Stage III NSCLC treatment options: too many choices

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Abstract

Stage III nonsmall cell lung cancer (NSCLC) represents a wide range of tumour (T1 to T4) and nodal (N0 to N3) components, requiring variable management and a multidisciplinary approach. Recent advancements in minimally invasive techniques, molecular biology and novel drug discoveries have accelerated the refinement of stage III NSCLC management. The latest developments in staging include the forthcoming update of the nodal component in the 9th TNM (tumour–node–metastasis) edition, which emphasises the critical role for endobronchial ultrasonography in mediastinal staging. Recent treatment developments include the use of immunotherapy and targeted molecular therapy in both the neoadjuvant and adjuvant setting, either in combination with other modalities or used alone as consolidation. Surgical and radiotherapy advancements have further enhanced patient outcomes. These developments have significantly improved the prognosis for patients with stage III NSCLC. Fast-changing recommendations have also brought about a challenge, with clinicians facing a number of options to choose from. Therefore, a multimodal approach by a multidisciplinary team has become even more crucial in managing stage III NSCLC.

Educational aims

- To understand the diversity and complexity of stage III nonsmall cell lung cancer and its impact on the advancement of treatment strategies
- To discuss the importance of proper staging and highlight the 9th edition of the TNM classification system
- To outline current neoadjuvant and adjuvant therapies for stage III NSCLC
- To outline current surgical and radiotherapeutic interventions for stage III NSCLC
- To discuss and explore future research directions for stage III NSCLC management

Introduction

Lung cancer has the highest incidence and mortality rate among all cancers worldwide [1–3]. It accounts for >2.4 million new cancer cases worldwide and 484 306 new cases in Europe annually, affecting both

sexes and displaying high mortality [1]. Nonsmall cell lung cancer (NSCLC) accounts for >80% of lung cancer cases, with adenocarcinoma being the most common histological subtype [2].

Approximately 53% of NSCLC cases are diagnosed at stage IV with distant metastasis; 20–35% are diagnosed at stage III. The 5-year survival rate for patients diagnosed at stage IV is around 8.9%, compared with 36%, 26% and 13% for stages IIIA, IIIB and IIIC, respectively. This varied survival rates reflect its broad classification, with treatment strategy and prognosis differing even within the same stage [4–6].

Until recently, locally advanced or stage III NSCLC treatment focused on radical treatment, encompassing a combination of chemotherapy and surgery or radiotherapy. Following the publication of the PACIFIC study, the combination of chemoradiotherapy (CRT) with adjuvant durvalumab became the preferred treatment combination in locally advanced unresectable NSCLC [7]. However, recent trials introduced new possibilities for stage III treatment; CheckMate 816 evaluated neoadjuvant immunotherapy, the ADAURA study evaluated adjuvant tyrosine kinase inhibitors (TKIs), and IMpower010 assessed adjuvant immunotherapy in this setting [8–10]. These innovations hold the potential to significantly improve survival rates. But this progress has introduced a challenge: which one is the optimal choice? The expanding array of treatment options has added further complication to the already complex treatment algorithm for stage III NSCLC. The availability of numerous treatment choices poses a dilemma for the multidisciplinary team (MDT) with regard to the optimal treatment option and informed decision-making by the patient.

The optimal positioning of these new developments will become even more complicated with the upcoming 9th TNM (tumour–node–metastasis) staging edition [11]. The review is a collaborative effort of an MDT of pulmonologists, oncologists, thoracic surgeons and radiotherapists. It aims to provide comprehensive information on recent developments in stage III NSCLC treatment, and to guide clinicians in optimal up-to-date management of this complex stage.

Stage III lung carcinoma: 9th TNM edition *versus* 8th TNM edition

The process of cancer staging offers a standardised classification system for describing the anatomical extent of malignancy. It serves as the universal language for both treatment strategies and prognosis. Staging involves three key components: tumour (T), nodal involvement (N), and metastasis to distant sites (M).

In recent years, the Staging and Prognostic Factors Committee of the International Association for the Study of Lung Cancer (IASLC) partnered with the not-for-profit organisation Cancer Research and Biostatistics (CRAB) in their third staging project. This collaboration aimed to update the 8th TNM staging system for lung cancer using data from 87 043 global cases recorded during 2010–2019 [12]. Among these, 84.1% and 6.4% had NSCLC and small cell lung cancer, respectively. Within the NSCLC subgroup, 71.1% had invasive adenocarcinoma and 21.7% had squamous cell carcinoma. The demographic distribution showed that 56% of the participants were Asian or Australian, 25% were from Europe, 16%

TABLE 1 Stages in lung cancer classification according to the 9th TNM (tumour–node–metastasis) edition *versus* the 8th TNM edition

T	Label	N0	N1	N2		N3
				N2a	N2b	
T1	T1a ≤1 cm	IA1	IIA	IIB	IIIA	IIIB
	T1b >1 to ≤2 cm	IA2	IIA	IIB	IIIA	IIIB
	T1c >2 to ≤3 cm	IA3	IIA	IIB	IIIA	IIIB
T2	T2a >3 to ≤4 cm	IB	IIB	IIIA	IIIB	IIIB
	T2b >4 to ≤5 cm	IIA	IIB	IIIA	IIIB	IIIB
T3	T3 >5 to ≤7 cm	IIB	IIIA	IIIA	IIIB	IIIC
	T3 invasion	IIB	IIIA	IIIA	IIIB	IIIC
	T3 satellite nodules	IIB	IIIA	IIIA	IIIB	IIIC
T4	T4 >7 cm	IIIA	IIIA	IIIB	IIIB	IIIC
	T4 invasion	IIIA	IIIA	IIIB	IIIB	IIIC
	T4 ipsilateral nodules	IIIA	IIIA	IIIB	IIIB	IIIC

Changes showing comparison to the 8th TNM classification are flagged accordingly. Blue signifies downstaging either from stage IIIA to IIB, or from stage IIIB to IIIA. Red signifies upstaging from stage IIIA to IIIB. For the scope of this review, alterations in stage I and II, as well as stage IV disease (M descriptor), were disregarded.

were from North America, 3% were from South/Central America, and 0.1% from Africa/the Middle East [12]. The proposed 9th TNM edition was presented at the World Conference on Lung Cancer in September 2023 [13], and will replace the 8th edition in 2024.

Several modifications have been introduced in the proposed 9th TNM edition concerning stage III lung cancers. Tumour descriptors (T) remained unchanged from the 8th edition. However, a crucial adjustment in staging for stage III lung cancer involved the subdivision of the N2 category based on quantification of lymph node involvement into N2a (involvement of a single N2 station) and N2b (involvement of multiple N2 stations) [11]. Since 1987, nodal involvement has only been categorised based on anatomical lymph node location: N0 for no involvement of lymph nodes; N1 for ipsilateral peribronchial, hilar, interlobar or intrapulmonary lymph node involvement; N2 for ipsilateral mediastinal or subcarinal node involvement; and N3 for contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular node involvement [14, 15]. In the 8th TNM edition, every lung cancer with N2 involvement was categorised as at least stage IIIA disease [15]. However, in the 9th edition, patients with a tumour diameter of ⩽3 cm, single-level N2 disease, and no distant metastases are now downgraded as having stage IIB lung cancer, due to significantly better prognosis in terms of survival compared with similar-sized tumours with multiple-node involvement (table 1). Another downgrade, from stage IIIB to IIIA, was made for T3 tumours with single-station N2 involvement. T2 tumours with multiple N2 station involvement are upgraded from stage IIIA to IIIB (table 1) [11].

Mediastinal staging

In the management of nonmetastatic NSCLC, precise mediastinal staging is vital for determining the most suitable treatment strategy. In addition to its role in prognostication, the N-status is a critical factor in determining eligibility for surgical intervention and differentiating between early stage and locally advanced disease (N2/N3 status) [16]. Pathological confirmation of tumour involvement in mediastinal lymph nodes, as indicated by computed tomography (CT) or positron emission tomography (PET) scans, is strongly recommended for patients who are potential candidates for resection. The methods employed for this evaluation, such as endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA), and mediastinoscopy, are vital in ensuring accurate staging and guiding the treatment strategy [17–19].

EBUS-TBNA has emerged over the past decade as the preferred minimally invasive method for sampling the mediastinum [20, 21]. EBUS-TBNA can access various mediastinal and hilar lymph node stations, including the upper and lower paratracheal nodes (stations 2R/2L and 4R/4L), the subcarinal nodes (station 7) and the hilar nodes (stations 10R/L and 11R/L). However, EBUS cannot image or sample subaortic (stations 5 and 6) and para-oesophageal (station 8) lymph nodes. Classic EUS with gastroscope can assess stations 4L (left inferior paratracheal), 7 (subcarinal), 8 (para-oesophageal) and 9 (pulmonary ligament). Several trials have extended the use of the EBUS scope to an oesophageal exploration (EUS-B) of these stations [22, 23].

EBUS is the first-line procedure for mediastinal staging unless prohibited by nodal position or if the patient is considered to be at high risk of nodal involvement despite previous EBUS results, particularly in patients being considered for radical resection. In such cases, mediastinoscopy can be considered as an alternative procedure. It can be video-assisted or performed through direct optic visualisation, providing access to the central mediastinal compartment. It facilitates the biopsy of upper paratracheal lymph nodes (stations 2R and 2L), right paratracheal lymph nodes (station 4R), left paratracheal lymph nodes superior to the aortic arch (station 4L), as well as the more challenging anterior subcarinal (station 7) and bilateral hilar nodes (stations 10R and 10L). These nodes can be sampled or removed for histological evaluation [21]. The choice between EBUS-TBNA and mediastinoscopy often depends on the specific lymph nodes that must be sampled and the overall clinical scenario. However, there is a trend towards reducing the number of mediastinoscopies up to 87% as EBUS emerged the primary option for staging the mediastinum over mediastinoscopy [24–26].

The complexity of lymph node evaluation increases in patients without apparent N2–3 lymph node involvement by both CT and PET criteria. Invasive staging is recommended for patients with central tumours, potentially resectable T2, T3, and T4 tumours, and those with tumours showing enlarged hilar lymph nodes *via* CT or clinical N1 involvement *via* PET. Nevertheless, the approach to preoperative pathological evaluation of mediastinal lymph nodes in patients with a peripheral T1a primary lesion and no N1 or N2–3 involvement remains a subject of debate [27, 28]. Some centres opt for primary resection without preoperative lymph node evaluation, given the low incidence of node involvement. Other centres advocate for preoperative evaluation due to the significant impact on treatment strategy if hidden lymph node metastases are detected [27, 28]. However, pretreatment pathological mediastinal evaluation is

deemed optional in peripheral tumours (an outer third of the lung) measuring ⩽3 cm where mediastinal lymph nodes are CT- and 2-fluoro-2-deoxy-ᴅ-glucose (FDG)-PET/CT-negative, as there is a low likelihood of them being positive [29].

The necessity for both EBUS and mediastinoscopy to thoroughly evaluate mediastinal lymph nodes in one patient requires careful consideration. EBUS has become the most commonly utilised diagnostic tool for mediastinal staging due to its minimally invasive technique with relatively high accuracy. Bᴏᴜsᴇᴍᴀ et al. [17] demonstrated that there is no need for confirmatory mediastinoscopy in patients with resectable NSCLC after negative systematically performed endosonography. The study showed that proceeding directly to resection after negative endosonography is noninferior to performing mediastinoscopy first to detect unforeseen N2 disease, with rates being 8.8% versus 7.7% ($P_{noninferior}$=0.0144), respectively. Moreover, quantifying programmed death-ligand 1 (PD-L1) expression from cytology specimens obtained via EBUS-TBNA yields reliable results comparable with specimens from surgical resection. Sᴀᴋᴀᴋɪʙᴀʀᴀ et al. [30] demonstrated the strong performance of EBUS-TBNA compared with transbronchial biopsy in showing large number of tumour cells, and demonstrated a good concordance with the corresponding primary tumour and lymph nodes metastasis.

The detailed decision-making process in NSCLC treatment underscores the delicate balance between comprehensive staging and over-treatment risk. Advances in diagnostic techniques, such as EBUS-TBNA, have markedly improved the accuracy of lung cancer staging, enabling more personalised treatment strategies and optimising patient outcomes.

Tumour PD-L1 expression level and molecular profiling

Thorough identification of tumour characteristics is crucial for effective treatment of the highly heterogeneous stage III NSCLC group. Although chemotherapy plus concurrent radiation therapy (chemoradiotherapy/CRT) has been considered the gold standard, perioperative treatment is now more relevant. In patients with epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) translocation, two TKIs, osimertinib and alectinib, are now used in the postoperative setting of stage III NSCLC. PD-L1 expression level and molecular profiling are essential to guide treatment, and this is true for stage III as well as for stage IV.

In stage III NSCLC patients treated with CRT, the PACIFIC study showed that progression-free survival was significantly longer with adjuvant durvalumab treatment than with placebo [7]. Effectiveness was higher in patients with a tumour PD-L1 expression level of ⩾1% than in those with a level of <1%. Nowadays, all patients are treated with immunotherapy after receiving CRT, regardless of whether their PD-L1 level is greater or less than 1% [29].

In resectable stage III patients, combined neoadjuvant treatment is the latest revolution in lung cancer treatment. The CheckMate 816 study, which included resectable stage III patients, demonstrated that, in comparison with chemotherapy alone, neoadjuvant chemotherapy and nivolumab resulted in significantly longer event-free survival and a higher percentage of patients with a pathological complete response. The improvement was more significant in patients with a tumour PD-L1 expression level of ⩾1% than in those with a level of <1%. Patients with an EGFR mutation or ALK translocation were not included [8]. Thus, for this group of patients, neoadjuvant chemotherapy combined with immunotherapy is the preferred first-line of therapy.

The adjuvant setting has also been impacted by the IMpower010 trial, which was published in 2021. The trial studied the survival benefit with atezolizumab versus best supportive care after adjuvant chemotherapy in patients with resected stage II–IIIA NSCLC. It demonstrated a more pronounced benefit in the subgroup whose tumours expressed PD-L1 on ⩾1% of tumour cells and in stage IIIA [10].

In 2023, the landmark trial KEYNOTE-671 was published, which had a perioperative immune checkpoint inhibitor (ICI) strategy. In patients with resectable, early stage NSCLC, neoadjuvant pembrolizumab plus chemotherapy followed by resection and adjuvant pembrolizumab significantly improved event-free survival, pathological response and pathological complete response compared with neoadjuvant chemotherapy alone followed by surgery [31].

For stage III patients with operable cancer, molecular profiling is now necessary as patients with EGFR mutations or ALK translocation may receive a TKI after surgery. The ADAURA study included postoperative stage III patients with EGFR mutation and showed that disease-free survival was significantly longer among those who received osimertinib than among those who received placebo [9].

TABLE 2 Recent landmark trials in stage III nonsmall cell lung cancer (NSCLC)			
Study	**Setting**	**Regimen**	**Comments**
PACIFIC [7]	Adjuvant	Chemoradiotherapy followed by durvalumab	Regardless of PD-L1 expression
CheckMate 816 [8]	Neoadjuvant	Chemotherapy and nivolumab	PD-L1 >1%
IMpower010 [10]	Adjuvant	Chemotherapy and atezolizumab	PD-L1 >1
KEYNOTE-671 [31]	Perioperative	Chemotherapy and pembrolizumab followed by resection and adjuvant pembrolizumab	
ADAURA [9]	Adjuvant	Osimertinib	EGFR mutation
ALINA [32]	Adjuvant	Alectinib	ALK translocation
PD-L1: programmed death-ligand 1; EGFR: epidermal growth factor receptor; ALK: anaplastic lymphoma kinase.			

The ALINA study included postoperative stage III patients with ALK translocation and showed that alectinib significantly improved disease-free survival compared with chemotherapy [32].

For all patients with stage III NSCLC, molecular profiling and PD-L1 status have become essential when considering the different NSCLC treatment options, whether for adjuvant or neoadjuvant treatments, or after CRT.

Table 2 summarises the recent landmark trials and highlights the subsequent changes proposed in clinical practice.

Developments in surgery for stage III NSCLC

Thoracic surgery has seen several developments in the treatment of stage III NSCLC. Minimally invasive techniques were initially employed for stage I lung cancer in the early 1990s, with video-assisted thoracoscopic surgery (VATS) used for anatomical resection [33]. Adoption was slow initially as there was a challenging learning curve to overcome in developing the required level of skill [34]. However, the technique has gradually evolved in parallel with the innovation of surgical equipment, such as 3D/4K high-definition endoscopic cameras, advanced energy systems and endo staplers for safe sealing of vessels and pulmonary tissue. In line with technique refinement and the development of better equipment, VATS has been employed for stage II and III lung cancer. The advantages include reduced postoperative pain, a shorter length of hospital stay, a faster return to daily activities, a better quality of life and, most importantly, fewer complications [35].

In recent years, robotic-assisted thoracic surgery (RATS) has gained widespread implementation in thoracic procedures as it offers improved visualisation and instrumentation. RATS facilitates the advanced resection that is as often required for stage III NSCLC. Pneumonectomy is a major thoracic procedure associated with potential risks and a high complication rate. Where possible, a sleeve lobectomy is preferable to decrease the risk of surgical mortality, reduce the occurrence of complications and increase quality of life [36]. Performing anastomosis may be technically challenging using traditional VATS. However, the advanced instrumentation of RATS facilitates this procedure.

In parallel with the improvement in minimally invasive techniques, enhanced recovery after surgery (ERAS) protocols have developed [37]. ERAS protocols are multidisciplinary perioperative care pathways designed to optimise patient outcome. Thesy focus on minimising surgical stress, optimising pain control, allowing early removal of the chest drain and facilitating early mobilisation. The guidelines of the European Society of Thoracic Surgeons (ESTS) for ERAS after pulmonary surgery recommend 45 items to optimise recovery [37]. Implementation of ERAS protocols has demonstrated benefits in reducing complications and accelerating recovery, with a median length of stay of 2 days after major pulmonary resections [38].

As already discussed, ICIs have become a promising alternative for the perioperative treatment of NSCLC, potentially enhancing the anti-tumour immune response during and after surgery. Although still a topic of debate, it is possible that neoadjuvant chemoimmunotherapy can convert initially unresectable tumours into resectable tumours, potentially broadening the pool of patients who can undergo curative surgical resection, while allowing for more pulmonary-sparing procedures. This may be particularly beneficial in patients with large-size tumours (T3 or T4) and N2-multilevel involvement who respond well to neoadjuvant chemoimmunotherapy [39]. Perioperative use of ICIs can also decrease microscopic disease

and micrometastases, therefore reducing the risk of recurrence and improving long-term outcome after surgery.

Multidisciplinary collaboration is essential for optimising treatment plans. Coordination between pulmonologists, thoracic oncologists and thoracic surgeons is crucial to optimise the timing of surgery following neoadjuvant therapy and to minimise the number of patients who are ineligible for surgery. There is no focused evidence on the intraoperative experience of surgeons performing surgical resection after novel neoadjuvant treatments. Therefore, questions remain regarding intraoperative tissue density, resection time and coagulation approaches [8]. The challenges for thoracic surgeons in this setting are still to optimise minimally invasive surgery, ensure radical resection and preserve lung tissue. This requires education, training and use of new technologies.

Surgical perspective: how to treat (single, multiple and bulky) N2 disease

Stage IIIa N2 patients are a heterogenous group in whom the optimal surgical approach is uncertain. Meticulous preoperative staging with PET-CT, EBUS, EUS and brain magnetic resonance imaging is important to ensure precise staging prior to making an MDT decision regarding therapeutic approach. This has been the preferred approach for resectable tumours since ROTH et al. [40] and ROSELL et al. [41] published the results of their randomised controlled trials in the late 1990s, which showed a significant survival benefit with neoadjuvant chemotherapy. Some surgeons advocate upfront surgery for resectable single-stage N2 (except where there is station 7 involvement), followed by adjuvant chemotherapy and/or radiation [42]. However, the evidence supporting this approach is sparse. In 2009, a randomised controlled trial comparing surgery to radiation after induction chemotherapy was published [43]. The study did not show a benefit for surgery. However, in a subgroup analysis, patients with a lobectomy showed significantly improved long-term survival in comparison with the pneumectomy group who had very high mortality. The study concluded that pneumonectomy in N2 patients should be avoided. Bulky N2 involvement is generally considered unresectable. In recent studies of adjuvant chemoimmunotherapy, the survival rate for N2 patients receiving surgery is very promising and the role of surgery may have to be reconsidered for patients with N2 involvement [8]. However, further studies are needed to clarify the future role of surgery in a modern multimodal setting.

Radiotherapy for stage III NSCLC

Radiation therapy can be applied to treat stage III NSCLC in the following settings: as a radical treatment in unresectable cases; as a neoadjuvant therapy in resectable disease; and as an adjuvant therapy for resected patients.

The 5-year survival results from the PACIFIC study (concurrent chemoradiation followed by durvalumab) showed a clear benefit for immunotherapy as an add-on treatment in irradiated patients with unresectable stage III disease. There was a clear advantage both in overall survival (plus 10% at 5 years; from 33% to 43%) and in progression-free survival (16.9 months *versus* 5.6 months). 33.1% of patients who were randomly assigned to durvalumab remained alive and free of disease progression at 5 years [44]. The benefits of immunotherapy after chemoradiation were also reported by the Chinese GEMSTONE-301 trial [45].

Real-world experience with durvalumab reproduced the benefits seen in the PACIFIC trial, even though 14% of the patients were treated with sequential chemoradiation [46]. This strategy was further explored in the PACIFIC-6 trial, which reported interesting survival results with a similar safety profile to durvalumab after concurrent treatment [47]. Phase III studies that are currently ongoing will shed light on the differences between sequential and concomitant approaches and further investigate the synergistic effects of ICI and radiotherapy.

Several studies are ongoing that use double immunotherapy as induction, concomitant or consolidation therapy [48]. In patients with a treatable driver mutation, such as EGFR, no survival benefit has been reported thus far when adding immunotherapy after chemoradiation, as documented by a *post hoc* subgroup analysis of the PACIFIC trial [49] and real-world experience [50]. Several studies have shown an advantage of adding TKIs before, after or concomitant to chemoradiation [51, 52]; randomised data are pending.

In addition to patient selection and pharmacological intensification, there has also been optimisation of radiotherapy treatment thanks to technological innovation in recent years. With the introduction of intensity-modulated radiation therapy (IMRT)/volumetric modulated arc therapy, curative treatments have increased compared with palliative treatments (2005–2008: 60% palliative and 40% curative; 2013–2020: 17% palliative and 83% curative) [53]. A secondary analysis of RTOG 0617, which investigated the long-term outcome of radiation techniques in locally advanced NSCLC, documented reduced incidence of

grade 3 pneumonitis and above with IMRT *versus* 3D (3.5% *versus* 8.2%) and a reduced heart dose that was clearly associated with 5-year survival [54].

Radiotherapy can be integrated into the neoadjuvant approach with concurrent chemotherapy and/or immunotherapy. Pathological complete response is a key point in this setting, ranging 17–37% in neoadjuvant chemoimmunotherapy studies [55, 56], 20–26% in radio-immunotherapy studies [57, 58] and 52–63% in radio-chemoimmunotherapy studies [59, 60]. Toxicity and survival data from the phase III trial are awaited. The definition of resectability is a key issue and the MDT should share their ideas for a final optimal decision [61]. As shown in figures 1 and 2, radiotherapy remains the backbone of treatment for patients with unresectable disease.

In resected pathological N2 (pN2) patients, the debate around adjuvant radiation therapy continues. Recent trials have confirmed that local failure is still a problem affecting about one-third of patients [62, 63]. Similar percentages were reported in adjuvant immunotherapy studies (KEYNOTE-091: 24–29% [64]; IMpower010: 17–23% [10]). Radiation therapy has clearly been shown to reduce mediastinal relapses by 50%. However, this does not appear to impact disease-free survival in the available randomised studies. In the Lung ART study, the increase in cardiopulmonary complications in postoperative radiotherapy (PORT) may have been due to application of the 3D technique, which subsequently increased the cardiac dose and cancelled out the expected benefits [65]. Figure 1 shows the optimal radiation dose distribution.

IMRT was used in a study by HIU *et al.* [66], who showed that the radiotherapy arm failed to improve disease-free survival in the intent-to-treat population, whereas the advantage was clear in both the per-protocol and as-treated analyses. An explanation could be that adherence to the protocol in the radiotherapy arm was only 76%, as 24% refused radiotherapy despite being randomised to this treatment arm.

### Radiation therapy: how to treat (single, multiple and bulky) N2

Currently, the management of radiologically/histologically proven N2 disease is one of the most debated topics in stage III disease. This is due to the difficulty of standardisation in the definition of resectability, and the variety of available therapeutic options. The role of CRT has certainly been explored more often in cases of multistation N2 involvement and bulky N2 disease. In these situations, where surgery has a questionable radical treatment intent, CRT plays a crucial role in optimising treatment outcome for patients with lung cancer.

A study conducted by SENAN *et al.* [67] focused on stage IIIA N2 patients in the PACIFIC trial, constituting 40% of the total participants. Their findings confirm the benefits associated with adding immunotherapy following chemoradiation in this specific subset of patients.

For lung cancer with a single N2 lymph node involved, two aspects must be underlined. The Lung ART PORT study certified that only 25% of patients had multistation N2 at clinical staging, compared with 52% at definitive histological examination. Although 45% of patients had single-station pN2, postoperatively, one out of three patients in the arm without radiotherapy experienced mediastinal recurrence [65]. These two elements confirm that both the risk of multistation disease and of recurrence of mediastinal disease in the absence of radiotherapy in the therapeutic programme could lead to unsatisfactory local control.

FIGURE 1 Dose distribution in a patient with unresectable stage III disease.
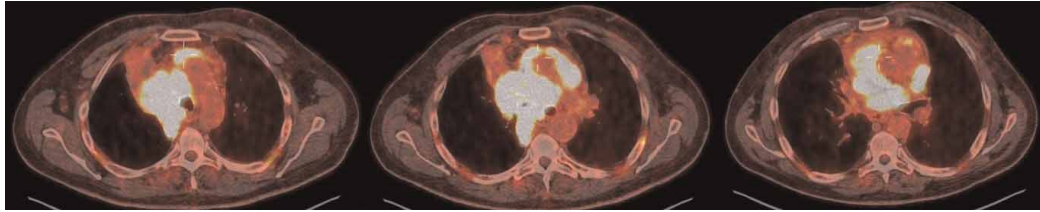
FIGURE 2 Imaging in unresectable stage III disease using positron emission tomography-2-fluoro-2-deoxy-D-glucose.

Discussion

The optimal treatment strategy for stage III NSCLC is rapidly advancing towards significant refinement. Until the arrival of immunotherapy, treatment for stage III NSCLC had not seen substantial changes for quite some time. However, the advancement of minimally invasive technology and the introduction of novel and effective drugs are now bringing further changes to the management of this condition. Doctors managing NSCLC patients need to be aware of these evolving strategies, and our review aims to provide an up-to-date and concise overview of these developments in stage III NSCLC management.

With the forthcoming 9th TNM edition, nodal staging will undergo modifications that might affect the therapeutic options available and subsequent prognosis, while the tumour component will remain unchanged. Patients with T1N2aM0 will be downgraded from stage IIIA to IIB, and those with T3N2aM0 will move from IIIB to IIIA. Meanwhile, patients with T2N2bM0 will be upgraded from IIIA to IIIB [11]. This proposed reclassification carries significant implications for future treatment decisions regarding multiple combination therapies. However, there is also skepticism regarding the applicability of trial results, as they were conducted with older TNM editions. Future research studies will explore the implications of these changes once the 9th TNM edition is officially released.

Mediastinal staging needs to be accurate and safe for patients with stage III NSCLC. EBUS-TBNA has become the preferred minimally invasive method for mediastinal staging. It can access multiple lymph nodes, including paratracheal, subcarinal and hilar nodes, with high accuracy and minimal complications. Previous studies have demonstrated that it can provide adequate tissue samples for diagnosis and molecular analysis, including PD-L1 expression, comparable to specimens obtained from surgical resection [30, 68]. EBUS-TBNA significantly improves staging accuracy and treatment selection while reducing the invasiveness of staging procedures.

Beyond staging, advancements in neoadjuvant therapy impact the treatment of previously unresectable cases. Neoadjuvant and adjuvant therapies for perioperative treatment are attracting considerable interest. Neoadjuvant chemoimmunotherapy, adjuvant immunotherapy, perioperative immunotherapy and adjuvant use of TKIs has shown promising results for patients with resectable stage III disease and will find their way into treatment algorithms and guidelines quickly, emphasising the importance of determining PD-L1 and molecular profiling in these patients.

For patients with unresectable stage III NSCLC, the use of various therapy options beyond surgery is pivotal. Concurrent CRT followed by consolidation immunotherapy is preferred for fit patients who are unlikely to benefit from resection, as shown in the PACIFIC trial [7]. Other approaches being investigated aim to optimise the effects of immunotherapy by combining them with monoclonal antibodies, such as ipilimumab, for advanced NSCLC [69–71]. It is important to consider patient characteristics, such as low performance or non-targetable oncogenic drivers, as well as patient preference when offering treatment options. Early palliative care should be initiated for patients in whom curative treatment is not feasible.

Ongoing studies are underway to investigate optimal neoadjuvant and adjuvant treatments for stage III NSCLC, with promising treatment combinations emerging. However, some of these treatments may pose higher toxicity risks than current treatments, and they are typically only recommended for fit patients. Despite this, in routine clinical practice, frail NSCLC patients with low performance scores of 2–4 are frequently encountered, mainly due to age and other comorbidities [72]. These patients require the MDT's special attention and should be included in research studies, as they are often excluded from clinical trials [73].

Another consideration pertains to specific populations, such as patients of Asian descent, who may require tailored management strategies and might not always have access to optimal treatments. PRABHASH *et al.*

[74] highlighted the regional differences in treatment approaches and survival rates across Asian countries, revealing that only 15% of all patients in their study were tested for PD-L1, of whom 50% tested positive. With the increase in costs due to expensive medications it has become more challenging for patients in low- and middle-income countries to receive optimal treatment, where even basic resources such as radiotherapy and surgery may be limited [2, 74]. Hence, the development of tailored approaches is imperative to address the diverse needs of different populations and countries.

Conclusion

We are living in an exciting era marked by rapid breakthroughs in lung cancer treatment, particularly over the past 5 years, which have the potential to continue further in the future. These breakthrough treatments have opened up possibilities for combining multiple therapies and have transformed the treatment of lung cancer, especially in stage III NSCLC, which is characterised by a diverse group of diseases with varying forms. However, the fast-changing treatment recommendations may create confusion for doctors and patients when choosing the best treatment in a shared decision-making. The decision for tumour resectability remains ambiguous, even though it plays a crucial role in management strategy. A multidisciplinary approach with a high awareness of fast-changing therapies is critical in selecting the optimal treatment for each individual patient.

Key points

- Stage III NSCLC presents a complex clinical decision path due to the fast-changing developments in staging classification, the forthcoming TNM 9th edition and treatment options.
- It is essential that resectability in stage III NSCLC is defined; currently, there is no clear definition, necessitating a multidisciplinary approach to decision-making.
- For resectable stage III NSCLC, there is growing interest in neoadjuvant and adjuvant therapies for perioperative treatment. Neoadjuvant chemoimmunotherapy, adjuvant immunotherapy and the adjuvant use of TKIs have shown promising results.
- For unresectable stage III NSCLC, concurrent CRT followed by adjuvant immunotherapy has shown a favourable outcome in fit patients, as seen in the PACIFIC trial.
- A MDT approach and staying alert to rapidly evolving therapies is essential for selection of the best treatment for each patient.

Self-assessment questions

1. What are the proposed changes in the upcoming 9th TNM edition compared with 8th edition?
2. When should endosonography be performed in patients with stage III NSCLC?
3. What is the role of the tumour PD-L1 expression level and molecular profiling in stage III NSCLC?
4. What are the latest advancements in neoadjuvant/adjuvant therapy for stage III NSCLC?

References

1   Global Cancer Observatory. Trachea, bronchus and lung fact sheet. https://gco.iarc.who.int/media/globocan/factsheets/cancers/15-trachea-bronchus-and-lung-fact-sheet.pdf Data last accessed: 1 February 2024.
2   Asmara OD, Tenda ED, Singh G, et al. Lung cancer in Indonesia. J Thorac Oncol 2023; 18: 1134–1145.
3   Hendriks LEL, Dingemans AC, De Ruysscher DKM, et al. Lung cancer in the Netherlands. J Thorac Oncol 2021; 16: 355–365.

4   Ganti AK, Klein AB, Cotarla I, *et al.* Update of incidence, prevalence, survival, and initial treatment in patients with non-small cell lung cancer in the US. *JAMA Oncol* 2021; 7: 1824–1832.

5   Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin* 2020; 70: 7–30.

6   Casal-Mouriño A, Ruano-Ravina A, Lorenzo-Gonzáles M, *et al.* Epidemiology of stage III lung cancer: frequency, diagnostic characteristics, and survival. *Transl Lung Cancer Res* 2021; 10: 506–518.

7   Antonia SJ, Villegas A, Daniel D, *et al.* Durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *N Engl J Med* 2017; 16377: 1919–1929.

8   Forde PM, Spicer J, Lu S, *et al.* Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer. *N Engl J Med* 2022; 386: 1973–1985.

9   Wu Y-L, Tsuboi M, He J, *et al.* Osimertinib in resected EGFR-mutated non-small-cell lung cancer. *N Engl J Med* 2020; 383: 1711–1723.

10   Felip E, Altorki N, Zhou C, *et al.* Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB–IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial. *Lancet* 2021; 398: P1344–P1357.

11   Huang J, Osarogiagbon RU, Giroux DJ, *et al.* The International Association for the Study of Lung Cancer Staging Project for Lung Cancer: proposals for the revision of the N descriptors in the forthcoming ninth edition of the TNM classification for lung cancer. *J Thorac Oncol* 2023; 19: 749–765.

12   Asamura H, Nishimura KK, Giroux DJ, *et al.* IASLC lung cancer staging project: the new database to inform revisions in the ninth edition of the TNM classification of lung cancer. *J Thorac Oncol* 2023; 18: 564–567.

13   Asamura H, Nishimura K. Abstract PL04.03: 9th Edition TNM staging classification: lung cancer. World Conference on Lung Cancer, 2023.

14   Mountain CF. A new international staging system for lung cancer. *Chest* 1986; 89: 225S–233S.

15   Goldstraw P, Chansky K, Crowley J, *et al.* The IASLC Lung Cancer Staging Project: proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer. *J Thorac Oncol* 2016; 11: 39–51.

16   Daly ME, Singh N, Ismaila N, *et al.* Management of stage III non-small-cell lung cancer: ASCO guideline. *J Clin Oncol* 2022; 40: 1356–1384.

17   Bousema JE, Dijkgraaf MGW, van der Heijden EHFM, *et al.* Endosonography with or without confirmatory mediastinoscopy for resectable lung cancer: a randomized clinical trial. *J Clin Oncol* 2023; 41: 3805–3815.

18   Remon J, Soria J-C, Peters S, *et al.* Early and locally advanced non-small-cell lung cancer: an update of the ESMO Clinical Practice Guidelines focusing on diagnosis, staging, systemic and local therapy. *Ann Oncol* 2021; 32: 1637–1642.

19   Postmus PE, Kerr KM, Oudkerk M, *et al.* Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2017; 28: Suppl. 4, iv1–iv21.

20   Silvestri GA, Gonzalez AV, Jantz MA, *et al.* Methods for staging non-small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013; 143: Suppl. 5, e211S–e2250.

21   Rami-Porta R, Call S, Dooms C, *et al.* Lung cancer staging: a concise update. *Eur Respir J* 2018; 51: 1800190

22   Hwangbo B, Lee GK, Lee HS, *et al.* Transbronchial and transesophageal fine-needle aspiration using an ultrasound bronchoscope in mediastinal staging of potentially operable lung cancer. *Chest* 2010; 138: 795–802

23   Oki M, Saka H, Ando M, *et al.* Endoscopic ultrasound-guided fine needle aspiration and endobronchial ultrasound-guided transbronchial needle aspiration: are two better than one in mediastinal staging of non-small cell lung cancer? *J Thorac Cardiovasc Surg* 2014; 148: 1169–1177

24   Navani N, Lawrence DR, Kolvekar S, *et al.* Endobronchial ultrasound-guided transbronchial needle aspiration prevents mediastinoscopies in the diagnosis of isolated mediastinal lymphadenopathy: a prospective trial. *Am J Respir Crit Care Med* 2012; 186: 255–260.

25   De Leyn P, Dooms C, Kuzdzal J, *et al.* Revised ESTS guidelines for preoperative mediastinal lymph node staging for non-small-cell lung cancer. *Eur J Cardiothorac Surg* 2014; 45: 787–798.

26   Dunne EG, Fick CN, Jones, DR. Mediastinal staging in non-small-cell lung cancer: saying goodbye to mediastinoscopy. *J Clin Oncol* 2023; 41: 3785–3790.

27   Lee PC, Port JL, Korst RJ, *et al.* Risk factors for occult mediastinal metastases in clinical stage I non-small cell lung cancer. *Ann Thorac Surg* 2007; 84: 177–181.

28   De Leyn P, Lardinois D, Van Schil P, *et al.* European trends in preoperative and intraoperative nodal staging: ESTS guidelines. *J Thorac Oncol* 2007; 2: 357–361.

29   National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Non-small cell lung cancer. www.nccn.org/professionals/physician_gls/pdf/nscl.pdf Date last updated: 2 February 2024. Date last accessed: 12 February 2024.

30   Sakakibara R, Inamura K, Tambo Y, *et al.* EBUS-TBNA as a promising method for the evaluation of tumor PD-L1 expression in lung cancer. *Clin Lung Cancer* 2017; 18: 527–534.

31   Wakelee H, Liberman M, Kato T, *et al.* Perioperative pembrolizumab for early-stage non-small-cell lung cancer. *N Engl J Med* 2023; 389: 491–503.

32   Solomon BJ, Ahn JS, Dziadziuszko R, *et al.* ALINA: efficacy and safety of adjuvant alectinib *versus* chemotherapy in patients with early-stage ALK+ non-small cell lung cancer (NSCLC). *Ann Oncol* 2023; 34: 1295–1296.

33   Cao C, D'Amico T, Demmy T, *et al.* Less is more: a shift in the surgical approach to non-small-cell lung cancer. *Lancet Respir Med* 2016; 4: e11–e12.

34   Petersen RH, Hansen HJ. Learning thoracoscopic lobectomy. *Eur J Cardiothorac Surg* 2010; 37: 516–520.

35   Falcoz PE, Puyraveau M, Thomas PA, *et al.* Video-assisted thoracoscopic surgery *versus* open lobectomy for primary non-small-cell lung cancer: a propensity-matched analysis of outcome from the European Society of Thoracic Surgeon database. *Eur J Cardiothorac Surg* 2016; 49: 602–609.

36   Chen J, Soultanis KM, Sun F, *et al.* Outcomes of sleeve lobectomy *versus* pneumonectomy: a propensity score-matched study. *J Thorac Cardiovasc Surg* 2021; 162: 1619–1628.

37   Batchelor TJP, Rasburn NJ, Abdelnour-Berchtold E, *et al.* Guidelines for enhanced recovery after lung surgery: recommendations of the Enhanced Recovery After Surgery (ERAS®) Society and the European Society of Thoracic Surgeons (ESTS). *Eur J Cardiothorac Surg* 2019; 55: 91–115.

38   Huang L, Kehlet H, Petersen RH. Reasons for staying in hospital after video-assisted thoracoscopic surgery lobectomy. *BJS Open* 2022; 6: zrac050.

39   Dickhoff C, Heineman DJ, Bahce I, *et al.* Unresectable stage III NSCLC can be reevaluated for resectability after initial treatment. *J Thorac Oncol* 2023; 18: 1124–1128.

40   Roth JA, Atkinson EN, Fossella F, *et al.* Long-term follow-up of patients enrolled in a randomized trial comparing perioperative chemotherapy and surgery with surgery alone in resectable stage IIIA non-small-cell lung cancer. *Lung Cancer* 1998; 21: 1–6.

41   Rosell R, Gomez-Codina J, Camps C, *et al.* A randomized trial comparing preoperative chemotherapy plus surgery with surgery alone in patients with non-small-cell lung cancer. *N Engl J Med* 1994; 330: 153–158.

42   Sanchez-Lorente D, Guzman R, Boada M, *et al.* N2 disease in non-small-cell lung cancer: straight to surgery? *Future Oncol* 2018; 14: 13–16.

43   Albain KS, Swann RS, Rusch VW, *et al.* Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomized controlled trial. *Lancet* 2009; 374: 379–386.

44   Spiegel DR, Corinne F-F, Gray JE, *et al.* Five-year survival outcomes from the PACIFIC trial: durvalumab after chemoradiotherapy in stage III non-small-cell lung cancer. *JCO* 2022; 40: 1301–1311.

45   Zhou Q, Chen M, Jiang O, *et al.* Sugemalimab *versus* placebo after concurrent or sequential chemoradiotherapy in patients with locally advanced, unresectable, stage III non-small-cell lung cancer in China (GEMSTONE-301): interim results of a randomised, double-blind, multicentre, phase 3 trial. *Lancet Oncol* 2022; 23: 209–219

46   Girard N, Mornex F, Christoph DC, *et al.* PACIFIC-R: first real-world study of patients with unresectable, stage III NSCLC treated with durvalumab after chemoradiotherapy. *Ann of Oncol* 2019; 30: Suppl. 2, 1137.

47   Garassino MC, Mazieres J, Reck M, *et al.* Durvalumab after sequential chemoradiotherapy in stage III, unresectable NSCLC: the phase 2 PACIFIC-6 trial. *J Thorac Oncol* 2022; 17: 1415–1427.

48   Cortiula F, Reyman B, Peters S, *et al.* Immunotherapy in unresectable stage III non-small-cell lung cancer: state of the art and novel therapeutic approaches. *Ann Oncol* 2022; 33: 893–908.

49   Naidoo J, Antonia S, Wu Y-L, *et al.* Brief report: durvalumab after chemoradiotherapy in unresectable stage III EGFR-mutant NSCLC: a *post hoc* subgroup analysis from PACIFIC. *J Thorac Oncol* 2023; 18: 657–663.

50   Peters S, Christoph DC, Field JK, *et al.* Real-world outcomes with durvalumab after chemoradiotherapy in unresectable stage III EGFR-mutated NSCLC (PACIFIC-R). *J Thorac Oncol* 2023; 18: Suppl., S83.

51   Lu S, Casarini I, Kato T, *et al.* Osimertinib maintenance after definitive chemoradiation in patients with unresectable EGFR mutation positive stage III non-small-cell lung cancer: LAURA trial in progress. *Clin Lung Cancer* 2021; 22: 371–375.

52   Govindan R, Hahn O, Choy H, *et al.* A randomized phase II study of individualized combined modality therapy for stage III non-small cell lung cancer (NSCLC). www.nrgoncology.org/Clinical-Trials/Protocol/rtog-1306?filter=rtog-1306 Date last accessed: 1 February 2024.

53   Fornacon-Wood I, Chan C, Bayman N, *et al.* Impact of introducing intensity modulated radiotherapy on curative intent radiotherapy and survival for lung cancer. *Front Oncol* 2022; 31: 835844.

54   Chun SG, Hu C, Choy H, *et al.* Long-term outcomes by radiation technique for locally-advanced non-small lung cancer: a secondary analysis of NRG oncology-RTOG 0617 at 5 years. *J Thorac Oncol* 2023; 18: Suppl., S83.

55   Heymach JV, Harpole D, Mitsudomi T, *et al.* Perioperative durvalumab for resectable non-small-cell lung cancer. *N Engl J Med* 2023; 389: 1672–1684

56   Provencio M, Nadal E, Gonzalez-Larriba JL, *et al.* Perioperative nivolumab and chemotherapy in stage III non-small-cell lung cancer. *N Engl J Med* 2023; 389: 504–513

57   Altorki NK, McGraw TE, Borczuk AC, *et al.* Neoadjuvant durvalumab with or without stereotactic body radiotherapy in patients with early-stage non-small-cell lung cancer: a single-centre, randomised phase 2 trial. *Lancet Oncol* 2021; 22: 824–835.

58   Mauti LA, Finazzi T, Holer L, *et al.* SAKK 16/18: Immune-modulatory radiotherapy to enhance the effects of neoadjuvant PD-L1 blockade after neoadjuvant chemotherapy in patients with resectable stage III(N2) non-small cell lung cancer (NSCLC). A multicenter phase II trial. *J Clin Oncol* 2023; 41: Suppl. 16, 8547.

59   Echevarria MI, Yang GQ, Chen D-T, *et al.* Phase 1 dose escalation of stereotactic body radiation therapy and concurrent cisplatin for reirradiation of unresectable, recurrent squamous cell carcinoma of the head and neck. *Int J Radiat Oncol Biol Phys* 2023; 117: 341–347.

60   Bahce I, Dickhoff C, Schneiders FL, *et al.* Ipilimumab plus nivolumab and chemoradiotherapy followed by surgery in patients with resectable and borderline resectable lung cancer: the INCREASE trial. *Ann Oncol* 2022; 33: Suppl. 7, S982.

61   Dingemans AM, Remon J, Hendriks L, *et al.* OA06.05 Consensual definition of stage III NSCLC resectability: EORTC-lung cancer group initiative with other scientific societies. *J Thorac Oncol* 2023; 18: S57–S58.

62   Kenmotsu H, Yamamoto N, Yamanaka T, *et al.* Randomized phase III study of pemetrexed plus cisplatin *versus* vinorelbine plus cisplatin for completely resected stage II to IIIA nonsquamous non-small-cell lung cancer. *J Clin Oncol* 2020; 38: 2187–2196.

63   Wakelee HA, Dahlberg SE, Keller S, *et al.* Adjuvant chemotherapy with or without bevacizumab in patients with resected non-small-cell lung cancer (E1505): an open-label, multicentre, randomised, phase 3 trial. *Lancet Oncol* 2017; 18: 1610–1623.

64   O'Brien M, Paz-Ares L, Marreaud S, *et al.* Pembrolizumab *versus* placebo as adjuvant therapy for completely resected stage IB-IIIA non-small-cell lung cancer (PEARLS/KEYNOTE-091): an interim analysis of a randomised, triple-blind, phase 3 trial. *Lancet Oncol* 2022; 23: 1274–1286.

65   Le Pechoux C, Pourel N, Barlesi F, *et al.* Postoperative radiotherapy *versus* no postoperative radiotherapy in patients with completely resected non-small-cell lung cancer and proven mediastinal N2 involvement (Lung ART): an open-label, randomised, phase 3 trial. *Lancet Oncol* 2022; 23: 104–114.

66   Hiu Z, Men Y, Hu C, *et al.* Effect of postoperative radiotherapy for patients with pIIIA-N2 non-small cell lung cancer after complete resection and adjuvant chemotherapy the phase 3 PORT-C randomized clinical trial. *JAMA Oncol* 2021; 7: 1178–1185.

67   Senan S, Özgüroğlu M, Daniel D, *et al.* Outcomes with durvalumab after chemoradiotherapy in stage IIIA-N2 non-small-cell lung cancer: an exploratory analysis from the PACIFIC trial. *ESMO Open* 2022; 7: 100410.

68   Heymann JJ, Bulman WA, Swinarski D, *et al.* PD-L1 expression in non-small cell lung carcinoma: comparison among cytology, small biopsy, and surgical resection specimens. *Cancer Cytopathol* 2017; 125: 896–907.

69   Borghael H, Ciuleanu TE, Lee JS, *et al.* Long-term survival with first-line nivolumab plus ipilimumab in patients with advanced non-small-cell lung cancer: a pooled analysis. *Ann Oncol* 2021; 34: 173–185.

70   Nivolumab and ipilimumab versus chemotherapy in first line treatment in PS 2 or Elderly in advanced NSCLC patients (eNERGY). https://clinicaltrials.gov/study/NCT03351361?cond=NSCLC,%20Stage%20III&term=ipilimumab&rank=6 Date last accessed: 16 February 2024.

71   A study of nivolumab and ipilimumab in untreated participants with stage 3 non-small cell lung cancer (NSCLC) that is unable or not planned to be removed by surgery. https://clinicaltrials.gov/study/NCT04026412?cond=NSCLC,%20Stage%20III&term=ipilimumab&rank=3&page=1 Date last accessed: 16 February 2024.

72   Gijtenbeek RGP, Noordhof AL, Asmara OD, *et al.* Immunotherapy in frail non-small-cell lung cancer patients. *Lancet* 2024; 403: 1986.

73   Gijtenbeek RGP, de Jong K, Venmans BJW, *et al.* Best first-line therapy for people with advanced non-small cell lung cancer, performance status 2 without a targetable mutation or with an unknown mutation status (review). *Cochrane Database Syst Rev* 2023; 7: CD013382.

74   Prabhash K, Tan DSW, Soo RA, *et al.* Real-world clinical practice and outcomes in treating stage III non-small cell lung cancer: KINDLE-Asia subset. *Front Oncol* 2023; 13: 1117348.

Suggested answers

1. The N2 category is subdivided based on quantification of lymph node involvement: N2a for single N2 station and N2b for multiple N2 stations. Patients with T1N2aM0 will be downgraded from stage IIIA to IIB, and those with T3N2aM0 from IIIB to IIIA. Meanwhile, patients with T2N2bM0 will be upgraded from IIIA to IIIB.
2. Endosonography is used for the diagnosis and staging of lung cancer, with enlarged or positive PET-FDG uptake lymph nodes, or as part of a systematic preoperative evaluation.
3. It is essential for guiding the treatment (the use of immunotherapy), both in unresectable and resectable NSCLC.
4. Immunotherapy, targeted therapy and a combination of different therapeutic modalities.