Guideline Resource Unit
guru@ahs.ca

Management of

Stage I, II, and Resectable Stage III NSCLC

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Background

Lung cancer is the overall leading cause of cancer mortality in Canadian men and women. By the end of 2024, almost 21,000 Canadian are expected to die of lung cancer.[1,2] In addition, more Canadian men and women will die from lung cancer as compared to prostate, breast, and colorectal cancers combined. In 2021, the latest year for which Alberta statistics are available, lung cancer was the leading cause of cancer death for both men and women.[3] Smoking remains the most important risk factor for lung cancer. [4]

Non-small cell lung cancer (NSCLC) accounts for 80% of all lung cancer cases and is categorized using the TNM staging system.[5] Approximately 30% of patients with newly diagnosed NSCLC will have stage IB to IIIA disease (by AJCC 7th edition).[6] Decisions regarding the treatment strategy should take into account the patient's age, performance status, comorbidities, prior therapy, and presence of actionable genomic alterations.[7]

Guideline Questions

- What are the diagnostic workup recommendations for patients with early stage non-small cell lung cancer (NSCLC)?
- What are the surgical recommendations for patients with early stage NSCLC?
- Is adjuvant or neoadjuvant treatment recommended in patients with early stage NSCLC?
- What are the follow-up and surveillance recommendations for patients with resected early stage NSCLC?

Search Strategy

The PubMed database was searched for relevant studies, guidelines and consensus documents published up to December 2024. The specific search strategy, search results, and evidence tables are available upon request. Online resources from oncology-based health organizations and guideline developers were also systematically searched, and relevant guidelines from the following organizations were considered in the development of our recommendations: American Society of Clinical Oncology (ASTRO),[8] European Society for Medical Oncology (ESMO),[9] American Society of Clinical Oncology (ASCO),[10] and the National Comprehensive Cancer Network (NCCN).[11]

Recommendations

DIAGNOSIS

Adequate staging is critical to determine therapeutic options for patients with NSCLC being treated with curative intent:

1. Initial stages I & II
   a. CT scan of the chest and FDG-PET is required. In some clinical scenarios, a PET scan may not be necessary.
   b. For stage II patients, mediastinal staging is required; endobronchial ultrasound is preferred over mediastinoscopy. Brain imaging should be considered.

2. Initial stage III [9,11]
   a. CT scan of the chest and FDG-PET is required.
   b. Routine imaging of the brain is required, with contrast enhanced MRI-brain or CT, depending on availability. MRI brain is preferred.
   c. Mediastinal staging is required after PET rules out distant metastases; (endobronchial ultrasound preferred over mediastinoscopy).

3. PD-L1 IHC expression alongside EGFR and ALK status is required to help individualize treatment decision making.

4. NSCLC-specific next generation sequencing (NGS) panel testing should be considered to help clarify likely benefit from neoadjuvant or adjuvant therapies.

MANAGEMENT OF STAGE I NSCLC

Surgery:

5. Surgical resection is recommended for patients with clinical stage I NSCLC and no medical contraindications to operative intervention.

6. All patients with stage I disease should be evaluated by a thoracic surgeon to determine whether they are an appropriate candidate for surgery.

7. Lobectomy is still considered the standard surgical treatment of tumours >2 cm in size that have a solid appearance on CT.

8. A sublobar resection is recommended over non-surgical interventions for patients with stage I NSCLC who cannot tolerate a lobectomy or anatomic pulmonary resection due to co-morbid disease or decreased pulmonary function. A sub-lobar resection for peripheral NSCLC ≤ 2cm should be considered. [12]

Adjuvant Chemotherapy:

9. Postoperative chemotherapy is not recommended for patients with completely resected stage IA NSCLC.

10. Postoperative adjuvant chemotherapy may be considered in select individuals with resected stage IB NSCLC with tumours >4 cm in diameter:
    - Cisplatin-based chemotherapy (i.e., cisplatin/vinorelbine for NSCLC or cisplatin/pemetrexed for adenocarcinomas) is the preferred treatment. A carboplatin-based chemotherapy regimen, such as carboplatin/paclitaxel, can be used as an alternative if there is a contraindication to cisplatin.
    - Chemotherapy should be administered within 12 weeks of surgical resection and ideally between 6 to 8 weeks.

11. Adjuvant osimertinib for 3 years should be considered after the completion of adjuvant platinum-based chemotherapy for patients with resected stage IB disease harbouring canonical sensitizing EGFR mutations (L858R or exon 19 deletion). Patients do not need to receive adjuvant chemotherapy to be eligible for adjuvant osimertinib.

Radiation Therapy:

12. Stereotactic body radiation therapy (SBRT), when available, is recommended for patients with node negative tumours ≤ 5 cm who are medically inoperable or who decline surgery. In certain cases, SBRT can be considered for tumours up to 7cm in size (stage II, node negative disease).

13. For peripheral tumours, the recommended dose is 48 Gy delivered in 4 fractions as per provincial practice in Alberta A number of other fractionation schedules can be considered based on radiation oncologist discretion (i.e. 54 Gy in 3 fractions or 50 Gy in 5 fractions).

14. For central tumours, the recommended dose is 60 Gy delivered in 10 fractions or less, although dosing for central tumours is evolving. Modification in dose fractionation may be required to ensure patient safety at the discretion of the Radiation Oncologist.

MANAGEMENT OF STAGE II NSCLC

Surgery:

15. Surgical resection is recommended for patients with clinical stage II NSCLC and no medical contraindications to operative intervention.

16. All patients with stage II disease should be evaluated by a thoracic surgeon and discussion at multidisciplinary tumour board rounds should be strongly considered.

Neoadjuvant or Adjuvant Chemotherapy:[13]

17. Patients with resectable stage II NSCLC not harbouring ALK/EGFR mutations should be considered for 3 cycles of neoadjuvant chemoimmunotherapy with platinum doublet with nivolumab immunotherapy followed by surgical resection. Other peri-operative chemoimmunotherapy regimens using durvalumab, nivolumab, or pembrolizumab are also options depending on regulatory approval and access.

18. For patients at high risk of recurrence, after surgical resection, that did not receive neoadjuvant chemoimmunotherapy, adjuvant chemotherapy regimens include up to 4 cycles of cisplatin (preferred) or carboplatin doublet chemotherapy.

19. Adjuvant osimertinib for 3 years should be considered after the completion of adjuvant platinum-based chemotherapy for patients with resected stage II disease harbouring canonical sensitizing EGFR mutations (L858R or exon 19 deletion). Patients do not need to receive adjuvant chemotherapy to be eligible for adjuvant osimertinib.

20. Patients with EGFR mutations or ALK re-arrangements should not receive neoadjuvant chemoimmunotherapy. These patients should receive upfront surgical resection followed by discussion regarding adjuvant systemic therapy. Select EGFR/ALK positive patients who are potentially resectable may be a candidate for neoadjuvant chemotherapy followed by surgical resection.

21. Adjuvant atezolizumab for up to 16 cycles or 1 year should be considered after the completion of adjuvant platinum-based chemotherapy in patients with PDL-1≥ 50% expression by the SP263 assay. These patients should not have EGFR mutations or ALK re-arrangements.

Radiation Therapy:

22. Radical radiation treatment is recommended if a patient refuses surgery in otherwise operable situations, or if the patient is medically unfit for thoracotomy. Concurrent chemotherapy can be considered for node positive disease based on extrapolation from clinical trials in stage III disease.

23. There is no significant role for stereotactic body radiation therapy in stage II, node positive NSCLC.

PERIOPERATIVE MANAGEMENT OF RESECTABLE STAGE III NSCLC

24. Patients should be seen by a thoracic surgeon to determine surgical resectability. Patients with resectable stage III disease should be presented at a Multidisciplinary Tumour Board for discussion between thoracic surgery, medical oncology, radiation oncology, radiology, pathology, nursing, palliative care and/or other disciplines as needed. [13]

25. Whenever possible, patients should be considered for enrollment into clinical trials.

Surgery:

26. Extended pulmonary resection may be performed in selected lesions. These include peripheral lesions invading the chest wall, apical lung carcinomas, central lesions with limited mediastinal invasion, or focal pericardial or phrenic nerve invasion. Carinal tumours and those within 2 cm of the carina occasionally may be amenable to resection with airway reconstruction. For multimodality therapy involving surgery, a thoracic surgeon needs to assess the patient for technical and medical operability.

Adjuvant Chemotherapy:

27. Patients with resectable stage III NSCLC not harbouring ALK/EGFR mutations should be considered for 3 cycles of neoadjuvant chemoimmunotherapy with platinum doublet and nivolumab immunotherapy followed by surgical resection. Other peri-operative chemoimmunotherapy regimens using durvalumab, nivolumab, or pembrolizumab are also options depending on regulatory approval and access.[13]

28. For patients at high risk of recurrence after resection that did not receive neoadjuvant chemoimmunotherapy, adjuvant chemotherapy regimens include up to 4 cycles of cisplatin (preferred) or carboplatin doublet chemotherapy.

29. Resectable stage III patients with EGFR mutations or ALK re-arrangements should not receive neoadjuvant chemoimmunotherapy. However, these patients may be a candidate for neoadjuvant chemotherapy followed by surgical resection.[13]

30. Adjuvant osimertinib for 3 years should be considered after the completion of adjuvant platinum-based chemotherapy for patients with resected stage IIIA disease harbouring canonical sensitizing EGFR mutations (L858R or exon 19 deletion). Patients do not need to receive adjuvant chemotherapy to be eligible for adjuvant osimertinib.

31. Adjuvant atezolizumab for up to 16 cycles or 1 year should be considered after the completion of surgical resection and adjuvant platinum-based chemotherapy in patients with PDL-1 ≥ 50% expression by the SP263 assay. These patients should not have EGFR mutations or ALK re-arrangements.

32. Patients with Pancoast tumors should be considered on a case-by-case basis based on the resectability of the lesion, the physiological reserve of the patient and the morbidity of various treatment modalities. Whilst the current standard of care includes chemoradiotherapy followed by surgical resection, neoadjuvant chemoimmunotherapy may be considered as an alternative option[13] [14]

Radiation Therapy:

33. Adjuvant radiotherapy after surgical resection is not routinely recommended. However, this treatment could be considered when there is microscopic involvement of the resection margin, including the bronchial resection margin.

FOLLOW-UP AND SURVEILLANCE

34. History, physical examination and CT Chest are suggested every 6 months during the first 2 years of surveillance, and then annually thereafter.[11]

35. Conventionally, patients are surveilled for 5 years.

Discussion

Adjuvant and Neoadjuvant Chemotherapy:

Based on recent randomized phase III trials, adjuvant chemotherapy has shown a significant survival benefit for stage II and IIIA NSCLC and is recommended for patients with a tumour size > 3-4 cm or with lymph node involvement. In an exploratory analysis from the CALGB 9633 trial,[15] which focused exclusively on patients with stage IB disease (T2N0), the investigators reported a statistically significant survival benefit in stage IB patients with tumours ≥ 4 cm in diameter who were treated with carboplatin plus paclitaxel compared to observation (HR 0.69; 90% CI 0.48-0.99, p=0.043). There was also a significant improvement in disease-free survival (DFS) in favour of the chemotherapy group (HR 0.69; 90% CI 0.49-0.97, p<0.035). Similarly, in an updated analysis of the JBR.10 trial, Butts *et al.* reported a non-significant trend in DSS in favour of adjuvant vinorelbine plus cisplatin chemotherapy for patients with completely resected stage IB tumours ≥ 4 cm in diameter (HR 0.66; 95% CI 0.39-1.14, p=0.13).[16]

Neoadjuvant therapy has been established as a standard of care in the treatment of stage IB to IIIA (by AJCC 7th) NSCLC. The Checkmate 816 trial reported an EFS improvement (median 31.6 months versus 20.8 months; HR 0.63, p=0.005) with nivolumab plus chemotherapy (chemoimmunotherapy) as compared to chemotherapy alone. The percentage of patients with a pathological complete response was also significantly increased (24.0% versus 2.2%) with chemoimmunotherapy compared to chemotherapy alone.[17]

The recent double-blind, phase III Keynote 671 trial evaluated the effect of pembrolizumab in patients with early-stage NSCLC. Patients with resectable stage II, IIIA, or IIIB (N2 stage) NSCLC were assigned in a 1:1 ratio to receive neoadjuvant pembrolizumab (N=397) or placebo (N=400) once every 3 weeks. One of the main outcomes was EFS at 24 months, which was 62.4% in the pembrolizumab group versus 40.6% in the placebo group (P<0.001). Major pathological responses were reported in 30.2% of patients in the pembrolizumab group versus 11.0% in the placebo group (P<0.0001). [18]

Tumours harboring canonical sensitizing EGFR (L858R/Exon19 deletion) mutations: The survival benefits associated with adjuvant osimertinib were confirmed by the phase III ADAURA trial.[19] In patients with stage IB to IIIA canonical sensitizing EGFR mutation–positive NSCLC, DFS was significantly longer among those who received osimertinib than among those who received placebo (89% versus 52%). This DFS benefit translated into a statistically significant and clinically meaningful improvement in OS at 5 years (88% versus 78%). The benefit of osimertinib was maintained irrespective of the receipt of post-operative adjuvant platinum-based chemotherapy.

Tumours that are PD-L1 positive (≥50% by SP263 assay): The IMpower010, open-label, phase III study investigated the expression of PD-L1 in the stage II–IIIA resected NSCLC patient population.[20] Atezolizumab improved DFS compared with placebo in patients in the stage II–IIIA population whose tumours expressed PD-L1 on 1% or more of tumour cells. All patients completed adjuvant platinum-based chemotherapy. The benefit in DFS was most pronounced in those expressing PD-L1 ≥ 50% staining (median DFS=not estimable atezolizumab versus 31.97 months best supportive care; HR 0.27, 95% CI 0.14-0.53). The subgroup analysis was not powered to show a trend for benefit in DFS in those with no smoking history, EGFR or ALK aberrations and those with PDL-1 <50% staining on tumours; OS data for this study remains immature.

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Development and Revision History

This guideline was reviewed and endorsed by the Alberta Provincial Lung Tumour Team. Members include medical oncologists, radiation oncologists, thoracic surgeons, radiologists, nurses, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Lung Tumour Team, external participants identified by the Working Group Lead, and a methodologist from the Guideline Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook.

This guideline was originally developed in 2025.

Levels of Evidence

I	Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, expert opinion

Strength of Recommendations

A	Strong evidence for efficacy with a substantial clinical benefit; strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit; generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.); optional
D	Moderate evidence against efficacy or for adverse outcome; generally not recommended
E	Strong evidence against efficacy or for adverse outcome; never recommended

Maintenance

A formal review of the guideline will be conducted in 2028. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

Abbreviations

AJCC, American Joint Committee on Cancer; ALK, anaplastic lymphoma kinase; CI, confidence interval; CT, computed tomography; DFS, disease-free survival; EGFR, epidermal growth factor receptor; FDG-PET, fluorodeoxyglucose positron emission tomography; HR, hazard ratio; IHC, immunohistochemistry; MRI, magnetic resonance imaging; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; OS, overall survival; PDL-1, programmed death ligand; TNM, tumour node metastasis

Disclaimer

The recommendations contained in this guideline are a consensus of the Alberta Provincial Lung Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

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Conflict of Interest Statements

Dr. Doreen Ezeife reports receiving honoraria from Pfizer, AstraZeneca, Bristol Myers Squibb, and Novartis, and is a member of the advisory board for Pfizer and Novartis.
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