A scoping review of lung cancer surgery with curative intent: workup, fitness assessment, clinical outcomes

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Lung cancer surgery with curative intent is mainly focused on minimally invasive techniques and relies on an efficient multidisciplinary team https://bit.ly/45EVfSW

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Abstract

Lung cancer surgery with curative intent has significantly developed over recent years, mainly focusing on minimally invasive approaches that do not compromise medical efficiency and ensure a decreased burden on the patient. It is directly linked with an efficient multidisciplinary team that will perform appropriate pre-operative assessment. Caution is required in complex patients with several comorbidities to ensure a meaningful and informed thoracic surgery referral leading to optimal patient outcomes.

Educational aim

To provide an overview of lung cancer surgery with curative intent, its pre-operative assessment and surgical approaches, for an audience of international healthcare professionals.

Introduction

Lung cancer is the predominant cause of cancer-related global mortality. It accounts for ∼15% of all new cancer diagnoses, and it is the second most common solid tumour after prostate cancer in men and breast cancer in women [1]. The mean age of lung cancer detection is 70 years old with men more likely to be affected, despite the rising incidence of lung cancer in women over recent years most probably due to an increased smoking habit. In addition to smoking, higher proportions of epidermal growth factor receptor (EGFR) mutations and oestrogen effects have made women more susceptible to lung cancer [1]. Nonsmall cell lung cancer (NSCLC) histology is the most frequently encountered lung malignancy, accounting for ∼85% of all cases. Surgery broadly remains the mainstay of treatment for early-stage disease at diagnosis, in patients with adequate baseline fitness [2].

Recently, the increasing use of ERAS (Enhanced Recovery After Surgery) protocols has improved the post-surgical outcome and quality of life in lung cancer patients. A recent systematic review and meta-analysis of randomised controlled trials showed that ERAS pathways in lung cancer surgery are correlated with lower incidence of complications and a shorter length of stay, eventually leading to a global cost saving [2, 3]. The authors of the ERAS guidelines highlighted the need to develop standardised, evidence-based guidelines for thoracic surgery to ensure all patients receive optimal treatment, thus avoiding any heterogeneity among the currently applied treatment protocols [3].

This review aims to provide a comprehensive summary of existing evidence and the main recommendations about pre- and post-operative care in lung cancer surgery with radical intent, focusing on workup, fitness evaluation and clinical outcomes.

Pre-operative workup

Prior to treatment, a multidisciplinary team (MDT) of specialists in the diagnosis and management of lung cancer, composed of thoracic surgeons, (interventional) pulmonologists, (interventional) radiologists, oncologists, nuclear medicine physicians, radiotherapists, pathologists and palliative care specialists, is required to determine the safest and most efficient route to tissue or to provide a consensus that histological confirmation is not feasible and to establish a clinical diagnosis of lung cancer where treatment is warranted [4]. A multidisciplinary approach is essential to provide the optimal treatment strategy ensuring improved clinical outcomes.

Imaging

In the realm of precision medicine, accurate pre-operative staging in patients with NSCLC is of paramount importance as it will lead to treatment options appropriate for the stage of the disease. It can also predict prognosis and treatment outcomes. The pre-operative diagnostic approach should be tailored according to a risk–benefit analysis, centre expertise and individual patient preferences. Ideally, centres with a dedicated MDT can provide an excellent forum of lung cancer specialists collaborating on key decision making and anticipated challenges, resulting in a more accurate pre-operative staging [5, 6]. Baseline noninvasive workup assessment should always include contrast-enhanced computed tomography (CT) of the chest, with detailed images of the liver and the adrenal glands. CT scans provide valuable information about the tumour size and extent with increased sensitivity (98–100%) and variable specificity (54–93%) [7]. Due to the accurate information, a chest CT scan needs to precede bronchoscopy, endobronchial ultrasound (EBUS) or mediastinoscopy to guide the appropriate route to tissue. CT should be followed by fluorodeoxyglucose (FDG) positron emission tomography–computed tomography (PET/CT) to facilitate accurate clinical staging (c-TNM). FDG-PET/CT is the single most sensitive noninvasive modality to detect locoregional lymph node involvement and metastatic disease with higher accuracy compared with CT alone. PET/CT has been reported to have 90% accuracy on mediastinal lymph node status and a sensitivity of 87–92% [8], thus orienting the physician on the need for further invasive investigation (*i.e.* EBUS, mediastinoscopy) for histological confirmation. In selected patients, combining PET/CT with EBUS–transbronchial needle aspiration can dramatically increase the diagnostic accuracy of mediastinal nodal staging.

A PET/CT scan provides valuable information for the presence of mediastinal or distal metastasis, and about the tumour's metabolic activity and differentiation between the tumour and other pathology. PET/CT sensitivity for detecting brain metastasis is limited; metastatic lesions in the brain can be disguised by increased FDG uptake of the brain as it consumes increased glucose quantities at its baseline. Therefore, current guidelines recommend head magnetic resonance imaging (MRI) with contrast to stage the patients' brain for stages IB–IIIA when they are candidates for treatment with curative intent. Pre-operative brain MRI is currently indicated as a favourable pre-operative assessment of brain metastasis in NSCLC only in patients with a high probability of extrathoracic disease spread, *i.e.* cStage II or greater, pure solid centrally located lesions, mediastinal lymph node involvement [9]. When MRI is unavailable, a brain CT with intravenous iodinated contrast is a valid alternative [4].

Pre-operative histology

An ongoing debate in lung cancer MDTs concerns the surgical resection of high-risk lung nodules without a preceding histological confirmation of malignancy.

In general, current guidelines favour a pre-operative biopsy in patients with a pulmonary nodule suspected for lung cancer to obtain pre-operative histology when technically feasible. In particular, when the risk of malignancy according to the Herder model after PET/CT is between 10% and 70% pre-operative biopsy is recommended [10].

With regards to peripheral lesions, CT-guided percutaneous biopsy could be considered for persistent or growing solid lesions larger than 8 mm or part-solid lesions larger than 15 mm. An absolute contraindication for the procedure is the presence of vascular lesions, while relative contraindications are coagulopathy, respiratory failure, a forced expiratory volume in 1 s (FEV_1) <35% predicted, severe emphysema, the presence of only one functional lung and uncooperative patients. In addition, guidelines suggest that if a part-solid lesion is strongly suspected for lung cancer, it is conceivable to perform surgery directly without pre-operative diagnosis [4, 11].

Bronchoscopy is another alternative to obtain a biopsy. However, its diagnostic yield in the evaluation of pulmonary nodules is usually low when there is no airway involvement, even if it can be increased with the use of fluoroscopy, EBUS or electromagnetic navigation [10].

EBUS or endoscopic ultrasound (EUS) is a valid and less invasive alternative to mediastinoscopy for mediastinal pre-operative staging, which is strongly recommended when mediastinal lymph nodes are enlarged at CT, or with increased FDG uptake at PET/CT, or when there is no suspicion of mediastinal involvement at pre-operative imaging but the tumour is bigger than 3 cm, is centrally located or there is evidence of cN1 disease [12]. Even though PET/CT is usually required prior to EBUS for mediastinal staging, evidence suggests that patients can be referred straight to EBUS after an initial chest CT and before PET/CT to reduce the time to treatment decision by providing both diagnosis and nodal stage at once with good clinical outcomes [13]. However, the current standard of care remains for PET/CT to precede EBUS.

Despite all these possible strategies for pre-operative staging, patients with a very high pre-test probability of stage IA lung cancer may not require a biopsy before surgery due to the increase in time to treatment, costs and procedural risk. Therefore, the most recent National Comprehensive Cancer Network guidelines suggest by-passing this procedure in this subgroup of selected patients [4]. In particular, when the nodule is characterised by large diameter, spiculated margins, absence of calcifications, increased FDG uptake or it has a part-solid aspect, surgical resection should be directly offered, possibly with intraoperative frozen section, in order to detect malignancy at an early stage and perform diagnosis and treatment with a single procedure without the added waiting time for a bronchoscopic or CT-guided biopsy and subsequent pathological confirmation that will not affect the decision to treat [14].

Fitness assessment

Pre-operative fitness assessment is pivotal in patients considered for lung cancer surgery. It is mainly based on the patient's general performance status, cardiological and pulmonary function parameters. Fitness assessment relies initially on the clinical evaluation of the referring healthcare professional [15].

Performance status

The Eastern Cooperative Oncology Group (ECOG) performance status is commonly used to assess the patient's overall health and ability to withstand surgery (table 1) [15]. Assessment can be made by trained healthcare professionals, including medical practitioners, nurses and physiotherapists.

Cardiological evaluation

Given the association between lung cancer and cardiovascular disease, cardiological evaluation is of paramount importance. ECG, echocardiography, and stress testing in high-risk patients assess cardiac function and fitness for surgery from a cardiological point of view.

All patients should initially be assessed with validated cardiological risk scores, such as the Revised Cardiac Risk Index (table 2). Patients with a poor functional status or history of cardiac disease should be submitted to noninvasive stress tests. If the results are consistent with the need for coronary intervention, lung surgery should be postponed for at least 6 weeks after the procedure. Furthermore, pre-operative

TABLE 1 Eastern Cooperative Oncology Group (ECOG) performance status

ECOG performance status	Grade
Fully active, no restrictions to carrying on any pre-disease activities	0
Restricted in physically strenuous activity, but ambulatory and able to carry out light or sedentary work (*e.g.* light housework, office work)	1
Up and about >50% of waking hours Unable to carry out any work activities, but ambulatory and capable of all selfcare	2
Confined to a bed or chair for >50% of waking hours Capable of only limited selfcare	3
Totally confined to a bed or chair Completely disabled and unable to carry on any selfcare	4
Deceased	5

Adapted from https://ecog-acrin.org/resources/ecog-performance-status/

TABLE 2 Detailed Revised Cardiac Risk Index (RCRI) breakdown and its clinical interpretation translating the index score into a specific risk of major cardiac event for each patient

Risk factor	Description	Points
History of ischaemic heart disease	History of myocardial infarction History of positive exercise test Current chest pain considered due to myocardial ischaemia Use of nitrate therapy or ECG with pathological Q waves	+1
History of congestive heart failure	Pulmonary oedema, bilateral rales or S3 gallop Paroxysmal nocturnal dyspnoea Chest radiograph showing pulmonary vascular redistribution	+1
Elevated-risk surgery	Intraperitoneal Intrathoracic Supra-inguinal vascular	+1
History of cerebrovascular disease	Prior transient ischaemic attack or stroke	+1
Pre-operative treatment with insulin		+1
Pre-operative creatinine >2 mg·dL^{-1}/ 176.8 µmol·L^{-1}		+1
Interpretation into practice		
RCRI score	**Risk of major cardiac event (95% CI)**	
0	3.9% (2.8–5.4%)	
1	6.0% (4.9–7.4%)	
2	10.1% (8.1–12.6%)	
⩾3	15% (11.1–20.0%)	

Adapted from [16].

echocardiography should be considered in cases suspected of left ventricular dysfunction, pulmonary hypertension or valvular diseases [17].

Pulmonary function tests

Pulmonary function tests are integral in determining a patient's lung function reserve. FEV_1 and diffusion capacity of the lung for carbon monoxide (D_{LCO}) are crucial parameters in the evaluation of a patient's ability to tolerate surgery. If they are both over 80% of the predictive value, resection up to pneumonectomy is feasible. If one of these values is <80% predicted, exercise tests (*i.e.* cardiopulmonary exercise testing (CPET)) with peak oxygen consumption (V'_{O_2}) evaluation are highly recommended. A peak V'_{O_2} value >75% of the predicted value or >20 mL·kg^{-1}·min^{-1} qualifies for up to pneumonectomy; a value <35% predicted or <10 mL·kg^{-1}·min^{-1} is related to high risk for any resection; for intermediate values, it is possible to predict post-operative lung function and assess the number of resected lung segments the patient could tolerate [17, 18]. The majority of patients undergoing lung cancer surgery have impaired lung function secondary to COPD; therefore, it is of vital importance for the surgeon to consider lung function in combination with optimal clinical outcome (table 3).

Although CPET is the gold standard test for exercise capacity measurement, it has limited availability, occasionally long waiting lists and it is resource intensive. In these cases, low-technology exercise tests (*e.g.* shuttle and 6-min walk tests, 30 s sit-to-stand test) may be used as an alternative to CPET [19].

Nutritional assessment

Malnutrition is common in cancer patients and can impact surgical outcomes. Current evidence strongly suggests that the pre-operative nutritional and immunological status not only impacts short-term post-operative complications but also significantly influences the long-term outcomes of cancer patients [20]. This association can be attributed to the link between systemic inflammation and nutritional impairment, characterised by increased catabolic process and energy consumption. Low levels of nutritional markers such as serum albumin, inhibited by systemic inflammation and cholesterol (an essential component of cellular membranes involved in cell homeostasis), can be indicative of poor prognosis. In the context of lung cancer, pre-operative nutritional scores like Prognostic Nutritional Index (PNI) and Controlling Nutritional Status (CONUT) score have emerged as independent prognostic factors [21]. Additionally, the albumin component of PNI indicates the nutritional status of cancer patients, with low levels associated

TABLE 3 Summary of cut-off values for pulmonary function tests that guide the thoracic surgeons' management plans for the extent of resection

Pulmonary function testing parameters	Cut-off values	Surgical management plan
Pre-operative FEV_1	>80% predicted	Candidate for lobectomy up to pneumonectomy
Pre-operative D_{LCO}	>80% predicted	Candidate for lobectomy up to pneumonectomy
Pre-operative FEV_1 and D_{LCO}	<80% predicted	Peak V'_{O_2} calculation
Peak V'_{O_2} value	>75% predicted or >20 $mL \cdot kg^{-1} \cdot min^{-1}$	Candidate for lobectomy up to pneumonectomy
Peak V'_{O_2} value	<35% or <10 $mL \cdot kg^{-1} \cdot min^{-1}$	High risk for any resection

FEV_1: forced expiratory volume in 1 s; D_{LCO}: diffusion capacity of the lung for carbon monoxide; V'_{O_2}: oxygen consumption.

with malnutrition and weight loss, ultimately contributing to poor overall survival and increased cancer-related mortality. The comprehensive understanding of these interconnections highlights the importance of PNI as a valuable prognostic marker in lung cancer and various other solid tumours.

In 2017, Galizia *et al*. [22] introduced the Naples Prognostic Score (NPS), a novel scoring system for colorectal cancer surgery patients, incorporating both inflammatory and nutritional biomarkers. This score incorporated pre-operative measures such as neutrophil-to-lymphocyte ratio, lymphocyte-to-monocyte ratio, serum albumin and total cholesterol, demonstrating a robust association with long-term survival. Elia *et al*. [23] recently investigated the same score with a retrospective score matching analysis of 260 patients undergoing surgery for NSCLC. The results showed a significant correlation between the NPS, overall survival (p=0.018) and cancer-related survival (p=0.007). Thus, highlighting the importance of pre-operative nutritional assessment for prediction of prognosis, further validated by the multivariate Cox regression analysis. In patients affected by NSCLC the nutritional index, calculated within the NPS proved to be a prognostic indicator for overall and cancer-related survival [23].

Surgical approaches

Lobectomy is still considered the standard of care for NSCLC. The introduction of video-assisted thoracic surgery (VATS) lobectomy led to the thoracoscopic approach to lung cancer. In this way, open surgical procedures requiring open thoracotomies (wider incisions) are avoided. Possible concerns about its oncological safety and adequacy have been clearly addressed and solved by the recently published VIOLET trial, which confirmed that the VATS approach is oncologically safe, showing no differences in both overall survival and disease-free survival in comparison with open procedures. The VIOLET trial also showed VATS performs better in terms of post-operative physical function and post-operative pain, without increasing post-operative complications [24].

Evidence is still lacking on whether a multiportal or uniportal approach is preferable, and it largely remains a surgeon's choice based on their own experience and expertise. A multiportal technique might bear greater post-operative pain due to the multiple sites of incision compared with the single one, but this is still a question of debate.

With the advent of robotic surgery, interest in robotic-assisted thoracic surgery (RATS) has been emerging. The ROMAN study, published in 2021, was the first international randomised controlled trial to compare the outcomes of RATS with those of VATS in early-stage lung cancer and although RATS was not superior to VATS, RATS allows for a more thorough lymph node dissection during surgery [25].

Recently, two multicentre randomised clinical trials, from Japan and the Alliance for Clinical Trials in Oncology Group in North America, showed that for early stage (T1a–b N0 M0, stage IA) NSCLC sublobar resection was noninferior to lobectomy for primary tumours measuring 2 cm or less in size [26–28]. These findings somehow change the consolidated "dogma" of better results after lobectomy for T1 N0 M0 NSCLC measuring up to 3 cm in size. Moreover, in a *post hoc* analysis by the Alliance trial there was no significant difference in the reported outcomes after segmentectomy *versus* wedge resection. Such results open a new scenario even though surgeons are now called to a more responsible approach in terms of selection of patients, negative resection margins, and precise nodal staging. In fact, the improvement of systemic therapy alternatives, *i.e.* immune checkpoint inhibitors (ICIs) and targeted therapies, requires a more extensive removal of N1 lymph nodes to warrant a proper adjuvant treatment.

The greater risk of local recurrence (micropapillary) or systemic progression (solid) after sublobar resection for some histological subtypes of adenocarcinoma should also be taken into consideration before planning the type of resection. However, it is now clear that the majority of published studies have shown that upfront videothoracoscopic parenchyma-sparing surgery, *i.e.* segmentectomy and wedge resections to diagnose/cure early-stage cancer, is a feasible strategy that has comparable results in terms of overall and disease-free survival *versus* standard lobectomy in selected patients with peripheral lesions [26–28]. Regardless of the type of surgical approach, all NSCLC cases with a tumour diameter ⩾4 cm and/or ⩾pN1 require programmed death-ligand 1 (PD-L1) testing and adenocarcinomas, in particular, require next-generation sequencing to inform the decision to treat [4].

Oligometastatic disease

The advances in systemic therapies, including targeted or immune therapy, have led to significant improvements in stage IV NSCLC survival. Even if systemic therapies are still the gold standard at this stage, surgery might be considered for patients with a limited burden of metastatic disease. There is no general consensus on the definition of oligometastatic disease. Nonetheless, the European Society of Radiotherapy and Oncology and American Society for Radiation Oncology recommended the use of this term when there are from one to five metastatic lesions and all the sites fall into surgical resectability. In these cases, the removal of both the primary tumour and the metastases, in selected patients after MDT discussion, might be related to improvements in overall survival, maintaining at the same time a low risk of post-operative mortality or morbidity thanks to the diffusion of mini-invasive approaches [29].

Non-intubated surgery

Current surgical strategies for radical lung cancer resection are increasingly based on minimally invasive surgery that include VATS anatomical or non-anatomical resections selectively performed through single, two or multiple ports, as well as robot-assisted surgical approaches. Recent technical advances are driving towards minimised surgical trauma by limiting the number and extension of the surgical accesses. In addition, it has been thought that by reducing the anaesthesia-related trauma as well optimised results can be achieved with minimised overall operative trauma. In this setting spontaneous ventilation (SV) anaesthesia protocols without tracheal intubation have been shown in initial series to reduce operative morbidity and hospital stay in patients with poor pulmonary function [30]. If compared with the pioneering strategies of the initial era, which entailed adoption of epidural catheter analgesia in fully awake patients, SV-VATS strategies continue to be refined to improve safety, reproducibility and patients' comfort in the operating room. Current anaesthesia protocols have entailed simple intercostal block analgesia with target control sedation under bi-spectral index monitoring, adoption of spontaneous ventilation with placement of a laryngeal mask without tracheal intubation, and even adjuvant negative-pressure ventilation to eliminate completely positive pressure ventilation and achieve full lung re-expansion at the end of the procedure [31].

Amongst the potential advantages of SV-VATS lung resection, a more rapid recovery to normal physiology with less impairment of immune system has been hypothesised. In this respect, following SV-VATS, total lymphocyte count and natural killer cells are better preserved than following intubated one-lung ventilation VATS. Non-intubated VATS surgery is associated with improved post-operative neurocognitive recovery, more stable intraoperative cerebral oxygenation, ameliorated perioperative inflammation and attenuated post-operative complication severity.

Long-term data comparing SV-VATS lung resection *versus* conventional VATS with intubation and one-lung ventilation are warranted to reinforce the encouraging early results published so far, although initial data have shown that SV-VATS lobectomy resulted in similar survival rates to those observed with intubated one-lung ventilation VATS [32].

No drain surgery

Thoracic drains have traditionally been placed in the thoracic cavity after surgical procedures in order to evacuate both fluid and air. However, they play a major role in increasing post-operative pain. Drain-related pain can increase post-operative complications, increasing sputum retention and limiting early mobilisation, rendering patients prone to respiratory infections and atelectasis. To improve post-operative outcomes, contribute to early recovery after thoracic surgery and shorten the length of stay, some groups have tried to overcome the need to place thoracic drains after surgery. While most studies in the literature refer to wedge resections, some authors have also implemented a drainless strategy in more complex procedures, such as lobectomy and segmentectomy for lung cancer. Nevertheless, these cases should always be carefully selected, and the absence of air leaks must be confirmed intraoperatively. Important criteria to take into account while selecting patients for drainless surgery are the absence of air leak during end-operative airtightness test, the absence of pleural adhesions, no history of previous thoracic surgery, and the absence of macroscopic emphysema or moderate-to-severe pulmonary obstructive or restrictive disease. Suture reinforcement and air sealants may also be used to improve sutures' airtightness, although there are no studies confirming its clinical efficacy [33].

The impact of neoadjuvant ICIs and targeted therapies in lung cancer surgery

Over the past few years there has been significant progress in the use of ICIs in the neoadjuvant setting with improved clinical outcomes [4]. Neoadjuvant targeted therapies and in particular EGFR-tyrosine kinase inhibitors (TKIs) are a novel area of interest which is currently studied in EGFR-mutated potentially resectable NSCLC and has yet to be adopted in daily clinical practice [34, 35]. Landmark trials have provided evidence regarding improved clinical outcomes with the use of ICIs in the neoadjuvant setting; however, there was no reference to the intraoperative surgical experience and the surgical outcome *per se* as both points were beyond the scope of those trials [36–38]. However, it has been reported that neoadjuvant ICIs seem to increase surgical complexity therefore leading to more invasive approaches. It has been shown that significant nodal response to neoadjuvant ICI therapy is linked with an increased possibility of more invasive and advanced surgical manoeuvres for the completion of vascular dissections due to a nodal sclerotic effect following induction treatment [39, 40]. In addition to the nodal sclerotic effect, surgeons raise concerns for nodal adherence and mediastinal fibrosis following neoadjuvant ICIs as well as increased frailty in the pulmonary artery, vein and trachea, which may further complicate surgical resection [40, 41].

Currently, there are no randomised controlled trials to support that these effects lead to an increased conversion rate to open thoracotomy, although it is of note that the majority of post-induction case series were initiated *via* open thoracotomies [39, 40].

Post-operative complications

Post-operative complications in thoracic surgery can range from 9% to 53.4%, although most of them are preventable [42]. The most important intra- and post-operative complications include bleeding, atelectasis, hospital-acquired infection and prolonged air leak (table 4). Early detection and appropriate intervention are critical for minimising adverse outcomes and reduce the length of hospital stay.

Bleeding is usually detected shortly after surgery either though clinical signs and haemoglobin drop, or profound blood in the chest drain, and it may be accompanied by haemodynamic instability. The rapid evolution to a haemothorax is associated with increased mortality (up to 17.8%) and usually occurs in 0.6–4.6% of cases [43]. Active bleeding requires immediate attention with intravenous blood and plasma administration as a bridge surgical exploration aimed at identifying the source of bleeding and treating it surgically.

Atelectasis and non-expansion of the operated lung can cause impairment in gas exchange and respiratory mechanics, and if it leads to lung collapse then this results in pneumonia and a prolonged hospital stay. Post-operative atelectasis is usually due to mucus plugging, lack of expectoration and reduced mobilisation after surgery. To avoid this, early mobilisation, respiratory physiotherapy, bronchoscopic removal of dense secretions, with a main emphasis in patients with COPD, good hydration and expectorants are measures that can prevent this adverse event. ERAS protocols are efficient in reducing post-operative atelectasis and

TABLE 4 The most important thoracic surgery complications and considerations on how to avoid them

Complications	Avoidance
Bleeding	Careful inspection of surgical field prior to closure by a minimum of two surgeons In the case of haemothorax, *i.v.* administration of plasma and tranexamic acid as a bridge to repeat surgery should this be required
Atelectasis	Early mobilisation Respiratory physiotherapy Expectorants ERAS approach
Hospital-acquired infections	Infection control measures implemented by all members of staff
Prolonged air leak	Use suction linked with the surgical chest drain, watchful waiting and prolong hospital stay

ERAS: Enhanced Recovery After Surgery.

subsequent pneumonia as their overall approach aims to minimise stress response, offer early mobilisation and reduce post-operative pulmonary complications with the view to improve patient outcomes [44].

Hospital-acquired infections are not specific to thoracic surgery as they can occur in the entire spectrum of hospital admissions, and they can prolong hospital stay and lead to adverse clinical outcomes. However, surgical site infections are more common in all surgical admissions, including thoracic surgery, and they can only be addressed by improved infection control and reduced hospital stay [45].

Prolonged air leak (*i.e.* >5 days after surgery) is the most common post-operative complication in patients undergoing lung cancer surgery and it has an overall incidence ranging from 5% to 25% [46]. Risk factors are related to the presence of emphysema, diabetes and long-term corticosteroids in combination with the extension of the surgical resection and the presence of pre-existing pleural adhesions [46]. Although one cannot prevent the pre-existing risk factors, the thoracic surgeon can reduce the risks related with the procedure *per se* with the conventional approach of reinforcing the staple line or even consider biological glues, although these have been debated in the literature. Prolonged air leak is usually managed with watchful waiting and suction application to the chest drain and subsequently a prolonged hospital stay [46].

Efficient lung cancer surgery relies on an efficient MDT

Thoracic surgery plays a pivotal role in the management of stage I and II lung cancer and it is a key player in the multimodality approach of stage III [4]. Its efficiency relies on the patients' fitness assessment, their accurate pre-operative staging, and the operating centre's expertise and resources [12, 15, 47]. Fitness assessment relies initially on the clinical evaluation of the referring respiratory physician, including performance status, comorbidities and lung function [15]. Continuing further, the diagnostic pathway leading to lung cancer surgery is a multidisciplinary activity involving radiologists, nuclear medicine specialists, bronchoscopists, lung function technicians, pathologists and surgeons (figure 1). To ensure an appropriate referral for surgical resection with radical treatment intent, the team must have expertise in the field, work seamlessly and meet certain standards [46, 47]. Despite the national shortages of dedicated chest radiologists, it is acknowledged that their special interest is important in meaningful radiology reporting that impacts on thoracic surgeons' views [48]. The bronchoscopist's learning curve and sensitivity impact on the accuracy of pre-operative staging, and they will affect the MDT discussion regarding the decision for surgical treatment [49]. Optimisation of EBUS samples processing and pathologists' expertise in reporting them also contributes to the decision to undergo surgical treatment of lung cancer [50].

In addition to pre-operative fitness assessment and accurate staging informing the surgical decision to treat with a radical intent, prognostic indicators of post-operative clinical outcomes seem to pave a promising

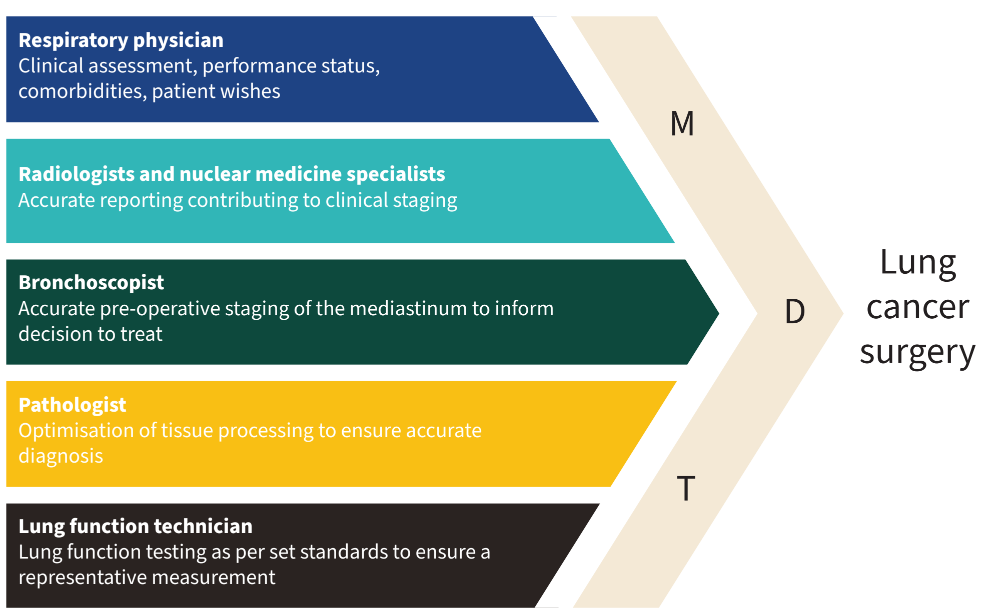

FIGURE 1 Key players contributing to an informed decision for lung cancer surgery.

way to identifying in advance the patients that will benefit the most from surgery. However, further clinical validation is required prior to implementation in daily clinical practice [14, 23].

Clinical outcomes in lung cancer surgery are closely associated with the centre's volume of cases and surgeon's experience. Patients undergoing lung cancer surgery in big centres present with a lower in-hospital mortality and higher 5-year survival [47]. Although the surgeon's volume has been associated with improved operative mortality in lobectomies, there has been a lack of a consistent agreement as there seems to be some evidence demonstrating that the volume does not associate with in-hospital mortality [51]. More recent evidence showed that low-volume thoracic surgeons present with higher in-hospital mortality compared with high-volume surgeons, with the caveat that most low-volume thoracic surgeons operate on black patients who have, by default, an independent risk factor for worse clinical outcomes [52]. This important observation adds an additional factor to consider when assessing clinical outcomes and deciding on centralisation of thoracic surgery services.

Conclusions

Lung cancer surgery with curative intent is an ever-evolving field that relies on an efficient MDT that will perform accurate staging. It will assess the patient's overall fitness including comorbidities and lung function to ensure an optimal surgical approach and clinical outcome. MDT input is essential as these patients frequently have significant comorbidities and complicated disease courses. Minimally invasive techniques have gained new ground as they do not compromise oncological efficacy and they have a significantly decreased burden on the patient.

Key points

- Lung cancer surgery with curative intent needs to involve an efficient and experienced multidisciplinary team.
- A thorough pre-operative staging in combination with pulmonary function and pre-operative assessment informs the surgeon's view on a tailored surgical management plan.
- Minimally invasive approaches are the mainstay of treatment.

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References

1 Thandra KC, Barsouk A, Saginala K, *et al.* Epidemiology of lung cancer. *Contemp Oncol (Pozn)* 2021; 25: 45–52.
2 Pu CY, Batarseh H, Zafron ML, *et al.* Effects of preoperative breathing exercise on postoperative outcomes for patients with lung cancer undergoing curative intent lung resection: a meta-analysis. *Arch Phys Med Rehabil* 2021; 102: 2416–2427.e4.
3 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.
4 National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Non-Small Cell Lung Cancer Version 5.2024 — April 23, 2024. Date last accessed: 5 June 2024. www.nccn.org/guidelines/category_1
5 de Castro G Jr, Souza FH, Lima J, *et al.* Does multidisciplinary team management improve clinical outcomes in NSCLC? A systematic review with meta-analysis. *JTO Clin Res Rep* 2023; 4: 100580.
6 Hardavella G, Frille A, Theochari C, *et al.* Multidisciplinary care models for patients with lung cancer. *Breathe* 2020; 16: 200076.
7 Stamatis G. Staging of lung cancer: the role of noninvasive, minimally invasive and invasive techniques. *Eur Respir J* 2015; 46: 521–531.
8 Al-Ibraheem A, Hirmas N, Fanti S, *et al.* Impact of 18F-FDG PET/CT, CT and EBUS/TBNA on preoperative mediastinal nodal staging of NSCLC. *BMC Med Imaging* 2021; 21: 49.
9 Bizzi A, Pascuzzo R. Is brain MRI unnecessary for early-stage non-small cell lung cancer? *Radiology* 2022; 303: 644–645.
10 Callister ME, Baldwin DR, Akram AR, *et al.* British Thoracic Society guidelines for the investigation and management of pulmonary nodules. *Thorax* 2015; 70: Suppl. 2, ii1–ii54.

11 Yoon SH, Lee SM, Park CH, *et al.* 2020 clinical practice guideline for percutaneous transthoracic needle biopsy of pulmonary lesions: a consensus statement and recommendations of the Korean Society of Thoracic Radiology. *Korean J Radiol* 2021; 22: 263–280.

12 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.

13 Navani N, Nankivell M, Lawrence DR, *et al.* Lung cancer diagnosis and staging with endobronchial ultrasound-guided transbronchial needle aspiration compared with conventional approaches: an open-label, pragmatic, randomised controlled trial. *Lancet Respir Med* 2015; 3: 282–289.

14 Elia S, Loprete S, De Stefano A, *et al.* Does aggressive management of solitary pulmonary nodules pay off? *Breathe* 2019; 15: 15–23.

15 Oken MM, Creech RH, Tormey DC, *et al.* Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982; 5: 649–655.

16 Duceppe E, Parlow J, MacDonald P, *et al.* Canadian Cardiovascular Society guidelines on perioperative cardiac risk assessment and management for patients who undergo noncardiac surgery. *Can J Cardiol* 2017; 33: 17–32.

17 Brunelli A, Charloux A, Bolliger CT, *et al.* ERS/ESTS clinical guidelines on fitness for radical therapy in lung cancer patients (surgery and chemo-radiotherapy). *Eur Respir J* 2009; 34: 17–41.

18 Hardavella G, Karampinis I, Styliara P, *et al.* Lung cancer surgery in patients with chronic obstructive pulmonary disease (COPD): surgical selection challenges and clinical outcomes. *Curr Respir Med Rev* 2019; 15: 140–146.

19 Butson G, Edbrooke L, Ismail H, *et al.* Exercise capacity prior to major cancer surgery: a cross-sectional observational study of the validity of the 6-minute walk and 30-second sit-to-stand tests. *Asia Pac J Clin Oncol* 2024; 20: 497–506.

20 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.

21 Yang Z, Zheng Y, Wu Z, *et al.* Association between pre-diagnostic serum albumin and cancer risk: results from a prospective population-based study. *Cancer Med* 2021; 10: 4054–4065.

22 Galizia G, Lieto E, Auricchio A, *et al.* Naples prognostic score, based on nutritional and inflammatory status, is an independent predictor of long-term outcome in patients undergoing surgery for colorectal cancer. *Dis Colon Rectum* 2017; 60: 1273–1284.

23 Elia S, Patirelis A, Hardavella G, *et al.* The Naples prognostic score is a useful tool to assess surgical treatment in non-small cell lung cancer. *Diagnostics (Basel)* 2023; 13: 3641.

24 Lim E, Batchelor TJP, Dunning J, *et al.* Video-assisted thoracoscopic or open lobectomy in early-stage lung cancer. *NEJM Evid* 2022; 1: EVIDoa2100016.

25 Veronesi G, Abbas AE, Muriana P, *et al.* Perioperative outcome of robotic approach *versus* manual videothoracoscopic major resection in patients affected by early lung cancer: results of a randomized multicentric study (ROMAN study). *Front Oncol* 2021; 11: 726408.

26 Altorki N, Wang X, Kozono D, *et al.* Lobar or sublobar resection for peripheral stage IA non-small-cell lung cancer. *N Engl J Med* 2023; 388: 489–498.

27 Hattori A, Suzuki K, Takamochi K, *et al.* Segmentectomy *versus* lobectomy in small-sized peripheral non-small-cell lung cancer with radiologically pure-solid appearance in Japan (JCOG0802/WJOG4607L): a *post-hoc* supplemental analysis of a multicentre, open-label, phase 3 trial. *Lancet Respir Med* 2024; 12: 105–116.

28 Saji H, Okada M, Tsuboi M, *et al.* Segmentectomy *versus* lobectomy in small-sized peripheral non-small-cell lung cancer (JCOG0802/WJOG4607L): a multicentre, open-label, phase 3, randomised, controlled, non-inferiority trial. *Lancet* 2022; 399: 1607–1617.

29 Antonoff MB, Deboever N, Werner R, *et al.* Surgery for oligometastatic non-small cell lung cancer. *J Thorac Cardiovasc Surg* 2024; 167: 508–516.e1.

30 Pompeo E, Rogliani P, Tacconi F, *et al.* Randomized comparison of awake nonresectional *versus* nonawake resectional lung volume reduction surgery. *J Thorac Cardiovasc Surg* 2012; 143: 47–54.

31 Taje R, Fabbi E, Sorge R, *et al.* Adjuvant transthoracic negative-pressure ventilation in nonintubated thoracoscopic surgery. *J Clin Med* 2023; 12: 4234.

32 Wang ML, How CH, Hung MH, *et al.* Long-term outcomes after nonintubated *versus* intubated thoracoscopic lobectomy for clinical stage I non-small cell lung cancer: a propensity-matched analysis. *J Formos Med Assoc* 2021; 120: 1949–1956.

33 Li R, Qiu J, Qu C, *et al.* Comparison of perioperative outcomes with or without routine chest tube drainage after video-assisted thoracoscopic pulmonary resection: a systematic review and meta-analysis. *Front Oncol* 2022; 12: 915020.

34 Liu W, Ren S, Xiao Y, *et al.* Neoadjuvant targeted therapy for resectable EGFR-mutant non-small cell lung cancer: current status and future considerations. *Front Pharmacol* 2022; 13: 1036334.

35 Grant C, Nagasaka M. Neoadjuvant EGFR-TKI therapy in non-small cell lung cancer. *Cancer Treat Rev* 2024; 126: 102724.

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

37 Provencio M, Nadal E, Insa A, *et al.* Neoadjuvant chemotherapy and nivolumab in resectable non-small-cell lung cancer (NADIM): an open-label, multicentre, single-arm, phase 2 trial. *Lancet Oncol* 2020; 21: 1413–1422.

38 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.

39 Feldman HA, Zhou N, Deboever N, *et al.* Intraoperative challenges after induction therapy for non-small cell lung cancer: effect of nodal disease on technical complexity. *JTCVS Open* 2022; 12: 372–384.

40 Gatteschi L, Iannopollo M, Gonfiotti A. Neoadjuvant immunotherapy in resectable non-small cell lung cancer. A narrative review. *Life (Basel)* 2021; 11: 1036.

41 Gao SJ, Corso CD, Wang EH, *et al.* Timing of surgery after neoadjuvant chemoradiation in locally advanced non-small cell lung cancer. *J Thorac Oncol* 2017; 12: 314–322.

42 Nilsson L, Risberg MB, Montgomery A, *et al.* Preventable adverse events in surgical care in Sweden: a nationwide review of patient notes. *Medicine (Baltimore)* 2016; 95: e3047.

43 Haager B, Passlick B, Schmid S. Postoperative Blutung nach thoraxchirurgischen Eingriffen [Postoperative haemothorax following thoracic surgery]. *Zentralbl Chir* 2019; 144: S20–S23.

44 Dinic VD, Stojanovic MD, Markovic D, *et al.* Enhanced recovery in thoracic surgery: a review. *Front Med (Lausanne)* 2018; 5: 14.

45 European Centre for Disease Prevention and Control. Healthcare-associated infections: surgical site infections – Annual Epidemiological Report for 2018–2020. Stockholm, ECDC, 2023. www.ecdc.europa.eu/en/publications-data/healthcare-associated-infections-surgical-site-annual-2018-2020

46 Aprile V, Bacchin D, Calabrò F, *et al.* Intraoperative prevention and conservative management of postoperative prolonged air leak after lung resection: a systematic review. *J Thorac Dis* 2023; 15: 878–892.

47 Al-Sahaf M, Lim E. The association between surgical volume, survival and quality of care. *J Thorac Dis* 2015; 7: Suppl. 2, S152–S155.

48 Rizzo S, Del Grande M, Espeli V, *et al.* Do oncologists prefer subspecialty radiology reports? A quality care study. *Insights Imaging* 2021; 12: 64.

49 Steinfort DP, Evison M, Witt A, *et al.* Proposed quality indicators and recommended standard reporting items in performance of EBUS bronchoscopy: an official World Association for Bronchology and Interventional Pulmonology Expert Panel consensus statement. *Respirology* 2023; 28: 722–743.

50 Bandiera A, Arrigoni G. The impact of pathological analysis on endobronchial ultrasound diagnostic accuracy. *Mediastinum* 2020; 4: 19.

51 Bach PB, Cramer LD, Schrag D, *et al.* The influence of hospital volume on survival after resection for lung cancer. *N Engl J Med* 2001; 345: 181–188.

52 Harrison S, Sun T, Kamel MK, *et al.* Do individual surgeon volumes affect outcomes in thoracic surgery? *Eur J Cardiothorac Surg* 2019; 56: 770–777.