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Follow-up and Surveillance of the Lung Cancer Patient Following Curative Intent Therapy: ACCP Evidence-Based Clinical Practice Guideline (2nd Edition)

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Follow-up and Surveillance of the Lung Cancer Patient Following Curative Intent Therapy*

ACCP Evidence-Based Clinical Practice Guideline (2nd Edition)

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Background: **To develop an evidence-based approach to follow-up of patients after curative intent therapy for lung cancer.**
Methods: **Guidelines on lung cancer diagnosis and management published between 2002 and December 2005 were identified by a systematic review of the literature, and supplemental material appropriate to this topic was obtained by literature search of a computerized database (Medline) and review of the reference lists of relevant articles.**
Results: **Adequate follow-up by the specialist responsible for the curative intent therapy should be ensured to manage complications related to the curative intent therapy and should last at least 3 to 6 months. In addition, a surveillance program should be considered to detect recurrences of the primary lung cancer and/or development of a new primary lung cancer early enough to allow potentially curative retreatment. A standard surveillance program for these patients, coordinated by a multidisciplinary tumor board and overseen by the physician who diagnosed and initiated therapy for the original lung cancer, is recommended based on periodic visits with chest imaging studies and counseling patients on symptom recognition. Smoking cessation and, if indicated, facilitation in participation in special programs is recommended for all patients following curative intent therapy for lung cancer.**
Conclusions: **The current evidence favors follow-up of complications related to curative intent therapy, and a surveillance program at regular intervals with imaging and review of symptoms. Smoking cessation after curative intent therapy to prevent recurrence of lung cancer is strongly supported by the available evidence.** ***(CHEST 2007; 132:355S–367S)***

Key words: lung cancer; metachronous tumors; recurrence; surveillance

Abbreviations: ACCC = Association of Community Cancer Centers; ACCP = American College of Chest Physicians; CXR = chest radiograph; NCCN = National Comprehensive Cancer Network; NSCLC = non-small cell lung cancer; PET = positron emission tomography

Approximately 172,000 new cases of lung cancer are diagnosed annually in the United States.[1] Unfortunately, only approximately 20% of patients with newly diagnosed lung cancer will have localized disease and will be candidates for potentially curative treatment.[2] Furthermore, some patients with localized non-small cell lung cancer (NSCLC) may either refuse potentially curative surgical therapy or may be

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unable to tolerate surgery because of limiting comorbid cardiopulmonary or other disease. Consequently, it has been estimated that only 35,000 patients underwent curative intent surgical resection for NSCLC in 1998.[3] Small numbers of patients will receive curative intent radiation therapy for localized NSCLC and some combination of curative intent chemotherapy and radiation therapy for localized small cell carcinoma.

Two distinctly different issues should be taken into account when planning patient care following curative intent therapy for lung cancer. First, adequate follow-up should be ensured to manage complications related to the curative intent therapy itself. This should be a specialist-directed process. The thoracic surgeon should be responsible for managing complications related to any surgical procedures performed, as should the radiation oncologist and the medical oncologist for managing complications related to radiation therapy and chemotherapy, respectively. In most cases, this specialist-directed follow-up should be transient.

Second, a surveillance program should be considered to detect recurrences of the primary lung cancer and/or development of a new primary lung cancer early enough to allow potentially curative retreatment. Numerous guidelines have been published regarding the management of lung cancer. Several of these guidelines include recommendations for a posttreatment surveillance program. These recommendations will be summarized and compared. Available data on rates, patterns, and diagnostic tools for identifying recurrence of the primary lung cancer and/or development of a second primary lung cancer will be reviewed as the basis for recommendations on an ongoing surveillance program following curative intent therapy for lung cancer. Issues related to follow-up for palliative therapy of lung cancer will not be discussed (see section on Palliative Treatment).

To update the previous recommendations on the follow-up and surveillance of lung cancer patients following curative intent therapy,[4] guidelines on lung cancer diagnosis and management published between 2002 and December 2005 were identified by a systematic review of the literature using search terms including "follow-up," "surveillance," "lung cancer," and "lung neoplasms" (see "Methodology for Lung Cancer Evidence Review and Guideline Development" chapter). Those guidelines including recommendations specific to the follow-up and surveillance of lung cancer after curative intent therapy were identified for inclusion in this section. Supplemental material appropriate to this topic was obtained by literature search of a computerized database (Medline) and review of the reference lists of relevant articles. Recommendations were developed by the section editor and writing committee, graded by a standardized method (see "Methodology for Lung Cancer Evidence Review and Guideline Development" chapter), and then reviewed by all section editors, the Executive Committee of the panel, and then further reviewed by the Thoracic Oncology Network, Health and Science Policy Committee, and Board of Reagents of the American College of Chest Physicians (ACCP).

Follow-up of Complications Related to the Original Mode of Curative Intent Therapy

Follow-up for complications should be performed by the specialist responsible for the curative intent therapy and should last at least 3 to 6 months.[5] Complications related to pulmonary resection include hospital readmission, loss of lung function, and chronic pain. Handsy et al[6] reported that 19% of patients discharged after pulmonary resection were readmitted within 90 days, most for pulmonary problems, postsurgical infections, and cardiac issues. Loss of lung function after surgery is directly related to the extent of the resection performed. Six months after lobectomy, FEV_1 is approximately 10 to 15% lower than preoperative values, and after pneumonectomy approximately 25 to 35% lower.[7] Similarly, maximal exercise capacity stabilizes at 6 months after lobectomy at a 10% reduction and a 20% decrease after pneumonectomy compared with preoperative value.[7] Postthoracotomy pain has been reported in 55% of patients at 18 to 24 months after resection, with 10% of patients requiring narcotic analgesia or more aggressive therapy, such as intercostal nerve blocks.[8–10] Patients undergoing resection for localized lung cancer have significantly lower baseline quality of life when compared with the normal population, and resection causes further deterioration in quality of life, especially during the first 3 to 6 months after surgery. Some studies[11,12] suggest that quality of life returns to baseline levels at 6 to 9 months after surgery, whereas others show significant impairments up to 12 months after surgery. Of note, persistent cigarette smoking after lung cancer resection significantly worsens quality of life measures.[13]

Unusual complications related to pulmonary resection may occur after hospital discharge. Case series[14,15] from the 1960s reported that persistent air in the pleural space was noted for weeks to months following lobectomy and pneumonectomy but usually resolved without complications. An autopsy series[16] from the same time period confirmed residual air in the pleural space after pneumonectomy in 27 of 37 cases, even

though surgery had been performed years before. In very rare situations, empyema may develop in these spaces.[14] Torsion of the mediastinum developing after pneumonectomy may lead to mainstem bronchus obstruction.[17]

Complications of radiation therapy with curative intent for lung cancer include acute radiation pneumonitis and radiation-induced pulmonary fibrosis, as well as injury to the skin, heart, pericardium, esophagus, and spinal cord. Pulmonary radiation toxicity is related to the volume of lung irradiated, the cumulative dose effects of radiation sensitizing agents, and undefined factors determining the biological predisposition of the patient. In a large study[18] using high-dose radiation therapy, acute toxicity was seen in 11% of the patients, with most injury relating to esophageal problems and only a third to lung toxicity. Acute radiation pneumonitis usually occurs within 3 months of treatment and is associated with nonproductive cough, dyspnea, and fever.[19] It may resolve without treatment, but severe cases may be responsive to corticosteroid therapy. Inoue et al[20] reported that 94 of 191 evaluable patients (49%) had acute radiation pneumonitis after thoracic radiotherapy for lung cancer, and 25 patients (13%) had severe cases. $PaO_2 < 80$ mm Hg prior to radiotherapy may have indicated an increased risk for acute radiation pneumonitis in this study. Severe radiation pneumonitis was associated with poorer overall survival. Other work[21] suggests that increased serum levels of KL-6 may be a useful marker of radiation pneumonitis. Radiation-induced fibrosis represents irreversible tissue damage, occurs in approximately 8% of patients treated with curative intent, and may present as early as 3 months and as late as 24 months after treatment.[18] Even without producing overt pneumonitis, effective radiation therapy may result in a loss of pulmonary function. Miller et al[22] described an average decrease in median FEV_1, FVC, and diffusing capacity of the lung for carbon monoxide of 10% at 6 months after irradiation therapy, similar to that reported after lobectomy. All values were closer to baseline at 1 year after treatment but continued to decline by 7 to 10%/yr.[22] However, Choi and Kanarek[23] found that patients with poor lung function before treatment had little decrease in FEV_1 after irradiation therapy.

Complications related to chemotherapeutic agents used for NSCLC and small cell lung cancer are usually detected during the course of therapy. A long-term morbidity of concern in patients who have completed chemotherapy is a mild-to-moderate peripheral neuropathy, which results from multiple treatments with the commonly used platin, vinca alkaloid, and taxane compounds. In addition, induction chemotherapy with cisplatinum and gemcitibine has been associated with a fall in diffusing capacity of the lung for carbon monoxide.[24]

Recommendation

1. In lung cancer patients treated with curative intent therapy, follow-up for complications related to the curative intent therapy should be managed by the appropriate specialist and should probably last at least 3 to 6 months. At that point, the patient should be reevaluated by the multidisciplinary tumor board for entry into an appropriate surveillance program for detecting recurrences and/or metachronous tumors. Grade of recommendation, 2C

Issues in Surveillance for Recurrence of the Original Lung Cancer and Development of New Primary Lung Cancers

Definitions

As previously reviewed,[4] a difficult but fundamental issue in surveillance of the lung cancer patient following curative intent therapy is distinguishing between recurrence of the original lung cancer and identification of a new primary, or metachronous, lung cancer. Martini and Melamed[25] proposed criteria for making this distinction in 1975. However, more recent considerations suggest that these criteria should be revised (Table 1). More definitive distinction will be possible in the future based on routine performance of analysis of panels of molecular, genetic markers, and/or proteomics. Whichever criteria are used, Martini and Melamed[25] remind us

Table 1—*Distinguishing Between Recurrence of the Original Lung Cancer and Development of a New Lung Cancer During Surveillance*

Metachronous Tumors, Martini and Melamed Criteria*	Metachronous Tumors, Proposed Revision
Histology different	Histology different
Histology the same, if:	Histology the same, if:
Free interval between cancers at least 2 years, or	Free interval between cancers at least 4 yr, or
Origin from carcinoma *in situ*, or	Origin from carcinoma *in situ*, and
Second cancer in different lobe or lung, but	No extrapulmonary metastases at time of diagnosis
No carcinoma in lymphatics common to both, and	
No extrapulmonary metastases at time of diagnosis	

*Adapted from Martini and Melamed.[25]

Table 2—*Recommendations for Surveillance Methods in Patients With NSCLC Following Curative Intent Therapy*

Guideline/Source	Baseline	First 2 yr	Years 3 to 5	After Year 5
ACCC[29]		Hx, PE, CXR, CBC, chemistries every 3 mo	Hx, PE, CXR, CBC, chemistries every 6 mo	Hx, PE, CXR, CBC, chemistries every 12 mo
ACCP[4]		Hx, PE, CXR or chest CT every 6 mo	Hx, PE, CXR or chest CT every 12 mo	Hx, PE, CXR or chest CT every 12 mo
ACR[27]	Chest CT at 3 mo after therapy	CXR every 2 to 4 mo; chest CT every 12 mo	CXR every 6 mo; chest CT every 12 mo	CXR every 12 mo; chest CT every 12 mo
ASCO[26]		Hx, PE every 3 mo	Hx, PE every 6 mo	Hx, PE every 12 mo
ESMO[30]		Hx, PE every 3 mo	Hx, PE every 6 mo	Hx, PE every 6 mo
NCCN[28]		Hx, PE, contrast CT every 6 mo	Hx, PE, non-contrast CT every 12 mo	Hx, PE, non-contrast CT every 12 mo

*ACR = American College of Radiology; ASCO = American Society of Clinical Oncology; ESMO = European Society for Medical Oncology; Hx = history; PE = physical examination.

that the distinction between a new primary lung cancer and recurrence of the original lung cancer is not as important as determining whether the tumor can be treated with curative intent.

Review of Current Guidelines

Five guidelines[26–30] provide specific recommendations for surveillance methods in patients with NSCLC (Table 2), and two guidelines[29,31] provide specific recommendations for patients with small cell lung cancer following curative intent therapy (Table 3). These guidelines were developed by consensus of expert panels and not necessarily by more rigorous metaanalysis. Two other guidelines[30,32] provided only general recommendations. One guideline[30] noted the lack of evidence that surveillance of the asymptomatic patient with small cell lung cancer following curative intent therapy is needed. Specific examinations in these patients should be performed as clinically indicated. The other guideline[32] supported the need for randomized clinical trials to define the most appropriate follow-up regimen, and to evaluate patient quality of life and the cost-effectiveness of the strategy.

The guidelines uniformly recommend more frequent visits during the first 2 years following curative intent therapy. Visits are less frequent for years 3 through 5 and decrease to a minimal level of annually after year 5. This pattern of visits is based on the expectation that recurrences of the original lung cancer will be more likely during the first 2 years after curative intent therapy but that there will be an increased lifelong risk of a new primary lung cancer developing. The guidelines uniformly emphasize symptoms as an extremely important indication of recurrence, with physical examination included as an adjunctive, but less valuable, tool for identifying recurrences or new primaries.

There is wide divergence among the guidelines regarding recommendations for chest imaging after curative intent therapy for lung cancer. The issues of radiographic detection of asymptomatic recurrent or metachronous cancer after treatment with curative intent are similar to those of early detection of primary cancer currently being investigated in high-risk patients (see section on "Screening for Lung Cancer"). Accordingly, the American Society of Clinical Oncology guidelines for NSCLC specifically state that there is no proven value for either chest radiograph (CXR) or CT in surveillance.[26] However, the Association of Community Cancer Centers (ACCC) guidelines recommend routine CXR for surveillance.[29] Guidelines from the American College of Radiology[27] recommend a postresection chest

Table 3—*Recommendations for Surveillance Methods in Patients With Small Cell Lung Cancer Following Curative Intent Therapy*

Guideline/Source	Baseline	First 2 yr	Years 3 to 5	After Year 5
ACCC[29]		Hx, PE, CXR, CBC, chemistries every 3 mo	Hx, PE, CXR, CBC, chemistries every 6 mo	Hx, PE, CXR, CBC, chemistries every 12 mo
ACCP[4]		Hx, PE, CXR, or chest CT every 6 mo	Hx, PE, CXR, or chest CT every 12 mo	Hx, PE, CXR or chest CT every 12 mo
NCCN[28]		Hx and PE (chest imaging and blood work as clinically indicated) every 2 to 3 mo	Hx and PE (chest imaging and blood work as clinically indicated) every 4 to 6 mo	Hx and PE (chest imaging as clinically indicated) every 12 mo

*See Table 2 for expansion of abbreviations.

CT scan to establish a new baseline and then annually in addition to interval CXR every 2 to 4 months. The most recent guidelines from the National Comprehensive Cancer Network (NCCN)[28] rely entirely on chest CT scanning for surveillance imaging (Table 2).

With regards to other tests, the ACCC guidelines incorporate regular complete blood counts and serum chemistries into surveillance monitoring for NSCLC. Other groups found little value in performing these tests routinely for NSCLC, but these tests are recommended routinely in small cell lung cancer surveillance. Sputum cytology and various bronchoscopic techniques were specifically not incorporated into guidelines for surveillance practices.

Patterns of Recurrence

Numerous studies[33–41] have reported on recurrence rates and patterns in patients with NSCLC treated with curative intent surgical resection. In patients with stage I disease confirmed at surgery, 5-year recurrence rates 20 to 39% have been reported.[34,37,38] Most of these recurrences were distant metastases.[34,37,39] Although most recurrences were detected within the first 4 years following curative intent surgery,[37,38] recurrences may be discovered $\geq$ 5 years following curative intent therapy.[34,37,39,40] In patients with nodal involvement, recurrence rates increase[35,36,41] and recurrences probably occur earlier.[33,35,41]

It has been estimated from published studies[42,43] on treatment outcomes that the approximate rate of a new primary lung cancer developing after curative intent therapy for a NSCLC is 1 to 2% per patient per year. Prospective lung cancer chemoprevention trials with vitamin A[44] and isotretinoin[45] also suggest similar rates for the development of metachronous tumors. In contrast, large population-based studies, such as the review of the regional cancer registry in Switzerland, suggest that in this population the rate may actually be slightly less than this estimate at approximately 0.5% per patient per year.[46] However, this type of study may underestimate the incidence rate of metachronous tumors because of incomplete surveillance and misclassification of tumors as recurrences.[45] Experience with long-term survivors of lung cancer indicate that new primary lung cancers may develop up to 20 years after the original cancer had been treated,[47] but the available data are unclear on whether the rate of development of metachronous tumors increases or decreases over time.[34,39,43] An important point is that following curative intent therapy for NSCLC, patients are also at increased risk for other aerodigestive cancers (*eg*, carcinoma of the oropharynx and esophagus).[46,48]

Roentgenographically occult lung cancers detected by sputum cytology have been reported to have an especially high rate of metachronous tumors. Saito et al[49] described 13 metachronous tumors occurring in a group of 127 patients who underwent surgical resection for roentgenographically occult NSCLC. The cumulative rate at 5 years of metachronous tumors was 11%, and the incidence per patient year of surveillance was 2.2%. Bechtel and colleagues[50] reported that seven metachronous tumors were identified in a group of 27 patients following surgical resection of a roentgenographically occult NSCLC. Consistent with these findings has been the observation that central lung cancers, treated with sleeve resection, may have a high rate of metachronous tumors approaching 7 to 8%.[51]

Patients treated for small cell lung cancer and surviving for 2 years have also been reported to have an especially high rate of metachronous NSCLCs developing. In two separate observational studies,[52] NSCLC was diagnosed in 12 to 15% of patients surviving at least 2 years after therapy for small cell lung cancer (six cases in one group of 40 patients, and six cases in another group of 47 patients). It has been estimated that the rate of NSCLC developing 2 years after effective therapy for small lung cancer is 2 to 13% per patient per year.[43] Another study[53] confirmed that the rate of NSCLC developing following therapy for small cell lung cancer was significantly greater than expected from population data. A more recent study[54] estimated that 10% of 2-year survivors of small cell lung cancer will eventually have NSCLC.

Curative Intent Therapy for Recurrence and/or New Primary

Most recurrences of lung cancer are found outside the thorax.[33–37,52,53] Effective treatment of isolated metastases may be possible (see section on "Special Treatment Issues"). However, locoregional intrathoracic recurrences are only infrequently treated with curative intent surgical therapy,[37,40,55] and more often are treated with radiation therapy.[56,57] Regardless of therapy, the available data indicate that survival with locoregional recurrence of lung cancer appears to be poor.[58]

Although curative intent surgical therapy may be possibly more feasible with metachronous lung tumors than with locoregional recurrences of the primary lung cancer,[47] patients with metachronous tumors often present with advanced stage disease or are unable to tolerate surgical resection due to pulmonary insufficiency.[43] Limited data suggest that, even controlling for stage of disease, survival following curative intent surgical resection of metachro-

nous lung tumors may not be as favorable as for the original lung cancer (Table 4). Despite limitations in the approach to curative intent therapy of metachronous lung cancers, 5-year survival rates of 25 to 53% (Table 4) have been reported when surgical resection is possible.

Intensity of the Surveillance Program

There may be differences in how recurrences and metachronous tumors are identified. Recurrences seem to be more often detected through assessment of symptoms. Pairolero et al[34] scheduled visits for their stage I NSCLC patients every 4 months for the first 2 years and then every 4 to 6 months thereafter following curative intent surgery. A history, physical examination, CXR, blood tests, urine analysis, and pooled sputum cytology were performed at each visit. Most recurrences were detected at scheduled visits (59%), but a substantial number of recurrences were detected at unscheduled visits. Most patients with recurrences were symptomatic (53%), and symptom assessment was the most sensitive method for detecting recurrences. The blood tests, urine analysis, physical examination, and sputum cytology added little to detecting recurrences. Others have reported similar findings. Chiu and colleagues[59] followed up 38 patients following curative intent surgical resection for NSCLC with a history, physical examination, sputum cytology, CXR, and CT at 3-month intervals for 2 years and then at 6-month intervals for the next 3 years. Of the 14 patients who had recurrences, 7 patients (50%) presented with symptoms. Ichinose[60] described a similarly intensive surveillance program and also reported that most recurrences were recognized by symptoms; neither CT nor standard blood tests provided appreciable additional benefit in identifying recurrences.

In contrast, some case series[61–63] have reported that 68 to 100% of patients with metachronous lung cancers were asymptomatic and had the new primary lung cancer detected by radiographic methods. Lamont et al[58] described a retrospective chart review of 124 patients following curative intent surgical resection of NSCLC. They had all been entered into a regular surveillance program, including a history, physical examination, and CXR at 4- to 6-month intervals and an annual CT. Of the 124 patients, metachronous lung cancers developed in 19 patients (15.3%; 2.1%/yr), and all 19 patients were asymptomatic at the time. Eleven of the 19 metachronous tumors were first detected by CT; 16 of the 19 patients had stage IA disease, and 14 patients underwent curative intent reoperation. Nine of 14 patients were alive without evidence of recurrent disease at a median of 20 months. These authors[58] recommended annual CT for detecting metachronous tumors because disease can be identified early and resected, although the study was not designed to show a survival advantage for this group.

Other studies have provided an expanded view of the methods used for detecting recurrences and/or metachronous tumors by considering the costs involved in a surveillance program. Walsh et al[64] retrospectively evaluated the course of 358 patients following curative intent surgical resection for NSCLC. There were 135 recurrences, and most (76%) were recognized through symptoms. Although the asymptomatic patients had a longer survival time following detection of the recurrence, the authors[64] believed that this reflected lead-time bias and not a

Table 4—*Survival After Surgical Resection for Metachronous Lung Cancers*

Source	Patients With Metachronous Tumors, No.	Patients Undergoing Surgical Resection, No. (%)	Patients With Stage I Disease, No. (%)	Five-Year Survival After Surgical Resection of Metachronous Cancer, % (Five-Year Survival After Surgical Resection of Primary Lung Cancer, %)
Rosengart et al[47]	78	54 (69)	60 (77)	23 (70)
Watanabe et al[55]	8	8 (100)	6 (75)	53*
Wu et al[103]	20	20 (100)	Notstated	42*
Van Bodegom et al[104]	89	45 (51)	35 (39)	Notstated
Deschamps et al[105]	44	44 (100)	34 (77)	34 (55)
Westermann et al[106]	8	8 (100)	7 (88)	Notstated
Antakli et al[61]	39	21 (54)	Notstated	23*
Adebonojo et al[62]	37	36 (97)	29 (78)	37*
Asaph et al[63]	37	37 (100)	25 (68)	33*
Van Rens et al[107]	127	127 (100)	90 (71)	26 (70)
Battafarano et al[108]	69	69 (100)	50 (73)	33 (61)

*Five-year survival comparative data following surgical resection of primary lung cancer not provided.

true survival benefit. Similar percentages of symptomatic (29%) and asymptomatic (30%) patients could be treated with curative intent. Seven metachronous lung cancers were recognized in this study, but information on therapy and survival for these patients was not provided. The authors[64] concluded that intensive surveillance was not cost-effective and suggested a reduced surveillance approach consisting of a history, physical examination, and CXR every 6 months for the first year following curative intent surgery and then annually. Egermann and colleagues[65] reached similar conclusions from their study of 563 patients who were cancer-free at 3 months following curative intent lobectomy for NSCLC. A history, physical examination, and CXR were performed at 3-month intervals for 2 years, and then at 6-month intervals for up to 5 years and then annually. Only 4.1% of the 361 patients had a potentially resectable lung cancer identified during follow-up. In 21 patients, metachronous tumors were detected and resected with curative intent. Survival analysis indicated a maximum survival benefit of 9 months; based on these data and estimated healthcare costs in Switzerland, a calculated cost for the surveillance plan was $56,000 (US dollars) per life-year gained. The authors believed that this cost was too high to justify this intensive follow-up and recommended follow-up at 6-month intervals. A decision-analysis model approach to estimating the cost-effectiveness of chest CT in following patients after resection of stage 1A NSCLC arrived at a similar theoretical cost ($47,676 per quality-adjusted life-year gained).[66] However, this analysis suggested that use of chest CT in surveillance might be cost-effective in patients < 65 years old; in clinical practices where the cost of chest CT was < $700, the annual incidence of second primary lung cancers was at least 1.6% per patient, and the false-positive rate of surveillance was < 14%.[66]

Virgo and colleagues[67] compared two groups retrospectively following surgery for NSCLC. One group of 120 patients had intensive surveillance, consisting of at least four visits with serum chemistries and CXR per year, and annual bronchoscopy and/or sputum cytology with CT. The other group of 62 patients had less intensive surveillance, with on average only two visits with serum chemistries and CXR per year. No differences were found between the groups in either time to detection of recurrences or metachronous tumors or survival time. They agreed that intensive surveillance was not cost-effective and supported the surveillance schedule suggested by Walsh et al.[64] Two other retrospective analyses of intensive surveillance methods provided similar results. Younes and colleagues[68] found that intensive surveillance yielded no survival advantage and was more expensive than a symptom-based approach, although more patients in the symptom-based group had disease identified through emergency room visits. Gilbert and coworkers[69] showed that more recurrences were found by family physicians based on symptomatic presentation than were identified through regularly scheduled surveillance visits to the surgical clinic. These investigators[69] also found that the costs of identifying recurrences would be much lower using family physicians than intensive surveillance through the surgical clinic. Reviews[70,71] of this topic have endorsed the concept of less intense surveillance because "more intensive diagnostic testing has yet to demonstrate survival and quality of life benefits."[70]

The concept of less intensive surveillance has been challenged by work by Westeel et al,[72] who instituted a very intensive surveillance program in 192 patients surviving 30 days after complete surgical resection for NSCLC. Visits were scheduled every 3 months for 3 years, with history, physical examination, and CXRs. Bronchoscopy and CT were performed at 6-month intervals. From the fourth year after surgery, visits with CXRs were at 6-month intervals, and CT and bronchoscopy were performed annually. At year 8, surveillance was reduced to a visit and CXR annually. They claimed good compliance with this surveillance regimen in a subset of the entire group. Of 136 patients with recurrent cancers, 35 cases (25.7%) were asymptomatic and detected by diagnostic procedures. Of these, 15 patients (11% of recurrences) had intrathoracic recurrences that could be treated with curative intent; these were diagnosed by CXR (n = 5), bronchoscopy (n = 5), or CT (n = 5). Survival after recurrence for the 36 patients with asymptomatic recurrences was significantly better than for the 100 patients with symptomatic recurrences. In their economic analysis, Westeel et al[72] suggested that this very intensive surveillance regimen provided an acceptable cost per additional year of life gained. However, the improved survival, as measured after time of recurrence rather than after time of resection, in the asymptomatic patients may have reflected lead-time bias, and the proposed costs for procedures used in the surveillance strategy were relatively low.

Reconciling the conflicting findings from these various studies in order to provide clinical guidance is difficult. To begin, a clinically intuitive but often not stated principle is that patients who have a poor performance status or inadequate pulmonary function are not candidates for curative resection of either recurrent or metachronous lung cancer. Consequently, such patients are not candidates for intensive and aggressive surveillance programs designed to detect asymptomatic tumors. Instead, they should

be educated to seek early attention and should have ready access to their providers for follow-up of new symptoms that might herald recurrent cancer. For patients with adequate performance status and lung function, the panel recognizes that periodic patient encounters following curative intent therapy for lung cancer are essential and strongly feels that imaging studies of the chest should be included in these visits. CT is accepted as more sensitive for detecting pulmonary nodules than CXR and has been shown to be more accurate for evaluating lung cancer response during chemotherapy.[73] Small series[59,74,75] have shown that CT can detect changes consistent with recurrence earlier than CXR. CT is also being widely studied as a method for early detection of lung cancer (see "Screening for Lung Cancer" section). Unfortunately, the performance characteristics of CT (*ie*, sensitivity and specificity) for distinguishing nonspecific posttreatment changes related to surgery, radiation therapy, and/or chemotherapy from a recurrence and/or metachronous lung cancer have not been defined. Many studies[58] report a high incidence of nodules in groups followed up with chest CT, and the appropriate protocols for differentiating benign from malignant nodules without excess morbidity and cost from diagnostic procedures have yet to be defined. Consequently, the panel was evenly divided between recommending CXR and CT as the imaging procedure of choice.

Recommendation

2. In lung cancer patients treated with curative intent therapy, and those having adequate performance and pulmonary function, surveillance with a history, physical examination, and imaging study (either CXR or CT) is recommended every 6 months for 2 years and then annually. All patients should be counseled on symptom recognition and be advised to contact their physician if worrisome symptoms are recognized. Grade of recommendation, 1C

Physician Factors Influencing Current Surveillance Methods

Numerous reports have evaluated individual factors that might influence the surveillance methods used by thoracic surgeons. These studies[76] showed that many thoracic surgeons do perform regular surveillance for detecting recurrences and/or metachronous lung cancers following curative intent surgical therapy. The most commonly used methods were the history, physical examination, CXR, CBC count, and serum chemistries. Infrequently used surveillance methods were CT, bronchoscopy, sputum cytology, bone scan, and head CT. There was wide variation in the frequency at which these methods were used. This wide variation was probably due to the common belief that the clinical benefits of a surveillance program, particularly in terms of improving survival, had not been demonstrated. Interestingly, the age of the surgeon, the geographic region of practice, and the stage of the original lung cancer did not seem to influence the surveillance methods used by individual thoracic surgeons.[77–79] Motivating factors for continued surveillance seemed to be pleasing the patient, avoiding malpractice litigation, and potentially improving the patient's quality of life.[80] A more important issue, not specifically addressed in the surveys, was articulated by Shields[81]: "The least desirable course of action (in regard to care of the lung cancer patient following curative intent surgical therapy) is to pass the patient from one team member to another without continued surveillance by the primary responsible physician."

Recommendation

3. Ideally, surveillance for recognition of a recurrence of the original lung cancer and/or development of a metachronous tumor should be coordinated through a multidisciplinary team approach. If possible, the physician who diagnosed the primary lung cancer and initiated the curative intent therapy should remain as the health-care provider overseeing the surveillance process. Grade of recommendation, 2C

Alternative Surveillance Techniques

There is considerable interest in developing noninvasive, easily performed, safe and accurate techniques for detecting recurrences and/or metachronous tumors at the earliest possible time. Positron emission tomography (PET) scanning is an established modality for identifying malignant pulmonary nodules, mediastinal nodal involvement in confirmed cases of lung cancer, and extrathoracic metastases (see sections on "Solitary Pulmonary Nodule" and "Noninvasive Staging"). As a metabolic imaging technique, PET may be able to distinguish recurrent cancer from the parenchymal scarring, distortion of bronchovascular anatomy, pleural thickening, and mediastinal fibrosis commonly seen on conventional imaging after initial treatment.[82] Pooled data from studies to date indicate that PET has 96% sensitivity and 84% specificity for detecting recurrent lung cancer after treatment with surgery, chemotherapy, or radiotherapy.[82–87] The accuracy of PET has been dependent on the standardized uptake value used to define a positive test result, the delay between initial treatment and the PET scan, and the size of recur-

rent lesions and prevalence of bronchoalveolar cell carcinoma.[84,85,87,88] Of note, the specificity of PET scan after definitive treatment is lower than at initial staging due to increased uptake on PET scan from inflammatory changes related to tumor necrosis and radiation pneumonitis.[82] In addition, uptake on PET scans has been reported in the pleura of the shielded, nonirradiated lung even in the absence of overt radiation pneumonitis.[89] It has been recommended that PET scans for evaluating recurrent disease not be performed after curative intent therapy for at least 3 to 6 months to minimize the possibility of false-positive findings, and that suspicious lesions on a surveillance PET scan be confirmed by CT imaging and biopsy.[82,90] Importantly, there are no data showing that incorporating PET scanning into a surveillance program improves either survival or quality of life following curative intent therapy for NSCLC.

Another approach to early identification of recurrences of lung cancer is based on measuring serum levels of tumor markers. Ichinose[60] has recommended using serum carcinoembryonic antigen levels as a marker of tumor recurrence. Others[91,92] have also shown that elevated carcinoembryonic antigen levels following curative intent surgery for NSCLC may suggest recurrence. Other serum markers potentially useful for detecting tumor recurrence are levels of cytokeratin-19 fragments,[93] serum amyloid A and macrophage migration inhibitory factor,[94] and levels of pro–gastrin-releasing peptide in small cell lung cancer.[95] Further studies will be needed to confirm the performance characteristics of tumor markers for identifying tumor recurrence.

Pilot studies[96,97] have been performed using fluorescence bronchoscopy to detect metachronous tumors after curative intent surgical resection of NSCLC. In a group of 73 patients who underwent fluorescence bronchoscopy at a median of 13 months following surgical resection, one invasive carcinoma and three cases of intraepithelial neoplasia were identified. The carcinoma was identified on routine white-light bronchoscopy, but fluorescence bronchoscopy was useful in identifying two of the three cases of intraepithelial neoplasia.[96] In a smaller study[97] of 25 patients studied on average about 20 months after curative intent surgery, fluorescence bronchoscopy was again found to be more sensitive that routine white-light bronchoscopy in detecting intraepithelial neoplasia. The impact of early detection of intraepithelial neoplasia on survival should be confirmed in larger studies before fluorescence bronchoscopy should be incorporated into surveillance programs.

Recommendation

4. In lung cancer patients following curative intent therapy, use of blood tests, PET scanning, sputum cytology, tumor markers, and fluorescence bronchoscopy is not currently recommended for surveillance. Grade of recommendation, 2C

Smoking Cessation

Smoking is common in patients with lung cancer. Gritz and colleagues[98] studied smoking behavior in 840 adults with stage I NSCLC who had participated in clinical trials. At the time of diagnosis, 60% of the patients were smokers. By 2 years after diagnosis, 40% of these smokers had quit smoking. Smoking cessation at the time of diagnosis of lung cancer may reduce the rate of development of metachronous tumors. Richardson et al[99] found that the relative risk of a second lung cancer developing following curative intent therapy of small cell lung cancer was lower for those who stopped smoking. Tucker and coworkers[100] found that continuing smoking increased the risk of metachronous lung cancers in small cell lung cancer survivors. Because smoking cessation remains a challenge for such patients, they should be offered intensive tobacco cessation programs, including counseling, behavioral therapy, the use of sustained-release bupropion and nicotine replacement, and telephone follow-up, which significantly increase successful abstinence.[101,102]

Recommendation

5. Lung cancer patients who smoke should be strongly encouraged to stop smoking, and offered pharmacotherapeutic and behavioral therapy, including follow-up. Grade of recommendation, 1A

Summary

Following curative intent therapy of lung cancer, patients should be followed up for at least 3 to 6 months by the appropriate specialist for potential complications. In addition to this follow-up, recurrence of the original lung cancer and/or development of a second primary lung cancer should be expected possibilities. Most recurrences of the original lung cancer will occur within 4 years of curative intent therapy, but occurrences may occur $\geq$ 5 years after surgery. Following curative intent therapy of lung cancer, the risk of a second primary, or metachro-

nous, lung cancer developing may be 1 to 2% per patient per year lifelong. The risk for metachronous lung cancer may be even higher when the original primary is either roentgenographically occult, central, treated by sleeve resection only, or a small cell carcinoma.

Curative intent therapy is less likely to be possible with locoregional recurrences of the original lung cancer than with metachronous tumors. Although survival is not as good with treatment of metachronous tumors as for the original primary, reasonable 5-year survival rates should be expected with surgical resection of metachronous lung cancers.

Benefits in terms of survival advantages or improvements in quality of life have not been demonstrated with intensive surveillance programs compared with either a symptom-based approach or a less intensive regimen. In addition, the intensive surveillance programs seem more expensive. A clinically reasonable and cost-effective surveillance approach would include a history, physical examination, and imaging study (either CXR or CT) every 6 months for 2 years and then annually, assuming no suspicious findings were seen. In addition, patients would be counseled on symptom recognition and be advised to contact the appropriate physician on symptom recognition. Further studies are needed to determine whether very intensive surveillance programs might be warranted in selected subsets of lung cancer patients: patients with roentgenographically occult primary lung cancers, and patients surviving >2 years with small cell lung cancer and a complete response to original therapy, who have a very high expected rate of metachronous lung cancer.

Ideally, surveillance programs for recognition of a recurrence of the original lung cancer and/or development of a metachronous tumor following curative intent therapy should be coordinated through a multidisciplinary team approach. If possible, the physician who diagnosed the primary lung cancer and initiated the curative intent therapy should remain as the health-care provider overseeing the surveillance process. Patients with either a recurrence of their original cancer or a new primary lung cancer identified through the surveillance process should be reevaluated by the entire multidisciplinary team for potentially curative retreatment.

Although advanced imaging techniques, such as PET scanning, appear to be more sensitive than CXR for identifying recurrences and/or metachronous tumors, their value in improving either survival or quality of life following curative intent therapy for NSCLC is as of yet unproven. Incorporating PET scanning into a surveillance program should await the results of adequately designed and controlled, prospective trials. Similarly, serum levels of various tumor markers and fluorescence bronchoscopy should be demonstrated to be sensitive and specific predictors of tumor recurrence in adequately designed and controlled, prospective trials before being incorporated into surveillance programs.

Summary of Recommendations

1. In lung cancer patients treated with curative intent therapy, follow-up for complications related to the curative intent therapy should be managed by the appropriate specialist and should probably last at least 3 to 6 months. At that point, the patient should be reevaluated by the multidisciplinary tumor board for entry into an appropriate surveillance program for detecting recurrences and/or metachronous tumors. Grade of recommendation, 2C

2. In lung cancer patients treated with curative intent therapy, and those having adequate performance and pulmonary functions, surveillance with a history, physical examination and imaging study (either CXR or CT) is recommended every 6 months for 2 years and then annually. All patients should be counseled on symptom recognition and be advised to contact their physician if worrisome symptoms were recognized. Grade of recommendation, 1C

3. Ideally, surveillance for recognition of a recurrence of the original lung cancer and/or development of a metachronous tumor should be coordinated through a multidisciplinary team approach. If possible, the physician who diagnosed the primary lung cancer and initiated the curative intent therapy should remain as the health-care provider overseeing the surveillance process. Grade of recommendation, 2C

4. In lung cancer patients following curative intent therapy, use of blood tests, PET scanning, sputum cytology, tumor markers, and fluorescence bronchoscopy is not currently recommended for surveillance. Grade of recommendation, 2C

5. Lung cancer patients who smoke should be strongly encouraged to stop smoking, and offered pharmacotherapeutic and behavioral therapy, including follow-up. Grade of recommendation, 1A

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