CHEST Supplement

DIAGNOSIS AND MANAGEMENT OF LUNG CANCER, 3RD ED: ACCP GUIDELINES

Follow-up and Surveillance of the Patient With Lung Cancer After Curative-Intent Therapy

Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

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Background: **These guidelines are an update of the evidence-based recommendations for follow-up and surveillance of patients after curative-intent therapy for lung cancer. Particular updates pertain to whether imaging studies, health-related quality-of-life (HRQOL) measures, tumor markers, and bronchoscopy improve outcomes after curative-intent therapy.**

Methods: **Meta-analysis of Observational Studies in Epidemiology guidelines were followed for this systematic review, including published studies on posttreatment outcomes in patients who received curative-intent therapy since the previous American College of Chest Physicians subject review. Four population, intervention, comparison, and outcome questions were formulated to guide the review. The MEDLINE and CINAHL databases were searched from June 1, 2005, to July 8, 2011, to ensure overlap with the search strategies used previously.**

Results: **A total of 3,412 citations from MEDLINE and 431 from CINAHL were identified. Only 303 were relevant. Seventy-six of the 303 articles were deemed eligible on the basis of predefined inclusion criteria after full-text review, but only 34 provided data pertaining directly to the subject of the questions formulated to guide this review. In patients undergoing curative-intent surgical resection of non-small cell lung cancer, chest CT imaging performed at designated time intervals after resection is suggested for detecting recurrence. It is recommended that treating physicians who are able to incorporate the patient's clinical findings into decision-making processes be included in follow-up and surveillance strategies. The use of validated HRQOL instruments at baseline and during follow-up is recommended. Biomarker testing during surveillance outside clinical trials is not suggested. Surveillance bronchoscopy is suggested for patients with early central airway squamous cell carcinoma treated by curative-intent photodynamic therapy and for patients with intraluminal bronchial carcinoid tumor who have undergone curative-intent bronchoscopic treatment with Nd:YAG laser or electrocautery.**

Conclusions: **There is a paucity of well-designed prospective studies specifically targeting follow-up and surveillance modalities aimed at improving survival or QOL after curative-intent therapy. Additional research is warranted to clarify which curative-intent treatment modalities affect HRQOL the most and to identify patients who are at the most risk for recurrence or impaired QOL after treatment. Further evidence is needed to determine how the frequency and duration of surveillance programs that include imaging studies, QOL measurements, tumor markers, or bronchoscopy affect patient morbidity, survival, HRQOL, and health-care costs.**

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Abbreviations: ACCP = American College of Chest Physicians; AFB = autofluorescence bronchoscopy; CDET = coincidence detection emission tomography; CEA = carcinoembryonic antigen; CIS = carcinoma in situ; CXR = chest radiograph; EORTC QLQ = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; HRCT = high-resolution CT; HRQOL = health-related quality of life; NSCLC = non-small cell lung cancer; OPN = osteopontin; PDT = photodynamic therapy; RCT = randomized controlled trial; SBRT = stereotactic body radiation therapy; SqCC = squamous cell carcinoma; SRS = somatostatin receptor scintigraphy; SUVmax = maximum standardized uptake value; WLB = white light bronchoscopy

Summary of Recommendations

3.5.1. In patients who have undergone curative-intent surgical resection of non-small cell lung cancer (NSCLC), it is suggested that chest CT be performed every 6 months for the first 2 years after resection and every year thereafter (Grade 2C).

3.5.2. For patients with NSCLC or carcinoid tumor who have undergone curative-intent therapy, it is recommended that the original treating physicians participate in the decision-making process during the follow-up and surveillance (Grade 1C).

3.5.3. After curative-intent therapy in patients with NSCLC or carcinoid tumors, routine surveillance with PET imaging, somatostatin receptor scintigraphy, or abdominal ultrasonography is not recommended (Grade 1C).

4.1.1. In NSCLC patients who have undergone curative-intent therapy, it is suggested that a validated health-related quality-of-life (QOL) instrument be used at baseline clinic visits and during follow-up (Grade 2C).

5.1.1. For lung cancer patients treated with curative intent, it is suggested that surveillance biomarker testing not be done (outside of clinical trials) (Grade 2C).

6.4.1. For patients with early central airway squamous cell carcinoma treated by curative-intent photodynamic therapy, it is recommended that surveillance bronchoscopy be done at 1, 2, and 3 months and thereafter at 3-month intervals during the first year, then every 6 months until 5 years (Grade 1C).

Remark: Autofluorescence bronchoscopy may be used if available (Grade 2C).

6.4.2. For patients with intraluminal bronchial carcinoid tumor who have undergone curative-intent bronchoscopic treatment using Nd:YAG or electrocautery, it is suggested that surveillance bronchoscopy be done within 6 weeks after endobronchial resection, every 6 months for 2 years, and annually thereafter (Grade 2C).

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Patients with lung cancer are burdened with symptoms of recurrence as well as with the threat of asymptomatic recurrence. The issues of whether surveillance is of benefit after patients have undergone curative-intent therapy, whether it should be done, and how to do it, therefore, are of the utmost importance. Indeed, despite improved survival in the first year after curative-intent therapy for lung cancer, 5-year survival remains poor, and lung cancer is now responsible for 23% of total cancer deaths in men and 11% in women globally.[2] In the United States, it is the most frequent cause of cancer-related death in both men and women (29% and 26%, respectively).[3] Less than 20% of patients receiving a new diagnosis of lung cancer will have localized disease amenable to potentially curative treatment.[4] Depending on the final pathologic stage, reported recurrence rates after complete surgical resection with curative intent range from 30% to 75%.[5] In recent years, therefore, a number of published guidelines have addressed follow-up and surveillance after treatment with curative intent.

Most guidelines suggest that follow-up should be done to manage complications related to the curative-intent therapy itself. This might be a specialist-directed process. For example, a thoracic surgeon might be responsible for managing complications related to any surgical procedures performed, whereas radiation and medical oncologists might be responsible for managing complications related to radiation therapy and chemotherapy, respectively. Guidelines also recommend surveillance to detect symptomatic or asymptomatic recurrence of the primary lung cancer and

to detect a new primary lung cancer early enough to allow potentially curative retreatment. Various surveillance strategies have been proposed,[6-8] including the use of drop-in clinics, follow-up by primary-care physicians in ambulatory care practice, specialist-led follow-up within an office-based or in-hospital setting, and a variety of imaging protocols (from chest radiograph [CXR] to whole-body, integrated PET/CT scan). The effectiveness of these strategies with regard to prolonging survival, detecting early recurrence or new primary tumors amenable to curative therapy, and alleviating emotional and psychologic distress related to the diagnosis and threat of recurrence itself continue to be debated.[9,10]

In this review, we summarize the recommendations made in the 2007 American College of Chest Physicians (ACCP) guidelines pertaining to lung cancer follow-up and surveillance after curative-intent therapy, provide a brief comparative summary of guidelines on the same subject from other professional medical associations published since 2010, and offer updated recommendations based on a systematic review of the literature published since June 1, 2005. Our purpose was to specifically address recent evidence, or the lack thereof, pertaining to whether specific surveillance modalities (defined as imaging studies, bronchoscopy, health-related quality-of-life [HRQOL] instruments, or biomarkers) improve or adversely affect outcomes in terms of survival; morbidity; and overall physical, mental, or emotional health during and after the first 2 years following curative-intent therapy. The recommendations resulting from this review are meant to supplement those proposed in the previously published 2007 ACCP guidelines.[11]

1.0 Methods

1.1 Study Identification

This study was undertaken to update the previous ACCP recommendations[11] regarding follow-up and surveillance of patients with lung cancer following curative-intent therapy. Meta-analysis of Observational Studies in Epidemiology guidelines were followed in the development of this systematic review.[12] Systematic methods were used to identify relevant studies, assess study eligibility for inclusion, and evaluate study quality.[13,14] We attempted to retrieve all published studies that reported on posttreatment outcomes for patients who had received curative-intent therapy since the previous ACCP review of this subject. We also sought to identify studies specifically focused on the benefits and potential adverse effects of specific surveillance strategies to detect recurrence. Thus, the following four population, intervention, comparison, and outcome (PICO) questions were developed to guide the review (Table S1):

1. Among patients with lung cancer after curative-intent therapy, do specific follow-up and surveillance interventions, such as imaging studies, HRQOL measures, tumor markers, and bronchoscopy, improve health outcomes (mortality and morbidity) over the short term (first 2 years after curative therapy)?
2. Among patients with lung cancer after curative-intent therapy, do specific follow-up and surveillance interventions, such as imaging studies, HRQOL measures, tumor markers, and bronchoscopy, improve health outcomes (mortality and morbidity) over the long term (beyond the first 2 years after curative therapy)?
3. Among patients with lung cancer after curative-intent therapy, do specific surveillance interventions and intervals worsen long-term health outcomes (anxiety, worry, etc)?
4. Among patients with lung cancer after curative-intent therapy and who have detected local recurrence, do specific interventions improve outcomes (mortality and morbidity)?

One investigator, with the help of a professional medical librarian and an ACCP staff methodologist, searched the MEDLINE and CINAHL databases for articles published between June 1, 2005, and July 8, 2011. The start date was selected to ensure overlap with the search strategy from the previously published ACCP guidelines (second edition). General search terms were used in order to be all inclusive. The specific terms entered for the searches are available on request. Articles that were repeated in different database searches were not tallied separately. Additional articles were captured by reviewing reference lists from identified studies and pertinent review articles.

1.2 Study Eligibility

Articles deemed potentially eligible were divided and reviewed by teams who independently assessed original research studies for eligibility according to predefined criteria. Thus, each potentially eligible manuscript was independently reviewed by two investigators, and disagreements were resolved after discussion among panelists, methodologists, and the topic editor.

1.3 Data Abstraction

Data were abstracted depending on the type of study; patient demographic characteristics; morphology and stage of lung cancer; surveillance strategies; length of follow-up; and reported outcomes, including benefits and harms. Data were abstracted into the evidence table template for intervention studies developed by ACCP for the Lung Cancer Guidelines according to type of follow-up method after curative-intent therapy, as follows: imaging, bronchoscopy, biomarkers, and HRQOL instruments. Specific outcomes were detection of recurrence, overall survival, complications, and change in QOL after curative-intent therapy. The population of interest for this review was adult patients who had been treated for primary lung carcinoma and were in follow-up. All patients with lung cancer who underwent curative-intent therapy for various stages and histologic types were included in the review. Curative-intent treatment options included surgery, conventional radiotherapy, stereotactic body radiation therapy (SBRT), radiofrequency ablation, chemotherapy, or any combination of these.

1.4 Study Quality

The ACCP quality assessment tool developed for randomized controlled trials (RCTs) was used to assess the quality of RCTs. The items included the appropriate design and implementation of the trial; appropriate randomization; explicit descriptions of inclusion and exclusion criteria; the intervention, outcomes, and statistical analyses; and potential biases and conflicts of interest. To measure the quality of observational studies, another inventory developed by the ACCP was used. The items included the study design, whether the setting and time frame were similar for the

comparator measure, whether the analysis was adjusted for potential confounders, whether the outcome was blinded to the assessors, and whether the number of patients lost to follow-up differed by the comparator measure. The Quality Assessment of Cohort Studies form was used when appropriate.[15] The assessment addressed the following items: subject selection, measurement of exposure, measurement of outcome, follow-up, adjustment for potential confounders, statistical analysis, funding, and conflict of interest. Quality of the study was based on the number of questions that could be answered affirmatively on a scale from 1 to 10 (good, 8-10; fair, 5-7; poor, <5).

1.5 Statistical Analysis

Information provided by each of the primary study authors was used to report hazard ratios, CIs, median values, and ranges for summary statistics. No attempt was made to pool data across studies because there was substantial heterogeneity in comparator and outcome measures, and few studies provided the raw data necessary for quantitative synthesis.

2.0 Summary of Other Published Guidelines

A patient-centered approach to cancer care mandates that health-care providers consider patient preferences in the decision-making process. Patients view follow-up favorably and prefer to be seen by medical staff in a clinic, with nurse-led care as an acceptable option. Follow-up by primary-care physicians or telephone calls are viewed less favorably.[16] The 2007 ACCP guidelines pertaining to follow-up and surveillance after curative-intent therapy summarized results from the guidelines of other organizations, most of which were developed by expert panel consensus. These guidelines emphasized symptoms as an indication for recurrence and uniformly recommended frequent follow-up visits during the first 2 years after curative-intent therapy, but they presented a wide divergence of views with regard to the use of chest imaging during this period of surveillance and beyond.[11,17]

During 2010 to 2011, four additional guidelines addressing surveillance and follow-up in patients with non-small cell lung cancer (NSCLC) after curative-intent therapy were published. These guidelines illustrate the continued emphasis on early surveillance within 6 weeks after completion of therapy and subsequent routinely scheduled follow-up focusing on eliciting clinical signs and symptoms of disease and initiating smoking cessation interventions. Recommendations from the 2007 ACCP guidelines in addition to those from these four guidelines are summarized in Fig 1.

3.0 The Role of Imaging Studies

Since the publication of the 2007 ACCP guidelines, several new studies were published that address the performance of imaging following curative-intent therapy (Table S2).

3.1 CT Imaging

No RCTs that evaluated the role of surveillance CT imaging for the follow-up of patients with lung cancer have been published since 2007. In a retrospective cohort study, however, Nakamura and colleagues[18] indirectly examined the effect of surveillance CT scan of the chest on survival in 1,398 patients who underwent resection of stage I to IIIB NSCLC. Of this large group of patients, 846 were followed by thoracic surgeons who performed periodic postoperative physical examination and CXR, and 552 were followed by pulmonologists who added chest CT imaging to this regimen. After a median follow-up period of 79 months, patients followed with chest CT scan had a significantly longer overall median and 5-year survival ($P = .0009$) than those followed by physical examination and CXR (hazard ratio,1.279; 95% CI, 1.086-1.507). This difference seemed to be attributable to patients with stage II and III disease and not to those with stage I disease. Multivariable analysis showed that age, sex, stage, Charlson comorbidity index score, adjuvant therapy, and type of physician follow-up (pulmonologist vs thoracic surgeon) independently influenced prognosis. Although this was a large study, it is limited by selection bias because both groups were not evenly matched with respect to many variables (eg, histology, sex).[18]

A role for surveillance chest CT imaging has also been studied after potentially curative chemoradiotherapy for locally advanced, unresectable NSCLC. Takigawa and colleagues[19] evaluated 92 patients from two phase 2 clinical trials of chemoradiotherapy for stage IIIA and IIIB unresectable NSCLC. Semiannual chest CT scan and annual brain MRI were performed. Median follow-up was 8.9 years. All but two patients completed curative-intent therapy. The most common site of recurrence was local (n = 28), and 28 patients survived >5 years. Of these 28 long-term survivors, second primary lung cancer developed in three, all of whom subsequently underwent curative-intent therapy. In another study of locally advanced NSCLC, 40 patients with stage III NSCLC from a single institution enrolled in two intergroup trials (INT 0160 and INT 0139) were compared with 35 similarly matched nontrial patients.[20] Trial patients were followed after therapy with a rigorous protocol that included multiple CT scans of the chest, whereas nontrial patients were followed with CXR. Trial patients were more likely to have asymptomatic, localized relapses detected and treated with curative intent, but overall survival between the two groups was not significantly different ($P = .67$).

FIGURE 1. [Section 2.0] Summary of recommendations for surveillance after curative-intent therapy of NSCLC (ACCP 2007 guidelines and other society guidelines published since 2010).

Organization	Summary of Recommendations
ACCP	• Follow-up for therapy-related complications should be managed by an appropriate specialist during the first 3-6 mo after therapy, then depends on results from multidisciplinary tumor board recommendations (Grade 2C). • Surveillance by clinical examination and choice of chest radiograph or CT scan should be arranged every 6 mo for 2 y then yearly for patients with good performance status and pulmonary function (Grade 1C). • Surveillance for recurrence or metachronous tumor should be arranged by a multidisciplinary team approach, with the health-care team that initiated lung cancer treatment overseeing the surveillance process (Grade 2C). • Blood tests, PET scans, sputum cytology, tumor markers, and fluorescence bronchoscopy were not recommended for surveillance (Grade 2C). • Patients with lung cancer who smoke should be encouraged to quit smoking and be offered pharmacotherapeutic and behavior therapy to assist with smoking cessation (Grade 1A).
ESMO	• Follow-up for treatment-related complications at 3 and 6 mo (2C). • History and physical examination and CT scan every 6 mo for 2 y, then annually (1C). • No PET/CT scan recommended because no correlation found between early detection of recurrence and survival benefit (2C). • Smoking cessation interventions recommended (1A).
GCS	• Multidisciplinary team follow-up with focus on symptoms. Psychosocial and social counseling should be integrated (expert opinion, Grade D). • Diffusion capacity and pulmonary function tests 4-6 wk after completion of therapy (weak recommendation, Grade C) • Surveillance by history and physical examination and appropriate imaging studies every 3 mo for 2 y, every 6 mo for years 3-5, and yearly thereafter for 5 y (weak recommendation). No general screening for brain metastases recommended (expert opinion). • Smoking cessation interventions recommended (Grade B).
NICE	• Scheduled follow-up with specialist within 6 wk after completion of therapy. Regular appointments should be offered thereafter rather than relying on patient recognition of symptoms. • Protocol-driven follow-up with a lung cancer clinical nurse specialist should be offered for patients with a life expectancy > 3 mo. • Patients should know how to contact surveillance program specialists between scheduled visits.
NCCN	• History & physical examination with contrast-enhanced CT scan every 4-6 mo for 2 y (2B), then history and physical examination and noncontrast-enhanced CT scan annually (2B). • PET scan or brain MRI not indicated during routine follow-up. • Smoking cessation interventions recommended. Annual influenza and pneumococcal vaccination with revaccination as appropriate.

ACCP = American College of Chest Physicians; ESMO = European Society of Medical Oncology; NCCN = National Comprehensive Cancer Network; NICE = National Institute for Health and Clinical Excellence; NSCLC = non-small cell lung cancer.

Korst and colleagues[7] identified all patients in their practice who underwent surveillance chest CT scan following curative resection of NSCLC (all stages) during a single calendar year. Patients were then followed for 3 additional years to determine the outcome of all abnormalities found on the scans. Of 168 scans performed in 140 patients, 105 in 92 patients were read as abnormal by the chest radiologist with respect to pulmonary nodules, pleural fluid, and lymphadenopathy. Only 30 of the 105 scans were considered potentially suspicious for lung cancer by the treating physician, with 14 of these actually representing recurrent disease. Of note, lung cancer did not develop in the area deemed abnormal by the radiologist during 3 years of further follow-up in any of the remaining patients with abnormal scans. The authors concluded that the performance of surveillance CT imaging produces a large number of abnormal scans (nearly two-thirds) and that the treating clinician's input helps to identify the minority of those signaling recurrent cancer. Results suggest that (1) potential harm can come to patients followed in this fashion if radiology reports are used solely to identify potential recurrence after resection of NSCLC and (2) the treating physician is a vital member of the surveillance team.

In summary, a large, retrospective, uncontrolled comparison study suggested that there may be a survival benefit to follow-up with periodic CT scans vs CXR for patients with resected stage I to IIIB lung cancer; however, there are many other possible explanations for this difference.[17] A smaller uncontrolled comparison of patients with stage III disease suggested

an increased rate of detection of asymptomatic local recurrences with frequent CT scans[19] but no difference in survival. One small noncomparative study[18] found a surprisingly high rate of local recurrence (30%) but little suggestion that this resulted in a survival benefit. Other studies found that only about 30% of local recurrences after resection are amenable to curative-intent treatment.[21,22] Therefore, data showing a benefit to follow-up with imaging for recurrence are only very weakly suggestive, and the quality of the data is poor. Involvement of the treating physician or at least a lung cancer expert seems to be of benefit in avoiding the relatively frequent misinterpretation of postoperative CT findings as recurrence.

Another potential benefit of surveillance is the early detection of new primary lung cancer. The incidence of a new primary lung cancer is fairly consistently about 2% per patient per year.[23] No studies have addressed the value of surveillance to detect such additional cancers, but given data that CT screening reduces lung cancer deaths in lower-risk populations (see Detterbeck et al,[24] "Screening for Lung Cancer," in the ACCP Lung Cancer Guidelines), there is reason to speculate that this may be of benefit. The question regarding overall duration (time limited or indefinite) of surveillance using CT imaging remains unanswered.

3.2 Functional Imaging Following Resection

Since publication of the 2007 ACCP guidelines, data regarding the use of functional imaging for following patients with lung cancer after curative-intent therapy have become available. An RCT by Monteil and colleagues[6] compared the use of coincidence detection emission tomography (CDET) (18-fludeoxyglucose functional scan using a γ camera) with conventional imaging (chest CT scan, abdominal ultrasound, radionuclide bone scan) at 6-month intervals following complete resection of stage I to IIIA NSCLC. A total of 69 patients were randomized, but no statistical power calculations were provided. Median follow-up was just >2 years. A significantly greater proportion of asymptomatic recurrences were detected in the CDET group compared with the conventional group. Recurrences were also detected earlier in the CDET group. Despite these findings, no significant difference in overall survival was found (CDET group, 26.5 ± 19.6 months; conventional group, 29 ± 17.1 months).

Functional imaging may be useful to detect asymptomatic recurrence following resection of NSCLC. In a retrospective case series from Korea, Cho and Lee[25] performed integrated PET/CT scanning in 86 asymptomatic patients for a median of 13 months after complete resection of stage I to IIIA NSCLC. Twenty-seven (31%) recurrences were found, with four patients undergoing potentially curative resection of their recurrence. Of note, 18 patients (21%) had either a false-positive or equivocal PET/CT scan, once again raising the issue of the specificity of post-treatment imaging.

Takenaka et al[26] compared standard imaging with whole-body CT scan, bone scintigraphy, and brain MRI with integrated PET/CT imaging at 6-month intervals in 92 patients with completely resected NSCLC. No significant differences in sensitivity (0.73 vs 0.82), specificity (0.91 vs 0.89), or accuracy (0.89 vs 0.88) were noted between standard and PET/CT imaging, respectively, for detecting recurrence, prompting the authors to conclude that integrated PET/CT imaging is a reasonable substitute for standard imaging.

Finally, Gorenberg and colleagues[27] investigated a possible role for detecting scar recurrence using integrated PET/CT imaging in 61 patients after resection of NSCLC. Imaging was performed at various time points. Only three patients developed scar recurrence, and many false-positive findings were noted.

In summary, studies using PET imaging after resection suggested little difference compared with more-traditional imaging, and many false-positive and equivocal findings were encountered. Given the expense of PET imaging (not to mention follow-up of findings), it seems better to reserve PET imaging for investigation of symptoms or specific areas of concern instead of as a routine surveillance tool.

3.3 Functional Imaging Following Curative-Intent Radiotherapy

In a small prospective pilot trial of 14 patients with medically inoperable stage I NSCLC, Henderson and colleagues[28] performed PET/CT scanning before SBRT and at 2 weeks, 6 months, and 12 months after treatment. Although the maximum standardized uptake value (SUVmax) in the tumor bed tended to decrease after treatment, no conclusions could be drawn because no cases of local recurrence were identified. In one instance, SUVmax rose significantly following SBRT, but biopsy specimens revealed necrosis. Similarly, Vahdat and colleagues[29] investigated 20 patients with stage IA NSCLC with PET/CT imaging before and after SBRT. They too demonstrated that SUVmax tended to decrease after treatment. One patient had documented local recurrence and a rising posttreatment SUVmax. Finally, van Loon and colleagues[30] performed PET/CT scans 3 months after initiating either radiotherapy or chemoradiotherapy in patients with stage I and II NSCLC. Progressive disease was detected radiographically in 24% of patients, but patients did not undergo confirmatory biopsies, and no PET/CT scan criteria for progressive disease were provided.

3.4 Miscellaneous Imaging

Aokage et al[31] investigated the use of abdominal ultrasonography as a surveillance tool following complete resection of NSCLC. This imaging modality is less expensive than CT scan and does not require contrast material. In a retrospective review of 265 consecutive patients followed by a single surgeon using yearly abdominal ultrasonography, only two of 59 with documented recurrent disease had their recurrence detected by abdominal ultrasonography. The authors concluded that this modality has no role in the postoperative surveillance of patients with NSCLC.

Venuta et al[32] used Doppler echocardiography to evaluate hemodynamic effects of lobectomy and pneumonectomy in 36 patients undergoing lobectomy and 15 undergoing pneumonectomy. Transthoracic echocardiography was performed periodically for up to 4 years following resection. Although patients who underwent lobectomy demonstrated no significant abnormalities, those who underwent pneumonectomy showed a progressive increase of right ventricular diastolic diameter and pulmonary artery systolic pressure. Findings had no clinical impact, and no ultrasound-detected recurrences were described.

Bini and colleagues[33] used somatostatin receptor scintigraphy (SRS) in 16 patients after resection of bronchial carcinoid tumors (15 typical, one atypical). Both SRS and CT scan were performed 12 months after surgery. Of three patients with positive SRS, two had confirmed recurrence and the third had sarcoidosis on biopsy specimen. There is no generally accepted surveillance protocol for patients with typical or atypical carcinoid tumors. In fact, recent guidelines from other societies vary in their recommendations for surveillance protocols in patients with resected carcinoid tumor. The European Society for Medical Oncology recommends CT scan or MRI once a year for up to 10 years in patients with either typical or atypical carcinoid tumor.[34] The National Comprehensive Cancer Network does not specifically address CT imaging surveillance for carcinoid tumor and does not recommend routine nuclear medicine (PET or octreotide) scanning following definitive resection.[35]

3.5 Recommendations

3.5.1. In patients who have undergone curative-intent surgical resection of NSCLC, it is suggested that chest CT be performed every 6 months for the first 2 years after resection and every year thereafter (Grade 2C)**.**

3.5.2. For patients with NSCLC or carcinoid tumor who have undergone curative-intent therapy, it is recommended that the original treating physicians participate in the decision-making process during the follow-up and surveillance (Grade 1C)**.**

3.5.3. After curative-intent therapy in patients with NSCLC or carcinoid tumors, routine surveillance with PET imaging, SRS, or abdominal ultrasonography is not recommended (Grade 1C)**.**

4.0 The Role of HRQOL

Only a handful of studies have assessed HRQOL following lung resection. Many analyses are limited by small study population size, cross-sectional study design, retrospective data analysis, or the use of nonvalidated assessments. Furthermore, the studies identified by our search addressed QOL after potentially curative interventions for patients with stage I to III lung cancer (Table S3). Although this reflects stages of disease appropriate for curative-intent treatment, it also signifies a heterogeneous study population subjected to follow-up QOL methodology. The paucity of data regarding the impact of follow-up on symptom control, symptom avoidance, or QOL may explain why only a few guidelines address these issues.

A recent systematic review and meta-analysis addressed published data on QOL,[9] finding only one study that reported QOL outcomes.[36] In this study, QOL was assessed at the end of treatment (baseline) and at monthly intervals with the core European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (EORTC QLQ-C30) and lung cancer-specific module (EORTC QLQ-LC13) (data were taken at monthly intervals for 1 year in patients with all stages of disease). This questionnaire has five functional scales (physical, role, emotional, cognitive, and social), three symptom scales (fatigue, nausea and vomiting, and pain), and a global health status and QOL scale. At 3 months, patients in the nurse-led arm of the trial rated dyspnea as less severe than did those in the conventional follow-up arm, but no other significant differences were found at this time point or at 6 months. At 12 months, however, patients in the nurse-led arm had improved scores for emotional functioning and less peripheral neuropathy than those in the conventional follow-up arm. This study used QOL as the primary outcome measure, showing that clinical nurse specialist follow-up of patients with lung cancer is safe, acceptable, and cost-effective and could lead to greater patient satisfaction and more appropriate and timely interventions at the same or no greater cost and with no detriment to QOL.

In a multicenter study, Kenny et al[37] followed 173 patients with clinical stage I and II NSCLC for a median of 2 years postoperatively to determine QOL, survival, and recurrence rate. QOL questionnaires

were obtained before surgery, at discharge, 1 month after surgery, and every 4 months for 2 years. Surgery substantially reduced QOL across all dimensions except emotional functioning. HRQOL improved in the 2 years after surgery for patients without disease recurrence, although approximately one-half continued to experience symptoms and functional limitations. For those with recurrence within 2 years, some early postoperative recovery in QOL was noted followed by deterioration across most dimensions. Patients who underwent pneumonectomy had substantially worse role and social functioning scores that persisted to the end of the follow-up period. By demonstrating that even disease-free survivors continued to report functional limitations and symptoms 2 years after surgery, this study shows that HRQOL instruments can be used to identify patients with persistent cough, dyspnea, fatigue, and associated functional limitations who might benefit from early referral for rehabilitation and supportive care services.

Similarly, Sarna et al[38] followed up 119 women who were surgically treated for NSCLC. Physical and emotional HRQOL was assessed at baseline and 3 and 6 months with the RAND Short-Form 36, and comorbidity was assessed with the Charlson comorbidity index, depression with the Center for Epidemiologic Studies and Depression Scale, and dyspnea with the Dyspnea Index. Depressed mood, comorbid conditions, and dyspnea were related to poorer physical and emotional QOL. Patients with these characteristics might benefit from greater supportive care postthoracotomy, highlighting the importance of continuous monitoring of patients after curative-intent surgery.

In a prospective cohort study using historical controls, Schulte et al[39] evaluated QOL in 131 elderly patients undergoing lobectomy or bilobectomy for NSCLC. Questionnaires were completed prior to resection and at 3, 6, 12, and 24 months after surgery using the EORTC QLQ-C30 and QLQ-LC13. The QOL of younger patients returned to preoperative levels significantly faster than that of elderly patients, but most QOL indicators, including physical function, pain, and dyspnea were significantly impaired in all patients after surgery and remained so for up to 24 months.

Follow-up led by a physician or nurse is likely to be beneficial when performed in the clinic. Subotic et al[8] followed up 88 patients who underwent resection for NSCLC, studying monthly phone contacts with patients and their families in addition to office visits every 3 months for the first year, every 4 months for the second and third years, and then every 6 months. Recurrence was noted in 50 patients (57%); 44 of these 50 recurrences occurred with symptoms, prompting the authors conclude that monthly phone calls were not helpful.

A significant proportion of patients with limited stage I or II lung cancer are not operable because of poor lung function or comorbid conditions. The impact on QOL of alternative treatments offered to these patients is relevant for informed decision-making. In a study of 39 patients with inoperable, pathologically confirmed T1,2 N0 M0 NSCLC[40] followed for a median of 17 months, the EORTC QLQ-C30 and QLQ-LC13 were used to investigate changes in QOL after SBRT; assessments were done before treatment; at 3 weeks; and at 2, 4, 6, 9, and 12 months after treatment until death or progressive disease. Emotional functioning improved significantly after treatment. Other function scores and QLQ-C30 and QLQ-LC13 lung symptoms, such as dyspnea and coughing, showed no significant changes, suggesting that these instruments can be used to monitor QOL in patients undergoing SBRT. Such instruments can also be used to follow QOL in long-term survivors of NSCLC treated by radical (for stage IIIA-B) or postoperative (for stage IIB) external beam radiation therapy.[41]

4.1 Recommendation

4.1.1. In NSCLC patients who have undergone curative-intent therapy, it is suggested that a validated HRQOL instrument be used at baseline clinic visits and during follow-up (Grade 2C)**.**

5.0 The Role of Tumor Markers

In solid tumors other than lung cancer, biomarkers help in diagnosis, determine response to treatment, and serve as a tool for detecting recurrence. These biomarkers include, but are not limited to, prostate-specific antigen in prostate cancer, carcinoembryonic antigen (CEA) in colon cancer, and cancer antigen 125 in ovarian cancer. Changes in biomarker levels in a specific individual during the disease course or after curative-intent therapy could be informative in estimating the efficacy of therapy and for the early detection of recurrent disease.[42] Continuous biomarker increases may be indicative of disease activity in terms of inefficient therapeutic response or tumor recurrence, whereas decreasing values often are associated with a reduction of disease activity.

In view of the known heterogeneity of NSCLC, a panel of tumor markers will likely be required to accurately predict patients most at risk for recurrent disease. The 2007 ACCP guidelines, however, do not support the use of blood tests, sputum cytology, or tumor markers for surveillance. Although certain serum biomarkers may correlate with increased risk of recurrence in patients with NSCLC, the evidence for recommending these as part of a follow-up algorithm remains poor to fair (Table S3).

European Society for Medical Oncology guidelines from 2010 recommend the use of biomarkers only for follow-up of carcinoid tumors after primary surgery. Patients with typical and atypical carcinoid tumors should be followed at least yearly up to 10 years (recommendation IIIC) to detect eventual surgically manageable recurrences. Biochemical markers such as chromogranin A should be determined every 3 to 6 months in cases where they are elevated at baseline, and CT scan or MRI should be performed once a year.[34] In the small cell lung cancer guidelines, the National Comprehensive Cancer Network does not comment on a specific follow-up strategy for lung neuroendocrine tumors. However, in a dedicated article on neuroendocrine tumors, chromogranin A is mentioned as a tumor marker that has been associated with recurrence, but panelists cautioned that rising chromogranin A levels in an asymptomatic patient with a tumor that appears stable by imaging does not necessarily indicate the need for treatment because chromogranin A levels have been reportedly elevated in other conditions, such as hepatic and renal insufficiency, or in the setting of concurrent proton pump inhibitor treatment.[35] Our review of the literature does not refute these recommendations, and we are unable to identify evidence supporting them. Although chromogranin A has been used as a marker for neuroendocrine tumors, the majority being gastroenteropancreatic, this has been mostly for diagnosis and not for surveillance.[43,44]

In a prospective case series of 96 patients, Blasberg et al[45] measured osteopontin (OPN) preoperatively and postoperatively in patients with resected early stage NSCLC. Recurrence (the primary outcome) occurred in five patients, three of whom had no OPN level available at the time of recurrence, but in the other two, OPN increased, suggesting that although OPN levels decrease after resection of lung cancer, they may increase again with recurrence. A prospective case series by D'Amico et al[46] evaluated several biomarkers in 196 patients with clinical stage I lung cancer who underwent resection. These biomarkers were measured preoperatively at the time of resection and at 1, 4, 6, 12, 18, and 24 months postoperatively in addition to routine clinical and imaging follow-up. Seventy-three patients had recurrence associated with decreasing levels of E-selectin and increasing levels of CD44 and urokinase plasminogen activator receptor. Ludovini et al[47] studied whether microsatellite alterations, p53 mutations, and circulating plasma DNA levels at diagnosis and follow-up are associated with disease-free survival and overall survival in surgically treated patients with NSCLC. Seventy-six consecutive patients with stage I to III NSCLC underwent surgical resection. Follow-up was a median of 23 months. Peripheral blood was drawn from each patient before surgery and at 3 and 12 months after surgery. Quantification of plasma DNA was believed to be useful in monitoring surgical patients during and after adjuvant therapy. The microsatellite alterations and p53 mutations detected in tumor DNA of NSCLC are associated with disease-free survival, correlate, and are more frequently detected in squamous histology and in smokers. The authors suggested that analysis of circulating DNA identifies patients with possible systemic disease at diagnosis and might thus be proposed as an early detection test of disease recurrence.

CEA was studied as part of a multimodal strategy, including physical examination, pertinent tumor markers, CXR, and PET/CT imaging.[48] The study included 819 patients who remained recurrence free for 5 years, with a median follow-up period of 40 months after the 5-year recurrence-free point; 87 (11%) had subsequent recurrence. The recurrence-free probabilities at 3 and 5 years from the point of 5 years after primary tumor resection were 92% and 87%, respectively. Recurrence was locoregional in 38 patients (43.7%) and distant in 49 (56.3%). The main conclusion of the study was that 5 years might not be a sufficient amount of time to declare cure of NSCLC, especially in patients with vascular invasion and node involvement. Although the study showed a statistically significant risk for recurrence in patients with preoperative elevated CEA, there was no comment on the value of CEA for surveillance or the nature of the pertinent tumor markers analyzed.

In addition to CEA, other markers (ie, Ki-67 labeling index, low podoplanin expression) have been described as prognosticators for early recurrence or survival in resected stage I NSCLC.[49,50] Our search, however, identified only one study that addressed the role of biomarkers in the surveillance of limited small cell lung cancer treated with curative-intent chemoradiotherapy.[51] In addition to physical examination and imaging studies, blood samples for neuron-specific enolase, soluble fragment of cytokeratin 19, progastrin-releasing peptide, and lactate dehydrogenase were obtained at 3 and 6 months after treatment. Although pretreatment neuron-specific enolase levels correlated with unfavorable prognosis, none of the biomarkers measured postoperatively were useful in predicting survival.

Surveillance may not always have recurrence or survival as an outcome. A prospective cohort study of 22 patients who underwent resection and were followed for a median of 217 days suggested that the combination of procalcitonin, brain natriuretic peptide, and IL-6 (recorded preoperatively and on days 1 and 5 postoperatively) seems to be useful for optimized postoperative monitoring (early postoperative complications).[52] After a follow-up of 6 months, overall

survival was 86% (n = 19). IL-6 levels were increased on day 1 and showed a slower decrease in patients with complications compared with those without complications (Table S3). Brain natriuretic peptide and procalcitonin levels were increased postoperatively after major pulmonary resection, but cardiac and infectious complications were associated with higher levels and a slower decrease of these markers compared with that seen in patients without complications.

5.1 Recommendation

5.1.1. For lung cancer patients treated with curative intent, it is suggested that surveillance biomarker testing not be done (outside of clinical trials) (Grade 2C)**.**

6.0 The Role of Bronchoscopy

The exact role for bronchoscopy as a follow-up method in all patients who undergo curative-intent therapy remains unclear. Only a few case series address this issue. Studies of surveillance protocols that used bronchoscopy in addition to CT scanning show that when the costs of retreatment (ie, surgical intervention) were included,[53] the cost per life-year gained was $56,000 compared with a (deemed) acceptable threshold of £20,000 to £30,000 per life-year gained in the United Kingdom and $50,000 per life-year gained in the United States. Westeel et al[54] evaluated patients by physical examination and CXR every 3 months and by bronchoscopy and CT scans every 6 months. Survival for the 36 detected asymptomatic recurrences was significantly better than for the 100 symptomatic recurrences. Cost analysis revealed that this surveillance protocol provided an acceptable cost per life-year gained.

A subgroup of patients may, in fact, benefit from surveillance bronchoscopy. This includes patients with initial central-type tumors (ie, visible during bronchoscopy) who underwent some form of curative-intent therapy (eg, surgery or photodynamic therapy [PDT]); patients at high risk for stump recurrence (eg, short tumor-free bronchus margin, nodal disease); and, possibly, patients with bronchial dysplasia or carcinoma in situ (CIS). Although evidence remains relatively weak, our literature search identified several research studies that may further clarify the role for bronchoscopy in surveillance protocols after curative-intent therapy (Tables S3).

6.1 Surveillance Autofluorescence Bronchoscopy for Bronchial Dysplasia or CIS

In the 2007 ACCP guidelines on follow-up and surveillance, white light bronchoscopy (WLB) or autofluorescence bronchoscopy (AFB) were not recommended for surveillance in patients after curative-intent therapy (Grade 2C). In the guidelines article on early central airway lung cancer, however, evidence was provided to justify a recommendation for bronchoscopic surveillance in patients with severe dysplasia and CIS: "For patients with known severe dysplasia or CIS in the central airways, standard WLB is recommended at periodic intervals (3 to 6 months) for follow-up and AFB should be used when available (2C)."[55]

AFB has improved the sensitivity of bronchial dysplasia and CIS detection by 1.5- to sixfold compared with WLB[56] and may, therefore, play a role in the surveillance of patients with known preinvasive lesions (bronchial dysplasia). In one study, 22 patients with 53 lesions were followed for 12 to 85 months. Eleven cancers were diagnosed in nine patients on the basis of AFB every 4 to 12 months in addition to annual chest CT scanning. Of 36 high-grade lesions (severe dysplasia and CIS), six progressed to invasive cancers, and five separate cancers developed at remote sites. The cumulative risk of developing lung cancer in a patient with a high-grade lesion was 33% and 54% at 1 and 2 years, respectively. Because all cancers were N0 M0, surveillance was useful to facilitate early detection and treatment with curative intent in most patients (eight of nine).[57]

6.2 Surveillance Bronchoscopy for Treated Endobronchial Lesions

Our review of the literature supports previous recommendations and suggests that studies of follow-up bronchoscopy for treated endobronchial lesions are necessary. Only the current guidelines from the German Respiratory Society and German Cancer Society recommend follow-up bronchoscopy in patients at risk for stump recurrence (eg, those who underwent sleeve resection), but the frequency and duration of follow-up were not described.[58] Another high-risk group is a subset of patients with previous early central squamous cell carcinoma (SqCC) for whom the reported rate of metachronous lesions appears even higher, with up to nearly 30% having a second central carcinoma develop within 4 years.[59]

In another study,[60] 13 patients with early central airway SqCC underwent PDT and had an AFB and a WLB at 1, 2, and 3 months then at every 3 months for the first year and every 6 months thereafter for a median follow-up of 30 months to detect local recurrence (Table S3). Treated patients met the following criteria: (1) histologically proven SqCC; (2) endoscopically visible distal tumor margins and accessibility to laser irradiation; (3) tumor size < 2 cm; (4) no metastasis in hilar or mediastinal lymph nodes and no distant

metastasis (stage 0, Tis N0 M0; stage I, T1 N0 M0) seen on chest and abdominal CT scan, brain MRI, and PET/CT scan; and (5) normal CXR and CT findings that did not detect primary lung tumor. The addition of AFB to WLB increased the sensitivity for detecting recurrence from 69% to 100%, but the specificity of WLB was higher than that of AFB (74% vs 41%), and many benign pathologic findings, such as fibrosis, were discovered with the use of AFB.

A retrospective case series by Endo et al[61] evaluated the role of follow-up bronchoscopy for radiographically occult SqCC after curative-intent PDT. Treated patients met the following criteria: (1) No metastatic lesions were observed, (2) the longitudinal extent of roentgenographically occult bronchogenic SqCC was < 10 mm, (3) the distal edge of roentgenographically occult bronchogenic SqCC was visible by bronchoscopy, and (4) bronchoscopy findings categorized the tumor as minute (< 2 mm height) or hidden (not visible with WLB, but diagnosed only through biopsy specimen, brushing, or AFB). Results showed that by applying the following protocol, local recurrence was detected in nine of 45 patients who initially had complete response after PDT: bronchoscopy with brushings and biopsy specimens at 1, 2, and 3 months after PDT then bronchoscopy, sputum cytology, and chest CT scan every 3 months for the first year and every 6 months for the second through fifth years; after that, sputum cytology and chest CT scan were done annually. Multiple primary cancers were detected in four of 48 patients.

Furukawa et al[62] used a similar algorithm to perform cytologic and histologic examinations through flexible bronchoscopy at 1, 2, and 3 months and then at 3-month intervals in the first year and 6-month intervals after the second year until 5 years after PDT. Recurrences after complete remission were detected in nine of 77 lesions (12%) even for those lesions that were < 1.0 cm in diameter. When recurrent tumor cells showed low to moderate atypia at the same site as that initially treated, complete remission could be obtained by performing a second PDT. Follow-up within the first year posttreatment as described in this study seems justified by the fact that in eight of nine lesions (89%), recurrence was detected within 12 months.

Bronchoscopic resection (reserved for a selected population with typical carcinoid tumors that are entirely endobronchial, forming a polypoid lesion with a small, < 1-cm base of implantation, no extraluminal growth, and no lymph node involvement noted by diagnostic imaging techniques) alone may provide prolonged recurrence-free survival for highly selected patients with a purely exophytic endoluminal bronchial carcinoid tumor.[63-66] In the largest prospective case series of 72 patients treated with this approach (57 with typical and 15 with atypical carcinoid tumors), initial bronchoscopic management resulted in complete tumor eradication in 33 (46%).[63] The follow-up strategy included flexible bronchoscopy in addition to high-resolution CT (HRCT) scan and tissue biopsy within 6 weeks after endobronchial resection; repeat evaluation was then performed every 6 months for 2 years and annually thereafter. Initial bronchoscopic treatment was considered successful when there were no signs of residual disease (by videobronchoscopy, biopsy specimen, thin-slice HRCT images, and radial endobronchial ultrasonography), although the authors did not specify whether all these tests were used in all patients. In cases of an atypical carcinoid tumor, residual tumor after bronchoscopic treatment, or recurrence, surgery was eventually required in 37 (including 11 of the 15 atypical carcinoid tumors), two for delayed recurrences at 9 and 10 years. At a median follow-up of 65 months, 66 (92%) patients were alive, and only one of the deaths was tumor related.

In a different retrospective series of 28 patients with typical bronchial carcinoid tumor, complete excision was confirmed on the basis of two successive negative bronchoscopy findings, both on macroscopic and microscopic grounds. Thereafter, patients underwent a 6-month checkup bronchoscopy and annual visits to the outpatient department to assess their condition and progress. During this visit, a targeted medical history was taken, and relevant clinical examination was carried out. A CXR was also taken. If there were concerns about either the history, examination, or CXR, a CT scan was performed with octreotide labeling. Recurrence was defined as either macroscopic or microscopic evidence of tumor after two consecutive negative checkup bronchoscopy findings.[65] At 1 and 10 years, 100% and 94% of patients, respectively, were disease free, and the 1- and 10-year survival rates were 89% and 84%, respectively.

6.3 Surveillance Bronchoscopy After Curative-Intent Surgical Treatment

In one retrospective series, Pasic et al[67] reported on 11 patients who had undergone radical surgery for N0 M0 lung tumors and were found to have CIS at the bronchial resection margins at the time of surgery. The median follow-up was 35 months (range, 15-89 months) during which time, regular (not further defined) WLB, AFB, and HRCT scan (every year) were performed. Suspicious lesions were visually scored and biopsied. Clinical parameters and the local extent of CIS at histology review were correlated with outcome. All the patients with CIS-A (extension of CIS down to the level of the glandular acini) developed stump recurrence in contrast to those with only CIS-S (superficial CIS, involving surface epithelium only).

Metachronous primary lesions in the contralateral lung developed in three patients with CIS-D (CIS involving the surface epithelium and extending into the bronchial gland ducts but not deeper), whereas the stump region remained free of tumor. Their results suggest that the risk of local recurrence after resection for lung carcinoma depends not only on the presence of CIS in the resection margin but also on the presence of gland involvement. The data also show a concurrent high risk of developing new primary carcinomas, potentially warranting more-intense follow-up in this group.

A prospective case series included 104 patients with completely resected NSCLC who were followed for a median of 30 months (range, 13-60 months).[68] All patients had bronchoscopy 1 year after resection to visualize the bronchial stump and a whole-body CT scan every 3 months. Eighteen patients had a recurrence, with four at the bronchial stump (all detected using bronchoscopy) and 14 elsewhere. Bronchial stump recurrence occurred in patients with either N1 or N2 disease at the time of resection. The authors concluded that although whole-body CT scan detects recurrences in 14% of patients, routine bronchoscopy after lobectomy detects stump recurrence in 4% at 1 year, and they found that short, tumor-free bronchial margins (< 1 cm) as well as nodal disease were independent risk factors for stump recurrence. Although this evidence is insufficient to justify a formal recommendation in the present guidelines, the study results warrant consideration, particularly because short bronchial margins cannot always be avoided in the realities of curative-intent surgical therapy. In our opinion, therefore, surveillance bronchoscopy at 1 year postresection should be considered in this population considered at risk for stump recurrence.

A retrospective case series addressed the role of bronchoscopy for evaluating suspected carcinoid tumor recurrence (on the basis of imaging studies) 3 and 12 months after surgical resection.[69] In this report of 104 patients (of whom 77% had central tumors [defined as tumor seen during bronchoscopy or tumors with atelectasis or postobstructive pneumonia]), there were 15 recurrences, but none were endobronchial, suggesting that bronchoscopic surveillance after surgical resection of carcinoid tumors may not be warranted. The optimal posttreatment surveillance strategy for carcinoid tumors is not yet clearly defined, and there is still no consensus on what tests should be ordered. Long-term follow-up (at least 10 years) may be warranted because local or distant recurrence can occur many years after initial treatment.[70]

6.4 Recommendations

6.4.1. For patients with early central airway SqCC treated by curative-intent PDT, it is recommended that surveillance bronchoscopy be done at 1, 2, and 3 months, and thereafter at 3-month intervals during the first year, then every 6 months until 5 years (Grade 1C)**.**

Remark: AFB may be used if available (Grade 2C).

6.4.2. For patients with intraluminal bronchial carcinoid tumor who have undergone curative-intent bronchoscopic treatment using Nd:YAG or electrocautery, it is suggested that surveillance bronchoscopy be done within 6 weeks after endobronchial resection, every 6 months for 2 years, and annually thereafter (Grade 2C)**.**

7.0 Questions for Future Research

Our review of the literature identifies the paucity of well-designed prospective studies and large rigorous case series specifically targeting follow-up and surveillance issues. Authors of future guidelines and, of course, practitioners and patients would greatly benefit from future investigations targeting these issues. Our literature search did not identify studies that could unequivocally answer the PICO questions described in the Methods section. In the following paragraphs, therefore, we ask questions that might help to identify areas for future research.

7.1 Which Curative-Intent Treatments With Similar Survival Benefits Most Favorably Affect HRQOL?

Because of the heterogeneity of the populations and treatment modalities studied, it remains difficult to determine which curative-intent treatment modality affects QOL the most and which patients are most at risk for impaired QOL after treatment. Research addressing QOL and treatment-related complications in a standardized manner would contribute to shared decision-making not only for discussing treatment alternatives but also for reinforcing the relevance of continuous monitoring (eg, clinical examinations, imaging studies, HRQOL instruments, bronchoscopy) for disease progression and to detect and potentially manage complications that can affect QOL (ie, bronchial stenosis, esophageal stricture, pericardial effusion). In patients with resectable NSCLC, for instance, if oncologic outcomes such as recurrence rates and survival are similar, then procedures with lesser adverse impact on QOL might be recommended. For example, findings from several retrospective cohort studies suggest that lobectomy by video-assisted thoracic surgery results in better QOL than by thoracotomy as assessed using Short Form-36 questionnaires at 3, 12, and 36 months postoperatively.[71]

For inoperable stage I NSCLC, SBRT has become an important treatment alternative because local tumor control rates > 90%[72] and 5-year overall survival rates of 47% are achieved.[73] These outcomes are reportedly better and obtained with less impairment of QOL than conventional external beam radiation therapy.[74] Randomized trials are needed to compare the effects of SBRT with other modalities (radiofrequency ablation and sublobar resection, if feasible) with regard to treatment-related changes in QOL, recurrence, and survival. Furthermore, because the reported 2-year local control rates are comparable to those achieved by surgery, QOL, in addition to survival, becomes an important outcome measure of future studies comparing surgery with SBRT in patients who are fit to undergo resection.[75]

For unresectable stage III NSCLC, modern high-dose, three-dimensional, conformal thoracic radiotherapy (60-90 Gy) used as part of combined modality treatment results in a median survival of 24.7 months. Late complications (after 90 days), however, occur in 24% of patients.[76] Studies are needed to identify surveillance protocols that will effectively identify and allow efficient management of these treatment-related complications.

7.2 How Do Specific Surveillance Modalities Affect Patient Outcomes?

Because QOL is an important prognostic factor for patients with lung cancer,[77,78] there may be potential in investigating whether improved QOL after treatment improves survival.[79] Surgical resection, for example, although potentially curative, could affect QOL separately from or in addition to disease effects because of postthoracotomy pain or limited physical activity resulting from reduced lung capacity. By focusing only on recurrence rates and survival, researchers and clinicians may be missing a valuable contribution to follow-up strategies.

Including QOL in the future evaluation of care after curative-intent therapy will eventually provide data that enable clinicians to knowledgeably inform patients about the potential consequences of each treatment alternative.[80,81] Patients with advanced NSCLC could benefit from early initiation of supportive care because of its potential for improving QOL and survival. Detecting early recurrence or second primary tumors amenable to repeat curative-intent therapy as well as detecting metastatic disease at an earlier stage when integrated oncologic care and palliative therapy are beneficial in terms of QOL and survival might also be warranted.[79] From a humanistic perspective, patient-centered outcomes such as QOL and psychologic well-being are probably just as relevant as survival and, thus, warrant designations as primary outcomes in future research.

Certain biomarkers (basic fibroblast growth factor, vascular endothelial growth factor) increase during disease progression, but it is not clear how often or when to test for these markers in order to improve survival or earlier detection of recurrence.[80] Several biomarkers analyzed on surgical specimens predict a higher risk for recurrence,[81-85] but questions regarding the frequency and mode of surveillance required in this high-risk group remain unanswered. Clinical, surgical, histologic, and biomarker data can be used to determine groups at high risk for recurrence, potentially warranting a more intense surveillance. In one study,[86] postoperative serum levels of CEA ≤ 2.5 ng/mL and absence of vascular invasion predicted no recurrence of stage I lung adenocarcinoma, suggesting a need for less-intense surveillance in this group. Setting the cutoff value for postoperative CEA levels at 2.5 ng/mL, nine of 16 cases (56%) showed disease recurrence, whereas six of 120 cases (5%) showed recurrence at levels ≤ 2.5 ng/mL. If results are replicated in additional studies, such a strategy might be recommended for selecting patients for more-intense follow-up as well as for selecting patients for adjuvant chemotherapy. Research is needed not only to identify specific and sensitive markers but also to clarify whether markers can predict locoregional and distant recurrence. Research is also needed to identify possible correlations between imaging studies (PET/CT imaging) and biomarker levels that might assist in identifying patients at higher risk for recurrence after curative therapy and who might thus be eligible for adjuvant therapy or more-intensive long-term surveillance.

Because conventional WLB is not useful for detecting mucosal changes that might be just a few cells thick or disease confined to below the tissue surface, studies targeting the use of combined multimodality bronchoscopic imaging platforms that include novel optical and acoustic modalities to allow visualization of airway abnormalities based on varying depth of penetration and resolution (eg, confocal endomicroscopy, optical coherence tomography, narrow band imaging, high-frequency endobronchial ultrasound, spectroscopy) are warranted. Combined modality imaging is already used in gastroenterology and laryngology, where white light and narrow band imaging are used together to detect various disease processes.[87,88] Other bronchoscopic technologies, such as Raman spectroscopy, that offer information on the biochemical composition of normal and diseased tissues[89] might eventually be shown to play a role in surveillance.

7.3 Which Patient Populations Should Be Followed?

The intensity of surveillance protocols after curative-intent therapy may need to be population specific. For instance, the existence of potential predictors for recurrence, such as pathologic stage, histologic type,

visceral pleural invasion, lymph node involvement, specific biomarkers (ie, CEA), and smoking habits,[48,90,91] highlight that lung cancer is a heterogeneous disease with a variety of possible outcomes after treatment. The discovery of oncogenic driver mutations may influence the development of late recurrences; tumor genotyping and phenotyping might stratify patients based on their risk for recurrence prior to personalizing surveillance protocols that are based on each individual patient's presumed or predicted risk.

Current follow-up radiologic imaging strategies are readily implemented because they are uniform and performed regularly. They do not, however, take into account prognostic factors associated with risk or time-to-treatment failure. The optimal interval for radiologic imaging studies during the surveillance period remains unknown. In fact, individualized surveillance protocols might be designed that first identify prognostic factors for time to recurrence and then model cumulative risk to plan visits according to the probability of recurrence.[92] Furthermore, current surveillance algorithms do not take into account the expected times of recurrent events or the prognostic factors that identify patient populations at a high or low risk of disease recurrence over time. Individualized models of surveillance can chart visits, imaging tests, biomarker measurements, or bronchoscopy at times when the risks of relapse are known to peak. Randomized trials are necessary to compare the effectiveness of current fixed-interval follow-up protocols with individualized protocols that are based on prognostic factors in terms of disease detection, effect on survival, impact on HRQOL, and health-care costs.

7.4 When and How Often Should Surveillance Studies Be Performed?

Particularly in the implementation of a personalized follow-up and surveillance strategy, the timing of surveillance interventions warrants further study. Recurrence patterns of NSCLC follow a specific dynamic at least in the first 4 years after curative-intent resection.[93] Recurrences seem to cluster at given times after surgery (ie, an initial surge at 9 months after surgery followed by two smaller peaks at the end of the second and fourth years), which contrasts with the pattern of second primary lung cancer where the hazard rate is essentially constant during the follow-up period. Although fixed-interval strategies for follow-up (eg, every 3-6 months) may be valuable for detecting second primary cancers, they do not take into account tumor biology and may thus miss the opportunity to detect recurrence in a more timely manner. The consequences of subsequent tumor detection on HRQOL and survival will also need to be specifically addressed.

7.5 How Long Should Patients Be Followed After Curative-Intent Therapy?

Although most recurrence from NSCLC occurs within the first 5 years after surgery, there is a growing body of evidence that this risk could be as high as 3.8% to 15% for patients surviving more than 5 years after complete resection.[35,90] Limiting follow-up to 5 years, therefore, is probably not advisable. Research that will help to identify patients at risk for late recurrence is warranted because of the effects of longer-term surveillance on QOL, health-care resource allocation, and cost of care.

Long-term follow-up is also relevant to carcinoid tumors. In one large study, for instance, after a median follow-up of 10 years, 8% of patients had recurrences most commonly in the liver (55%), followed by lung (25%), bone (20%), adrenal gland (10%), pericardium (10%), and mediastinal lymph nodes (10%).[70] Recurrent cancer developed preferentially in atypical carcinoid tumors (17.9% vs 3.4% in typical carcinoid tumors, $P = .0001$) and in patients with positive nodes, but no bronchial recurrences were seen, highlighting the need for clarifying an optimal surveillance modality that is based on specific risk factors for recurrence. Recommendations from other societies vary with regard to the use of imaging studies in patients with resected atypical or typical carcinoid tumors, and prospective randomized studies pertaining to bronchoscopic surveillance are lacking. Similar to NSCLC, there is a need for developing plasma or genetic tests to predict or identify early recurrence.[94]

8.0 Summary

The goals of follow-up and surveillance programs after patients have undergone curative-intent therapy are to identify and potentially manage treatment-associated morbidity, detect and potentially treat disease recurrence or new primary tumors, enhance QOL, and improve survival. Much of the evidence supporting various aspects of surveillance protocols, however, remains relatively weak and based on studies of lesser quality. In this review, we chose to complement the existing ACCP guidelines on this topic by searching the literature for evidence pertaining specifically to the use of HRQOL assessments, radiologic imaging studies, tumor markers, and flexible bronchoscopy. Our review of the evidence has prompted several recommendations and suggestions that are directly relevant to patient care.

As the increasingly accepted paradigm of personalized lung cancer treatment evolves, we propose that individualized surveillance programs will also need to be designed. These programs may be based on tumor biology, individually identified risk factors for

recurrence or disease progression, and the evidence supporting the particular use of medical tests and assessments. Future surveillance protocols may be initiated at different times during the follow-up period and may vary from patient to patient according to diagnosis, tumor histology, and many of the parameters mentioned in this article. Deliberate randomized trials will be necessary to compare the effectiveness of these individually designed programs with more traditional, yet from our review of the evidence, insufficiently studied surveillance protocols. The challenges facing health-care providers caring for patients with lung cancer after curative-intent treatment, therefore, are real but not insurmountable. Higher-quality research can successfully address specific issues pertaining to the value of surveillance and its impact on HRQOL, morbidity, survival, and health-care costs as well as determine with greater certainty those medical tests, assessments, and protocols that are most likely to benefit patients touched by the effects of lung cancer and its treatment.

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Dr Murgu: contributed as deputy editor and collected and analyzed data from eligible studies.
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