Special Treatment Issues in Lung Cancer*

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

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Background: **This chapter of the guidelines addresses patients who have particular forms of non-small cell lung cancer that require special considerations. This includes patients with Pancoast tumors, T4N0,1M0 tumors, satellite nodules in the same lobe, synchronous and metachronous multiple primary lung cancers (MPLCs), solitary brain and adrenal metastases, and chest wall involvement.**

Methods: **The nature of these special clinical cases is such that in most cases, metaanalyses or large prospective studies of patients are not available. For ensuring that these guidelines were supported by the most current data available, publications that were appropriate to the topics covered in this chapter were obtained by performance of a literature search of the MEDLINE computerized database. When possible, we also referenced other consensus opinion statements. Recommendations were developed by the writing committee, graded by a standardized method (see "Methodology for Lung Cancer Evidence Review and Guideline Development" chapter), and reviewed by all members of the lung cancer panel before approval by the Thoracic Oncology NetWork, Health and Science Policy Committee, and the Board of Regents of the American College of Chest Physicians.**

Results: **In patients with a Pancoast tumor, a multimodality approach seems to be optimal, involving chemoradiotherapy and surgical resection, provided appropriate staging has been conducted. Patients with central T4 tumors that do not have mediastinal node involvement are uncommon. Such patients, however, seem to benefit from resection as part of the treatment as opposed to chemoradiotherapy alone when carefully staged and selected. Patients with a satellite lesion in the same lobe as the primary tumor have a good prognosis and require no modification of the approach to evaluation and treatment than what would be dictated by the primary tumor alone. However, it is difficult to know how best to treat patients with a focus of the same type of cancer in a different lobe. Although MPLCs do occur, the survival results after resection for either a synchronous presentation or a metachronous presentation with an interval of < 4 years between tumors are variable and generally poor, suggesting that many of these patients may have had a pulmonary metastasis rather than a second primary lung cancer. A thorough and careful evaluation of these patients is warranted to try to differentiate between patients with a metastasis and a second primary lung cancer, although criteria to distinguish them have not been defined. Selected patients with a solitary focus of metastatic disease in the brain or adrenal gland seem to benefit substantially from resection. This is particularly true in patients with a long disease-free interval. Finally, in patients with chest wall involvement, as long as tumors can be completely resected and there is absence of N2 nodal involvement, primary surgical treatment should be considered.**

Conclusions: **Carefully selected patients may benefit from an aggressive surgical approach.**

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Key words: adrenal metastasis; brain metastasis; carina; metachronous primary lung cancers; multiple primary lung cancer; Pancoast tumor; satellite nodules; superior sulcus tumor; superior vena cava; synchronous primary lung cancers; T4N0,1M0 tumor

Abbreviations: ACCP = American College of Chest Physicians; MPLC = multiple primary lung cancer; NSCLC = non-small cell lung cancer; PET = positron emission tomography; WBRT = whole-brain radiotherapy

In general, patients with an early stage non-small cell lung cancer (NSCLC) without mediastinal nodal involvement (stage I and II) are treated primarily with surgery, whereas those with a locally advanced lung cancer with mediastinal nodal involvement (stages IIIA and IIIB) are treated with chemotherapy and radiation. However, there are several relatively unusual presentations of NSCLC in which the anatomic and biological issues seem to dictate a different approach. In addition, the presence of an isolated, second focus of cancer in a patient with lung cancer presents a situation in which the biology of this phenomenon is often not clear and, therefore, the approach to treatment is difficult.

This section addresses patients with particular forms of NSCLC that require special considerations. This includes patients with Pancoast tumors, T4N0,1M0 tumors, satellite nodules in the same lobe, synchronous and metachronous multiple primary lung cancers (MPLCs), and solitary metastases.

Materials and Methods

A formal metaanalysis was not available for any of the particular forms of NSCLC that are the subject of this chapter, and resources did not permit the American College of Chest Physicians (ACCP) to conduct such an analysis independently. Clinical guidelines from other organizations were available only with regard to Pancoast tumors. These involve primarily consensus opinion statements and are discussed in the "Pancoast Tumors" section.[1–6] However, a systematic review of the most recent literature in each of these areas was performed. The recommendations in this section rely heavily on the data from this review.

The data regarding the approach to these special situations were reviewed, summarized, and used to define management recommendations by the writing committee. This document was then reviewed by three independent reviewers, and further changes were made. The revised document and recommendations were further reviewed by the entire ACCP Guidelines Committee to ensure that it met the requirements of a balanced, accurate, and generally acceptable representation of the issues with regard to these particular forms of NSCLC.

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Results

Pancoast Tumors

Definitions: Lung cancers that occur in the apex of the chest and invade apical chest wall structures are called superior sulcus tumors, or Pancoast tumors. The classic description of such patients involves a syndrome of pain radiating down the arm as a manifestation of brachial plexus involvement. With improvements in radiographic techniques, earlier diagnosis, and a more detailed understanding of the anatomy, a tumor can be classified as a Pancoast tumor when it invades any of the structures at the apex of the chest, including the most superior ribs or periosteum, the lower nerve roots of the brachial plexus, the sympathetic chain near the apex of the chest, or the subclavian vessels. These tumors are now divided into anterior, middle, and posterior compartment tumors depending on the location of the chest wall involvement in relation to the insertions of the anterior and middle scalene muscles on the first rib.[7] A syndrome of pain radiating down the arm is no longer a prerequisite for an apical tumor to be designated a Pancoast tumor.

Workup: No data specifically address the reliability of the clinical examination in patients with Pancoast tumors with regard to the presence of distant metastases. Given that benign lesions such as granulomas, fungal infections, and small cell lung cancer can masquerade as NSCLC in the superior sulcus region, it is recommended that a histologic diagnosis of the mass be obtained before initiation of any treatment. In the absence of data to the contrary, the panel thought that Pancoast tumors should be treated like most other resectable lung cancers, meaning that imaging tests for distant metastases are not routinely necessary in the presence of a negative clinical evaluation. There are also no data regarding the reliability of CT or positron emission tomography (PET) scans for mediastinal node involvement specifically in patients with Pancoast tumors. The reader is referred to the "Noninvasive Staging of Non-small Cell Lung Cancer" chapter for additional discussion regarding the sensitivity and specificity of CT and PET scans in lung cancer staging. The consensus of the panel is that mediastinoscopy should be performed in all patients who are being considered for an attempt at a curative resection, regardless of whether the CT or PET scan suggests involvement of the mediastinal lymph nodes. The argument for this approach to surgically staging the mediastinum in all patients with a Pancoast tumor is that it is consistent with the general recommendation for accurate staging before initiation of a major intervention such as resection and consistent with data demonstrating

that N2,3 node involvement is a major negative prognostic factor. No firm recommendation can be made about whether mediastinoscopy should be done before or after preoperative therapy. An MRI demonstrates involvement of apical chest wall structures better than a CT scan,[8] but CT provides more information about the presence of nodal enlargement and pulmonary, hepatic, and adrenal metastases; therefore, both chest CT and MRI are indicated to assess the resectability of a Pancoast tumor.

Treatment: The classic approach to curative treatment of Pancoast tumors has been preoperative radiotherapy followed by surgical resection. This dates back to an experience published in 1961 by Shaw et al,[9] in which 12 of 18 patients who were treated with this approach were still alive at the time the article was written. However, the follow-up was < 2 years in 90% of the patients.[9] Alternatives are treatment with radiation alone, preoperative chemoradiotherapy and resection, or chemoradiotherapy without resection.

Treatment with radiation alone has achieved good palliation of pain in approximately 75% of patients.[10] In general, very few patients who are treated with radiation alone are long-term survivors (approximately 5%).[11] However, many of these series have included patients with advanced-stage tumors. Among studies[10,12–14] that have involved primarily patients who had a reasonable chance of cure, the average median survival time was 16 months and the average 5-year survival was 20% (range, 15 to 23%).

Treatment with preoperative radiation and resection has resulted in an average median survival time of 22 months and a 5-year survival of 27%.[11] In these series, approximately one third of patients underwent an incomplete (R1 or R2) resection, and approximately one third of the resections involved only a limited resection of the affected lobe of the lung.[11] Retrospective analysis[15] found that a complete resection with negative margins (R0) and a pulmonary resection involving at least a lobectomy are major factors associated with better survival. Furthermore, N2,3 lymph node involvement is a major negative prognostic factor and should generally be considered a contraindication to surgery.[11] Patients with vertebral body or subclavian vessel involvement have traditionally not been consider for resection, but it seems that with improved surgical approaches to these structures, a few experienced centers[16,17] have been able to achieve reasonable survival in such patients. The presence of Horner syndrome is also associated with poor survival.[11]

A large phase II study[18] of preoperative chemoradiotherapy in patients with Pancoast tumors showed a complete resection rate of 92% and a good 2-year survival rate compared with historical controls of radiotherapy followed by surgery. Furthermore, local recurrences were seen in only 33% of patients with a recurrence, whereas in series[18] involving preoperative radiotherapy alone, the majority of recurrences involved the tumor bed. These data, in combination with the data for non-Pancoast stage III NSCLC, suggest that preoperative chemoradiotherapy is a significant improvement over preoperative radiotherapy, particularly in light of the fact that there are insufficient numbers of patients with a Pancoast tumor to be able to complete a randomized comparison. The Southwest Oncology Group is accruing patients with Pancoast tumors into a phase II study of induction chemotherapy with cisplatin/etoposide and concurrent radiation followed by surgical resection, followed by consolidation docetaxel (S0220).

A single-institution, retrospective report[19] using high-dose three-dimensional radiation as part of induction chemotherapy and radiation therapy followed by surgery strategy showed that doses up to 60 Gy could be tolerated by most patients without any significant increase in postoperative complications. In 37 patients with pretreatment Pancoast tumors stages IIB to IV, the authors[19] reported a complete resection rate of 97.3%, with a complete response rate of 40.5%. Overall median survival time was 2.6 years, and 7.8 years in the group with a pathologic complete response. The overall recurrence rate was higher than most other series at 50%, with 50% of those being in the brain.

Other published guidelines[3] have recommended that patients with Pancoast tumors be evaluated by a thoracic surgeon. If there is no evidence of mediastinal node involvement[1] or extensive local invasion,[5] then patients should undergo resection in combination with radiotherapy or chemoradiotherapy.[1,4,5] Patients with inoperable, painful Pancoast tumors should be treated with radiotherapy with or without chemotherapy for palliation of their pain.[2] The last two recommendations were rated grade B, whereas the strength of the other statements was rated grade C. Other guidelines have reached the same conclusions as this ACCP document, although the recommendations in those other documents were less detailed and more vaguely worded.

In summary, the available data suggest that the best survival is achieved by preoperative chemoradiotherapy followed by surgical resection in carefully selected patients. Preoperative radiotherapy followed by surgical resection is a reasonable alternative. Involvement of subclavian vessels or the vertebral column is associated with poor survival after resection. However, a few centers have gained experience with improved surgical approaches to these

structures and have reported reasonable survival rates after resection. Involvement of mediastinal nodes is associated with poor survival after resection. At the time of resection, it is important to carry out a complete resection that should involve at least a lobectomy. There are no data on how unresectable yet still potentially curable Pancoast tumors should be managed. However, extrapolation from the data for non-Pancoast stage III NSCLC suggests that chemoradiotherapy is the best approach. For patients in whom cure is not believed to be possible, radiotherapy offers good palliation of pain.

Recommendations

1. In patients with a Pancoast tumor, it is recommended that a tissue diagnosis be obtained before initiation of therapy. Grade of recommendation, 1C

2. In patients who have a Pancoast tumor and are being considered for curative intent surgical resection, an MRI of the thoracic inlet and brachial plexus is recommended to rule out tumor invasion of unresectable vascular structures or the extradural space. Grade of recommendation, 1C

3. In patients with a Pancoast tumor involving the subclavian vessels or vertebral column, it is suggested that resection be undertaken only at a specialized center. Grade of recommendation, 2C

4. In patients who have a Pancoast tumor and are being considered for curative resection, invasive mediastinal staging and extrathoracic imaging (head CT/MRI plus either whole-body PET or abdominal CT plus bone scan) are recommended. Involvement of mediastinal nodes and/or metastatic disease represents a contraindication to resection. Grade of recommendation, 1C

5. In patients with a potentially resectable, nonmetastatic Pancoast tumor (and good performance status), it is recommended that preoperative concurrent chemoradiotherapy be administered before resection. Grade of recommendation, 1B

6. In patients who undergo resection of a Pancoast tumor, it is recommended that every effort be made to achieve a complete resection. Grade of recommendation, 1A

7. It is recommended that resection of a Pancoast tumor consist of a lobectomy (instead of a nonanatomic wedge resection) as well as the involved chest wall structures. Grade of recommendation, 1C

8. In patients with either a completely or incompletely resected Pancoast tumor, postoperative radiotherapy is not recommended because of lack of demonstrated survival benefit. Grade of recommendation, 2C

9. In patients who have an unresectable but nonmetastatic Pancoast tumor and good performance status, definitive concurrent chemotherapy and radiotherapy is recommended. Grade of recommendation, 1C

10. In patients who have Pancoast tumors and are not candidates for curative intent treatment, palliative radiotherapy is recommended. Grade of recommendation, 1B

T4N0,1M0 Tumors

Patient Selection and Workup: Most patients with involvement of T4 structures have mediastinal node involvement as well. These patients should be treated with chemoradiotherapy, as is generally recommended for patients with stage IIIB NSCLC. However, very selected patients with T4 involvement but without mediastinal node involvement can be viewed as candidates for surgery. Although many reports have demonstrated the technical feasibility of resection of T4 structures, fewer series have provided long-term survival data. The largest experience of resection for T4 involvement involves carinal resections, usually together with a right pneumonectomy. Since 1980, there have been 12 published series of carinal resections for lung cancer. Four of the largest series[20–24] have been published since 2000 and provide long-term survival data on 395 patients. A moderate experience is available with left atrial involvement (88 patients)[25–29] and involvement of the superior vena cava (189 patients),[30–33] and a smaller experience has been reported with tumors invading the aorta (60 patients)[34–37] and vertebral bodies (48 patients).[38–41] That so few patients have been reported with long-term survival statistics underscores that patients who are candidates for a surgical approach are extremely rare and highly selected.

Mediastinoscopy should be performed even if a CT suggests no N2,3 involvement in patients who have T4 tumors and are being considered for a surgical approach. This argument is based on the fact that CT evaluation of the mediastinum in central tumors has a high false-negative rate. Furthermore, a consistent finding is that survival for patients with T4N2,3 disease is so poor that the presence of positive N2 disease should be considered a contraindication to aggressive surgical therapy. In patients who are being considered for carinal resection, it may be best to perform mediastinoscopy at the same

time as resection to prevent scarring and therefore lack of mobility of the airways at the time of reconstruction.

Outcomes After Surgery: In a fairly large series[25] involving an aggressive approach to T4 tumors from Japan, approximately one third of patients were able to undergo complete (R0) resection, one third a microscopically incomplete resection (R1), and one third a grossly incomplete resection (R2). The 5-year survival rates for these groups were 22%, 18%, and 0%, respectively.[25] Two small series from Japan on highly selected patients who had T4 tumors invading the aorta and underwent *en bloc* aortic resection reported complete resection rates of 50%[22] and 75%.[21] The 5-year survival rates were significantly better in patients who underwent complete resection and in those who had no N2 or N3 mediastinal lymph node disease.

The data regarding the outcome after resection in patients with carinal involvement show an average 5-year survival of 28%. However, the survival comes at a price of an average operative mortality of 17% (range, 7 to 29%). It should be noted, however, that the survival statistics have included all operative deaths as well. That the best reported 5-year survival (44%) comes from the largest series[24]—which also reported an operative mortality of only 7%—can be interpreted to suggest that such resections should be undertaken only in experienced centers. Survival data for resections involving other T4 structures have involved fewer patients, making interpretation of the data difficult (Table 1). The survival of patients with left atrial involvement has been less favorable. In general, however, the survival of patients with involvement of other T4 structures has been similar to that reported for patients with carinal involvement.

Patients with involvement of T4 structures should be very carefully selected before surgical resection is undertaken because of the limited survival and the high mortality. This means that these patients should have a high likelihood of being able to tolerate a major operation from a general medical standpoint. This also means that the evaluations to rule out either mediastinal or extrathoracic metastases should be especially thorough and that the threshold for pursuing subtle abnormalities seen on imaging tests should be low.

Preoperative chemotherapy or chemoradiotherapy in patients with T4 tumors has been reported in several trials. A 5-year survival of 20% was reported among all patients in the largest trial[34] (57 patients; 62% of whom underwent complete resection). These results are encouraging, however, given that 60% of the patients entered in the study had T4N2M0 tumors by careful surgical staging. By comparison, 5-year survival results for chemoradiotherapy without surgery in patients with stage IIIA and IIIB tumors have been approximately 9 and 14% in large, randomized trials involving sequential or concurrent chemoradiotherapy trials, respectively.[38] However, these latter series included patients both with stage IIIA and IIIB disease and did not report data separately or report any data specifically in patients with T4N0,1 tumors. A retrospective analysis[42] of the Southwest Oncology Group experience suggested that patients with T4N0,1M0 tumors benefited from preoperative chemoradiotherapy and surgery compared with chemoradiotherapy alone (2-year survival, 64% vs 33%).

Recommendations

11. In patients who have a clinical T4N0,1M0 NSCLC and are being considered for curative resection, it is recommend that invasive mediastinal staging and extrathoracic imaging (head CT/MRI plus either whole-body PET or abdominal CT plus bone scan) be undertaken. Involve-

Table 1—*Results of Resection of Patients With T4 Involvement From NSCLC**

Structure	Studies, No.	Patients, No.	Hospital Mortality, %	5-yr Survival, %		
				Average	Highest	Lowest
Any	1	101	13	13	23 (R0)	0 (R2)
Carina	12	722	17	28	44	13
Left atrium	4	88	3.5	15	22	10
Superior vena cava	4	189	12	25	31	21
Vertebral bodies	3	48	0	50†		
Aorta	3	60	13	27	37	17
Esophagus	1	7		14		
Main pulmonary artery	1	7		0		

*R0 = complete resection; R2 = incomplete resection with gross residual disease.
†Two-year survival.

ment of mediastinal nodes and/or metastatic disease represents a contraindication to resection. Grade of recommendation, 1C

12. In patients with a T4N0,1M0 NSCLC, it is recommended that resection be undertaken only at a specialized center. Grade of recommendation, 1C

Satellite Nodules and MPLCs

Occasionally, patients present with more than one focus of cancer within the lung. The American Joint Committee on Cancer staging system classifies a second focus of cancer within the same lobe as T4, whereas a second focus in another lobe is classified as M1. However, the classification does not help in grouping tumors according to similar biological situations. Although the secondary focus may represent a hematogenously spread metastasis, it may also be a second primary lung cancer or a second focus that is a manifestation of local spread. Distinguishing these situations is difficult. In this section, these tumors are classified according to clinical presentation, which is a method that at least has practical relevance in defining an approach to these patients. This section distinguishes a synchronous lesion within the same lobe as the primary tumor, two synchronous foci of cancer in different lobes, and two metachronous foci of cancer in the lung. Circumstances can be identified for each of these clinical presentations to allow them to be defined reasonably as satellite lesions and synchronous and metachronous MPLCs. In this document, as well as in the published literature, a satellite lesion is any additional focus of lung cancer of the same histologic type within the same lobe, regardless of the relative size or location in different segments and regardless of whether it is discovered by the radiologist, the surgeon, or the pathologist.

Definitions for satellite lesions within the same lobe as the primary tumor, synchronous second primary lung cancers, and metachronous second primary lung cancers are given in Table 2. In general, these criteria are relatively well accepted, but some authors have varied slightly in some details (*eg*, the minimum interval between metachronous MPLCs). Many data are available regarding the incidence of a second primary lung cancer and the recurrence rates and patterns of resected lung cancer. Therefore, the incidence of a second primary cancer and the incidence of a solitary pulmonary metastasis can be estimated for different stages of the primary lung cancer and by location of the second focus of cancer, as is shown in Figure 1. Although such estimates are based on extrapolations from known data, the resulting incidences and distributions between synchronous and metachronous presentations or same histology and different histologic types both are internally consistent and very close to what is actually observed. Analysis of these rates suggests that the biological situation (*ie*, new primary vs locally or hematogenously spread metastasis) can be defined clearly in some clinical presentations (*eg*, satellite lesions, MPLCs of different histologic types, metachronous tumors with a $\geq$ 4-year interval). In other clinical presentations, the biological situation is very unclear.

Table 2—*Definition of Satellite Nodules, MPLCs, and Pulmonary Metastases*

Satellite nodules from primary tumor
Same histology
And same lobe as primary cancer
And no systemic metastases
MPLCs
Same histology, anatomically separated
Cancers in different lobes
And no N2,3 involvement
And no systemic metastases
Same histology, temporally separated
$\geq$ 4-yr interval between cancers
And no systemic metastases from either cancer
Different histology
Different histologic type
Or different molecular genetic characteristics
Or arising separately from foci of carcinoma *in situ*
Hematogenously spread pulmonary metastases
Same histology and multiple systemic metastases
Same histology, in different lobes
And presence of N2,3 involvement
Or $<$ 2-yr interval

Small pulmonary lesions are frequently seen in addition to the primary tumor on the chest CT. This occurred in 16% of patients with potentially operable clinical stages I to IIIA NSCLC in one large study.[43] The lesions were not calcified and ranged from 4 to 12 mm. A definitive diagnosis (biopsy or follow-up of $>$ 24 months) was established in only 20% of the patients, the remainder being unavailable for follow-up or having unavailable pathology reports. Of the lesions for which a definitive diagnosis was available, 86% were found to be benign. In another study,[44] 10% of patients had a second lesion detected preoperatively, nearly 60% of which were found to be benign. Therefore, a patient should not be denied a curative approach on the basis of a second pulmonary nodule without a definitive tissue diagnosis.

In this section, a prospective approach is formulated for patients with cI to III NSCLC in whom a second intraparenchymal focus of cancer not only is identified radiographically but also is proved to be malignant by cytologic studies. Patients with disseminated disease (extrathoracic metastases) are ex-

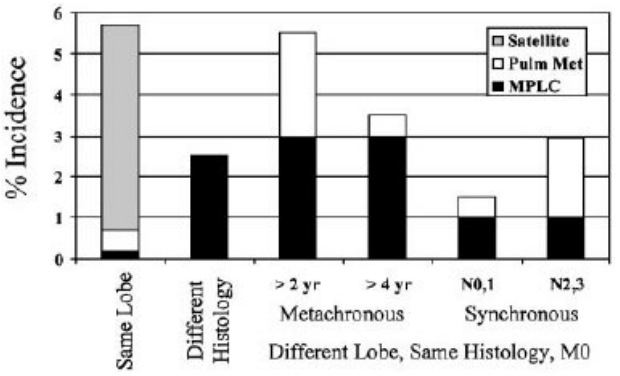

FIGURE 1. Estimated incidence of MPLCs, solitary pulmonary metastases (Pulm Met), and satellite lesions in different clinical presentations. These estimates are based on data concerning recurrence rates by stage and time interval, location of metastases, and the observed incidence of MPLCs and satellite lesions for each clinical presentation. Adapted from Detterbeck et al.[45]

cluded. In addition, the 30% of patients who had synchronous MPLCs and in whom the second cancer was found incidentally at thoracotomy are excluded for obvious reasons. Patients with bronchioloalveolar carcinoma should also be considered separately. Finally, it must be emphasized that the majority (57 to 86%) of additional nodules seen radiographically in patients with cI to III NSCLC are benign lesions.[43,44] Therefore, the considerations noted in the following discussion are relevant only when a histologic diagnosis of an MPLC has been made.

Satellite Nodules of Cancer in the Same Lobe:

Studies that have reported on long-term survival specifically of patients with satellite nodules in the same lobe as the primary tumor have generally reported good survival. The overall 5-year survival rate of all patients, approximately 60% of whom have N1 or N2 involvement, is 34%.[45] The 5-year survival for patients with satellite nodules and no node involvement is 64% (range, 54 to 70%), which is similar to the survival for patients with stage I NSCLC without satellite nodules.[45] Direct comparisons have generally demonstrated a slightly inferior survival in patients with satellite nodules, stage for stage, compared with patients without satellite nodules.[46] Nevertheless, the survival of patients with satellite nodules in the same lobe is consistently higher than that reported for patients with a second cancer nodule in a separate lobe (5-year survival, approximately 10%; range, 0 to 23% for all patients).[45]

In general, no additional diagnostic workup is necessary in patients with a secondary lesion in the same lobe. The available data indicate that most secondary lesions in the same lobe as the primary tumor were found to be benign. Furthermore, the prognosis in patients who are found to have a satellite nodule of cancer is only slightly inferior to those without a satellite focus, which argues that resection should be undertaken even in patients who do, in fact, have a satellite focus of cancer. Therefore, there is little reason to attempt to diagnose definitively a second lesion preoperatively in patients who have cI and II tumors and a second radiographic nodule in the same lobe. Furthermore, there is little reason to perform any additional preoperative staging investigations (*eg*, mediastinoscopy, CT of the head, bone scan) in patients with a second nodule in the same lobe as the primary tumor, other than what is dictated by the patient's clinical status and the primary tumor.

RECOMMENDATIONS

13. In patients with suspected or proven lung cancer and a satellite nodule within the same lobe, it is recommend that no further diagnostic workup of a satellite nodule be undertaken. Grade of recommendation, 1B

14. In patients with a satellite lesion within the same lobe as a suspected or proven primary lung cancer, evaluation of extrathoracic metastases and confirmation of the mediastinal node status should be performed as dictated by the primary lung cancer alone and not modified because of the presence of the satellite lesion. Grade of recommendation, 1C

15. In patients with NSCLC and a satellite focus of cancer within the same lobe (and no mediastinal or distant metastases), resection via a lobectomy is the recommended treatment. Grade of recommendation, 1B

Synchronous Second Primary Lung Cancer

Definition: A synchronous second focus of lung cancer in a different lobe is easily defined as a second primary lung cancer when the two sites are of different histologic types. Cancers may also be distinguished on the basis of different molecular genetic characteristics. In the absence of molecular analysis, it is difficult to distinguish two synchronous cancers that are of the same histologic type as separate primary lung cancers. One proposed requirement for classification as synchronous second primary lung cancers is that there be no mediastinal node involvement and no sites of distant metastases when the two cancers are of the same histologic type.[45] It can be estimated that the incidence of a second primary cancer using this definition is slightly

higher than the incidence of an isolated pulmonary metastasis, given what is known about the incidence of MPLCs and the rate and sites of spread of lung cancer.[45] Conversely, when mediastinal node involvement is present, the incidence of an isolated pulmonary metastasis is higher than that of a second primary cancer.[45] Although the exact incidence of multiple primary cancers and isolated pulmonary metastasis may not be fully defined by these estimates, at the very least it is clear that the identification of two synchronous foci of cancer of the same histologic type is difficult.

Patient Selection and Treatment Results: The survival of patients with synchronous (different lobe) MPLCs (either same or different histologic types) is highly variable, consistent with the difficulty of reliably classifying these tumors.[45] The 5-year survival for all patients ranges from 0 to 70%, and the survival of patients in whom both tumors are classified as stage I ranges from 0 to 79%.[47–50] These data suggest that a great deal of caution is necessary in classifying two synchronous foci of cancer as two separate primary lung cancers. Approximately one third of the second foci of cancer are found incidentally at the time of resection.[45] Approximately 60% of synchronous second primary lung cancers are squamous cell cancers; in approximately 60% of the cases, the tumors are of the same histologic type.[45]

The first issue to consider in approaching patients with a synchronous second focus of lung cancer in a different lobe is the accuracy of the diagnosis. If two histologic types of primary NSCLC are diagnosed preoperatively, then it must be remembered that the accuracy of determining lung cancer cell type by cytologic studies is only 60 to 80%.[51–54] A histologic or core needle diagnosis should be obtained, especially when there is evidence of mediastinal lymph node involvement. Mediastinal lymph node involvement increases the probability that a second focus of tumor is an isolated pulmonary metastasis. Even when a diagnosis of synchronous second primary lung cancers is secure, careful staging with distant organ scanning and mediastinoscopy should be carried out because the survival of patients with synchronous MPLC is poor, even in patients who have cancers of different histologic types.[55]

Patients with a synchronous second cancer of similar histologic type present a conundrum. These patients should undergo an extensive search for mediastinal involvement, distant metastases, or an extrapulmonary primary cancer. Genetic marker analysis may be useful in distinguishing between MPLC and a metastasis. In the absence of distant metastases, lymph node involvement, or evidence that the second focus of cancer is a metastasis, resection is reasonable, although the reported long-term survival is generally poor.

Occasionally, patients who are not suspected of having a second primary cancer are found intraoperatively to have a second cancer. It is usually difficult to determine whether the histologic type of the two cancers is the same or different on frozen-section examination. No published data specifically address this situation. The panel believes that it is reasonable to proceed with a resection of each lesion when each seems to be a resectable primary lung cancer, given that the patient has already been exposed to the morbidity of a thoracotomy. However, this can be recommended only when the patient has adequate pulmonary reserve to tolerate the resection, when there is no mediastinal nodal involvement, and when there is no clinical evidence of distant metastases. Concerns about the adequacy of pulmonary reserve may make it necessary to perform a limited resection (segmentectomy or wedge) of one or both of the lesions. Nevertheless, the resection must be a complete resection; if this cannot be achieved, then nothing more than a biopsy of the lesions for diagnosis is indicated. The prognosis after resection in such situations has not been defined but is likely to be poor, similar to the survival of patients with synchronous primary lung cancers that are recognized or at least suspected preoperatively.

Recommendations

16. In patients who have two synchronous primary NSCLCs and are being considered for curative surgical resection, invasive mediastinal staging and extrathoracic imaging (head CT/MRI plus either whole-body PET or abdominal CT plus bone scan) are recommended. Involvement of mediastinal nodes and/or metastatic disease represents a contraindication to resection. Grade of recommendation, 1C

17. In patients suspected of having two synchronous primary NSCLCs, a thorough search for an extrathoracic primary cancer to rule out the possibility that both of the lung lesions represent metastases is recommended. Grade of recommendation, 1C

18. In patients (not suspected of having a second focus of cancer) who are found intraoperatively to have a second cancer in a different lobe, resection of each lesion is recommended, provided that the patient has adequate pulmonary reserve and there is no N2 nodal involvement. Grade of recommendation, 1C

Metachronous Second Primary Lung Cancer

Definition: A metachronous second focus of lung cancer is easily defined as a second primary lung

cancer when the two tumors are of different histologic types. When they are of the same type, the second focus can be reliably defined as a second primary when there is no evidence of systemic metastases and at least a 4-year interval between the two.[45] Some authors[56] have included patients with > 2-year interval, but the estimated incidence of a solitary pulmonary metastasis from the previous lung cancer is practically the same as the estimated incidence of a new primary lung cancer.[45] Therefore, an interval of 2 to 4 years represents a gray area, where it is difficult to determine whether a new lesion is a second primary. If the interval is < 2 years, then it is much more likely that the lesion is a metastasis from the original cancer than a second primary lung cancer.

Patient Selection and Treatment Results: Among studies that have reported on metachronous second primary lung cancers, approximately two thirds of these have been tumors of the same histologic type (most often squamous cell).[45] The average time interval between tumors in these studies is 48 months. Approximately 80% of second primary lung cancers are found on a routine chest radiograph, and approximately 75% are stage I.[45–47] Approximately 65% of second primary lung cancers are able to be resected, with approximately one third of the resections involving a limited resection. The operative mortality for the resection has been reported to average 7%.[45] The 5-year survival of all patients who present with a second primary is approximately 20%.[48,50,57,58] The survival of patients who are able to undergo resection of the second primary is 36%.[48–50,55,59–62] The survival of patients who are found to have a second primary lung cancer that is stage pI is also only 36% (range, 20 to 50%).[48,49,55,58,59,61]

A careful search for sites of recurrence should be conducted in patients who present with a nodule that is suspected of being a metachronous second primary lung cancer. This is particularly important when the histologic type is the same as the primary cancer and when the interval between cancers has been < 4 years. A new cancer that appears in < 2 years should be assumed to be a metastasis unless it is clearly of different histologic type. Although some cancers that appear between 2 and 4 years after the first primary lung cancer are probably MPLC, a fair amount of doubt about this exists until the interval has been > 4 years. Resection of a second primary lung cancer that is early stage should be undertaken, although the prognosis is not as good as that of an early stage single primary lung cancer.

RECOMMENDATION

19. In patients who have a metachronous NSCLC and are being considered for curative surgical resection, invasive mediastinal staging and extrathoracic imaging (head CT/MRI plus either whole-body PET or abdominal CT plus bone scan) are recommended. Involvement of mediastinal nodes and/or metastatic disease represents a contraindication to resection. Grade of recommendation, 1C

Isolated Brain Metastasis

Patient Selection and Workup: Approximately 25% of patients with stage IV NSCLC have a brain metastasis as well as other sites of metastatic disease.[63] The median survival of patients with a brain metastasis is approximately 2 months when treated with steroids alone and 3 to 6 months when treated with whole-brain radiotherapy (WBRT).[63] Because the survival of patients with a brain metastasis is so short, there is reason to consider aggressive treatment of the brain metastasis with either surgical resection or radiosurgery as a palliative treatment to prolong survival. However, a subset of patients with stage IV disease have a brain metastasis as the only site of metastatic disease. In this group, it is reasonable to consider aggressive therapy of both the primary lesion and the isolated metastatic site as a potentially curative therapy. This latter group is the focus of this section. Patients who have a brain metastasis and are treated with surgery or radiosurgery of the brain metastasis as a palliative treatment are discussed in the "Palliative Care in Lung Cancer" chapter.

Aggressive treatment of a brain metastasis may involve either surgical resection of the metastasis or ablation of the metastasis by radiosurgery. This latter technique involves a precisely focused beam of radiation with a steep fall-off of the dose outside the target area, hence the name radiosurgery. Although no randomized trial of surgery vs radiosurgery has ever been completed, comparison of the results of these techniques in patients who have been treated palliatively suggests that they are similar with regard to survival, local control, morbidity, and mortality.[64,65] A number of technical issues often favor one of these treatments over the other; therefore, they are best viewed as complementary modalities. In the discussion in this section, they are considered together as similar methods of aggressive treatment of a brain metastasis.

Patients with a brain metastasis should be selected for curative treatment only after a thorough search for other sites of disease has been negative. Furthermore, it is fairly obvious that only patients in whom

both the brain metastasis and the primary tumor can be completely resected can be considered candidates for curative treatment (synchronous presentation). It seems reasonable to assume that patients with N2,3 involvement and a brain metastasis are not good candidates for curative therapy, although data demonstrating this are lacking.[65] Therefore, it seems reasonable to perform mediastinoscopy in selecting patients for resection of the brain metastasis and the primary lesion. The histologic subtype does not play a role.[65] The number of brain metastases may not play a role as long as the number is small (≤ 3) and they all can be completely resected (as has been demonstrated by several retrospective studies in patients who were treated for palliation).[66–69]

The outlook is likely to be more optimistic for patients who are younger or female or have a metachronous presentation.[65] The outlook may also be better in patients with supratentorial lesions and those with a brain metastasis < 3 cm in diameter. However, these considerations are relative and should not necessarily exclude patients who are otherwise fit and in whom a complete resection is likely to be achieved.

Treatment Outcomes: Survival statistics of patients who have a brain metastasis and were treated with curative intent have been reported by a number of studies.[65] The overall survival for all patients is fairly consistent and averages 14% (range, 8 to 21%). The 5-year survival for patients in whom complete resection has been achieved averages 21% (range, 16 to 30%).[65] The operative mortality in these studies has been low, averaging 2%.[65] Approximately two thirds of the cases involved a metachronous presentation.[65]

There are conflicting data regarding the role of adjuvant WBRT after resection of an isolated brain metastasis. Retrospective analyses of patients who were primarily treated with curative intent have suggested either no survival benefit[70] or a significant benefit.[71] The rate of intracranial recurrence among patients who were treated primarily with palliative intent was lower after WBRT in a randomized study,[72] whereas retrospective analyses[65] in such patients have shown conflicting results. It is likely that a benefit might be seen only in patients without other sites of metastases, given the experience with prophylactic cranial irradiation in patients with small cell lung cancer. There are no data regarding the role of adjuvant chemotherapy in patients who have undergone curative resection of a brain metastasis.

Recommendations

20. In patients who have an isolated brain metastasis from NSCLC and are being considered for curative resection of a stage I or II lung primary tumor, invasive mediastinal staging and extrathoracic imaging (head CT/MRI plus either whole-body PET or abdominal CT plus bone scan) are recommended. Involvement of mediastinal nodes and/or metastatic disease represents a contraindication to resection. Grade of recommendation, 1C

21. In patients with no other sites of metastases and a synchronous resectable N0,1 primary NSCLC, resection or radiosurgical ablation of an isolated brain metastasis is recommended (as well as resection of the primary tumor). Grade of recommendation, 1C

22. In patients with no other sites of metastases and a previously completely resected primary NSCLC (metachronous presentation), resection or radiosurgical ablation of an isolated brain metastasis is recommended. Grade of recommendation, 1B

23. In patients who have undergone a curative resection of an isolated brain metastasis, adjuvant WBRT is suggested, although there are conflicting and insufficient data regarding a benefit with respect to survival or the rate of recurrent brain metastases. Grade of recommendation, 2B

24. In patients who have undergone curative resections of both the isolated brain metastasis and the primary tumor, adjuvant chemotherapy may be considered. Grade of recommendation, 2C

Isolated Adrenal Metastasis

Highly selected patients who have undergone resection of an adrenal metastasis from NSCLC with intent to cure have been reported.[65,73,74] The overall 5-year survival for these patients has been 10 to 23%. Survival after resection of the primary and the adrenal metastasis seems to be good primarily in patients without nodal involvement.[65,74] Other factors such as the histologic type, synchronous vs metachronous presentation, and ipsilateral vs contralateral location do not have prognostic value in the limited number of reported patients who underwent this treatment.[65,73,74]

One report[75] from a single institution suggested that a disease-free interval > 6 months is an independent and significant predictor of increased survival in patients who undergo resection of an isolated solitary adrenal metastasis from NSCLC. The overall 5-year survival was 23.3% in the 23 patients treated but was 38% after resection of an isolated adrenal metastasis that occurred > 6 months after lung resection. All patients with a disease-free interval of

< 6 months died within 2 years of the operation, most commonly from progression of their disease.

Recommendations

25. In patients who have an isolated adrenal metastasis from NSCLC and are being considered for curative intent surgical resection, invasive mediastinal staging and extrathoracic imaging (head CT/MRI plus either whole-body PET or abdominal CT plus bone scan) are recommended. Involvement of mediastinal nodes and/or metastatic disease represents a contraindication to resection. Grade of recommendation, 1C

26. In patients with a synchronous resectable N0,1 primary NSCLC and no other sites of metastases, resection of the primary tumor and an isolated adrenal metastasis is recommended. Grade of recommendation, 1C

27. In patients with no other sites of metastases and a previously completely resected primary NSCLC (metachronous presentation), resection of an isolated adrenal metastasis is the recommended treatment when the disease-free interval is > 6 months and complete resection of the primary NSCLC has been achieved. Grade of recommendation, 1C

Tumors That Invade the Chest Wall

Patient Selection and Workup: Lung cancers that invade the chest wall are usually peripheral in location, and hilar and mediastinal lymph nodes are less likely to be involved in this group of patients. Tumors that extend to invade the parietal pleura, muscles, and ribs of the chest wall and can be completely resected with *en bloc* resection techniques are classified as T3. Significant numbers of these patients are amenable to treatment by resection, and because of their favorable survival after resection, their disease has been recategorized as stage IIB as long as no lymph nodes are involved. Factors that influence survival in this group of patients include the following: (1) the extent of invasion of the chest wall, (2) completeness of resection of the tumor, and (3) the presence or absence of regional lymph node metastases.

Once lymph node involvement is present, the overall survival after resection of tumors that invade the chest wall is worse and survival is comparable to patients with stage IIIA disease. In patients who are being considered for extensive chest wall resections, it is essential to identify nodal involvement by noninvasive imaging or minimally invasive biopsy techniques before subjecting patients to extensive chest wall resections. Hilar and mediastinal lymph nodes can be assessed before surgery using CT, MRI, and PET scans. Mediastinoscopy remains the most sensitive and specific test for evaluating mediastinal nodes and should be considered before undertaking a major chest wall resection.

The use of spirometry, xenon scanning, and exercise oxygen testing are helpful in identifying patients who are not suitable for surgery on the basis of their pulmonary function. No studies, however, have accurately predicted the increased postoperative pulmonary compromise of patients who have T3 lesions and require chest wall resections. The overall effect on chest wall mechanics can be significant and must be taken into account when evaluating the medical condition of the patient and the extent of the pulmonary resection.

Treatment Outcomes: Overall 5-year survival rates for patients with complete resection range from 18 to 61%.[76–79] Long-term results are affected most importantly by complete resection to microscopically negative margins and by absence of N2 nodal involvement. In those in whom resection was incomplete or not possible, the 5-year survival in the two largest series[77,79] was virtually zero. The addition of postoperative radiation therapy in these patients does not seem to have an impact on their ultimate survival. In most series, depth of invasion of the tumor affects survival rates, with invasion limited to the pleura being an independent factor favoring long-term survival only when compared with deeper invasion.

Recommendations

28. In patients who have an NSCLC invading the chest wall and are being considered for curative intent surgical resection, invasive mediastinal staging and extrathoracic imaging (head CT/MRI plus either whole-body PET or abdominal CT plus bone scan) are recommended. Involvement of mediastinal nodes and/or metastatic disease represents a contraindication to resection, and definitive chemoradiotherapy is recommended for these patients. Grade of recommendation, 2C

29. At the time of resection of a tumor invading the chest wall, we recommend that every effort be made to achieve a complete resection. Grade of recommendation, 1B

Conclusions

The available data for patients with Pancoast tumors suggest that the best survival is achieved by

preoperative chemoradiotherapy followed by surgical resection in carefully selected patients. Preoperative radiotherapy followed by surgical resection is a reasonable alternative. Involvement of subclavian vessels, vertebral column, or mediastinal lymph nodes is associated with poor survival after resection. At the time of resection, it is important to perform a complete resection that should involve at least a lobectomy. There are no data on how unresectable yet still potentially curable Pancoast tumors should be managed. However, extrapolation from the data for non-Pancoast stage III NSCLC suggests that chemoradiotherapy is the best approach. For patients in whom cure is not believed to be possible, radiotherapy offers good palliation of pain.

Although most patients with T4 NSCLC have N2,3 or M1 involvement, surgical resection should be pursued in highly selected patients with T4N0,1M0 tumors. The survival of such patients in whom a complete resection is achieved seems to be better than after treatment with chemoradiotherapy alone. However, the operative mortality is relatively high, and patients must be carefully staged and selected. In patients with complete resection and an absence of N2 mediastinal lymph nodes, long-term survival is possible. Preoperative chemoradiotherapy may also be beneficial.

An additional small pulmonary nodule is not an infrequent finding on a CT scan in patients with an NSCLC. Most of these lesions are benign. If the lesion is within the same lobe as the lung cancer, then no special workup is necessary other than what would usually be done because lobectomy is associated with good survival even when a second focus of cancer is present (satellite lesion). When a second lesion in another lobe is suspected of being malignant, it is difficult to define whether this represents a synchronous second primary lung cancer vs a manifestation of systemic disease. The patient should undergo a thorough investigation for evidence of metastatic disease before making a decision regarding treatment. The prognosis and whether resection should be undertaken are difficult to define when two lesions of the same histologic type are present in different lobes. Resection of both lesions may be appropriate, but the prognosis is likely to be much worse than for similarly staged isolated primary lung cancers.

A careful search for sites of recurrence should be conducted in patients who present with a nodule that is suspected to be a metachronous second primary lung cancer. This is particularly important when the histologic type is the same as the primary cancer and when the interval between cancers has been < 4 years. A new cancer that appears in < 2 years should be assumed to be a metastasis unless it is clearly of a different histologic type. Although some cancers that appear between 2 and 4 years after the first primary lung cancer may be MPLC, a fair amount of doubt about this exists until the interval has been > 4 years. Resection of an early stage second primary lung cancer should be undertaken, although the prognosis is not as good as that for an early stage single primary lung cancer.

Patients who have previously undergone complete resection of the primary tumor but are subsequently found to have a solitary cranial or adrenal metastasis should be evaluated for resection of the metastasis with curative intent. In addition, patients who present with a resectable primary lung cancer and a solitary metastasis to the brain and possibly also the adrenal gland should be evaluated for possible resection of both lesions with curative intent. It is necessary to perform a careful search for other sites of metastases, and patients with mediastinal node involvement should be excluded from such an approach. Five-year survival rates of 15 to 20% have consistently been reported in patients who have undergone resection of a solitary metastasis (as well as resection of the primary tumor).

Summary of Recommendations

1. In patients with a Pancoast tumor, it is recommended that a tissue diagnosis be obtained before initiation of therapy. Grade of recommendation, 1C

2. In patients who have a Pancoast tumor and are being considered for curative intent surgical resection, an MRI of the thoracic inlet and brachial plexus is recommended to rule out tumor invasion of unresectable vascular structures or the extradural space. Grade of recommendation, 1C

3. In patients with a Pancoast tumor involving the subclavian vessels or vertebral column, it is suggested that resection be undertaken only at a specialized center. Grade of recommendation, 2C

4. In patients who have a Pancoast tumor and are being considered for curative resection, invasive mediastinal staging and extrathoracic imaging (head CT/MRI plus either whole-body PET or abdominal CT plus bone scan) are recommended. Involvement of mediastinal nodes and/or metastatic disease represents a contraindication to resection. Grade of recommendation, 1C

5. In patients with a potentially resectable, nonmetastatic Pancoast tumor (and good performance status), it is recommended that preoperative concurrent chemoradiotherapy be given before resection. Grade of recommendation, 1B

6. In patients who undergo resection of a Pancoast tumor, it is recommended that every effort be made to achieve a complete resection. Grade of recommendation, 1A

7. It is recommended that resection of a Pancoast tumor consist of a lobectomy (instead of a nonanatomic wedge resection) as well as the involved chest wall structures. Grade of recommendation, 1C

8. In patients with either a completely or incompletely resected Pancoast tumor, postoperative radiotherapy is not recommended because of lack of demonstrated survival benefit. Grade of recommendation, 2C

9. In patients who have an unresectable but nonmetastatic Pancoast tumor and good performance status, definitive concurrent chemotherapy and radiotherapy is recommended. Grade of recommendation, 1C

10. In patients who have Pancoast tumors and are not candidates for curative intent treatment, palliative radiotherapy is recommended. Grade of recommendation, 1B

11. In patients who have a clinical T4N0,1M0 NSCLC and are being considered for curative resection, it is recommend that invasive mediastinal staging and extrathoracic imaging (head CT/MRI plus either whole-body PET or abdominal CT plus bone scan) be undertaken. Involvement of mediastinal nodes and/or metastatic disease represents a contraindication to resection. Grade of recommendation, 1C

12. In patients with a T4N0,1M0 NSCLC, it is recommended that resection be undertaken only at a specialized center. Grade of recommendation, 1C

13. In patients with suspected or proven lung cancer and a satellite nodule within the same lobe, it is recommend that no further diagnostic workup of a satellite nodule be undertaken. Grade of recommendation, 1B

14. In patients with a satellite lesion within the same lobe as a suspected or proven primary lung cancer, evaluation of extrathoracic metastases and confirmation of the mediastinal node status should be performed as dictated by the primary lung cancer alone and not modified because of the presence of the satellite lesion. Grade of recommendation, 1C

15. In patients with NSCLC and a satellite focus of cancer within the same lobe (and no mediastinal or distant metastases), resection via a lobectomy is the recommended treatment. Grade of recommendation, 1B

16. In patients who have two synchronous primary NSCLCs and are being considered for curative surgical resection, invasive mediastinal staging and extrathoracic imaging (head CT/MRI plus either whole-body PET or abdominal CT plus bone scan) are recommended. Involvement of mediastinal nodes and/or metastatic disease represents a contraindication to resection. Grade of recommendation, 1C

17. In patients suspected of having two synchronous primary NSCLCs, a thorough search for an extrathoracic primary cancer is recommended to rule out the possibility that both of the lung lesions represent metastases. Grade of recommendation, 1C

18. In patients (not suspected of having a second focus of cancer) who are found intraoperatively to have a second cancer in a different lobe, resection of each lesion is recommended, provided that the patient has adequate pulmonary reserve and there is no N2 nodal involvement. Grade of recommendation, 1C

19. In patients who have a metachronous NSCLC and are being considered for curative surgical resection, invasive mediastinal staging and extrathoracic imaging (head CT/MRI plus either whole-body PET or abdominal CT plus bone scan) are recommended. Involvement of mediastinal nodes and/or metastatic disease represents a contraindication to resection. Grade of recommendation, 1C

20. In patients who have an isolated brain metastasis from NSCLC and are being considered for curative resection of a stage I or II lung primary tumor, invasive mediastinal staging and extrathoracic imaging (head CT/MRI plus either whole-body PET or abdominal CT plus bone scan) are recommended. Involvement of mediastinal nodes and/or metastatic disease represents a contraindication to resection. Grade of recommendation, 1C

21. In patients with no other sites of metastases and a synchronous resectable N0,1 primary NSCLC, resection or radiosurgical ablation of an isolated brain metastasis is recommended (as well as resection of the primary tumor). Grade of recommendation, 1C

22. In patients with no other sites of metastases and a previously completely resected primary NSCLC (metachronous presentation), resection or radiosurgical ablation of an isolated brain metastasis are recommended. Grade of recommendation, 1B

23. In patients who have undergone a curative resection of an isolated brain metastasis, adjuvant WBRT is suggested, although there are conflicting and insufficient data regarding a benefit with respect to survival or the rate of recurrent brain metastases. Grade of recommendation, 2B

24. In patients who have undergone curative resections of both the isolated brain metastasis and the primary tumor, adjuvant chemotherapy may be considered. Grade of recommendation, 2C

25. In patients who have an isolated adrenal metastasis from NSCLC and are being considered for curative intent surgical resection, invasive mediastinal staging and extrathoracic imaging (head CT/MRI plus either whole-body PET or abdominal CT plus bone scan) are recommended. Involvement of mediastinal nodes and/or metastatic disease represents a contraindication to resection. Grade of recommendation, 1C

26. In patients with a synchronous resectable N0,1 primary NSCLC and no other sites of metastases, resection of the primary tumor and an isolated adrenal metastasis is recommended. Grade of recommendation, 1C

27. In patients with no other sites of metastases and a previously completely resected primary NSCLC (metachronous presentation), resection of an isolated adrenal metastasis is the recommended treatment when the disease-free interval is > 6 months and complete resection of the primary NSCLC has been achieved. Grade of recommendation, 1C

28. In patients who have an NSCLC invading the chest wall and are being considered for curative intent surgical resection, invasive mediastinal staging and extrathoracic imaging (head CT/MRI plus either whole-body PET or abdominal CT plus bone scan) are recommended. Involvement of mediastinal nodes and/or metastatic disease represents a contraindication to resection, and definitive chemoradiotherapy is recommended for these patients. Grade of recommendation, 2C

29. At the time of resection of a tumor invading the chest wall, we recommend that every effort be made to achieve a complete resection. Grade of recommendation, 1B

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