Stage I and II nonsmall cell lung cancer treatment options

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Shareable abstract (@ERSpublications)
Chest radiography, CT scan and PET-CT are required for staging NSCLC. Stage IA tumours should be resected. Stereotactic body radiotherapy may be used if surgery is not possible. Stage IB to IIB disease require multimodality approaches. https://bit.ly/3RVbQMu

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Abstract

Chest radiography, computed tomography (CT) and positron emission tomography (PET)-CT are required for staging nonsmall cell lung cancers. Stage I cancers may be up to 4 cm in maximal diameter, with stage IA tumours being up to 3 cm and stage IB up to 4 cm. A lung cancer becomes stage II if the tumour is between 4 and ⩽5 cm (stage IIA), or it spreads to ipsilateral peribronchial or hilar lymph nodes (stage IIB). Stage IA tumours should be surgically resected, ideally using minimally invasive methods. Lobectomy is usually performed, although some studies have shown good outcomes for sublobar resections. If surgery is not possible, stereotactic body radiotherapy is a good alternative. This involves delivering a few high-dose radiation treatments at very high precision. For stage IB to IIB disease, combinations of surgery, chemotherapy or immunotherapy and radiotherapy are used. There is evidence that neoadjuvant treatment (immunotherapy with nivolumab and chemotherapy for stage IB and II) optimises outcomes. Adjuvant chemotherapy with a platinum-based doublet (typically cisplatin+vinorelbine) should be offered for resected stage IIB tumours and considered for resected IIA tumours. Adjuvant pembrolizumab is used for stage IB–IIIA following resection and adjuvant platinum-based chemotherapy. Osimertinib may be used for resected stage IB to IIIA cancers which have relevant mutations (epidermal growth factor receptor exon 19 deletions or exon 21 (L858R) substitution). There are no fixed guidelines for follow-up, but most centres recommend 6-monthly CT scanning for the first 2–3 years after definitive treatment, followed by annual scans.

Educational aims

- To understand the staging of nonsmall cell lung cancer (NSCLC).
- To learn about all the possible treatments for stage I and II NSCLC: surgery, radiotherapy and chemotherapy, including new types of drugs.
- To get an idea of suggested follow-up protocols.

Introduction

Lung cancer (LC) is the most common cause of death among all types of solid organ malignancies accounting for 18% of cancer-related deaths worldwide [1]. It is the leading cause of cancer death in men, and the second most common cause of cancer death after breast cancer in women, globally and in Europe. It is the leading cause of cancer death in women in the USA and UK. LC has one of the lowest 5-year survival rates due to late stage at the time of diagnosis, when the disease is less likely to be cured. In the USA, only 23% of LC cases are diagnosed at an early stage when the 5-year survival rate is higher (59%) and this has increased 33% over the past 5 years nationally following LC screening implementation and

improved participation rates among high-risk individuals [2]. The wider implementation of LC screening worldwide, either through national programmes or through pilot studies, is anticipated to further increase the early-stage diagnosis rates up to 70% similar to the results of landmark LC screening trials [3–8].

The mainstay of treatment for stage I and II LC is surgery with curative intent. Early-stage patients who are deemed inoperable or decline surgery can be offered definitive radiotherapy as an alternative. A multimodal approach, where required, including surgery, radiotherapy and medical treatment, may provide improved clinical outcomes for early-stage LC. Regardless of the treatment pathway, a multidisciplinary approach is required to ensure optimal treatment plans. This manuscript aims to highlight all treatment options available, to date, for stage I and II nonsmall cell lung cancer (NSCLC).

Definitions and staging

NSCLC is the most common type of LC, the main histological subtypes of which are adenocarcinoma, squamous cell carcinoma and large cell carcinoma. The TNM system of staging is used to describe LC: T for the extent of the tumour, N for lymph node involvement and M for distant metastases.

Stage I and II (as well as stage III) LC, by definition, will be M0. The eighth edition of the TNM staging divides stage I LC into stage IA and IB. Stage IA is now subdivided into stage IA1 (T1aN0M0 or T1(mi) N0M0), stage IA2 (T1bN0M0) and IA3 (T1cN0M0). Stage IB corresponds to T2aN0M0. T1(mi) is a new T category, which stands for "minimally invasive" [9, 10]. Stage II LC is subdivided into stage IIA (T2bN0M0) and IIB (T(1–2)N1M0 or T3N0M0).

The T staging of tumours is based on size, in 1 cm increments from T1a (⩽1 cm) to T2b (⩽5 cm). There is no longer the factor of the 2 cm distance from the carina as a limit to differentiate T2 and T3 tumours. However, a tumour should not extend proximal to the lobar bronchus and must be surrounded by lung or visceral pleura to be considered T1. If the tumour invades the visceral pleura, extends into the main bronchus or it causes distal atelectasis or post-obstructive pneumonitis, it is staged as T2. Another change compared with the seventh edition, is that N1 lymph node (*i.e.* ipsilateral hilar and peribronchial lymph node) involvement for T1 and T2a tumours is now categorised as stage IIB (previously stage IIA). T2b tumours without lymph node involvement are categorised as stage IIA.

Table 1 provides a summary of the eighth TNM edition for LC stages I and II.

Decision-making process and investigations required for localised treatments

To improve outcomes in patients with NSCLC, the decision-making process should be based on accessibility, quality and efficiency [11]. To receive optimal treatment, minimum quality standards must be met, such as the development and follow-up of clinical practice guidelines taking into account the biological heterogeneity of each individual and their preferences when deciding what treatment they will receive [12]. Both the European Society for Medical Oncology and the National Comprehensive Cancer Network in the USA include in their evidence-based clinical practice guidelines specific recommendations for pretreatment diagnostic evaluation in patients with stage I and II NSCLC [13–15]. Although patients with LC in clinical practice usually differ from those included in clinical trials, there are studies that suggest that non-adherence to clinical guidelines has a negative impact on pre- and post-treatment outcomes, mainly in older patients [16, 17].

TABLE 1 Summary of the tumour (T) and nodal (N) characteristics of stage I and II lung cancers

Tumour size	Invasion	T	Stage	
			No N1 nodes	N1 nodes involved
0– ⩽1 cm	None	1a	IA1	IIB
>1– ⩽2 cm	None	1b	IA2	IIB
>2– ⩽3 cm	None	1c	IA3	IIB
>3– ⩽4 cm	None	2a	IB	IIB
>4– ⩽5 cm	None	2b	IIA	IIB
⩽3 cm	Main bronchus or visceral pleura	2_{Centr} or $2_{Visc\ Pl}$	IB	IIB

Within the quality standards of LC diagnosis and treatment clinics, a decision-making process based on the consensus of a multidisciplinary team (MDT) is considered indispensable today [18]. An MDT consists of healthcare professionals from various specialties who convene at a designated time to collectively discuss and contribute to the diagnostic and treatment decisions concerning a specific patient [19]. There are heterogeneous results in the literature, but most studies concluded that MDT meetings significantly influence management plans, processes and patient outcomes, including survival from LC [20, 21]. A meta-analysis from De Castro *et al*. [22] showed that MDT LC discussion was associated with better quality of care outcomes and longer overall survival (OS).

The MDT meetings are particularly important in cases of early-stage LC where surgical resection is performed without prior histological confirmation. An experienced and focused MDT approach for indeterminate pulmonary nodules significantly reduces the number of benign resections [23]. MDT discussion can modify the clinical hypothesis in oncological thoracic surgery settings for one-in-ten cases [24].

Investigations required by stage

All patients with suspected stage I and II NSCLC require an initial evaluation that should include history and physical examination, assessing comorbidities and performance status; computed tomography (CT) of the chest and upper abdomen with contrast (including adrenals); a complete blood count with platelets, haemoglobin, electrolyte, liver function and calcium levels; and smoking cessation advice [15, 25].

The pretreatment evaluation in stage IA should include a [^{18}F]-2-fluoro-2-deoxy-D-glucose-positron emission tomography (FDG-PET)/CT scan, a pulmonary function test with diffusing capacity of the lungs for carbon monoxide (D_{LCO}), a preoperative bronchoscopy if necessary, and an optional mediastinal lymph node evaluation. In stage IB–II, the pathological mediastinal lymph node evaluation is mandatory, the patient should be evaluated for perioperative systemic therapy, and a brain MRI with contrast is recommended for stage II and optional for stage IB [15].

The pretreatment tissue procurement should be as minimally invasive as possible, including bronchoscopy, endobronchial ultrasound (EBUS)/endoscopic ultrasound (EUS), CT-guided biopsy or mediastinoscopy. The technique selected will depend on the experience of each centre and its diagnostic accuracy. A preoperative histological diagnosis is strongly recommended, except for cases with stage IA with a very high pre-test probability assessed by a multidisciplinary approach. If malignancy is not confirmed, an intraoperative biopsy will be necessary before the definitive resection is performed [14, 15].

Invasive mediastinal staging is recommended for centrally located lesions, tumours >3 cm, or abnormal mediastinal and/or hilar lymph nodes at CT and/or PET. Needle aspiration guided by EBUS and/or EUS is preferred and recommended over surgical staging. If there is a high clinical suspicion of nodal involvement and EBUS/EUS yields negative results, clinicians should indicate mediastinoscopy [13].

Surgical management of NSCLC

Patients with early-stage NSCLC are divided into two groups, each with unique clinical and research inquiries. For individuals in the very early stage of the disease (stage IA1–IA2), the focus revolves around determining and defining the optimal extent of resection and implementing minimally invasive methods without affecting oncological outcomes. Video-assisted thoracoscopic surgery (VATS) has now become the standard of care, rather than open surgery. Many centres are now developing robot-assisted thoracoscopic surgical techniques. For patients with stage IB–IIB disease, there is a significantly higher risk of recurrence. In this context, even though surgery remains pivotal in treatment, there is an emphasis on combining systemic therapy, radiation and surgery safely to achieve maximum benefit through multimodal approaches.

Lobectomy has been considered the most effective treatment for early-stage tumours since the Lung Cancer Study Group's publication in 1995, which compared lobectomy with limited resection for stage I NSCLC [26]. However, due to advancements in staging technology and improved understanding of disease biology and subtyping, there is renewed interest in sublobar resections because of increased accuracy and availability of imaging techniques like CT and FDG-PET scans [27].

Over the past 20 years, several extensive database studies, single-institution retrospective studies and meta-analyses have illustrated the similarity in cancer treatment outcomes between sublobar resection and lobectomy for stage IA NSCLC patients [28–30]. Studies have highlighted the significant role of tumour size, grade, and histological subclassification when making a choice between sublobar resection and lobectomy [31, 32]. However, conducting retrospective research in this area is associated with limitations

due to potential influences from patient comorbidities on the decision-making process regarding the procedure of choice. In addition, there is considerable heterogeneity regarding the surgical definitions and inclusion criteria in the literature. For example, sublobar resection may serve as an elective procedure for patients capable of undergoing lobectomy or as a compromise for those who cannot undergo lobectomy. The bias derives from the lack of pulmonary function data or information about surgical intent in many comprehensive databases. Additionally, categorising segmentectomy under sublobar resection further complicates analyses since it encompasses simple and complex segmentectomies.

Two randomised studies, JCOG0802/WJOG4607 and CALGB/Alliance trial 140503, have compared lobectomy with sublobar resection for stage IA NSCLC, and are expected to significantly influence surgical treatment for early-stage care in the future. Both trials mandated CT and FDG-PET for staging and set a limit on tumour size at <2 cm, which is smaller than the 3 cm boundary in the Lung Cancer Study Group trial.

The Japanese study, JCOG0802/WJOG4607, randomly allocated 1106 patients to either lobectomy or segmentectomy (wedge resections were not permitted) and found similar short-term surgical outcomes for both procedures in terms of procedural characteristics, perioperative morbidity and mortality [33, 34]. The primary end-point was the 5-year OS and was enhanced in the segmentectomy group (hazard ratio (HR) 0.66 (95% CI 0.47–0.92)), with a tendency towards improved survival observed across all subgroups analysed. In addition, the incidence of local recurrence was higher in the segmentectomy cohort (6.9% *versus* 3.1%), but most could be further managed. The trial suggests an overall health benefit from preserved lung tissue.

The CALGB/Alliance North American cooperative group conducted a trial where 697 patients were randomly assigned to either lobectomy or sublobar resection (either segmentectomy or wedge resection). The study found no significant differences in short-term perioperative morbidity or mortality between lobectomy and sublobar resection. Their primary focus was on disease-free survival, and after a median follow-up period of 7 years, they did not observe any difference (63.6% *versus* 64.1%; HR 1.01 (95% CI 0.83–1.24)) [35, 36]. In this study wedge resections accounted for nearly 60% of the sublobar resections.

One common characteristic of these two trials was their emphasis on thorough lymph node assessment when considering sublobar resection. The pathological nodal stage holds great significance as a prognostic factor in resectable NSCLC. Patients in both trials were registered prior to surgery, with random assignment taking place during the operation after confirming N0 status through frozen section evaluation of hilar and mediastinal lymph nodes. While this approach of evaluating lymph nodes *via* frozen section before conducting planned sublobar resections is not widely practised in clinical settings, it raises concerns about the validity of results if this step is not incorporated into routine operative care. Finally, the highly precise localisation of small nonpalpable lung nodules within the segmental boundaries of surgical resection represents a significant consideration, leading to the development of new localisation technologies and changing the paradigm of LC resections. These technologies range from preoperative three-dimensional imaging platforms [37], to intraoperative imaging adjuncts like thoracoscopic ultrasound, physical markers such as hook wires and microcoils, or parenchymal dyes/tattoos and molecular targeting agents that are systemically delivered and visualised with fluorescence imaging intraoperatively [38, 39].

Taking everything into consideration, early-stage NSCLC treatment is increasingly personalised, focusing on a customised resection approach. New evidence advocates for sublobar resection in carefully selected peripheral stage I tumours <2 cm, emphasising the crucial role of operative lymph node evaluation and tumour localisation.

Radiation therapy for stage I and II NSCLC

As patients with LC are often elderly and may have comorbidities, a surgical approach is not always feasible. In cases where patients are deemed inoperable, or for those who decline surgery, stereotactic body radiotherapy (SBRT), also known as stereotactic ablative radiotherapy (SABR), is an effective alternative therapy with a curative aim [40]. When discussing treatment options, particularly the choice between surgery and radiation therapy, it is crucial to understand and communicate the fundamental differences in both the procedures and the potential side-effects associated with each treatment.

Treatment preparation and planning of radiation therapy

In modern radiotherapy, which relies on precise calculations, the development of a radiation treatment plan prior to therapy is essential. This involves performing a planning CT scan that serves as the reference

image for the radiation calculations. Ensuring accurate patient positioning and clear tumour depiction for the planning CT is vital. Another important factor that needs to be considered is the movement of the tumour while the patient is breathing. To address this, four-dimensional imaging techniques can be used to depict the position of the tumour in each phase of the breathing cycle [41].

During treatment planning, target volume as well as organs at risk and other critical structures are defined for the radiation plan. For early-stage LC, the targeted volume intended to receive a high dose of radiation is typically small, encompassing the tumour and a minimal safety margin around it. Nevertheless, creating a safe and viable radiation plan can be challenging, depending on the tumour's location and various patient-specific factors, such as prior treatments or existing lung and/or heart comorbidities.

A "stereotactic" (in comparison to non-stereotactic) radiotherapy typically involves delivering a few high-dose radiation treatments at very high precision. Commonly used treatment regimens usually comprise three to eight fractions (*e.g.* 3 × 13.5 Gy, 3 × 18 Gy, 5 × 11 Gy or 8 × 7.5 Gy) [42].

Possible complications and side-effects

Radiotherapy, especially to small volumes not adjacent to critical structures (oesophagus, central bronchi) is rarely associated with significant side-effects, although fatigue may sometimes be observed. More severe side-effects of SBRT are generally rare and dependent on the location of the tumour, they may include acute oesophagitis or late-onset (and potentially permanent) side-effects such as chest wall pain, rib fracture or brachial plexopathy [43].

Another rare, yet serious, side-effect is the development of a radiation pneumonitis, which can cause symptoms such as cough, dyspnoea, fever and pleuritic pain and may require corticosteroid therapy. The risk is also related to the volume of lungs being irradiated [44].

Special situations: central tumour lesions, stage II N1

While SBRT is a highly effective treatment option for many patients, there are also situations where its application can be challenging. For tumours located near the central bronchial tree, major blood vessels, the heart or the oesophagus there may be an increased risk of side-effects, including life-threatening complications like haemorrhage, fistulas or bronchial strictures [45].

Furthermore, in specific scenarios involving early-stage NSCLC with N1 lymph node involvement, the use of SBRT may not always be the most suitable approach. Instead, treatment with more fractions or even a combination of radiation and chemotherapy, similar to treatments used in more advanced stage NSCLC, might be considered.

Generally, the risk of treatment-related side-effects increases with the size of the target volume and the proximity of critical structures. Therefore, certain situations in early-stage LC require careful consideration, to balance treatment efficacy with potential adverse effects. When SBRT is performed with precision and safety, severe side-effects are rare in modern radiotherapy. Furthermore, SBRT may even be applied multiple times in cases of tumour recurrence or the emergence of a second lung tumour malignancy [46].

Comparison of surgery and SBRT

Direct comparisons between surgery and SBRT in stage I NSCLC were undertaken in the STARS trial [47] and in the ROSEL trial [48]. Unfortunately, both trials were prematurely terminated due to insufficient patient enrolment. In a pooled analysis of both trials, the estimated rates of OS at 3 years were 86% for SBRT and 80% for surgery [49]. In the revised STARS trial, which was a single-arm trial comparing operable stage I NSCLC patients treated with SBRT to a surgical cohort in a propensity matched analysis, non-inferiority regarding 3-year OS at 91% was reported [50]. In another propensity matched comparative analysis from 2019, 792 patients aged >65 years with stage I NSCLC underwent VATS lobectomy or SBRT with a benefit on OS shown for the VATS lobectomy group [51]. Despite interesting results, retrospective analyses cannot replace randomised controlled trials. Overall, there is limited reliable data comparing the oncological outcomes of SBRT to surgery.

Currently, surgery is recommended as the standard treatment for medically operable patients, as per international guidelines. Beyond outcome, surgery allows for the histological examination of the tumour, which may be helpful in situations where no histology could be obtained with the primary diagnostics.

TABLE 2 European Society of Medical Oncology (ESMO) updated recommendations in early-stage lung cancers including the level and grade of recommendation

Treatment	Recommendation	Level/grade
Adjuvant chemotherapy	Adjuvant chemotherapy should be offered to patients with resected stage IIB–III NSCLC (TNM eighth edition)	I, A
	Adjuvant chemotherapy should be considered in patients with stage IIA resected primary tumour >4 cm (TNM eighth edition)	II, B
	If adjuvant chemotherapy is used, a cisplatin-based doublet is preferred (trials targeted a cumulative dose of up to 300 mg·m^{-2})	I, A
	When cisplatin is not feasible, carboplatin is an accepted alternative	IV, B
	Although cisplatin–vinorelbine is the most common regimen studied, other cisplatin-based combinations can be used (with gemcitabine, docetaxel, pemetrexed)	II, B
	Carboplatin–paclitaxel combination is a potential option for T2bN0, stage IIA resected primary tumour >4 cm	IV, B
Adjuvant osimertinib	Adjuvant osimertinib is indicated in patients with completely resected stage IB–IIIA NSCLC who harbour EGFR exon 19 deletion or exon 21 (L858R) substitution mutations	I, A

ESMO levels of evidence: I (at least one randomised controlled trial of good methodological quality or meta-analyses of well-conducted randomised trials without heterogeneity); II (small randomised trials or large randomised trials with a suspicion of bias or meta-analyses of such trials with demonstrated heterogeneity); III (prospective cohort studies); IV (retrospective cohort studies or case–control studies); and V (studies without control group, case reports, expert opinions). ESMO grades of recommendation: A (strong evidence for efficacy with substantial clinical benefit, strongly recommended); B (strong or moderate evidence for efficacy with limited clinical benefit, generally recommended); C (insufficient evidence for efficacy or benefit does not outweigh the risk of disadvantages, optional); D (moderate evidence against efficacy, generally not recommended); and E (strong evidence against efficacy or for adverse outcome, never recommended). NSCLC: nonsmall cell lung cancer; TNM: tumour, node, metastasis; EGFR: epidermal growth factor receptor. Information from [14].

The treatment processes of surgery and SBRT are very different. Surgery requires hospitalisation and anaesthesia, whereas SBRT involves several outpatient visits, typically spanning 1–2 weeks. While surgery remains the preferred treatment for early-stage LC, SBRT stands as a viable alternative for patients who are either inoperable or choose not to undergo surgery [52].

Systemic therapy

Patients with early-stage resectable NSCLC have high rates of recurrence and mortality depending on the stage at diagnosis. In a prospective study of 1640 consecutive patients with resected stage I–IIIA NSCLC, recurrence rates were 20% in stage I–II and 52% in stage IIIA disease. Distant recurrence was more common than local or regional recurrence, suggesting early seeding of micrometastatic disease during the perioperative stage of surgery [53, 54]. Despite radical curative surgery, early recurrence and cancer-related deaths remain high in this cohort. Therefore, the availability of effective neoadjuvant and adjuvant therapies remains an area of unmet need. In this section, we will discuss the approved and upcoming systemic therapies for stage I–II resectable NSCLC (tables 2 and 3) [14, 56, 57].

There are different advantages and disadvantages to neoadjuvant (preoperative) compared with adjuvant (post-operative) treatment [58]. One of the main advantages of neoadjuvant treatment is elimination of micrometastatic disease, downstaging the primary lesion, improving complete resection rates, and testing treatment sensitivity *in vivo*. However, the main concern with neoadjuvant treatment is the development of

TABLE 3 European Medicines Agency (EMA) extended indications for immune checkpoint inhibitors and targeted therapies in early-stage lung cancers

Treatment	Recommendation
Neoadjuvant nivolumab with chemotherapy	Indicated for the neoadjuvant treatment of resectable stage IB–IIIA NSCLC (TNM seventh edition) with PD-L1 ⩾1%
Adjuvant pembrolizumab monotherapy	Indicated for the adjuvant treatment of stage IB–IIIA NSCLC (TNM seventh edition) following complete resection and adjuvant platinum-based chemotherapy
Adjuvant osimertinib	Indicated for the adjuvant treatment of stage IB to IIIA NSCLC (TNM seventh edition) following complete resection where tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations

NSCLC: nonsmall cell lung cancer; TNM: tumour, node, metastasis; PD-L1: programmed death ligand 1; EGFR: epidermal growth factor receptor. Information from [55–57].

severe toxicities that would delay or preclude patients from receiving curative surgery. Preoperative treatment may also impact the surgical field, making it more technically difficult for complete and safe tumour resection. With adjuvant treatment, all patients would have already received curative surgery. The primary purpose would therefore be to eliminate residual micrometastatic disease. While this formed the basis of neoadjuvant/adjuvant chemotherapy, the availability of novel targeted agents and immunotherapy requires a new approach to clinical trial designs. With immunotherapy, there may be a greater rationale for neoadjuvant immunotherapy due to the reactivation of already primed tumour-infiltrating lymphocytes within the primary tumour [59]. Adjuvant immunotherapy may have the advantage of overcoming the post-operative immunosuppressive environment and activating T-cells to target residual micrometastatic disease [60].

In the pre-immunotherapy era, adjuvant/neoadjuvant platinum-based chemotherapy doublet was the standard of care in resectable NSCLC. The LACE meta-analysis demonstrated a 5-year absolute OS and disease-free survival (DFS) benefit of ∼5% with adjuvant cisplatin-based chemotherapy compared with placebo with hazard ratios of 0.89 (95% CI 0.82–0.96; p=0.005) and 0.84 (95% CI 0.78–0.91; p<0.001), respectively. No benefit was observed in stage IA and IB disease [61]. In the CALGB-9633 trial, 344 patients with resected stage IB (pT2N0M0) received either carboplatin–paclitaxel or observation. Although the OS was not significantly different, subgroup analysis of tumours >4 cm demonstrated a significant improvement in OS and DFS [62]. Following CALGB-9633 and other smaller studies, adjuvant chemotherapy may be considered in patients with stage IB disease. However, this was based on the seventh edition of the TNM staging and tumours >4 cm are now reclassified as T2b (equivalent to stage IIA in T2bN0M0 disease). When considering adjuvant chemotherapy in resected NSCLC, it is also important to recognise that chemotherapy-associated mortality in these trials was ∼1–2% [63, 64].

Although neoadjuvant chemotherapy is offered in resectable NSCLC, its evidence is less robust. Most trials in this setting are relatively small and use a range of different chemotherapy regimens. The NSCLC meta-analysis collaborative group conducted a meta-analysis of 15 randomised trials totalling 2385 patients (10 neoadjuvant trials, five perioperative trials). The absolute 5-year OS and recurrence-free survival benefits were 5% and 6%, respectively [65]. In an indirect comparison of 32 trials involving neoadjuvant *versus* adjuvant chemotherapy, there was no significant difference in OS between the two options (HR 0.99 (95% CI 0.81–1.21); p=0.91) [66].

In the era of precision medicine, the success of immune checkpoint inhibitors (ICI) and targeted therapies have changed the way we approach early-stage LC. While several phase 3 trials have met their primary end-points, it is important to acknowledge that this area is evolving very quickly with ongoing updates in survival outcomes as the data matures. We have summarised the major trials in the following paragraphs, with the most up-to-date survival data at the time of writing this review (table 4).

In CheckMate-816, the addition of neoadjuvant nivolumab (anti-programmed cell death protein 1 (anti-PD-1)) to chemotherapy extended median event-free survival (EFS) from 18.4 months (95% CI 14.0–26.7) to 43.8 months (95% CI 30.6–not reached (NR)) (HR 0.66; p=0.005) in patients with resectable stage IB (⩾4 cm)–IIIA NSCLC [67]. Median OS from the 4-year survival update also showed a trend towards improvement but did not reach the significance boundary at interim analysis. Further exploratory analysis demonstrated that survival benefit is greatest in the programmed death ligand 1 (PD-L1) ⩾1% group, stage III NSCLC, and non-squamous histologies [68]. The CheckMate-816 protocol is the first neoadjuvant chemoimmunotherapy approved for early-stage NSCLC and has the longest follow-up in the neoadjuvant/perioperative setting.

Recently, there have been several phase 3 ICI/chemotherapy trials in the perioperative setting. In KEYNOTE-671, the addition of perioperative pembrolizumab (anti-PD-1) with neoadjuvant chemotherapy was the first trial to report any OS benefit [75]. The KEYNOTE-671 protocol, using four cycles of neoadjuvant pembrolizumab with chemotherapy followed by up to 1 year of adjuvant pembrolizumab, extended the median OS from 52.4 months (95% CI 45.7–NR) to NR (95% CI NR–NR) (HR 0.72; p=0.02) [70]. Other perioperative ICI trials (AEGEAN, CheckMate-77T, RATIONALE-315, Neotorch) demonstrated EFS benefits with combination anti-PD-(L)1 therapies with chemotherapy [71, 75–77]. All ICI arms had an adjuvant treatment phase of up to 1-year post-operation and used primarily neoadjuvant platinum-chemotherapy doublet as its comparator. In all four trials, the ICI arm had improved pathological complete response (pCR) and major pathological response, which correlated with EFS.

In the adjuvant ICI trials in stage IB–IIIA resected NSCLC, both IMpower-010 and KEYNOTE-091/PEARLS demonstrated improved median DFS with ICI [73, 78].

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TABLE 4 Summary of major phase 3 trials of neoadjuvant, perioperative and adjuvant chemoimmunotherapy trials

Study	ICI agent (+ chemotherapy)	Cycles	Subjects (n)	Stage	Stage (%)	Surgery (%)	Median follow-up (months)	OS (months)	EFS (months)	pCR (%)
Neoadjuvant chemoimmunotherapy										
CheckMate-816 [67]	Nivolumab	3	358	IB (⩾4 cm)–IIIA (AJCC 7)	IB/II=36.3% IIIA=63.1%	83.2	57.6	NR *versus* NR (HR 0.71)[#]	43.8 *versus* 18.4 months (HR 0.66) IB–II (HR 0.87)[#] [68]	24 *versus* 2.2 IB–II (21.4) [68]
Perioperative chemoimmunotherapy										
CheckMate-77T [69]	Nivolumab	4 (+13)	461	IIA–IIIB (AJCC 8)	II=35.4% IIIA/B=63.8%	77.7	25.4	NA	NR *versus* 18.4 (HR 0.58) II (HR 0.81)[#]	25.3 *versus* 4.7 II (25.9)
KEYNOTE-671 [70]	Pembrolizumab	4 (+13)	797	II–IIIB (AJCC 8)	II=29.7% IIIA/B=70.3%	82.1	25.2	NR *versus* 52.4 (HR 0.72) II (HR 0.67)[#]	47.2 *versus* 18.3 (HR 0.59) II (HR 0.59)	18.1 *versus* 4.0
AEGEAN [71]	Durvalumab	4 (+12)	740	II–IIIB (AJCC 8)	II=28.4% IIIA/B=81.3%	77.6	11.7	NA	NR *versus* 25.9 (HR 0.68) II (HR 0.76)[#]	17.2 *versus* 4.3 II (16.6)
Adjuvant chemoimmunotherapy										
IMpower-010 [72]	Atezolizumab	16	1005	IB (⩾4 cm)–IIIA (AJCC 7)	II=55.0% IIIA=39.6%	100	65.0	NR *versus* NR (HR 0.97)	65.6 *versus* 47.8 (HR 0.85)[#]	
KEYNOTE-091/ PEARLS [73, 74]	Pembrolizumab	18	1177	IB (⩾4 cm)–IIIA (AJCC 7)	IB/II=60.3% IIIA=29.7%	100	51.7	NR *versus* NR (HR 0.87)[#]	53.8 *versus* 43.0 (HR 0.81) IB (HR 1.01)[#] II (HR 0.78)	

ICI: immune checkpoint inhibitor; OS: overall survival; EFS: event-free survival; pCR: pathological complete response; AJCC: American Joint Committee on Cancer; NR: not reached; NA: not available. [#]: not statistically significant.

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TABLE 5 Summary of surveillance recommendations by various scientific societies

Guidelines	Surveillance recommendations				Comments
ASCO 2019 [84]		Year 1–2		Year 3 onwards	No role for: CT abdomen and pelvis Circulating biomarkers Brain MRI
	Frequency: Every 6 months	Modality: Chest CT including adrenals with contrast	Frequency: Annually	Modality: LDCT without contrast	
NCCN 2023 [15]		Year 1–3		Year 4–5	Surveillance continues after 5 years with H&P and annual LDCT without contrast
First treatment surgery ±chemotherapy	Frequency: Every 6 months	Modality: H&P, chest CT±contrast	Frequency: Annually	Modality: H&P and LDCT without contrast	
First treatment radiotherapy	Frequency: Every 3–6 months	Modality: H&P, chest CT±contrast	Frequency: Every 6 months	Modality: H&P and chest CT±contrast	
ESMO 2021 [14]		Year 1–2		Year 3 onwards	Optional [^{18}F]2-fluoro-2-deoxy-D-glucose-PET at 12 and 24 months
	Frequency: Every 6 months At 12 and 24 months	Modality: H&P, contrast-enhanced volume chest CT Abdominal CT scan with contrast	Frequency: Annually	Modality: H&P, chest/upper abdominal CT scan	
NICE 2023 [85]		Year 1–2		Year 3 onwards	
	Frequency: Not stated	Modality: Not stated	Frequency: Not stated	Modality: Not stated	

ASCO: American Society of Clinical Oncology; NCCN: National Comprehensive Cancer Network; ESMO: European Society for Medical Oncology; NICE: National Institute for Health and Care Excellence; CT: computed tomography; LDCT: low-dose CT; MRI: magnetic resonance imaging; H&P: history and physical examination; PET: positron emission tomography.

The decision of which chemoimmunotherapy strategy to use in early-stage NSCLC is nuanced and will depend on several factors including treatment licensing, local protocols, tumour characteristics (*e.g.* PD-L1 %, stage, nodal status), fitness and patient choice. All patients considered for chemoimmunotherapy should have potentially resectable disease at the start. When interpreting the trial results, it is important to recognise that ∼80% of patients underwent surgical resection in the neoadjuvant/perioperative trials while all patients in the adjuvant trials had already their resection [68, 70, 71, 76, 77, 79]. Cross-trial comparisons should be avoided between neoadjuvant, perioperative and adjuvant trials due to patient and protocol differences. A recent meta-analysis suggested that a perioperative approach seems to be the most effective strategy and was the only one to demonstrate a survival benefit in an unselected cohort of early-stage NSCLC [80]. The addition of immunotherapy in the neoadjuvant or perioperative setting seems to have consistent benefits across all subgroups including stage IB–II and PD-L1 negative [81]. By contrast, adjuvant chemoimmunotherapy seems to mainly benefit the PD-L1 positive subgroups compared with chemotherapy alone [72, 73]. The question of whether 1 year of adjuvant immunotherapy is required in patients with a pCR remains unanswered. Once more data matures, we will likely have more information for determining which patients will benefit most from the neoadjuvant, perioperative and adjuvant strategies.

There have been two major practice-changing adjuvant targeted therapy trials: ADAURA and ALINA. In ADAURA, patients with resected non-squamous stage IB–IIIA NSCLC with the epidermal growth factor receptor (EGFR) mutations Ex19del or L858R were given osimertinib (a third-generation irreversible EGFR-tyrosine kinase inhibitor (TKI)) *versus* placebo for up to 3 years or until disease relapse. 5-year OS was 88% with osimertinib *versus* 78% with placebo (HR 0.40; p<0.001). Median DFS in the intention-to-treat (ITT) population was 65.8 months with osimertinib *versus* 28.1 months with placebo [82]. In ALINA, patients with resected stage IB–IIIA NSCLC with anaplastic lymphoma kinase (ALK) rearrangement were given alectinib (a second-generation ALK-TKI) for up to 2 years *versus* cisplatin-based doublet chemotherapy. At a median follow-up of 27.8 months, there was a significant benefit with adjuvant alectinib compared with chemotherapy in the ITT population: 3-year DFS was 88.3% with alectinib *versus* 53.3% with chemotherapy. Central nervous system DFS HR was 0.22 (95% CI 0.08–0.58). DFS benefit with alectinib was observed across all subgroups including stage IB and II [83].

The evolving landscape of systemic treatments in early-stage NSCLC is becoming more complicated and careful patient selection is vital. There remain uncertainties about whether patients with stage IB or some stage II patients require systemic therapy. Current investigations into prognostic biomarkers may help identify patients who can have treatment de-escalation. In addition, neoadjuvant or perioperative ICI/chemotherapy achieves a pCR of ∼20–25%, which suggests there may be some patients who can have treatment de-escalation as well. With so many ICI/chemotherapy trials, deciding which treatment regimen will become even more complicated and cross-trial comparisons must be done very cautiously, especially due to variations in systemic therapy regimens and heterogenous patient characteristics.

Follow-up protocols

Various surveillance protocols have been proposed following LC treatment [14, 15, 84, 85]. Table 5 summarises the frequencies and modalities of follow-up as per each guideline. There is a common preference for more frequent chest CT scans (6-monthly) in the first 2–3 years following treatment and this changes to annual surveillance thereafter as the risk of recurrence decreases significantly. There is no specific guidance regarding the timing to stop surveillance; however, the American Society of Clinical Oncology guidelines allude to patient fitness and comorbidities' assessments that may identify a non-reversible reason to stop surveillance.

Conclusion

The diagnosis of stage I and II LC has become more accurate and efficient by the development of investigation strategies including PET-CT, EBUS and improved pathological methodology. Surgical management has developed with the use of VATS and now robot-assisted procedures. Improved radiotherapy techniques such as SBRT now provide a truly viable alternative to surgery for patients who cannot have an operation or who choose not to. For stage IB and II disease, better multimodality protocols of care have been developed, and are being further refined. In many cases, neoadjuvant chemoimmunotherapy has been shown to improve outcomes with perioperative and adjuvant chemoimmunotherapy soon becoming alternative options. Adjuvant TKIs have also shown significant benefit in LCs with EGFR and ALK mutations. Although stage I and II LCs may be curable, there is still a risk of recurrence and follow-up is required. Further work continues in all these areas to further improve outcomes.

Self-evaluation questions

1. In the treatment of stage I and II NSCLC, when is SBRT considered a viable alternative to surgery?
   a) SBRT is preferred for all patients due to its higher efficacy.
   b) SBRT is used only when patients have comorbidities that make surgery risky.
   c) SBRT is considered for patients who are inoperable or refuse surgery.
   d) SBRT is a mandatory preliminary treatment before any surgical procedure.
   e) SBRT should only be used for recurrence after primary surgery.
2. In evaluating the effectiveness of SBRT compared with surgery in treating stage I NSCLC lung cancer, what critical information can be inferred from the outcomes of two randomised controlled trials, considering their premature termination?
   a) The definitive superiority of SBRT over surgery is established due to the higher survival rates observed in these trials.
   b) Despite the trials' early cessation, a pooled analysis indicates non-inferiority of SBRT to surgery in terms of 3-year OS.
   c) The trials conclusively prove that surgery is more effective than SBRT for stage I and II lung cancer.
   d) The trials' termination indicates the inherent risks of SBRT, making surgery the preferable option.
   e) We cannot yet draw any conclusions whatsoever from these trials.
3. Which subgroups of patients are least likely to benefit from neoadjuvant/adjuvant ICI/chemotherapy?
   a) Performance status 0–1
   b) Performance status 2
   c) Stage II
   d) PD-L1 $\geqslant$1%
   e) PD-L1 $\geqslant$50%
4. What is the proportion of patients who underwent curative surgery following neoadjuvant or perioperative ICI/chemotherapy?
   a) 60%
   b) 70%
   c) 80%
   d) 90%
   e) 100%
5. According to most follow-up protocols, what is the preferrable frequency and imaging modality for stage I and II NSCLC?
   a) Contrast-enhanced CT of head, chest, abdomen and pelvis every 6 months.
   b) Noncontrast chest of chest and abdomen every 6 months.
   c) Chest CT with/without contrast including adrenals every 6 months.
   d) LDCT every 3–6 months.
   e) FDG-PET annually.

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Suggested answers

1. c.
2. b.
3. b.
4. c.
5. c.