

# NON-SMALL CELL LUNG CANCER STAGE II

Effective Date: July, 2014

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update in progress

The recommendations contained in this guideline are a consensus of the Alberta Provincial Thoracic Tumour Team 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.

## BACKGROUND

Lung cancer is the second most common cancer in both males and females in Canada. By the end of 2013, an estimated 25,500 new cases of lung cancer were diagnosed in Canada.<sup>1</sup> In addition, lung cancer is the leading cause of cancer death for both sexes; an estimated 20,200 Canadian men and women died from their disease in 2013.<sup>1</sup> While lung cancer death rates are decreasing among Canadian men, they continue to climb among Canadian women. Despite many research and clinical advances in lung cancer treatments, the age-standardized five-year survival rate for all types and stages of lung cancer combined is only 17 percent for Canada overall, and 14 percent for Alberta.<sup>2</sup> The economic impact of lung cancer care is equally as staggering: the mean cost associated with the care of each patient diagnosed with lung cancer in Alberta has been reported to be \$15,023 for non-small cell lung cancer, and \$18,243 for small cell lung cancer, not including end of life care.<sup>3</sup> Smoking remains the largest single risk factor for lung cancer, and is responsible for 90 percent of lung cancers in men and 80 percent of lung cancers in women in Canada. Exposure to specific industrial and atmospheric pollutants, including second-hand tobacco smoke, also increases an individual's risk of lung cancer.

## GUIDELINE QUESTIONS

- What are the diagnostic workup recommendations for patients with stage II non-small cell lung cancer?
- What are the surgical recommendations for patients with stage II non-small cell lung cancer?
- When is adjuvant treatment recommended in patients with stage II non-small cell lung cancer?
- What are the recommendations for medically inoperable patients with stage II non-small cell lung cancer?
- What are the follow-up and surveillance recommendations for patients with stage II non-small cell lung cancer?

## DEVELOPMENT AND REVISION HISTORY

This guideline was reviewed and endorsed by the Alberta Provincial Thoracic Tumour Team. Members of the Alberta Provincial Thoracic Tumour Team include medical oncologists, radiation oncologists, surgical oncologists, nurses, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Thoracic Tumour Team and a Knowledge Management Specialist from the Guideline Utilization Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the [Guideline Utilization Resource Unit Handbook](#).

This guideline was originally developed in July, 2008. This guideline was revised in September, 2009, June, 2011 and July, 2014.

## SEARCH STRATEGY

For this guideline update, two search strategies were used. The first was a general search using MEDLINE (1946 to January 30, 2014), EMBASE (1974 to January 30, 2014), PubMed (1975 to January 30, 2014), and the Cochrane Database of Systematic Reviews electronic databases; the references and bibliographies of articles identified through these searches were scanned for additional sources. The search terms were carcinoma, non small cell lung [MeSH] OR lung neoplasms [MeSH] AND stage II or

early stage [key term]. The search was limited to the following: clinical trial, all OR meta analysis OR randomized controlled trial OR systematic reviews. The working group excluded articles from the final review if they were not available through the library system.

The second strategy was more focused and used the MEDLINE (1946 to March 10, 2014), EMBASE (1974 to March 20, 2014), PubMed (1975 to March 20, 2014), and the Cochrane Database of Systematic Reviews electronic databases; the references and bibliographies of articles identified through these searches were scanned for additional sources. The search terms were SBRT OR stereotactic body radiation therapy OR SABR OR stereotactic ablative radiotherapy OR ablative radiotherapy [key terms] AND carcinoma, non small cell lung [MeSH] AND inoperable [key term]. The search was limited to the following: clinical trial, all OR meta analysis OR randomized controlled trial OR systematic reviews. The working group excluded articles from the final review if they were not available through the library system.

A search for new or updated practice guidelines published since June 2011 was also conducted.

The working group reviewed the currency and acceptability of all relevant literature and updated published guidelines for the treatment for stage II non-small cell lung cancer; we then circulated a draft of the updated guideline to the entire provincial tumour team for final feedback and approval.

## TARGET POPULATION

The recommendations in this guideline apply to adult patients over the age of 18 years.

## RECOMMENDATIONS

1. Surgical resection is the cornerstone of treatment and the best option for achieving cure in patients with clinically operable non-small cell lung cancer (NSCLC).
2. In circumstances where surgical resection may not be feasible, patients may be presented at a Multidisciplinary Tumour Board for further discussion between surgery, medical oncology, radiation oncology, nursing, palliative care and/or other disciplines as needed.
3. Whenever possible, patients should be considered for enrollment into clinical trials.

## Diagnosis and Clinical Staging

4. A PET-CT is recommended for all patients with suspected stage II NSCLC to rule out advanced disease.
5. A pulmonary function test is indicated for all surgical candidates.
6. Invasive staging for mediastinal lymph biopsy, via endobronchial ultrasound, mediastinoscopy, or VATS, is indicated for all patients with clinical stage T2Nx or TxN1/2 or greater disease to achieve pathological confirmation of true lymph node status. Please refer to the [Non-Small Cell Lung Cancer Staging](#) document for appropriate staging definitions.
7. Please also refer to the [AHS Lung Cancer Requirements for a Referral to a Cancer Centre](#) document for more information.

## **Surgery**

8. Systematic mediastinal lymph node sampling or dissection should be performed for accurate pathologic staging of patients undergoing resection for stage II NSCLC.
9. Surgical resection is recommended for patients with clinical stage II NSCLC and no medical contraindications to operative intervention.
10. All patients with stage II disease should be evaluated by a thoracic surgeon to determine whether they are an appropriate candidate for surgery.
11. A lobectomy or anatomic pulmonary resection is recommended over a sublobar resection for patients with stage II NSCLC who are medically fit for surgery.
12. A sublobar resection is recommended over non-surgical interventions for patients with stage II NSCLC who cannot tolerate a lobectomy or anatomic pulmonary resection due to co-morbid disease or decreased pulmonary function.
13. For patients with an anatomically appropriate (central) tumour, a sleeve lobectomy is the preferred treatment; a pneumonectomy is an acceptable alternative.
14. For medically operable patients with T3 NSCLC with chest wall involvement, complete resection of the tumour should be the aim by either extrapleural or en bloc chest wall resection.
15. Re-resection is recommended for patients with positive margins in resected stage II NSCLC; if re-resection is not possible, radiotherapy should be considered.
16. Patients who are inoperable or refuse surgery should be referred to a Radiation Oncologist for consideration of radiotherapy.

## **Adjuvant Chemotherapy**

17. Post-operative adjuvant platinum-based chemotherapy is recommended for patients with completely resected stage II NSCLC.
  - Cisplatin-based chemotherapy (ie. cisplatin/vinorelbine) 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 post-surgery.

## **Radiotherapy**

18. Radical radiation treatment is recommended if a patient refuses surgery in otherwise operable situations, or if the patient is medically unfit for thoracotomy.

## **Stereotactic Body Radiation Therapy**

19. There is no significant role for stereotactic body radiation therapy in stage II NSCLC.

## **Chemoradiation**

20. Concurrent chemoradiation may be considered for selected medically inoperable stage II NSCLC patients, especially if they are node positive, have a large tumour ( $\geq 5$  cm), and are reasonably fit.

## Follow-up and Surveillance

21. Follow-up for stage II NSCLC treated with curative intent therapy should involve one of the following protocols:
  - a. A physical examination and chest x-ray every 3 months for 2 years post-treatment, then every 6 months for the third year post-treatment, then annually up to the fifth year post-treatment; the frequency is dependent on risk factors for recurrence and may be more or less frequent.
  - b. A physical examination and high resolution CT scan every 6 months for the first 2 years and then a low-dose CT scan annually up to 5 years post-treatment; the frequency is dependent on risk factors for recurrence and may be more or less frequent.
22. Each follow-up visit should also include an assessment of the patient's smoking status, as well as counseling and referral to smoking cessation programs.

## DISCUSSION

### Diagnosis and Classification

A PET-CT is indicated for all patients with suspected stage II NSCLC. Surgical candidates should also receive a pulmonary function test to ensure adequate lung function for resection. NSCLC accounts for 80 percent of all lung cancer cases, and is categorized using the seventh edition TNM staging system.<sup>4</sup> In 2010, the Alberta Cancer Registry reported 261 patients with stage II NSCLC.<sup>5</sup> The stage definitions and groups for NSCLC are summarized in a supporting document ([Non-Small Cell Lung Cancer Staging](#)).

### Surgery

Systematic mediastinal lymph node sampling or dissection should be performed for accurate pathologic staging of patients undergoing resection for stage II NSCLC. In a pooled analysis of three studies comparing mediastinal lymph node dissection to systematic sampling, Manser and colleagues reported a significant reduction in the risk of death in patients with stages I to IIIA NSCLC undergoing dissection, with a pooled hazard ratio (HR) of 0.63 (95% CI 0.51-0.78;  $p < 0.0001$ ).<sup>6</sup> Similarly, in a case series involving 100 consecutive patients, Lardinois *et al.* reported that mediastinal lymph node dissection was associated with longer disease-free survival and better local tumour control rates compared to mediastinal lymph node sampling after complete resection for N0-1 disease, with no increase in morbidity.<sup>7</sup> In a prospective randomized trial completed by the American College of Surgery Oncology Group (ACOSOG Z0030 trial), the investigators also reported that morbidity is not increased with complete lymph node dissection, and recommended that the number of lymph nodes resected during mediastinal lymph node dissection be 12 or more, with nodes removed from stations 2R, 4R, 7, 8, 9 and 10R for right-sided cancers, and stations 4L, 5, 6, 7, 8, 9 and 10L for left-sided cancers.<sup>8,9</sup> Published data from the ACOSOG study showed little difference in median survival between patients in the mediastinal lymph node sampling group compared to the dissection group (8.1 years vs. 8.5 years,  $p = 0.25$ ).<sup>10</sup> Five-year disease-free survival rates were also similar (69% vs. 68%,  $p = 0.92$ ), and there were no differences in local, regional, or distant recurrences between the two groups.<sup>10</sup> The investigators concluded that, for patients undergoing resection for N0 or nonhilar N1, T1, or T2 NSCLC, and for whom systematic and thorough presection sampling of the mediastinal and hilar lymph nodes is negative, mediastinal lymph node dissection does not improve survival in patients with early stage disease.

Surgical resection is the treatment of choice for patients with early stage NSCLC, and offers the best potential for long-term survival and cure.<sup>11,12</sup> Five-year survival rates ranging from approximately 29 to 51 percent have been reported for patients with stage II disease who undergo surgical resection, with more favourable results for individuals with single node involvement and smaller (< 3 cm) lesions.<sup>13-15</sup> All patients with early stage disease should be evaluated by a thoracic surgeon to determine whether they are an appropriate candidate for surgery.<sup>11</sup>

A lobectomy, the surgical removal of a single lobe, is the optimal procedure for the management of early stage disease because it preserves pulmonary function.<sup>12</sup> Although conclusions about the efficacy of different surgical methods for patients with local or locoregional NSCLC are limited by both the small number of included participants in trials and methodological weaknesses of published trials, there is agreement among current published guidelines that a lobectomy is preferred over a sublobar resection for patients who are medically fit for surgery. This recommendation has been adopted from recommendations made by the American College of Chest Physicians (ACCP) and the National Comprehensive Cancer Network (NCCN).<sup>11,12</sup> A systematic review by the Cochrane Collaboration reported the results of 13 trials involving 2290 patients who underwent surgery for stages I to IIIA NSCLC.<sup>6</sup> A pooled analysis of three relevant trials included in this review showed that overall survival was superior in patients who underwent surgical resection (lobectomy or pneumonectomy) and complete mediastinal lymph node dissection compared with those who underwent surgical resection and lymph node sampling (hazard ratio (HR)=0.63; 95% CI 0.51-0.78,  $p < 0.0001$ ).<sup>6</sup>

The surgical procedure used will depend on the extent of the disease, location of the tumour, and cardiopulmonary reserve of the patient. Members of the Alberta Provincial Thoracic Tumour Team agree with recommendations from both the NCCN and ACCP stating that for patients with an anatomically appropriate tumour, a sleeve lobectomy is the preferred alternative to pneumonectomy, in order to conserve lung function.<sup>11,12</sup> In addition, for patients with T3 NSCLC with chest wall involvement, complete resection of the tumour should be the aim by either extrapleural or en bloc chest wall resection.

Several retrospective series and comprehensive reviews have concluded that video-assisted thoracic surgery (VATS) lobectomy for early stage NSCLC is safe, and is associated with fewer complications, less pain, and more rapid return of normal functioning when compared to open thoracotomy.<sup>16-18</sup> There are few randomized trials comparing the two procedures and, consequently, evidence for a survival difference is limited. Where facilities exist, video-assisted thoracic surgery (VATS), by experienced surgeons, or open thoracotomy are both appropriate resection techniques for either lobectomy or segmentectomy for patients with stage II NSCLC who are appropriate surgical candidates.

The members of the Alberta Provincial Thoracic Tumour Team recommend that patients with positive margins following resection of stage II disease should be considered for re-resection; for cases where additional surgery is not an option, tumour team members recommend radical radiotherapy.

### **Adjuvant Chemotherapy**

The results of several large randomized controlled trials have established a clear benefit for adjuvant chemotherapy following surgery in patients with stage II NSCLC. The JBR.10 trial, conducted by the National Cancer Institute of Canada Clinical Trials Group, reported the most striking survival benefit for their subset of 263 patients with stage II disease treated with chemotherapy compared to observation (80 months vs. 41 months; HR=0.59; 95% CI 0.42-0.85,  $p = 0.004$ ).<sup>19</sup> In an updated analysis from this trial,

Butts and colleagues reported that, at a median follow-up of 9.3 years, patients with stage II disease treated with chemotherapy versus observation continued to show a significant survival benefit (median survival=6.8 vs. 3.6 years; HR=0.68; 95% CI 0.50-0.92, p=0.01), corresponding to an absolute benefit of 20 percent at five years.<sup>20</sup> Similarly, the ANITA clinical trial reported five-year survival rates of 52 and 39 percent for patients with stage II disease treated with chemotherapy or observation, respectively (HR=0.71; 95% CI 0.49-1.03, p=0.07), corresponding to an absolute benefit of 13 percent at 5 years.<sup>21</sup> The survival benefits associated with adjuvant chemotherapy were further examined in a large review by the LACE Collaborative Group.<sup>22</sup> In this meta-analysis based on individual patient data, the investigators used pooled data from five clinical trials representing 4584 patients, 1616 of which had stage II disease.<sup>22</sup> With a median follow-up of 5.2 years, the HR for death was 0.83 (95% CI 0.73-0.95, p=.04), corresponding to an absolute survival benefit of 10 percent at five years.<sup>22</sup> Based on the results of these clinical trials and meta-analysis, the Alberta Provincial Thoracic Tumour Team members recommend the use of platinum-based chemotherapy regimens as post-operative adjuvant therapy in the management of patients with completely resected stage II NSCLC. Tumour team members currently view the combination of cisplatin and vinorelbine as standard, as was used in both the JBR.10, and ANITA studies.<sup>19,21</sup> The combination of carboplatin and paclitaxel, such as was used in the CALGB 9633 trial, is an acceptable alternative for individuals with a contraindication to cisplatin.<sup>23</sup> Chemotherapy should ideally start 6 to 8 weeks post-surgery, but certainly before 12 weeks.

### **Radiotherapy**

Patients with stage II NSCLC who are medically inoperable or who refuse surgery should be assessed for the appropriateness of radical radiotherapy. In one randomized trial of 169 patients with stages I and II disease, continuous hyperfractionated accelerated radiotherapy (CHART; 1.5 Gy three times daily/ 12 days) resulted in superior survival rates when compared to conventionally fractionated radiotherapy (60Gy/ 30 fractions over 6 weeks).<sup>24</sup> However, CHART is often not a feasible option, due to lack of equipment and manpower, as well as low patient compliance. In a systematic review of one randomized and 26 non-randomized studies, Rowell and colleagues concluded that when CHART is not available, patient with early stage NSCLC who are medically inoperable but suitable for radical radiotherapy should be offered conventional fractionated radiotherapy.<sup>25</sup> Techniques such as hypofractionated conformal 3D radiotherapy have also been associated with favourable overall survival rates, high rates of local control, and low toxicity in inoperable patients with early stage disease.

Patients with stage II NSCLC who are medically inoperable but not suitable for radical radiotherapy should be offered palliative radiation for symptom management, when appropriate.<sup>26</sup> Detailed recommendations can be found in the [Palliative Radiotherapy Clinical Practice Guideline](#).

### **Stereotactic Body Radiation Therapy**

There is no significant role for stereotactic body radiation therapy (SBRT) in stage II NSCLC. In very rare T3N0 cases, it may be appropriate to treat with SBRT if the patient is medically inoperable.

### **Chemoradiation**

The National Comprehensive Cancer Network recommends concurrent chemoradiation for inoperable, node positive stage II NSCLC patients.<sup>12</sup> A recent systematic review of over 3700 stage I to III NSCLC patients treated within a randomized controlled trial demonstrated a survival benefit for concurrent

chemoradiation.<sup>27</sup> However, the study authors did note that of the 25 trials included in the review, only four included patients with stage I and II disease; therefore, patient selection is an important consideration due to added toxicity. As such, the Alberta Provincial Thoracic Tumour Team recommends that concurrent chemoradiation may be considered for selected medically inoperable stage II NSCLC patients, especially if they are node positive, have a large tumour ( $\geq 5$  cm), and are reasonably fit.

### **Follow-up and Surveillance**

The incidence of local recurrence following surgical resection of early stage NSCLC was documented in an 11-year study of 975 consecutive patients treated at a single institution.<sup>28</sup> In this study, a local failure was defined as a recurrence at the surgical margin, in the ipsilateral hilum, or in the mediastinum. The 5-year incidence of any local recurrence after surgery was 23 percent, with a median time to recurrence of 14 months.<sup>28</sup> In addition, the 5-year risk of any treatment failure, including local or distant relapses and second primary lung cancers, was 42 percent. First sites of recurrence were local only in 25 percent of cases, local and distant in 29 percent of cases, and distant only in 46 percent of cases.

Due to high rates of post-treatment recurrence, long-term follow-up and surveillance is recommended for patients with early stage NSCLC. To date there are no randomized trials assessing different surveillance strategies in patients with stage I NSCLC. One prospective study examined the feasibility and impact on patient survival of an intensive surveillance program of 192 NSCLC patients.<sup>29</sup> The follow-up consisted of physical examination and chest roentgenogram every 3 months and fiberoptic bronchoscopy and thoracic CT scan with sections of the liver and adrenal glands every 6 months. Seventy-one percent of patients developed a recurrence; 26 percent were asymptomatic of which all but one were detected by a scheduled follow-up procedure. From the date of recurrence, 3-year survival was 13 percent in all patients and 31 percent in asymptomatic patients whose recurrence was detected by a scheduled follow-up procedure. The study authors concluded that intensive follow-up and surveillance may improve survival through early detection of potentially curable recurrences.<sup>29</sup> The members of the Alberta Provincial Thoracic Tumour Team recommend that patients undergo a physical examination and chest x-ray every 3 months for the first year post-treatment, then every 6 months for the second year post-treatment, then annually up to the fifth year post-treatment.

Debate exists regarding the sensitivity and specificity of CT scans in identifying post-treatment changes, as well as the appropriate protocols for the use of CT scans to distinguish between benign and malignant nodules without excess morbidity and cost.<sup>30-32</sup> As a result, various guideline publications and consensus statements differ in their recommendations regarding follow-up schedules and types of imaging required for patients treated with curative intent.<sup>12,32-34</sup> The NCCN recommends a chest CT  $\pm$  contrast every 6 to 12 months for 2 years, then non-contrast-enhanced chest CT annually.<sup>12</sup> Similarly, the American Association for Thoracic Surgery recommends high-resolution CT scans every 6 months for 4 years after surgical resection, followed by annual low-dose CT scans for the remainder of the patient's life as long as they have functional status and pulmonary reserve needed to treat a new lung cancer.<sup>35</sup> Given the state of the current evidence, the members of the Alberta Provincial Thoracic Tumour Team suggest that an alternative surveillance regimen be a high-resolution CT scan every 6 months for the first 2 years and then a low-dose CT scan annually up to 5 years post-treatment; the frequency is dependent on risk factors for recurrence and may be more or less frequent.

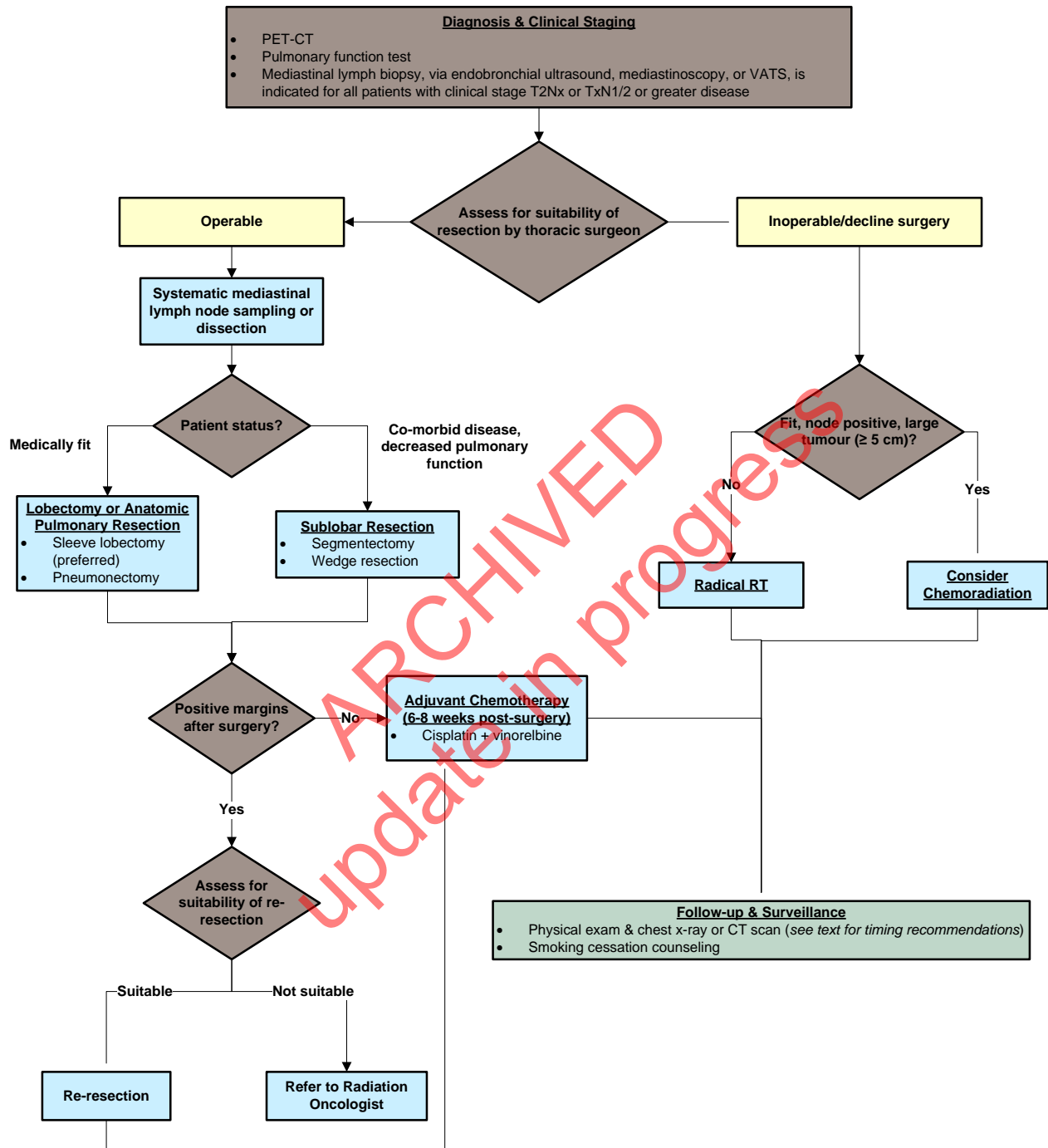
Smoking cessation also increases the efficacy of treatment, decreases the risk of complications, and reduces the risk of second primary malignancies; therefore each follow-up visit should also include an assessment of the patient's smoking status, as well as counseling and referral to smoking cessation



programs.<sup>12,32-34</sup> Health care professionals, patients, and caregivers can refer to [AlbertaQuits](#) for smoking cessation information and resources.

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**TREATMENT ALGORITHM**



In circumstances where surgical resection may not be feasible, patients may be presented at a Multidisciplinary Tumour Board for further discussion between surgery, medical oncology, radiation oncology, nursing, palliative care and/or other disciplines as needed

Whenever possible, patients should be considered for eligibility in ongoing clinical trials.

## GLOSSARY OF ABBREVIATIONS

Acronym	Description
AACP	American College of Chest Physicians
ACOSOG	American College of Surgery Oncology Group
ANITA	Adjuvant Navelbine International Trialists Association study
CALGB	Cancer and Leukemia Group B
CHART	continuous hyperfractionated accelerated radiation therapy
CI	confidence interval
CT	computed tomography scan
Gy	gray
HR	hazard ratio
IASLC	International Association for the Study of Lung Cancer
JBR.10	National Cancer Institute of Canada Clinical Trials Group trial # JBR.10
LACE	Lung Adjuvant Cisplatin Evaluation
NCCN	National Comprehensive Cancer Center
NSCLC	non-small cell lung cancer
PET	positron emission tomography scan
PFT	pulmonary function testing
PS	performance status
RT	radiotherapy
SBRT	stereotactic body radiotherapy
TNM	tumour-node-metastasis
VATS	video-assisted thoracic surgery
VQ	ventilation/perfusion scan

## DISSEMINATION

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta.

## MAINTENANCE

A formal review of the guideline will be conducted at the Annual Provincial Meeting in 2016. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

## CONFLICT OF INTEREST

Participation of members of the Alberta Provincial Thoracic Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Thoracic Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

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