

Navigating controversies in stage III NSCLC: a multidisciplinary case discussion on evolving treatment paradigms

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ABSTRACT

Background: The management of stage III non-small cell lung cancer (NSCLC) has become increasingly complex, driven by advances in neoadjuvant and perioperative chemo-immunotherapy as well as targeted therapies. These evolving treatment paradigms have introduced new challenges for multidisciplinary teams (MDTs), regarding patient selection, treatment sequencing, surgical planning and definitions of operability and resectability.

Case presentation: We present a case of a 69-year-old male with cT3N2aM0 (single-station N2) adenocarcinoma NSCLC with a programmed death-ligand 1 (PD-L1) tumour proportion score of 100%. Following discussion in MDT, he received 3 cycles of neoadjuvant carboplatin, paclitaxel, and nivolumab. The initial surgical plan was for a pneumonectomy due to tumour proximity to the right main bronchus, a procedure associated with perioperative risk and long-term functional compromise. Restaging computed tomography (CT) scan demonstrated a partial response, with a 60% reduction in axial tumour dimensions. This downstaging facilitated a change in surgical plan from pneumonectomy to the less extensive right upper lobectomy, resulting in a pathological complete response (ypT0ypN0).

Discussion: The case was discussed during an academic webinar in August 2025. Expert faculty from respiratory medicine, thoracic surgery and medical and radiation/clinical oncology highlighted key discussion points and challenges. This included: 1) evolving definitions of operability and resectability, 2) perioperative systemic therapy selection, 3) the risk of not proceeding to surgery, and 4) the role of postoperative radiotherapy (PORT) and salvage therapy in case of progression.

Conclusion: The case underscores current controversies in the management of stage III NSCLC and the critical role of the MDT. While neoadjuvant and perioperative chemo-immunotherapy offers an opportunity for less extensive surgical resection and improved oncological outcomes, this strategy is not without risks and validated biomarkers to guide decision making are lacking. Concurrent chemoradiotherapy (cCRT) followed by durvalumab remains the standard for fit patients with unresectable or inoperable stage III disease. Future progress depends on clinical trials, biomarker development, and real-world data collection and national audits.

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1. Introduction

Stage III non-small-cell lung cancer (NSCLC) represents 20% of lung cancer diagnoses, encompasses a heterogeneous group of locally advanced disease and is associated with poor outcomes [1]. Management options include either curative-intent multimodality treatment (involving surgery or radiotherapy) or palliative approaches such as systemic anti-cancer therapy (SACT) and palliative radiotherapy [2]. Curative decisions depend on resectability and operability: operable patients with resectable disease may receive surgery, while inoperable and/or unresectable cases are considered for radiotherapy-based treatment (see Fig. 1). Clear definitions of resectability and operability are essential to standardise care and improve access to curative treatment, and are provided here:

- Resectability refers to the technical feasibility of completely removing the tumour with negative margins (R0 resection), based on tumour location, involvement of adjacent structures and nodal disease.
- Operability assesses a patient's fitness to undergo surgery and tolerate its physiological consequences, based on functional status, comorbidities, and associated risks.

The European Organisation For Research and Treatment of Cancer (EORTC) has produced TNM-based guidelines defining resectability, though a grey-zone remains for N2b (multi-station mediastinal nodal) disease [3,4]. Surgical fitness assessments are integrated into diagnostic pathways and are used to assess operability. For radiotherapy, fitness

assessment incorporates performance status, pulmonary function, comorbidities, and tumour characteristics. However, while surgical risk stratification benefits from objective measures such as predicted post-operative forced expiratory volume in one second (FEV₁) and cardio-pulmonary exercise testing (CPET), consensus-based objective criteria for radiotherapy fitness are less well-defined, and decisions often rely on clinician experience and multidisciplinary risk–benefit discussion [6]. This disparity highlights an important area for future research and guideline development.

The PACIFIC trial established concurrent chemoradiotherapy (cCRT) followed by a year of consolidation durvalumab as the standard of care for unresectable stage III disease, achieving a 5 year survival rate of approximately 40% [5]. More recently, neoadjuvant and perioperative chemo-immunotherapy trials have changed the management of resectable stage III NSCLC by demonstrating improved pathological complete response (pCR) rates and survival outcomes [6].

The evolving evidence base raises several pertinent clinical questions for lung cancer multidisciplinary teams (MDTs):

- Can neoadjuvant chemo-immunotherapy convert unresectable disease to resectable disease?
- Can neoadjuvant chemo-immunotherapy influence surgical planning, for example by avoiding pneumonectomy?
- What is the role of adjuvant immunotherapy after neoadjuvant chemo-immunotherapy in patients achieving pCR?
- How to integrate postoperative radiotherapy (PORT) and salvage radiotherapy in the chemo-immunotherapy era?

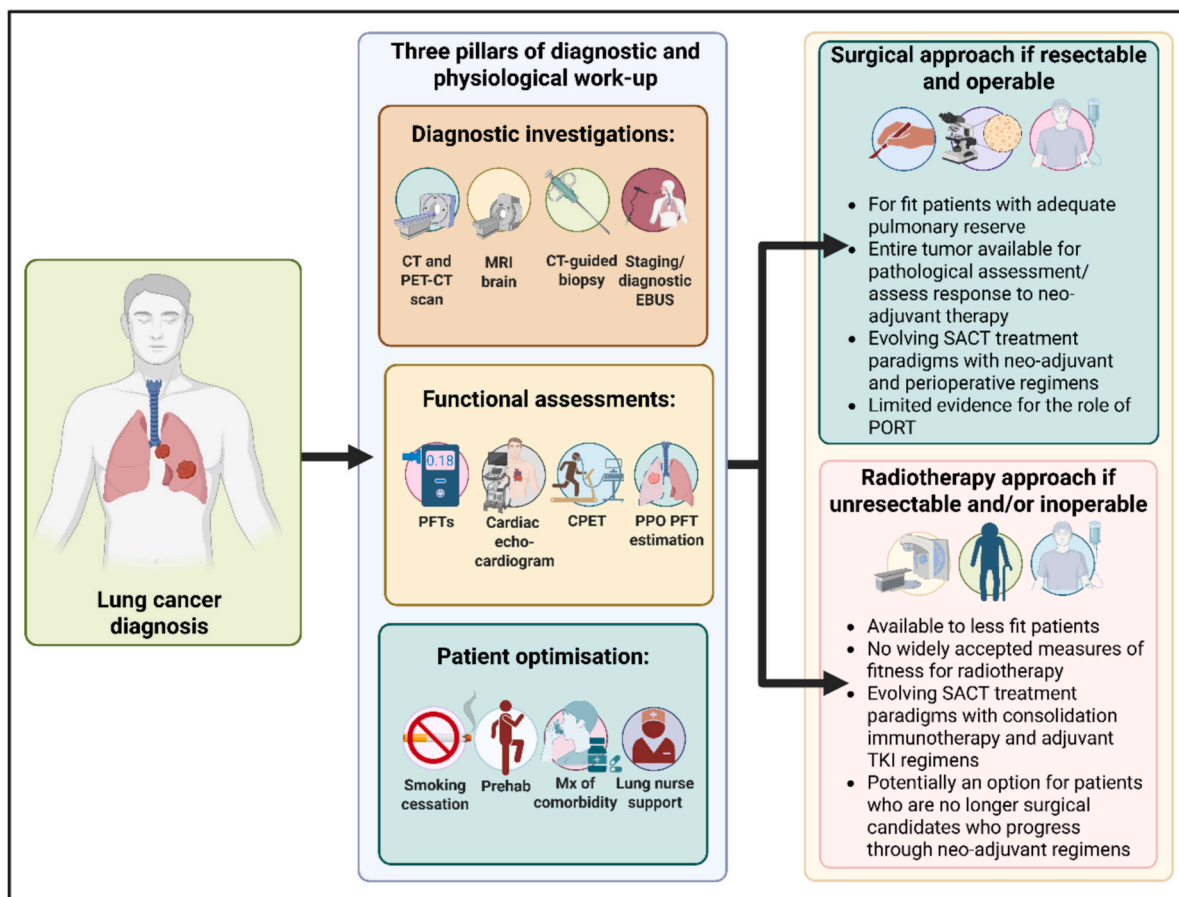


Fig. 1. Summary of lung cancer diagnostic and treatment pathways. CT; computed tomography, PET-CT; positron emission tomography CT, MRI; magnetic resonance imaging, EBUS; endobronchial ultrasound, PFTs; pulmonary function tests, CPET; cardio-pulmonary exercise testing, PPO; predicted postoperative, SACT; systemic anti-cancer therapy, PORT; postoperative radiotherapy, TKI; tyrosine-kinase inhibitors. Created in BioRender. Horne, A. (2026) <https://BioRender.com/gw67cz9>.

The aim of this manuscript is to present a lung cancer case and summarise the perspectives of different members of the lung cancer MDT. It was initially discussed during a UK-based academic webinar that took place in August 2025 and describes a patient undergoing surgical management for stage III NSCLC. This manuscript incorporates controversies and perspectives relevant to MDT practice.

1.1. Webinar format and case discussion methodology

The case presented in this manuscript was discussed during a live, UK-based academic webinar held in August 2025, which was attended by over 200 healthcare professionals with an interest in thoracic oncology. The webinar format was designed to simulate and explore MDT decision-making.

The session was chaired by AH and IG-R and began with a detailed presentation of the case by RM (author). Following this, four expert faculty members, representing respiratory medicine (E O'D), thoracic surgery (RM), medical oncology (AF), and radiation/clinical oncology (PJ), each delivered a 10-minute perspective on the case. Each expert

focused on the key considerations from their respective specialty perspectives.

After the presentations, the expert panel engaged in a moderated discussion and responded to questions submitted by the online audience. The discussion was recorded and transcribed, and the key themes were subsequently synthesised to form the basis of this manuscript.

1.2. Case presentation

A 69-year-old patient with a 25-pack-year smoking history presented with cough. A chest x-ray was performed that prompted further investigation including computed tomography (CT) chest/abdomen with contrast, positron emission tomography-CT (PET-CT), magnetic resonance imaging (MRI) brain and bronchoscopy/EBUS (endobronchial ultrasound) (See Fig. 2 for diagnosis, investigations and management pathway). The patient was staged using TNM8 and was diagnosed with a right upper lobe cT3N2M0 adenocarcinoma NSCLC (cT3N2aM0 using TNM9 – reflecting the single-station N2 node) [7,8]. Programmed death-ligand 1 (PD-L1) tumour proportion score was 100% and no actionable

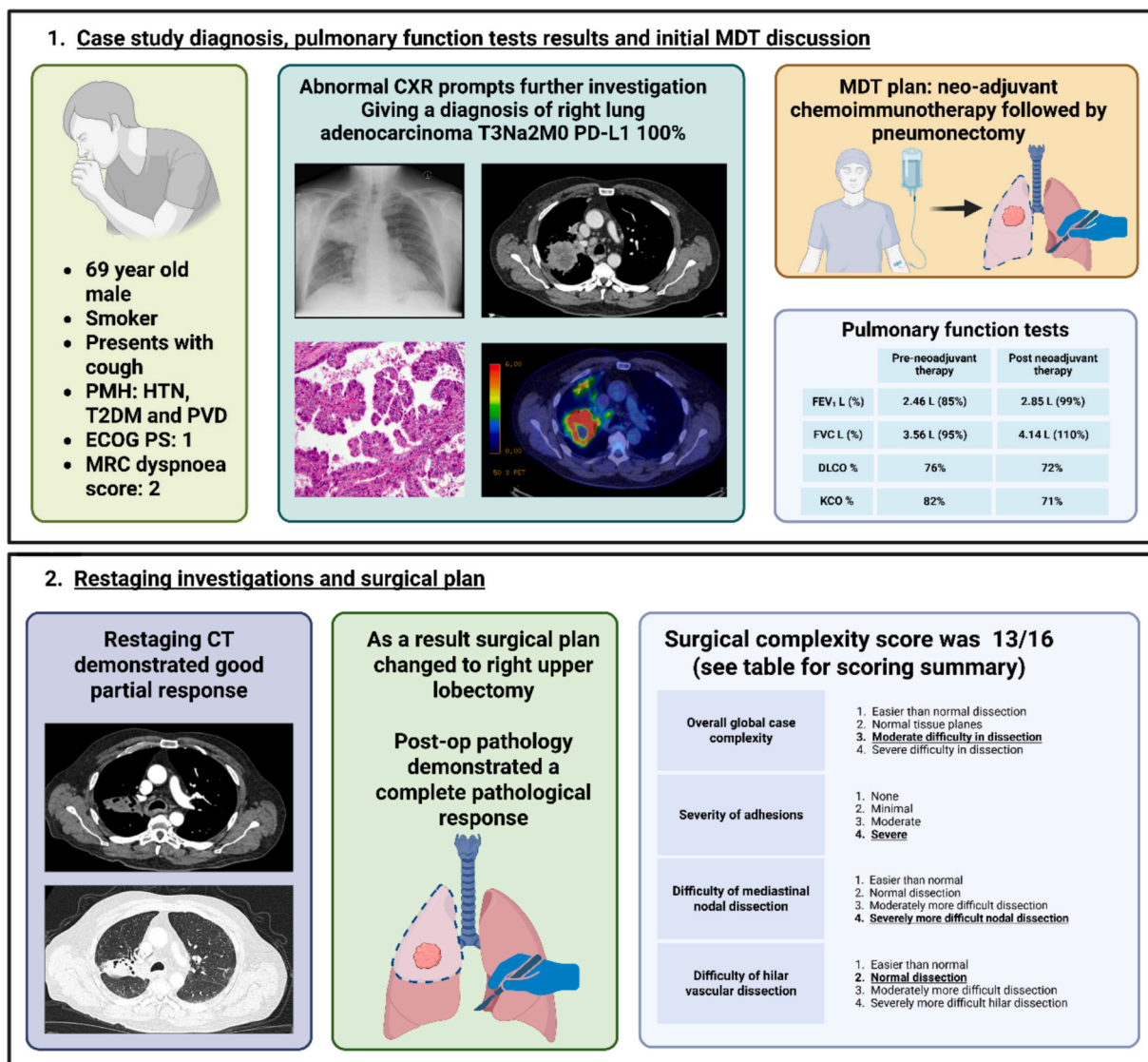


Fig. 2. Summary of diagnosis, investigations and management pathway. PMH; past medical history, HTN; hypertension, T2DM; type 2 diabetes mellitus, PVD; peripheral vascular disease, ECOG PS: European Cooperative Oncology Group Performance Status, MRC; Medical Research Council, CXR; chest x-ray, TNM; tumour, node, metastasis, PD-L1; programmed death-ligand 1, MDT; multidisciplinary team, FEV₁; forced expiratory volume in 1 s, FVC; forced vital capacity, DLCO; diffusing capacity of the lungs for carbon monoxide, KCO; carbon monoxide transfer coefficient, CT; computed tomography. Created in BioRender. Horne, A. (2026) <https://BioRender.com/kyva81t>.

gene alterations (AGAs) were detected. Comorbidities included hypertension, type 2 diabetes mellitus, and peripheral vascular disease. He had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 1 and a Medical Research Council (MRC) dyspnoea score of 2.

The proximity of the primary tumour to the right main bronchus was discussed at MDT meeting, raising concern that a pneumonectomy would be required. As a result, the patient was referred for discussion at the local high-risk lung cancer MDT. Although not available in all cancer centres, these MDTs allow for extended, focused discussion of complex cases, promoting enhanced clinical engagement and peer support [9]. Such an MDT requires an optimal multidisciplinary skill mix which can include radiation/clinical and medical oncologists, therapeutic radiographers, dietician, respiratory physician, surgeons, anaesthetists and specialist nursing support.

Comprehensive investigations were performed to evaluate surgical fitness. Lung function was assessed using pulmonary function tests (PFTs). The results were satisfactory with a FEV₁ of 2.46 L (85% predicted), forced vital capacity (FVC) of 3.56 L (95% predicted), diffusing capacity for carbon monoxide (DLCO) of 76%, and transfer coefficient for carbon monoxide (KCO) of 82%. CPET demonstrated an intermediate oxygen consumption (peak VO₂: 13.5 mL/kg/min), reduced anaerobic threshold (AT: 11.4 mL/kg/min) and elevated ventilatory equivalent of carbon dioxide (VE/VCO₂: slope of 35), indicating reduced ventilatory efficiency, associated with increased risk of postoperative cardiopulmonary complications. The predicted postoperative (PPO) FEV₁ following pneumonectomy was 40%. Cardiac echocardiogram demonstrated the left ventricular ejection fraction at 58% with no significant structural abnormalities identified.

Following high-risk MDT discussion, the patient was referred to prehabilitation and received smoking cessation advice. He was referred to medical oncology and received three cycles of carboplatin, paclitaxel and nivolumab based on the results of the Checkmate-816 study [10]. Restaging imaging demonstrated a partial response based on tumour size, with a 60% reduction in axial dimensions and resolution of associated parenchymal obstructive changes. Repeat PFTs demonstrated an improvement in FEV₁ (2.85 L, 99% predicted) and FVC (4.14 L, 110% predicted) consistent with the resolution of bronchial obstruction. DLCO and KCO reduced slightly to 72% and 71%.

Due to treatment response, the surgical plan was de-escalated from pneumonectomy to right upper lobectomy with the PPO FEV₁ increasing to 71%. Surgery was attempted via video-assisted thoracoscopic surgery (VATS) but was converted to an open thoracotomy due to dense adhesions, resulting in a high surgical complexity score of 13/16 [11]. A right upper lobectomy was performed, with pathology confirming ypT0N0 pCR. At 24 months of follow-up, the patient remains disease free and has been successful in smoking cessation.

2. The MDT discussion

2.1. The respiratory physician's perspective

Respiratory physicians manage the diagnostic and physiological work-up that determines both the staging of patients with lung cancer and the treatments they receive [12]. This role rests on three pillars: 1) performing diagnostic investigations to identify cancer type and stage the extent of the disease, 2) coordinating functional assessment to assess for treatment fitness and 3) optimising patients via prehabilitation, smoking cessation support, and management of comorbidities (see Fig. 1). Lung cancer nurse specialists play a complementary role as patient advocates and provide holistic support while guiding patients through each of these pillars.

Appropriate staging investigations, including whole body PET-CT, reduces futile thoracotomy and improve radiotherapy target delineation [13,14]. For patients with stage III disease considered for curative-intent treatment, MRI brain is recommended because of its greater sensitivity than CT and a reported rate of occult brain metastases of up to

11% [15]. Systematic mediastinal staging using EBUS-TBNA (\pm endoscopic ultrasound with fine needle aspiration (EUS-FNA)) demonstrates high accuracy comparable to mediastinoscopy and should follow PET-CT [16,17]. Although recommended by most guidelines, systemic mediastinal staging is resource-intensive and as a result not available for every patient [2].

Initial functional assessment includes spirometry and gas transfer measurements (see Table 1 for selected parameters commonly used when assessing fitness for lung resection [18]). When surgery is being considered, predicted postoperative lung function and CPET help stratify operative risk [19]. In contrast, radiotherapy suitability is usually assessed using ECOG PS, pulmonary reserve, comorbidity, tumour extent and anticipated dosimetry rather than a single fixed threshold. These assessments should inform, rather than replace, multidisciplinary clinical judgement.

Short, structured prehabilitation programmes (including aerobic and strength exercise \pm inspiratory muscle training) can improve fitness and reduce postoperative pulmonary complications, with benefits observed even over a few weeks [20]. Nutritional support and correction of anaemia further reduce deconditioning. Smoking cessation is crucial: preoperative abstinence reduces pulmonary and wound complications, improves cancer outcomes and should be initiated as early as possible [20,21].

The role of vaping in cessation remains controversial. Recent guidance from the Clinical Oncology Society of Australia advises against routine recommendation due to emerging evidence of carcinogenic potential [22]. Updates from other health advisory groups are awaited.

In addition, respiratory physicians optimise coexisting respiratory disease to improve treatment tolerance, including management of chronic obstructive pulmonary disease (COPD), airway obstruction and secretion clearance. They also provide specialist support for patients with interstitial lung disease (ILD). Formal discussion at an ILD MDT is recommended, as baseline impairment and radiological inflammation predict increased risk from surgery, radiotherapy and immunotherapy [23,24].

Respiratory case discussion: Baseline fitness assessments suggested intermediate operative risk for pneumonectomy, which justified referral to a high-risk MDT. The respiratory team therefore prioritised smoking cessation, prehabilitation and reassessment after induction therapy. Following neoadjuvant treatment, spirometry improved consistent with relief of bronchial obstruction and an increase in lung capacity. The planned resection was deescalated from pneumonectomy to lobectomy. This illustrates the value of structured physiological reassessment after systemic therapy.

Table 1

Summary of pulmonary function test results and surgical fitness.

Pulmonary function test	Result threshold	Interpretation
FEV ₁ (%) / DLCO (%)	Both \geq 80	Fit without further physiologic testing
	Either value < 80	Proceed to exercise assessment
PPO FEV ₁ (%) / DLCO (%)	\geq 30	Usually operable
	<30	Further functional assessment needed
VO ₂ peak (mL/kg/min)	>20	Fit for resection
	10–20	Intermediate risk
	<10	High risk for surgery
VE/VCO ₂ slope	<35	Normal
	\geq 35	Abnormal; impaired gas exchange

FEV₁; forced expiratory volume in 1 s, DLCO; diffusing capacity of the lungs for carbon monoxide, PPO; predicted postoperative, VO₂; oxygen consumption, VE/VCO₂; ventilatory equivalent of carbon dioxide. Adapted from the ERS/ESTS clinical guideline on fitness for radical therapy in lung cancer [18].

2.2. The thoracic surgeon's perspective

The thoracic surgeon plays a pivotal role in the curative-intent management of patients with NSCLC [2]. The primary surgical objective is to achieve an R0 resection, defined as the complete removal of all macroscopic disease with negative microscopic margins and systematic dissection of relevant thoracic and mediastinal lymph nodes.

Lobectomy remains the standard approach for tumours confined to a single lobe where an R0 resection is achievable. Pneumonectomy involves removal of an entire lung and is reserved for more extensive or centrally located tumours in which lung preservation is not possible. This includes tumours that involve the main bronchus or pulmonary artery. Despite advances in technique, perioperative care and patient selection, pneumonectomy continues to carry a higher risk of perioperative morbidity, long-term functional decline, cor pulmonale and increased mortality [25,26].

Sleeve lobectomy is a lung-preserving alternative for selected patients with central tumours involving the lobar bronchus and extending into the main bronchus. It entails resection of the affected lobe and lobar bronchus, reconstructing the proximal airway via an end-to-end anastomosis and attaches the unaffected lobe(s) directly to the trachea. Compared with pneumonectomy, it is associated with lower morbidity and mortality but is technically demanding and requires an experienced surgical team [27].

Surgical case discussion: High-risk MDTs present a valuable opportunity to discuss the nuances of treatments, including different surgical techniques and radiotherapy. In this case, the patient was considered resectable at baseline but required a pneumonectomy due to tumour centrality. Following a good response to neoadjuvant chemo-immunotherapy, the original MDT plan was modified, and a lobectomy was performed instead of pneumonectomy. It is important to distinguish this from converting an unresectable tumour to a resectable one, which remains an area of investigation [28]. The conversion from VATS to thoracotomy due to dense SACT-related adhesions underscores the potential risk of increased technical complexity associated with surgery after neoadjuvant immunotherapy. This was reflected in the high intra-operative complexity score and highlights the importance of experienced thoracic surgical teams. Several surgical complexity scoring systems have been developed for lung cancer resection after neoadjuvant therapy, but none have been prospectively validated. The scoring system used in this case is employed locally and is adapted from published criteria [29]. However, the lack of formal validation, potential for inter-surgeon variability in score allocation and uncertain clinical utility are acknowledged. Standardised collection of surgical quality data, including pneumonectomy rates and complexity scoring, remains valuable for auditing local outcomes and has the potential to facilitate inter-centre comparisons. Future studies should assess inter-rater reliability and establish the optimal scoring system in multi-centre cohorts.

2.3. The medical oncologist's perspective

The medical oncologist plays a leading role in selecting and delivering SACT based on tumour biology, disease stage and patient factors [2]. The role of SACT in early-stage and stage III NSCLC has shifted with the introduction of immunotherapy and targeted agents. Previously, adjuvant platinum-doublet chemotherapy has been the standard for tumours ≥ 4 cm with or without nodal involvement but it provides only a modest absolute overall survival (OS) benefit of 5% at 5 years and is associated with an increased risk of non-cancer-related mortality [30].

Recently, immunotherapy targeting programmed cell death protein 1 (PD-1) or its ligand (PD-L1) has demonstrated clinically meaningful benefit in the surgical setting. The landmark phase III Checkmate 816 trial evaluated 3 cycles of neoadjuvant nivolumab plus chemotherapy versus chemotherapy alone [10,31,32]. The results demonstrated an improved pCR (24.0% vs 2.2%; OR 13.94), median event-free survival (EFS) (59.6 months vs 21.1 months; HR 0.68), and 5-year OS (65.4% vs 55.0%; HR 0.72).

Perioperative chemo-immunotherapy strategies have also established clinical benefit. In KEYNOTE-671, pembrolizumab added to neoadjuvant chemotherapy and continued postoperatively for up to 1

year significantly improved pCR (18.1% vs 4.0%; OR 5.45), EFS at 48 months (51.9% vs 28.1%; HR 0.57) and the 4 year OS (68.0% vs 56.7%; HR 0.73) compared with neoadjuvant chemotherapy alone [33–35]. Other phase III perioperative trials, including AEGEAN (durvalumab) and Checkmate 771 (nivolumab), have also reported positive results, although OS data remain immature [36–39] (see Table 2 for a summary of key neoadjuvant and perioperative trials).

These novel approaches require balancing of potential benefits against associated risks. Immune-related toxicities can be persistent. In KEYNOTE-671, treatment-related toxicity of Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 3 occurred in 45% of patients receiving chemo-immunotherapy [43]. Additionally, approximately 20% of patients who start perioperative or neoadjuvant chemo-immunotherapy do not proceed to planned surgery due to tumour progression or toxicity [44]. These observations highlight the importance of appropriate patient selection, particularly given the lack of validated biomarkers to reliably predict response or progression during treatment.

The role of adjuvant immunotherapy after neoadjuvant chemo-immunotherapy remains unresolved. While outcomes correlate with pathological response, no direct prospective data exist to guide adjuvant therapy decisions based on pCR status. Retrospective analyses and meta-analyses suggest that patients achieving a pCR may derive limited additional benefit from consolidation immunotherapy, whereas those with residual disease appear more likely to benefit [45]. A recent systematic review reported comparable outcomes between perioperative and neoadjuvant-only immunotherapy, with the shorter, neoadjuvant-only approach offering pragmatic logistical and financial advantages [46]. Response-adapted approaches are being evaluated in ongoing trials. For example, the academic ADOPT-lung study (NCT06284317) randomises patients to observation versus adjuvant immunotherapy following neoadjuvant chemo-immunotherapy and surgery [47]. Other trials, such as DNA-PREDICT (NCT06902272), are evaluating circulating tumour DNA as a minimal residual disease marker to guide adjuvant therapy postoperatively [48].

Patients with non-squamous NSCLC with an AGA represent a distinct subgroup [2]. For classic AGAs, adjuvant targeted therapy offers the clearest survival benefit, while immunotherapy does not confer significant benefit. In ADAURA, 3 years of adjuvant Osimertinib significantly improved OS compared with placebo in completely resected epidermal growth factor receptor (EGFR)-mutant NSCLC [49]. Similarly, ALINA demonstrated marked disease-free survival (DFS) benefit with 2 years of adjuvant alectinib in resected anaplastic lymphoma kinase (ALK)-positive NSCLC [50]. These findings highlight the importance of expedited molecular profiling to identify the best perioperative approach.

Medical oncology case discussion: For this patient with a high PD-L1 expressing tumour, the MDT recommended a neoadjuvant approach based on the Checkmate-816 regimen. The objectives were to increase the probability of pCR, reduce tumour and nodal burden, facilitate less morbid surgery and improve survival outcomes. Treatment was delivered over 3 cycles with close monitoring for progression and toxicity. Radiological regression and physiological improvement after neoadjuvant therapy allowed for surgical de-escalation to a right upper lobectomy, and final pathology confirmed pCR (ypT0N0). We await the results of response-adapted studies to better personalise adjuvant therapy strategies in the perioperative setting.

2.4. The radiation/clinical oncologist's perspective

Radiation/clinical oncologists are involved in the management of both unresectable and resectable stage III NSCLC [2]. The aim of curative-intent radiotherapy is to deliver a tumouricidal dose while minimising exposure to normal tissues, thereby maximising local control and survival while reducing treatment-related toxicity. A key unanswered question relates to the optimal role of definitive chemo-radiotherapy versus surgery in patients with resectable disease, as there are currently no contemporary randomised data addressing this question.

Table 2

Summary of the key neoadjuvant (CheckMate 816) and perioperative (KEYNOTE-671, AEGEAN and CheckMate 77 T) randomised, phase III clinical trials.

Trial	Patients	Regimen	Key efficacy outcomes	Selected safety and surgery results
Checkmate 816 [10,31] Neoadjuvant trial (<i>Nivolumab</i>)	Resectable IB–IIIA N = 358	Neoadjuvant: 3 cycles of neoadj. nivolumab + CTx vs neoadj. CTx	pCR: 24.0% vs 2.2% (OR 13.94) Median EFS: 59.6 m vs 21.1 m (HR 0.68) 5 yr OS: 65.4% vs 55.0% (HR 0.72)	TRAEs G3-4: 43.2% vs 44.9% (OR n/d) TRAEs G5: 0% vs 1.7% (OR n/d) No surgery: 16.8% vs 24.6% Pneumonectomy: 16.8% vs 25.2%
KEYNOTE-671 [33–35,40] perioperative trial (<i>Pembrolizumab</i>)	Resectable II–IIIB N = 786	Perioperative: 4 cycles of neoadj. pembrolizumab + CTx and 1 yr adj. pembrolizumab vs 4 cycles of neoadj. CTx	pCR: 18.1% vs 4.0% (OR 5.45) 48 m EFS: 51.9% vs 28.1% (HR 0.57) 4 yr OS: 68.0% vs 56.7% (HR 0.73)	TRAEs G3-4: 44.1% vs 37.1% (OR n/d) TRAEs G5: 1.0% vs 0.8% (OR n/d) No surgery: 17.9% vs 20.6% Pneumonectomy: 11.4% vs 12.3%
AEGEAN [37,38,41] Perioperative trial (<i>Durvalumab</i>)	Resectable II–IIIB N = 802	Perioperative: 4 cycles of neoadj. durvalumab + CTx and 1 yr adj. durvalumab vs 4 cycles of neoadj. CTx	pCR: 17.2% vs 4.3% (OR 4.7) 2 yr EFS: 63.3% vs 52.4% (HR 0.68) OS data immature	TRAEs G3-4: 43.6% vs 43.2% (OR n/d) TRAEs G5: 1.7% vs 0.5% (OR n/d) No surgery: 19.4% vs 19.3% Pneumonectomy: 9.2% vs 9.6%
Checkmate 77 T [36,39,42] Perioperative trial (<i>Nivolumab</i>)	Resectable IIA–IIIB N = 461	Perioperative: 4 cycles of neoadj. nivolumab + CTx and 1 yr adj. nivolumab vs 4 cycles of neoadj. CTx	pCR: 25.3% vs 4.7% (OR 6.64) 30 m EFS: 61% vs 43% (HR 0.61) OS data immature	TRAEs G3-4: 32.5% vs 25.2% (OR n/d) TRAEs G5: 0.9% vs 0% (OR n/d) No surgery: 22% vs 23% Pneumonectomy: 9.0% vs 13.5%

Neoadj.; neoadjuvant, CTx; platinum-based chemotherapy, pCR; pathological complete response, OR; odds ratio, EFS; event-free survival, m; months, HR; hazard ratio, yr; year, OS; overall survival, TRAEs; treatment-related adverse events, G; grade, n/d; not documented.

For fit patients with unresectable stage III NSCLC and no actionable driver mutations, the PACIFIC regimen, remains the standard of care [2]. Notably, the European Medicines Agency (EMA) restricts durvalumab to tumours expressing PD-L1 $\geq 1\%$, a decision based on an unpowered subgroup analysis, which is not aligned with Food and Drug Administration (FDA) approval or wider expert consensus [51–53]. Progression remains a challenge, with a 5-year progression-free survival of only 33.1% in the durvalumab arm (versus 19.0% with placebo) [5]. For patients who are less fit or when concurrent treatment is contraindicated, radiotherapy alone or sequential chemoradiotherapy can be considered. However, these approaches are associated with inferior outcomes [54].

In the LAURA phase III trial, adjuvant Osimertinib following cCRT demonstrated a progression-free survival (PFS) benefit in EGFR-mutant stage III NSCLC (39.1 months vs 5.6 months; HR 0.16) [55]. However, interpretation of these results requires caution. OS data remain immature, and the strategy effectively implies prolonged, potentially lifelong, treatment with osimertinib, raising important questions regarding long-term side-effects, financial toxicity, cost-effectiveness, and patient acceptability [56,57]. Furthermore, the optimal patient population for this approach remains uncertain, as the trial enrolled a selected cohort of patients with EGFR-mutant disease who had not progressed after definitive chemoradiotherapy. While the regimen has been approved by the FDA and EMA, its implementation in routine practice may be challenging, given both the economic implications of indefinite targeted therapy and the logistical burden associated with long-term monitoring and toxicity management.

Radiation/clinical oncologists also deliver postoperative radiotherapy (PORT). Following the LungART trial, PORT is not routinely recommended after complete resection of N2 disease [58]. The trial demonstrated no improvement in OS and reported an increased risk of cardiovascular toxicity and mortality in the radiotherapy arm. However,

PORT should be considered for patients with positive microscopic (R1) or macroscopic (R2) bronchial resection margins [2]. Its role for patients with isolated extracapsular nodal spread and positive vascular resection margins remains unclear and warrants an individualised, multidisciplinary approach. Discussion within the MDT, particularly with the surgeon and pathologist, is essential to understand risk of relapse based on surgical and pathological findings.

Radiation/clinical oncology case discussion: Histology demonstrated ypT0N0, indicating a pathological complete response (pCR). Consequently, PORT was not considered, in line with the findings of the lungART study [58]. An alternative treatment strategy for this patient would have been curative-intent chemoradiotherapy followed by adjuvant durvalumab. Assessment of fitness for radiotherapy is nuanced and lacks validated objective measures. While an ECOG PS of 0–1 and PFT thresholds (e.g., FEV₁ $\geq 40\%$, DLCO $\geq 40\%$) are often cited in clinical trials, they should be guidance rather than absolute exclusion criteria in routine practice. This is reflected in European Respiratory Society (ERS) guidance that suggests not excluding patients from curative radiotherapy based solely on strict PFT thresholds [18]. The final decision should include an overall assessment of functional capacity and an informed discussion of risks, benefits, and alternatives. This case raises several key questions regarding optimal management after neoadjuvant therapy. For the 20% of patients who do not proceed to surgery after neoadjuvant treatment, critical questions remain: 1) Should patients be re-staged with EBUS and PET-CT? 2) Should the radiotherapy volume include the original tumour or the residual disease? and 3) Should these patients receive adjuvant durvalumab after chemo-radiotherapy given prior treatment with induction chemo-immunotherapy? Given the paucity of prospective data addressing optimal management in this scenario, we refer readers to recent papers that discuss these challenges and potential approaches [6,59].

3. Discussion

The management of stage III NSCLC is complex and continually evolving, requiring close multidisciplinary collaboration. The case study discussed during the webinar and expanded upon in this article

illustrates how treatment decision-making must adapt to evolving treatment paradigms. Four key themes emerged from the discussion.

3.1. Redefining operability and resectability

Traditionally, operability and resectability were static assessments made at diagnosis. However, these definitions are becoming dynamic and are being influenced by response to systemic therapy. This case demonstrates how neoadjuvant chemo-immunotherapy can facilitate surgical de-escalation, converting a planned pneumonectomy to a lobectomy in a patient with initially resectable disease. It is important to distinguish this scenario from the concept of true conversion, where initially unresectable disease becomes resectable after induction therapy. While this case does not demonstrate the latter, it illustrates the potential for neoadjuvant approaches to reduce surgical morbidity. This distinction raises important discussion points. Firstly, can disease considered borderline resectable or unresectable by the MDT at baseline could be converted to resectable disease following induction chemo-immunotherapy? The MDT Bridge trial (84 patients with stage IIb-IIIb NSCLC; 56 patients deemed resectable and 28 unresectable by the MDT) demonstrated that neoadjuvant chemo-immunotherapy is feasible, safe, and enables most patients (85% of the overall cohort, 92% of the resectable cohort, and 71% of the borderline resectable cohort) to proceed to surgery within highly specialised MDTs [28,60]. However, this approach should be applied cautiously in routine practice, as the number of borderline resectable patients was limited, and randomised trials supporting neoadjuvant or perioperative chemo-immunotherapy have so far been conducted in patients with initially resectable disease [31,36,37,43].

A second question concerns the timing and method for assessing resectability. Should it occur after, rather than before, neoadjuvant therapy? In MDT-BRIDGE, patients were reassessed after 2 cycles of induction chemo-immunotherapy with a restaging CT scan, but more detailed investigations, such as repeat EBUS or PET-CT, were not mandated. In this context, establishing a clear, guideline-driven definition of technical resectability is essential to standardise inclusion criteria and enable meaningful comparisons across clinical trials [3,4,61].

3.2. Systemic therapy decisions

While the benefit of neoadjuvant and perioperative chemo-immunotherapy has been established, optimal patient selection is not well defined. PD-L1 status may influence outcomes, yet no validated biomarkers currently exist to guide the choice of treatment regimen. Emerging technologies, such as liquid biopsy, radiomic analysis of routine imaging and immune profiling, hold promise to refine clinical decision-making and enable more personalised treatment approaches. In addition, this case highlights uncertainty regarding adjuvant therapy following pCR. Whether an additional year of immunotherapy meaningfully improves outcomes, or simply adds toxicity and cost, remains unknown. Results from response-adapted trials such as ADOPT-Lung and DNA-PREDICT are eagerly awaited to define the minimum effective therapy and reduce risk of overtreatment [47,48].

3.3. Surgical risks and complexity

Although neoadjuvant therapy can enable less extensive resections, it also introduces new perioperative challenges. Approximately 20% of patients enrolled in perioperative trials do not proceed to surgery, primarily due to treatment-related side effects or disease progression [44]. This underscores the importance of careful patient selection and close monitoring during neoadjuvant treatment.

The proportion of patients undergoing pneumonectomy varies across trials (Table 2), ranging from 9 to 17% in the immunotherapy arms of recent studies [30,32,35,36]. This variation is likely due to differences in patient selection, tumour characteristics and institutional surgical

practice and experience. Centres with high-volume thoracic surgical teams and expertise in lung-preserving techniques, such as sleeve lobectomy, could achieve lower pneumonectomy rates without compromising oncological outcomes [28]. The decision to proceed with pneumonectomy should be carefully assessed, particularly in the context of neoadjuvant immunotherapy, where tumour response can enable lung-sparing techniques. Standardised reporting of surgical procedures, including pneumonectomy indications and intraoperative complexity scores, should be incorporated into routine practice and clinical trials to facilitate comparisons and quality assurance across centres. However, existing complexity scores lack prospective validation and the optimal scoring system remains undefined. Future studies should prioritise validation of standardised, reproducible complexity metrics before widespread implementation.

In the case study, SACT caused adhesions and inflammatory changes that increased operative complexity, as demonstrated by the conversion from VATS to thoracotomy and the high surgical complexity score. This highlights the importance of experienced thoracic surgical teams familiar with the challenges of operating after immunotherapy. For those unable to proceed to surgery, the optimal salvage radiotherapy approach either to initial or residual volumes, and the role of consolidation durvalumab after prior immunotherapy remain areas of active investigation.

3.4. Evolving role of radiotherapy

For patients unsuitable for surgery, the PACIFIC regimen remains the standard of care [5]. However, variation in durvalumab access (e.g., restriction to PD-L1 \geq 1%) and uncertainty around PORT continue to generate debate. PORT should be reserved for patients with microscopic (R1) bronchial resection margins or macroscopic (R2) residual disease, though its role in cases of extracapsular nodal extension and R1 vascular margins is less defined. Future research should prioritise biomarker-driven patient selection and the integration of modern radiotherapy techniques, using more conformal treatment volumes to minimise side-effects and maximise the therapeutic ratio for high-risk patients [6].

Unlike surgery, there are no validated or objective measures of radiotherapy fitness, highlighting an important gap in current practice. Accordingly, comprehensive fitness assessments should be routinely integrated into radiotherapy-based trials to better characterise patient populations and define parameters of radiotherapy suitability.

Other key priorities for the radiation/clinical oncology community include: 1) establishing management strategies for complex cases (e.g. ILD, large tumour volumes, or vascular invasion), 2) investigating novel dose-escalation, such as SABR boost to the primary tumour alongside conventional radiotherapy [62], 3) exploring innovative radiotherapy-drug combinations (as exemplified by the CONCORDE trial with DNA damage response inhibitors) [6] and 4) determining if radiotherapy de-escalation strategies such as clinical target volume (CTV)-free planning or lower doses to mediastinal lymph nodes can reduce side-effects without compromising efficacy (64).

This case also underscores the vital role of the MDT and highlights that coordinated multidisciplinary, evidence-based decision-making is a hallmark of modern oncology practice. The process begins with accurate staging and prehabilitation led by respiratory physicians, followed by careful surgical planning informed by evolving anatomical and functional data, and extends to the optimal integration of SACT and radiotherapy. As treatment options expand, the MDT must continue to evolve, incorporating access to high-risk MDTs capable of reassessing disease biology, patient fitness and treatment response as a dynamic, iterative process.

While limited by discussing a single case, this article reflects broader trends and challenges faced by clinicians managing patients with stage III NSCLC. New treatment approaches are improving cure rates but also introducing new uncertainties regarding operability, sequencing, and adverse events. As an MDT, we have identified future research and

healthcare priorities, including: 1) the development of predictive biomarkers to improve patient selection, 2) response-adapted and pragmatic trials to determine optimal treatment choice and duration, 3) the re-evaluation of indications for PORT in the immunotherapy era and 4) the need to ensure equitable access to high quality MDT care through national audit and standardisation.

Ultimately, the integration of systemic, surgical, and radiotherapy advances must be guided by robust evidence, sound clinical judgment, and patient-centred collaboration. The ability for the MDT to re-evaluate its processes and decision-making is essential to translate scientific progress into real-world benefit for patients with stage III NSCLC.

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CRedit authorship contribution statement

Ashley Horne: Writing – review & editing, Writing – original draft, Conceptualization. **Igor Gomez-Randulfe:** Writing – review & editing, Writing – original draft, Conceptualization. **Amy Ford:** Writing – review & editing, Writing – original draft. **Richard Milton:** Writing – review & editing, Writing – original draft. **Petra Jankowska:** Writing – review & editing, Writing – original draft. **Emma O’Dowd:** Writing – review & editing, Writing – original draft. **Alastair Greystoke:** Writing – review & editing, Writing – original draft. **Corinne Faivre-Finn:** Writing – review & editing, Writing – original draft.

Declaration of competing interest

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