherapy concomitant with radiotherapy is recommended (level of evidence: I, recommendation grade: A) [73]. In patients in whom concomitant treatment is not possible, the alternative is a sequential administration.

The recommended chemotherapy regimen is a cisplatin regimen with vinorelbine or etoposide [89, 94]. Most randomised studies comparing sequential versus concomitant treatment use cisplatin with etoposide or cisplatin with vinorelbine [92, 95]. It is recommended to administer two to four cycles of chemotherapy concurrent with radiotherapy (level of evidence I, recommendation grade: A) [89].

Cisplatin can be replaced by carboplatin in patients with comorbidities that contraindicate treatment with cisplatin (carboplatin and paclitaxel is one of the most used regimens). In unresectable patients, cisplatin and pemetrexed regimens have not shown better results than standard treatment with cisplatin and etoposide concomitant with radiotherapy [96].

Age does not justify administering a suboptimal treatment in elderly patients. Therefore, the most convenient treatment should be administered according to the patient's illness and comorbidities (level of evidence: I, recommendation grade: A).

Radiotherapeutic treatment of stage III NSCLC

Radiotherapy volumes

Gross tumour volume (GTV) includes the primary tumour and the affected lymph nodes, when there is lymph node involvement. The clinical target volume (CTV) includes the GTV with a three-dimensional margin that incorporates the microscopic extension of the disease. The planning target volume (PTV) includes the CTV with a three-dimensional margin that considers the tumour movement and the uncertainties in the patient's daily positioning. Improving the immobilisation systems, respiratory movement control and image-guided radiation therapy (IGRT) can reduce the PTV margin [97].

Prophylactic irradiation of non-affected lymph node areas is not recommended, especially if PET/CT with ^{18}F-FDG has been performed during staging, since it does not increase survival and causes more toxicity [98, 99].

When post-operative radiotherapy is administered, the CTV should include the bronchial stump and the ipsilateral, subcarinal and contralateral hilar and paratracheal nodal areas [60, 100].

A correct definition of the healthy organs is a priority to minimise side effects, especially respiratory and cardiac [101, 102]. A useful source is the RTOG volume contouring atlas [103].

New technological advances such as 4D radiotherapy, the use of PET/CT with ^{18}F-FDG for the simulation, intensity-modulated radiotherapy (IMRT) or volumetric-modulated arc therapy (VMAT), IGRT and the control of respiratory movement permit the administration of radical doses and reduce the impact on healthy organs, and should be used whenever available [104].

Radiotherapy dose

As part of a radical treatment, doses of 60–66 Gy at 2.0 Gy/day are recommended. Higher doses do not improve results and increase side effects [91]. In the case of sequential radiation therapy, accelerated radiotherapy schemes should

be evaluated [105]. In post-operative irradiation, doses of 50–54 Gy at 1.8–2.0 Gy/day are usually indicated, although higher doses may be administered when there is extracapsular involvement or involvement of resection margins [60]. If radiation therapy is administered as part of an induction therapy, doses of 45–54 Gy at 1.8–2.0 Gy/day are usually used. A team of experienced thoracic surgeons is required when administering higher doses as induction therapy to avoid possible post-operative complications [106, 107].

Surgical treatment of stage III NSCLC

Surgery in patients with stage IIIA and IIIB non-N3 NSCLC should be considered in a multidisciplinary approach, especially if the R0 is feasible without pneumonectomy [19, 81, 82, 108–111]. The best results are obtained after an adequate selection of the optimal therapeutic scheme and when the surgery is performed at hospitals that have trained surgical teams with anaesthesiology, thoracic surgery, nursing, rehabilitation, etc. [81–83, 108, 109, 111].

It is important to assess the resectability of the lesion and the operability of the patient. As mentioned previously, there are updated guidelines for this purpose in which predictable ppoFEV1 and ppoDLCO values and oxygen consumption have a central role in decision-making. There is not a single value or scale (Thoracoscore, ThRCRI, etc.) that indicates operability. The determination of the patient's general condition using the ECOG scale or the Karnofsky index as well as their expectations and socio-family environment will help to make individualised decisions regarding the surgical options [112, 113].

The standard anatomical resection is lobectomy or bilobectomy (level of evidence: I, recommendation grade: A). Anatomical segmental resection is considered in situations of impairment of the cardiopulmonary reserve. Pneumonectomy can be avoided, as far as possible, with bronchoplastic and angioplastic resections, since this procedure (especially if it is right pneumonectomy) has a significant impact on the results [114, 115].

The setting for the surgical approach would be the least invasive one, such as muscle-sparing thoracotomies, video-assisted thoracic surgery (VATS) or robot-assisted thoracic surgery (RATS). The purpose of this approach is to be the least aggressive possible and to manage these patients, who must necessarily receive neo- or coadjuvant treatments, safely. Anaesthetic and peri-operative care are crucial in the future for these patients [115]. In this context, there are multimodal rehabilitation protocols established, such as fast-track or enhanced recovery after surgery (ERAS) [116].

Consolidation treatment in unresectable stage III NSCLC

Until recently, consolidation treatment with chemotherapy [92, 117], targeted therapy or some types of immunotherapy [118] failed to increase survival in patients with stage III NSCLC [119].

Recently, the administration of the anti-PD-L1 drug durvalumab as consolidation treatment for 1 year in patients with unresectable stage III NSCLC treated with radical chemoradiotherapy and with no progressive disease has been established as a new standard (level of evidence: I, recommendation grade: A). This is based on the results of a phase III clinical trial, in which durvalumab compared with placebo increased both the PFS (17.2 months vs. 5.6 months, respectively, HR, 0.51, 95% CI 0.41–0.63) and the 2-year overall survival of 66.3% (95% CI 61.7–70.4) with durvalumab to 55.6% (95% CI 48.9–61.8) with placebo (HR, 0,68; 99.73% CI 0,47–0,997; $p = 0.0025$). The benefit was consistent in all the pre-specified subgroups. Durvalumab was well tolerated, with a 15.4% of treatment discontinuation due to toxicity, and with grades 3–4 toxicity of 30.5% in patients treated with durvalumab and 26% of patients in the placebo group [120]. The European Medicines Agency (EMA) has approved durvalumab as a consolidation treatment in patients with locally advanced or unresectable NSCLC with expression of PD-L1 $\geq 1\%$ of tumour cells and whose disease has not progressed after platinum-based chemoradiotherapy, based on an unplanned post hoc analysis of PD-L1 expression.

Follow-up of patients with stage III NSCLC

A key point in the follow-up of the patients diagnosed with a pulmonary neoplasm is quitting smoking, since this improves the prognosis of the disease [121]. Of note, it has been shown that a causal relationship may be inferred between smoking and increased mortality from any cause and mortality associated with cancer, as well as regarding the appearance of second lung neoplasms [121]. There is also a relationship, although it cannot be considered a cause, between smoking and an increased risk of recurrence, worse response to treatment and greater probability of suffering treatment-related toxicity [121].

The follow-up frequency of patients with lung cancer is controversial. SEOM and SERAM recommend that patients treated with surgery undergo follow-up with CT scan every 6–12 months during the first 2 years, and annually thereafter [5, 122]. Some authors suggest that performing a PET/CT with ^{18}F-FDG 1 year after surgery is more sensitive than CT alone to detect recurrence [123].

Table 3 Recommendations for the clinical management of patients with stage III NSCLC

Non-invasive staging of stage III NSCLC:

CT scan of the thorax and upper abdomen with intravenous contrast is the preferred technique in the initial assessment when lung cancer is suspected

PET/CT with ^{18}F-FDG is the most sensitive technique to explore mediastinal lymphadenopathy

Brain MRI is indicated in patients with lung neoplasm who are going to be treated with curative intent

Invasive staging of stage III NSCLC:

Non-surgical invasive staging methods are the first choice due to their lower associated morbidity and mortality.

In cases in which the result of invasive non-surgical techniques is negative or non-assessable, surgical staging methods should be recommended, as they remain the standard of excellence in stage III NSCLC staging

Pre-treatment functional assessment:

Before conducting surgery on the patient, it is necessary to ensure that their cardiac function is adequate and to estimate the risk derived from pulmonary resection by means of a pulmonary function study

The FEV1 and the DLCO predicted after the scheduled surgery will be calculated

Functional assessment prior to radiotherapy is less defined, but the lung and heart doses should be minimised

Multimodal management of stage III NSCLC

Incidental Stage IIIA (N2):

In stage IIIA with incidental N2 involvement, the recommended treatment is surgical resection and adjuvant chemotherapy (level of evidence: I, recommendation grade: A)

The administration of sequential post-operative radiotherapy after completing chemotherapy has shown to increase local control of the disease, without being clear whether it provides an OS benefit (level of evidence: II, recommendation grade: C)

Potentially resectable stage IIIA (N2):

In potentially resectable stage IIIA-N2, initial surgical resection is not recommended (level of evidence: I, recommendation grade: A)

In potentially resectable stage IIIA-N2, the recommended treatment is induction chemotherapy, followed by surgery if there is improvement of the stage (level of evidence: I, recommendation grade: A), followed by adjuvant radiotherapy according to the findings after surgery (level of evidence: IV, recommendation grade: C)

Neoadjuvant chemotherapy/radiotherapy achieves a greater downstaging of mediastinal disease volume with respect to induction chemotherapy, without an impact on OS (level of evidence: I, recommendation grade: C)

Unresectable stages IIIA (N2); IIIB and IIIC:

In patients with ECOG 0–1, without weight loss > 5% and with irradiation volumes that do not compromise cardiopulmonary functionality, the administration of concomitant platinum-based chemotherapy/radiotherapy is recommended (level of evidence: I, recommendation grade: A), followed by consolidation treatment with durvalumab, if there is no disease progression

The administration of radiotherapy at doses higher than 66 Gy is not recommended (level of evidence: I, recommendation grade: A)

Systemic treatment of stage III NSCLC

The recommended chemotherapy regimens, either adjuvant, induction or radical combined with radiotherapy, are cisplatin doublets

Radiotherapeutic treatment of stage III NSCLC:

The recommended radiotherapy dose in radical chemoradiotherapy is 60–66 Gy at 2 Gy/day. If administered sequentially, accelerated schemes that reduce the total duration of treatment are recommended

In post-operative irradiation, doses of 50–54 Gy at 1.8–2.0 Gy/day are recommended. In case of extracapsular involvement or resection margins, higher doses may be administered

In case of induction radiotherapy, doses of 45–54 Gy are usually used

Surgical treatment of stage III NSCLC:

The standard anatomical resection is lobectomy or bilobectomy (level of evidence: I, recommendation grade: A).

Surgery in patients with stage III NSCLC is considered in a multidisciplinary and personalised treatment environment, especially if R0 is feasible without pneumonectomy

This surgery should be carried out at hospitals that have trained surgical teams

Stage III NSCLC consolidation treatment:

Durvalumab is recommended as consolidation treatment for 1 year in patients with unresectable stage III NSCLC with expression of PDL1 ≥ 1% in tumour cells and without progression after radical chemoradiotherapy (level of evidence: I, recommendation grade: A)

Follow-up of patients with stage III NSCLC:

Quitting smoking should be advised to patients undergoing treatment for lung cancer

It is recommended to carry out a CT scan every 6–12 months during the first 2 years and later annually

PET/CT with ^{18}F-FDG shows better results in the assessment of patients treated with chemoradiotherapy

The evaluation criteria for response to systemic treatments (RECIST, iRECIST) should be used according to the type of systemic therapy used

CT Computed tomography, *DLCO* diffusing capacity of the lung for carbon monoxide, *EBUS* endobronchial ultrasound, *ECOG* Eastern Cooperative Oncology Group, *EUS* endoscopic ultrasound, *FEV1* forced expiratory volume in the first second, *MRI* magnetic resonance imaging, *NSCLC* non-small cell lung cancer, *PET* positron-emission tomography, PET/CT with ^{18}F-FDG, *OS* overall survival, *R0* complete resection

In patients treated with radiotherapy or chemoradiotherapy, an initial PET/CT with ^{18}F-FDG and during follow-up is useful for predicting areas with greater potential for recurrence or treatment failure [124]. On the other hand, treatment response can be assessed early with a post-treatment PET/CT with ^{18}F-FDG [125–127].

The response assessment criteria will be established based on the systemic treatment received. In most cases, the RECIST 1.1 criteria will apply [128], but for patients who have received immunotherapy, iRECIST criteria should be used [129]. In these patients, successive controls should be carried out in the event of tumour growths, given the possibility of pseudoprogression. However, to verify that these are true progressions and not peritumoural inflammatory reactions, controls should not be performed before 4 weeks after the last assessment.

Conclusions

Stage III NSCLC is a very heterogeneous disease in which multidisciplinary management is essential. A multimodal approach is necessary when establishing treatment for stage III NSCLC. This will depend on the stage III subtype (incidental, potentially resectable or unresectable), and may include surgery, chemotherapy and radiotherapy, as detailed in Table 3. Recently, consolidation therapy with durvalumab has become the new standard treatment for unresectable NSCLC after radical chemoradiotherapy and without disease progression.

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Compliance with ethical standards

Conflict of interest M Majem reports personal fees from AstraZeneca, Roche, Eli Lilly, Bristol-Myers Squibb, Pfizer, Boehringer Ingelheim, Novartis, Tesaro, Takeda, Vifor Pharma, AbbVie, outside the submitted work. M Provencio has received honoraria from Roche, Eli Lilly, Boehringer Ingelheim, AstraZeneca, and Bristol-Myers Squibb, outside the submitted work. The rest of the authors declare that they have not conflicts of interest.

Ethical statement The study has been performed in accordance with the ethical standards of the Declaration of Helsinki and its later amendments. This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study formal consent is not required.

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