Evidence-Based Series 26-3 IN REVIEW

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Follow-up and Surveillance of Curatively Treated Lung Cancer Patients

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An assessment conducted in December 2018 placed Evidence-Based Series (EBS) 26-3 IN REVIEW. This means that it is undergoing a review for currency and relevance. It is still appropriate for this document to be available while this updating process unfolds. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

EBS 26-3 is comprised of 3 sections. You can access the summary and full report here:

Section 1: Guideline Recommendations
Section 2: Evidentiary Base
Section 3: Development Methods, Recommendations Development and External Review Process

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GUIDELINE OBJECTIVES
The primary objective of this guideline is to develop recommendations for optimal clinical and imaging surveillance and disease control after curative-intent treatment for lung cancer. In addition, the guideline includes an assessment of late toxicity from cancer treatments, quality of life of lung cancer survivors and the benefit of smoking cessation interventions.

TARGET POPULATION
Studies of both small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) patients after curative-intent treatment were considered.

INTENDED USERS
This guideline is targeted to thoracic surgeons, medical and radiation oncologists specializing in lung cancer, radiologists, family physicians, respirologists, nurses and psychosocial care providers.

RECOMMENDATIONS, KEY EVIDENCE, AND JUSTIFICATION
Table 1 summarizes the recommended evaluations and intervals for the routine surveillance of NSCLC and SCLC survivors. These recommendations are based on the expert opinion of the authors, interpretation of the available evidence, and feedback obtained from health care professionals across Ontario through an extensive review process (described in Section 3 of this document). There is currently no data demonstrating improvements in survival from routine surveillance. There are however clinical options for managing local or locoregional recurrence. Therefore, routine surveillance schedules have been designed in order to detect local or locoregional recurrence and new primary lung cancers that are amenable to salvage therapy in asymptomatic patients during follow-up care. Survivors who develop symptoms suggestive of recurrence, should be evaluated according to those symptoms.
RECOMMENDATION 1
Following curative-intent treatment for NSCLC, survivors should receive scheduled follow-up visits that include a medical history, physical examination and chest imaging. Clinical evaluations should be conducted every three months in years 1 and 2, every six months in year 3 and annually thereafter.

Summary of Key Evidence for Recommendation 1
One systematic review with meta-analysis found no survival benefit with a more intense follow-up schedule for NSCLC survivors (hazard ratio [HR], 0.83; 95% confidence interval [CI], 0.66-1.05; p=0.13) (1). However, asymptomatic recurrence detection was associated with a longer survival time (HR, 0.61; 95%CI, 0.50-0.74; p<0.01) (1). Other research has determined that in both NSCLC and SCLC, the majority of recurrences are diagnosed in the first two years (2).

A systematic review that evaluated the role of computed tomography (CT) follow-up one year after lobectomy did not find a clear survival benefit for CT scans (3). However, a more recent study points to a role for minimal-dose CT (MnDCT) scans, which showed higher sensitivity (94.2% vs. 21.2%; p<0.0001) and negative predictive value (99.7% vs. 96.2%; p=0.007) than chest x-ray for detecting new primary tumours and recurrent lung cancer at an early stage (4).

Justification for Recommendation 1
There is very little high level evidence to inform this recommendation. NSCLC survivors should be followed after curative-intent treatment in order to detect local or locoregional recurrence and new primary lung cancers, which are amenable to resection or radical radiation therapy for salvage. For this reason, the Working Group valued overall survival rate over recurrence detection rate. Visits should include medical history with attention to new symptoms in the aerodigestive tract, physical examination and chest imaging. Due to the lack of evidence to inform which frequency is most appropriate, a consensus approach was used to make a recommendation on the appropriate timing of follow-up evaluations in the expert opinion of the Working Group. The consensus process incorporated the evidence that most recurrences are detected in the first two years following curative treatment (2), the indication that asymptomatic recurrence detection is associated with longer survival (1) and the clinical experience of the Working Group members. Additionally, even though data for surveillance beyond five years is limited, the Working Group feels confident in recommending ongoing annual surveillance after year five as this population of patients remains at a heightened risk of developing new lung cancers. Data from the National Lung Screening Trial (5,6) for screening high risk populations for lung cancer recommended low dose CT scans to reduce mortality rates from lung cancer.

Due to the limited evidence, there is no clear indication of the most appropriate chest imaging modality for surveillance. However, based on the limited evidence and expert opinion, Qualifying Statements with imaging modality suggestions have been included for NSCLC survivors. Although there is no clear evidence from studies focusing on recurrence rate detection, the clinical standard among Ontario health care professionals is CT scan, with the appropriate dose and use of contrast IV remaining controversial. Due to radiation dose concerns when performing CT scans for surveillance, lower dose CT scan protocols are of great interest. The best evidence for the value of low-dose CT (LDCT) surveillance comes from the National Lung Screening Trial (5,6), which indicated that LDCT was better than chest radiography in detecting early-stage lung cancers. The Working Group concluded that the cohort study that demonstrated the superiority of MnDCT over chest x-ray for follow-up of NSCLC survivors (4) paired with the success of LDCT in screening (5,6) provide rationale to
suggest either LDCT or MnDCT rather than chest x-ray in follow-up care of NSCLC survivors. The suggestion to include chest CT as a reasonable option for appropriate surveillance imaging of NSCLC survivors is in agreement with recommendations published by the American Association for Thoracic Surgery (AATS) (7), the American College of Chest Physicians (ACCP) (8), the European Society for Medical Oncology (ESMO) (9) and the National Comprehensive Cancer Network (NCCN) (10).

Qualifying Statements for Recommendation 1 (Table 1)
Selection of an appropriate imaging modality should reflect the competing risk of locoregional recurrence, which is potentially curative versus distant recurrence, which is not curative. A cohort study (4) and the National Lung Screening Trial (5,6) indicated that MnDCT and LDCT detect pulmonary lesions better than chest x-ray, yet no demonstrated survival benefit has been established in patients treated by surgical resection with curative intent. Thus, for routine surveillance, LDCT or MnDCT without IV contrast may be a reasonable option instead of chest x-ray. The MnDCT cohort study conducted chest CTs at three months post-treatment, followed by six months post-treatment, then at six month intervals until the end of year 2, followed by annually until year 5. As this is the best available schedule at this time, the intervals are considered reasonable, with the addition of annual surveillance exceeding year 5, as outlined in the Justification section. Even though surveillance is recommended annually until end of life, health care professionals should use their own discretion in determining the applicability of annual surveillance in patients who are not well enough to undergo treatment if a new cancer is detected. When recurrent disease or new disease is suspected, either from constitutional symptoms or chest imaging findings, diagnostic chest CT plus upper abdomen CT scan is suggested to identify local recurrence or a new lung primary.

RECOMMENDATION 2
Following curative-intent treatment for SCLC, survivors should receive scheduled follow-up visits that include a medical history, physical examination and chest imaging. Clinical evaluations should be conducted every three months in years 1 and 2, every six months in year 3 and annually thereafter.

Summary of Key Evidence for Recommendation 2
One systematic review with meta-analysis found no survival benefit with a more intense follow-up schedule for SCLC survivors (1). Other research has determined that in both NSCLC and SCLC, the majority of recurrences are diagnosed in the first two years (2).

Justification for Recommendation 2
There was very little high level evidence to inform this recommendation. SCLC survivors should be followed after curative treatment in order to detect new primary lung cancers and local recurrences that may be amenable to further curative treatment. For this reason, follow-up schedules that result in a high detection rate for recurrence are only of value if this translates into an increase in overall survival. Thus, overall survival rate is valued over recurrence detection rate by the Working Group. Visits should include medical history with attention to new symptoms in the aerodigestive tract, physical examination and chest imaging. A consensus approach was used to determine the appropriate timing of follow-up evaluations in the expert opinion of the Working Group. The consensus process incorporated both the evidence that most recurrences are detected in the first two years following curative treatment (2) and that more intense follow-up schedules do not result in a
longer overall survival time (1), as well as incorporating the clinical experience of the Working Group members.

Due to a lack of evidence, there is no clear indication in the literature on the appropriate surveillance imaging modality for SCLC survivors. The clinical standard among Ontarian oncologists is to perform a CT scan, but there is no evidence to support this choice in a lung cancer survivor population. Based on extrapolation from screening data and expert opinion, Qualifying Statements with imaging modality suggestions have been included for SCLC survivors. Data from the National Lung Screening Trial (5,6) indicated that LDCT was better than radiography in detecting early-stage lung cancers. Based on the superiority of CT to chest x-ray for screening in a high-risk population, in the expert opinion of the Working Group, surveillance of SCLC survivors with CT scans for detection of recurrence or progression may be a reasonable option. Since this suggestion is based on expert opinion and interpretation of data from a screening population, and not the target population of the guideline, a specific radiation dose cannot be included. The suggestion to include chest CT as a reasonable option for appropriate surveillance imaging of SCLC survivors is in agreement with the ESMO guideline for SCLC patients, which states that survivors should be followed with CT scans (11).

Qualifying Statements for Recommendation 2 (Table 1)

Selection of an appropriate imaging modality should reflect the competing risk of locoregional recurrence, which is potentially curative versus distant recurrence, which is not curative. Based on the clinical experience of the Working Group and results from the National Lung Screening Trial (5,6), for routine surveillance, diagnostic CT without IV contrast is preferable to chest x-ray for detection of pulmonary lesions, though no survival benefit has been established. Also based on the clinical experience of the Working Group, diagnostic CT with contrast is suggested for detection of recurrence in mediastinal lymph nodes. In the expert opinion of the Working Group, CT imaging may be conducted three months post-treatment, followed by six months post-treatment, then at six month intervals until the end of year 2, followed by annually thereafter. Beyond year 2, LDCT or MnDCT could be considered rather than a diagnostic CT. Even though surveillance is recommended annually until end of life, health care professionals should use their own discretion in determining the applicability of annual surveillance in patients who are not well enough to undergo treatment if a new cancer is detected. When recurrent disease or new disease is suspected, either from constitutional symptoms or chest imaging findings, diagnostic chest CT plus upper abdomen CT scan is suggested to identify local recurrence or a new lung primary.
Table 1. Evaluations and intervals for routine surveillance of lung cancer survivors after curative-intent therapy.

<table>
<thead>
<tr>
<th></th>
<th>NSCLC</th>
<th>SCLC</th>
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<tr>
<td>Clinical visit evaluations</td>
<td>Medical history, physical exam and chest imaging</td>
<td>Medical history, physical exam and chest imaging</td>
</tr>
<tr>
<td>Clinical visit frequency</td>
<td>Years 1-2: every 3 months; Year 3: every 6 months; Years 4+: annually</td>
<td>Years 1-2: every 3 months; Year 3: every 6 months; Years 4+: annually</td>
</tr>
<tr>
<td>Medical imaging modality</td>
<td>LDCT\textsuperscript{ii} or MnDCT\textsuperscript{iii} without contrast may be a reasonable option over chest x-ray for detection of pulmonary lesions</td>
<td>Diagnostic CT without contrast may be a reasonable option over chest x-ray for detection of pulmonary lesions\textsuperscript{ii}</td>
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<td></td>
<td>Diagonal CT with contrast is suggested to detect recurrence in mediastinal lymph nodes</td>
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<tr>
<td>Surveillance imaging frequency</td>
<td>Year 1: 3, 6 and 12 months post-treatment</td>
<td>Year 1: 3, 6 and 12 months post-treatment</td>
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<td></td>
<td>Year 2: every 6 months (18 and 24 months post-treatment)</td>
<td>Year 2: every 6 months (18 and 24 months post-treatment)</td>
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<td>Years 3+: annually\textsuperscript{iii}</td>
<td>Years 3+: annually\textsuperscript{iii}</td>
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<td>Medical imaging when recurrent disease or new disease is suspected</td>
<td>Diagnostic chest CT with contrast plus upper abdomen scan is suggested to detect local recurrence or new primary lung cancer</td>
<td>Diagnostic chest CT with contrast plus upper abdomen scan is suggested to detect local recurrence or new primary lung cancer</td>
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<tr>
<td></td>
<td>If patient is symptomatic, imaging modality specific to patient’s symptoms is recommended</td>
<td>If patient is symptomatic, imaging modality specific to patient’s symptoms is recommended</td>
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</table>

\textsuperscript{1} Based on consensus of expert opinion.
\textsuperscript{2} Based on extrapolation data from the National Lung Screening Trial (5,6).
\textsuperscript{3} Based on a MnDCT vs. chest x-ray cohort study (4).

Abbreviations: LDCT, low-dose computed tomography; MnDCT, minimal-dose computed tomography; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

**RECOMMENDATION 3**

For both NSCLC and SCLC survivors, no recommendation can be made in relation to positron emission tomography (PET)/CT.

**Summary of Key Evidence for Recommendation 3**

The only identified studies that assessed PET/CT surveillance of lung cancer survivors were in NSCLC survivor populations. Two PET/CT diagnostic studies indicated a benefit for PET/CT over CT alone for recurrence detection (12,13), while another demonstrated a benefit for PET/CT over non-contrast CT for detection of extrathoracic and mediastinal metastases (14). One study, looking at the ability to detect local recurrence, found that almost 26% of the recurrences diagnosed by PET/CT were recurrences within the ipsilateral lung (12). In another diagnostic study, PET/CT scanning led to the detection of lung cancer recurrence that was amenable to salvage therapy in a small proportion (3% of total) of the patients enrolled (13).
Justification for Recommendation 3

The Working Group was unable to provide a recommendation for PET/CT surveillance of NSCLC and SCLC survivors based on the identified evidence. Diagnostic studies have shown better sensitivity, specificity and accuracy of PET/CT compared with CT alone and point to a role for PET/CT in diagnosing local and locoregional recurrences, which may be amenable to salvage therapy (12, 13). However, due to the low percentage of local recurrence detected by PET/CT in these studies and the higher doses of radiation patients would receive with PET/CT compared with CT alone, the Working Group feels that the evidence does not point to a clinically important difference in patient outcomes with PET/CT and the data are not strong enough upon which to base a recommendation.

RECOMMENDATION 4

In the expert opinion of the authors, any new and persistent or worsening symptom warrants the consideration of a recurrence, especially:

Constitutional symptoms:
- Dysphagia
- Fatigue (new onset)
- Nausea or vomiting (unexplained)
- New finger clubbing
- Suspicious lymphadenopathy
- Sweats (unexplained)
- Thrombosis
- Weight loss or loss of appetite

Pain:
- Bone pain
- Chest pain
- Caveat shoulder pain not related to trauma

Neurological symptoms:
- Headaches (if persistent)
- New neurological signs suggestive of brain metastasis or cord compression such as leg weakness or speech changes
- Headache or focal neurological symptoms

Respiratory symptoms:
- Cough (despite use of antibiotics)
- Dyspnea
- Hemoptysis
- Hoarseness
- Signs of superior vena cava obstruction
- Stridor

Summary of Key Evidence for Recommendation 4

Only one prospective cohort study was identified to inform this recommendation. This PET/CT diagnostic study recorded the symptoms experienced by patients who had developed
progressive disease and found that these patients experienced more pain and neurological issues than did those without progressive disease (13).

**Justification for Recommendation 4**
The included study enrolled a modest sample size of 100 patients, with only 24 patients developing progressive disease (13). Due to the lack of evidence and small sample size of the included study, the Working Group decided to use expert opinion in a consensus process to list the potential symptoms of recurrence.

**RECOMMENDATION 5**
Health-related quality of life (QoL) is very important for long-term survivors suffering from late side effects of their curative-intent therapy (including surgery, chemotherapy and radiation therapy). The following is a summary of issues reported by survivors. Health care professionals need to aid lung cancer survivors in handling these symptoms to improve QoL.

**Constitutional Issues:**
- Anxiety
- Cough
- Decline in appetite
- Decrease in general health
- Depression
- Dysphagia
- Esophageal stricture
- Fatigue
- Pain
- Physical ability restrictions
- Reduced sleep quality
- Shortness of breath

**Long-Term Chemotherapy Effects:**
- Hearing loss
- Neuropathies
- Renal impairment

**Long-Term Radiation Effects:**
- Breathing complications
- Breathlessness/Dyspnea

**Long-Term Surgery Effects:**
- Empyema
- Oxygen dependence
- Post-thoracotomy pain syndrome
- Reduced exercise tolerance or activity limitations
- Shortness of breath

**Summary of Key Evidence for Recommendation 5**
When overall QoL profiles of lung cancer survivors were analyzed, it was found that survivors of both NSCLC and SCLC experienced a reduction in the physical domains of the QoL
questionnaires for up to one year post surgery (15,16). There was an increase in the QoL mental domain level above that experienced pre-surgery by two years, but this level was still lower than an age-matched reference population (16). When only NSCLC survivors were followed after lobectomy, 66% of survivors experienced improved or stable QoL scores, while 71% of survivors experienced improved or stable scores following pneumonectomy or bilobectomy (17).

A systematic review that assessed the specific treatment-related long-term effects found that survivors of lung cancer report physical ability restrictions, depression, decreases in general health and vitality, and increased body pain (2). Prospective cohort studies evaluating non-recurrence related issues found that lung cancer survivors experienced long-term dyspnea (18-20), cough (18,20), fatigue (18,20), impaired breathing (21), increased pain (20,21), decline in appetite (20,21) and reduced sleep efficiency (19). Studies that focused solely on survivors of NSCLC found that a majority of these survivors experienced some degree of pneumonitis (22) and a sustained decrease in multiple QoL domains (23).

**Justification for Recommendation 5**

The literature search on this question was designed to assess both the QoL and treatment-related symptom burden of lung cancer survivors, which quite often go hand-in-hand. The studies that informed the research question ranged from systematic reviews and randomized controlled trials (RCTs) to non-randomized prospective cohort studies. All the included studies used prospective data collection and analyzed the study population through comparisons either between groups or within the study group, across time. Unfortunately, since all non-randomized studies carry an unclear risk of bias and most of the studies relied on the use of self-reported QoL tools, which inherently introduce recall bias, it was believed that the studies informing this evidence were of low quality. The Working Group does recognize that this is the best data available as QoL and late treatment effect data are generally not included in treatment trials a priori. However, due to the low quality of studies discovered, the Working Group decided to use both the literature and their clinical experience to summarize the late side-effects and QoL issues reported by long-term survivors of lung cancer.

**RECOMMENDATION 6**

For lung cancer survivors who have completed curative-intent therapy, surveillance is required and may be provided by specialists, family physicians or hospital-based nurses.

**Summary of Key Evidence for Recommendation 6**

The literature was searched for studies that compared follow-up care provided by a specialist with care provided by family physicians or nurses. The search returned no studies focusing on lung cancer survivors that compared family physician follow-up with specialist-led care. However, one RCT which compared hospital-based nurse-led follow-up care with specialist-led follow-up care following treatment for SCLC or NSCLC was identified (24). The study found that both QoL and recurrence outcomes were not different between the two groups, indicating that nurse-led follow-up did not negatively impact QoL or recurrence detection.

**Justification for Recommendation 6**

Unfortunately, the identified RCT is more than 10 years old, and when it was conducted, no effective salvage therapy and no effective second-line chemotherapy were available, which may account for the lack of difference in overall survival being detected.
Also, nurses within the study were supervised by specialists and the study allowed for additional visits to the family physician, which may have confounded some of the direct comparisons. Finally, the study included a more advanced disease population than was our target population. The Working Group considered the study limitations and even though this patient population would be managed differently today due to new treatment options, the group accepts this study as it is the best available evidence. Additionally, for this research question, QoL and satisfaction with care are highly valued. Thus, the Working Group believes that a weak recommendation for care provided by non-specialists is warranted.

**Qualifying Statements for Recommendation 6**

Although the identified literature only evaluated hospital-based nurse-led care models, expert opinion supports family physician-led care models. Additionally, family physicians should be included in all survivorship care models. There is no evidence to support timing for when lung cancer survivors can be transitioned into non-specialist care, thus no recommendation can be made for when transition is appropriate.

**RECOMMENDATION 7**

Smoking cessation counselling is recommended for patients who have completed curative-intent therapy for NSCLC and SCLC. Although verbal cessation advice from a health care professional is of benefit, interventions that involve behavioural and pharmacotherapy support in addition to verbal advice is recommended.

**Summary of Key Evidence for Recommendation 7**

Systematic reviews that assessed the efficiency of smoking cessation counselling concluded that any intervention is better than no cessation advice from a health care professional (25), and that an intensive intervention that adds further follow-up visits is more effective than brief intervention (25). When pharmacotherapy and behavioural support are added to advice from a health care professional alone, the benefit of the counselling is increased (26). The three systematic reviews and one cohort study that evaluated the benefits of smoking cessation after diagnosis of lung cancer or prior to surgery all concluded that smoking cessation improved clinical outcomes (27-30). Cohort studies that looked at the association between smoking cessation and QoL found that never-smokers reported the best QoL after curative treatment (31,32). However, patients who quit smoking within one year prior to diagnosis or during follow-up reported better overall QoL and symptom scales, compared with survivors who continued to smoke (31-33).

**Justification for Recommendation 7**

Even though none of the identified studies directly evaluated the value of smoking cessation counselling directly, the Working Group members agreed that taken together, the evidence for the benefit of smoking cessation counselling, the evidence for the benefits of cessation in lung cancer survivors and the evidence for the QoL benefits of cessation can be combined to adequately inform this recommendation.

**HOW THIS GUIDELINE CONTRIBUTES TO THE CARE OF PATIENTS**

Studies showing the benefits of surveillance after treatment for lung cancer are fairly new. For this reason, many physicians have not favoured intensive follow-up or advanced imaging because it was thought to be of little value. In the current era, improved treatment options exist, producing a larger population of lung cancer survivors and thus making follow-up more important. However, there is currently great variability in the follow-up care being
provided to lung cancer survivors in Ontario due to a lack of high-quality evidence to support one surveillance schedule. Additionally, there is a lack of high-quality evidence to inform which clinical evaluations should be performed at follow-up visits. The current evidence-based guidance document provides recommendations on appropriate follow-up schedules and evaluations for survivors of NSCLC and SCLC. This guidance document also outlines specific symptoms that may indicate recurrence or progression of lung cancer and that should be further investigated by an appropriate health care professional. Lung cancer survivors have specific post-treatment health-related QOL issues. Physicians and other health care professionals can assist patients with these issues. Finally, health care professionals can positively impact the rate of smoking cessation in lung cancer survivors by ensuring that smoking cessation counselling occurs.

FUTURE RESEARCH

High-quality literature for this topic was very limited. As such, many of the recommendations are based on clinical standards and expert opinion. Research into better salvage therapies, as well as detection of recurrent disease and second primary cancers at an earlier stage is greatly needed. Additionally, very little evidence was identified that assessed symptoms of lung cancer recurrence or development of second primary tumours. Research into these areas will allow for better guidance for health care professionals. Additionally, studies that investigate other issues experienced by cancer survivors, such as fear of recurrence, sexual health, return to work and psychosocial coping, have not been addressed in solely lung cancer survivor groups, presenting an area in need of future work. Finally, although survivorship follow-up care plans facilitate continuity of care and may minimise adverse outcomes as survivors transition into non-specialist follow-up care, care plans have not been extensively evaluated in lung cancer survivor populations, presenting another area in need of future research.

RELATED GUIDELINES

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REFERENCES


1.0. INTRODUCTION

Lung cancer is the second most commonly diagnosed cancer in men and women in Canada and the leading cause of death in both (1). It is estimated that there will be 25,500 new cases in 2013 (13,300 men and 12,200 women) and 20,200 deaths (10,700 men, 9,500 women) (1). More than 80% of diagnosed lung cancers are non-small cell lung cancer (NSCLC), while the remainder are mostly small cell lung cancer (SCLC) (2). SCLC typically spreads early and is treated using nonsurgical approaches (2). Early-stage NSCLC (stage I or II) patients are potential candidates for resection (2). Patients with stage III NSCLC that present with good performance status and minimal weight loss are candidates for curative-intent combined modality treatment, involving chemotherapy, radiation therapy, and occasionally, surgery (2). Some patients with limited-stage SCLC may also be candidates for curative-intent therapy with chemotherapy and radiation (2). These curative-intent treatments for NSCLC and SCLC provide a subset of cancer survivors who have special follow-up needs related to surveillance for recurrent or new cancer, and on-going management of cancer-therapy effects and residual disease-related symptom burden.

Lung cancer survivors are at an increased risk of developing recurrent lung cancer, as well as second primary lung cancers and other primary cancers in the aerodigestive tract (3). Recurrent lung cancer may occur locally, regionally, in distant sites or any combination of the three. When recurrence is local, it may still be amenable to curative-intent salvage therapy either with further surgery or radical radiation (3). These recurrences occur in the operative field or within the same hemithorax (3). Recurrences that occur in the lymphatic drainage basins within the chest or neck are defined as regional recurrences and may also be amenable to salvage therapy; however, this presentation is often an indication of more widespread disease (3). Finally, although not generally curable, prompt treatment for distant recurrence is important for the palliation of symptoms and to ensure the best possible health-related quality of life (QoL) (3). Due to the frequency of second primary lung cancers and recurrent disease, follow-up schedules must be designed to detect disease that is amenable to curative-intent therapy.

There is no high-quality evidence to support one surveillance schedule for follow-up visits for lung cancer survivors, which results in great variability in guideline recommendations from different organizations. Similarly, as there is little high-quality
evidence related to which tests should be performed at the follow-up visits, there is much variability as to which imaging tests are recommended for lung cancer survivors and at what frequency. The current authors sought to create an evidence-based follow-up protocol for survivors who have received curative-intent treatment following a diagnosis of NSCLC or SCLC. The authors also sought to address which health care professional should be the most responsible for lung cancer survivors, common symptoms and signs of recurrence and commonly experienced non-recurrence related issues. Additionally, although continued smoking has been linked to an increased risk of developing recurrent disease and second primary lung cancers (3), some lung cancer survivors continue to smoke after treatment (4). Thus, there is potential value in promoting smoking cessation to lung cancer survivors. This review will examine the evidence surrounding whether cessation counselling by clinicians is beneficial in helping lung cancer survivors to quit.

In order to make recommendations as part of a clinical practice guideline, the Working Group of the Lung Cancer Follow-up Guideline Development Group developed this evidentiary base upon which those recommendations are founded. Based on the objectives of the guideline, the Working Group derived the research questions outlined below.

1.1. RESEARCH QUESTIONS
In survivors who have received curative-intent treatment for non-small cell lung cancer (NSCLC) or small cell lung cancer (SCLC):

1. What clinical activities are effective at detecting recurrence or progression of lung cancer, including detection of metastases in lung cancer survivors?
2. What is the relationship between frequency and timing of any diagnostic/laboratory test in the management of recurrence in lung cancer survivors? Are recurrences associated with symptomatic versus asymptomatic presentation?
3. What symptoms are indicative of possible recurrence or development of any other primary cancer that warrant further evaluation?
4. What are the common non-recurrence related issues experienced by lung cancer survivors?
5. Is there a relationship between the clinician and/or setting of follow-up care and the effective detection and management of recurrent or metastatic disease?
6. Is there a value to smoking cessation counselling for lung cancer survivors?

2.0. METHODS
This evidentiary base was developed using a planned two-stage method, summarized here and described in more detail below.

1. Search and evaluation of existing systematic reviews: If one or more existing systematic reviews were identified that addressed the research questions and were of reasonable quality, then those systematic reviews formed the core of the evidentiary base.
2. Systematic review of the primary literature: This review focused on those areas not covered by existing reviews if any were located and accepted.

The PEBC is supported by the Ontario Ministry of Health and Long-Term Care. All work produced by the PEBC and any association Programs is editorially independent from the Ministry.

2.1. Search for Existing Systematic Reviews
An electronic search employing OVID was used to systematically search the MEDLINE and EMBASE databases for systematic reviews on the follow-up care of curatively treated lung
cancer patients. OVID was searched from 2000 to week 4 of 2014 using the following keywords: “lung cancer,” “surveillance,” “follow up,” “after care,” “survivor,” “recurrence,” and “late effects.” In addition, websites/databases of specific guideline developers and systematic review producers were also searched, using the same keywords and for the same time period. These websites/databases included: Cochrane Database of Systematic Reviews (CDSR), Scottish Intercollegiate Guideline Network (SIGN), American Society of Clinical Oncology (ASCO), European Society of Clinical Oncology (ESMO), American Society for Radiation Oncology (ASTO), European Society for Radiotherapy and Oncology (ESTRO), American Association for Thoracic Surgery (AATS), American Thoracic Society (ATS), European Society of Thoracic Surgeons (ESTS), Society of Thoracic Surgeons (STS) and American College of Chest Physicians (ACCP). When multiple reviews were found with overlapping outcomes, only the most recent systematic review was chosen for further evaluation.

Identified systematic reviews that required further consideration based on the criteria above were assessed using the Assessing the Methodological Quality of Systematic Reviews (AMSTAR) tool (5). The results of the AMSTAR assessment were used to determine whether or not an existing review could be incorporated as part of the evidentiary base.

Any identified reviews that did not meet the criteria above, whose AMSTAR assessment indicated important deficiencies in quality, or that was otherwise not incorporated as part of the evidence base would be reported in the reference list, but not further described or discussed.

2.2. Primary Literature Systematic Review

Assuming that no existing systematic reviews were identified, or that the identified reviews were incomplete in some fashion, a systematic review of the primary literature was also planned. This review was reduced in scope, such as a reduction in subject areas covered, time frames covered, etc., based on the scope of incorporated existing reviews. The criteria described below are written assuming no existing reviews were incorporated.

2.2.1. Literature Search Strategy

OVID was used to systematically search the MEDLINE and EMBASE databases for articles related to follow-up care of curatively treated lung cancer patients, published between 2000 and week 4 of 2014. Due to the variation in the research questions, separate searches were conducted for each question. Common to each search were terms to retrieve articles on lung cancer and survivor follow-up care. A complete literature search strategy for each question can be found in Appendix 2. In addition to the MEDLINE and EMBASE databases searches, reference lists of included systematic reviews and primary literature were scanned for potentially useful studies.

2.2.2. Study Selection Criteria and Protocol

All hits from the OVID literature search were imported into reference management software (EndNote X6), where the citations underwent de-duplication. Table 1 describes the details of the inclusion criteria and outcome variables for each question addressed in this evidence summary. For each research question, only full publications on patients treated with curative-intent therapy for NSCLC or SCLC were included. However, for Research Question 6, studies that described smoking cessation strategies did not need to limit enrolment to lung cancer survivors. Due to the limited amount of data expected to be found, the Working Group searched for randomized controlled trials (RCTs), as well as non-randomized studies, except for Research Question 5, which only included RCTs data a priori. Letters and editorials, as well as studies not in English, were excluded from the evidentiary base.
A review of the titles and abstracts that resulted from the search was done by one reviewer (LS). For those items that warranted full-text review, one reviewer (LS) reviewed each item, and then the list was checked by the entire Working Group. Once the full-text review was completed, the Working Group re-evaluated the types of studies included in the evidence summary and decided to exclude retrospective and case series studies, as well as prospective studies that enrolled fewer than 30 patients. Additionally, studies that enrolled survivors of multiple cancer types and that did not separately analyze lung cancer survivors were excluded.

### Table 1. Details of inclusion criteria and outcome variables.

<table>
<thead>
<tr>
<th>Research Question</th>
<th>Inclusion Criteria</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| Q1. Clinical activities for detection of recurrence, progression or metastasis. | • RCTs comparing follow-up tests  
• Non-randomized reviews describing follow-up tests | • Overall and/or recurrence-free survival  
• Rate of detection of potentially curable relapse/progression/metastasis  
• Positive and negative predictive values  
• Specificity and reproducibility of tests |
| Q2. Frequency and timing of diagnostic/laboratory tests. | • RCTs comparing follow-up frequencies  
• Non-randomized reviews describing follow-up frequencies | • Overall and/or recurrence-free survival  
• Positive and negative predictive values  
• Rate of diagnosed recurrence or progression  
• QoL or patient satisfaction |
| Q3. Symptoms of recurrence or development of any second primary. | • RCTs collecting data on relapse symptoms or development of second primary tumours  
• Non-randomized reviews reporting on symptom burden of lung cancer survivors experiencing relapse | • Incidence of second primary tumour  
• Predictive value and/or likelihood ratio of recurrence for symptom or symptom combination |
| Q4. Non-recurrence related issues. | • RCTs comparing late toxicity or QoL after different treatment modalities  
• Non-randomized reviews describing QoL or on-going symptom burden of lung cancer survivors | • Rate of late treatment effect  
• QoL changes  
• Lung cancer survivor symptom burden |
| Q5. Most responsible care provider. | • RCTs comparing specialist-led follow-up to follow-up led by nurse or family physician | • Overall and/or recurrence-free survival  
• Rate of late effects, or recurrence or metastasis  
• QoL or patient satisfaction  
• Health care provider satisfaction |
| Q6. Value of smoking cessation counselling. | • RCTs comparing smoking cessation strategies or impact of smoking status on lung cancer survivor QoL  
• Non-randomized reviews reporting on smoking cessation strategies or impact of smoking status on lung cancer survivor QoL  
• Study participants did not need to be lung cancer survivors for studies | • Likelihood of smoking cessation  
• Risk of recurrence  
• QoL of lung cancer survivors |
2.2.3. Data Extraction and Assessment of Study Quality and Potential for Bias

Data were extracted from all studies that passed full-text review by one reviewer (LS) and checked by the rest of the Working Group. All extracted data and information were audited by an independent auditor. Important quality features, such as study design, lung cancer type, comparison type, group allocation method, and sources of funding were extracted for each study. Since randomized and non-randomized, as well as diagnostic studies were included in this review, no specific quality assessment tool was used. Instead, the above quality features were extracted. For diagnostic studies, the quality features extracted were based on a modified form from the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy. For non-randomized studies, the study designs were defined by the Cochrane Collaborations schema (Handbook Table 13.2a). The Working Group anticipated that the non-randomized studies would not carry the weight of randomized trials when creating recommendations, but agreed that this was the best evidence to be found.

2.2.4. Synthesizing the Evidence

Due to the anticipated large variation in study quality and outcomes measured, pooling the data was not planned.

3.0. RESULTS

3.1. Search for Existing Systematic Reviews

The search for existing systematic reviews identified 28 reviews on the follow-up care of curatively treated lung cancer patients.

3.1.1 Quality of Systematic Reviews

Of the 39 systematic reviews identified by the literature search, only 10 met the inclusion criteria, were assessed with the AMSTAR tool and are included in this evidence summary (Figure 1, Table 2). The AMSTAR assessment for these 10 included systematic reviews can be found in Appendix 3. One systematic review focused on computed tomography (CT) follow-up after lobectomy (6), another focused on positron emission tomography (PET)/CT detection of metastases (7), and a third focused on the frequency of lung cancer survivor follow-up (8). Two systematic reviews discussed QoL issues in lung cancer survivors (9,10) and five focused on aspects of smoking cessation (11-15). Even though most of the systematic reviews scored well using the AMSTAR tool, many of them included studies of low quality design.

3.2. Primary Literature Systematic Review

The primary literature systematic review was used to address outcomes of interest not covered by the included systematic reviews. Where systematic reviews existed, a search of the primary literature was conducted from the end date of the search in the reviews.

3.2.1. Literature Search Results

Twenty-one studies were identified that met inclusion criteria (16-36) (Figure 1). Table 2 summarizes the number and types of studies included per research question, the intervention addressed by the studies and the type of lung cancer diagnosed in the enrolled patients. Both systematic reviews and primary studies were identified for all the research questions except for Research Questions 3 and 5 (Table 2). For Research Question 1, a
systematic review was identified that summarized studies focused on fluorodeoxyglucose (FDG) PET/CT detection of metastases, so the primary literature was searched for PET/CT studies on detection of metastases after the search date of the systematic review, as well as for studies investigating the role of PET/CT in detection of recurrence for the entire search period (Table 2). For Research Question 2, where a systematic review evaluating intensive follow-up schedules was identified, the primary literature was searched for additional studies after the search date of the systematic review (Table 2). However, for Research Questions 4 and 6, in addition to searching for studies after the search date of the identified systematic reviews, the primary literature was also searched for outcomes not addressed by the reviews (Tables 1 and 2).

The majority of the studies (12/21; 57%) enrolled only NSCLC patients (16,19,22-25,29,31,32,34-36). Eight of the studies focused on both NSCLC and SCLC patients (18,20,21,26-28,30,33), and only one enrolled solely SCLC patients (17).
Figure 1. Selection of systematic reviews and primary literature from the search results of MEDLINE and EMBASE.

* Studies that were picked up by the systematic review but were found to have already been included in a systematic review included in the evidentiary base.
<table>
<thead>
<tr>
<th>Question</th>
<th>Intervention</th>
<th>Number of Studies, Type of Lung Cancer (ref)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1. Clinical activities for detection of recurrence, progression or metastases.</td>
<td>FDG-PET</td>
<td>2 - FPDC, NSCLC (23,25)</td>
</tr>
<tr>
<td></td>
<td>FDG-PET/CT</td>
<td>1 - SR, NSCLC (7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 - FPDC, NSCLC (19,31)</td>
</tr>
<tr>
<td></td>
<td>FDG-PET/CT vs. non-contrast CT</td>
<td>1 - FPDC, NSCLC (35)</td>
</tr>
<tr>
<td></td>
<td>CT</td>
<td>1 - SR, NSCLC (6)</td>
</tr>
<tr>
<td></td>
<td>Minimal-dose CT</td>
<td>1 - FPDC, NSCLC (36)</td>
</tr>
<tr>
<td>Q2. Frequency and timing of diagnostic/laboratory tests.</td>
<td>Intensive follow-up</td>
<td>1 - SR, NSCLC and SCLC (8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 - BAC, NSCLC (29)</td>
</tr>
<tr>
<td>Q3. Symptoms of recurrence or development of any second primary tumour.</td>
<td>Symptoms of progressive disease</td>
<td>1 - FPDC, NSCLC (31)</td>
</tr>
<tr>
<td>Q4. Non-recurrence-related issues.</td>
<td>Impact of resection on long-term QoL</td>
<td>1 - SR, NSCLC and SCLC (9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 - BAC, NSCLC and SCLC (26)</td>
</tr>
<tr>
<td></td>
<td>Impact of neoadjuvant therapy and lung resection on QoL</td>
<td>1 - RCT, NSCLC (22)</td>
</tr>
<tr>
<td></td>
<td>Late lung toxicity after concurrent chemoradiotherapy</td>
<td>1 - RCT, NSCLC (32)</td>
</tr>
<tr>
<td></td>
<td>QoL of survivors</td>
<td>1 - SR, NSCLC and SCLC (10)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 - BCA, NSCLC (24)</td>
</tr>
<tr>
<td></td>
<td>Physical activity and QoL</td>
<td>1 - BAC, NSCLC and SCLC (28)</td>
</tr>
<tr>
<td></td>
<td>Sleep patterns</td>
<td>1 - CCS, NSCLC and SCLC (21)</td>
</tr>
<tr>
<td></td>
<td>Ongoing symptoms</td>
<td>3 - BAC, NSCLC and SCLC (18,30,33)</td>
</tr>
<tr>
<td>Q5. Most responsible care provider.</td>
<td>Nurse-led vs. specialist-led follow-up</td>
<td>1 - RCT, NSCLC and SCLC (27)</td>
</tr>
<tr>
<td>Q6. Value of smoking cessation counselling.</td>
<td>Effects of cessation after diagnosis</td>
<td>1 - SR, NSCLC and SCLC (11)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 - SR, NSCLC (15)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 - SR, NA (14)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 - CBA, NSCLC (34)</td>
</tr>
<tr>
<td></td>
<td>Effectiveness of physician counselling</td>
<td>1 - SR, NA (12)</td>
</tr>
<tr>
<td></td>
<td>Effectiveness of counselling paired with medication</td>
<td>1 - SR, NA (13)</td>
</tr>
<tr>
<td></td>
<td>Effects of smoking on QoL</td>
<td>1 - CBA, NSCLC (16)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 - CBA, SCLC (17)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 - CBA, NSCLC and SCLC (20)</td>
</tr>
</tbody>
</table>

Abbreviations: BAC, before-and-after comparison; CBA, controlled before-and-after study; CCS, case-control study; CT, computed tomography; FDG, fluorodeoxyglucose; FPDC, fully paired diagnostic cohort study; NA, not applicable; NSCLC, non-small cell lung cancer; PET, positron emission tomography; QoL, quality of life; RCT, randomized controlled trial; SCLC, small cell lung cancer; SR, systematic review.

### 3.2.2. Study Design and Quality

The primary literature returned 21 studies that met the inclusion and exclusion criteria. A description of the study design and quality of the studies can be found in Appendix 4. The evidentiary base included six diagnostic studies, as well as three RCTs and 12 non-randomized prospective cohort studies. When evaluating the quality of diagnostic studies, the PEBC endorses the methods described in the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy. All six of the fully published diagnostic studies (19,23,25,31,35,36) used a cohort recruitment method and fully-paired comparison model (all patients received all interventions), minimizing selection bias (Appendix 4). However, two
Additionally, the definition of “intensive follow-up” was not consistent throughout the included studies. For early-stage NSCLC survivors, four studies were pooled to determine that there was no survival benefit with a more intense follow-up schedule (hazard ratio [HR], 0.83; 95% confidence interval [CI], 0.66-1.05; p=0.13). Similarly, three RCTs included in the evidentiary base more strongly informed the recommendations on the follow-up care of lung cancer survivors. The 12 non-randomized studies were further defined using the Cochrane Collaborations schema (Handbook Table 13.2a; available from: http://handbook.cochrane.org/) as before-and-after comparisons (six studies), controlled before-and-after studies (five studies) and case-control studies (one study) (Appendix 4). All the included non-randomized studies used prospective data collection and employed a comparison either within the group across time or between the survivor group and a control group (Appendix 4). The controlled before-and-after studies made comparisons between groups as well as across time, resulting in less risk of bias than the before-and-after comparisons, which only compared across time within the group (Appendix 4). However, all non-randomized studies carry an unclear risk of bias, which was taken into consideration when drafting the recommendations. In addition, the studies looking at QoL and symptom burden of lung cancer survivors mostly relied on the use of self-reported QoL tools, which may have resulted in an increased risk of recall bias in these studies, as survivors were required to recall symptoms experienced over a period of time. All three RCTs and 12 non-randomized studies were included in the evidentiary base.

3.3. Questions 1 & 2: What clinical activities are effective at detecting recurrence or progression of lung cancer, or occurrence of metastases in lung cancer survivors? What is the relationship between frequency and timing of any diagnostic/laboratory test in the management of recurrence in lung cancer survivors? Are recurrences associated with symptomatic versus asymptomatic presentation?

Three systematic reviews were identified to inform this research question. One systematic review discussed overall survival and symptomatic versus asymptomatic recurrence when comparing intensive with less intensive follow-up (8), while another evaluated the survival benefits of CT follow-up (6), and the third summarized the diagnostic value of FDG-PET/CT for metastasis detection (7). The systematic review of the primary literature identified a non-randomized prospective cohort study that evaluated an intensive follow-up schedule and its role in relapse treatment (29), as well as two studies that assessed the role of PET in imaging lung cancer relapse (19,31), one study that compared minimal-dose CT with chest X-ray for detection of recurrent or new cancer (36) and one study that compared PET/CT with non-contrast CT for surveillance after lobectomy (35).

3.3.1. Frequency of Follow-Up Care

3.3.1.1. Systematic Reviews

A systematic review with meta-analysis that compared more intensive to less intensive follow-up for lung cancer survivors of both NSCLC and SCLC was identified (8). This meta-analysis investigated overall survival and symptomatic versus asymptomatic recurrence when comparing intensive with less intensive follow-up schedules. Subsets of eight observational studies and one RCT, published before August 2008, were pooled for multiple analyses. The authors noted that the meta-analysis was based primarily on observational studies, introducing the potential for bias. Additionally, the definition of “intensive follow-up” was not consistent throughout the included studies. For early-stage NSCLC survivors, four studies were pooled to determine that there was no survival benefit with a more intense follow-up schedule (hazard ratio [HR], 0.83; 95% confidence interval [CI], 0.66-1.05; p=0.13). Similarly,
there was no survival benefit with an intensive follow-up schedule for SCLC and advanced-stage NSCLC survivors (HR, 0.86; 95%CI, 0.65-1.13; p=0.27) when two studies were pooled. Only two studies reported time to disease progression after curative treatment, and analysis determined that more intensive follow-up did not affect time to detection of recurrence (HR, 0.85; 95%CI, 0.50-1.42; p=0.52). In fact, there was a high rate of relapse across all included studies (21%-71%), with detection being as likely to occur during an unscheduled consultation as during a routine appointment. However, when the four studies that reported on overall survival with asymptomatic versus symptomatic recurrence after curative treatment for NSCLC were pooled, the meta-analysis found that asymptomatic recurrence was associated with a longer survival time (HR, 0.61; 95%CI, 0.50-0.74; p<0.01). From the pooled studies, the reviewers were unable to determine whether the survival benefit was due to earlier intervention to treat the recurrent disease or if lead time bias was a factor in the extended survival of the asymptomatic patients.

3.3.1.2. Non-Randomized Prospective Studies for NSCLC

One before-and-after comparison study that enrolled NSCLC survivors was conducted after the Calman et al review (8) search date and evaluated whether intensive follow-up resulted in earlier relapse treatment (29). Intensified follow-up was defined as regular monthly phone contacts, clinic visits every month for the first three months, then every three months until end of the first post-operative year. The control group followed the same clinic schedule, but did not receive the monthly phone contact. In years 2 and 3, intensified follow-up was combined with regular out-patient visits at four-month intervals. The enrolled patients were originally diagnosed with stage I-IIIA NSCLC (10.2% stage IB, 4.5% IIA, 45.5% IIB, 39.8% IIIA). Fifty of the 88 enrolled patients developed relapse. Forty-four of the relapsed patients had symptoms, while the other six did not. When comparing NSCLC stage, 77.1% of stage IIIA (27/35), 52.55% (21/40) of stage IIB and 22.22% (2/9) of stage IB patients experienced relapse. The intensified follow-up did not increase the proportion of patients detected with asymptomatic relapse or the number of patients treated for relapse.

3.3.2. Imaging of Lung Cancer Recurrence or Progression

3.3.2.1. Systematic Reviews for NSCLC

Two systematic reviews that evaluated imaging modalities for NSCLC recurrence or progression were identified. One summarized studies focused on CT follow-up after lobectomy to determine if CT surveillance resulted in a survival benefit for NSCLC survivors (6). Five studies were identified as the best evidence, while an additional three studies were used as supportive evidence. The included studies reported conflicting results, with only three concluding that CT scanning may improve survival by detecting local and distant recurrences at an asymptomatic stage. However, two included studies found no survival benefit for CT scanning, regardless of site of recurrence. The remaining studies supported the use of CT scans for recurrent disease screening but did not directly address survival rates. The limited and contradictory evidence points to a substantial lack in the literature.

A second systematic review, which included a meta-analysis, assessed the diagnostic value of FDG-PET/CT in detecting metastatic lesions in NSCLC survivors (7). Diagnostic accuracy was compared between PET/CT and PET or CT alone in nodal staging. The meta-analysis pooled 56 studies, including 46 that reported on lymph node metastases and 13 that reported on extra-thoracic metastases. When 27 studies that reported on mediastinal staging were pooled, the sensitivity of PET/CT was 0.72 (95%CI, 0.65-0.78) and the specificity was 0.91 (95%CI, 0.86-0.94). Three of these pooled studies compared the diagnostic performance of FDG-PET/CT with FDG-PET, and it was determined that the overall sensitivity of PET/CT
was significantly higher than PET (0.83 vs. 0.69; p<0.05), while the specificity was significantly lower (0.82 vs. 0.90; p<0.05). Six mediastinal staging studies compared the efficacies of contrast-enhanced CT and PET/CT, and pooling found that PET/CT demonstrated significantly higher sensitivity (0.78 vs. 0.53; p<0.0001) and specificity (0.73 vs. 0.87; p<0.0001) than did contrast-enhanced CT. Intrathoracic staging data were pooled from 18 studies and showed a sensitivity of 0.71 (95%CI, 0.60-0.80) and specificity of 0.83 (95%CI, 0.77-0.88) for PET/CT. Pooling of three studies, which compared the accuracies of PET/CT to PET in intrathoracic staging, determined that PET/CT had significantly higher sensitivity (0.83 vs. 0.70; p=0.0337) and specificity (0.75 vs. 0.59; p=0.0152) than did PET. Similarly, when data from four studies that compared PET/CT to contrast-enhanced CT in intrathoracic staging were pooled, PET/CT showed significantly higher sensitivity (0.73 vs. 0.57; p=0.0056) and specificity (0.80 vs. 0.52; p<0.0001) than did contrast-enhanced CT. Only four included studies evaluated the use of PET/CT in the detection of extrathoracic metastases. The pooled sensitivity of PET/CT was 0.77 (95%CI, 0.47-0.93) and the pooled specificity was 0.95 (95%CI, 0.92-0.97). None of the pooled studies compared PET/CT diagnostic accuracy to PET or CT for detection of extrathoracic metastases. Meta-analysis results indicate that FDG-PET/CT is beneficial in detecting lymph node metastases and extrathoracic metastases in NSCLC survivors.

3.3.2.2. Fully-Paired Diagnostic Cohort Studies for NSCLC

Three fully paired diagnostic cohort studies were discovered that discussed FDG-PET/CT follow-up in NSCLC survivors. One used FDG-PET/CT to detect recurrence by imaging one year post resection or earlier if recurrence was suspected (19). Twenty-seven of the 86 enrolled patients developed recurrences that were identified by PET/CT and confirmed by histopathologic examination of samples from surgery or biopsy. The PET/CT scan identified 29 positive findings, 27 of which were recurrences and 2 in patients who developed extrathoracic double-primary cancer. More than half of the recurrences were diagnosed in the lung parenchyma, with 33.3% of recurrences occurring in the contralateral lung and lymph node and 25.9% occurring in the ipsilateral lung and lymph node. The remaining recurrences occurred in the liver (18.5%), bone (14.8%), brain (11.1%) and adrenal gland (7.4%). The 86 enrolled patients had predominantly stage IB NSCLC (41.9%), followed by 23.3% with stage IA, 17.4% stage IIIA, 13.9% stage IIB and only 3.5% stage IIA. This study indicates that PET/CT may be beneficial for detecting early locoregional lung cancer recurrence.

A second study looked at the ability of FDG PET/CT to detect progressive disease (PD) starting at approximately three months (16 ± 3.1 weeks) after start of radiotherapy (RT), compared to detection with CT alone (31). Patients were followed every three months for two years, then every six months until five years post-treatment. The study enrolled predominantly late-stage patients (25% stage IIIA, 61% stage IIB, 1% stage IV), with few stage I (4% IA, 6% IB) or stage II (0% IIA, 3% IIB) NSCLC patients. Twenty-four of 100 survivors developed PD, 17 detected by CT alone. The other seven cases required PET scan, as the CT results were negative or inconclusive. Seventeen patients developed locoregional recurrences, with 10 (59%) being inside the RT-field, six (35%) being outside the RT-field, and one patient (6%) developing recurrence both inside and outside the RT-field. Seventeen patients (some of whom developed locoregional recurrence) developed distant metastases, with six having metastasis at more than one site. Of the 24 patients with PD, eight were asymptomatic, with four requiring PET scan to detect PD. Sixteen of the 24 patients were symptomatic when PD was detected, and three of these required PET scan to detect PD. Three of the asymptomatic patients (38%) had PD that was amenable to salvage therapy. In addition, 36 of the 100 enrolled patients showed post-RT effects, which the study authors stated were easily distinguished from PD by combination PET-CT images. In this study, PET-
CT scanning led to the detection of lung cancer progression that was amenable to salvage therapy in a small proportion (3% of total) of the patients enrolled.

The third study focusing on FDG-PET/CT, compared FDG-PET/CT to non-contrast CT for recurrence surveillance after lobectomy in stage I NSCLC survivors (35). Ninety patients received PET/CT and non-contrast CT scans one year after lobectomy. All patients were originally diagnosed with either stage IA or stage IB NSCLC; however, 21 (23.3%) were upstaged to stage II or III based on the pathology results from their lobectomy. The reference standard for detection of recurrent disease was a multidisciplinary tumour board who had access to all imaging and clinical data, who determined that there were 16 true recurrences. Six of the recurrences were in stage I survivors and 10 recurrences in those survivors upstaged to stage II and III. Thus, the recurrence rate of stage I NSCLC survivors one year after lobectomy was 8.7%. The recurrence rate of survivors upstaged to stage II or III NSCLC one year after lobectomy was 47.6%. PET/CT scans identified all 16 recurrences plus five false-positive reports (sensitivity, 100%; specificity, 93.2%), while non-contrast CT identified nine of the 16 recurrences, plus three false-positive reads (sensitivity, 56.3%; specificity, 95.9%). Of the six recurrences in the survivors with stage I disease, non-contrast CT did not detect one, which was a hypermetabolic pulmonary nodule in a patient with many pulmonary nodules. Of the 10 recurrences in the stage II or III survivors, non-contrast CT did not detect six; five extrathoracic metastases and one anterior mediastinal mass. When including all patients, non-contrast CT was 56.3% (95%CI, 37-87%; p=0.16) as sensitive as PET/CT in detecting recurrence, with no significant difference in specificity between the modalities (103%; 95%CI, 22-165%; p=0.62). For survivors of stage I NSCLC, there was no significant difference in the sensitivity (83.3%; 95%CI, 52-124%; p=0.31) or specificity (102%; 95%CI, 15.7-188%; p=0.56) of non-contrast CT compared with PET/CT. However, for survivors upstaged to stage II or III disease after lobectomy, non-contrast CT was 40% as sensitive (95%CI, 18.7-85.4%; p=0.03) as PET/CT, with no significant difference in specificity (110%; 95%CI, 58.8-285%; p=0.31) between the modalities. This study indicates that in advanced-stage NSCLC survivors, PET/CT may be helpful in detecting distant metastases.

A final cohort study compared minimal-dose CT scan (MnDCT) to chest x-ray (CXR) for detection of new or recurrent lung cancer in patients after resection (36). Enrolled survivors of NSCLC received follow-up with MnDCT and CXR at three, six, 12, 18, 24, 36, 48 and 60 months after surgery. Diagnosis of new or recurrent lung cancer was confirmed by full-dose CT and/or tissue biopsy. MnDCT showed a higher sensitivity than did CXR for the diagnosis of new or recurrent lung cancer after surgical resection (94.2%; 95%CI, 84.1-98.8%; vs. 21.2%; 95%CI, 11.1-34.72%; p<0.0001). MnDCT also had a higher negative predictive value compared with CXR (99.7%; 95%CI, 99.0-99.9%; vs. 96.2%l 95%CI, 94.9-97.2%; p=0.007). However, positive predictive value (86%; 95%CI, 83.7-88.1%; vs. 99.9%; 95%CI, 99.5-99.9%; p<0.0001) and specificity (25.1%; 95%CI, 19.2-31.8%; vs. 91.7%; 95%CI, 61.5-99.8%; p=0.0001) were lower for MnDCT than for CXR. Nevertheless, the investigators noted that surgeons were able to recognize false-positive results with high accuracy, and only half the positive MnDCT studies led to further clinical investigation. More than 20% (23.2%; 63/271) of the survivors developed new or recurrent lung cancer, and 78% (49/63) of these were asymptomatic, which were only detected by MnDCT. The majority of asymptomatic patients (67.3%, 32/49) were diagnosed with MnDCT within the first year, while 26.5% (13/49) were diagnosed within the second year. Due to detection of the new or recurrent cancer at a subclinical stage, most of the asymptomatic patients (75%, 37/49) were treated with curative-intent surgery or radiation and had a median survival of 69 months (range 12-76 months) from the initial resection. This study points to a potential beneficial role for MnDCT in detecting new primary tumours and recurrent lung cancer at a time when curative treatment is possible, leading to long-term survival.
3.3.3. Study Summary

Two reports were found that discussed overall survival and symptomatic versus asymptomatic recurrence when comparing intensive with less intensive follow-up. A meta-analysis (8) found that asymptomatic recurrence was associated with longer survival time, but that intensive follow-up schedules did not increase overall survival time, nor asymptomatic recurrence detection. Similarly, a NSCLC cohort study (29) found that intensified follow-up did not result in an increase in the number of patients treated for relapse nor an increase in the proportion of patients detected with asymptomatic relapse. In terms of imaging lung cancer recurrence or progression, identified systematic reviews and primary literature focused on CT or PET/CT. For CT imaging, one systematic review (6) evaluated the role of CT follow-up in surveillance after lobectomy in NSCLC survivors and found conflicting results for a survival benefit. A cohort study indicated a role for MnDCT scans in detecting new primary tumours and recurrent lung cancer at an early stage (36). For PET/CT imaging, one meta-analysis and three studies were included. The meta-analysis (7) indicated that PET/CT is beneficial in detecting lymph node metastases and extrathoracic metastases in NSCLC survivors. Two cohort studies that assessed PET/CT for imaging lung cancer relapse in NSCLC survivors found that PET/CT may show more benefit than CT alone (19,31), while a third cohort study found that PET/CT was more sensitive than non-contrast CT for detecting recurrence in advanced-stage NSCLC survivors (35).

3.4. Question 3: What symptoms are indicative of possible recurrence or development of any other primary cancer that warrant further evaluation?

The literature search did not return any systematic reviews or studies that looked specifically at symptoms of recurrence or development of a secondary primary cancer in lung cancer survivors. However, one of the diagnostic studies, which was discussed while addressing Research Questions 1 and 2, listed the symptoms experienced by patients at detection of PD (31). The van Loon study (31) described the percentage of patients with specific symptoms at detection of PD versus the percentage of patients experiencing the symptom that did not have PD. Patients with PD experienced significantly more pain (45.8% vs. 5.3%, p<0.001) and more neurological issues (16.7% vs. 2.6%, p=0.01). Although four patients presented with brain metastases, the study did not indicate if the patients with neurological issues corresponded to those with brain metastases. More patients with PD also had the presence of a palpable mass (4.2% vs. 0.0%) compared to patients without PD; however, due to the small sample size, this difference was not significant (p=0.07). Symptoms that were not different between patients with and those without PD included cough (12.5% vs. 19.7%, p=0.42), dyspnea (12.5% vs. 14.5%, p=0.81), dysphagia (4.2% vs. 2.6%, p=0.70), malaise (4.2% vs. 1.3%, p=0.38) and fatigue (0.0% vs. 1.3%, p=0.57). Thus, the study concluded that patients with PD experienced more pain and neurological issues that those without PD.

3.5. Question 4: What are the common non-recurrence related issues experienced by lung cancer survivors?

This question focused on late treatment toxicities (at least 6 months post-treatment) and on-going QoL issues experienced by lung cancer survivors. The search for systematic reviews returned two: one discussed the impact of lung resection on QoL of lung cancer survivors (9) and the other discussed health and QoL of long-term survivors (10). The systematic review of primary literature returned nine studies: one before-and-after comparison that focused on the impact of resection on QoL (26), one RCT on the impact of neoadjuvant therapy and lung resection on QoL (22), one RCT on late lung toxicity after concurrent chemoradiotherapy (32), one controlled before-and-after study looking at QoL
(24), one before-and-after comparison on physical activity and QoL (28), one case-control study on sleep patterns of lung cancer survivors (21) and three before-and-after comparisons that focused on on-going symptoms (18,30,33).

3.5.1. Studies Assessing General QoL Scales for NSCLC and SCLC Survivors

3.5.1.1. Systematic Reviews

The systematic review discussed the impact of lung resection on QoL of lung cancer survivors (9). Data was extracted from 15 studies, none of which were RCTs, comparing QoL pre- and post-pulmonary lobectomy or pneumonectomy. The reviewers concluded that pulmonary lobectomy had a transient negative influence on QoL, while pneumonectomy had a larger negative impact that did not recover over the follow-up period (Table 3).

3.5.1.2. Non-Randomized Prospective Cohort Studies

A before-and-after comparison examined QoL after lung resection in NSCLC and SCLC survivors (26). The majority of enrolled patients (62.6%) were diagnosed with tumour stage I or II, while a smaller percentage (7.2%) were diagnosed with stage III. Patients filled out SF-36 (short form 36) questionnaires pre-surgery, then six months and two years post-surgery. Both the change in SF-36 physical (PCS) and mental (MCS) component summary scores were calculated. In addition to comparing within the group across time, QoL was also compared with an age and gender-matched reference population (RP). Survivors experienced decreased PCS scores that never returned to baseline levels and were lower than the RP (Table 3). The MCS scores increased after surgery but were still lower than the RP (Table 3). Thus lung cancer survivors treated with surgery experienced an early decrease in the physical domain of QoL that did not improve after two years. A moderate, and clinically relevant, improvement in the mental domain of QoL was experienced by survivors after surgery for lung cancer (Table 5).

3.5.2. Studies Assessing General QoL Scales for NSCLC Survivors

The Gralla RCT assessed the QoL changes in NSCLC patients after neoadjuvant therapy and lung resection (22). The study was a follow-up to the Gemcitabine in Neoadjuvant Early Stage Trials (GINEST). Patients were randomized to receive one of two neoadjuvant therapy regimens involving Gemcitabine followed by resection for all patients. The majority of the enrolled patients were diagnosed with stage IB (49%) NSCLC, followed by 26% of patients diagnosed with stage IIB, 21% with stage IA, and 3% with stage IIA. QoL was assessed using the Lung Cancer Symptom Scale (LCSS). Patients filled out the questionnaire at baseline, then three, six and 12 months post-surgery. Two potentially overlapping groups were analyzed separately, leading to potential risk of bias. One group, defined as the LRM (last recorded measurement) group, consisted of 43 patients who completed baseline LCSS plus at least one LCSS post-surgery, while the ASBI (average-symptom-burden index) group of 25 patients completed baseline plus at least two post-surgery LCSS assessments. The study did not specify at what time point the post-surgery LCSS assessed occurred. Following lobectomy, pneumonectomy or bilobectomy, the majority of the enrolled patients reported improved or stable QoL scores (Table 3).
Table 3. Studies assessing overall QoL profiles of lung cancer survivors.

<table>
<thead>
<tr>
<th>Study</th>
<th>QoL Assessment Tool</th>
<th>Major QoL Findings</th>
</tr>
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<tbody>
<tr>
<td><strong>Survivors of NSCLC and SCLC</strong></td>
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<tr>
<td><strong>Systematic Reviews</strong></td>
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</table>
| Brunelli et al, 2012 (9)                   |                    | • 6 studies: EORTC C30 + LC13                                                                                             • Following lobectomy                          o Reduction in physical functioning at 6 and 12 months  
• 9 studies: SF36 +/- QLI                    |                    | • Following pneumonectomy                           o Decline in physical domains up to 12 months post-surgery  
                                                                                                           o Decline in emotional and mental domains compared with pre-surgery values |
| **Non-Randomized Prospective Cohort Studies** |                    |                                                                                                                                                                                                                   |
| Moller and Sartipy, 2012 (26)              | SF36               | • Physical component summary (PCS)                                                                                       o Decreased at 6 months vs. pre-surgery (p<0.001)  
                                                                                                           o Remained low at 2 years post-surgery (p<0.001)  
                                                                                                           o Lower than reference population at 2 years (p=0.013)  
• Physical role function subscale                  |                    | • Physical role function subscale                           o Dropped at 6 months vs. pre-surgery (p<0.001)  
                                                                                                           o Increased at 2 years post-surgery compared with 6 months (p<0.001), but not to pre-surgery level  
                                                                                                           o Changes considered clinically relevant  
• Mental component summary (MCS)               |                    | • Mental component summary (MCS)                                                                                       o Increased at 6 months vs. pre-surgery (p=0.001)  
                                                                                                           o Further improved at 2 years (p=0.005)  
                                                                                                           o Lower than reference population at 2 years (p=0.01)  
• Mental health subscale                     |                    | • Mental health subscale                                                                                                      o Improved trend at 6 months vs. pre-surgery (p=0.114)  
                                                                                                           o Significant improvement from 6 months to 2 year post-surgery (p<0.001)  
                                                                                                           o 2-year change deemed clinically relevant  
| **Survivors of NSCLC**                      |                    |                                                                                                                                                                                                                   |
| **Randomized Controlled Trials**            |                    |                                                                                                                                                                                                                   |
| Gralla et al, 2009 (22)                     | LCSS               | • Following lobectomy                                                                                                  o 65% of survivors experienced improved or stable scores  
                                                                                                           o 35% experienced worsening symptoms  
                                                                                                           o Difference not statistically significant  
• Following pneumonectomy or bilobectomy       |                    | • Following pneumonectomy or bilobectomy                                                                                                    o 71% of survivors experienced improved or stable scores  
                                                                                                           o 29% experienced worsening symptoms  
                                                                                                           o Difference not statistically significant  

Abbreviations: EORTC, European Organization for the Research and Treatment of Cancer; LC13, lung cancer module (13 questions); LCSS, Lung Cancer Symptom Scale; QLI, Quality of Life Index; SF-36, Short Form 36.

3.5.3. Studies Assessing Specific Symptoms Experienced by NSCLC and SCLC Survivors

3.5.3.1. Systematic Reviews

The one systematic review identified looked at health and QoL of lung cancer survivors that were at least five years post-diagnosis (10). The reviewers found little data available on treatment-related late toxicities, but some evidence indicated that lung cancer survivors experienced physical ability restrictions, depression, decreases in general health and vitality and increased body pain (Table 4). The prevalence and severity of comorbidities was very high in lung cancer survivors, and comorbidities were related to reduced functioning as measured in the physical and mental domains of the QoL tools. The majority of recurrences
in lung cancer survivors were detected within two years. Stage I NSCLC survivors showed a recurrence incidence rate of 2%-3% per patient-year, while the incidence of second primary lung cancer after resection for NSCLC was 1%-2% per patient-year. The cumulative risk of second primary lung cancer or other smoking-related cancers was 13%-20% at six to eight years after NSCLC resection. The review also found that the risk of a second primary lung cancer is high for SCLC survivors with the cumulative risk being 30% at 10-12 years after initial treatment. Risk is increased by chest RT and continued smoking in SCLC survivors. The review concluded that lung cancer survivors are at an elevated risk of premature death and reduced QoL.

3.5.3.2. Non-Randomized Prospective Cohort Studies

A before-and-after comparison study examined the relationship between physical activity and QoL in long-term lung cancer survivors. Patients were enrolled in the Epidemiology and Genetics of Lung Cancer Research Program at the Mayo Clinic in Rochester, MN (28). Most survivors had been originally diagnosed with early-stage (49% stage I and 9% stage II) disease, with fewer experiencing late-stage tumours (21% stage III, 14% stage IV). Enrolled patients completed questionnaires on at least two time points, one before or during treatment and at least one during follow-up. Questionnaires assessed smoking status, physical activity, QoL and symptom control. In terms of smoking status, patients were classified as a current smoker, past smoker, or never smoker. Physical activity level was defined as “state of change for physical activity level” and assessed by a four-item measure related to current activity level and intention for future activity. QoL was assessed by the Linear Analog Self-Assessment (LASA) questionnaire. Symptom control was based on six symptoms and rated on a 10-point scale. The study concluded that there was a significant link between increased physical activity and QoL, as well as symptom control for lung cancer survivors (Table 4).

A before-and-after comparison by Cheville and colleagues sought to identify a persistent symptom cluster in lung cancer survivors (18). As with the Solberg study (28), patients were enrolled in the Epidemiology and Genetics of Lung Cancer Research Program at the Mayo Clinic in Rochester, MN. However, unlike the Solberg study, this study provided more detail on the original tumour stage and disease type of the participants. More than forty percent (41.2%) of the patients were diagnosed with stage I NSCLC, 8.8% with stage II NSCLC, 28.2% with stage III NSCLC or limited-disease SCLC and 21.8% with stage IV NSCLC or extensive SCLC. Data were collected six months after diagnosis and then annually. Patients completed LCSS, which assessed appetite, fatigue, coughing, dyspnea, hemoptysis and pain. Patients also completed the LASA, which rated cognitive, emotional and social well-being, plus sleep quality and overall QoL. Additionally, with each assessment, patients were asked about tobacco use (current/previous use, duration, average number smoked per day, years since quitting). A non-parametric cluster analysis detected a single symptom cluster (SxCl), which included dyspnea, cough, and fatigue (Table 4). The SxCl had a stable prevalence within the lung cancer survivor population up to five years after diagnosis (Table 4).

A case-control study looked at sleep patterns of lung cancer survivors compared with non-cancer controls (NCC) (21). Sleep data were obtained over the phone using the Pittsburgh Sleep Quality Index (PSQI) questionnaire. Due to the study design, stage data were not provided. The study assessed sleep quality, insomnia, sleep apnea, limb movement disorder, daytime consequences of sleep deprivation and medication use. The study also calculated sleep efficiency, defined as wake time minus bedtime, divided by the time spent sleeping. Symptoms related to sleep disturbances, including pain severity, depression and dyspnea, as well as overall perception of QoL, were also assessed by the study. Lung cancer survivors were found to have lower sleep efficiency than did NCCs (Table 4). The decrease in
sleep efficiency was attributed to increased wakefulness after sleep onset; lung cancer survivors reported waking up in the middle of the night more often than did NCCs (40.8% vs. 21.8%, p=0.01) (Table 4). Poor sleep quality was associated with lower QoL for both groups.

Another before-and-after comparison looked at QoL and symptom burden of long-term lung cancer survivors within three and five years post-diagnosis (33). Similar to the Cheville (18) and Solberg (28) studies, patients were enrolled at the Mayo Clinic and were followed within six months of diagnosis and then annually until death, using the LCSS questionnaire to assess QoL. The majority of the enrolled patients were diagnosed with early-stage disease (67.8% stage I, 11.4% stage II), while a smaller percentage were diagnosed with late-stage disease (16.8% stage III, 4.0% stage IV). Thirty-five percent of patients reported a decrease in overall QoL over time, with only 15% reporting an improvement. For those lung cancer survivors who reported a decreased QoL, symptom burden included increased fatigue, pain, cough, and dyspnea, and a decline in appetite. Multiple logistics regression modelling indicated that older age; lung cancer progression; recurrence; and poor scores in fatigue, dyspnea, and pain were significantly associated with poor overall QoL (Table 4). The study authors concluded that lung cancer survivors suffer from a substantial symptom burden.

A before-and-after comparison examined patients’ perspectives on symptom intensity and distress in survivors of primary inoperable lung cancer (30). Patients completed self-report instruments at six points: before treatment initiation (T1), two weeks after T1 (T2), one month after T1 (T3), three months after T1 (T4), six months after T1 (T5), and one year after T1 (T6). At study enrollment, 14.0% of the patients had been diagnosed with SCLC, while 85% were diagnosed as NSCLC. For the remaining 1%, type of diagnosed lung cancer was missing. In terms of stage, 3% had stage I disease, 5% stage II, 9% stage IIIA, 19% stage IIIB, and 41% stage IV, with 6% of patients having an unclassified tumour and 17% missing stage data. A research nurse was present at each assessment point. Self-reported symptom distress and intensity were measured by the McCorkle and Young Symptom Distress Scale (SDS) and Thurstone Scale of Symptom Distress-Lung Cancer (TSSD-LC). Self-report data were supplemented with field documentation by the research nurse. Breathing, pain, and fatigue were reported as the most distressing symptom across all time points, while fatigue was recorded as the most intense symptom (Table 4).

3.5.4. Studies Assessing Specific Symptoms Experienced by NSCLC Survivors

3.5.4.1. Randomized Controlled Trials

An RCT examined late lung toxicity in patients with inoperable NSCLC (stage II and III), treated with concurrent chemoradiotherapy (32). Patients were recruited from those enrolled in four Radiation Therapy Oncology Group (RTOG) clinical trials. The RCT looked at acute esophagitis within three months of initiating RT and pneumonitis (PN) after three months. Since late treatment effects were the focus of this research question, only PN data was extracted. PN was scored according to the scale used for RTOG clinical trials with toxicity scores assessed as Grade 0 through Grade 4. Medium follow-up was 1.4 years (range, 0.3-12.2 years). Fifty-nine percent of patients experienced some degree of PN, with 18% experiencing severe PN (Grade 3 or 4; Table 4). No new cases developed after two years. The risk of late Grade 2 or 3 lung toxicity was associated with increased total RT dose (odds ratio [OR], 1.05; p=0.002 and OR, 1.05; p=0.045).

3.5.4.2. Non-Randomized Comparative Prospective Cohort Studies

A controlled before-and-after study by Ilonen and colleagues evaluated short- and long-term QoL in post-resection NSCLC patients to determine if there was a link between QoL and pre-operative pulmonary function tests (PFTs) (24). Patients completed pre-operative
spirometry, which included forced expiration volume in 1 second (FEV1), forced vital capacity (FVC), FEV1/FVC and pulmonary diffusion capacity for carbon monoxide (DL\textsubscript{CO}). QoL was assessed using the 15D QoL instrument pre-operatively, then at three, 12 and 48 months postoperatively. The majority of enrolled patients were stage I (35.4% stage IA, 31.3% stage IB), with 10.4% having a stage IIB tumour, and the remaining patients were diagnosed with stage III NSCLC (20.8% stage IIIA, 2.1% stage IIIB). The median survival of patients who died over the study period was 28 months (range, 5-61 months). QoL scores were compared with an age-standardized general population. The study found that resection was associated with a significant and sustained decrease in multiple QoL domains (Table 4).

Table 4. Studies assessing long-term symptom burden experienced by lung cancer survivors

<table>
<thead>
<tr>
<th>Study</th>
<th>QoL Tool: Symptom(s) Assessed</th>
<th>Time of Assessment</th>
<th>Major Symptom Burden Findings</th>
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<tr>
<td><strong>Survivors of NSCLC and SCLC</strong></td>
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<td>Systematic Reviews</td>
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<tr>
<td>Sugimura and Yang, 2006 (10)</td>
<td>General health, vitality, physical function, bodily pain and chronic post-thoracotomy pain</td>
<td>NA</td>
<td>• 25% of lung cancer survivors report physical ability restrictions and depression</td>
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<td>• Evidence shows that lung cancer survivors experience a decrease in general health, vitality, physical function and bodily pain 12 months post-resection</td>
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<td>• 30% of lung cancer survivors report chronic post-thoracotomy pain beyond 4 years post-surgery</td>
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<td><strong>Non-Randomized Prospective Cohort Studies</strong></td>
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<tr>
<td>Solberg Nes et al, 2012 (28)</td>
<td>LAAS: frequency of pain, severity of pain, dry cough, cough with phlegm, shortness of breath and level of fatigue; physical activity level</td>
<td>Before or during treatment and at least once during follow-up</td>
<td>• Survivors reporting a decrease in physical activity level experienced:</td>
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<td></td>
<td>o Decreased mental well-being (p&lt;0.001)</td>
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<td>o Decreased physical well-being (p&lt;0.001)</td>
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<td>o Decreased emotional well-being (p&lt;0.001)</td>
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<td>o Decreased social well-being (p&lt;0.001)</td>
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<td>o Decreased spiritual well-being (p&lt;0.001)</td>
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<td>o Decreased overall QoL (p&lt;0.001)</td>
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<td>o Increased frequency of pain (p=0.03)</td>
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<td>o Increased severity of pain (p=0.002)</td>
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<td>o Increased frequency of dry cough (p=0.03)</td>
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<td>o Increased coughing with phlegm (p&lt;0.001)</td>
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<td>o Increased shortness of breath (p=0.003)</td>
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<td>o Increased level of fatigue (p&lt;0.001)</td>
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<td>• Survivors reporting an increase in physical activity level experienced:</td>
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<td>o Increased mental well-being (p=0.005)</td>
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<td>o Increased social well-being (p&lt;0.001)</td>
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<td>o Increased emotional well-being (p=0.02)</td>
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<td>o Increased spiritual well-being (p=0.02)</td>
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<td>o Increased overall QoL (p&lt;0.001)</td>
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<td>o Reduced pain frequency (p=0.005)</td>
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<td>o Reduced pain severity (p=0.006)</td>
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<td>Study</td>
<td>QoL Tool: Symptom(s) Assessed</td>
<td>Time of Assessment</td>
<td>Major Symptom Burden Findings</td>
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| Cheville et al, 2011 (18)     | LCSS and LASA: Appetite, fatigue, coughing, dyspnea, hemoptysis, pain sleep quality; cognitive, emotional and social well-being | 6 months after diagnosis, then annually | * Identified symptom cluster (SxCl)*  
  o Dyspnea, cough, fatigue  
 * Experienced by:*  
  o Year 1: 14.6% of lung cancer survivors  
  o Year 2: 12.9% of lung cancer survivors  
  o Year 3: 14.1% of lung cancer survivors  
  o Year 4: 14.6% of lung cancer survivors  
  o Year 5: 15.4% of lung cancer survivors |
| Gooneratne et al, 2007 (21)   | PSQI: Sleep quality and symptoms related to sleep disturbances - pain, depression, dyspnea, QoL perception | At least 5 years post-diagnosis       | * Survivors experienced lower sleep efficiency than non-cancer controls (NCC; p<0.001)*  
  o Survivors spent more time in bed (8.4 ± 1.3 hr vs. 7.3 ± 1.2 hr, p=0.01), but less time asleep (6.5 ± 1.4 hr vs. 7.0 ± 1.4 hr, p=0.02)*  
 * More survivors rated sleep quality as bad compared with NCC (25.3% vs. 11.7%, p=0.03) and were more likely to use sleep medications (19.7% vs. 11.5%, p=0.03)*  
  o Verified by higher PSQI scores for survivors compared with NCC, where a score greater than 5 indicates poor sleep quality (6.3 ± 4.1 vs. 4.5 ± 3.1, p=0.002)*  
 * Dyspnea was found to cause more problems for survivors compared with NCC (2.6 ± 3.4 vs. 1.1 ± 2.5, p=0.003)*  
 * Similar levels of depression and QoL between groups* |
| Yang et al, 2012 (33)         | LCSS: appetite, fatigue, cough, dyspnea, hemoptysis, pain, symptom distress, activity reduction and overall QoL | Within 6 months of diagnosis, then annually | * 35% of survivors reported decreased overall QoL over time with the following symptom burden (change of at least 10 points on LCSS):*  
  o 69% experienced increased fatigue  
  o 59% experienced increased pain  
  o 58% experienced increased dyspnea  
  o 49% experienced decline in appetite  
  o 42% experienced increased cough  
 * 15% of survivors reported improved overall QoL over time*  
  o No specific function or symptom changed more than 10 points on the LCSS and thus not considered clinically relevant* |
| Tishelman et al, 2005 (30)    | SDS and TSSD-LC: fatigue, insomnia, appetite, mobility, concentration, mood, outlook, appearance, pain, nausea, bowel function, cough and breathing | Before treatment, 2 weeks after treatment, 1, 3, 6 and 12 months after treatment | * Breathing, pain and fatigue most distressing symptoms across all time points*  
 * According to lung cancer survivors, symptom intensity was not equivalent to symptom distress*  
 * Fatigue recorded as most intense symptom by SCLC and NSCLC survivors*  
  o Higher levels for SCLC survivors at 3-12 months post-treatment*  
 * At 1 year post-treatment:*  
  o SCLC survivors ranked breathing, pain and cough as top distressing symptoms  
  o Women reported higher levels of pain and appetite disturbances than did men  
  o Young survivors reported higher levels of bowel problems than did older survivors* |
<table>
<thead>
<tr>
<th>Study</th>
<th>QoL Tool: Symptom(s) Assessed</th>
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<td><strong>Randomized Controlled Trials</strong></td>
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<tr>
<td>Werner-Wasik et al, 2011 (32)</td>
<td>Pneumonitis (PN) scored Grade 0 through Grade 4</td>
<td>3 months after treatment through 48 months</td>
<td>No new cases of PN developed after 2 years</td>
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<td>Late Grade 2 or 3 lung toxicity risk was associated with increased total radiotherapy dose (OR, 1.05; p=0.002 and OR, 1.05; p=0.045, respectively)</td>
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<td><strong>Non-Randomized Comparative Prospective Cohort Studies</strong></td>
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<tr>
<td>Ilonen et al, 2010 (24)</td>
<td>Pulmonary function test and 15D: Lung function, moving, seeing, hearing, breathing, sleeping, eating, speech, elimination, usual activities, mental function, discomfort and symptoms, depression, distress, vitality and sexual activity</td>
<td>Pre-resection then 3, 12 and 48 months post-resection</td>
<td>At pre-resection:</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>o No overall QoL differences between NSCLC-S and reference population (RP)</td>
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<td></td>
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<td></td>
<td>o Differences between groups for following dimensions: breathing (p=0.001), mental function (p=0.001), discomfort and symptoms (p=0.021), and distress (p=0.028)</td>
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<td></td>
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<td>o Decrease in QoL compared with pre-operative scores over 2-year follow-up (p=0.001 at 3 months post-operation (MPO), p=0.019 at 12MPO, p=0.001 at 24MPO). Altered dimensions included:</td>
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<td>o Reduced mobility at 3MPO (p=0.001) and 24MPO (p=0.008)</td>
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<td>o Increased breathing impairment at 3MPO (p=0.002) and 24MPO (p=0.001)</td>
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<td></td>
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<td>o Reduced ability to perform usual activities at 3MPO (p=0.001), 12MPO (p=0.004) and 24MPO (p=0.019)</td>
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<td></td>
<td>o Sexual activity reduction at 24MPO (p=0.019)</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>• More depression reported at month 3 (p=0.004)</td>
</tr>
</tbody>
</table>

Abbreviations: LASA, Linear Analog Self-Assessment; LCSS, Lung Cancer Symptom Scale; NA, not applicable; NSCLC, non-small cell lung cancer; NSCLC-S, NSCLC survivors; OR, odds ratio; PSQI, Pittsburgh Sleep Quality Index; QoL, quality of life; SCLC, small cell lung cancer; SCLC-S, SCLC survivors; SDS, McCorkle and Young Symptom Distress Scale; TSSD-LC, Thurstone Scale of Symptom Distress - Lung Cancer.

### 3.5.5. Study Summary

When evaluating overall QoL profiles, the search for systematic reviews returned one, which found that survivors of SCLC and NSCLC experience a reduction in physical ability for up to a year post-surgery (9) (Table 3). A before-and-after cohort study found that NSCLC and SCLC survivors treated with surgery experienced an improvement in the mental domain of QoL, but also an early decrease in physical ability (26) (Table 3). An RCT that focused on NSCLC survivors found that following lobectomy, 65% of survivors experienced improved or stable QoL scores, while 71% of survivors experienced improved or stable scores following pneumonectomy or bilobectomy (22) (Table 3).
When assessing specific symptoms experience by lung cancer survivors, the search for systematic reviews identified one review, which found that lung cancer survivors report physical ability restrictions, depression, decreases in general health and vitality and increased body pain (10) (Table 4). Identified cohort studies found that survivors of NSCLC and SCLC experience long-term dyspnea (18,21,33), cough (18,33), fatigue (18,33), impaired breathing (30), increased pain (30,33), decline in appetite (30,33) and reduced sleep efficiency (21). Studies that focused solely on survivors of NSCLC found that a majority of these survivors experienced some degree of pneumonitis (32) and a sustained decrease in multiple QoL domains (24).

3.6. Question 5: Is there a relationship between the clinician and/or setting of follow-up care and the effective detection and management of recurrent or metastatic disease?

This research question was designed to determine the most responsible health care professional and follow-up location for lung cancer survivors. For the purposes of this systematic review, a specialist was defined as a physician certified by the Royal College of Physician and Surgeon of Canada (RCPSC). The search for published systematic reviews returned one review (37) that looked at nurse-led follow-up compared with specialist-led follow-up. This review included multiple cancer types and only included one study with lung cancer survivors, so the actual RCT (27) will be discussed in this evidence summary and not the systematic review. The RCT by Moore and colleagues (27) was also the only study that was found through the systematic review of the primary literature that discusses the most responsible health care professional for lung cancer survivors. Although the RCT enrolled a population with a more advanced disease stage than our target population, the RCT was included as the best available evidence.

The study conducted by Moore and colleagues randomized post-treatment lung cancer patients who were expected to live at least three months, into either a nurse-led follow-up arm or a conventional specialist-led follow-up arm, following treatment (27). The enrolled patients were diagnosed with either NSCLC (72.8%), limited SCLC (8.4%), extensive SCLC (8.9%), mesothelioma (6.9%) or not known (no histology, 3.0%). In terms of stage for the NSCLC patients, 12.9% of tumours were stage I or II, 10.4% were stage IIIA, 31.7% were stage IIIB, 18.8% were stage IV, and 2.0% were unknown. The nurse-led model included a clinical visit with a nurse specialist or telephone follow-up once a month, while the specialist-led follow-up included an out-patient appointment with the specialist every two or three months. Nurse-led patients also had open access to the nurse specialist. Both population arms continued to visit their family physician as needed. The data was analyzed at three, six and 12 months. At three months, patients rated dyspnea as less severe in the nurse-led group compared with the conventional group (p=0.03). There were no other differences at month 3. There were no differences between the two patient groups at month 6. At 12 months, the nurse-led group had better emotional functioning scores (p=0.03) and less peripheral neuropathy (p=0.05) than the specialist-led group. Satisfaction with care was high in both groups. At three months, 78% of nurse-led patients reported they would prefer nurse-led care if asked, while only 17% of specialist-led patients reported preferring to see a doctor only. Mortality during the 12-month follow-up was 70% overall (n=141/202), which included 73% (n=72/98) of the nurse-led and 67% (n=69/103) of the specialist-led patients. When looking at progression, median time to symptomatic progression was 6.0 months (range, 4.7-7.3 months) for nurse-led patients and 10.2 months (range, 5.9-14.6 months) for specialist-led patients (p=0.01), while median time to objective progression was 8.3 months (range, 5.5-12.2) for nurse-led and 10.2 months (range, 5.9-14.5) for specialist-led patients (p=0.47), indicating that nurses recorded symptoms sooner than specialists. No difference in overall cost of care was found between groups even though nurse-led patients had fewer medical consultations.
with hospital doctors at three months (p=0.004), fewer radiographs at three months (p=0.04) and six months (p=0.03), and were more likely to have had RT at three months (p=0.01). More nurse-led patients died at home (40%), compared with specialist-led patients (23%, p=0.04). When family physicians were surveyed on satisfaction, 46% indicated a preference for future follow-up provided by both clinical nurse specialist and oncologist (9% oncologist alone, 18% nurse-led service alone). The study authors concluded that nurse-led follow-up care within an institutional setting was acceptable to patients and family physicians and did not negatively impact quality of care.

3.7. Question 6: Is there a value to smoking cessation counselling for lung cancer survivors?

The search for existing systematic reviews returned five systematic reviews on aspects of smoking cessation: three on effects of cessation after diagnosis (11,14,15), one on the effectiveness of counselling (12) and one on the effectiveness of counselling paired with medication (13). The systematic search for primary literature returned four studies relating to aspects of smoking cessation in lung cancer survivors: one controlled before-and-after study on effects of cessation after diagnosis (34) and three controlled before-and-after studies on effects of smoking on QoL of lung cancer survivors (16,17,20).

3.7.1. Studies Investigating the Benefits of Smoking Cessation

3.7.1.1. Systematic Reviews

The systematic review by Parsons reviewed the effects of smoking cessation after diagnosis of primary lung cancer (11). Data was extracted from RCTs and longitudinal observational studies. The majority of patients enrolled in most included studies were diagnosed with early-stage lung tumours. For NSCLC, continued smoking after diagnosis was associated with increased risk of mortality from all causes (HR, 2.94; 95%CI, 1.15-7.54) and recurrence (HR, 1.86; 95%CI, 1.01-3.41). For limited-stage SCLC, continued smoking was associated with increased mortality from all causes (HR, 1.86; 95%CI, 1.33-2.59), development of a second primary tumour (HR, 4.31; 95%CI, 1.09-16.98), and recurrence (HR, 1.26; 95%CI, 1.06-1.5). Estimation based on life table modeling for NSCLC indicated a 33% five-year survival in 65-year-old patients who continue to smoke, compared with 70% five-year survival for those who quit. Estimation based on life table modeling for limited-stage SCLC indicated 29% five-year survival for persistent smokers, compared with 63% five-year survival for those who quit. This review provides evidence that smoking cessation after a diagnosis of early-stage lung cancer improves outcomes.

A Cochrane Collaboration systematic review assessed the effects of pre-operative smoking intervention on smoking cessation and on post-operative complications (14). The population of these studies were not lung cancer survivors, but instead, any smoker of any age who was scheduled for elective surgery. The review only extracted data from RTCs that recruited smokers before surgery. Intensive interventions were defined as those which included weekly counselling sessions provided pre-operatively and continuing over four to eight weeks. Brief interventions were provided in relation to routine pre-operative evaluations and involved at least one face-to-face, telephone counselling, interactive computer counselling session, or letter about the risk of smoking in relation to surgery. Studies reported smoking status at time of surgery and 12 months post-operatively. A subgroup analysis indicated that both intensive and brief interventions increased smoking cessation at the time of surgery (intensive intervention: Relative Risk [RR], 10.76; 95%CI, 4.55-25.46; brief intervention: RR, 1.41; 95%CI, 1.22-1.63). When looking at post-operative complications, pooled RRs from five studies were 0.70 (95%CI, 0.56-0.88) for any complication...
and 0.70 (95%CI, 0.51-0.95) for wound complications. Intensive intervention showed a significant effect on any complication (RR, 0.42; 95%CI, 0.27-0.65) and on wound complications (RR, 0.31; 95%CI, 0.16-0.62). Brief interventions, did not show a statistically significant effect, but CIs did not rule out a clinically significant effect (any complication: RR, 0.96; 95%CI, 0.74-1.25; wound complications: RR, 0.99; 95%CI, 0.70-1.40). This review indicates that pre-operative smoking cessation intervention resulted in increased smoking cessation and a subsequent reduction in post-operative morbidity.

A brief systematic review by Zaman and colleagues reviewed studies examining if timing of smoking cessation in patients undergoing lung resection predicted incidences of post-operative pulmonary complications (PPCs) (15). The risk of PPCs and hospital death declined with smoking cessation; however, no optimal interval of smoking cessation has been identified. Evidence suggests that risk declines with a longer smoke-free period. Two of the seven included studies pointed to a smoking abstinence greater than four weeks needed to ensure reduced risk of PPCs. The review authors concluded that all patients should be counselled in smoking cessation before lung resection.

3.7.1.2. Non-Randomized Comparative Prospective Cohort Studies

A controlled before-and-after study in early-stage NSCLC patients examined the association between smoking cessation and overall survival and recurrence-free survival (34). Patients completed a modified version of the detailed American Thoracic Society health questionnaire at recruitment to determine smoking status. The majority of enrolled patients were diagnosed with stage IA NSCLC (51.0%), followed by 29.3% being diagnosed with stage IB and 19.7% having stage IIA/IIIB. Patients’ smoking status was categorized as 1) never smokers (smoked <100 cigarettes in lifetime), 2) ex-smokers (stopped smoking one year before diagnosis), or 3) current smokers. Ex-smokers were further divided into ex-smokers who quit one to eight years previous, nine to 17 years previous, and more than 18 years before diagnosis. The study examined overall survival, calculated from date of surgery to date of last follow-up or death (from any cause) and recurrence-free survival, defined as the time from surgery to the first date of recurrence or death (any cause). Five-year overall survival rates were 50% (43%-58%) for current smokers, 58% (52%-64%) for ex-smokers and 76% (63%-90%) for never smokers (p=0.02). Five-year recurrence-free survival rates were 38% (31%-45%) for current smokers, 50% (44%-57%) for ex-smokers and 60% (45%-76%) for never smokers (p=0.01). For overall survival, smoking cessation was associated with better overall survival rate (but not significant, p=0.09). A beneficial effect of smoking cessation on overall survival was observed only among women (p=0.01). Adjusted HRs for ex-smokers who quit one to eight years previously (HR, 0.82; 95%CI, 0.59-1.13), nine to 17 years (HR, 0.69; 95%CI, 0.49-0.97), at least 18 years (HR, 0.66; 95%CI, 0.45-0.95), and never smokers (HR, 0.54; 95%CI, 0.29-0.996) were significantly different from current smokers (p=0.004). Smoking cessation was associated with significantly better recurrence-free survival (p=0.03). Again, the beneficial effect of smoking cessation on recurrence-free survival was observed only among women (p=0.01). The study authors concluded that smoking cessation leads to improved survival and that the advantage is directly proportional to the length of time since cessation.

3.7.2. Studies Investigating the Effectiveness of Physician Counselling on Smoking Cessation

A Cochrane systematic review assessed the effectiveness of physician counselling in promoting smoking cessation in all smokers (12) (Table 5). Data were extracted from RCTs that examined smoking status at least six months after advice from medical practitioners. The reviewers found that cessation advice was provided most commonly by primary care practitioners, while less common settings included hospital wards, outpatient clinics and
industrial clinics. Advice was categorized as brief, brief plus printed material or intensive (parameters explained in Table 5). Both brief intervention and intensive intervention improved quit rates, with a small but significant advantage to intensive intervention compared with brief intervention. The review also indirectly compared studies using additional aids (demonstration, PFT, self-help manuals) with studies that did not use additional aids and found no difference between the subgroups.

Another Cochrane review, by the same lead author as the previous, assessed the effectiveness of combining behavioural support and medication to aid smoking cessation (13) (Table 5). Data were extracted from both RCTs and quasi-RCTs that examined combinations of pharmacotherapy and behavioural support for smoking cessation. Most studies recruited patients in healthcare settings or with specific health needs. The systematic review excluded studies that recruited only pregnant women or adolescents. Reviewers found that there was a significant benefit to combination pharmacotherapy and behavioural support compared with brief intervention or behavioural support alone (Table 5). When studies were pooled, studies that recruited patients in healthcare settings showed more benefit (RR, 2.06; 95%CI, 1.81-2.34) than studies that recruited patients in community settings (RR, 1.53; 95%CI, 1.33-1.76).

Table 5. Systematic reviews assessing the efficiency of smoking cessation counselling.

<table>
<thead>
<tr>
<th>Review</th>
<th>Counselling Intervention</th>
<th>Efficiency of Counselling</th>
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</table>
| Stead et al, 2008 (12) | • Brief Intervention o Advice included a verbal “stop smoking” message  
• Brief Intervention PLUS Printed Material o Verbal message plus printed material OR o Verbal message plus additional advice from a support health worker OR o Verbal advice plus referral to cessation clinic  
• Intensive Intervention o Smoking cessation manual plus additional visits or longer consultation | • Quit rates increased for brief intervention compared with no advice (RR, 1.66; 95%CI, 1.42-1.94)  
• Quit rates higher for intensive intervention compared with no advice (RR, 1.84; 95%CI, 1.60-2.13)  
• Small (but significant) advantage to intensive intervention compared with brief (RR, 1.37; 95%CI, 1.20-1.56)  
• Addition of further follow-up visits to brief intervention increased odds of quitting (RR, 1.52; 95%CI, 1.08-2.14)  
  o When data from five studies were pooled but not individually by study |
| Stead and Lancaster, 2012 (13) | • Brief Intervention o Advice included a verbal “stop smoking” message  
• Behavioural Support o Brief intervention PLUS o Between 4 and 8 sessions (30-300 min) with a cessation counselling specialist  
• Pharmacotherapy PLUS Counselling o Medication plus o Behavioural support | • Benefit to combination pharmacotherapy and behavioural support compared with brief intervention, or behavioural support alone (RR, 1.82; 95%CI, 1.66-2.00)  
• Weak evidence that studies offering more counselling session had a larger benefit on cessation  
• No clear evidence that increasing the duration of contact with a cessation counsellor increases the benefit of cessation counselling |

Abbreviations: CI, confidence interval; RR, relative risk.

3.7.3. Studies Investigating the Effects of Smoking Status on QoL in Lung Cancer Survivors

3.7.3.1. Non-Randomized Comparative Prospective Cohort Studies

A controlled before-and-after study involving survivors of NSCLC and SCLC examined the relationship between smoking and QoL after lung cancer diagnosis (20). Six assessments
were mailed to enrolled patients: at six months post-treatment, one year post-treatment, then annually for a total of five years. Enrolled patients had been diagnosed with stage IA (29.3%), stage IB (17.3%), stage IIA (3.0%), stage IIIB (7.8%), stage IIIA (14.1%), stage IIIB (7.6%), or stage IV (12.6%) NSCLC; limited-stage SCLC (5.3%); or extensive-stage (2.4%) SCLC. QoL was assessed with the patient portion of the LCSS (version 2). Tobacco use was assessed by self-report, and patients were categorized as never-smokers, former smokers, or current smokers (Table 6). In order to distinguish changes in smoking habits, study designers described former and current smokers more fully as former smokers, relapsed former smokers, persistent smokers, or abstinent smokers (Table 6). At diagnosis, 18% of patients were never-smokers, 58% were former smokers and 24% were current smokers. At the first follow-up, 95% of former smokers remained smoke-free, but 5% had relapsed (relapsed former smoker). Seventy percent of current smokers at time of diagnosis quit by first follow-up (abstinent smokers); however, 30% continued to smoke at follow-up (persistent smoker). Overall QoL scores were better for never smokers compared with persistent smokers (Table 6). However, former smokers also saw an increase in QoL, compared with persistent smokers (Table 6). The study authors concluded that persistent smoking after treatment for lung cancer negatively impacts QoL.

3.7.3.2. Non-Randomized Comparative Prospective Cohort Studies for Survivors of NSCLC

A controlled before-and-after study in NSCLC patients evaluated the effects of smoking status on QoL after surgery (16). The majority of enrolled patients had early-stage disease (28.6% stage IA, 22.9% stage IB, 25.7% stage IIA, 15.7% stage IIIB), with only 7.1% having been diagnosed with stage IIIA disease. Smoking status was determined by two questionnaires, and patients were categorized as non-smokers, former smokers, recent quitters, or current smokers (Table 6). To assess QoL, patients completed the Dutch version of the European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire - Cancer Patients (30 questions) (QLQ-C30) and the EORTC Quality of Life Questionnaire - Lung Cancer Module (13 questions) QLQ-LC13 one day before surgery, then at one, three, six and 12 months post-operation (MPO). At baseline, 13% of patients were non-smokers, 29% were former smokers, 8% were recent quitters and 50% were current smokers. All survivors, except for non-smokers, noted fatigue for the first three months after surgery. Non-smokers experienced the fastest recovery, with all QoL scores returning to baseline by 3MPO (Table 6). Former smokers complained of a decrease in physical functioning for three months, a decrease in role functioning up to 12MPO, but also less dyspnea the first six months (Table 6). Recent quitters found that physical functioning did not return to baseline for six months, while dyspnea levels remained high for three months (Table 6). Current smokers noted the worst QoL scores in physical functioning, role functioning and social functioning, all of which did not return to baseline levels even after completion of the 12-month follow-up (Table 6). Current smokers also experienced a persistent increase in dyspnea for the 12 months, an increase in general pain for 6MPO and increased thoracic pain up to 12MPO (Table 6). The study concluded that smoking cessation was beneficial at any stage of treatment and that continued smoking greatly impaired postoperative QoL.

3.7.3.3. Non-Randomized Comparative Prospective Cohort Studies for Survivors of SCLC

Only one controlled before-and-after study enrolled solely SCLC patients (61.9% limited-stage, 38.1% extensive-stage) post-diagnosis (17). The study examined the relationship between smoking and QoL profiles. Data were collected within six months after diagnosis and then annually. Smoking status was determined through a questionnaire at each follow-up point. Patients were categorized as never smoker, early quitter, recent quitter, late quitters or never quitters (Table 6). As part of the follow-up questionnaire, QoL was
assessed. The LCSS was used at the beginning of the study (1999), but replaced with the LASA in 2005. Data in the study were analyzed based on overlap between tools: pain, fatigue, cough, dyspnea and overall QoL. The study also determined Eastern Cooperative Oncology Group (ECOG) performance status and appetite change. The QoL values for the SCLC survivors were compared to a control population of lung cancer-free heavy smokers over 50 years of age. At enrolment, 3% of patients were never smokers, 44% were former smokers, and 53% were current smokers. All SCLC survivors reported a worse QoL than the matched control population (Table 6). However, among smoker subgroups, early quitters reported the best overall QoL, while recent quitters reported the best symptom scores (Table 6). Late quitters and never quitters reported the worst QoL and the highest percentage of reduced appetite (Table 6). Thus, the study indicated that smoking cessation around the time of diagnosis could improve overall QoL and symptom of SCLC survivors.

Table 6. Studies assessing the effects of smoking status on QoL of lung cancer survivors.

<table>
<thead>
<tr>
<th>Study; LC Type</th>
<th>Smoking Status Categorization</th>
<th>Major QoL and Symptom Burden Findings</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Never smoker</td>
<td>QoL scores better for never-smokers compared with persistent smokers (p&lt;0.001)</td>
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<td></td>
<td>o Smoked fewer than 100 cigarettes in lifetime and not currently smoking</td>
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<td></td>
<td>Former smoker</td>
<td>Former smokers (abstinent and relapsed) recorded LCSS scores similar to never-smokers</td>
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<tr>
<td></td>
<td>o Smoked more than 100 cigarettes in lifetime but not currently smoking at diagnosis or follow-up</td>
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<tr>
<td></td>
<td>Current smoker</td>
<td>Never-smokers recorded best QoL levels and persistent smokers worst QoL levels for the following domains:</td>
</tr>
<tr>
<td></td>
<td>o Not smoking at diagnosis, but smoking at follow-up</td>
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<tr>
<td></td>
<td>Persistent smoker</td>
<td>o Appetite, fatigue, cough, shortness of breath, lung cancer symptoms, illness affecting normal activities and overall QoL (p&lt;0.001)</td>
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<tr>
<td></td>
<td>o Current smoker at diagnosis and follow-up</td>
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<tr>
<td></td>
<td>Relapsed former smoker</td>
<td>o Hemoptysis and pain were also significantly different but not clinically relevant as there was less than a 10-point LCSS scale difference</td>
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<tr>
<td></td>
<td>o Not smoking at diagnosis, but smoking at follow-up</td>
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<tr>
<td></td>
<td>Abstinent smoker</td>
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<td></td>
<td>o Smoker at diagnosis, but not at follow-up</td>
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<tr>
<td>Garces et al, 2004 (20); NSCLC and SCLC</td>
<td>Non-smoker</td>
<td>At baseline (1 day before surgery):</td>
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<tr>
<td></td>
<td>o Never smoked</td>
<td>o QoL was similar across smoking subgroups</td>
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<tr>
<td></td>
<td>Former smoker</td>
<td>o Non-smokers reported higher thoracic pain vs. former smokers (p=0.01)</td>
</tr>
<tr>
<td></td>
<td>o Quit before NSCLC diagnosis</td>
<td>o Non-smokers reported lower role functioning vs. former smokers (p=0.03) and current smokers (p=0.02)</td>
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<tr>
<td></td>
<td>Recent quitter</td>
<td>Non-smokers:</td>
</tr>
<tr>
<td></td>
<td>o Quit between diagnosis and curative surgery for NSCLC</td>
<td>o Return to baseline QoL scores 1 month post-operation (MPO)</td>
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<tr>
<td></td>
<td>Current smoker</td>
<td>▪ Except for temporary decline in physical function at 1MPO (p=0.01) and social functioning at 3MPO (p=0.03)</td>
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<td></td>
<td></td>
<td>Former smokers:</td>
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<td></td>
<td></td>
<td>o Decrease in physical functioning (1MPO p=0.01, 3MPO p=0.01), which returned to baseline at 6MPO</td>
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<tr>
<td></td>
<td></td>
<td>o General QoL perception, emotional, cognitive and social functioning returned to baseline at 1MPO</td>
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<tr>
<td>Study; LC Type</td>
<td>Smoking Status Categorization</td>
<td>Major QoL and Symptom Burden Findings</td>
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<tr>
<td></td>
<td></td>
<td>o Role functioning did not return to baseline levels</td>
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<td></td>
<td></td>
<td>o Patients reported comparable coughing and shoulder functioning before and after surgery</td>
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<tr>
<td></td>
<td></td>
<td>o Temporary increase in general pain (p=0.03) and thoracic pain (p=0.04) at 1MPO</td>
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<tr>
<td></td>
<td></td>
<td>o Increase in fatigue for the first 3 months (1MPO p=0.01, 3MPO p=0.04)</td>
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<tr>
<td></td>
<td></td>
<td>o Decreased in dyspnea for the first 6 months (1MPO p=0.01, 3MPO p=0.01, 6MPO p=0.01)</td>
</tr>
<tr>
<td>Chen et al, 2012 (17); SCLC</td>
<td>Never smoker</td>
<td>o Less than 100 cigarettes in lifetime</td>
</tr>
<tr>
<td></td>
<td>Early quitter</td>
<td>o Quit more than 1 year prior to SCLC diagnosis</td>
</tr>
<tr>
<td></td>
<td>Recent quitter</td>
<td>o Quit within 1 year surrounding SCLC diagnosis</td>
</tr>
<tr>
<td></td>
<td>Late quitter</td>
<td>o Quit after 1 year post SCLC</td>
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<tr>
<td></td>
<td>SCLC survivors reported worse QoL compared with matched controls (p&lt;0.0001)</td>
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</tr>
<tr>
<td></td>
<td>Over a five-year follow-up, overall QoL and symptom scales of pain, fatigue, cough and dyspnea were stable</td>
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<tr>
<td></td>
<td>Among smoker subgroups:</td>
<td>o Early quitters reported best overall QoL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Recent quitters reported best symptom scales</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Late quitters and never quitters reported worst QoL and highest reduced appetite</td>
</tr>
</tbody>
</table>
### Study; LC Type | Smoking Status Categorization | Major QoL and Symptom Burden Findings
--- | --- | ---
 | diagnosis | • Never quitter | 

**Abbreviations:** LC, lung cancer; LCSS, Lung Cancer Symptom Scale; MPO, months post-operation; NSCLC, non-small cell lung cancer; QoL, quality of life; SCLC, small cell lung cancer.

#### 3.7.4. Study Summary

The search for existing systematic reviews returned five on aspects of smoking cessation. Three systematic reviews that evaluated the benefits of smoking cessation after diagnosis of lung cancer or prior to surgery all concluded that smoking cessation improved prognostic outcomes \((11,14,15)\). Systematic reviews that assessed the efficiency of smoking cessation counselling concluded that any intervention is better than no cessation advice from a health care professional \((12)\), with an intensive intervention that added further follow-up visits being more effective than brief intervention \((12)\). When pharmacotherapy and behavioural support are added to advice from a health care professional alone, the benefit of the counselling is increased \((13)\). The systematic search for primary literature returned four studies relating to aspects of smoking cessation in lung cancer survivors. The cohort study by Zhou and colleagues \((34)\), which looked at the effects of smoking cessation after NSCLC diagnosis, agreed with the systematic reviews and found an association between smoking cessation and improved survival. The remaining cohort studies, which all assessed the effects of smoking status on lung cancer survivors, found that never-smokers reported the best QoL after curative treatment \((16,20)\). However, patients who quit smoking within one year prior to diagnosis or during follow-up reported better overall QoL and symptom scales compared with survivors that continued to smoke \((16,17,20)\).

#### 4.0. DISCUSSION

4.1. Questions 1 & 2: What clinical activities are effective at detecting recurrence or progression of lung cancer, or occurrence of metastases in lung cancer survivors? What is the relationship between frequency and timing of any diagnostic/laboratory test in the management of recurrence in lung cancer survivors? Are recurrences associated with symptomatic versus asymptomatic presentation?

4.1.1. Survivors of NSCLC

A meta-analysis by Calman and colleagues \((8)\) found no association between increased overall survival with an intensive follow-up schedule when studies only comparing intensive to regular follow-up schedules were pooled. However, when studies examining detection of symptomatic versus asymptomatic recurrence were pooled, asymptomatic recurrence was associated with higher overall survival \((8)\). The Calman et al meta-analysis \((8)\) did have limitations related to the types and quantity of studies pooled, but results suggest that it is the early detection of asymptomatic recurrence that leads to increased survival. NSCLC survivors should be followed after curative treatment in order to detect local or locoregional recurrence, as they may be amenable to resection or radical radiation therapy for salvage. For this reason, follow-up schedules that result in higher overall survival are more valuable than schedules that merely result in a higher rate of recurrence detection.
Scheduled follow-up visits for NSCLC survivors should include a medical history, physical examination, and chest imaging (Table 7). This recommendation is in agreement with the latest clinical practice guidelines produced by ESMO (38) and the National Comprehensive Cancer Network (NCCN) (39). Due to the lack of evidence to inform which frequency is most appropriate, a consensus approach was used to determine the appropriate timing of follow-up evaluations based on the expert opinion of the Working Group (Table 7). Other research has determined that in both NSCLC and SCLC, the majority of recurrences are diagnosed in the first two years (10). The consensus process is described in Section 3 and incorporated the timing of recurrence diagnosis (10), the indication that asymptomatic recurrence detection is associated with a longer survival time (8), and the clinical experience of the Working Group members. The Working Group agrees that NSCLC survivors should have scheduled follow-up visits every three months for the first two years following curative-intent therapy (Table 7). Follow-up visit should occur every six months in year 3, then annually until end of life (Table 7). Although the Working Group agrees that annual surveillance should occur until the end of life, health care professionals should use their own discretion in determining the applicability of annual surveillance in patients who are not well enough to undergo treatment if a new cancer is detected. The high frequency of follow-up visits in the first two years is in agreement with the ESMO guideline for early-stage and locally advanced NSCLC (38), which recommend visits every three to six months in the first two to three years.

For NSCLC survivors, there is currently not enough high-quality evidence to inform the best imaging modality that should be used for the detection of recurrence. The clinical standard among oncologists is a CT scan, but the evidence to support this modality is conflicting. A systematic review that evaluated the role of CT follow-up one year after lobectomy did not find a clear survival benefit for CT scans (6). The best evidence for the value of CT surveillance comes from the National Lung Screening Trial (40,41), which indicated that low-dose CT (LDCT) was better than radiography in detecting early-stage lung cancers, which theoretically can be extrapolated to recurrent disease. A recent study also points to a role for MnDCT scans, which showed higher sensitivity and negative predictive value than chest X-ray for detecting new primary tumours and recurrent lung cancer at an early stage (36). The Working Group concluded that appropriate chest imaging for follow-up should include either LDCT or MnDCT (Table 7). The recommendation to include chest CT as the most appropriate imaging modality for NSCLC survivors is in agreement with recommendations produced by the American Association for Thoracic Surgery (AATS) (42), ACCP (43), ESMO (38) and NCCN (39).

Other included studies focused on the diagnostic accuracy of PET/CT for surveillance after curative-intent therapy. A meta-analysis that pooled studies comparing PET/CT with PET or CT alone found that for mediastinal staging, PET/CT had higher sensitivity than both PET or CT alone and higher specificity than PET alone (7). For intrathoracic staging, PET/CT showed higher sensitivity and specificity than both PET and CT alone (7). Finally, when evaluating extrathoracic staging, no studies compared PET/CT with PET or CT alone, but pooled data determined that PET/CT had high sensitivity and specificity for diagnosing these types of metastases (7). There were three additional diagnostic studies identified by the systematic review of the primary literature. Two studies indicated a benefit for PET/CT over CT alone for recurrence detection (19,31), while the other demonstrated a benefit for PET/CT over non-contrast CT for detection of extrathoracic and mediastinal metastases (35). When looking at the ability to detect local recurrence, one study found that almost 26% of the recurrences diagnosed by PET/CT were recurrences within the ipsilateral lung (19). In the other diagnostic study, PET/CT scanning led to the detection of lung cancer progression that was amenable to salvage therapy in a small proportion (3%) of the patients enrolled (31). Thus, these studies point to a role for PET/CT in diagnosing local and locoregional
recurrences, which may be amenable to salvage therapy. Additionally, both the PET/CT diagnostic studies were of fairly good quality, and all used a fully-paired design to minimize the risk of bias. However, due to the low percentage of local recurrence detected by PET/CT and the higher doses of radiation patients would receive with PET/CT compared with CT alone, the Working Group believes that the evidence from these two studies is not strong enough upon which to base a recommendation for recurrence surveillance (Table 7). A search of ongoing trials identified the Positron Emission Tomography/Computed Tomography (PET/CT) for the Diagnosis of Recurrent Cancer: a Feasibility Study (PETREC) trial (http://clinicaltrials.gov/ct2/show/NCT00686465A?term=PETREC&amp;rank=1). This trial was designed to study the feasibility of using PET/CT to aid in diagnosing recurrent cancer when standard imaging tests are inconclusive. The trial is now closed, but no publication is yet available. The Working Group is aware that the enrolled population for this feasibility study is not the appropriate population for this guideline, but the study results may indicate a role for PET/CT when other imaging tests fail to detect recurrence. A further systematic review (44), based on the systematic review portion of a PEBC guideline (EBS 7-20), looked at the use of PET in the diagnosis and staging of both NSCLC and SCLC. This systematic review expanded on the Institute for Clinical Evaluation Sciences’ (ICES) 2001 report entitled Health Technology Assessment of Positron Emission Tomography in Oncology (45) and looked at the role of PET in NSCLC, but not SCLC. Neither systematic reviews looked at the role of PET in diagnosing recurrence; however, the role of PET in diagnosing distant metastases was evaluated, and it was concluded that the evidence was conflicting (44).

4.1.2. Survivors of SCLC

The meta-analysis by Calman et al (8) found no association between increased overall survival with an intensive follow-up schedule when analyzing studies that compared intensive with regular follow-up schedules in SCLC populations. Thus, follow-up schedules that result in a high recurrence rate are only of value if this translates into an increase in overall survival.

Scheduled follow-up visits for SCLC survivors should include a medical history, physical examination and chest imaging (Table 7). This recommendation is in agreement with the latest clinical practice guideline produced by ESMO (46). Due to the lack of evidence to inform which frequency is most appropriate, a consensus approach was used to determine the appropriate timing of follow-up evaluations based on the expert opinion of the Working Group (Table 7). The consensus process is described in Section 3 and incorporated the research that determined that the majority of recurrences are diagnosed in the first two years (10), the indication that longer survival is associated with asymptomatic recurrences detection (8), and the clinical experience of the Working Group members. The Working Group agrees that SCLC survivors should have scheduled follow-up visits every three months for the first two years following curative-intent therapy (Table 7). Follow-up visits should occur every six months in year 3, then annually until end of life (Table 7). These recommendations do not differ greatly from those recommended by NCCN (47), which state that SCLC should receive follow-up visits every three to four months in the first two years, every six months in years three through five and then annually. Similarly, the ESMO guideline for SCLC patients (46) recommends follow-up every three to six months in the first two years, then longer intervals continuing until year 5, when follow-up should be annual.

No studies that evaluated the most appropriate chest imaging for recurrence or progression in SCLC survivors were identified by the current literature search. One again, the clinical standard amongst oncologist is a CT scan, but the evidence to support this modality is lacking. The only evidence that supports a role for CT surveillance comes from the National Lung Screening Trial (40,41), which indicated that LDCT was better than radiography in detecting early-stage lung cancers, which theoretically can be extrapolated to recurrent
disease. In the expert opinion of the Working Group, SCLC survivors should be followed with CT scans for detection of recurrence or progression based on the superiority of CT to chest X-ray for screening (Table 7). This recommendation is in agreement with the ESMO guideline for SCLC patients, which states that survivors should be followed with CT scans (46). Although PET imaging may eventually emerge as beneficial for imaging of recurrent SCLC, there is insufficient evidence available at this time. A PEBC Recommendation Report, in collaboration with the Ontario PET Steering Committee, was written in 2009 and is now in the process of being reviewed to determine if the Recommendation Report should be updated (48). This Recommendation Report included a question on whether PET or PET/CT provides a benefit to the clinical management of suspected SCLC recurrence, but no recommendation was made for or against the use of PET for evaluation of recurrence due to lack of evidence.

Table 7. Evaluations and intervals for routine surveillance of lung cancer survivors after curative-intent therapy.

<table>
<thead>
<tr>
<th></th>
<th>NSCLC</th>
<th>SCLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical visit evaluations</td>
<td>Medical history, physical exam and chest imaging</td>
<td>Medical history, physical exam and chest imaging</td>
</tr>
<tr>
<td>Clinical visit frequency</td>
<td>Years 1-2: every 3 months, Year 3: every 6 months, Years 4+: annually</td>
<td>Years 1-2: every 3 months, Year 3: every 6 months, Years 4+: annually</td>
</tr>
<tr>
<td>Medical imaging modality</td>
<td>LDCT or MnDCT without contrast may be a reasonable option over chest x-ray for detection of pulmonary lesions</td>
<td>Diagnostic CT without contrast may be a reasonable option over chest x-ray for detection of pulmonary lesions</td>
</tr>
<tr>
<td></td>
<td>Diagnostic CT with contrast is suggested to detect recurrence in mediastinal lymph nodes</td>
<td>Diagnostic CT with contrast is suggested to detect recurrence in mediastinal lymph nodes</td>
</tr>
<tr>
<td>Surveillance imaging frequency</td>
<td>Year 1: 3, 6 and 12 months post-treatment, Year 2: every 6 months (18 and 24 months post-treatment), Years 3+: annually</td>
<td>Year 1: 3, 6 and 12 months post-treatment, Year 2: every 6 months (18 and 24 months post-treatment), Years 3+: annually</td>
</tr>
<tr>
<td>Medical Imaging when recurrent disease or new disease is suspected</td>
<td>Diagnostic chest CT with contrast plus upper abdomen scan is suggested to detect local recurrence or new primary lung cancer</td>
<td>Diagnostic chest CT with contrast plus upper abdomen scan is suggested to detect local recurrence or new primary lung cancer</td>
</tr>
<tr>
<td></td>
<td>If patient is symptomatic, imaging modality specific to patient’s symptoms is recommended</td>
<td>If patient is symptomatic, imaging modality specific to patient’s symptoms is recommended</td>
</tr>
</tbody>
</table>

Abbreviations: LDCT, low-dose computed tomography; MnDCT, minimal-dose computed tomography; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

4.2. Question 3: What symptoms are indicative of possible recurrence or development of any other primary cancer that warrant further evaluation?

The literature search did not return any systematic reviews or studies that looked specifically at symptoms of recurrence or the development of a second primary cancer in lung cancer survivors. However, one of the diagnostic studies looking at the role of PET/CT listed the symptoms experienced by patients at detection of PD (31). The study found that patients experiencing PD had more pain and neurological issues than those without disease progression (31). Unfortunately, the study enrolled a modest sample size of 100 patients, with only 24 patients developing PD. Due to the lack of evidence, the Working Group decided to use a
consensus process (described in Section 3) to list the potential symptoms of recurrence in their expert opinion. The symptoms are listed in Table 8 and are organized into constitutional, neurological, and respiratory symptoms, as well as types of pain.

Table 8. Potential symptoms of recurrence or development of new primary cancer.

<table>
<thead>
<tr>
<th>Constitutional Symptoms:</th>
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<tbody>
<tr>
<td>• Dysphagia</td>
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<tr>
<td>• Fatigue (new onset)</td>
</tr>
<tr>
<td>• Hoarseness</td>
</tr>
<tr>
<td>• Nausea or vomiting (unexplained)</td>
</tr>
<tr>
<td>• New finger clubbing</td>
</tr>
<tr>
<td>• Suspicious lymphadenopathy</td>
</tr>
<tr>
<td>• Sweats (unexplained)</td>
</tr>
<tr>
<td>• Thrombosis</td>
</tr>
<tr>
<td>• Weight loss or loss of appetite</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Pain:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Bone pain</td>
</tr>
<tr>
<td>• Chest pain</td>
</tr>
<tr>
<td>• Caveat shoulder pain not related to trauma</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Neurological Symptoms:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Headaches (if persistent)</td>
</tr>
<tr>
<td>• New neurological signs suggestive of brain metastasis or cord compression such as leg weakness or speech changes</td>
</tr>
<tr>
<td>• Headache or focal neurological symptoms</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Respiratory Symptoms:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Cough (despite use of antibiotics)</td>
</tr>
<tr>
<td>• Dyspnea</td>
</tr>
<tr>
<td>• Hemoptysis</td>
</tr>
<tr>
<td>• Signs of superior vena cava obstruction</td>
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<td>• Stridor</td>
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4.3. Question 4: What are the common non-recurrence-related issues experienced by lung cancer survivors?

The Working Group is concerned that the long-term needs of lung cancer survivors are not being met. The literature search for Research Question 4 was designed to assess both the QoL and treatment-related symptom burden of lung cancer survivors, which quite often go hand-in-hand. When evaluating overall QoL profiles, studies found that survivors of both NSCLC and SCLC show a reduction in the physical ability domain (9,26) and an increase in the mental ability domain (26) of QoL tools following resection (Table 3). One study that focused solely on NSCLC survivors found that following lobectomy, 65% of survivors experienced improved or stable QoL scores, while 71% of survivors experienced improved or stable scores following pneumonectomy or bilobectomy (22) (Table 3). A systematic review that assessed the specific treatment-related long-term effects found that survivors of lung cancer report physical ability restrictions, depression, decreases in general health and vitality and increased body pain (10) (Table 4). Prospective cohort studies evaluating non-recurrence-related issues found that survivors experience long-term dyspnea (18,21,33), cough (18,33), fatigue (18,33),
impaired breathing (30), increased pain (30,33), decline in appetite (30,33) and reduced sleep efficiency (21) (Table 4). Studies that focused solely on survivors of NSCLC found that a majority of these survivors experienced some degree of pneumonitis after radiation therapy (32) and a sustained decrease in multiple QoL domains after all therapy (24) (Table 4). The studies that inform this research question range from systematic reviews and RCTs to non-randomized prospective cohort studies. All the included studies used prospective data collection and analyzed the study population through comparisons either between groups or within the study group, across time. Unfortunately, since all non-randomized studies carry an unclear risk of bias and most of the studies relied on the use of QoL tools that survivors filled out at home, increasing the risk of recall bias, it is believed that the studies informing this evidence are of low quality. The Working Group does recognize that this is the best data available, as QoL and late treatment effect data are generally not included in treatment trials a priori. However, due to the low quality of studies discovered, the Working Group decided to use both the literature and their clinical experience to summarize the late side effects and QoL issues reported by long-term survivors of lung cancer. The non-recurrence-related issues experienced by lung cancer survivors are listed in Table 9 and are organized into treatment-related effects (chemotherapy, radiation, surgery) or constitutional issues. The lack of high-quality data to inform this research question is a short-coming of the literature. Health-related QoL is very important for long-term survivors suffering from late side effects of their curative-intent therapy. Future research should be designed to fill this gap in knowledge. Additionally, studies that investigate other issues experienced by cancer survivors, such as fear of recurrence, sexual health, return to work and psychosocial coping, have not been addressed in solely lung cancer survivor groups, presenting another area in need of future work.

Table 9. Non-recurrence related issues reported by lung cancer survivors.

<table>
<thead>
<tr>
<th>Constitutional Issues:</th>
</tr>
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<tbody>
<tr>
<td>• Anxiety</td>
</tr>
<tr>
<td>• Cough</td>
</tr>
<tr>
<td>• Decline in appetite</td>
</tr>
<tr>
<td>• Decrease in general health</td>
</tr>
<tr>
<td>• Depression</td>
</tr>
<tr>
<td>• Dysphagia</td>
</tr>
<tr>
<td>• Esophageal stricture</td>
</tr>
<tr>
<td>• Fatigue</td>
</tr>
<tr>
<td>• Pain</td>
</tr>
<tr>
<td>• Physical ability restrictions</td>
</tr>
<tr>
<td>• Reduced sleep quality</td>
</tr>
<tr>
<td>• Shortness of breath</td>
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<table>
<thead>
<tr>
<th>Long-term Chemotherapy Effects:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Hearing loss</td>
</tr>
<tr>
<td>• Neuropathies</td>
</tr>
<tr>
<td>• Renal impairment</td>
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<tr>
<th>Long-term Radiation Effects:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Breathing complications</td>
</tr>
<tr>
<td>• Breathlessness/Dyspnea</td>
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<tr>
<th>Long-term Surgery Effects:</th>
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</thead>
<tbody>
<tr>
<td>• Empyema</td>
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<tr>
<td>• Oxygen dependence</td>
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</table>
4.4. Question 5: Is there a relationship between the clinician and/or setting of follow-up care and the effective detection and management of recurrent or metastatic disease?

The literature search for this research question returned only one RCT. The RCT conducted by Moore and colleagues (27) enrolled patients of advanced-stage lung cancer who were expected to survive at least three months. Patients were randomized to receive either a nurse-led follow-up or a conventional specialist-led follow-up after treatment. The study found that both QoL and recurrence outcomes were not different between the two groups, indicating that nurse-led follow-up did not negatively impact QoL or recurrence detection. Moreover, patients were satisfied with both arms of follow-up care. When family physicians were surveyed on satisfaction, 46% indicated a preference for future follow-up provided by both clinical nurse specialist and oncologist (9% oncologist alone, 18% nurse-led service alone) (27). Upon quality assessment, it was found that the RCT was of good methodological quality. However, the study is more than 10 years old and when conducted, no effective salvage therapy and no effective second-line chemotherapy were available, which may have led to no difference in overall survival being detected. Also, follow-up care was not provided exclusively by nurses or specialists. The study allowed for additional visits to the family physician, which though beneficial for the survivors, may have confounded some of the findings. Finally, the study included a more advanced disease population than was our target population. The Working Group considered the study limitations, and even though this patient population would be managed differently today due to new treatment options and shared care models, the Working Group accepts this study as it is the best available evidence. Additionally, for this research question, QoL and satisfaction with care are valued highly. Although the identified literature only evaluated hospital-based nurse-led care models, expert opinion supports family physician-led care models. Thus, the Working Group believes that transition from specialist-led care to family physicians or hospital-based nurses may be a reasonable option for lung cancer survivors, following curative treatment.

4.5. Question 6: Is there a value to smoking cessation counselling for lung cancer survivors?

The literature search did not find any systematic reviews or studies that looked specifically at the value of smoking cessation counselling for lung cancer survivors. Instead, separate evidence was found on the efficiency of smoking cessation counselling in a broader population, in addition to evidence for the value of smoking cessation in lung cancer survivors. Systematic reviews that assessed the efficiency of smoking cessation counselling concluded that any intervention is better than no cessation advice from a health care professional (12), with an intensive intervention that included additional follow-up visits being more effective than a brief intervention (12) (Table 5). When pharmacotherapy and behavioural support are added to advice from a health care professional alone, the benefit of the counselling is increased (13) (Table 5). The three systematic reviews and one cohort study that evaluated the benefits of smoking cessation after diagnosis of lung cancer or prior to surgery all concluded that smoking cessation improved prognostic outcomes (11,14,15,34) (Table 6). Cohort studies that looked at the association between smoking cessation and QoL found that never-smokers reported the best QoL after curative treatment (16,20) (Table 6). However, patients who quit smoking within one year prior to diagnosis or during follow-up reported better overall QoL and symptom scales compared with survivors who continued to smoke (16,17,20) (Table 6). The included systematic reviews that inform the efficiency of
smoking cessation counselling aspect of this research question and the systematic reviews that inform the benefits of smoking cessation aspect of the research question were all of good quality. The cohort studies looking at QoL of lung cancer survivors in relation to their smoking status were of lesser quality as the studies relied on patient reported QoL tools, introducing recall bias. Additionally, smoking status was not clinically verified in any of the cohort studies. The Working Group is concerned that none of the studies identified in the literature review directly informed the question of whether smoking cessation counselling is beneficial to survivors. Studies looking at the efficiency of counselling were not conducted in lung cancer survivor populations, while studies looking at the QoL of survivor in relation to their smoking status did not include cessation interventions. The Working Group members agreed that taken together, the evidence for the benefit of smoking cessation counselling, the evidence for the clinical benefits of cessation and the evidence for the QoL benefits of cessation can be combined to adequately inform this research question. Thus, smoking cessation counselling should be offered to patients who have completed curative-intent therapy for NSCLC and SCLC. Although verbal cessation advice from a health care professional is of benefit, interventions that involve behavioural and pharmacotherapy support in addition to verbal advice are recommended.

5.0. CONCLUSIONS

Based on the available evidence and expert opinion, the Working Group makes the following recommendations for adult patients who have completed primary treatment for NSCLC or SCLC and who are without evidence of disease:

5.1. Clinical evaluations and timing (Table 7):

1. Following curative-intent treatment for NSCLC, survivors should receive scheduled follow-up visits that include a medical history, physical examination and chest imaging. Clinical evaluations should be conducted every three months in years 1 and 2, every six months in year 3 and then annually.
   a. For routine surveillance, LDCT or MnDCT without IV contrast may be a reasonable option instead of chest x-ray. Chest CT may be conducted at three months post-treatment, followed by six months post-treatment, then at six month intervals until the end of year 2, followed by annually thereafter.

2. Following curative-intent treatment for SCLC, survivors should receive scheduled follow-up visits that include a medical history, physical examination and chest imaging. Clinical evaluation should be conducted every three months in years 1 and 2, every six months in year 3 and then annually.
   a. For routine surveillance, diagnostic CT without contrast may be a reasonable option instead of chest x-ray for pulmonary lesion detection. Diagnostic CT with contrast is suggested for detection of recurrence in mediastinal lymph nodes. CT imaging may be conducted three months post-treatment, followed by six months post-treatment, then at six month intervals until the end of year 2, followed by annually thereafter. Beyond year 2, LDCT or MnDCT can be considered rather than diagnostic CT.

3. Due to a lack of evidence, no recommendation can be made for or against PET/CT.

5.2. Symptoms of recurrence or development of new primary:

4. In the expert opinion of the Working Group, any new and persistent or worsening symptom warrants the consideration of a recurrence, especially those symptoms listed in Table 8.
5.3. Non-recurrence related issues:
   5. Health-related QoL is very important for long-term survivors suffering from late side effects of their curative-intent therapy (including surgery, chemotherapy and radiation therapy). Table 9 lists a summary of the issues that survivors may be experiencing. Health care professionals need to aid lung cancer survivors in handling these issues to improve QoL.

5.4. Most responsible health care professional and care location:
   6. For lung cancer survivors who have completed curative-intent therapy, surveillance is required and may be provided by specialists, family physicians, or hospital-based nurses.

5.5. Value of smoking cessation counselling:
   7. Smoking cessation counselling is recommended for patients who have completed curative-intent therapy for NSCLC and SCLC. Although verbal cessation advice from a health care professional is of benefit, interventions that involve behavioural and pharmacotherapy support in addition to verbal advice are recommended.

6.0. CONFLICT OF INTEREST
   Information regarding conflict of interest declarations can be found at the end of Section 3.

7.0. ACKNOWLEDGEMENTS AND AUTHORSHIP
   The Follow-up and Surveillance of Curatively Treated Lung Cancer Patients Expert Panel and the Working Group would like to thank the following individuals for their assistance in developing this report:
   - Melissa Brouwers, Medhat El-Mallah, Bill Evans, John Goffin, Richard Malthaner, Sheila McNair, Hans Messersmith, Marko Simunovic, David Stewart and Kazuhiro Yasufuku for providing feedback on draft versions.
   - Esaba Kashem for conducting a data audit.
   - Heather Hepplewhite and Bruce Histed for copyediting.

A complete list of the members of the Lung Cancer Follow-up Expert Panel and the Working Group, with their affiliations and conflict of interest information, is provided in Section 3, Appendix 1.
REFERENCES


Evidence-Based Series 26-3: Section 3

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Follow-up and Surveillance of Curatively Treated Lung Cancer Patients: Development Methods, Recommendations Development and External Review Process

Y.C. Ung, L.H. Souter, G. Darling, J. Dobranowski, L. Donohue, N. Leighl, P.M. Ellis and the Lung Cancer Follow-up Expert Panel

Report Date: August 29, 2014

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, termed Disease Site Groups (DSGs), as well as other groups or panels called together for a specific topic, all mandated to develop the PEBC products. These panels are comprised of clinicians, other health care providers and decision makers, methodologists, and community representatives from across the province.

The PEBC produces evidence-based and evidence-informed guidelines, known as Evidence-Based Series (EBS) reports, using the methods of the Practice Guidelines Development Cycle (1,2). The EBS report consists of an evidentiary base (typically a systematic review), an interpretation of and consensus agreement on that evidence by our Groups or Panels, the resulting recommendations, and an external review by Ontario clinicians and other stakeholders in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each document, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original guideline information.

This EBS is comprised of the following sections:

- **Section 1: Guideline Recommendations.** Contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the Group or Panel involved and a formalized external review in Ontario by review participants.
- **Section 2: Evidentiary Base.** Presents the comprehensive evidentiary/systematic review of the clinical and scientific research on the topic and the conclusions reached by the Group or Panel.
• **Section 3: Development Methods, Recommendations Development, and External Review Process.** Summarizes the EBS development process, the recommendations development process and the results of the formal external review of the draft version of the EBS.

**FORMATION OF GUIDELINE DEVELOPMENT/WORKING GROUP**

The Survivorship Program of Cancer Care Ontario asked the PEBC to develop a guideline on follow-up care of lung cancer survivors. In consultation with the Survivorship Program, a Working Group was identified from the Lung DSG membership, plus outside expertise, suggested by the DSG chairs. This Working Group consisted of one radiation oncologist, two medical oncologists, one surgeon, one radiologist, one family physician and one methodologist. The Working Group, Survivorship Program Expert Panel, representatives from the Lung DSG and representatives from the Cancer Imaging Program also formed the Lung Cancer Follow-up Guideline Development Group. This group would take responsibility for providing feedback on the guideline as it was being developed and acted as Expert Panel for the document at Internal Review, reviewing the document and requiring changes as necessary before approving it.

**OBJECTIVES AND RESEARCH QUESTIONS**

This Working Group developed the following objective for this guideline in consultation with CCO’s Survivorship Program:

- To determine which test should be done at which intervals for optimal cancer surveillance and control
- To determine what quality of life (QoL) issues are experienced by lung cancer survivors following curative-intent treatment

From these objectives, the following research questions were derived to direct the search for available evidence to inform recommendations to meet the objectives:

**In survivors who have received curative treatment for non-small cell lung cancer (NSCLC) or small-cell lung cancer (SCLC):**

1. What clinical activities are effective at detecting recurrence or progression of lung cancer or occurrence of metastases in lung cancer survivors?
2. What is the relationship between frequency and timing of any diagnostic/laboratory test in the management of recurrence in lung cancer survivors? Are recurrences associated with symptomatic versus asymptomatic presentation?
3. What symptoms are indicative of possible recurrence or development of any other primary cancer that warrant further evaluation?
4. What are the common non-recurrence-related issues experienced by lung cancer survivors?
5. Is there a relationship between the clinician and/or setting of follow-up care and the effective detection and management of recurrent or metastatic disease?
6. Is there a value to smoking cessation counselling for lung cancer survivors?

**GUIDELINE REVIEW**

Almost all PEBC document projects begin with a search for existing guidelines that may be suitable for adaptation. The PEBC defines adaptation, in accordance with the ADAPTE Collaboration, as “the use and/or modification of (a) guideline(s) produced in one cultural and organizational setting for application in a different context” (3). This includes a wide spectrum of potential activities from the simple endorsement, with little or no change, of an existing guideline, to the use of the evidence base of an existing guideline with de novo recommendations development.
For this document, a search was conducted of the Inventory of Cancer Guidelines (www.cancerguidelines.ca) and the National Guidelines Clearinghouse (www.guideline.gov). In addition, the websites of several known high-quality guideline developers, including Scottish Intercollegiate Guideline Network (SIGN), American Society of Clinical Oncology (ASCO), European Society of Clinical Oncology (ESMO), National Comprehensive Cancer Network (NCCN), American Society for Radiation Oncology (ASTO), European Society for Radiotherapy and Oncology (ESTRO), American Association for Thoracic Surgery (AATS), American Thoracic Society (ATS), European Society of Thoracic Surgeons (ESTS), Society of Thoracic Surgeons (STS) and American College of Chest Physicians (ACCP), were searched. Finally, an electronic search employing OVID was used to systematically search the MEDLINE and EMBASE databases from 2000 to week 49 of 2012 using the following keywords: “lung cancer,” “surveillance,” “follow up,” “after care,” “survivor,” “recurrence,” and “late effects”. Only guidelines published after 2000 were considered. Additionally, only the most recent clinical practice guidelines from each organization, when multiple guidelines were found with overlapping outcomes, were chosen for further evaluation. A priori methodology planned that the Appraisal of Guidelines for Research and Evaluation (AGREE II) Instrument (4) would be applied to any clinical practice guideline that was considered for inclusion. Since none of the identified guidelines were incorporated into the evidentiary base of our systematic review (Section 2), AGREE II scores were not calculated for any guidelines.

Quality of Clinical Practice Guidelines

Twenty-three clinical practice guidelines underwent full-text review. Eleven were found to be outdated guidelines with the newest version retained. Three others were removed due to only including treatment and not follow-up guidance. Retained clinical practice guidelines were published by groups affiliated with ACCP (5), ESMO (6-8), AATS (9), ASCO (10), the joint effort of the German Respiratory Society and German Cancer Society (GRS & GCS) (11) and NCCN (12,13) (Appendix 5). The guideline produced by GRS & GCS (11) covered both NSCLC and SCLC patients. Guidelines published by ESMO separated the guidelines into SCLC (6), NSCLC (8) and early-stage and locally advanced NSCLC (7), and guidelines published by NCCN separated the guidelines by SCLC (12) and NSCLC (13). The guideline sponsored by AATS (9) focused on NSCLC survivors and high-risk screening populations. The ASCO guideline (10) was targeted for patients with unresectable NSCLC, while the guideline produced by ACCP (5) was targeted for NSCLC survivors after curative-intent therapy. All of the found guidelines were included here for completeness; however, it should be noted that the quality of the guidelines was variable.

Based on the quality assessment of the clinical practice guidelines, three of the guidelines will not be summarized in this section. The ESMO guideline on NSCLC (8) and the ASCO guideline for unresectable NSCLC (10) were both at least five years old and considered outdated. The guideline sponsored by the collaboration between GRS and GCS (11) will not be discussed further due to quality concerns. When the supplemental data that detailed the methodology and recommendation evidence were obtained for this guideline, it was discovered that this information was only in German; thus, the Working Group was not able to assess the quality of the guideline.

The ACCP guideline for all NSCLC patients after curative-intent therapy included a high-quality systematic review that focused on detection of recurrence and progression, as well as a summary of QoL aspects of follow-up care (5). The AATS guideline focused on the use of low-dose computer tomography (LDCT) scan for screening in lung cancer survivors and high-risk populations (9). The guideline builds on the work of the National Lung Screening Trial and the NCCN. Recommendations were separated into Tier 1 and Tier 2 based on the quality of the available evidence to inform the recommendation. The recommendations for
the lung cancer survivor population were based on level 2 (case-control and non-randomized trials) and level 3 (authors’ consensus opinion) evidence. The literature search returned two guidelines sponsored by ESMO: one targeted to SCLC patients (6), and one focused on early-stage and locally advanced NSCLC patients (7). Both guidelines looked at diagnosis, treatment, and follow-up with very little data provided in the follow-up section. For the SCLC guideline (6), recommendations for follow-up care were based solely on expert opinion, while recommendations for NSCLC populations (7) were informed by recurrence rate and low-quality evidence. The Working Group included the above guidelines here for completeness, but note that they are of low quality.

The NCCN has produced clinical practice guidelines for diagnosis, treatment, and follow-up of both SCLC (12) and NSCLC (13). While NCCN guidelines are consensus documents and as such, the guidelines did not explicitly state how evidence was identified and considered in formulating their recommendations, for completeness, the Working Group could not ignore the existence of the NCCN guidelines, as their recommendations in this subject matter are in common use and are well known in clinical practice. Thus, the NCCN guidelines have been included here.

**Clinical Practice Guideline Recommendations**

**Clinical Practice Guidelines for NSCLC**

The recommendations for the four clinical practice guidelines on the follow-up care of survivors of NSCLC are shown in Table 1. The ESMO early-stage and locally advanced NSCLC guideline (7) focused on all aspects of patient care, with a small section on follow-up after curative-intent treatment. Similarly, the NCCN guideline (13) on NSCLC patients focused on all aspects of care, with a section dedicated to post-treatment care. The ACCP guideline was targeted specifically for follow-up care after curative-intent therapy in NSCLC patients (5), while the AATS guideline focused on the use of LDCT scan for screening in lung cancer survivors and high-risk populations (9). The ESMO guideline (7) recommended the most intense follow-up schedule, with the AATS (9), ACCP (5), and NCCN (13) recommending similarly less intense follow-up frequencies. All four guidelines recommended CT as the imaging modality, with AATS (9) and NCCN (13) including more specific recommendations on CT dose and use of contrast enhancement. Both the ACCP (5) and NCCN (13) guideline stated the positron emission tomography (PET) surveillance was not recommended (Appendix 5).

Table 1. Published clinical practice guideline recommendation on follow-up evaluation for NSCLC survivors.

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Evaluations at follow-up appointment</td>
<td>CT scan</td>
<td>CT scan</td>
<td>History, physical examination, and imaging</td>
<td>History, physical examination, and chest imaging</td>
</tr>
</tbody>
</table>
Follow-up Evaluation | AATS (2012)
---|---|---|---|---|---
Frequency of follow-up | Every 6 months for 3 years, then annually | Every 6 months for 2 years, then annually | Every 3-6 months for 2-3 years, then annually | Every 6-12 months for 2 years, then annually
Imaging test | High-resolution CT for 4 years, then low dose CT | Chest CT | Chest CT preferred with chest x-ray also being appropriate | Chest CT with or without contrast first 2 years, then non-contrast-enhanced chest CT annually

Abbreviations: AATS, American Association for Thoracic Surgery; ACCP, American College of Chest Physicians; CT, computed tomography; ESMO, European Society of Medical Oncology; LDCT, low-dose computed tomography; NCCN, National Comprehensive Cancer Network; NSCLC, non-small cell lung cancer.

Clinical Practice Guidelines for SCLC
Two identified clinical practice guidelines made recommendations on the care of SCLC survivors; Table 2 summarizes the relevant recommendations. The ESMO SCLC guideline (6) covered all aspects of SCLC care, including diagnosis, treatment and follow-up. The NCCN guideline (12) also covered all aspects of SCLC patient care. The ESMO guideline only specified that CT scans were to occur at follow-up visits (6), while the NCCN guideline recommended a more thorough evaluation (12). The frequency of follow-up visits did not differ dramatically between the guidelines; however, only the ESMO guideline recommended the use of CT scan for surveillance (6), while the NCCN guideline did not make a recommendation of the appropriate chest imaging modality (12).

Table 2. Published clinical practice guideline recommendations on follow-up care for SCLC survivors.

<table>
<thead>
<tr>
<th>Follow-up Evaluation</th>
<th>ESMO (2013)</th>
<th>NCCN (2014)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluations at follow-up appointment</td>
<td>CT scan</td>
<td>History, physical examination, chest imaging and blood work as clinically indicated</td>
</tr>
<tr>
<td>Frequency of follow-up</td>
<td>Every 3-6 months for 2 years with longer intervals between thereafter. Annual scans after 5 years.</td>
<td>Every 3-4 months during first 1-2 years, every 6 months years 3-5, then annually</td>
</tr>
</tbody>
</table>
Follow-up Evaluation | ESMO (2013)\(^6\) SCLC | NCCN (2014)\(^{12}\) SCLC
--- | --- | ---
Imaging test | CT scan with low-dose CT being recommended after 5 years. | Not specified

Abbreviations: CT, computed tomography; ESMO, European Society of Medical Oncology; NCCN, National Comprehensive Cancer Network; SCLC, small cell lung cancer.

EVIDENTIARY BASE DEVELOPMENT

Using the research questions described above, a search for existing systematic reviews and systematic review of the primary literature was conducted, as described in Section 2 of this EBS.

INITIAL RECOMMENDATIONS

Using the evidentiary base in Section 2, the Working Group developed a set of initial recommendations. These initial recommendations were developed through a consideration of the aggregate evidence quality and the potential for bias in the evidence, and the likely benefits and harms of follow-up care interventions for patients after curative-intent treatment for NSCLC or SCLC. The Working Group considered the values they used in weighing benefits compared with harms, and then made a considered judgement. This process is described in detail for each topic area described below. When there was little evidence identified, the Working Group used a consensus process to make a recommendation in their expert opinion. In general, the consensus process involved a form with recommendations broken down by statement that all Working Group members used to vote. Possible responses included agree, disagree, or agree with alterations, with space to detail the alteration. Working Group members returned the forms to the methodologist (LS), who pooled final recommendations for approval based on the majority. The Working Group then voted on the initial recommendations as a whole. Specifics for each consensus process are detailed below.

Topic Area 1: Follow-up Evaluations and Frequency for Survivors of NSCLC

Key Evidence for Benefits and Harms

One systematic review with meta-analysis found no survival benefit with a more intense follow-up schedule for NSCLC survivors (hazard ratio [HR], 0.83; 95%CI, 0.66-1.05; p=0.13) (14). However, asymptomatic recurrence detection was associated with a longer survival time (HR, 0.61; 95%CI, 0.50-0.74; p<0.01) (14). Other research has determined that in both NSCLC and SCLC, the majority of recurrences are diagnosed in the first two years (15).

A systematic review that evaluated the role of CT follow-up one year after lobectomy did not find a clear survival benefit for CT scans (16). However, a more recent study points to a role for minimal-dose CT (MnDCT) scans, which showed higher sensitivity (94.2% vs. 21.2%; p<0.0001) and negative predictive value (99.7% vs. 96.2%; p=0.007) than chest x-ray for detecting new primary tumours and recurrent lung cancer at an early stage (17).

Aggregate Evidence Quality and Potential for Bias

The Calman (14) systematic review with meta-analysis was based primarily on observational studies, introducing a high risk of bias. Additionally, for the included studies,
there was not a constant definition for intensive follow-up schedules (14). Similarly, the systematic review on the role of CT was based on primarily observational studies (16). The PET diagnostic studies were of fairly good quality, and all used a fully paired design to minimize the risk of bias.

Values of the Working Group

The Working Group believes that NSCLC survivors should be followed after curative treatment in order to detect local or locoregional recurrence as they are potentially amenable to resection or radical radiation therapy for salvage. For this reason, overall survival rate is valued over recurrence detection rate.

Considered Judgement

There is very little high-level evidence to inform this recommendation. Visits should include medical history with attention to new symptoms in the aerodigestive tract, physical examination and chest imaging. Due to the lack of evidence to inform which frequency is most appropriate, a consensus approach was used to make a recommendation on the appropriate timing of follow-up evaluations in the expert opinion of the Working Group. The consensus process incorporated the evidence that most recurrences are detected in the first two years following curative treatment (15), the indication that asymptomatic recurrence detection is associated with longer survival (14), and the clinical experience of the Working Group members. The high frequency of follow-up visits in the first two years is in agreement with the ESMO guideline for early-stage and locally advanced NSCLC (7), which recommend visits every three to six months in the first two to three years. Additionally, even though data for surveillance beyond five years is limited, the Working Group feels confident in recommending annual surveillance after three years as the population under discussion is at a heightened risk of developing new cancers and screening protocols for populations at high risk recommend annual CT scans.

Due to the limited evidence, there is no clear indication of the most appropriate chest imaging modality for surveillance. Although there is no clear evidence from studies focusing on recurrence detection, the clinical standard among Ontario health care professionals is CT scan, with the appropriate dose and use of contrast IV remaining controversial. Due to radiation dose concerns when performing CT scans for surveillance, lower dose CT scan protocols are of great interest. The best evidence for the value LDCT surveillance comes from the National Lung Screening Trial (18,19), which indicated that LDCT was better than radiography in detecting early-stage lung cancers. The Working Group concluded that the cohort study that demonstrated the superiority of MnDCT over chest x-ray in NSCLC survivors (17) paired with the success of LDCT in screening (18,19) provide rationale to suggest either LDCT or MnDCT over chest x-ray for pulmonary lesion detection in NSCLC survivor populations. The MnDCT cohort study conducted chest CTs at three months post-treatment, followed by six months post-treatment, then at six month intervals until the end of year 2, and then annually until year 5. As this is the best available schedule at this time, the intervals are considered reasonable, with the addition of annual surveillance exceeding year 5. Even though surveillance is recommended annually until end of life, health care professionals should use their own discretion in determining the applicability of annual surveillance in patients who are not well enough to undergo treatment if a new cancer is detected. When recurrent disease or new disease is suspected, either from constitutional symptoms or chest imaging findings, diagnostic chest CT plus upper abdomen scan is suggested to identify local recurrence or a new lung primary. The suggestion to include chest CT as a reasonable option for appropriate surveillance imaging of NSCLC survivors is in agreement with recommendations published by AATS (9), ACCP (5), ESMO (7) and NCCN (13).
Initial (DRAFT) Recommendation 1
Following curative-intent treatment for NSCLC, survivors should receive scheduled follow-up visits that include a medical history, physical examination and chest imaging. Clinical evaluations should be conducted every three months in years 1 and 2, every six months in year 3, and annually thereafter.

Topic Area 2: Follow-up Evaluations and Frequency for Survivors of SCLC

Key Evidence for Benefits and Harms
One systematic review with meta-analysis found no benefit with a more intense follow-up schedule for SCLC survivors (14). Other research has determined that in both NSCLC and SCLC, the majority of recurrences are diagnosed in the first two years (15).

Aggregate Evidence Quality and Potential for Bias
There was little evidence found to inform this question. The Calman (14) systematic review with meta-analysis was based primarily on observational studies, with only two studies being pooled for the SCLC analysis.

Values of the Working Group
The Working Group believes that SCLC survivors should be followed after curative treatment in order to detect new primary lung cancers that are amenable to further curative treatment. For this reason, follow-up schedules that result in a high recurrence rate are only of value if this translates into an increase in overall survival, and overall survival rate is valued over recurrence detection rate. The clinical experts on the Working Group commonly use chest CT over chest x-ray for follow-up imagining, but recognize that there is no evidence to support chest CT as the gold standard.

Considered Judgement
There was very little high-level evidence to inform this recommendation. Visits should include medical history with attention to new symptoms in the aerodigestive tract, physical examination and chest imaging. A consensus approach was used to determine the appropriate timing of follow-up evaluations in the expert opinion of the Working Group. The consensus process incorporated the evidence that most recurrences are detected in the first two years following curative treatment (15), that more intense follow-up schedules do not result in a longer overall survival time (14), and the clinical experience of the Working Group members.

Due to a lack of evidence, there is no clear indication in the literature on the appropriate surveillance imaging modality for SCLC survivors. The clinical standard among Ontarian oncologists is a CT scan, but there is no evidence to support this choice in a lung cancer survivor population. Based on extrapolation from screening data and expert opinion, Qualifying Statements with imaging modality suggestions have been included for SCLC survivors. Data from the National Lung Screening Trial (18,19) indicated that LDCT was better than radiography in detecting early-stage lung cancers. Based on the superiority of CT to chest x-ray for screening in a high risk population, in the expert opinion of the Working Group, surveillance of SCLC survivors with diagnostic CT scans for detection of further pulmonary lesions may be a reasonable option. Based on the clinical experience of the Working Group, diagnostic CT with contrast is suggested for detection of recurrence in mediastinal lymph nodes. In the expert opinion of the Working Group, CT imaging may be conducted three months post-treatment, followed by six months post-treatment, then at six month intervals until the end of year 2, followed by annually thereafter. Even though surveillance is recommended annually until end of life, health care professionals should use...
their own discretion in determining the applicability of annual surveillance in patients who are not well enough to undergo treatment if a new cancer is detected. When recurrent disease or new disease is suspected, either from constitutional symptoms or chest imaging findings, diagnostic chest CT plus upper abdomen scan is suggested to identify local recurrence or a new lung primary. The suggestion to include chest CT as a reasonable option for appropriate surveillance imaging of SCLC survivors is in agreement with the ESMO guideline for SCLC patients, which states that survivors should be followed with CT scans (6).

**Initial (DRAFT) Recommendation 2**
Following curative-intent treatment for SCLC, survivors should receive scheduled follow-up visits that include a medical history, physical examination and chest imaging. Clinical evaluations should be conducted every three months in years 1 and 2, every six months in year 3, and then annually thereafter.

**Topic Area 3: Role of Positron Emission Tomography (PET)/CT in Follow-up Care of Lung Cancer Survivors**

*Key Evidence for Benefits and Harms*

The only identified studies that assessed PET/CT surveillance of lung cancer survivors were in NSCLC survivor populations. Two PET/CT diagnostic studies indicated a benefit for PET/CT over CT alone for recurrence detection (20,21), while another demonstrated a benefit for PET/CT over non-contrast CT for detection of extrathoracic and mediastinal metastases (22). One study, looking at the ability to detect local recurrence, found that almost 26% of the recurrences diagnosed by PET/CT were recurrences within the ipsilateral lung (20). In another diagnostic study, PET/CT scanning led to the detection of lung cancer recurrence that was amenable to salvage therapy in a small proportion (3% of total) of the patients enrolled (21).

*Aggregate Evidence Quality and Potential for Bias*

The PET diagnostic studies were of fairly good quality and all used a fully-paired design to minimize the risk of bias.

*Values of the Working Group*

Overall survival rate is valued over recurrence detection rate. The goal of surveillance is to detect new primary lung cancers or local and locoregional recurrences that are amenable to further curative treatment.

*Considered Judgement*

The Working Group was unable to provide a recommendation for PET/CT surveillance of NSCLC and SCLC survivors based on the identified evidence. Diagnostic studies have shown better sensitivity, specificity and accuracy of PET/CT compared with CT alone and point to a role for PET/CT in diagnosing local and locoregional recurrences, which may be amenable to salvage therapy (20,21). However, due to the low percentage of local recurrence detected by PET/CT in these studies and the higher doses of radiation patients would receive with PET/CT compared with CT alone, the Working Group feels that the evidence from these two studies is not strong enough upon which to base a recommendation.

**Initial (DRAFT) Recommendation 3**
For both NSCLC and SCLC survivors, no recommendation can be made in relation to PET/CT.
Topic Area 4: Symptoms of Recurrence or Development of Any Second Primary Tumour

Key Evidence for Benefits and Harms

A prospective cohort study found that patients with progressive disease experienced more pain and neurological issues that did those without progressive disease (21).

Aggregate Evidence Quality and Potential for Bias

Evidence comes from a PET diagnostic study that was of fairly good quality and used a fully paired design to minimize the risk of bias. However, the study enrolled a modest sample size of 100 patients, with only 24 patients developing progressive disease.

Values of the Working Group

The Working Group was concerned by the lack of data to inform this question, in addition to the small sample size of the included study.

Considered Judgement

Due to the lack of data, the Working Group decided to use a consensus process to list the symptoms in their expert opinion. During the project planning stage of the guideline, the clinical experts provided the methodologist with a list of symptoms to use when designing the literature search. The methodologist created a draft list of symptoms, which the clinical experts then voted on including.

Initial (DRAFT) Recommendation 4

In the expert opinion of the authors, any new and persistent or worsening symptom warrants the consideration of a recurrence, especially:

Constitutional Symptoms:
- Dysphagia
- Fatigue (new onset)
- Hoarseness
- Nausea or vomiting (unexplained)
- New finger clubbing
- Suspicious lymphadenopathy
- Sweats (unexplained)
- Thrombosis
- Weight loss or loss of appetite

Pain:
- Bone pain
- Chest pain
- Caveat shoulder pain not related to trauma

Neurological Symptoms:
- Headaches (if persistent)
- New neurological signs suggestive of brain metastasis or cord compression such as leg weakness or speech changes
- Headache or focal neurological symptoms

Respiratory Symptoms:
- Cough (despite use of antibiotics)
Dyspnea
Hemoptysis
Signs of superior vena cava obstruction
Stridor

Topic Area 5: Non-Recurrence-Related Issues Experienced by Lung Cancer Survivors

Key Evidence for Benefits and Harms

When overall QoL profiles of lung cancer survivors were analyzed, it was found that survivors on unspecified type lung cancer experienced a reduction in physical domains for up to one year post surgery (23,24). There was an increase in mental domains above pre-surgery by two years, but this domain was still lower than an age-matched reference population (24). When only NSCLC survivors were followed after lobectomy, 65% of survivors experienced improved or stable QoL scores, while 71% of survivors experienced improved or stable scores following pneumonectomy or bilobectomy (25).

A systematic review that assessed the specific treatment-related long-term effects found that survivors of lung cancer report physical ability restrictions, depression, decreases in general health and vitality and increased body pain (15). Prospective cohort studies evaluating non-recurrence-related issues found that survivors experience long-term dyspnea (26-28), cough (26,28), fatigue (26,28), impaired breathing (29), increased pain (28,29), decline in appetite (28,29) and reduced sleep efficiency (27). Studies that focused solely on survivors of NSCLC found that a majority of these survivors experienced some degree of pneumonitis (30) and a sustained decrease in multiple QoL domains (31).

Aggregate Evidence Quality and Potential for Bias

The studies that inform this research question range from systematic reviews and randomized controlled trials (RCTs) to non-randomized prospective cohort studies. All the included studies used prospective data collection and analyzed the study population through comparisons either between groups or within the study group, across time. Unfortunately, since all non-randomized studies carry an unclear risk of bias and most of the studies relied on the use of QoL tools that survivors filled out at home, increasing the risk of recall bias, it is believed that the studies informing this evidence are of low quality.

Values of the Working Group

The Working Group is concerned that the long-term needs of survivors are not being met. QoL is valued very highly in the follow-up care of these patients.

Considered Judgement

The Working Group does recognize that this is the best data available, as QoL and late treatment effect data are generally not included in treatment trials a priori. However, due to the low quality of studies discovered, the Working Group decided to use both the literature and their clinical experience to summarize the late side effects and QoL issues reported by long-term survivors of lung cancer. During the project planning stage of the guideline, the clinical experts provided the methodologist with a list of known late treatment-related effects to use when designing the literature search. The methodologist pooled these effects with the effects identified by the literature to create a list, which the clinical experts then voted upon including.
Initial (DRAFT) Recommendation 5

Health-related QoL is very important for long-term survivors suffering from late side effects of their curative-intent therapy (including surgery, chemotherapy and radiation therapy). The following is a summary of issues reported by survivors. Health care professionals need to aid lung cancer survivors in handling these symptoms to improve QoL.

Constitutional Issues:
- Anxiety
- Cough
- Decline in appetite
- Decrease in general health
- Depression
- Dysphagia
- Esophageal stricture
- Fatigue
- Pain
- Physical ability restrictions
- Reduced sleep quality
- Shortness of breath

Long-term Chemotherapy Effects:
- Hearing loss
- Neuropathies
- Renal impairment

Long-term Radiation Effects:
- Breathing complications
- Breathlessness/Dyspnea

Long-term Surgery Effects:
- Empyema
- Oxygen dependence
- Post-thoracotomy pain syndrome
- Reduced exercise tolerance or activity limitations
- Shortness of breath

Topic Area 6: Most Responsible Follow-up Health Care Professional and Setting

Key Evidence for Benefits and Harms

One RCT informed this question. The Moore et al study (32) compared institution-based nurse-led follow-up care with specialist-led follow-up care following treatment for SCLC or NSCLC. The study found that both QoL and recurrence outcomes were not different between the two groups, indicating that nurse-led follow-up did not negatively impact QoL or recurrence detection.

Aggregate Evidence Quality and Potential for Bias

The RCT was of good methodological quality. Unfortunately, the study is more than 10 years old, and when conducted, no effective salvage therapy and no effective second-line chemotherapy were available, which may have led to no difference being detected for overall survival. Also, the study allowed for additional visits to a family physician, which though
beneficial for the survivors, may have confounded some of the findings. Finally, the study included a more advanced disease population than was our target population.

**Values of the Working Group**

The Working Group is concerned about the lack of evidence to inform this question. Additionally, the included study had limitations in the treatments available. The Working Group valued QoL of survivors above all other outcomes for this question. Patient satisfaction with care is also valued highly. The Working Group also notes that family physicians play an integral part in survivor follow-up and should be included in all care models.

**Considered Judgement**

The Working Group considered the study limitations and even though this patient population would be managed differently today due to new treatment options, the Working Group accepts this study as it is the best available evidence. Additionally, for this research question, QoL and satisfaction with care are highly valued. Thus, the Working Group believes that a weak recommendation for healthcare provided by non-specialists is warranted. Although the identified literature only evaluated hospital-based nurse-led care models, expert opinion supports family physician-led care models. Additionally, family physicians should be included in all survivorship care models. There is no evidence to support timing for when lung cancer survivors can be transitioned into non-specialist care, thus no recommendation can be made for when transition is appropriate.

**Initial (DRAFT) Recommendation 6**

For lung cancer survivors who have completed curative-intent therapy, surveillance is required and may be provided by specialists, family doctors or hospital-based nurses.

**Topic Area 7: Value of Smoking Cessation Counselling for Lung Cancer Survivors**

**Key Evidence for Benefits and Harms**

Systematic reviews that assessed the efficiency of smoking in cessation counselling concluded that any intervention is better than no cessation advice from a health care professional (33), with an intensive intervention that added further follow-up visits being more effective than brief intervention (33). When pharmacotherapy and behavioural support are added to advice from a health care professional alone, the benefit of the counselling is increased (34). The three systematic reviews and one cohort study that evaluated the benefits of smoking cessation after diagnosis of lung cancer or prior to surgery all concluded that smoking cessation improved prognostic outcomes (35-38). Cohort studies that looked at the association between smoking cessation and QoL found that never-smokers reported the best QoL after curative treatment (39,40). However, patients who quit smoking within one year prior to diagnosis or during follow-up reported better overall QoL and symptom scales compared with survivors who continued to smoke (39-41).

**Aggregate Evidence Quality and Potential for Bias**

The included systematic reviews that inform both aspects of the research question were all of good quality. The cohort studies looking at QoL of lung cancer survivors in relation to their smoking status were of lesser quality, as the studies relied on patient reported QoL tools, introducing recall bias. Additionally, smoking status was not clinically verified in any of the cohort studies.
Values of the Working Group

The Working Group is concerned that none of the discovered studies directly informed the question of whether smoking cessation counselling is beneficial to survivors. Instead, separate evidence was found on the efficiency of smoking cessation counselling and the evidence for the value of smoking cessation in lung cancer survivors. Studies looking at the efficiency of counselling were not conducted in lung cancer survivor populations, while studies looking at the QoL of survivor in relation to their smoking status did not include cessation interventions.

Considered Judgement

Even though neither of the types of studies found for this research question directly answered the research question, the Working Group members agreed that taken together, the evidence for the benefit of smoking cessation counselling, the evidence for the prognostic benefits of cessation and the evidence for the QoL benefits of cessation can be combined to adequately inform this recommendation.

Initial (DRAFT) Recommendation 7
Smoking cessation counselling is recommended for patients who have completed curative-intent therapy for NSCLC and SCLC. Although verbal cessation advice from a health care professional is of benefit, interventions that involve behavioural and pharmacotherapy support in addition to verbal advice are recommended.

INTERNAL REVIEW

Almost all PEBC documents undergo internal review. This review is conducted by the Expert Panel and the Report Approval Panel. The Working Group was responsible for incorporating the feedback and required changes of both of these panels, and both panels had to approve the document before it could be sent to External Review.

Expert Panel Review and Approval

The Lung Cancer Follow-up Expert Panel acted as the Expert Panel for this document. The members of this group were required to submit conflict of interest declarations prior to reviewing the document. These declarations are described in Appendix 1. The document must be approved by formal vote. In order to be approved, 75% of the Lung Cancer Follow-up Expert Panel membership must cast a vote or abstain, and of those who voted, 75% must approve the document. At the time of the voting, the Lung Cancer Follow-up Expert Panel members could suggest changes to the document, and possibly make their approval conditional on those changes. In those cases, the Working Group was responsible for considering the changes, and if those changes could be made without substantially altering the recommendations, the altered draft would not need to be resubmitted for approval.

The Lung Cancer Follow-up Expert Panel reviewed the draft document over a six-week period at the end of 2013. During this review the Lung Cancer Follow-up Expert Panel provided the following key feedback.

1. Originally, Recommendations 1 and 2 did not include CT as the recommended imaging modality, based on a lack of evidence. Expert Panel members believed that even though there wasn’t sufficient data to recommend CT as the imaging modality of choice, CT at least had to be described as the current standard of care. Further, Expert Panel members believed that since the recommendation for timing of follow-up was based on expert opinion, that a definitive imaging modality could be based on expert opinion as well.
2. One reviewer wanted to know if the Working Group considered including the Boston data about early referral to palliative care.
3. Expert Panel members believed that Section 1 did not state clearly enough that there is a lack of good evidence for this topic.
4. Two Expert Panel members identified new studies not included in the evidentiary base.
5. One Expert Panel member believed the recommendation for chest imaging at every follow-up visit to be excessive.
6. One Expert Panel member believed that Research Question 4, which focused on long-term side-effects of lung cancer treatment, was too specific and ignored broader survivorship issues.

In response to this feedback, the Working Group made the following changes.

1. The Working Group agreed with the Expert Panel members and altered the recommendations to include CT scans for both NSCLC and SCLC. For NSCLC, the recommendation includes LDCT, backed by the lung cancer screening data, or MnDCT, backed by a cohort study. The decision to include a radiation dose for NSCLC survivors was debated at length among the Working Group members. The Working Group members believed that the dose recommendation was justified, but are prepared to further discuss this based on external review feedback. For SCLC, the recommendation was altered to include CT without a dose recommendation and is backed by the lung screening data.
2. The Working Group did not consider including the early referral to palliative care data, as this data was not in our population of interest.
3. Statements about the lack of high-quality data to inform the research questions were included in Section 1 in both the “Justification for Recommendation” and the “Future Research” section.
4. As the literature search for this clinical practice guideline was almost eight months old when internal review was initiated, an update of the search was planned. The literature search was updated to week 4 of 2014 and identified the new studies provided by the Expert Panel members.
5. In the absence of good evidence on the appropriate timing of chest imaging for surveillance, the Working Group relied on expert opinion and the frequency of CT scans in the only cohort study that enrolled NSCLC survivors. The timing of imaging compared with clinical evaluations was debated at length among Working Group members. The decision to recommend CT scans at every follow-up visit is in agreement with other clinical practice guidelines, but Working Group members are prepared to further discuss imaging frequency based on the external review feedback.
6. The original inclusion criteria stated that studies had to be conducted solely in lung cancer survivor populations. Since the broader survivorship issues have not been studied in lung cancer survivor populations specifically, no studies were identified. Discussion of this short-coming of the literature was added to the “Future Research” paragraph in Section 1 and the “Discussion” in Section 2.

On January 13, 2014 by email, the Lung Cancer Follow-up Expert Panel considered a draft of the document incorporating the changes described above, and formally approved the document by vote. Of the 15 members of the Lung Cancer Follow-up Expert Panel, 13 members cast votes and two abstained, for a total of 86.7% response. Of those who cast votes, 13 approved the document (100%).
Report Approval Panel Review and Approval

The purpose of the Report Approval Panel (RAP) review is to ensure the methodological rigour and quality of PEBC documents. The RAP consists of nine clinicians with broad experience in clinical research and guideline development, and the Director of the PEBC. For each document, three RAP members review the document: the Director and two others. RAP members must not have had any involvement in the development of the guideline prior to Internal Review. All three RAP members must approve the document, although they may do so conditionally. If there is a conditional approval, the Working Group is responsible for ensuring the necessary changes are made, with the Assistant Director of Quality and Methods, PEBC, making the final determination that the RAP’s concerns have been addressed.

In December 2013 the RAP reviewed this document. The RAP approved the document on January 17, 2014. Key issues raised by the RAP included the following:

1. Section 2 of the guideline includes many different subheadings within questions. One RAP reviewer did not find the format of the subheading clear.
2. One RAP reviewer believed that recurrence in the aerodigestive tract should have been added to multiple places within the guideline.
3. One RAP reviewer was concerned with the explanation of the Calman et al meta-analysis (14), as the explanation made it appear that intensive follow-up led to asymptomatic recurrence detection and longer survival time.

The Working Group made the following changes in response to the RAP review:

1. Section 2 was altered so that it now follows a numbering system for subheadings.
2. The Working Group does recognize the importance of recurrences in the aerodigestive tract; however, since the original literature search was not designed to specifically search for studies on this type of recurrence, it would have been misleading to insert “recurrences in the aerodigestive tract” to many locations within Section 2. Within Section 1, the “Justification for Recommendations 1 and 2” were altered to incorporate aerodigestive tract recurrence. Additionally, the Introduction of Section 2 was altered to incorporate recurrence in the aerodigestive tract.
3. All text that mentioned the Calman et al meta-analysis (14) was rewritten to ensure that the study findings were clear.

External Review by Ontario Clinicians and Other Experts

The PEBC external review process is two-pronged and includes a targeted peer review that is intended to obtain direct feedback on the draft report from a small number of specified content experts and a professional consultation that is intended to facilitate dissemination of the final guidance report to Ontario practitioners.

Following approval of the document at Internal Review, the Lung Cancer Follow-up Expert Panel circulated the draft document with recommendations modified as noted under Internal Review, above, to external review participants for review and feedback.

Methods

Targeted Peer Review: During the guideline development process, nine targeted peer reviewers from Ontario considered to be clinical and/or methodological experts on the topic were identified by the Working Group. Several weeks prior to completion of the draft report, the nominees were contacted by email and asked to serve as reviewers. Five reviewers agreed and the draft report and a questionnaire were sent via email for their review. The questionnaire consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be
approved as a guideline. Written comments were invited. The questionnaire and draft document were sent out on April 9, 2014. Follow-up reminders were sent at two weeks (email) and at four weeks (telephone call). The Lung Cancer Follow-up Expert Panel reviewed the results of the survey.

**Professional Consultation**: Feedback was obtained through a brief online survey of health care professionals who are the intended users of the guideline. The PEBC database was used to identify professionals who had reported being interested in both lung cancer and either survivorship, systemic therapy, radiation, surgery, primary care, imaging, nursing, or post-treatment follow-up. Additionally, lung cancer survivors were identified through Lung Cancer Canada. All identified professionals and survivors were contacted by email to inform them of the survey. Of the 126 individuals informed of the survey, 114 were from Ontario, with the other 12 from other provinces. Participants were asked to rate the overall quality of the guideline (Section 1) and whether they would use and/or recommend it. Written comments were invited. Participants were contacted by email and directed to the survey website where they were provided with access to the survey, the guideline recommendations (Section 1), and the evidentiary base (Section 2). The notification email was sent on April 9, 2014. The consultation period ended on May 9, 2014. The Lung Cancer Follow-up Expert Panel reviewed the results of the survey.

**Results**

**Targeted Peer Review**: Five responses were received from five reviewers. Key results of the feedback survey are summarized in Table 3.

<table>
<thead>
<tr>
<th>Table 3. Responses to nine items on the targeted peer reviewer questionnaire.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Question</td>
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<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Question</td>
</tr>
<tr>
<td>1. Rate the guideline development methods.</td>
</tr>
<tr>
<td>2. Rate the guideline presentation.</td>
</tr>
<tr>
<td>3. Rate the guideline recommendations.</td>
</tr>
<tr>
<td>4. Rate the completeness of reporting.</td>
</tr>
<tr>
<td>5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?</td>
</tr>
<tr>
<td>6. Rate the overall quality of the guideline report.</td>
</tr>
<tr>
<td>7. I would make use of this guideline in my professional decisions.</td>
</tr>
<tr>
<td>8. I would recommend this guideline for use in practice.</td>
</tr>
<tr>
<td>9. What are the barriers or enablers to the implementation of this guideline report?</td>
</tr>
</tbody>
</table>
Summary of Written Comments

The main points contained in the written comments were as follows:

1. Three reviewers were concerned about the applicability of the timing for CT scans with the lack of strong evidence. Due to the lack of high-quality evidence, the radiation exposure, lack of scanners, and cost, the reviewers did not agree with the frequency of scans. One reviewer was especially concerned with SCLC survivors due to the lack of evidence. Another reviewer felt that QoL issues for an increased CT surveillance schedule should have been considered.

2. One reviewer would like more clarification on whether CT scans should be chest or chest and abdomen CT and whether the scans should be with or without-contrast.

3. One reviewer found the symptoms and side-effects in Recommendations 4 and 5 to be too general. The reviewer would also like to see the location aspect of bony pain removed as hip and back are not mentioned but are also appropriate. Finally, the reviewer also suggests inclusion of headache or focal neurological symptoms under the “Neurological” subheading.

Professional Consultation: Twenty-one responses were received. Key results of the feedback survey are summarized in Table 4.

Table 4. Responses to four items on the professional consultation survey.

| Number (%) |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| General Questions: Overall Guideline Assessment | Lowest Quality (1) | (2) | (3) | (4) | Highest Quality (5) |
| 1. Rate the overall quality of the guideline report. | 1 (4.8%) | 2 (9.5%) | 5 (23.8%) | 5 (23.8%) | 8 (38.1%) |
| 2. I would make use of this guideline in my professional decisions. | Strongly Disagree (1) | (2) | (3) | (4) | Strongly Agree (5) |
| 3. I would recommend this guideline for use in practice. | 3 (14.3%) | 2 (9.5%) | 3 (14.3%) | 7 (33.3%) | 6 (28.6%) |
| 4. What are the barriers or enablers to the implementation of this guideline report? | 3 (14.3%) | 3 (14.3%) | 1 (4.8%) | 5 (23.8%) | 9 (42.8%) |

Summary of Written Comments

The main points contained in the written comments were as follows:

1. One reviewer feels that “Intended Users” should be expanded to include cytopathologists and surgical pathologists who first diagnosed the disease and who perform the subsequent restaging.

2. One reviewer would like clarification on whether surveillance is until death as Recommendations 1 and 2 read “annually thereafter.”

3. Two reviewers asked why studies involving family physician follow-up of lung cancer survivors were not included in the guideline.
**Modifications/Actions**

1. The Working Group has modified the recommendations to only recommend chest imaging with details on the reasonable option to use CT within “Qualifying Statements” of Recommendations 1 and 2 only.
2. Qualifying statements for Recommendation 1 and 2 now also include expert opinion suggestions on use contrast and abdomen scans.
3. The Working Group admits that Recommendations 4 and 5 are very general, but feel that the generality is necessary for guidance. Suggestions for bony pain and neurological symptoms have been incorporated into Recommendation 4 and 5.
4. The Working Group did not add pathologists to the “Intended Users” as it was felt that these individuals do not provide follow-up care for NSCLC or SCLC survivors.
5. Qualifying Statements for Recommendations 1 and 2 also now include clarification on follow-up being recommended until end of life, but this being at the health care professional’s discretion for those unable to be re-treated.
6. The original literature was designed to identify family physician care models, but as none were identified, they were not discussed in Section 1. Statements explaining that family physician studies were searched have been added to the “Summary of Key Evidence for Recommendation 6.”

**Conclusion**

This EBS report reflects the integration of feedback obtained through the external review process with final approval given by the Lung Cancer Follow-up Expert Panel and the Report Approval Panel of the PEBC. Updates of the report will be conducted in accordance with the PEBC Document Assessment and Review Protocol.

**Conflict of Interest**

In accordance with the PEBC Conflict of Interest (COI) Policy, the guideline authors, Lung Cancer Follow-up Expert Panel members, and internal and external reviewers were asked to disclose potential conflicts of interest. All authors and internal reviewers declared they had no conflicts of interest. For the Expert Panel, 14 members declared they had no conflict of interest, and one (MR) declared a conflict. MR reported receiving $10,000 in 2011 for consulting on lung cancer follow-up. The conflict of interest declared by MR did not disqualify the individual from performing her role in the development on this guideline, in accordance with the PEBC COI Policy. All external reviewers declared that they had no conflict of interest. To obtain a copy of the policy, please contact the PEBC office by email at ccopgi@mcmaster.ca.
REFERENCES


Appendix 1: Members of the Lung Cancer Follow-up Guideline Development Group.

**Working Group Members**

<table>
<thead>
<tr>
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<th>Contact Information</th>
<th>Conflict of Interest</th>
</tr>
</thead>
<tbody>
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<td>None</td>
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**Report Approval Panel Members**

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<tr>
<td>Robert Zeldin</td>
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<td></td>
<td>Toronto, ON M4C 3E7</td>
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Appendix 2: Literature Search Strategies.

1. (((lung$ or respiratory or bronch$ or pulmonary or pleural or tracheal or pneumo$ or peribronch$ or alveobronch$) adj2 (neoplasm$ or cancer$ or tumor$ or tumour$ or carcinoma$ or adenocarcinoma$ or angiosarcoma$ or chondrosarcoma$ or sarcoma$ or teratoma$ or lymphoma$ or blastoma$ or microcytics or carcinogenesis)).tw.
2. exp Lung Neoplasms/
3. exp Bronchial Neoplasms/
4. exp Carcinoma, Bronchogenic/ or exp Carcinoma, Small Cell/
5. exp Carcinoma, Non-Small-Cell Lung/
6. or/1-5
7. care.mp.
8. continuity.mp.
9. follow up.mp.
10. shared care.mp.
11. (after care or aftercare).mp.
12. surveillance.mp.
13. survivo$.mp.
14. or/7-13
15. recurrence/
16. neoplasm recurrence, local/
17. recurrence$.mp.
18. metastas$.mp.
19. (locoregional or local-regional) recurrence.mp
20. Local recurrence.mp
21. Second$ primary tumour$.mp
22. Second$ primary tumor$.mp
23. or/15-22
24. 14 or 23
25. exp "sensitivity and specificity"/
26. (sensitivity or specificity).tw.
27. exp Diagnostic Errors/
28. predictive value$.tw.
29. predictive value$ of test$.tw.
30. (false adj (negative or positive)).tw.
31. accuracy.tw.
32. reference value$.tw.
33. likelihood ratio$.tw.
34. ((pre-test or pretest) adj probability).tw.
35. post-test probability.tw.
36. Diagnosis, differential/
37. Diagnostic tests, routine/
38. or/25-37
40. (CT adj scan$).mp.
41. (PET adj CT).mp.
42. tomosynthesis.mp.
43. bronchoscopy.mp.
44. exp Blood Test/
45. (genetic adj biomarker$).mp.
46. Or/39-45
47. 38 or 46
48. frequency.mp
49. intense$.mp
50. 49 or 50
51. dysphagia/
52. chest pain/ or shoulder pain/
53. cough/
54. ((chest or shoulder) adj3 pain$).tw.
55. exp body weight changes/
56. (weight adj1 (loss or gain or change$)).tw.
57. (appetite adj loss).tw.
58. neurological symptoms.tw.
59. finger clubbing.tw.
60. lymphadenopathy.tw.
61. Dyspnea/
62. dyspn$.tw.
63. cough$.tw.
64. boney pain.tw.
65. headach$.tw.
66. hemoptysis/
67. (hemoptysis or haemoptysis).tw.
68. hoarseness/
69. hoarse$.tw.
70. superior vena cava obstruction.tw.
71. stridor.tw.
72. fatigue.tw.
73. respiratory sounds/
74. wheez$.tw.
75. "signs and symptoms"/
76. or/51-75
77. 47 or 50 or 76
78. 6 and 24 and 77
79. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt
80. 78 not 79
81. Limit 80 to English
82. Animal/
83. Human/
84. 82 not 83
85. 81 not 84
86. Limit 85 to yr="2000-2012"

1. (((lung$ or respiratory or bronch$ or pulmonary or pleural or tracheal or pneumo$ or peribronch$ or alveobronch$)
adj2 (neoplasm$ or cancer$ or tumor$ or tumour$ or carcinoma$ or adenocarcinoma$ or angiosarcoma$ or chondrosarcoma$ or sarcoma$ or teratoma$ or lymphoma$ or blastoma$ or microcytic$ or carcinogenesis)).tw.
2. exp lung tumor/
3. exp bronchus tumor/
4. exp lung carcinoma/
5. exp lung non small cell cancer/
6. exp small cell carcinoma/
7. or/1-6
8. care.mp.
9. continuity.mp.
10. (follow-up or follow up).mp.
11. exp follow up/
12. shared care.mp.
13. after care/
14. long term care/
15. (after care or aftercare).mp.
16. surveillance$ .mp.
17. survivor$.mp.
18. or/8-17
19. exp recurrent cancer/ or exp recurrent disease/
20. recurrence$.mp.
21. neoplasm recurrence, local/
22. metastas$.mp.
23. local recurrence.mp
24. (locoregional or local-regional) recurrence.mp
25. second$ primary tumor$.mp
26. second$ primary tumour$.mp
27. or/19-26
28. 18 or 27
29. "sensitivity and specificity"/
30. sensitivity.tw.
31. specificity.tw.
32. exp "prediction and forecasting"/
33. predictive value$.tw.
34. predictive value$ of test$.tw.
35. exp diagnostic error/
36. (false adj (positive or negative)).tw.
37. diagnostic accuracy/
38. accuracy.tw.
39. reference value/
40. reference value$ .tw.
41. likelihood ratio$.tw.
42. ((pre-test or pretest) adj probability).tw.
43. post-test probability.tw.
44. differential diagnosis/
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46. (chest adj X-ray$).mp.
47. (CT adj scan$).mp.
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50. bronchoscopy.mp.
51. exp blood test/
52. (genetic adj biomarker$).mp.
53. Or/46-52
54. 45 or 53
55. Frequency.mp
56. Intense$.mp
57. 55 or 56
58. dysphagia/
59. exp pain/ and (chest or shoulder$).tw.
60. ((chest or shoulder) adj3 pain$).tw.
61. coughing/ or irritatihemve coughing/
62. cough$.tw.
63. cough/
64. weight change/ or weight gain/ or weight reduction/
65. (weight adj1 (loss or gain or change$)).tw.
67. neurological symptom$.tw.
68. finger clubbing.tw.
69. lymphadenopathy.tw.
70. dyspnea/
71. dyspn$.tw.
72. boney pain.tw.
73. (bone$ adj pain$).tw.
74. headache$.tw.
75. hemoptysis/
76. (hemoptysis or haemoptysis).tw.
77. hoarseness/
78. hoarse$.tw.
79. (superior vena cava adj obstruction).tw.
80. stridor.tw.
81. fatigue.tw.
82. respiratory sounds/
83. wheezing/
84. clinical feature$ or symptom$ /
85. or/58-84
86. 54 or 57 or 85
87. 7 and 28 and 86
88. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt
89. 87 not 88
90. Limit 89 to English
91. Animal/
92. Human/
93. 91 not 92
94. 90 not 93
95. Limit 94 to yr="2000-2012"
1. ((lung$ or respiratory or bronch$ or pulmonary or pleural or tracheal or pneumo$ or peribronch$ or alveobronch$) adj2 (neoplasm$ or cancer$ or tumor$ or tumour$ or carcinoma$ or adenocarcinoma$ or angiosarcoma$ or chondrosarcoma$ or sarcoma$ or teratoma$ or lymphoma$ or blastoma$ or microcytics$ or carcinogenesis)).tw.

2. exp Lung Neoplasms/
3. exp Bronchial Neoplasms/
4. exp Carcinoma, Bronchogenic/ or exp Carcinoma, Small Cell/
5. exp Carcinoma, Non-Small-Cell Lung/
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9. follow up.mp.
10. shared care.mp.
11. (after care or aftercare).mp.
12. surveillance.mp.
13. survivo$.mp.
14. or/7-13
15. (late adj2 effect$).mp
17. Second$ primary tumor$.mp
18. Second primary tumour$.mp
19. Dysphagia/
20. Esophageal stricture.mp.
21. (weight adj gain).mp
22. Radiation induced malignanc$.mp
23. Short$ of breath.mp
24. Lung toxicity.mp
25. Thrombosis.mp
26. (breath$ adj complication$).mp
27. Post-thoracotomy pain syndrome.mp
28. Neuropath$.mp
29. Renal impairment.mp
30. Renal function.mp
31. Hearing loss.mp
32. Quality of life.mp
33. Quality of life/
34. Or/15-33
35. 6 and 14 and 34
36. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt
37. 35 not 36
38. Limit 37 to English
39. Animal/
40. Human/
41. 39 not 40
42. 38 not 41

43. Limit 42 to yr="2000-2012"

1. ((lung$ or respiratory or bronch$ or pulmonary or pleural or tracheal or pneumo$ or peribronch$ or alveobronch$) adj2 (neoplasm$ or cancer$ or tumor$ or tumour$ or carcinoma$ or adenocarcinoma$ or angiosarcoma$ or chondrosarcoma$ or sarcoma$ or teratoma$ or lymphoma$ or blastoma$ or microcytics$ or carcinogenesis)).tw.

2. exp lung tumor/
3. exp bronchus tumor/
4. exp lung carcinoma/
5. exp lung non small cell cancer/
6. exp small cell carcinoma/
7. or/1-6
8. care.mp.
9. continuity.mp.
10. (follow-up or follow up).mp.
11. exp follow up/
12. shared care.mp.
13. after care/
14. (after care or aftercare).mp.
15. surveillance$.mp.
16. survivor$.mp.
17. or/8-16
18. (late adj2 effect$).mp.
19. secondary primar$.mp.
20. Second$ primary tumor$.mp
21. Second$ primary tumour$.mp
22. dysphagia/
23. esophageal stricture.mp.
24. (weight adj gain).mp.
25. radiation induced malignanc$.mp.
26. short$ of breath.mp.
27. lung toxicity.mp.
28. thrombosis.mp.
29. (breath$ adj complication$).mp.
30. post-thoracotomy pain syndrome.mp.
31. neuropath$.mp.
32. renal impair$.mp.
33. renal function.mp.
34. (hearing adj loss).mp.
35. Quality of life.mp
36. Quality of life/
37. or/18-36
38. 7 and 17 and 37
39. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt
1. meta-analysis as topic/
2. meta analysis.pt.
3. (meta analysis$ or metaanaly$).tw.
4. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes$ or quantitative overview).tw.
5. (systematic adj (review$ or overview$)).tw.
6. (exp Review Literature as topic/ or review.pt. or exp review/) and systematic.tw.
7. or/1-6
8. (cochrane or embase or psychlit or psychinfo or cinahl or science citation index or scisearch or bids or sigle or cancerlit).ab.
9. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$s).ab.
10. (selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
11. (study adj selection).ab.
12. 10 or 11
13. review.pt.
14. 12 and 13
15. 7 or 8 or 9 or 14
16. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.
17. 15 not 16
18. ((lung$ or respiratory or bronch$ or pulmonary or pleural or tracheal or pneumo$ or peribronch$ or alveobronch$) adj2 (neoplasm$ or cancer$ or tumor$ or tumour$ or carcinoma$ or adenocarcinoma$ or angiosarcoma$ or chondrosarcoma$ or sarcoma$ or teratoma$ or lymphoma$ or blastoma$ or microcytics$ or carcinogenesis)).tw.
19. exp Lung Neoplasms/
20. exp Bronchial Neoplasms/
21. exp Carcinoma, Bronchogenic/ or exp Carcinoma, Small Cell/
22. exp Carcinoma, Non-Small-Cell Lung/
23. or/18-22
24. care.mp.
25. continuity.mp.
26. follow up.mp.
27. shared care.mp.
28. (after care or aftercare).mp.
29. surveillance.mp.
30. survivo$.mp.
31. or/24-30
32. recurrence/
33. neoplasm recurrence, local/
34. recurren$.mp.
35. metastas$.mp.
36. or/32-35
37. 31 or 36
38. primary health care/
39. general practitioner/
40. ((family or general) adj practitioner$).mp.
41. gp.mp.
42. family physician/
43. family physicians.mp.
44. family doctor$.mp.
45. general practice/
46. ((family or general) adj practice$).mp.
47. primary care.mp.
48. primary health care.mp.apn.mp
49. tertiary care.mp.
50. tertiary health care.mp.
51. specialist/
52. medical oncologist$.mp.
53. specialist.mp.
54. radiation oncologist$.mp.
55. oncologist$.mp.
56. radiologist$.mp.
57. surgeon$.mp.
58. nurse$.mp.
59. registered nurse$.mp.
60. nurse/
61. rn.mp.
62. apn.mp.
63. advanced practice nurse.mp.
64. advanced practice registered nurse.mp.
65. nurse practitioner.mp.
66. (community adj care).mp.
67. (hospital adj care).mp.
68. (institution$ adj care).mp.
69. cancer centre.mp.
70. outpatient clinic.mp.
71. outpatient clinic.mp.
72. clinic.mp.
73. or/38-72
74. 17 and 23 and 37 and 73
75. limit 74 to English
76. Animal/
77. Human/
78. 76 not 77
79. 75 not 78
80. limit 79 to yr="2000-2012"

1. exp meta analysis/ or exp "systematic review"/
2. (meta analy$ or metaanaly$).tw.
3. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthesis or quantitative overview).tw.
4. (systematic adj (review$ or overview$)).tw.
5. exp "Review"/ or review.pt.
6. (systematic or selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
7. (study adj selection).ab.
8. 5 and (6 or 7)
9. or/1-4,8
10. (cochrane or embase or psychlit or psyclit or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
11. (reference list$ or bibliograph$ or handsearch$ or relevant journals or manual search$).ab.
12. 9 or 10 or 11
13. (editorial or note or letter erratum or short survey).pt. or abstract report/ or letter/ or case study/
14. 12 not 13
15. (((lung$ or respiratory or bronch$ or pulmonary or pleural or tracheal or pneumo$ or peribronch$ or alveobronch$) adj2 (neoplasm$ or cancer$ or tumor$ or tumour$ or carcinoma$ or adenocarcinoma$ or angiosarcoma$ or chondrosarcoma$ or sarcoma$ or teratoma$ or lymphoma$ or blastoma$ or microcytic$ or carcinogenesis$)).tw.
16. exp lung tumor/
17. exp bronchus tumor/
18. exp lung carcinoma/
19. exp lung non small cell cancer/
20. exp small cell carcinoma/
21. or/15-20
22. care.mp.
23. continuity.mp.
24. (follow-up or follow up).mp.
25. exp follow up/
26. shared care.mp.
27. after care/
28. long term care/
29. (after care or aftercare).mp.
30. surveillance$.mp.
31. survivor$.mp.
32. or/22-31
33. exp recurrent cancer/ or exp recurrent disease/
34. recurrence$.mp.
35. neoplasm recurrence, local/
36. metastas$.mp.
37. or/33-36
38. 32 or 37
39. exp primary health care/
40. general practitioner/
41. ((family or general) adj practitioner$).mp.
42. gp.mp.
43. family physician/
44. family physician$.mp.
45. family doctor$.mp.
46. general practice/
47. ((family or general) adj practice$).mp.
48. primary care.mp.
49. primary health care.mp.
50. tertiary care.mp.
51. tertiary health care.mp.
52. specialist/
53. medical oncologist$.mp.
54. specialist$.mp.
55. radiation oncologist$.mp.
56. oncologist$.mp.
57. radiologist$.mp.
58. surgeon$.mp.
59. nurse$.mp.
60. registered nurse$.mp.
61. nurse/
62. rn.mp.
63. apn.mp.
64. advance$ practice nurse.mp.
65. advance$ practice registered nurse.mp
66. nurse practitioner.mp.
67. (community adj care).mp.
68. (hospital adj care).mp.
69. (institution$ adj care).mp.
70. cancer centre.mp.
71. out-patient clinic.mp.
72. outpatient clinic.mp.
73. clinic.mp.
74. or/39-73
75. 14 and 21 and 38 and 74
76. Limit 75 to English
77. Animal/
78. Human/
79. 77 not 78
80. 76 not 79
81. Limit 80 to yr="2000-2012"

1. (((lung$ or respiratory or bronch$ or pulmonary or pleural or tracheal or pneumo$ or peribronch$ or alveobronch$) adj2 (neoplasm$ or cancer$ or tumor$ or tumour$ or carcinoma$ or adenocarcinoma$ or angiosarcoma$ or chondrosarcoma$ or sarcoma$ or teratoma$ or lymphoma$ or blastoma$ or microcytics$ or carcinogenesis)).tw.
2. exp Lung Neoplasms/
3. exp Bronchial Neoplasms/
4. exp Carcinoma, Bronchogenic/ or exp Carcinoma, Small Cell/
5. exp Carcinoma, Non-Small-Cell Lung/
6. or/1-5
7. care.mp.
8. continuity.mp.
9. follow up.mp.
10. shared care.mp.
11. (after care or aftercare).mp.
12. surveillance.mp.
13. survivor$.mp.
14. Or/7-13
15. recurrence/
16. neoplasm recurrence, local/
17. recurrence.mp.
18. metastas$.mp.
19. or/15-18
20. 14 or 19
21. smoking cessation/
22. smoking cessation.mp.
23. smoking/
24. smoking.mp.
25. smok$ cessation.mp.
26. smok$.mp.
27. smok$ counsel$.mp.
29. (smok$ adj3 (tumour or tumor)).mp.
30. (smok$ adj3 neoplasm$).mp.
31. Smok$-related malignanc$-related.mp
32. Smok$-related tumour$.mp
33. Smok$-related tumour$.mp
34. Smok$-related neoplasm$.mp
35. or/21-34
36. and 20 and 35
37. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt
38. 36 not 37
39. limit 38 to English
40. Animal/
41. Human/
42. 40 not 41
43. 39 not 42
44. limit 43 to yr="2000-2012"

1. (((lung$ or respiratory or bronch$ or pulmonary or pleural or tracheal or pneumo$ or peribronch$ or alveobronch$) adj2 (neoplasm$ or cancer$ or tumor$ or tumour$ or carcinoma$ or adenocarcinoma$ or angiosarcoma$ or chondrosarcoma$ or sarcoma$ or teratoma$ or lymphoma$ or blastoma$ or microcytics$ or carcinogenesis)).tw.
2. exp lung tumor/
3. exp bronchus tumor/
4. exp lung carcinoma/
5. exp lung non small cell cancer/
6. exp small cell carcinoma/
7. or/1-6
8. care.mp.
9. continuity.mp.
10. (follow-up or follow up).mp.
11. exp follow up/
12. shared care.mp.
13. after care/
14. long term care/
15. (after care or aftercare).mp.
16. surveillance$.mp.
17. survivor$.mp.
18. or/8-17
19. exp recurrent cancer/ or exp recurrent disease/
20. recurrence.mp.
21. neoplasm recurrence, local/
22. metastas$.mp.
23. or/19-22
24. 18 or 23
25. Smoking cessation/
26. Smoking cessation.mp
27. Smoking/
28. Smoking.mp
29. Smok$ cessation.mp
30. Smok$.mp
31. Smok$ counsel$.mp
32. (smok$ adj3 malignanc$).mp
33. (smok$ adj3 (tumour or tumor)).mp
34. (smok$ adj3 neoplasm$).mp
35. Smok$-related malignanc$-related.mp
36. Smok$-related tumour$.mp
37. Smok$-related tumour$.mp
38. Smok$-related neoplasm$.mp
39. Or/25-38
40. 7 and 24 and 39
41. (comment or letter or editorial or note or
    erratum or short survey or news or
    newspaper article or patient education
    handout or case report or historical
    article).pt
42. 40 not 41
43. Limit 42 to English
44. Animal/
45. Human/
46. 44 not 45
47. 43 not 46
48. Limit 47 to yr="2000-2012"
## Appendix 3: AMSTAR Quality Assessment of Included Systematic Reviews

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
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<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1. Was an ‘a priori’ design provided?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Q2. Was there duplicate study selection and data extraction?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>CA</td>
<td>Yes</td>
<td>Yes</td>
<td>CA</td>
<td>Yes</td>
<td>CA</td>
<td>CA</td>
</tr>
<tr>
<td>Q3. Was a comprehensive literature search performed?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Q4. Was the status of the publication used as an inclusion criterion?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>CA</td>
<td>Yes</td>
<td>Yes</td>
<td>CA</td>
</tr>
<tr>
<td>Q5. Was a list of studies (included and excluded) provided?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Q6. Were the characteristics of the included studies provided?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Q7. Was the scientific quality of the included studies assessed and documented?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Q8. Was the scientific quality of the included studies used appropriately in formulating conclusions?</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Q9. Were the methods used to combine the findings of studies appropriate?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Q10. Was the likelihood</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Q11. Was the conflict of interest stated?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Abbreviations: CA, can't answer.
Reference numbers are in accordance with numbering from Section 2.
### Appendix 4: Quality Assessment for Included Studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>LC Type and Sample Size</th>
<th>Comparison Type</th>
<th>Group Allocation Method</th>
<th>Intervention</th>
<th>Country</th>
<th>Funding Body</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Randomized Controlled Trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gralla et al, 2009 (22)</td>
<td>Randomized controlled trial</td>
<td>NSCLC, n=43</td>
<td>Between groups and within groups across time</td>
<td>Concealed randomization</td>
<td>QoL</td>
<td>USA</td>
<td>Sponsored by Eli Lilly and Company</td>
</tr>
<tr>
<td>Moore et al, 2002 (26)</td>
<td>Randomized controlled trial</td>
<td>SCLC and NSCLC, n=203</td>
<td>Between groups and within groups across time</td>
<td>Concealed randomization</td>
<td>Nurse-led follow-up</td>
<td>UK</td>
<td>Funded by NHS Research and Development National Cancer Programme</td>
</tr>
<tr>
<td>Werner-Wasik et al, 2011 (32)</td>
<td>Randomized controlled trial</td>
<td>NSCLC, n=528</td>
<td>Between group and within groups across time</td>
<td>Concealed randomization</td>
<td>Late lung toxicity</td>
<td>USA</td>
<td>Supported by Medimmune Inc. and research grants from unspecified source</td>
</tr>
<tr>
<td><strong>Non-Randomized Comparative Prospective Cohort Studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Balduyck et al, 2011 (16)</td>
<td>Controlled before-and-after study</td>
<td>NSCLC, n=70</td>
<td>Between groups and within groups across time</td>
<td>Allocated based on smoking status</td>
<td>QoL</td>
<td>Belgium</td>
<td>Funding not specified</td>
</tr>
<tr>
<td>Chen et al, 2012 (17)</td>
<td>Controlled before-and-after study</td>
<td>SCLC, n=223</td>
<td>Between groups and within groups across time</td>
<td>Allocated based on smoking status</td>
<td>QoL</td>
<td>USA</td>
<td>Funded by grant from US National Institutes of Health and Mayo Clinic Foundation Funds</td>
</tr>
<tr>
<td>Garces et al, 2004 (20)</td>
<td>Controlled before-and-after study</td>
<td>SCLC and NSCLC, n=1028</td>
<td>Between groups and within groups across time</td>
<td>Allocated based on smoking status</td>
<td>QoL</td>
<td>USA</td>
<td>Funding not specified</td>
</tr>
<tr>
<td>Gooneratne et al, 2007 (21)</td>
<td>Case-control study</td>
<td>SCLC and NSCLC, n=154</td>
<td>Between survivors and control population</td>
<td>Allocation by disease</td>
<td>Sleep patterns</td>
<td>USA</td>
<td>Funded by grants from the National Institute of Health and the Veterans Affairs Competitive Pilot Project Fund</td>
</tr>
<tr>
<td>Ilonen et al, 2010 (24)</td>
<td>Controlled before-and-after study</td>
<td>NSCLC, n=53</td>
<td>Between groups and within groups across time</td>
<td>Allocation by treatment differences</td>
<td>QoL</td>
<td>Finland</td>
<td>Funded by grant from the special governmental subsidy for health sciences research</td>
</tr>
</tbody>
</table>
### Study Design

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>LC Type and Sample Size</th>
<th>Comparison Type</th>
<th>Group Allocation Method</th>
<th>Intervention</th>
<th>Country</th>
<th>Funding Body</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhou et al, 2006 (34)</td>
<td>Controlled before-and after study</td>
<td>NSCLC, n=543</td>
<td>Between groups and within groups across time</td>
<td>Allocation based on smoking status</td>
<td>Smoking status and survival</td>
<td>USA</td>
<td>Funded by grants from National Institutes of Health, Flight Attendants Medical Research Institute, American Institute for Cancer Research and Doris Duke Charitable Foundation</td>
</tr>
<tr>
<td>Cheville et al, 2011 (18)</td>
<td>Before-and-after comparison</td>
<td>SCLC and NSCLC, n=2405</td>
<td>Within group across time</td>
<td>NA</td>
<td>Symptom burden</td>
<td>USA</td>
<td>Funded by grant from the National Cancer Institute of the National Institutes of Health</td>
</tr>
<tr>
<td>Moller and Sartipy, 2012 (26)</td>
<td>Before-and-after comparison</td>
<td>SCLC and NSCLC, n=249</td>
<td>Within group across time</td>
<td>NA</td>
<td>QoL</td>
<td>Sweden</td>
<td>Funded by grants from Karolinska Institutet and Signe and Olof Wallenius Foundation</td>
</tr>
<tr>
<td>Solberg et al, 2012 (28)</td>
<td>Before-and-after comparison</td>
<td>SCLC and NSCLC, n=1937</td>
<td>Within group across time</td>
<td>NA</td>
<td>Physical activity and QoL</td>
<td>USA</td>
<td>Funded by grants from the National Cancer Institute</td>
</tr>
<tr>
<td>Subotic et al, 2009 (29)</td>
<td>Before-and-after comparison</td>
<td>NSCLC, n=88</td>
<td>Within group across time</td>
<td>NA</td>
<td>Intensive follow-up schedule</td>
<td>Serbia</td>
<td>Funding not specified</td>
</tr>
<tr>
<td>Tishelman et al, 2005 (30)</td>
<td>Before-and-after comparison</td>
<td>SCLC and NSCLC, n=400</td>
<td>Within group across time</td>
<td>NA</td>
<td>Symptom burden</td>
<td>Sweden</td>
<td>Funded by grants from The Swedish Cancer Society, The Swedish Heart-Lung Foundation and the Swedish Foundation for the Health Care Sciences and Allergy Research</td>
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<tr>
<td>Yang et al, 2002 (33)</td>
<td>Before-and-after comparison</td>
<td>SCLC and NSCLC, n=447</td>
<td>Within group across time</td>
<td>NA</td>
<td>QoL and symptom burden</td>
<td>USA</td>
<td>Funded by grants from the US National Institute of Health</td>
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</tbody>
</table>

### Diagnostic Cohort Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>LC Type and Sample Size</th>
<th>Comparison Type</th>
<th>Intervention</th>
<th>Country</th>
<th>Funding Body</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cho and Lee, 2010 (19)</td>
<td>Fully paired diagnostic cohort study</td>
<td>NSCLC, n=86</td>
<td>Patients received all interventions</td>
<td>NA</td>
<td>PET/CT detected recurrence confirmed by</td>
<td>Korea</td>
</tr>
<tr>
<td>Study</td>
<td>Study Design</td>
<td>LC Type and Sample Size</td>
<td>Comparison Type</td>
<td>Group Allocation Method</td>
<td>Intervention</td>
<td>Country</td>
</tr>
<tr>
<td>----------------------</td>
<td>-----------------------</td>
<td>-------------------------</td>
<td>------------------------------------------------</td>
<td>-------------------------</td>
<td>--------------------------------------------------</td>
<td>--------------------------</td>
</tr>
<tr>
<td>Dane et al, 2013 (35)</td>
<td>Fully paired diagnostic cohort study</td>
<td>NSCLC, n=100</td>
<td>Patients received all interventions</td>
<td>NA</td>
<td>FDG PET/CT compared with non-contrast CT</td>
<td>USA</td>
</tr>
<tr>
<td>Hanna et al, 2014 (36)</td>
<td>Fully paired diagnostic cohort study</td>
<td>NSCLC, n=271</td>
<td>Patients received all interventions</td>
<td>NA</td>
<td>Minimal-dose CT compared with chest x-ray</td>
<td>Canada</td>
</tr>
<tr>
<td>Hellwig et al, 2006 (23)</td>
<td>Fully paired diagnostic cohort study</td>
<td>NSCLC, n=62</td>
<td>Patients received all interventions</td>
<td>NA</td>
<td>FDG-PET detected recurrence confirmed by conventional staging</td>
<td>Germany</td>
</tr>
<tr>
<td>Keidar et al, 2004 (25)</td>
<td>Fully paired diagnostic cohort study</td>
<td>NSCLC, n=42</td>
<td>Patients received all interventions</td>
<td>NA</td>
<td>FDG-PET/CT detected recurrence compared with PET with side-by-side CT</td>
<td>Israel</td>
</tr>
<tr>
<td>Van Loon et al, 2009 (31)</td>
<td>Fully paired diagnostic cohort study</td>
<td>NSCLC, n=100</td>
<td>Patients received all interventions</td>
<td>NA</td>
<td>FDG-PET-CT compared with CT</td>
<td>Netherlands</td>
</tr>
</tbody>
</table>

Note: Studies are grouped by study design in descending order according to the study quality as a consequence of the design. Non-randomized studies were further defined using the Cochrane Collaboration schema (Handbook Table 13.2a) as controlled before-and-after studies (provided comparisons between groups), case-control studies (comparison between case and controls) and before-and-after comparison (used longitudinal data collection with the group). All included non-randomized studies used prospective data collection and a form of comparison; however, since the comparison is within the group for before-and-after comparisons, this study designs carries the highest risk of bias. All RCT and non-randomized studies with QoL as an outcome relied on the use of QoL tools that survivors filled out at home, resulting in potential recall bias. The WG does recognize however that for QoL studies, this is the best available evidence. Although not of a lower quality than the non-randomized studies, diagnostic cohort studies are included at the end of the table. All diagnostic cohort studies used a fully paired model so that all patients received all interventions, thus reducing selection bias. Reference numbers are in accordance with numbering from Section 2.

Abbreviations: CT, computed tomography; FDG, fluorodeoxyglucose; LC, lung cancer; NA, not applicable; NSCLC, non-small cell lung cancer; PET, positron emission tomography; QoL, quality of life; SCLC, small cell lung cancer.
### Appendix 5: Clinical Practice Guideline Recommendations.

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Frequency of follow-up</strong></td>
<td>Every 6 months for 3 years, then annually</td>
<td>Every 6 months for 2 years, then annually</td>
<td>Every 3-6 months for 2 years with lengthening interval thereafter. Annually by year 5</td>
<td>Every 3-6 month for 2-3 years, then annually</td>
<td>Every 3-4 months during first 1-2 years, every 6 months years 3-5, then annually</td>
<td>Every 6-12 months for 2 years, then annually</td>
</tr>
<tr>
<td><strong>Evaluations at follow-up appointment</strong></td>
<td>CT scan</td>
<td>Chest CT scan</td>
<td>Chest CT scan</td>
<td>History, physical examination and imaging</td>
<td>History, physical examination, chest imaging and blood work as clinically indicated</td>
<td>History, physical examination and chest imaging</td>
</tr>
<tr>
<td><strong>Imaging test</strong></td>
<td>High-resolution CT annually for 4 years, then low dose CT</td>
<td>Chest CT</td>
<td>Chest CT for first 4 years, then low-dose CT starting in year 5</td>
<td>Chest CT scan preferable but chest X-Ray also appropriate</td>
<td>Not specified</td>
<td>Chest CT with or without contrast first 2 years, then non-contrast-enhanced chest CT annually</td>
</tr>
<tr>
<td><strong>Testing NOT recommended</strong></td>
<td>NS</td>
<td>Routine PET surveillance, somatostatin receptor scintigraphy, ultrasoundography and biomarker testing</td>
<td>NS</td>
<td>NS</td>
<td>PET/CT</td>
<td>PET or brain MRI</td>
</tr>
<tr>
<td><strong>Smoking cessation</strong></td>
<td>N/A</td>
<td>NS</td>
<td>Smoking cessation is recommended</td>
<td>NSCLC patients should be offered smoking cessation counselling, with a combination of behaviour technique and pharmacotherapy being the preferred approach</td>
<td>Smoking cessation recommended</td>
<td>Smoking cessation advice, counselling and pharmacotherapy should be offered as needed</td>
</tr>
</tbody>
</table>

**Abbreviations:** AATS, American Association for Thoracic Surgery; ACCP, American College of Chest Physicians; CT, computed tomography; ESMO, European Society of Clinical Oncology; MRI, magnetic resonance imaging; N/A, not applicable question for the guideline; NCCN, National Comprehensive Cancer Network; NS, outcome not specified by guideline; NSCLC, non-small cell lung cancer; PET, positron emission tomography; SCLC, small cell lung cancer.
### Appendix 6: List of Abbreviations.

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AATS</td>
<td>American Association for Thoracic Surgery</td>
</tr>
<tr>
<td>AGREE II</td>
<td>Appraisal of Guideline for Research and Evaluation version 2</td>
</tr>
<tr>
<td>AMSTAR</td>
<td>A Measurement Tool to Assess Systematic Reviews</td>
</tr>
<tr>
<td>ASBI</td>
<td>Average symptom-burden index</td>
</tr>
<tr>
<td>BAC</td>
<td>Before-and-after comparison study</td>
</tr>
<tr>
<td>CBA</td>
<td>Controlled before-and-after study</td>
</tr>
<tr>
<td>CCS</td>
<td>Case-control study</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>CXR</td>
<td>Chest x-ray</td>
</tr>
<tr>
<td>ECOG</td>
<td>Eastern Cooperation Oncology Group</td>
</tr>
<tr>
<td>EORTC</td>
<td>European Organization for the Research and Treatment of Cancer</td>
</tr>
<tr>
<td>EP</td>
<td>Expert Panel</td>
</tr>
<tr>
<td>FEV1</td>
<td>Forced expiration volume in 1s</td>
</tr>
<tr>
<td>FDG</td>
<td>Fluorodeoxyglucose</td>
</tr>
<tr>
<td>FPDPC</td>
<td>Fully-paired diagnostic cohort study</td>
</tr>
<tr>
<td>FVC</td>
<td>Forced vital capacity</td>
</tr>
<tr>
<td>GDG</td>
<td>Guideline Development Group</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard ratio</td>
</tr>
<tr>
<td>LASA</td>
<td>Linear Analog Self-Assessment</td>
</tr>
<tr>
<td>LCSS</td>
<td>Lung Cancer Symptom Scale</td>
</tr>
<tr>
<td>LRM</td>
<td>Last recorded measurement</td>
</tr>
<tr>
<td>MCS</td>
<td>Mental component scale</td>
</tr>
<tr>
<td>MnDCT</td>
<td>Minimal-dose CT</td>
</tr>
<tr>
<td>MPO</td>
<td>Months post operation</td>
</tr>
<tr>
<td>NCC</td>
<td>Non-cancer control</td>
</tr>
<tr>
<td>NSCLC</td>
<td>Non-small-cell lung cancer</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>PCS</td>
<td>Physical component scale</td>
</tr>
<tr>
<td>PD</td>
<td>Progressive disease</td>
</tr>
<tr>
<td>PET</td>
<td>Positron emission tomography</td>
</tr>
<tr>
<td>PFT</td>
<td>Pulmonary function test</td>
</tr>
<tr>
<td>PN</td>
<td>Pneumonitis</td>
</tr>
<tr>
<td>PPC</td>
<td>Post-operative pulmonary complications</td>
</tr>
<tr>
<td>PSQI</td>
<td>Pittsburgh Sleep Quality Index</td>
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<tr>
<td>QLI</td>
<td>Quality of Life Index</td>
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<tr>
<td>QLQ-C30</td>
<td>Quality of Life Questionnaire - Cancer Patients (30 questions)</td>
</tr>
<tr>
<td>QLQ-LC13</td>
<td>Quality of Life Questionnaire - Lung Cancer Module (13 question)</td>
</tr>
<tr>
<td>QoL</td>
<td>Quality of life</td>
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<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
</tr>
<tr>
<td>RR</td>
<td>Relative risk</td>
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<tr>
<td>RT</td>
<td>Radiation therapy</td>
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<tr>
<td>SCLC</td>
<td>Small-cell lung cancer</td>
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<tr>
<td>SDS</td>
<td>McCorkle and Young Symptom Distress Scale</td>
</tr>
<tr>
<td>SF-36</td>
<td>Short form 36</td>
</tr>
<tr>
<td>SR</td>
<td>Systematic review</td>
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<tr>
<td>TSSD-LC</td>
<td>Thurstone Scale of Symptom Distress - Lung Cancer</td>
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</tbody>
</table>