

**American College of Radiology
ACR Appropriateness Criteria®**

Clinical Condition:

Follow-Up of Non-Small-Cell Lung Cancer

Variant 1:

Middle aged patient, 3 months postoperative for stage II squamous cell cancer of lung, asymptomatic. Still smoking, KPS 90-100.

Radiologic Procedure	Rating	Comments
Frequency of follow-up every 2-4 months for 2 years, then every 6 months for 5 years, then yearly for life	8	
X-ray chest every 6 months for 5 years, then yearly for life	8	
CT chest single postoperative scan, then yearly for life	8	The frequency of follow-up CT scans is controversial and may be impacted by many clinical factors. Chest CT may replace a routine chest x-ray.
CT head	2	
MRI head	2	
3-day pooled sputum cytologies	2	
NUC Tc-99m bone scan whole body	2	
FDG-PET whole body	2	
Serum tumor markers (TPA, NSE)	2	
<u>Rating Scale:</u> 1=Least appropriate, 9=Most appropriate		

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Clinical Condition:**Follow-Up of Non-Small-Cell Lung Cancer****Variant 2:**

Elderly patient, never smoked, postoperative 3 months neoadjuvant chemotherapy irradiation and surgery for stage IIIA adenocarcinoma of lung. No residual disease at surgery. KPS 80.

Radiologic Procedure	Rating	Comments
Frequency of follow-up every 2-4 months for 2 years, then every 6 months for 5 years, then yearly for life	8	
X-ray chest every 6 months for 5 years, then yearly for life	8	
CT chest single postoperative scan, then yearly for life	8	The frequency of follow-up CT scans is controversial and may be impacted by many clinical factors. Chest CT may replace a routine chest x-ray.
CT head	2	
MRI head	2	
3-day pooled sputum cytologies	2	
NUC Tc-99m bone scan whole body	2	
FDG-PET whole body	2	
Serum tumor markers (TPA, NSE)	2	
Rating Scale: 1=Least appropriate, 9=Most appropriate		

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Clinical Condition:**Follow-Up of Non-Small-Cell Lung Cancer****Variant 3:**

Middle aged patient, heavy smoker, unresectable stage 3A adenocarcinoma. Treated with concurrent chemoradiotherapy to 66 Gy using conformal technique.

Radiologic Procedure	Rating	Comments
Frequency of follow-up every 2-4 months for 2 years, then every 6 months for 5 years, then yearly for life	8	
X-ray chest every 6 months for 5 years, then yearly for life	8	
CT chest post treatment scan, then every 6 months for 5 years, then yearly for life	5	The frequency of follow-up CT scans is controversial and may be impacted by many clinical factors. Chest CT may replace a routine chest x-ray. The value of post-therapy screening should be discussed with the patient.
FDG-PET whole body one after treatment only	4	This modality is currently under study and may be impacted by many clinical factors. The value of post-therapy screening should be discussed with the patient.
CT head	2	
MRI head	2	
3-day pooled sputum cytologies	2	
NUC Tc-99m bone scan whole body	2	
Serum tumor markers (TPA, NSE)	2	
Rating Scale: 1=Least appropriate, 9=Most appropriate		

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FOLLOW-UP OF NON-SMALL-CELL LUNG CANCER

Expert Panel on Radiation Oncology–Lung; William W. Thoms, Jr, MD¹; Ritsuko U. Komaki, MD²; Richard M. Gewanter, MD³; Ramesh S. Gopal, MD⁴; Benjamin Movas, MD⁵; Kenneth E. Rosenzweig, MD⁶; Thomas H. Weisenburger, MD⁷; Harvey B. Wolkov, MD⁸; Larry R. Kaiser, MD⁹; Joan H. Schiller, MD.¹⁰

Summary of Literature Review

New technologies are being introduced into the follow-up of patients with non-small cell lung cancer (NSCLC) at a rapid pace. Very few of these have been examined in a scientifically justified and cost-effective manner. Nevertheless, their impact on day-to-day oncology practice is undeniable. This section examines the evidence supporting or refuting their integration into the current follow-up recommendations. It is important to stress that many of these technologies are unquestionably valuable in assessing symptomatic patients with recurrence after initial treatment. The relevant question is whether and how they should be used in routine follow-up of the asymptomatic patient after primary curative treatment of NSCLC.

Rationale for Follow-up Recommendations

Despite the proliferation of treatment options including surgery, chemotherapy, post-operative chemotherapy, pre-operative chemoradiotherapy, and primary chemoradiotherapy, the patterns of failure remain relatively unchanged; many patients fail in the first 2 years post-therapy, long term survival percentages are often under 50%, salvage interventions are less efficacious than the initial therapy, and second primary cancers including metachronous lung cancers are common among long-term survivors [1-7]. For example, Hotta et al [4] reviewed a single institution experience of 743 resected patients for NSCLC and found only 43 with isolated locoregional recurrence. The median time to recurrence was 13.6 months and the most frequent site of recurrence was mediastinal nodes in 49% of recurrences. Only two were treated with re-resection. Median survival after diagnosis of recurrence was 10.5 months and median time to distant recurrence after locoregional recurrence was 8.4 months. For the purposes of this report, one can segment follow-up discussions into recommendations for

postoperative patients and those with therapy for unresectable cancer.

One might expect the best outcomes among patients treated with surgery, such that incrementally more rigorous follow-up might be expected to enhance survival. The justification for this assumption is controversial. Younes et al [7] evaluated 130 patients divided retrospectively into routine versus symptomatic follow-up regimens after curative resection. Most patients' recurrences were diagnosed based on symptoms rather than routine tests. Survivals of patients with recurrent cancer were poor and unaffected by follow-up regimen. The authors questioned the value of routine follow-up imaging based on these data. Lamont et al [8] retrospectively evaluated 124 patients with resected NSCLC using physical examination and chest radiography every 3 months for 2 years and every 6 months for an additional 3 years. Annual chest computed tomography (CT) scans were done. Only 14 patients with second malignant tumors could be treated surgically, and 9 of these were alive and without evidence of disease at a median of 20 months follow-up. The median size of resected tumors was 14 mm. The authors also concluded that locally recurrent lung cancers are infrequently resectable. Westeel et al [6] followed postoperative patients with physical examination and chest x-ray every 3 months, fiberoptic bronchoscopy and chest and abdominal CT scans every 6 months. Recurrence was found in 71% of patients and only 11% of these could have re-resection for curative intent. Recurrence was found in asymptomatic patients by a scheduled follow-up procedure in 26% of all recurrences. Three-year survival was 31% in these patients versus 13% for all patients. These authors used this data to justify an intensive follow-up schedule. A similar analysis by Egermann et al [2] in 563 patients with curative resection who were followed for 10 years with regular clinic visits and chest radiography found that only 3.8% of patients were able to undergo a second curative resection based on this program. The calculated cost per life-year gained was approximately \$75,000. This cost was far above other large-scale surveillance programs in their country, and the intensity and duration of follow-up were reduced.

With respect to second primary lung cancers (SPLC) alone, one may identify highly selected subsets of patients who can benefit from aggressive follow-up. Rice et al [9] analyzed the records of the NCI Intergroup trial NCI#I91-0001 examining the effectiveness of isotretinoin A for chemoprevention of second primary tumors after complete resection of pathologic stage I NSCLC. All of these patients had rigorous follow-up designed to detect SPLCs. Among the 569 patients randomized to the placebo arm, second primary tumors of all kinds were

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found in 88 (15%) patients. Only 49 of these patients had SPLC (incidence of 1.99/100 patient-years). Despite semi-annual follow-up with chest radiographs, 12 (24%) patients had metastatic disease at the time of diagnosis and only 31 (63%) patients underwent surgery. Median survival was 4.1 years for those patients who had surgery and 1.4 years for those who did not and this difference was highly significant. On the whole, these data support regular clinical exams and chest radiographs for post-resection follow-up.

The value of chest spiral CT has been evaluated as a screening tool in high-risk smokers, but it has a high false positive rate and is not sensitive for detecting endobronchial disease or preinvasive disease [10-12]. It is attractive to speculate that applying this technology to follow-up of resected lung cancer patients might identify recurrences earlier, resulting in more curative re-resections. There is no doubt this is being done to some extent in daily practice. No controlled trials on use of low-dose spiral CT in follow-up of lung cancer patients have been done. Smaller experiences confirm the usefulness of this modality in confirming recurrence when compared to chest radiography, but the impact on survival is unknown [13]. For now, it may be reasonable to replace a follow-up chest radiograph with chest CT scans in high-risk patients after resection.

If the case for avoiding aggressive follow-up in resected patients is controversial, then it is surely less so in patients with unresectable NSCLC treated with chemotherapy, chemoradiotherapy, or other combined modality approaches. These patients tend to fail soon after therapy with symptomatic metastases, and most imaging is focused on restaging the patient for salvage therapy [3,5]. Routine post-therapy imaging of asymptomatic patients outside of clinical trials cannot be recommended until more effective salvage regimens are developed.

New imaging technologies are being investigated, but no controlled clinical trials establish their use in routine follow-up. Positron emission tomography (PET) has been evaluated in follow-up of NSCLC primarily in unresected patients [14-19]. It is felt to be less sensitive for evaluating metastatic or recurrent cancer than it is in initial staging. It is probably more accurate than CT in distinguishing tumor from fibrotic scar or pneumonitis in NSCLC patients [13,14]. Patz et al [19] demonstrated a significantly improved survival in patients with a negative PET scan after first line treatment. The combination of PET/CT improves the diagnostic accuracy over that of either test alone [16]. Other modalities such as 99mTc-tetrofosmin scintigraphy [20,21], Tc99m MIBI [22] and thallium-201 chloride SPECT [22], and whole-body magnetic resonance imaging (MRI) have been investigated but have no proven clinical usefulness in routine follow-up.

Since the previous edition of the ACR guidelines, the American Society of Clinical Oncology has published guidelines for treatment of unresectable NSCLC [23]. They recommended maintaining regular physical exams but did not advocate regular imaging in asymptomatic patients. They acknowledged the investigational nature of low-dose spiral chest CT as a routine follow-up study. Many of the interventions described above, including fiberoptic bronchoscopy, sputum cytologies, tumor markers, and more established imaging studies, continue to have value in follow-up of symptomatic patients or in clinical trials. These recommendations acknowledge the disappointing efficacy of salvage regimens after first therapy despite early diagnosis of recurrence, as well as, their additional cost to the patient. Under the circumstances, similar recommendations from this report are justifiable.

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