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American Society of Clinical Oncology Treatment of Unresectable Non–Small-Cell Lung Cancer Guideline: Update 2003

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INTRODUCTION

The American Society of Clinical Oncology (ASCO) previously published evidence-based guidelines for the treatment of unresectable non–small-cell lung cancer (NSCLC) [1]. ASCO guidelines are updated periodically by the responsible Expert Panel (Appendix) [2].

For the 2003 update, a methodology similar to that applied in the original ASCO practice guidelines for treatment of unresectable NSCLC was used. Pertinent information published from 1996 through March 2003 was reviewed. The MEDLINE database (1996 through October 2002; National Library of Medicine, Bethesda, MD) was searched to identify relevant information from the published literature for this update. A series of searches was conducted using the medical subject headings, "carcinoma, non–small-cell lung," "diagnostic imaging," "neoplasm staging," "mediastinoscopy," "bone neoplasms," "brain neoplasms," "liver neoplasms," "adrenal gland neoplasms," "non–small-cell lung cancer," "radionuclide imaging," "bisphosphonates," "radiotherapy," "smoking," "chemoprevention," and the text words "chemotherapy," "bone scan," "PET," and "zoledronic acid." These terms were combined with the study design–related subject headings or text words "meta-analysis" and "randomized controlled trial." Search results were limited to human studies and English-language articles. The Cochrane Library was searched in October 2002 using the phrase "lung cancer." Directed searches based on the bibliographies of primary articles were also performed. Randomized trials published in the literature since October 2002, as well as data presented at ASCO Annual Meetings, were added to the evidence for these guidelines at the discretion of members of the Expert Panel.

The entire update committee met once to discuss strategy and assign responsibilities for the update. A writing committee subsequently met to further review the literature searches, collate different sections of the update, and refine the manuscript. A draft update was circulated to the full Expert Panel for review and approval. The final document was also reviewed by ASCO's Health Services Research Committee and the ASCO Board of Directors.

Each recommendation from the 1997 guideline is listed below, and is followed by an updated (2003) recommendation, if applicable. "No change" is indicated if a particular recommendation has not been revised. A summary of the evidence follows thereafter. In order to preserve the framework of the 1997 guideline, information and recommendations regarding major topics, such as fluorodeoxyglucose positron emission tomography (FDG-PET), have been divided and distributed to the appropriate section of the text.

ASCO considers adherence to these guidelines to be voluntary. The ultimate determination regarding their application is to be made by the physician in light of each

patient's individual circumstances. In addition, these guidelines describe evaluations and administration of therapies in clinical practice; they cannot be assumed to apply to interventions performed in the context of clinical trials, given that such clinical studies are designed to test innovative management strategies in a disease for which better treatment is sorely needed. However, by reviewing and synthesizing the latest literature, this practice guideline serves to identify questions for further research and the settings in which investigational therapy should be considered.

PRACTICE RECOMMENDATIONS

DIAGNOSTIC EVALUATION OF PATIENTS WITH ADVANCED LUNG CANCER

Staging Locoregional Disease

1997 Recommendations:

1. A chest x-ray and chest computed tomography (CT) scan with infusion of contrast material are recommended to stage locoregional disease. The CT scan should extend inferiorly to include the liver and adrenal glands.

2. For patients with clinically operable NSCLC, biopsy is recommended of mediastinal lymph nodes found on chest CT scan ≥ 1.0 cm in shortest transverse axis.

2003 Recommendations:

1. A chest x-ray and chest CT scan with infusion of contrast material are recommended to stage locoregional disease. The CT scan should extend inferiorly to include the liver and adrenal glands. *Assuming there is no evidence of distant metastatic disease on CT scan, FDG-PET scanning complements CT scan and is recommended.*

2. For patients with clinically operable NSCLC, biopsy is recommended of mediastinal lymph nodes found on chest CT scan to be greater than 1.0 cm in shortest transverse axis, *or positive on FDG-PET scanning. Negative FDG-PET scanning does not preclude biopsy of radiographically enlarged mediastinal lymph nodes.*

Evidence Summary

Despite advances in noninvasive methods of staging locoregional disease, including FDG-PET scan, mediastinoscopy remains important for the accurate detection of cancer in mediastinal lymph nodes. There have been numerous, nonrandomized studies of FDG-PET to evaluate mediastinal lymph nodes using surgery (mediastinoscopy and/or thoracotomy with mediastinal lymph node dissection) as the gold standard of comparison [3-32]. These studies vary in quality and design, but the predominant theme is that the accuracy of FDG-PET alone is consistently superior to CT scanning alone, with an excellent negative predictive value (NPV; reported range, 87% to 100%) [21-32]. Granted, the patient populations varied among studies; however, a common trend found the positive predictive value (PPV) of FDG-PET to be lower than the NPV, with PPVs less than 80% reported in several studies [23,26,27,32]. A prospective trial studied the impact of FDG-PET on the staging of 102 patients with NSCLC, and found that the sensitivity, specificity, NPV, and PPV of FDG-PET alone for detection of mediastinal metastases were 91%, 86%, 95%, and 74%, respectively, as compared with CT scan alone, which had a sensitivity of 75% and a specificity of 66% [32]. False-negative results from FDG-PET were seen in small tumors, or when FDG-PET was unable to distinguish the primary lesion from contiguous lymphadenopathy. False-positive results were often caused by the presence of benign inflammatory disease. These results have been corroborated by other studies [33,34].

Data published since the 1997 guideline confirm the inadequacy of CT scan alone in staging the mediastinum [35,36]. One retrospective study of 235 patients who underwent mediastinoscopy despite normal-sized mediastinal lymph nodes on CT (≤ 1.5 cm) found that malignant lymph nodes were still present in 20% of patients, with higher rates of mediastinal disease associated with larger primary tumors [37]. While the accuracy of FDG-PET is superior to CT scan, the anatomic information provided by CT scan is vital to treatment planning, and therefore both tests are recommended as part of initial staging for these patients. The metabolic information provided by FDG-PET is complementary to the anatomic information provided by CT scan, and allows for distinction between central tumors and adjacent lymph nodes, thereby improving overall accuracy compared with FDG-PET alone [24,25].There are insufficient data to mandate simultaneous, so-called fusion FDG-PET and CT scans, though machines which generate such images are currently in use [23,38].

When added to CT scan, the additional information provided by FDG-PET alters patient management. A randomized, prospective study in Europe assigned 188 patients to either conventional work-up (including contrast-enhanced CT scan), or conventional work-up plus FDG-PET. Those who had FDG-PET had a significant reduction in the number of unnecessary thoracotomies (relative reduction, 51%; 95% CI, 32% to 80%; $P = .003$) [39]. Other smaller, nonrandomized studies have found similar results [25,40,41]. FDG-PET may also prove useful in planning radiation treatment for patients with localized disease by minimizing treatment volumes, and/or identifying regional lymph nodes which might otherwise not be included in the treatment field [42-44]. A nonrandomized, prospective study of 153 patients with unresectable NSCLC who were candidates for radical radiation therapy after conventional staging found that FDG-PET detected unsuspected metastasis in 20%, strongly influenced choice of treatment strategy, frequently impacted radiotherapy planning, and was a powerful predictor of survival [45].

In reviewing the rapidly evolving data for locoregional staging of NSCLC, the Panel agrees that FDG-PET provides information which impacts on both staging and management. The Panel still regards mediastinoscopy as necessary for the detection of cancer in mediastinal lymph nodes when the results of the CT scan and FDG-PET do not corroborate each other. Similarly, the Panel was uncomfortable excluding mediastinoscopy in patients with positive CT and positive FDG-PET in the mediastinum, in the absence of a medical contraindication to the procedure or the availability of more easily accessible biopsy tissue that would define management. The reported PPVs of FDG-PET alone are lower than the NPVs, a concern not entirely addressed by the addition of information from CT, as benign inflammatory conditions have been reported even with bulky, FDG-PET–positive mediastinal disease [23,26,27,32]. Thus, the utility of FDG-PET is to corroborate a negative CT scan or to redirect a biopsy by identifying an otherwise undetected site of metastasis. If the results of FDG-PET will not affect management, such as when distant metastatic disease is demonstrated on CT scan, the Panel does not recommend obtaining FDG-PET.

Decision analyses demonstrate that FDG-PET may reduce the overall costs of medical care by identifying patients with falsely negative CT scans in the mediastinum, or otherwise undetected sites of metastases [46-48]. However, these studies concluded that the money saved by forgoing mediastinoscopy in FDG-PET–positive mediastinal lesions was not justified due to the unacceptably high number of false-positive results [46-48].

While many new techniques for mediastinal lymph node sampling are being studied, none have acquired sufficient evidence to supplant mediastinoscopy. Transbronchial needle biopsy of mediastinal nodes is currently being utilized at some centers [49]. This technique, along with endoscopic ultrasound-guided fine-needle aspiration, seem to be lower-risk procedures that can give cytologic evidence of malignant mediastinal disease in place of mediastinoscopy [50-55]. A retrospective review of 194 patients undergoing transbronchoscopic needle aspiration concluded that this technique could replace more invasive procedures, with overall sensitivity and diagnostic accuracy of 71% and 73%, respectively [56]. Transbronchial needle biopsy and mediastinoscopy are often complementary, in that some nodes cannot be sampled with mediastinoscopy (ie, subcarinal nodes). Cytologic evidence of benign cells is of limited diagnostic value. Still, early positive results using transbronchial biopsy or endoscopic ultrasonography-guided fine-needle aspiration can limit cost, or provide easier preoperative evaluation of contralateral mediastinal nodes [57-60].

Another potential tool to assist in locoregional staging is video-assisted thoracoscopic surgery (VATS). VATS has proven useful for assessment of the pleura and mediastinum, biopsy of peripheral lesions, and biopsy of suspicious contralateral lesions [61]. Prospective, nonrandomized studies have demonstrated the added benefit of VATS compared with CT staging alone in patients with histologically confirmed NSCLC and negative mediastinoscopy [62].

It should be noted that the International System for Staging of Lung Cancer has been revised since the last guideline was published, based on information from a clinical database of more than 5,000 patients [63]. Patients with T3N0 tumors are now categorized as stage IIB instead of stage III. This takes into account the slightly superior prognosis of these patients and the fact that many patients with invasion of the parietal pleura or chest wall due to pleural-based or superior sulcus tumors (T3), but with negative lymph nodes (N0), are often treated with surgery, sometimes combined with radiotherapy, and with results similar to those of patients with resected stage II disease [63-65]. Furthermore, the presence of satellite tumor(s) in the ipsilateral lung, in a distant, nonprimary tumor lobe, is now categorized as M1 disease, consistent with the poorer prognosis of this patient population [63].

Staging Distant Metastatic Disease

1997 Recommendations:

1. *Bone*: A bone scan should be performed only in patients who complain of (A) bone pain, or (B) chest pain, or who have (C) an elevated serum calcium level or (D) an elevated serum alkaline phosphatase level.

2. *Brain*: Head CT or magnetic resonance imaging (MRI) brain imaging with and without infusion of contrast material should be obtained only in patients who have signs or symptoms of CNS disease.

3. *Adrenal*: The finding of an isolated adrenal mass on ultrasonographic or CT scan requires biopsy to rule out metastatic disease if the patient is otherwise considered to be potentially resectable.

4. *Liver*: The finding of an isolated liver mass on ultrasonographic or CT scan requires biopsy to rule out metastatic disease if the patient is otherwise considered to be potentially respectable.

2003 Recommendations:

1. General: For the staging of distant metastatic disease, an FDG-PET scan is recommended when there is no evidence of distant metastatic disease on CT scan of the chest.

2. Bone: A bone scan is optional in patients who have evidence of bone metastases on FDG-PET scanning, unless there are suspicious symptoms in regions not imaged by FDG-PET. In patients with a surgically resectable primary lung lesion, bone lesions discovered on bone scan or FDG-PET require histologic confirmation, or corroboration by additional radiologic testing (x-ray, CT, and/or MRI).

3. Brain: Head CT or MRI brain imaging with and without infusion of contrast material is recommended in patients who have signs or symptoms of CNS disease, as well

as asymptomatic patients with stage III disease who are being considered for aggressive local therapy (chest surgery or radiation).

4. *Adrenal:* The finding of an isolated adrenal mass on ultrasonography, CT scan, *or FDG-PET scan* requires biopsy to rule out metastatic disease if the patient is otherwise considered to be potentially resectable.

5. *Liver:* The finding of an isolated liver mass on ultrasonography, CT scan, *or FDG-PET scan* requires biopsy to rule out metastatic disease if the patient is otherwise considered to be potentially resectable.

Evidence Summary

Despite the existence of practice guidelines, there is still great variability in practice patterns for extrathoracic imaging of patients with NSCLC. Available data indicate that asymptomatic patients frequently undergo bone scans, CT, or MRI of the brain, and abdominal CT scans, even though the rate of discovery of distant metastases is more than three times higher among patients with clinical or laboratory signs of disease before imaging [66]. The rising use of FDG-PET during the last 5 years has made contemporary staging of patients with metastatic disease even more diverse. FDG-PET scans performed to evaluate locoregional disease commonly extend through the pelvis, and thereby screen for distant sites of metastasis [67-70]. This changes the paradigm whereby symptoms, physical or laboratory findings, or perceived risk of distant metastasis prompt an active decision to evaluate for distant disease spread, as the additional information from FDG-PET scan is often unsolicited.

There is a lack of randomized, controlled studies to evaluate FDG-PET, and other radiologic techniques as well, in the staging of distant metastatic disease. However, similar to the case in staging locoregional disease, numerous nonrandomized, prospective and retrospective studies have demonstrated that FDG-PET seems to offer diagnostic advantages over conventional imaging in staging distant metastatic disease, and the more accurate staging has an impact on choice of therapy and outcome. In the previously mentioned, nonrandomized prospective study of 102 patients with resectable NSCLC, FDG-PET correctly identified metastases in extracranial sites in 11 patients in whom the usual methods of staging had found none. The sensitivity and specificity of FDG-PET for detecting distant metastases were 82% and 93%, respectively [32]. In a retrospective study of 157 patients selected for radical radiotherapy to the chest, those patients selected after staging with FDG-PET had significantly lower 1-year cancer mortality (17%) than those selected using conventional imaging (32%) [71]. Other nonrandomized, prospective and retrospective studies of FDG-PET have demonstrated its usefulness in differentiating benign versus malignant pulmonary nodules, as well as in distinguishing benign from malignant pleural effusions [72-75]. The utility of FDG-PET may vary depending on the site being evaluated, and the availability of other testing modalities.

Bone: A nonrandomized, prospective study comparing FDG-PET with bone scan in 53 patients with lung cancer found that PET was superior to bone scan in detecting bone metastases, producing no false-negatives, which is in contrast to six false-negatives produced by bone scan [76]. A nonrandomized, retrospective study of 110 consecutive patients who underwent both FDG-PET and bone scan found FDG-PET to have superior accuracy in detecting bone metastases (96% *v* 66%) suggesting that whole-body FDG-PET may be a useful substitute for bone scanning in detecting bone metastases [77]. It should be noted that standard FDG-PET scans often do not extend below the pelvis, thereby neglecting detection of bone metastases in the long bones of the lower extremities.

Brain: Because the metabolic tracer used in FDG-PET scanning accumulates in the brain and urinary tract, FDG-PET is not reliable for detection of metastases in these sites [15]. The 1997 guidelines recommend contrast-enhanced head CT or MRI only in patients with abnormal neurologic signs or symptoms. Nevertheless, brain imaging is commonly performed in asymptomatic patients, especially those being considered for aggressive local therapy such as surgery or radiation. Although early detection of brain metastases has never been shown to improve survival, it may avoid morbidity by allowing earlier treatment of the brain, or by precluding unnecessary chest surgery or radiation.

Asymptomatic brain metastases occur more frequently in patients with more advanced stages of disease, with rates as high as 30% at 2 years in stage II-III patients. Higher stage and nonsquamous histology have been identified as risk factors for brain metastases [78,79]. In asymptomatic patients, gadolinium-enhanced MRI of the brain seems to be superior to CT for the detection of occult brain metastases. A recent study randomized 332 patients with potentially operable NSCLC, but without neurological symptoms, to brain CT or MRI imaging in order to detect occult brain metastasis before lung surgery. MRI showed a trend toward a higher preoperative detection rate than CT ($P = .069$), with an overall detection rate of approximately 7% from pretreatment to 12 months after surgery. Patients with stage I or II disease had a detection rate of 4% (8 of 200), while for individuals with stage III disease, the rate was 11.4% (15 of 132). The mean maximal diameter of the brain metastases was significantly smaller in the MRI group [80]. Whether the improved detection rate of MRI translates into improved outcome remains unknown. Not all patients are able to tolerate MRI, and for these patients, contrast-enhanced CT scan is a reasonable substitute.

Adrenal: Biopsy remains the gold standard to evaluate abnormal adrenal lesions identified on CT. One retrospective study of 443 patients, in which 32 were found to have an abnormal adrenal mass on CT, concluded that CT-guided

biopsy was necessary in the evaluation of suspicious adrenal masses due to the poor positive predictive values of unenhanced CT and standard MRI [81]. FDG-PET may offer a noninvasive way of distinguishing benign from malignant adrenal masses observed on CT scan. Two small, nonrandomized studies, one of which was prospective, have demonstrated a 100% sensitivity, and an 80% to 90% specificity of FDG-PET in identifying adrenal metastases, using CT-guided biopsy or clinical follow-up as the gold standard [82,83]. Noncontrast CT scanning may also be used to evaluate adrenal masses, with benign adrenal lesions tending to be lower in density—10 Hounsfield units (HU) or less [84]. Chemical shift MRI (CSMRI), also known as in-phase and opposed-phase gradient echo imaging, has also been used to evaluate suspicious but equivocal adrenal lesions seen on CT scan, or found incidentally on FDG-PET scanning. A prospective study of 42 patients undergoing biopsy of suspicious adrenal lesions found CSMRI to be 96% sensitive for adrenal adenoma, and 100% specific [85]. A decision analysis model has been used to study the most cost-effective way to evaluate an adrenal mass in patients with NSCLC [86]. Sequences which moved straight to needle biopsy after only one negative radiologic test were not cost-effective in this analysis, with unenhanced CT, CSMRI, and CT-guided biopsy being the diagnostic options. FDG-PET was not included as a diagnostic option [86]. Further validation of such an approach is required before incorporation into practice is recommended.

Liver: Biopsy remains the gold standard to evaluate abnormal liver lesions identified on CT. Use of gadolinium–contrast enhancement and CSMRI is also being used to distinguish benign versus malignant liver lesions, and technological advancements may make MRI more reliable in this regard in the future [87-89].

TREATMENT

The Role of Chemotherapy

1997 Recommendations:

1. Outcome:

Unresectable stage III NSCLC. A. Chemotherapy in association with definitive thoracic irradiation is appropriate for selected patients with unresectable, locally advanced NSCLC.

Stage IV NSCLC. A. Chemotherapy is appropriate for selected patients with stage IV NSCLC.

2. Patient Selection:

Unresectable stage III NSCLC. A. In unresectable stage III disease, chemotherapy plus radiotherapy prolongs survival compared with radiation alone and is most appropriate for individuals with good performance status (Eastern Cooperative Oncology Group [ECOG]/Zubrod performance status 0 or 1, and possibly 2).

Stage IV NSCLC. A. In stage IV disease, chemotherapy prolongs survival and is most appropriate for individuals with good performance status (ECOG/Zubrod performance status 0 or 1, and possibly 2).

3. Selection of Drugs:

Chemotherapy given to NSCLC patients should be a platinum-based combination regimen.

4. Duration of Therapy:

Unresectable stage III NSCLC. A. In patients with unresectable stage III NSCLC who are candidates for combined chemotherapy and radiation, the duration of chemotherapy should be two to eight cycles.

B. In the absence of compelling data, the Panel consensus is that in patients with unresectable stage III NSCLC who are candidates for combined chemotherapy and radiation, the duration of chemotherapy should be no more than eight cycles.

Stage IV NSCLC. A. In the absence of compelling data, the Panel consensus is that chemotherapy should be administered for no more than eight cycles in patients with stage IV NSCLC.

5. Timing of Treatment:

Unresectable stage III NSCLC A. In patients with unresectable stage III disease, chemotherapy may best be started soon after the diagnosis of unresectable NSCLC has been made. Delaying chemotherapy until performance status worsens or weight loss develops may negate the survival benefits of treatment.

Stage IV NSCLC. A. In patients with stage IV disease, if chemotherapy is to be given, it should be initiated while the patient still has good performance status.

6. Second-Line Therapy:

There is no current evidence that either confirms or refutes that second-line chemotherapy improves survival in nonresponding or progressing patients with advanced NSCLC. Second-line treatment may be appropriate for good performance status patients for whom an investigational protocol is not available or desired, or for patients who respond to initial chemotherapy and then experience a long progression-free interval off treatment.

7. Role of Investigational Agents/Options:

Initial treatment with an investigational agent or regimen is appropriate for selected patients with stage IV NSCLC, provided that patients are crossed over to an active treatment regimen if they have not responded after two cycles of therapy.

8. Histology:

NSCLC histology is not an important prognostic factor in patients with advanced, unresectable disease. The use of newer, putative prognostic factors such as *RAS* mutations or *p53* mutations is investigational and should not be used in clinical decision-making.

2003 Recommendations:

1. Outcome:

Unresectable stage III NSCLC. A. No change.

Stage IV NSCLC. A. No change.

2. Patient Selection:

Unresectable stage III NSCLC. A. No change.

Stage IV NSCLC. A. No change.

3. Selection of Drugs:

Unresectable stage III NSCLC. A. No change.

Stage IV NSCLC. A. First-line chemotherapy given to patients with advanced NSCLC should be a two-drug combination regimen. Non–platinum-containing chemotherapy regimens may be used as alternatives to platinum-based regimens in the first line. For elderly patients or patients with ECOG/Zubrod performance status 2, available data support the use of single-agent chemotherapy.

4. Duration of Therapy:

Unresectable stage III NSCLC. A. In patients with unresectable stage III NSCLC, who are candidates for combined chemotherapy and radiation, the duration of chemotherapy should be *two to four cycles of initial, platinum-based chemotherapy*.

B. In the absence of compelling data, the Panel consensus is that in patients with unresectable stage III NSCLC who are candidates for combined chemotherapy and radiation, the duration of *initial platinum-based chemotherapy should be no more than four cycles.*

Stage IV NSCLC. A. In patients with stage IV NSCLC, first-line chemotherapy should be stopped at four cycles in patients who are not responding to treatment. The Panel consensus is that first-line chemotherapy should be administered for no more than six cycles in patients with stage IV NSCLC.

5. Timing of Treatment:

Unresectable stage III NSCLC. A. No change.

Stage IV NSCLC. A. No change.

6. Second-Line Therapy:

Docetaxel is recommended as second-line therapy for patients with locally advanced or metastatic NSCLC with adequate performance status who have progressed on first-line, platinum–based therapy. Gefitinib is recommended for the treatment of patients with locally advanced or metastatic non–small-cell lung cancer after failure of both platinum-based and docetaxel chemotherapies.

7. Role of Investigational Agents/Options:

No change.

8. Histology:

No change.

Evidence Summary

Combined-Modality Therapy for Stage III Disease (Without Malignant Pleural/Pericardial Effusion):

The benefit of adding chemotherapy to radiation therapy for stage III disease is well-established, and since 1997 has been corroborated by two additional prospective phase III trials [90-92]. The largest of the prospective trials was sponsored by the Radiation Therapy Oncology Group (RTOG), ECOG, and the Southwest Oncology Group (SWOG), and allocated 490 patients to receive 2 months of cisplatin + vinblastine chemotherapy followed by 60 Gy of radiation at 2 Gy per fraction; or one of two radiation-alone arms. Overall survival was statistically superior for the patients receiving chemotherapy and radiation versus the other two arms of the study (13.2 months *v* 12 months, *v* 11.4 months, respectively; $P = .04$) [91]. However, the survival benefit of combined modality treatment in this trial was substantially less than that seen in the original Cancer and Leukemia Group B (CALGB) trial [93]. Patterns of first failure showed less distant metastasis for patients who received chemotherapy compared with the radiotherapy-alone arms [94]. The results of a Cochrane review were also consistent with a survival benefit for the addition of chemotherapy in this setting [95].

Administration of chemotherapy concurrently with radiation therapy theoretically improves local control by sensitizing the tumor to radiation, while simultaneously treating systemic disease, albeit at the expense of greater local toxicity. Two large phase III studies suggest improvement in both local control and survival with concurrent chemoradiotherapy as compared with sequential chemotherapy followed by radiation for patients with stage III NSCLC. RTOG 94-10 randomized 611 patients to three arms: sequential cisplatin + vinblastine followed by thoracic radiation to a total dose of 60 Gy delivered in daily fractions; concurrent cisplatin + vinblastine with radiation to a total dose of 60 Gy delivered in daily fractions; or cisplatin + etoposide concurrent with radiation to a total dose of 69.6 Gy delivered in twice-a-day fractions. Although rates of nonhematologic toxicity were higher on the concurrent arms, median survival time trended toward superiority in the concomitant chemotherapy plus daily radiation arm compared with the sequential arm (17 months *v* 14.6 months; $P = .08$), while the concomitant chemotherapy plus twice-daily radiation arm demonstrated intermediate survival compared with the other study arms [96]. A phase III study from Japan randomized 320 patients to receive either concurrent or sequential chemoradiotherapy. The concurrent arm received cisplatin, vindesine, and mitomycin throughout 5 weeks, with concurrent radiation consisting of two, 28-Gy courses (2 Gy per fraction for 14 days, 5 days per week) separated by a 10-day rest period. The sequential arm received the same chemotherapy, but radiation was initiated after completing chemotherapy, and consisted of 56 Gy (2 Gy per fraction and 5 fractions per week

for a total of 28 fractions) [97]. The concurrent arm demonstrated statistically significant superiority in response rate (84% *v* 66%, $P = .0002$) and median survival time 16.5 *v* 13.3, $P = .040$), but suffered greater myelosuppression.

Other chemotherapy regimens have been tested with concomitant radiation, and proven safe in phase II testing, including carboplatin + paclitaxel, gemcitabine + cisplatin, cisplatin + paclitaxel, and cisplatin + vinorelbine [98-100].These chemoradiotherapy regimens await phase III testing. One source of debate is whether the addition of induction or consolidation chemotherapy adds anything to concomitant chemoradiotherapy, with numerous intergroup trials underway [100,101]. CALGB has completed a randomized phase II study of two cycles of induction chemotherapy followed by two additional cycles of the same drugs with concomitant radiotherapy. The three treatment arms included four cycles of cisplatin (80 mg/m^2) combined with either gemcitabine, paclitaxel, or vinorelbine. Radiotherapy was completed during the last two cycles to a total of 66 Gy. Response rates were similar, and median survival for all patients was 17 months with no clearly superior arm evident in this randomized phase II trial [102]. The CALGB is currently conducting a phase III trial comparing induction chemotherapy plus concomitant chemoradiotherapy versus concomitant chemoradiotherapy alone, using carboplatin + paclitaxel in both arms. One prospective, randomized trial compared sequential cisplatin + vinblastine chemotherapy followed by radiation, versus sequential cisplatin + vinblastine plus concomitant carboplatin and radiation in 283 patients with inoperable stage III NSCLC, and was unable to demonstrate benefit with the addition of concomitant carboplatin after cisplatin-based induction [103]. A randomized trial directly comparing concomitant chemoradiotherapy with radiotherapy alone has yet to be performed, and will probably not be pursued due to the superiority of concurrent chemoradiotherapy compared with historical data of single-modality therapy, and no worse than comparable results between concurrent and sequential chemoradiotherapy in randomized trials, the latter of which has been demonstrated to be superior to radiation alone.

The optimal duration of chemotherapy for patients with unresectable stage III NSCLC being treated with combined-modality therapy remains a matter of debate. The 1997 guideline recommended between two and eight cycles of chemotherapy based on the number of cycles utilized among cisplatin-based combined-modality studies included in the Non-Small Cell Lung Cancer Collaborative Group meta-analysis, and the lack of benefit seen in studies when chemotherapy was continued until progression of disease. No prospective, randomized trials have addressed this question since the 1997 guideline was published. Treatment protocols tested in recent years have used between two and four cycles of platinum-based chemotherapy combined with radiation, with results as detailed above. Trials which measure the additional benefit, if any, of induction or consolidation chemotherapy are currently underway. In the absence of compelling data, the Panel consensus was to change the recommendation for duration of initial chemotherapy to between two and four cycles of platinum-based therapy, with an upper limit of four cycles.

The role of surgery following induction chemotherapy or chemoradiotherapy for patients with initially unresectable cancer is being explored. In phase II testing, the use of concomitant chemoradiotherapy has led to improved resectability and overall survival compared with historical controls in patients with T3 to T4 NSCLC tumors of the superior sulcus [104]. Accumulated data from surgical series suggest that induction chemotherapy does not result in increased risk of anastomotic complications in bronchoplastic or angioplastic surgical procedures, and is unlikely to limit the type of surgery which can be performed [105]. Two prospective, randomized trials support the inclusion of induction chemotherapy for patients with stage IIIA disease. One trial randomized patients with N2 disease to three cycles of preoperative mitomycin, ifosfamide, and cisplatin chemotherapy versus surgery alone (n = 60) [106]. A second trial randomized similar patients to six cycles of perioperative cyclophosphamide, etoposide, and cisplatin (three cycles before and three cycles after surgery) (n = 60) [107,108]. Both trials documented statistically significant improvements in overall survival with the use of induction chemotherapy, versus surgery alone. Another randomized trial studied induction chemotherapy with mitomycin, ifosfamide, and cisplatin, versus no chemotherapy, in 355 patients with disease ranging from stage IB to IIIA. All patients with T3 or N2 disease at thoracotomy went on to receive adjuvant radiation. This trial failed to show a significant benefit of induction chemotherapy for the subgroup of patients with stage IIIA disease [109]. Ongoing trials will determine whether patients with locally advanced tumors are better served with induction chemoradiotherapy followed by surgical resection, or chemoradiotherapy alone [110].

Chemotherapy for Stage IV Disease (or IIIB With Pleural/Pericardial Effusion):

Given the large number of prospective, randomized controlled trials of chemotherapy for metastatic NSCLC that have been published in the last 5 years, there is much better evidence to support changes to the guidelines for treatment than there are for diagnostics. Numerous phase III trials have confirmed the superiority of systemic chemotherapy over best supportive care for patients with metastatic NSCLC who have good performance status (ECOG/Zubrod 0 to 1), and a Cochrane review also demonstrated a survival benefit [95,111-114]. Similarly, phase III trials have been used to test the best chemotherapy drugs, combinations of drugs, and schedules.

The prior recommendation to use a platinum-based combination for the treatment of patients with metastatic NSCLC was based on the historical single-agent activity of cisplatin against NSCLC, as well as the results of meta-analyses suggesting a unique benefit of platinum-based chemotherapy over other DNA alkylating agents [115]. Several new chemotherapy agents, including paclitaxel, docetaxel, gemcitabine, vinorelbine, and irinotecan, have demonstrated single-agent activity, with arguably less toxicity than cisplatin. These drugs have been incorporated into combination regimens with carboplatin and cisplatin, and studied in several randomized phase III trials.

Much of the data suggest that the newer regimens provide higher response rates and longer survival times than single agent cisplatin, or first-generation cisplatin-based regimens [116-126]. No particular two-drug, platinum-based combination has been identified as superior in terms of efficacy, nor have three-drug combinations proven superior despite increased toxicity [127-131]. A recent phase III trial compared four platinum-based doublets in patients with metastatic NSCLC—cisplatin + paclitaxel, carboplatin + paclitaxel, cisplatin + docetaxel, and cisplatin + gemcitabine—and documented statistically equivalent response rates ranging from 17% to 22% with median survivals of approximately 8 months [132]. Cost analyses of chemotherapy continue to support the cost-effectiveness of combination and single-agent chemotherapy for patients with metastatic disease compared with best supportive care [133-135]. Given the relative equivalence in efficacy and toxicity of the platinum-based doublets, economic analyses have been performed in an attempt to identify the most cost-effective chemotherapy regimens [136,137].

Data from prospective, randomized phase III trials have been published in abstract form demonstrating that combining one of the new chemotherapy agents (paclitaxel or gemcitabine) with carboplatin is superior in terms of response rate and survival to using the new chemotherapy agent alone [138,139]. One small phase III trial (n = 169) showed equivalence in response rate and survival between single-agent gemcitabine and cisplatin + vindesine combination, with lower toxicity in the single-agent arm [140]. While data on single-agent chemotherapy versus platinum doublets continues to evolve, there are phase III trials which suggest that non–platinum-containing doublets may be equivalent to platinum doublets in terms of efficacy. In the last three years, there have been numerous phase III trials of nonplatinum combinations. A randomized trial with 441 patients compared the nonplatinum combination of docetaxel + gemcitabine with docetaxel + cisplatin at standard doses [141]. Response rates in the two treatment arms were similar (35% *v* 33%, respectively), with no differences seen in response duration, time to progression, or survival (median survival times, 10 *v* 9.5 months, respectively). However, patients treated with the docetaxel + gemcitabine regimen had less nonhematologic toxicity, such as nausea, vomiting, and diarrhea. Similarly, a phase III comparison (n = 509) of gemcitabine + paclitaxel versus carboplatin + paclitaxel showed no difference in survival (10.4 *v* 9.8 months), with comparable toxicity [142].

Still, the nonplatinum combinations carry higher toxicity than single-agent chemotherapy, and may not be appropriate for patients with poor performance status (ECOG/Zubrod 2). Single-agent vinorelbine, docetaxel, and paclitaxel have each demonstrated excellent tolerability and improved survival in phase III comparisons versus best supportive care. Docetaxel as a single agent resulted in superior survival versus best supportive care (two-year survival of 12% *v* 0%), as well as a quality of life benefit [143]. A randomized, phase III trial compared single-agent paclitaxel versus best supportive care and showed significant improvement in survival (6.8 *v* 4.8 months) and functional activity score, with good tolerance [144]. Therefore, one could argue that single-agent chemotherapy would be sufficient for patients with performance status (PS) 2.

There have been no randomized trials which compare combination chemotherapy versus single-agent chemotherapy in patients with PS 2. Subgroup analyses from some randomized trials suggest that patients with PS 2 have a significantly higher rate of toxicity, and lower rate of response and survival than patients with PS 0 to 1 [132,145-147]. In contrast, a subgroup analysis from a recent randomized trial has shown that PS 2 patients have significantly superior survival when they receive combination carboplatin + paclitaxel compared with single agent paclitaxel (4.7 *v* 2.4 months, respectively, $P < .05$) [138].

It is important to distinguish performance status from age. Age is not an independent predictor of survival or response in randomized controlled trials of chemotherapy for advanced NSCLC. Subgroup analyses from randomized trials have documented the benefits of combination chemotherapy in all patients with good performance status, regardless of their age [148,149]. However, older patients have higher rates of comorbid illness and may be more susceptible to the toxic side effects of chemotherapy. Given that the median age of patients with advanced NSCLC is 68 and rising, some clinical trials have decided to focus on the elderly population by limiting enrollment to patients who are 70 years of age or older. In an elderly population, single agent vinorelbine has been shown to be well-tolerated, and improves survival versus best supportive care in phase III testing [150,151]. Subgroup analysis of elderly patients (70 years of age or older) in one randomized trial suggested superiority of combination carboplatin + paclitaxel over single-agent paclitaxel (8.0 *v* 5.8 months, respectively) but this result did not reach statistical significance [138]. Early randomized data also suggested the superiority of combination chemotherapy (vinorelbine + gemcitabine) over single-agent vinorelbine in terms of response rate, survival,

and quality of life in patients over the age of 70 [152]. However, a larger, 3-arm trial with nearly 700 patients over the age of 70 —identified after the completion of our original literature search — concluded that the combination of vinorelbine + gemcitabine did not provide a survival benefit over single-agent vinorelbine, or single-agent gemcitabine, and that the two-drug combination was more toxic than single-agent therapy in this elderly population [153]. Approximately 20% of the elderly patients enrolled in this study were PS 2, and subgroup analysis based on PS in this elderly population was not reported [153].

Based on the available evidence, the Expert Panel recommends combination chemotherapy for patients with good performance status (ECOG/Zubrod 0 to 1). Nonplatinum containing combinations may be used as alternatives to platinum-based combination regimens in the first line. For elderly patients, or patients with PS 2, available data support the use of single-agent chemotherapy.

The optimal duration of chemotherapy remains a matter of debate. Prolonged chemotherapy can lead to cumulative toxicity, with no proven advantage in efficacy. In a recent phase III study, Socinski et al randomized 230 patients to receive carboplatin + paclitaxel delivered every 3 weeks for 4 cycles only, versus identical doses delivered every 3 weeks until progression [154]. At progression, all patients received weekly paclitaxel. No significant differences in response or survival were detected between the two treatment arms; however, continuous, uninterrupted therapy was not possible in the majority of patients, and an increase in grade 3 to 4 neuropathy accompanied prolonged therapy. Another phase III trial from the United Kingdom randomized 308 patients to receive either 3 or 6 cycles of a combination of mitomycin, vinblastine, and cisplatin [155]. There were slight differences in response rate (31% *v* 38%, respectively), and survival (6 months *v* 7 months, respectively) between the 3- and 6-cycle groups, which did not reach statistical significance.

Both of these trials demonstrated that the majority of patients failed to have a major response, or became intolerant of chemotherapy, by the third or fourth cycle. Survival and response rates were similar between short duration and long duration groups, and additional chemotherapy resulted in cumulative toxicity. Neither trial addressed the more specific question of whether patients who are responding to chemotherapy, and tolerating chemotherapy well, benefit from treatment beyond three to four cycles. Also, the potential benefit of switching stable or responding patients to an alternative chemotherapy, perhaps with a different side effect profile to avoid cumulative toxicity after 3 to 4 cycles, has not been well-studied. The available data suggest that, for most patients, the benefits accrued beyond three to four cycles of chemotherapy will be modest at best, and may be offset by added toxicity in this palliative setting. As such, stopping chemotherapy after three to four cycles in patients who are not responding to chemotherapy is quite defensible. Furthermore, in light of new evidence that supports the use of second-line chemotherapy at the time of recurrence, the Panel consensus was to change the prior recommendation, and advocate no more than six cycles of initial chemotherapy, even in patients who have responded to treatment.

Second-Line Chemotherapy for Stage IV (or IIIB With Pleural/Pericardial Effusion)

Recent trials now indicate that several new chemotherapy agents may be useful for the treatment of NSCLC refractory to, or recurrent following platinum-based chemotherapy. Promising results of phase II trials of docetaxel in previously treated patients prompted two phase III trials which have established docetaxel as the first chemotherapeutic agent with proven benefit for patients with recurrent, or refractory disease following initial chemotherapy. The TAX 320 trial randomized 373 patients with disease progression following platinum chemotherapy to receive either docetaxel (arm 1 = 100 mg/m^2, arm 2 = 75 mg/m^2), versus a control arm treated with vinorelbine or ifosfamide (V/I) at standard doses (arm 3) [156]. Patients were stratified by performance status and best response to previous platinum therapy. Patients who had received prior paclitaxel therapy were included in this trial, and composed approximately 40% of patients in each arm. Response rates to docetaxel were low (11% on arm 1 and 7% on arm 2) yet significantly higher than the response rate with V/I, which was only 1%. Overall survival was not significantly different among the groups (approximately 6 months). Only when survival analysis was censored at the time of administration of additional poststudy chemotherapy, a posthoc analysis with its related limitations, were significant differences in 1-year survival rates detected favoring docetaxel-treated patients (32% *v* 10%, $P < .01$). Overall, patients treated on either docetaxel arm enjoyed a quality of life benefit as measured by the Lung Cancer Symptom Scale (LCSS) questionnaire [157].

In another phase III trial, Shepherd et al randomized 204 patients, similarly stratified by performance status and best response to prior platinum–based chemotherapy, to receive either salvage docetaxel (100 mg/m^2) or best supportive care [158]. Patients who had received prior paclitaxel therapy were excluded. An interim analysis identified a significant increase in toxicity in the treatment arm, requiring dose reduction to 75 mg/m^2 in the second half of the trial. At final analysis, the objective response rate of patients with measurable disease was 7%, similar to that observed in the TAX 320 trial. Treated patients experienced a significant improvement in median survival (7 *v* 5 months), as well as quality of life measured by the LCSS questionnaire [159]. The Cochrane review on this topic only included the Shepherd et al study, excluding the Fossella et al trial since no comparison to best supportive care or placebo alone was included [160]. The Cochrane group concluded that second-line docetaxel could

be offered to good performance status patients who should be appraised of the modest survival benefit and potential toxicities, but that there were no data to support this approach in patients with poor performance status.

Although the response rate to docetaxel in this patient population is low, the expert panel felt the observed benefit in 1-year survival and apparent quality-of-life improvement for treated patients justify its consideration for platinum-refractory disease. The phase III dose was 75 mg/m^2, infused over 1 hour, every 3 weeks. Phase II trials of docetaxel in this setting using weekly schedules have shown similar results [161].

Phase II data for gemcitabine, paclitaxel, and irinotecan as second-line agents in the treatment of advanced NSCLC have not merited phase III testing [162-165]. Similarly, combinations of gemcitabine + docetaxel, or gemcitabine + vinorelbine, have been studied in phase II with promising results, but have yet to be compared, either with each other, or with single-agent docetaxel in phase III randomized trials [166-171].

Gefitinib (ZD1839), an orally active inhibitor of the epidermal growth factor receptor tyrosine kinase, has been the subject of two phase II studies in previously treated patients, one conducted in the United States, and a second in Japan/Europe [172,173]. In the US trial, patients were entered after demonstrating intolerance or disease progression following at least two prior chemotherapy regimens, including both a platinum agent, and docetaxel. One hundred forty-two patients received gefinitib at a dose of either 250 mg daily, or 500 mg daily. The overall response rate was approximately 10%, and the 500 mg dose did not appear to yield a higher response rate. The most common side effects were mild to moderate diarrhea and acneiform skin rash, worse in the 500-mg arm of the trial. The study in Japan/Europe was of similar size (N = 210) and design (randomization to either a 250-mg or 500-mg oral daily dose), but differed slightly in that a little more than half of the patients enrolled had received only one prior platinum-containing chemotherapy. The overall response rate was approximately 19% in this study, with no differences noted between low-dose/high-dose arms, or second-/third-line patients. Similar to the US study, the 250-mg dose was better tolerated in this study. Cases of interstitial lung disease have been reported in approximately 1% of patients receiving gefitinib, which is consistent with the overall rate of pneumonitis in patients with advanced NSCLC on supportive care only.

On May 5, 2003, based on the results of the phase II trial in the United States, the US Food and Drug Administration approved single-agent gefitinib (250-mg oral tablet, daily) for the treatment of patients with locally advanced or metastatic NSCLC after failure of both platinum-based and docetaxel chemotherapies. The approval was dependent on assurances by the drug's manufacturer to conduct randomized, controlled clinical trials of gefitinib, with end points to demonstrate clinical benefit, such as improved survival or symptom improvement. The package insert for gefitinib includes a warning to discontinue therapy in the event of acute onset or worsening of pulmonary symptoms, including dyspnea or cough. Preliminary results of randomized trials combining gefitinib with standard chemotherapy in previously untreated patients have not demonstrated benefit, and the role of gefitinib in combination with other chemotherapy drugs remains investigational [174,175].

While the phase II data for gefitinib are promising, it is clear that gefitinib is similar to other chemotherapies used as salvage therapy, namely it benefits only the minority of patients. While the US Food and Drug Administration indication allows gefitinib to be used for any patient with NSCLC intolerant or resistant to both platinum-based and docetaxel chemotherapy, preliminary data suggest that the population best suited for treatment with gefitinib remains to be defined. In the phase II trials of gefitinib, the majority of responders were women with adenocarcinoma [172,173]. There are currently little or no data to support the use of gefitinib in, for example, male patients with squamous cell histology.

Prognostic Factors

The main prognostic factors in patients with lung cancer remain tumor stage and performance status. Degree of weight loss, sex (women fare better), serum concentration of lactate dehydrogenase, and the presence of bone and liver metastases are also of importance [176,177]. Other factors are being explored to complement these factors in predicting response to therapy and assessing prognosis. FDG-PET scanning before or after definitive therapy is currently under investigation [178-180]. Molecular markers for disease prognosis are becoming available, though the data remain insufficient to recommend incorporation of any molecular markers into standard practice [181-189]. Within the last 2 years, the first studies of DNA microarray analysis of early-stage NSCLC have been published [190,191]. The impact of this new technology on the diagnosis and treatment of patients with advanced disease has yet to be defined.

Ancillary Medications

ASCO has published several evidence-based guidelines for the use of ancillary medications for patients receiving chemotherapy for various forms of cancer. Topics have included reviews of the use of bisphosphonates for the treatment of breast cancer and multiple myeloma, recommendations for antiemetic therapy in a spectrum of settings, as well as chemoprotectant agents, and hematopoietic growth factors including granulocyte stimulating factors and erythropoietin [192-200]. The literature search for this guideline revealed a lack of prospective, randomized trials of these agents specific to lung cancer therapy. Given the availability of related guidelines, further discussion of ancillary medications specific to lung cancer therapy is beyond the scope of this update.

Radiotherapy

1997 Recommendations:

1. Radiation for Locally Advanced Unresectable NSCLC:

Radiation therapy should be included as part of treatment for selected patients with unresectable locally advanced NSCLC.

2. *Patient Selection:*

Candidates for definitive thoracic radiotherapy with curative intent should have performance status 0, 1, or possibly 2, adequate pulmonary function, and disease confined to the thorax. Patients with malignant pleural effusions and those with distant metastatic disease are not appropriate candidates for definitive thoracic radiotherapy.

3. Dose and Fractionation:

Definitive-dose thoracic radiotherapy should be no less than the biologic equivalent of 60 Gy, in 1.8-Gy to 2.0-Gy fractions.

4. Local- and Distant-Site Palliative Effects of External-Beam Radiation:

Local symptoms from primary or metastatic NSCLC can be relieved by a variety of doses and fractionations of external-beam radiotherapy. In appropriately selected patients, hypofractionated palliative radiotherapy (of one to five fractions instead of 10) may provide symptomatic relief with acceptable toxicity in a more time-efficient and less costly manner.

2003 Recommendations:

1. Radiation for Locally Advanced Unresectable NSCLC:

No change.

2. Patient Selection:

No change.

3. Dose and Fractionation:

No change.

4. Local- and Distant-Site Palliative Effects of External-Beam Radiation:

No change.

Evidence Summary

Definitive Treatment for stage III Disease (Without Malignant Pleural/Pericardial Effusion):

Altered fractionation radiation programs with definitive intent have been receiving increased attention since the original guidelines were published. A European, prospective randomized trial investigated the CHART regimen (continuous hyperfractionated accelerated radiotherapy) and found a survival advantage and lack of additional morbidity compared with standard radiotherapy alone [201-203]. CHART delivers radiotherapy three times daily for 12 consecutive days. The generalizability of this data is questionable in that more than 33% of the patients had early-stage disease (stages I-II), another 38% had stage IIIA, and most had squamous-cell histology [201]. Trials are ongoing to add chemotherapy to CHART, as well as adjustment of the schedule to provide weekends off for patients and caregivers [204] (eg, noncontinuous hyperfractionated accelerated radiation, known as HART, delivers radiation three times a day for 12 days out of 15 [205]). Other investigators have also evaluated the tolerance and efficacy of innovative radiation fractionation schedules combined with chemotherapy with encouraging results [206,207]. The precise roles and contributions of each modality are still being defined. Technological improvements in radiation therapy delivery, such as three-dimensional conformal radiation therapy/intensity-modulated radiation therapy, may allow the delivery of higher doses of radiation while still permitting the use of concurrent chemotherapy [92,208-210].

Palliative Treatment for Stage III-IV Disease:

While radiation therapy is useful in treating local symptoms, phase III data suggest that prophylactic radiation, before symptoms occur, is not helpful. Falk et al randomized 230 asymptomatic patients, who were not candidates for curative treatment, to receive immediate palliative radiation to the chest, or therapy delayed until the onset of symptoms. The median time to start was 15 days in the immediate treatment group, and 125 days in the delayed treatment group. There was no difference between the two groups in terms of symptom control, quality of life, or survival; however, adverse events were more common in the immediate treatment group [211].

Other randomized studies have evaluated a variety of different dose and fractionation schedules in the palliative setting [212-216], a frequent focus being the relief of chest symptoms. Hypofractionated radiation schedules offer potential effective and efficient palliation. However, there may be a trade-off in survival compared with that obtained with radiation schedules employing a larger number of lower-dose fractions, with a higher reported cumulative dose [212,213]. For example, a phase III randomized study in Canada compared 10-Gy single-fraction radiation with 20-Gy in five fractions for the palliation of thoracic symptoms from lung cancer in 230 patients with advanced disease unsuitable for curative treatment. There was no difference between the two arms in the primary end point, which was palliation of thoracic symptoms at 1 month after radiation evaluated by a patient-completed daily diary card, nor in treatment-related toxicity. However, patients who received five fractions survived, on average, 2 months longer than patients who received one fraction [212]. In a randomized study from the United Kingdom, 17 Gy delivered in two fractions 1 week apart, in patients with localized but inoperable NSCLC, lead to more rapid symptom palliation and less treatment-related dysphagia than 39 Gy administered in 13 fractions, 5 days per week. But reported survival was superior with the latter radiation schedule [213]. Other investigators have failed to demonstrate a difference in median survival between treatment groups [214,216].

A Cochrane review evaluating the role of palliative radiotherapy to the chest felt that a meta-analysis of identified trials could not be attempted because of considerable heterogeneity among the trials [217]. The reviewers found that higher dose regimens were associated with a modest survival benefit at the expense of greater acute toxicity, but evidence was lacking that any particular schedule lead to better palliation.

The role of brachytherapy, photodynamic therapy, and the laser in the treatment and palliation of advanced NSCLC is evolving, and has been tested only in nonrandomized comparisons to more conventional therapy. All three modalities have been found to produce effective palliation of symptomatic endobronchial disease, with palliation of cough, hemoptysis and dyspnea, even in critically ill patients [218-222]. One study compared photodynamic therapy (PDT) and Nd-YAG (neodymium-yttrium aluminum garnet) laser resection in patients with NSCLC and airway obstruction, and found equivalent efficacy and toxicity profiles [223].

Brain metastases develop in approximately one-third of patients with NSCLC. External beam radiation is the treatment of choice for brain metastases, which are not amenable to surgical resection. Historically, whole-brain radiation therapy (WBRT) has been the standard treatment, and provides palliation of symptoms and improved survival compared with untreated historical controls [224]. A phase III comparison of early, versus delayed WBRT in 176 patients with NSCLC metastatic to the brain receiving cisplatin and vinorelbine chemotherapy, concluded that the timing of WBRT with chemotherapy did not influence survival [225]. Stereotactic radiosurgery (SRS) is an alternative to surgical resection. It is being used as primary therapy followed by surveillance, or WBRT. It can also be used in patients who have already received WBRT to treat recurrent solitary or oligo ($n = 2$ to 4) metastases. While no randomized comparisons of SRS versus surgery or WBRT are available, case series of patients with solitary and oligo brain metastases from NSCLC undergoing SRS followed by WBRT have demonstrated comparable survival and rates of local control compared with historical data of surgical resection plus WBRT [226]. Consistent findings in these retrospective studies include reliable local control by SRS ($> 80\%$), as well as poor prognosis in patients with low performance status or active disease outside of the brain at the time of SRS [227-231]. Prospective, randomized trials are needed to compare SRS with surgical resection, and assess the role of SRS with and without WBRT, in order to control for problems unique to SRS, such as radionecrosis [232-234].

Surgery

1997 Recommendation:

1. *Role of resection for distant metastases:* In patients with controlled disease outside of the brain who have an isolated cerebral metastasis in a resectable area, resection followed by WBRT is superior to WBRT alone.

2003 Recommendations:

1. Role of resection for distant metastases: A. In patients with controlled disease outside of the brain who have an isolated cerebral metastasis in a resectable area, resection followed by WBRT is superior to WBRT alone.

B. While feasible in selected patients, there is insufficient evidence to support routine resection of solitary adrenal metastases.

Evidence Summary

The results of large case series continue to support the resection of limited brain metastases. A retrospective look at 220 patients who underwent surgical treatment for brain metastases from NSCLC showed a median survival of 24 months, with a 21% five-year survival proportion. The majority of the patients in this series had metachronous disease, with only 28 (13%) of patients operated on for synchronous brain disease [235]. Patients without intrathoracic lymph node involvement fared better. A series of 103 patients operated on for between one and three synchronous brain metastases, followed by resection of the lung primary, showed a five-year survival proportion of 11% [236]. Univariate and multivariate analyses showed that patients with adenocarcinoma fared better, with a trend toward a better prognosis for patients with small pulmonary tumors and absence of intrathoracic nodal metastases [236].

Only small, nonrandomized case series support resection of solitary adrenal metastases, with long-term survival reported in selected patients following unilateral adrenalectomy [237-242]. Minimally invasive, laparoscopic approaches to adrenalectomy have become more common for the surgical treatment of benign adrenal disease, and may be useful in patients with advanced NSCLC to minimize the morbidity of adrenalectomy [243,244].

SURVEILLANCE AND FOLLOW-UP CARE FOR PATIENTS WITH ADVANCED LUNG CANCER

1997 Recommendations

1. History and Physical Examination:

For patients treated with curative intent, in the absence of symptoms, a history and physical examination should be performed every 3 months during the first 2 years, every 6 months thereafter through year 5, and yearly thereafter.

2. Chest Radiographs:

For patients treated with curative intent, there is no clear role for routine studies in asymptomatic patients and for those in whom no interventions are planned. A yearly chest x-ray to evaluate for potentially curable second primary cancers may be reasonable.

3. Other Diagnostic Studies:

There is no role for routine studies in most asymptomatic patients and those patients not undergoing therapeutic interventions. CT scan of the chest/abdomen; CT scan/MRI

of the brain; bone scan; bronchoscopy; CBC; and routine chemistries, including liver function tests, should only be performed as indicated by the patient's symptoms.

2003 Recommendations

1. History and Physical Examination:

No change.

2. Chest Radiographs:

For patients treated with curative intent, there is no clear role for routine studies in asymptomatic patients and for those in whom no interventions are planned.

3. Other Diagnostic Studies:

There is no role for routine studies in most asymptomatic patients and those patients not undergoing therapeutic interventions. CT scan of the chest/abdomen; CT scan/MRI of the brain; *FDG-PET scan*; bone scan; bronchoscopy; CBC; and routine chemistries, including liver function tests, should only be performed as indicated by the patient's symptoms.

3A. Low-dose helical chest CT is more sensitive than chest x-ray for the identification of second primary cancers, but at this time remains investigational as part of the routine follow-up of patients with a history of unresectable NSCLC.

Evidence Summary

There have been no randomized, controlled trials of lung cancer follow-up completed since the ASCO guidelines were last published, but studies using less rigorous designs are available. Large, retrospective series have questioned the benefits of aggressive surveillance [245-247]. One prospective study of 192 patients in which postoperative surveillance included chest radiographs every 3 months and bronchoscopy and CT scans every 6 months found that recurrence developed in 136/192 (71%), and was asymptomatic in 36/192 (26%) [248]. In asymptomatic patients, the recurrence was detected by CT scan in 10 of 35 (28% of recurrences, but 5% of total), and by bronchoscopy in 10. Fifteen (43% of recurrences, 8% of 192 total) had a thoracic recurrence that could be treated with curative intent. From the date of recurrence, the 3-year survival was 13% in all patients and 31% in those patients whose recurrence was detected while asymptomatic. The authors concluded that this intensive follow-up was feasible, and may have improved survival. Given the likelihood of lead and detection time bias, and the small overall number who might benefit, a large randomized controlled trial would be necessary to answer this question.

Similarly, there is no prospective, randomized, or controlled evidence that early treatment of asymptomatic brain metastases—even with the use of newer techniques such as stereotactic radiosurgery—improves survival and/or palliation of symptoms. Therefore, more aggressive strategies of CNS surveillance cannot be advocated at this time. The reliability of FDG-PET for following the response of disease after chemotherapy and/or radiotherapy, or for early detection of recurrence, is also under investigation [249-254].

Screening for Second Primary Cancers:

Long-term survival in patients with unresectable non–small-cell lung cancer is infrequent. However, patients who achieve long-term survival have a high risk of second primary lung cancer (1% to 2% per year) [255,256]. Screening is performed to detect disease at a stage when cure or control is possible. Although survival from the time of diagnosis of the disease is commonly reported in screening trials, this measure may be affected by lead-time, length-time, and overdiagnosis biases [257]. An effect on lung cancer mortality rather than survival is necessary to validate potential screening methods.

Data regarding the utility of low-dose, helical CT are evolving, with the first large scale prospective, randomized studies currently underway. Beginning in 1993, the Early Lung Cancer Action Project (ELCAP) screened 1,000 high-risk patients ($\geq$ 60 years of age with $\geq$ 10 pack-year smoking history) with low-dose helical CT [258-260]. Results have confirmed that CT–based screening markedly enhances the detection of lung cancer at earlier stages compared with traditional chest radiography. There was a high false-positive rate on baseline screening, with 233 patients (23%) found to have suspicious findings, but only 27 (2.7%) of these patients eventually found to have a nodule-associated malignancy. Notably, 20 of the 27 CT-detected malignancies were not seen on chest radiography. The incidence of false-positive results fell dramatically with repeat annual screening, with only 3% of patients found to have suspicious nodules on their second scan, and a higher true-positive rate (43%). More than 80% of the malignancies detected were stage IA. There were no instances of symptom-promoted interim diagnosis of nodule-associated malignancy. There were, however, two symptom-prompted interim diagnoses of lung cancer related to endobronchial lesions, suggesting that CT screening for lung cancer may be effectively supplemented with cytologic screening.

Two nonrandomized studies from Japan that used chest radiography and low-dose CT for screening have also confirmed that CT scanning is more sensitive than conventional chest radiography for the detection of lung nodules, and that some of these nodules proved to be lung cancer [261,262]. Once again, it was found that CT detected more cases of lung cancer, and at an earlier stage. It remains to be seen whether there will be a stage shift with CT scanning (ie, if the prevalence of advanced disease will decrease in the screened-positive population).

Several additional studies of CT-based screening are currently underway, including randomized trials sponsored by the National Cancer Institute, and the American College of Radiology Imaging Network [257,263]. Despite aggressive attempts to identify small, early-stage tumors for re-

section, one study has found that tumor size is not an independent predictor of survival [264]. Another study found no statistically significant relation between the stage distribution and the size of the primary lesion [265].

Laser-induced fluorescence emission (LIFE) techniques detect the autofluorescence of dysplastic tissue, and are being studied to improve detection of malignancy over white-light bronchoscopy (WLB) [266,267]. A randomized study of this technique in 55 patients found that LIFE was significantly more sensitive than WLB for detecting moderate to severe dysplasia (69% *v* 22%, $P < .001$), especially certain forms of dysplasia such as angiogenic squamous dysplasia. However, LIFE was slightly less specific than WLB (70% *v* 78%, $P = .45$) [268]. A nonrandomized study comparing 53 patients receiving standard WLB, versus 39 patients who had LIFE + WLB, concluded that biopsies from sites with normal and abnormal LIFE imaging were equivalent, and that individuals examined by LIFE imaging had no improvement in the detection of dysplasia or metaplasia compared with WLB [269].

Other methods of early diagnosis are being pursued—including analysis of sputum, bronchoalveolar lavage fluid, bronchial biopsy specimens, and even serum specimens—using techniques such as immunohistochemistry, gene mutation analyses, telomerase activity, microsatellite instability, and abnormal DNA methylation [266,270-275]. None of these analyses has been tested in a large trial as the sole detection technique, and the sensitivity and specificity of these tests remain to be elucidated.

LIFESTYLE CHANGES TO PREVENT RECURRENT LUNG CANCER

1997 Recommendations

1. Smoking Cessation:

Smoking cessation, never initiating smoking, and avoidance of occupational and environmental exposure to carcinogenic substances are recommended as effective interventions to reduce the risk of second primary NSCLC in curatively treated patients. In patients with distant metastatic NSCLC, the outlook is poor and smoking cessation has little effect on overall prognosis, but may improve respiratory symptoms.

2. Chemopreventive Agents:

The use of antioxidants and/or chemopreventive agents for NSCLC is investigational, and their clinical use off-study is not recommended.

2003 Recommendations

1. Smoking Cessation:

Smoking cessation, never initiating smoking, and avoidance of occupational and environmental exposure to carcinogenic substances are recommended as effective interventions to reduce the risk of second primary NSCLC in curatively treated patients. *Of these interventions, the first two have the largest public health impact*. In patients with distant metastatic NSCLC, the outlook is poor, and smoking cessation has little effect on overall prognosis but may improve respiratory symptoms.

2. Chemopreventive Agents:

No change.

Evidence Summary

Occupational and environmental exposure to carcinogenic substances (eg, radon, asbestos) may increase the risk of lung cancer, but this risk is small compared with that associated with tobacco use [276-280]. Our understanding of the molecular mechanisms by which tobacco smoke causes lung cancer continues to grow [281-285]. Heavy smokers have been reported to have greater frequency of aneuploid tumors than light or nonsmokers, but no statistical association has been shown between survival and lifetime total cigarette consumption [286]. Eckhardt et al evaluated the smoking histories and outcomes of patients in four clinical trials. Patients with no or remote smoking history had an increased probability of a partial response to chemotherapy compared with those with recent smoking history. There was also an advantage in time to progression and longer survival in those ceasing to smoke. Multivariate analysis confirmed smoking as an independent variable. This may be related to cigarette-smoking implication in mutation of *p53* tumor suppression gene and the *k-ras* proto-oncogene, and may lead to less sensitivity to chemotherapy [287,288]. A recent study of markers of lung epithelial proliferation by bronchoscopic biopsy and Ki-67 immunostaining in former and current smokers found that active smoking increased epithelial proliferation, and that increased proliferation was still detectable for more than 20 years, even in the absence of squamous metaplasia [289].

A retrospective study examined the 6-month tobacco abstinence rate among lung cancer patients treated clinically for nicotine dependence. The intervention involved consultation with a nicotine dependence counselor, followed by individualized treatment including provision of behavioral and social strategies, stress management techniques, and pharmacologic therapy. The results suggested that the majority of lung cancer patients were motivated to stop smoking, and were more likely to succeed in quitting than matched controls who did not have lung cancer, however the rate of abstinence at 6 months was only 22% even among patients with lung cancer [290].

There have been no positive chemoprevention trials since the publication of the last guideline. A four-arm, prospective randomized study from the Netherlands enrolled over 1,000 patients with treated, early-stage NSCLC (as well as 1,500 patients with head and neck cancer). The treatment arms included two years of adjuvant treatment

with oral vitamin A (retinyl palmitate), *N*-acetylcysteine, both, or neither. No benefits in terms of survival, event-free survival, or incidence of second primary tumor were observed for any tumor type [291]. The patients were primarily former smokers (93%), with a substantial number of active smokers (25%). A randomized trial of over 1100 patients with resected, stage I NSCLC compared 3 years of oral, adjuvant treatment with isotretinoin with placebo. There were no statistically significant differences between the placebo, and isotretinoin arms with respect to the time to second primary tumors, recurrence, or mortality [292]. Subset analyses suggested that isotretinoin was harmful in current smokers, and beneficial in never smokers. A small (n = 160) case-control study has suggested that aspirin use is useful in preventing lung cancer in women [293].

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Authors' Disclosures of Potential Conflicts of Interest

The following authors or their immediate family members have indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. Acted as a consultant within the last 2 years: Andrew T. Turrisi, Aventis, AstraZeneca.

Table 1. Summary of Guidelines

Specific Guidelines	1997 Recommendations	2003 Recommendations
Diagnostic evaluation of patients with advanced lung cancer		
Staging locoregional disease	A chest x-ray and chest CT scan with infusion of contrast material are recommended to stage locoregional disease. The CT scan should extend inferiorly to include the liver and adrenal glands.	A chest x-ray and chest (CT) scan with infusion of contrast material are recommended to stage locoregional disease. The CT scan should extend inferiorly to include the liver and adrenal glands. Assuming there is no evidence of distant metastatic disease on CT scan, FDG-PET scanning complements CT scan and is recommended.
	For patients with clinically operable NSCLC, biopsy is recommended of mediastinal lymph nodes found on chest CT scan ≥ 1.0 cm in shortest transverse axis.	For patients with clinically operable NSCLC, biopsy is recommended of mediastinal lymph nodes found on chest CT scan to be greater than 1.0 cm in shortest transverse axis, or positive on FDG-PET scanning. Negative FDG-PET scanning does not preclude biopsy of radiographically enlarged mediastinal lymph nodes.
Staging distant metastatic disease		
General		For the staging of distant metastatic disease, an FDG-PET scan is recommended when there is no evidence of distant metastatic disease on CT scan of the chest.
Bone	A bone scan should be performed only in patients who report (a) bone pain, or (b) chest pain, or who have (c) an elevated serum calcium level, or (d) an elevated serum alkaline phosphatase level.	A bone scan is optional in patients who have evidence of bone metastases on FDG-PET scanning, unless there are suspicious symptoms in regions not imaged by FDG-PET. In patients with a surgically resectable primary lung lesion, bone lesions discovered on bone scan or FDG-PET require histologic confirmation, or corroboration by additional radiologic testing (x-ray, CT, and/or MRI).
Brain	Head CT or MRI brain imaging with and without infusion of contrast material should be obtained only in patients who have signs or symptoms of CNS disease.	Head CT or MRI brain imaging with and without infusion of contrast material is recommended in patients who have signs or symptoms of CNS disease, as well as asymptomatic patients with stage III disease who are being considered for aggressive local therapy (chest surgery or radiation).
Adrenal	The finding of an isolated adrenal mass on ultrasonographic or CT scan requires biopsy to rule out metastatic disease if the patient is otherwise considered to be potentially resectable.	The finding of an isolated adrenal mass on ultrasonography, CT scan, or FDG-PET scan requires biopsy to rule out metastatic disease if the patient is otherwise considered to be potentially resectable.
Liver	The finding of an isolated liver mass on ultrasonographic or CT scan requires biopsy to rule out metastatic disease if the patient is otherwise considered to be potentially respectable.	The finding of an isolated liver mass on ultrasonography, CT scan, or FDG-PET scan requires biopsy to rule out metastatic disease if the patient is otherwise considered to be potentially resectable.

Table 1. Summary of Guidelines (continued)

Specific Guidelines	1997 Recommendations	2003 Recommendations
Treatment		
Chemotherapy		
Outcome		
Unresectable stage III	Chemotherapy in association with definitive thoracic irradiation is appropriate for selected patients with unresectable, locally advanced NSCLC.	No change.
Stage IV	Chemotherapy is appropriate for selected patients with stage IV NSCLC.	No change.
Patient selection		
Unresectable stage III	In unresectable stage III disease, chemotherapy plus radiotherapy prolongs survival compared with radiation alone and is most appropriate for individuals with good performance status (ECOG/Zubrod performance status 0 or 1, and possibly 2).	No change.
Stage IV	In stage IV disease, chemotherapy prolongs survival and is most appropriate for individuals with good performance status (ECOG/Zubrod performance status 0 or 1, and possibly 2).	No change.
Selection of drugs		
Unresectable stage III	Chemotherapy given to NSCLC patients should be a platinum-based combination regimen.	No change.
Stage IV		First-line chemotherapy given to patients with advanced NSCLC should be a two-drug combination regimen. Non—platinum containing chemotherapy regimens may be used as alternatives to platinum-based regimens in the first line. For elderly patients, or patients with ECOG/Zubrod performance status 2, available data support the use of single-agent chemotherapy.
Duration of therapy		
Unresectable stage III	In patients with unresectable stage III NSCLC, who are candidates for combined chemotherapy and radiation, the duration of chemotherapy should be two to eight cycles.	In patients with unresectable stage III NSCLC, who are candidates for combined chemotherapy and radiation, the duration of chemotherapy should be two to four cycles of initial, platinum-based chemotherapy.
	In the absence of compelling data, the Panel consensus is that in patients with unresectable stage III NSCLC who are candidates for combined chemotherapy and radiation, the duration of chemotherapy should be no more than eight cycles.	In the absence of compelling data, the Panel consensus is that in patients with unresectable stage III NSCLC who are candidates for combined chemotherapy and radiation, the duration of initial platinum-based chemotherapy should be no more than four cycles.
Stage IV	In the absence of compelling data, the Panel consensus is that chemotherapy should be administered for no more than eight cycles in patients with stage IV NSCLC.	In patients with stage IV NSCLC, first-line chemotherapy should be stopped at 4 cycles in patients who are not responding to treatment. The Panel consensus is that first-line chemotherapy should be administered for no more than six cycles in patients with stage IV NSCLC.
Timing of treatment		
Unresectable Stage III	In patients with unresectable stage III disease, chemotherapy may best be started soon after the diagnosis of unresectable NSCLC has been made. Delaying chemotherapy until performance status worsens or weight loss develops may negate the survival benefits of treatment.	No change.
Stage IV	In patients with stage IV disease, if chemotherapy is to be given it should be initiated while the patient still has good performance status.	No change.
Second-line therapy	There is no current evidence that either confirms or refutes that second-line chemotherapy improves survival in non-responding or progressing patients with advanced NSCLC. Second-line treatment may be appropriate for good performance status patients for whom an investigational protocol is not available or desired, or for patients who respond to initial chemotherapy and then experience a long progression-free interval off treatment.	Docetaxel is recommended as second-line therapy for patients with locally advanced or metastatic NSCLC with adequate performance status who have progressed on first-line, platinum-based therapy. Gefitinib is recommended for the treatment of patients with locally advanced or metastatic NSCLC after failure of both platinum-based and docetaxel chemotherapies.
Role of investigational agents/options	Initial treatment with an investigational agent or regimen is appropriate for selected patients with stage IV NSCLC, provided that patients are crossed over to an active treatment regimen if they have not responded after two cycles of therapy.	No change.

Table 1. Summary of Guidelines (continued)

Specific Guidelines	1997 Recommendations	2003 Recommendations
Histology	NSCLC histology is not an important prognostic factor in patients with advanced, unresectable disease. The use of newer, putative prognostic factors such as *RAS* mutations or *p53* mutations is investigational and should not be used in clinical decision-making.	No change.
Radiotherapy		
Radiation for locally advanced unresectable NSCLC	Radiation therapy should be included as part of treatment for selected patients with unresectable locally advanced NSCLC.	No change.
Patient selection	Candidates for definitive thoracic radiotherapy with curative intent should have performance status 0, 1, or possibly 2, adequate pulmonary function, and disease confined to the thorax. Patients with malignant pleural effusions and those with distant metastatic disease are not appropriate candidates for definitive thoracic radiotherapy.	No change.
Dose and fractionation	Definitive-dose thoracic radiotherapy should be no less than the biologic equivalent of 60 Gy in 1.8- to 2.0-Gy fractions.	No change.
Local and distant site palliative effects of external-beam radiation	Local symptoms from primary or metastatic NSCLC can be relieved by a variety of doses and fractionations of external-beam radiotherapy. In appropriately selected patients, hypofractionated palliative radiotherapy (of one to five fractions instead of 10) may provide symptomatic relief with acceptable toxicity in a more time efficient and less costly manner.	No change.
Surgery		
Role of resection for distant metastases	In patients with controlled disease outside of the brain who have an isolated cerebral metastasis in a resectable area, resection followed by whole-brain radiotherapy is superior to whole-brain radiotherapy alone.	No change. While feasible in selected patients, there is insufficient evidence to support routine resection of solitary adrenal metastases.
Surveillance and follow-up care for patients with advanced lung cancer		
History and physical examination	For patients treated with curative intent, in the absence of symptoms, a history and physical examination should be performed every 3 months during the first 2 years; every 6 months thereafter through year 5; and yearly thereafter.	No change.
Chest radiographs	For patients treated with curative intent, there is no clear role for routine studies in asymptomatic patients and for those in whom no interventions are planned. A yearly chest x-ray to evaluate for potentially curable second primary cancers may be reasonable.	For patients treated with curative intent, there is no clear role for routine studies in asymptomatic patients and for those in whom no interventions are planned.
Other diagnostic studies	There is no role for routine studies in most asymptomatic patients and those patients not undergoing therapeutic interventions. CT scan of the chest/abdomen; CT scan/MRI of the brain; bone scan; bronchoscopy; complete blood cell count; and routine chemistries, including liver function tests, should only be performed as indicated by the patient's symptoms.	There is no role for routine studies in most asymptomatic patients and those patients not undergoing therapeutic interventions. CT scan of the chest/abdomen; CT scan/MRI of the brain; FDG-PET scan; bone scan; bronchoscopy; complete blood cell count; and routine chemistries, including liver function tests, should only be performed as indicated by the patient's symptoms. Low-dose helical chest CT is more sensitive than chest x-ray for the identification of second primary cancers, but at this time remains investigational as part of the routine follow-up of patients with a history of unresectable NSCLC.
Lifestyle changes to prevent recurrent lung cancer		
Smoking cessation	Smoking cessation, never initiating smoking, and avoidance of occupational and environmental exposure to carcinogenic substances are recommended as effective interventions to reduce the risk of second primary NSCLC in curatively treated patients. In patients with distant metastatic NSCLC, the outlook is poor and smoking cessation has little effect on overall prognosis, but may improve respiratory symptoms.	Smoking cessation, never initiating smoking, and avoidance of occupational and environmental exposure to carcinogenic substances are recommended as effective interventions to reduce the risk of second primary NSCLC in curatively treated patients. Of these interventions, the first two have the largest public health impact. In patients with distant metastatic NSCLC, the outlook is poor and smoking cessation has little effect on overall prognosis, but may improve respiratory symptoms.
Chemopreventive agents	The use of antioxidants and/or chemopreventive agents for NSCLC is investigational and their clinical use off-study is not recommended.	No change.

Abbreviations: CT, computed tomography scan; FDG-PET, fluorodeoxyglucose positron emission tomography; NSCLC, non–small-cell lung cancer; MRI, magnetic resonance imaging; ECOG, Eastern Cooperative Oncology Group.

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