CHEST Supplement

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

Special Treatment Issues in Non-small Cell Lung Cancer

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

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Background: **This guideline updates the second edition and addresses patients with particular forms of non-small cell lung cancer that require special considerations, including Pancoast tumors, T4 N0,1 M0 tumors, additional nodules in the same lobe (T3), ipsilateral different lobe (T4) or contralateral lung (M1a), synchronous and metachronous second primary lung cancers, solitary brain and adrenal metastases, and chest wall involvement.**

Methods: **The nature of these special clinical cases is such that in most cases, meta-analyses or large prospective studies of patients are not available. To ensure that these guidelines were supported by the most current data available, publications appropriate to the topics covered in this article were obtained by performing a literature search of the MEDLINE computerized database. Where possible, we also reference other consensus opinion statements. Recommendations were developed by the writing committee, graded by a standardized method, and reviewed by all members of the Lung Cancer Guidelines panel prior to approval by the Thoracic Oncology NetWork, Guidelines Oversight Committee, and the Board of Regents of the American College of Chest Physicians.**

Results: **In patients with a Pancoast tumor, a multimodality approach appears to be optimal, involving chemoradiotherapy and surgical resection, provided that appropriate staging has been carried out. Carefully selected patients with central T4 tumors that do not have mediastinal node involvement are uncommon, but surgical resection appears to be beneficial as part of their treatment rather than definitive chemoradiotherapy alone. Patients with lung cancer and an additional malignant nodule are difficult to categorize, and the current stage classification rules are ambiguous. Such patients should be evaluated by an experienced multidisciplinary team to determine whether the additional lesion represents a second primary lung cancer or an additional tumor nodule corresponding to the dominant cancer. Highly selected patients with a solitary focus of metastatic disease in the brain or adrenal gland appear to benefit from resection or stereotactic radiosurgery. This is particularly true in patients with a long disease-free interval. Finally, in patients with chest wall involvement, provided that the tumor can be completely resected and N2 nodal disease is absent, primary surgical resection should be considered.**

Conclusions: **Carefully selected patients with more uncommon presentations of lung cancer may benefit from an aggressive surgical approach.** ***CHEST 2013; 143(5)(Suppl):e369S–e399S***

Abbreviations: AAH = adenomatous alveolar hyperplasia; ACCP = American College of Chest Physicians; BAC = bronchioloalveolar carcinoma; GGO = ground glass opacity; IASLC = International Association for the Study of Lung Cancer; MFLC = multifocal lung cancer; NSCLC = non-small cell lung cancer; SPLC = second primary lung cancer; SVC = superior vena cava; UICC = International Union Against Cancer; WBRT = whole-brain radiotherapy

Pancoast Tumor

2.4.1. In patients with a Pancoast tumor, it is recommended that a tissue diagnosis be obtained prior to the initiation of therapy (Grade 1C)**.**

2.4.2. In patients with a Pancoast tumor being considered for curative-intent surgical resection, an MRI of the thoracic inlet and brachial plexus is recommended to characterize possible tumor invasion of vascular structures or the extradural space (Grade 1C)**.**

2.4.3. In patients with a Pancoast tumor 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 (Grade 1C)**.**

Remark: Involvement of mediastinal nodes and/or metastatic disease represents a contraindication to resection.

2.4.4. In patients with a potentially resectable Pancoast tumor (and good performance status), it is suggested that preoperative concurrent chemoradiotherapy is given prior to resection (Grade 2B)**.**

2.4.5. In patients undergoing resection of a Pancoast tumor, it is recommended that every effort be made to achieve a complete resection (Grade 1B)**.**

2.4.6. In patients undergoing resection of a Pancoast tumor, it is suggested that the resection consist of a lobectomy (instead of a nonanatomic wedge resection), as well as the involved chest wall structures (Grade 2C)**.**

2.4.7. In patients with an unresectable, nonmetastatic Pancoast tumor who have good performance status, definitive concurrent chemotherapy and radiotherapy are suggested (Grade 2C)**.**

2.4.8. In patients with Pancoast tumors who are not candidates for curative-intent treatment, palliative radiotherapy is suggested (Grade 2B)**.**

Tumors Invading Chest Wall

3.3.1. In patients with a non-small cell lung cancer (NSCLC) invading the chest wall who 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 suggested (Grade 2C)**.**

3.3.2. In patients with an NSCLC invading the chest wall, involvement of mediastinal nodes and/or metastatic disease represent a contraindication to resection, and definitive chemoradiotherapy is suggested for these patients (Grade 2C)**.**

3.3.3. At the time of resection of a tumor invading the chest wall, it is recommended that every effort be made to achieve a complete resection (Grade 1B)**.**

Central T4 N0,1 M0 Tumors

4.3.1. In patients with a clinical T4 N0,1 M0 NSCLC being considered for curative resection, it is recommended that extrathoracic imaging (head CT/MRI plus either whole-body PET or abdominal CT plus bone scan) be undertaken (Grade 1C)**.**

Remark: Metastatic disease represents a contraindication to resection.

4.3.2. In patients with a clinical T4 N0,1 M0 NSCLC without distant metastases being considered for curative resection, it is suggested

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that invasive mediastinal staging be undertaken. Involvement of mediastinal nodes represents a contraindication to primary resection (Grade 2C)**.**

Remark: Preoperative chemotherapy and resection has resulted in long-term survival in experienced centers in patients with mediastinal nodal involvement.

4.3.3. In patients with a clinical T4 N0,1 M0 NSCLC being considered for curative resection, it is suggested that resection be undertaken only at a specialized center (Grade 2C)**.**

Second Primary Lung Cancer

5.2.4.1. In patients with two foci typical of a primary lung cancer (either proven or suspected, ie, solid, spiculated masses), it is suggested that identification of these as second primary lung cancers (either synchronous or metachronous) should be based on the judgment of a multidisciplinary team, taking into account clinical, radiologic, and (if available) tumor cytologic/histologic features (Grade 2C)**.**

Remark: The multidisciplinary team should include a thoracic radiologist, pulmonologist, thoracic surgeon, and pathologist.

5.2.4.2. In patients with two primary NSCLCs (synchronous or metachronous) being considered for curative surgical resection, invasive mediastinal staging and extra-thoracic imaging (head CT/MRI plus either whole-body PET or abdominal CT plus bone scan) are recommended (Grade 1B)**.**

Remark: Involvement of mediastinal nodes and/or metastatic disease represents a contraindication to resection.

5.2.4.3. 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 suggested, provided the patient has adequate pulmonary reserve and there is no N2 nodal involvement (Grade 2C)**.**

Additional Tumor Nodules in the Same Lobe ($T3_{Satell}$)

5.3.2.3.1. In patients with suspected or proven lung cancer and an additional (suspected) tumor nodule within the same lobe, it is recommended that no further diagnostic workup of the additional nodule is undertaken (Grade 1B)**.**

5.3.2.3.2. In patients with an additional (suspected) tumor nodule within the same lobe as a suspected or proven primary lung cancer, it is recommended that evaluation of extrathoracic metastases and confirmation of the mediastinal node status should be carried out as dictated by the primary lung cancer alone and not modified due to the presence of the additional lesion (Grade 1C)**.**

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

Ipsilateral Different Lobe Tumor Nodules ($T4_{Ipsi\ Nod}$)

5.3.3.3.1. In patients with suspected or proven lung cancer and an ipsilateral different lobe nodule(s), it is recommended that the judgment of a multidisciplinary team should reasonably exclude the possibility that this represents a benign lesion or a synchronous primary lung cancer, taking into account clinical, radiologic, and (if available) tumor cytologic/histologic features (Grade 1C)**.**

Remark: The multidisciplinary team should include a thoracic radiologist, pulmonologist, thoracic surgeon, and pathologist at a minimum.

5.3.3.3.2. In patients with an ipsilateral different lobe tumor nodule(s), it is suggested that evaluation for possible extrathoracic metastases (eg, PET and brain MRI/CT) should be carried out (Grade 2C)**.**

Remark: The presence of distant metastases indicates the pulmonary nodule most likely represents metastatic (M1b) disease.

5.3.3.3.3. In patients with an ipsilateral different lobe tumor nodule(s), it is suggested that invasive evaluation to rule out mediastinal node involvement should be carried out (Grade 2C)**.**

Remark: Such involvement rules out curative-intent treatment.

5.3.3.3.4. In patients with NSCLC and an ipsilateral different lobe tumor nodule(s) (and no mediastinal or distant metastases), resection of each lesion is recommended, provided the patient has adequate pulmonary reserve (Grade 1B)**.**

Contralateral Lobe Tumor Nodules ($M1a_{Contr\ Nod}$)

5.3.4.3.1 In patients with a contralateral lobe tumor nodule(s), it is suggested that evaluation

of extrathoracic metastases (eg, PET and brain MRI/CT) and invasive evaluation to rule out mediastinal node involvement should be carried out (Grade 2C)**.**

Remark: Such involvement represents a contraindication curative-intent treatment.

5.3.4.3.2. In patients with NSCLC and a contralateral lobe tumor nodule(s) (and no mediastinal or distant metastases), resection of each lesion is suggested, provided the patient has adequate pulmonary reserve (Grade 2C)**.**

Multifocal Lung Cancer

5.4.4.1. In patients with multiple lesions that are at least partially ground glass and are suspected to be malignant, it is suggested that these are classified as multifocal lung cancer (MFLC) (Grade 2C)**.**

5.4.4.2. In patients with suspected or proven MFLC who have a negative clinical evaluation and normal mediastinum by CT, it is suggested that distant and mediastinal staging are not routinely necessary (Grade 2C)**.**

5.4.4.3. In patients with suspected or proven MFLC, it is suggested that curative-intent treatment should be pursued (Grade 2C)**.**

5.4.4.4. In patients with suspected or proven MFLC, it is suggested that sublobar resection of all lesions suspected of being malignant be performed, if feasible (Grade 2C)**.**

Isolated Brain Metastasis

6.3.1. In patients with an isolated brain metastasis from NSCLC being considered for curative treatment, invasive mediastinal staging and extrathoracic imaging (either whole-body PET or abdominal CT plus bone scan) are suggested (Grade 2C)**.**

Remark: Involvement of mediastinal nodes and/or metastatic disease represents a contraindication to curative-intent treatment.

6.3.2. 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 1C)**.**

6.3.3. 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 1C)**.**

6.3.4. In patients who have undergone a curative resection of an isolated brain metastasis, adjuvant whole-brain radiotherapy is suggested (Grade 2B)**.**

Remark: Adjuvant chemotherapy is reasonable in patients with a good performance status with the goal of decreasing the incidence of brain recurrences, although no studies have specifically addressed this.

6.3.5. In patients who have undergone a curative resection of an isolated brain metastasis, adjuvant chemotherapy is suggested (Grade 2B)**.**

Remark: Adjuvant chemotherapy is reasonable in patients with a good performance status, although no studies have specifically addressed this.

Isolated Adrenal Metastasis

7.2.1. In patients with an isolated adrenal metastasis from NSCLC 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 suggested (Grade 2C)**.**

Remark: Involvement of mediastinal nodes and/or other sites of distant metastases represent a contraindication to resection.

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

7.2.3. In patients with no other sites of metastases and a previously completely resected primary NSCLC (*metachronous* presentation), resection of an isolated adrenal metastasis is recommended (Grade 1C)**.**

7.2.4. In patients who have undergone a curative resection of an isolated adrenal metastasis, adjuvant chemotherapy is suggested (Grade 2B)**.**

Remark: Adjuvant chemotherapy is reasonable in patients with a good performance status, although no studies have specifically addressed this.

In general, the primary therapy of localized tumors (stages I and II) is complete surgical resection. The majority of patients with lung cancer involving the mediastinal lymph nodes (stage III) are treated with

chemotherapy and radiation.[2] However, there are several relatively unusual presentations of non-small cell lung cancer (NSCLC) for which the anatomic and biologic issues dictate a different approach. In addition, the presence of an isolated second focus of cancer in a patient with lung cancer presents a situation where the biology of this phenomenon is often not clear, and therefore, the approach to treatment is difficult.

This article addresses patients with particular forms of NSCLC that require special considerations, including patients with Pancoast tumors, T4 N0,1 M0 central tumors, chest wall involvement, additional pulmonary tumor nodules, synchronous and metachronous second primary lung cancers (SPLCs), multifocal lung cancer (MFLC), and solitary metastases.

1.0 Methods

A formal meta-analysis was not available for any of the particular forms of NSCLC that are the subject of this article. Clinical guidelines from other organizations were available and are discussed. These involve primarily consensus opinion statements.[3-7] However, a systematic review of the most recent literature in each of these areas was performed. Using Ovid MEDLINE, each subject area was searched (details available on request), and articles published since the previous American College of Chest Physicians (ACCP) Lung Cancer Guidelines from January 1, 2007, to January 1, 2012, were included. Articles were included if they reported on the key outcome measures in a sufficient sample size as outlined in each table herein. The recommendations in this article are based 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. In particular, the committee carefully reviewed the published literature produced since the second edition of these guidelines published in 2007.[8] The document and recommendations were further reviewed by the entire ACCP Lung Cancer Guidelines panel 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.

Although each subject area in this article was searched systematically, the following questions were specifically identified a priori (Table S1):

1. In patients with a Pancoast tumor, does induction chemoradiation therapy improve complete resection rates and improve 5-year survival compared with preoperative radiotherapy or no preoperative therapy (with or without adjuvant therapy)?
2. Do patients with $T3_{Satell}$ tumors have similar survival to those with $T4_{Ipsi\ Nod}$ disease?
3. How do we determine whether a contralateral tumor lesion is a synchronous primary NSCLC or an $M1a_{Contr\ Nod}$ lesion, and does it matter?

2.0 Pancoast Tumors

2.1 Definition

The formal definition of a superior sulcus tumor (Pancoast tumor) is as follows: a lung cancer arising in the apex of the lung that involves structures of the apical chest wall.[9] Invasion of apical chest wall structures is required at the level of the first rib or above, but it is not necessary to have Horner syndrome or pain radiating down the arm. These lesions frequently invade the brachial plexus, subclavian vessels, or spine. Of note, the stage classification designates such a tumor as T3 if it involves the T1 or T2 nerve roots or first rib and as T4 if there is involvement of C8 or higher nerve roots, cords of the brachial plexus, subclavian vessels, vertebral bodies, or lamina (see Detterbeck et al,[10] "The Stage Classification of Lung Cancer," in the ACCP Lung Cancer Guidelines).

The anatomic location and extension of the tumor determines the presenting signs and symptoms. Most patients with superior sulcus tumors present with shoulder or chest wall pain. These tumors may invade the lower brachial plexus (C8-T1) and present with radicular pain or neurologic findings of the ulnar hand. Hand swelling is a sign of subclavian or brachiocephalic vein compression. Horner syndrome may be present as a result of invasion of the stellate ganglion. Posteroanterior and lateral chest radiographs may demonstrate nothing more than apical pleural thickening because tumors can hide behind the first rib. However, CT scan and MRI can detect small lesions and provide excellent anatomic detail. 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.[9,11]

2.2 Workup

Most superior sulcus tumors are diagnosed through transcutaneous needle biopsy performed under CT imaging guidance. Transbronchial biopsy is less useful because the lesions are usually too peripheral. The majority of tumors are NSCLC, but other lesions, such as granulomas, fungal infections, and small cell lung cancer, can masquerade as NSCLC in the superior sulcus region.[12,13] Therefore, it is recommended that a histologic diagnosis of the mass be obtained prior to initiating any treatment.

Pancoast tumors should be treated like most other resectable lung cancers by performing a thorough preoperative evaluation. Although there are no data regarding the reliability of CT or PET scans for mediastinal node involvement, specifically in patients with Pancoast tumors, the consensus of the panel is that invasive mediastinal staging should be performed in all patients being considered for curative resection, regardless of whether the CT or PET scan suggests involvement of the mediastinal lymph nodes. The

argument to invasively stage 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 (see Silvestri et al,[14] "Methods for Staging Non-small Cell Lung Cancer," in the ACCP Lung Cancer Guidelines), 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 or endobronchial ultrasound/esophageal ultrasound should be done before or after preoperative therapy. An MRI demonstrates involvement of apical chest wall structures, such as the brachial plexus, better than a CT scan,[15] but CT imaging provides more information about the presence of nodal enlargement and pulmonary, hepatic, and adrenal metastases. Therefore, both a chest CT scan and an MRI are indicated to assess the resectability of a Pancoast tumor. No new data have been published regarding the presentation, imaging, diagnosis, or staging workup of Pancoast tumors since the second edition of the ACCP Lung Cancer Guidelines.

2.3 Treatment

The initial results with superior sulcus tumors were quite poor until Shaw et al[16] and Paulson[17] demonstrated that preoperative radiation facilitates surgical resection and improves 5-year survival to 30%. This was the classic approach for curative intent, but alternatives were radiation alone, preoperative chemoradiotherapy followed by resection, and definitive chemoradiotherapy without resection.

Treatment with radiation alone has achieved good palliation of pain in about 75% of patients.[18] In general, very few patients treated with radiation alone are long-term survivors (about 5%).[19] However, many of these series have included patients with advanced-stage tumors. Among studies including primarily patients with a reasonable chance of cure, the average median survival time is 16 months, and the average 5-year survival is 20% (range, 15%-23%).[18,20,21]

Treatment with preoperative radiation and resection has resulted in an average median survival time of 22 months and a 5-year survival of 27%.[19] In these series, approximately one-third of patients underwent an incomplete resection (R1 or R2), and approximately one-third of the resections involved only a limited resection of the affected lobe of the lung. A retrospective analysis demonstrated that a complete resection with negative margins (R0) and a pulmonary resection involving at least a lobectomy are major factors associated with better survival.[22] Furthermore, N2 or N3 lymph node involvement is a negative prognostic factor and should generally be considered a contraindication to surgery.[19] An exception to this rule may be patients with ipsilateral supraclavicular N3 lymph node involvement.[9] Patients with vertebral body or subclavian vessel involvement have traditionally been considered to have an unresectable tumor, but it appears that with improved surgical approaches to these structures, a few experienced centers have been able to achieve reasonable survival in such patients.[23-26] Such patients should be referred to a specialized center with experience in performing this type of resection.

The largest reported series of surgically resected superior sulcus tumors included 225 patients.[27] Only 55% of these patients were treated with preoperative radiation therapy and only 20% with induction chemotherapy. The 5-year survival was 46% for T3 N0 (stage IIB) and $<15\%$ for stage III with T4 or N2 disease. Survival was influenced by T and N status and completeness of resection. However, a pathologic complete resection (R0) was achieved in only 64% of T3 N0 and 39% of T4 N0 tumors, with locoregional disease being the most common form of relapse.

A prospective, multiinstitutional trial involved induction chemoradiation therapy followed by resection[28] in 111 patients with mediastinoscopy-negative T3,4 N0,1 superior sulcus tumors (two cycles of cisplatin and etoposide concurrent with 45-Gy radiation). Patients with stable or responding disease (75%) underwent thoracotomy 3 to 5 weeks later. The procedure of choice was a lobectomy with en bloc resection of involved chest wall structures. One-third of resections showed a complete pathologic response, and 92% had a complete resection. This report demonstrated that induction chemoradiation is feasible in a multiinstitutional setting, improves resectability, and improves the 2-year survival to 70% for those with a complete resection. Further follow-up for these patients demonstrated that disease recurrence occurs primarily at distant sites, and the 5-year survival was 44%. In patients with a complete resection following induction therapy, the 5-year survival was 54%.[29] Other series involving induction chemoradiotherapy identified by the literature review reported very similar results. These studies involved induction chemoradiation therapy followed by surgery and used platinum-based doublets, and the most common radiation dose was 45 Gy. The results from these induction therapy trials are summarized in Figure 1[30-35] and Table S2. These studies were performed by dedicated thoracic surgeons and other specialists in a formal, multidisciplinary setting. Therefore, these results may not be generalizable to all community centers and physicians, and referral to or at least discussion with a larger center should be strongly considered for these patients if a center sees Pancoast tumors infrequently (eg, ≤ 2 per year).

FIGURE 1. [Section 2.3] Results of multimodality treatment of Pancoast tumors.

First Author	Year	No.	% N2,3	% T4	Induction therapy, # of cycles	RT dose (Gy)	% Drop-out[a]	% of operated patients		% 5 y Survival		% Local recurrence
								R0	pCR	2 yr	5 yr	
Rusch[29]	2007	110	0	29	EP x2	45	20	94	34	55	44	9
Kunitoh[32]	2008	76	few	26	MVdP x2	45	24	89	21	67	56	10
Fisher[30]	2008	44	2	32	EP x2	45	-	89	30	67	59	10
Wright[34]	2002	15	0	47	P based	51	-	93	66	93	84[b]	0
Martinez[35]	1994	18	-	50	MVdP x2	45-50	11	76	71	56	56[b]	9
Kappers[31]	2009	39	13	46	P qd	66	44	100	62	70	37	0
Marra[33]	2007	31	29	19	P based	45	7	100	45	-	46	6
Average							**21**	**92**	**47**	**68**	**55**	**6**

Inclusion criteria were studies from December 1989-April 2012 of ≥ 20 patients with Pancoast tumors treated with neoadjuvant chemoradiotherapy and reporting survival data. EP = etoposide, cisplatin; MVdP = mitomycin, vindesine, cisplatin; P = cisplatin; pCR = pathologic complete response; R0 = microscopic complete resection; RT = radiotherapy; y, year.

[a]Patients dropping out of planned treatment prior to resection.

[b]Four-year survival.

No randomized controlled trials have compared different treatment strategies in Pancoast tumors and likely will never be performed given the rarity of the disease. Comparison across series, however, consistently shows better complete resection rates, decreased local recurrence rates, and better overall survival with preoperative chemoradiotherapy as opposed to preoperative radiotherapy followed by resection. The consistency of the data suggests that concurrent chemoradiotherapy followed by complete resection in an experienced center is the best treatment strategy.

A review of all published guidelines through 2012 showed that all recommend that patients with Pancoast tumors be evaluated by a thoracic surgeon. If there is no evidence of mediastinal node involvement, patients should undergo resection following induction radiotherapy or chemoradiotherapy.[3-5] These procedures are technically complicated, and these patients should be evaluated by a thoracic surgeon with the experience and capacity to perform a complete resection, including reconstruction of subclavian vessels, en bloc resection of vertebral bodies, and sacrificing lower cervical and upper thoracic nerve roots.[9] Patients with inoperable, painful Pancoast tumors should be treated with radiotherapy with or without chemotherapy for palliation of their pain.[7] The latter two recommendations from other guidelines were rated grade B, whereas the strength of the other statements was rated grade C. Thus, other guidelines have reached the same conclusions as the ACCP Lung Cancer Guidelines, although the recommendations in the other guidelines have been 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 has traditionally been 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 patients with unresectable, yet potentially curable Pancoast tumors should be treated. 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.

2.4 Recommendations

2.4.1. In patients with a Pancoast tumor, it is recommended that a tissue diagnosis be obtained prior to the initiation of therapy (Grade 1C)**.**

2.4.2. In patients with a Pancoast tumor being considered for curative-intent surgical resection, an MRI of the thoracic inlet and brachial plexus is recommended to characterize possible tumor invasion of vascular structures or the extradural space (Grade 1C)**.**

2.4.3. In patients with a Pancoast tumor 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 represent a contraindication to resection (Grade 1C)**.**

2.4.4. In patients with a potentially resectable Pancoast tumor (and good performance status), it is suggested that preoperative concurrent chemoradiotherapy is given prior to resection (Grade 2B)**.**

2.4.5. In patients undergoing resection of a Pancoast tumor, it is recommended that every effort be made to achieve a complete resection (Grade 1B)**.**

2.4.6. In patients undergoing resection of a Pancoast tumor, it is suggested that the resection consist of a lobectomy (instead of a nonanatomic wedge resection) as well as the involved chest wall structures (Grade 2C)**.**

2.4.7. In patients with an unresectable, but nonmetastatic Pancoast tumor who have good performance status, definitive concurrent chemotherapy and radiotherapy is suggested (Grade 2C)**.**

2.4.8. In patients with Pancoast tumors who are not candidates for curative-intent treatment, palliative radiotherapy is suggested (Grade 2B)**.**

3.0 Tumors Invading the Chest Wall

3.1 Patient Selection and Workup

Chest wall involvement occurs in $<8\%$ of patients with newly diagnosed NSCLC. In the absence of metastatic spread, en bloc anatomic surgical resection of the involved lung and chest wall is the primary treatment for most patients. These lesions are T3 tumors and, if node negative (N0), have been reclassified as stage IIB disease.[36,37] If lymph node involvement is present, the overall survival following resection of T3 tumors is reduced such that T3 N1,2 tumors remain in the stage IIIA category. Factors identified in our literature review that influence survival in this group of patients were completeness of resection, the extent of chest wall invasion, and the presence of regional lymph node metastasis.[38,39]

No studies specifically addressed the need for distant and mediastinal staging in patients with a chest wall tumor. However, in general, data support further imaging for distant metastases (eg, PET scan) and invasive mediastinal staging for lung cancer.[14] These techniques are carefully reviewed in the NSCLC staging article of these guidelines.[14]

The use of spirometry, quantitative perfusion scanning, and exercise testing are helpful in identifying patients who are at higher risk of perioperative mortality on the basis of their pulmonary function. No studies, however, could accurately predict the increased postoperative pulmonary compromise of patients with T3 lesions who require chest wall resections. In general, the recommendations cited by Brunelli et al,[40] "Physiologic Evaluation of the Patient With Lung Cancer," in the ACCP Lung Cancer Guidelines should apply to chest wall resections.

3.2 Treatment Outcomes

The average 5-year survival of patients with T3 N0 tumors is around 40%, whereas that of patients with T3 N1 tumors is around 20%.[19] However, the 5-year survival of patients with T3 N0 (chest wall) tumors undergoing complete resection has been consistently reported to be 50% to 60%,[41-50] with few exceptions.[51] Long-term results are affected most importantly by complete resection to microscopically negative margins and by absence of N2 nodal involvement.[43] The depth of invasion, as determined histologically, also appears to be a significant factor that influenced survival in most studies,[47,50,52-54] although the largest series found no difference among patients who received complete resections.[48]

In studies of patients in whom resection was incomplete, or not possible, the 5-year survival was consistently $<5\%$.[36,42,47,48,51,55-58] Adjuvant radiation in patients who received incomplete resection did not result in long-term survival,[44,47,56] and local recurrence rates of 30% to 40% at the site of a positive margin were seen, despite the use of radiation (dose not reported).[44,58]

Some controversy remains about whether an en bloc resection of chest wall (vs parietal pleura only) is required for adequate resection of those tumors in which only the parietal pleura is involved.[59] There are no randomized data to answer this question, but retrospective data from most studies showed better survival for complete en bloc resections.[44,60,61] In addition, the ability to assess an adequate margin intraoperatively was poor in some series of extrapleural resections.[44,56] Because the chest wall resection typically adds minimal morbidity,[19] we recommend performing a chest wall resection if there is any question of achieving a complete resection.

3.3 Recommendations

3.3.1. In patients with an NSCLC invading the chest wall who 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 suggested (Grade 2C)**.**

3.3.2. In patients with an NSCLC invading the chest wall, involvement of mediastinal nodes and/or metastatic disease represent a contraindication

to resection, and definitive chemoradiotherapy is suggested for these patients (Grade 2C).

3.3.3. At the time of resection of a tumor invading the chest wall, it is recommended that every effort be made to achieve a complete resection (Grade 1B).

4.0 T4 N0,1 M0 Tumors (Central Tumor With Direct Invasion)

4.1 Patient Selection and Workup

Most patients with involvement of T4 structures have mediastinal node involvement making T4 N0,1 tumors rare. Patients with N2 disease should be treated with chemoradiotherapy, as is generally recommended for other patients with stage IIIB NSCLC[2]; these patients have not been separated from the general cohort of patients with N2 and N3 disease, but there is no reason to believe that the T4 N2,3 cohort represents a special subgroup. However, carefully selected patients with T4 involvement and without mediastinal lymph node involvement can be viewed as candidates for surgery. Although many reports demonstrated the technical feasibility of resection of T4 structures, fewer series have provided long-term survival data. Figure 2 summarizes the data regarding treatment of T4 N0,1 tumors reported from 1980 to 2012 and identified in our search. The largest experience of resection for T4 involvement involves carinal resections, usually together with a right-sided pneumonectomy. Since 1980, there have been 12 published series of carinal resections for lung cancer. Four of the largest series were published since 2000 and provided long-term survival data in 395 patients.[62-65] A modest experience is available with left-side atrial involvement[66-68] and involvement of the superior vena cava (SVC),[69,70] and a smaller experience has been reported with tumors invading the aorta[66,69,71] and vertebral bodies.[72-75] The observation that long-term survival statistics are available in so few patients underscores the fact that patients who are candidates for a surgical approach are extremely rare and highly selected.

Mediastinoscopy or endobronchial ultrasound/esophageal ultrasound should be performed even if a CT or PET scan suggests no N2,3 involvement in patients with T4 tumors 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 (about 25%).[76] Furthermore, a consistent finding is that survival for patients with T4 N2,3 disease is so poor (< 10% after resection) that the presence of positive N2 disease should be considered a contraindication to aggressive surgical therapy.[77] In patients who are being considered for carinal resection, it may be best to perform a mediastinoscopy at the same time as the planned resection to prevent scarring and, therefore, lack of mobility of the airways for tracheobronchial reconstruction, if indicated.

4.2 Outcomes After Surgery

Surgical outcomes for patients with carinal involvement show an average 5-year survival of 28%. Contributing to this survival is a high perioperative mortality rate averaging 10% (range, 7%-29%). Of importance, the highest reported 5-year survival (44%) comes from one of the largest series,[63] which also reported a low operative mortality of only 7%. Looking across studies, the operative mortality has been decreasing and is consistently < 10% in more recent reports.[77]

The largest reported series of en bloc vertebral resections included 54 consecutive patients operated on over a 20-year period.[72] A complete resection was achieved in 91% of patients, and one-half of the patients received induction therapy. The estimated 5-year survival was 31%, and the most important predictor of survival was a complete resection. Other series reported similar results[23,78-80] in Pancoast tumors.

Figure 2. [Sections 4.1, 4.2] Results of resection of patients with T4 involvement from NSCL.

Structure	No. of Studies	No. of Patients	Hospital Mortality %	% 5-year survival		
				Highest	Lowest	Average
Carina	12	722	10	44	13	**33**
Left atrium	4	88	3.5	22	10	**15**
Superior vena cava	4	189	12	31	21	**25**
Vertebral bodies	4	102	0	31	21	**27**
Aorta	3	60	13	50	17	**31**
Mixed	10	1216	-	38	14	**25**

NSCLC = non-small cell lung cancer.

The SVC is a relatively common T4 structure that is approached for surgical resection (Fig 2). The 5-year survival is about 20% to 25%,[81-83] and the operative mortality is 10% to 14%.[70,81,82] Studies suggested that both long-term survival (28%-31%) and operative mortality (6%-8%) have improved over time.[81,83,84] Multivariable analysis found the extent of surgery (pneumonectomy) and the extent of SVC resection (complete resection with graft replacement) to be negative prognostic factors (but not age, N status, R0 resection, or neoadjuvant therapy) in a retrospective multicenter analysis of 109 patients from 1963 to 2000.[81] Another study of 39 patients undergoing SVC resection identified carinal resection and squamous histology as the only negative prognostic factors (not N status, although 5-year survival was 20% vs 38% with and without N2 involvement, respectively).[83] Several studies found that the presence of N2 lymph nodes identified postoperatively did not significantly affect survival.[70,81,82]

Among those studies focusing specifically on aortic resection, the overall 5-year survival was 25% to 50%.[85,86] The use of neoadjuvant therapy varied from 20% to 62%, with no clear conclusions drawn, and the use of adjuvant therapy was not described. Absence of N2 involvement appears to be associated with better survival (5-year survival of 70% for N0 vs 17% for N1 and 0%-9% for N2,3 disease).[85,86] Complete resection has also been associated with better survival (36% vs 0%).[87] In a series involving a subadventitial resection, the 5-year survival was reported to be 0%.[88]

In general, survival data for resections involving T4 structures have involved relatively few patients, making interpretation of the data difficult (Fig 2). The survival of patients with left-side atrial involvement has been less favorable, and the survival of patients with involvement of other T4 structures has been similar to that reported for patients with carinal involvement. A systematic review of circulatory bypass for the resection of these central tumors demonstrated an overall 5-year survival of 37% and improved outcome when bypass is planned rather than used for intraoperative complications.[89]

Patients with central T4 tumors should be carefully selected before undertaking surgical resection because of the limited long-term survival and the technical difficulty of the surgery. These patients need an excellent performance status with a high likelihood of being able to tolerate such a major operation. It is also prudent to perform a thorough staging evaluation to rule out mediastinal or extrathoracic metastases, and the threshold for pursuing subtle abnormalities seen on imaging tests should be low. Given the rarity of the disease, the complexity of the resection, and the relatively high operative mortality yet possibility of long-term cure, these patients should be seen at an experienced and very-high-volume specialized center.

A systematic review of preoperative chemotherapy or chemoradiotherapy for patients with T4 N0,1 tumors found three trials. A 5-year survival of 20% was reported among all patients in the largest trial (57 patients of whom 62% underwent complete resection).[71] These results are encouraging, given that 60% of the patients entered in the study had T4 N2 M0 tumors by careful surgical staging. By comparison, 5-year survival results for chemoradiotherapy without surgery in patients with stage IIIA,B tumors have been about 9% and 14% in large randomized trials involving sequential or concurrent chemoradiotherapy trials, respectively.[8] However, these latter series included both stage IIIA and IIIB disease and did not report data separately or any data specifically in patients with T4 N0,1 tumors. A retrospective analysis of the Southwest Oncology Group trial suggested that patients with T4 N0,1 M0 tumors benefited from preoperative chemoradiotherapy and surgery compared with chemoradiotherapy alone, with an overall 5-year survival of 54% and 44%, respectively, after complete resection (R0).[29] For comparison, a large number (15) of studies reported on preoperative chemotherapy with and without radiotherapy for patients with T4 or N3 disease, as summarized in a recent review.[77] Approximately two-thirds of patients underwent resection (50% an R0 resection), and the 5-year survival was 25% overall and 40% after R0 resection. These results are impressive for such extensive disease. Collectively, these data suggest that preoperative therapy may be useful for T4 tumors being considered for resection.

4.3 Recommendations

4.3.1. In patients with a clinical T4 N0,1 M0 NSCLC being considered for curative resection, it is recommended that extrathoracic imaging (head CT/MRI plus either whole-body PET or abdominal CT plus bone scan) be undertaken (Grade 1C)**.**

Remark: Metastatic disease represents a contraindication to resection.

4.3.2. In patients with a clinical T4 N0,1 M0 NSCLC without distant metastases being considered for curative resection, it is suggested that invasive mediastinal staging be undertaken. Involvement of mediastinal nodes represents a contraindication to primary resection (Grade 2C)**.**

Remark: Preoperative chemotherapy and resection has resulted in long-term survival in experienced centers in patients with mediastinal nodal involvement.

4.3.3. In patients with a clinical T4 N0,1 M0 NSCLC being considered for curative resection, it is suggested that resection be undertaken only at a specialized center (Grade 2C)**.**

5.0 Additional Nodules and Multiple Primary Lung Cancers

5.1 Categories of Patients and General Approach

Patients who present with a lung cancer and additional nodules or lesions often are a challenge to manage clinically. The different categories of such patients are easily confused. This topic is difficult because the terms and definitions are ambiguous, and usage varies over time and between centers. Further detail regarding the classification of these lesions is provided by Detterbeck et al[10] in the ACCP Lung Cancer Guidelines. An outline of the categories and general approach to patients with additional lesions is shown in Figure 3.

Patients with multiple nodules are categorized on the basis of their clinical presentation. The first category involves patients with a typical (ie, solid, spiculated), potentially operable lung cancer who have an additional small lesion identified on CT scan. Studies that have addressed this reported that the large majority of these additional lesions are benign.[90-92] (Details of some of these studies are described in the second edition of these guidelines.[8]) The experience with CT screening for lung cancer also shows that the majority of nodules, especially if <8 mm, are benign.[93,94] Thus, one must be very careful not to assign a designation that is based on an assumption of malignancy (eg, T3, T4, M1a) in the majority of patients. The difficulty lies in identifying which patients have additional lesions that need to be considered differently. Benign lesions typically are small, subcentimeter nodules. Experience from the workup of solitary pulmonary nodules has shown that an experienced clinical team can make an accurate assessment about which lesions are likely benign and appropriate for observation vs those that are likely malignant and require investigation.[95,96] The physicians most commonly making this judgment are radiologists, pulmonologists, and thoracic surgeons. Therefore, we suggest that a multidisciplinary panel comprising these specialties evaluates such additional small lesions.

Another category of patients is those with additional nodules and a clinical presentation highly suggestive of distant metastatic disease, including patients with several lesions that appear typical for metastatic disease (ie, by PET/CT scan, brain MRI) and a typical clinical presentation (usually a locally advanced, dominant lung cancer and symptoms, eg, anorexia, fatigue). In general, the clinical staging is reliable for

FIGURE 3. [Section 5.1] Approach to patients with additional nodules.

Presentation	Data Summary	Suggested Approach	Outcome	Category	Management
Typical solid cancer and additional nodule on CT	Large majority are benign	Judgment by a multidisciplinary team[a]	Judged very likely benign	Benign lesion	Treatment of Primary lung Cancer, observation of nodule per Fleishner Guidelines.
Locally advanced lung cancer, nodule(s) and presentation suspicious for stage IV	No formal data	PET and Judgment by a multidisciplinary team	Judged very likely stage IV	Stage IV	Stage IV treatment (i.e. chemotherapy)
			Judged unclear	Suspicious for Stage IV	Biopsy of nodule and other potential sites (N2,3 or M1b)
Typical solid cancer and additional typical solid cancer	~1.5% incidence	Judgment by multidisciplinary team[a], thorough work-up to rule out N2,3 or M1b	Meets criteria for synchronous primaries after thorough evaluation	synchronous primaries	Manage each primary accordingly, and as patient will tolerate physiologically
Typical solid cancer and additional solid nodule	IASLC database, but patients poorly defined, survival after resection better than for solitary distant metastasis	Judgment by a multidisciplinary team[a], thorough work-up to rule out N2,3 or M1b	Judged unlikely to be synchronous 2nd primary, but lesion suspected (or proven) malignant with same histology	Lung Cancer with additional cancer nodule	Manage aggressively if T3 or T4 (consider resection), unclear if M1a (contralateral lung)
Lung Cancer with GGO component and additional GGO (or semisolid) lesions	Indirect data, patients poorly defined	Judgment by a multidisciplinary team[a]	Fits a pattern of multifocal disease	Multiple (Multifocal) lung cancer	Manage primary accordingly, manage additional lesions according to guidelines for GGO

GGO = ground glass opacity.
[a]Team should include a chest radiologist, pulmonologist, and thoracic surgeon.

a patient with a dominant lung cancer and multiple metastases on radiographic imaging. Of note, the International Association for the Study of Lung Cancer (IASLC) database specifically excluded patients believed to have metastatic disease from the category of additional foci of cancer.[36,97] In other words, additional lung nodules consistent with distant metastasis in a patient who otherwise also has a presentation compatible with distant metastasis should be classified as M1b. If the presentation is suspicious but atypical either clinically or radiographically, biopsy specimens should be obtained from distant sites, pulmonary nodules, or mediastinal nodes to clarify the situation. An experienced multidisciplinary team can make a reliable clinical diagnosis in the majority of situations.

Patients with additional lesions judged highly likely to be benign or as having distant metastases are not discussed further in this article (for further discussion see Gould et al,[97] "Evaluation of Individuals With Pulmonary Nodules: When Is It Lung Cancer?," and Rivera et al,[98] "Establishing the Diagnosis of Lung Cancer," in the ACCP Lung Cancer Guidelines). The remaining categories are dealt with in detail in the subsequent sections.

FIGURE 4. [Section 5.2.1] T3 tumors, T4 tumors, pulmonary metastases, and multiple primary lung cancers.[100]

T3 Tumors (multiple foci)
Same lobe as primary tumor
and same histology
T4 Tumors (multiple foci)
Different ipsilateral lobe from primary tumor
and anatomically separated
and same histology
Pulmonary metastases
Same histology and multiple systemic metastases
Or
Same histology, in different lobes
and presence of N2, N3 involvement
Or
< 2-year interval
Multiple primary lung cancers
Same histology, tumor in different lobe as primary
and no N2,N3 involvement
and no systemic metastases
Or
Different histology, molecular genetic characteristics or arising from a separate focus of carcinoma in situ
Or
Same histology, temporarily separated
and ≥ 4-year interval between cancers
and no systemic metastases

5.2 Second Primary Lung Cancer

5.2.1 Definitions: This section deals with lesions that are believed to represent SPLCs with either a synchronous or metachronous presentation. This should not be confused with the classification of additional nodules in the IASLC database.[36,97] The seventh edition classification specifically excluded second primary cancers from the cohort of patients with additional nodules; these will be discussed in the next section.

How does one decide whether two foci of lung cancer represent two primary cancers? Traditionally, this has been decided by the treating clinicians usually on the basis of criteria proposed empirically by Martini and Melamed[99] > 35 years ago. In 2003, on the basis of indirect data, the ACCP guidelines proposed slightly modified criteria (Fig 4).[100] Second primary tumors are easy to define when the tumors are histologically different cell types (eg, adenocarcinoma, squamous cell carcinoma). However, it must be recognized that the majority of reports of SPLC have involved tumors of the same cell type.[101-115] Furthermore, there is consistently no difference in outcomes in these series between tumors classified as SPLC on the basis of different histology vs other features,[102-106,112,115-120] suggesting that the traditional criteria for identifying SPLC have worked reasonably well.

There has been a suggestion that adenocarcinomas be distinguished on the basis of the proportion of different histologic subtypes (eg, lepidic, papillary, acinar).[120-127] This suggestion seems reasonable and should be included in the judgment about how to classify a particular pair of tumors, but it has not yet been extensively studied as a method of identifying SPLC. The 2012 International Union Against Cancer (UICC) supplement mentions lung cancer subtyping as a factor to consider.[128]

More recently, there has been interest in using genetic analysis to identify SPLC. Studies that used specific molecular markers or mutations showed conflicting results.[129-135] Furthermore, if an SPLC develops in a patient, it seems likely that there will be similarities as a result of contributing genetic predispositions and environmental factors. However, the importance of histologic type and genetic fingerprinting are called into question by recent data showing tumor heterogeneity and that tumors not only can acquire new mutations but also can transform from an adenocarcinoma to a small cell lung cancer.[136] It is clear that our understanding of these factors is rudimentary and requires further study. At this point, the data regarding molecular genetic features of cancers should be taken into account but should not be regarded as definitive by themselves or to obviate the consideration of other clinical and radiographic features.

A metachronous second focus of lung cancer is easily defined as an SPLC when the two tumors are of different histologic types. When the tumors have

identical histologies, the second focus can be reliably defined as a second primary if there is no evidence of systemic metastases and at least a 4-year interval between the two different occurrences of lung cancer.[8,9] Some authors included patients with a >2-year interval,[99] but the estimated incidence of a solitary pulmonary metastasis from the previous lung cancer is similar to the estimated incidence of a new primary lung cancer. Therefore, an interval of 2 to 4 years represents a gray area, during which it is difficult to determine whether a new lesion is a second primary or a metastasis. If the interval is <2 years, it is much more likely that the lesion is a metastasis from the original cancer. The stage of the original tumor appears to play little role in the likelihood of a metachronous lesion being a new primary cancer once 2 years have passed since curative treatment of the first cancer.[19]

Although it may be reasonable to obtain a biopsy specimen of both tumors, one should first consider whether the interpretation of the situation will be any different if both lesions are of the same histology. This is important because the majority of SPLCs are of similar histology. Furthermore, the ability to determine lung cancer histology by cytologic studies of limited samples can be inaccurate.[98] There are no data on whether classification of two lung cancers in resected specimens can be applied to limited preoperative biopsy samples. Therefore, clinical judgment is critically important, with biopsy results playing a supplementary role.

The clinical judgment of an experienced multidisciplinary team is the most important factor in the definition of SPLC. This team should include a thoracic radiologist, pulmonologist, and thoracic surgeon because they usually are most experienced in the clinical judgment of whether a lesion is a primary lung cancer. The team should also include a thoracic pathologist and, if available, a review of the biopsy material. The team's assessment, taking all features (histologic, genetic, radiologic, and clinical) into account, is critical because the decision of how to approach the patient must be made prior to resection, and the reliability of classification using small biopsy specimens is unclear. The ability to differentiate between SPLC and metastases is reasonably good, but formal assessment is hampered by the lack of a gold standard test that can provide the truth.

5.2.2 Metachronous SPLCs

5.2.2.1 Patient Evaluation—A careful search for sites of recurrence should be conducted in patients who present with a nodule that is suspected of being a metachronous SPLC, especially if the histologic type is the same as the primary cancer and if the interval between cancers has been <4 years. A new cancer appearing in <2 years generally should be assumed to be a metastasis, unless it is clearly of different histologic type. Patients suspected of having a metachronous SPLC should undergo PET scan and brain MRI or CT scan. The role of mediastinal staging is less clear and should probably be determined by the characteristics of the second primary tumor. If the tumors are histologically different or the time interval is long (ie, >5 years), the extent of distant and mediastinal staging should be determined according to the second cancer as outlined by Silvestri et al,[14] "Methods for Staging Non-small Cell Lung Cancer" in the ACCP Lung Cancer Guidelines.

5.2.2.2 Outcomes and Treatment Approach—The majority of studies reporting on metachronous SPLC over the past 25 years demonstrated that approximately two-thirds of these have been tumors of the same histologic type (most often squamous cell).[101-115] The average time interval between tumors in these studies was 48 months.[117,137] Approximately 80% of SPLCs are found on a routine chest radiograph, and about 75% are stage I (Fig 5).[103,113,114,138-145] Approximately 80% of SPLCs are resectable, with about 40% involving a limited resection.[8]

The 5-year survival of all patients who present with a second primary tumor is about 30% (Fig 5). The 5-year survival of patients able to undergo resection of the second primary tumor is about 40%. The survival of patients who are found to have an SPLC that is stage pI is also only about 40% (range, 20%-70%). No data on outcomes of patients who did not undergo resection are available, but it is likely to be worse given the available natural history data.[148] In conclusion, resection of an early stage SPLC should be undertaken, although the prognosis is not as good as that of an early stage single primary lung cancer. Stereotactic body radiosurgery is emerging as another option for treatment, particularly when there is limited pulmonary reserve (see Howington et al,[149] "Treatment of Stage I and II Non-small Cell Lung Cancer," in the ACCP Lung Cancer Guidelines).

5.2.3 Synchronous SPLCs

5.2.3.1 Patient Evaluation—The survival of patients with synchronous (different lobe) SPLC is fairly variable, suggesting that a thoughtful approach is necessary in classifying two synchronous foci of cancer as two separate primary lung cancers. Thus, patients believed to have synchronous SPLC should undergo a careful clinical and radiographic assessment for distant and mediastinal node metastases (ie, PET scan, if available; brain MRI or CT scan; invasive mediastinal staging, preferably with a thorough mediastinoscopy).

5.2.3.2 Outcomes and Treatment Approach—Approximately 60% of synchronous SPLC reported in the past 25 years are squamous cell cancers, and in about 60% of the cases, the tumors are of the same

histologic type.[101,103,104,108-109,113,147] Approximately 90% have undergone resection, and this involved a sublobar resection of at least one of the tumors in about 30% (Fig 5).

The 5-year survival for all patients ranges from 0% to 70%, and the survival of patients in whom both tumors were classified as stage I ranges from 0% to 79% (Fig 6). The average 5-year survival of patients who undergo resection is only about 25%, and that of patients with stage pI disease is about 40%. Nevertheless, this appears to be better than the natural history of untreated lung cancer.[148] In the absence of distant metastases, lymph node involvement, or evidence that the second focus of cancer is a metastasis, resection is preferable to observation according to the available data.

FIGURE 5. [Sections 5.2.2.2, 5.2.3.2] Survival of patients with second primary lung cancers.

First Author	No.	% incidental[a]	% resected	% limited resection[b]	% Operative mortality	% 5-year Survival		
						All	Resected	pI
Synchronous								
Finley[120]	175	42	(100)[c]	27	1	52	52	64[d]
Trousse[194]	125	-	(100)[c]	14	11	34	34	-
Riquet[114]	118	-	(100)[c]	16	5	26	26	-
Rostad[113]	94	79	(100)[c]	16	9	33	33	-
Chang[133]	92	-	(100)[c]	11	1	35	35	-
Van Rens[138]	85	32	(100)[c]	13	14	20	20	23
Fabian[139]	67	-	(100)[c]	60	2	53	53	89
van Bodegom[101]	64	-	50	34	-	-	-	24[e]
Voltolini [140]	50	-	>90	65	7	31	34	-
Shah[49]	47		(100)[c]	41	2	29	29	90
De Leyn[112]	36	-	(100)[c]	72	3	38	38	-
Deschamps[103]	36	42	(100)[c]	21	6	-	16	-
Vansteenkiste[146]	35	-	(100)[c]	23	9	33	33	-
Rosengart[104]	33	-	91	33	-	44	-	-
Jung[142]	32	3	(100)[c]	53[f]	9	61	61	31
Ferguson[147]	28	18	68	47	0	0	0	0
Okada[107]	28	39	(96)[c]	7	0	70	-	79[e]
Kocaturk[143]	26		92	38	8	50	50	-
Antakli[108]	26	19	92	42	-	5	12	-
Ribet[109]	24	-	63	40	4	-	-	-
Average		**34**	**79**	**34**	**5**	**36**	**33**	**51**
Metachronous								
Riquet[114]	116	-	(100)[c]	30	13	32	32	-
von Bodegom[103]	89	-	51	16	9	-	20	20[e]
Mathisen[102]	80	80	(100[c]	61[f]	8[f]	33	-	-
Rosengart[104]	78	-	73	37	2	23	38	38
Battafarano[119]	69		(100)[c]	49	6	33	33	-
Lee[113]	58	-	(100)[c]	50	-	66	66	70
Ribet[109]	51	63	33	35	11	-	58	-
Deschamps[103]	44	86	(100)[c]	43	5	-	34	41
Aziz[144]	41	-	(100)[c]	-	7	44	44	48
Verhagen[105]	40	90	83	18	15	18	-	27[e]
Antakli[108]	39	-	54	49	-	8	23	-
Adebonojo[106]	37	100	97	22	6	-	37	39
Okada[107]	29	-	(100)[c]	-	0	-	33	50[e]
Bae[145]	23	-	(100)[c]	15	5	77	77	65
Wu[113]	20	55	(100)[c]	30	-	-	42	-
Average[g]		**79**	**65**	**35**	**7**	**37**	**41**	**44**

Inclusion criteria were studies from December 1989-April 2012 of ≥ 20 patients with synchronous or metachronous second primary lung cancers reporting survival data. pI = pathologic stage I.

[a]Percentage found incidentally at time of resection (synchronous) or found by routine follow-up chest radiograph (metachronous).

[b]Percentage of patients who underwent wedge resection or segmentectomy.

[c]Surgical series with ≥ 90% of patients who received a resection.

[d]Stage Ia only.

[e]Stages I and II.

[f]Includes patients with synchronous second primary cancers (11%).

[g]Excluding values in parentheses.

Approximately one-third of the second foci of cancer is found incidentally at the time of resection (Fig 6). Usually, it is 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 if an R0 (microscopically negative) resection can be obtained for each tumor and there is no N2 nodal disease. A sublobar resection (segmentectomy or wedge) of one or both lesions may be necessary, depending on a patient's pulmonary reserve. If an R0 resection cannot be achieved, then only a diagnostic biopsy of the lesions should be performed.

5.2.4 Recommendations

5.2.4.1. In patients with two foci typical of a primary lung cancer (either proven or suspected, ie, solid, spiculated masses), it is suggested that identification of these as SPLCs (either synchronous or metachronous) should be based on the judgment of a multidisciplinary team, taking into account clinical, radiologic, and (if available) cytologic/histologic features (Grade 2C)**.**

Remark: The multidisciplinary team should include a thoracic radiologist, pulmonologist, thoracic surgeon, and pathologist.

5.2.4.2. In patients with two primary NSCLCs (synchronous or metachronous) 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 (Grade 1B)**.**

Remark: Involvement of mediastinal nodes and/or metastatic disease represents a contraindication to resection.

5.2.4.3. 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 suggested, provided the patient has adequate pulmonary reserve and there is no N2 nodal involvement (Grade 1C)**.**

FIGURE 6. [Sections 5.3.2.2, 5.3.3.2] Additional tumor nodules in the same lobe.

First Author	No. of Patients	% with Multiple Nodules	Continent	% Survival 2-Year	% Survival 5-Year
Nagai[165]	316	-	Asia	46	27
Okumura[166]	152	-	Asia	52	34
Okada[151]	51	-	Asia	52	30
Yano[167]	39	-	Asia	57	36
Shimizu[168]	37	-	Asia	41	27
Osaki[152]	36	-	Asia	46	27
Watanabe[153]	24 [a]	-	Asia	36	22
Lee [113]	23	-	Asia	-	30
Yoshino[169]	22	-	Asia	34	34
Fukuse[170]	20	12	Asia	58	37
Ruffini[154]	50	-	Europe	-	28
Oliaro[172]	39	49	Europe	49	20
Trousse[155]	35	-	Europe	-	52
Terzi[156]	32	-	Europe	70	42
Port[172]	53	19	N. Am	73	48
Pennathur[157]	51	-	N. Am	-	26
Rao[158]	35	-	N. Am	-	57
Battafarano[116]	27	-	N. Am	70	(66) [b]
Bryant[159]	26	-	N. Am	75	57
Average [c]				**54**	**37**
Registry Database Studies [d]					
IASLC[160]	363	-	Global	50	28
CCR[161]	422	-	N. Am	40	23
SEER[162]	633	-	N. Am	44	35
SEER[163]	2,285	-	N. Am	43	24

Inclusion criteria were studies of ≥ 20 patients with an additional nodule in the same lobe as the dominant primary lung cancer from December 1989-April 2012. CCR = California Cancer Registry; IASLC = International Association for the Study of Lung Cancer; SEER = Surveillance, Epidemiology, and End Results.

[a]Most were same lobe.

[b]Three-year survival.

[c]Excluding values in parentheses.

[d]Majority of patients in each study who underwent resection.

5.3 Multiple Tumor Nodules (T3, T4, M1a)

5.3.1 Definitions: The classification of additional nodules in the seventh edition of the lung cancer staging system focuses attention on these tumor nodules in a way that may be potentially misleading. Such nodules accounted for only 2.5% of cases in the IASLC database. It is important to recognize that the cohort with additional nodules in the IASLC database specifically excluded patients with synchronous primary cancers as well as those with systemic spread.[97] How these categories were defined, however, was left to the interpretation of the submitting institution. It is unclear whether the additional tumor nodule designation is meant to apply only to lesions that can be recognized grossly or also to lesions detected solely by the pathologist because this is defined in conflicting ways in the IASLC, American Joint Committee on Cancer, and UICC manuals. Furthermore, it is not specified whether the term "recognized grossly" means radiographically visible or able to be palpated. The IASLC manual and the lung-specific sections of the UICC supplement manual allow nodules identified only by the pathologist to be included.

The ACCP panel suggests that the additional nodule designations be used for patients with a dominant classic lung cancer (ie, solid, spiculated) and an

additional solid nodule identified clinically or on pathologic examination[150] (see Detterbeck et al[10] in the ACCP Lung Cancer Guidelines). This provides a clearer definition than existed previously. It must be emphasized that the additional nodule classification should not be applied to synchronous second primary cancers, patients with clear distant metastases, or lesions that are imaged but are most likely benign.

5.3.2 T3 Same Lobe Additional Tumor Nodules

5.3.2.1 Patient Evaluation—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 are benign. Furthermore, the prognosis for patients with an additional tumor nodule in the same lobe is only slightly inferior to those without an additional focus, which argues that resection should be performed for an ipsilateral additional focus of cancer. Therefore, there is little reason to perform additional diagnostic tests for patients with a second radiographic nodule in the same lobe. Furthermore, there is little reason to perform additional preoperative staging investigations (eg, mediastinoscopy, brain MRI) 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.

5.3.2.2 Outcomes and Treatment Approach—Data on additional nodules in the same lobe ($T3_{Satell}$) are summarized in Figure 6.[116,151-164] The overall 5-year survival rate for these patients is about 30% (about 60% have N1 or N2 involvement). This figure is corroborated by results from population-based registries and large regional or international databases. These data involve patients primarily treated by surgical resection, regardless of nodal status or completeness of resection.

In general, studies in the past 25 years found a moderate decrease in the survival of patients with vs without an ipsilobar additional tumor nodule in each stage (ignoring the nodule in the stage classification).[160,163,166-168,172,173] This appears to be about a 10% to 15% decrease in 5-year survival, although the magnitude of the difference is difficult to define precisely. This is due to the limited number of studies, the long time intervals involved, variability in survival results potentially stemming from small cohorts when divided by stage, and different editions of the stage classification system used. One of the more recent studies reported 5-year survival for stage I, II, and III disease (ignoring the additional nodule in the stage classification) of 64%, 31%, and 0%, respectively.[172] In summary, these studies supported surgical resection of $T3_{Satell}$ tumors in the absence of N2 node involvement.

Prognostic factors for this subclassification of NSCLCs are not well defined. Nodal involvement appears to have a similar effect in patients with and without a same lobe additional tumor nodule (see previous paragraph). No difference in survival is seen whether there is one or several ipsilobar additional tumor nodules.[115,172,174] Survival may be better in women.[172]

5.3.2.3 Recommendations

5.3.2.3.1 In patients with suspected or proven lung cancer and an additional (suspected) tumor nodule within the same lobe, it is recommended that no further diagnostic workup of the additional nodule is undertaken (Grade 1B)**.**

5.3.2.3.2 In patients with an additional (suspected) tumor nodule within the same lobe as a suspected or proven primary lung cancer, it is recommended that evaluation of extrathoracic metastases and confirmation of the mediastinal node status should be carried out as dictated by the primary lung cancer alone and not modified due to the presence of the additional lesion (Grade 1C)**.**

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

5.3.3 T4 Ipsilateral Different Lobe Nodules

5.3.3.1 Patient Evaluation—No data specifically address the evaluation of patients with $T4_{Ipsi\ Nod}$ tumors. However, given the difficulties in categorization of patients with additional nodules and the limited outcomes (see next subsection), it seems reasonable to stage these patients with a thorough search for distant and mediastinal metastases (ie, PET scan, if available; brain MRI or CT scan; mediastinoscopy).

5.3.3.2 Outcomes and Treatment Approach—The average 5-year survival for ipsilateral different lobe additional nodules is 13% (Fig 7). Many of the reports of additional nodules have come from Asia, suggesting a possibly different tumor etiology and different biologic behavior. It could also be due to an increased prevalence of CT screening. However, no differences in outcomes are apparent between continents, although the data are limited. No data suggest that a more limited resection in the face of a different lobe nodule accounts for the poor survival.[19]

The long-term survival of patients with resected ipsilateral different lobe additional tumor nodules is clearly less than for same lobe additional tumor nodules. This is seen by comparing Figures 6 and 7,

FIGURE 7. [Section 5.3.3.2] Additional ipsilateral (different lobe) tumor nodules.

First Author	No. of Patients	% with Multiple Nodules	Continent	% Survival 2-Year	% Survival 5-Year
Nagai[165]	129	-	Asia	42	22
Okumura[166]	48	-	Asia	31	11
Okada[107]	38	-	Asia	49	23
Ruffini[154]	36	-	Europe	-	28
Oliaro[171]	35	49	Europe	49	10
Lee[118]	26	-	Asia	42	31
Fukuse[170]	21	12	Asia	41	0
Tung[164]	20	-	Asia	40	28
Average				**42**	**19**
Registry Database Studies					
IASLC[160]	180	-	Global	40	22
CCR[161]	745	-	N. Am	(26)[a]	(9)[a]
SEER[162]	3,010	-	N. Am	(18)[a]	(7)[a]
SEER[163]	3,019	-	N. Am	(26)[a]	(8)[a]

Inclusion criteria were studies of ≥ 20 patients with an additional nodule in a different ipsilateral lobe as the dominant primary lung cancer from December 1989-April 2012. See Figure 6 legend for expansion of abbreviations.

[a]The majority of patients did not undergo resection.

is consistent with other reviews,[19] and is observed in population-based registries (8% vs 24% 5-year survival in the Surveillance, Epidemiology, and End Results database).[163] Individual studies consistently showed worse survival for different-lobe vs same lobe additional tumor nodules, which is statistically significant in some[116,146] and a trend in others (probably because of sample size).[115,167,169-171]

The survival of patients with $T4_{Ipsi\ Nod}$ disease who undergo resection is better than that found in a series of patients who did not undergo resection (Fig 7). However, this may represent a benefit from resection, selection of a cohort with better prognosis, or differences in staging definitions used in different series. Nevertheless, it cautiously suggests that resection is warranted for patients with sufficient pulmonary reserve.

Multivariable analysis has demonstrated worse survival with multiple vs single additional different lobe nodules as well as for positive mediastinal lymph nodes.[174] Only two studies of > 20 patients reported on patients with another tumor in an ipsilateral different lobe who also had node involvement ($T4_{Ipsi\ Nod}$ N1,2 M0).[165,171] Both studies found that any node involvement (N1 or N2) is associated with worse long-term survival than N0 node involvement (5-year survival, 10% and 10% vs 16% and 42%, respectively).[165,171] However, the impact of nodal involvement appears to be less for ipsilateral different lobe tumor nodules than for same lobe additional tumor nodules perhaps because of the already poor survival of patients with ipsilateral different lobe nodules. Because these results demonstrate that survival is poor for N2 involvement, thorough mediastinal staging should be performed prior to resection to ensure that these nodes are negative for disease.

5.3.3.3 Recommendations

5.3.3.3.1. In patients with suspected or proven lung cancer and an ipsilateral different lobe nodule(s), it is recommended that the judgment of a multidisciplinary team should reasonably exclude the possibility that this represents a benign lesion or a synchronous primary lung cancer, taking into account clinical, radiologic, and (if available) cytologic/histologic features (Grade 1C)**.**

Remark: The multidisciplinary team should include a thoracic radiologist, pulmonologist, thoracic surgeon, and pathologist at a minimum.

5.3.3.3.2. In patients with an ipsilateral different lobe tumor nodule(s), it is suggested that evaluation for possible extrathoracic metastases (eg, PET and brain MRI/CT) should be carried out (Grade 2C)**.**

Remark: The presence of distant metastases indicates the pulmonary nodule most likely represents metastatic (M1b) disease.

5.3.3.3.3. In patients with an ipsilateral different lobe tumor nodule(s), it is suggested that invasive evaluation to rule out mediastinal node involvement should be carried out (Grade 2C)**.**

Remark: Such involvement rules out curative-intent treatment.

5.3.3.3.4. In patients with NSCLC and an ipsilateral different lobe tumor nodule(s) (and no mediastinal or distant metastases), resection of each lesion is recommended, provided the patient has adequate pulmonary reserve (Grade 1B)**.**

5.3.4 M1a Contralateral Additional Tumor Nodules

5.3.4.1 Patient Evaluation—Only a few studies have reported data on patients with contralateral pulmonary tumor nodules (Fig 8).The panel suggests that a careful search with further imaging be undertaken in all such patients and that invasive mediastinal staging is performed. Given that the histologic type is not a major prognostic factor, it does not appear to be necessary to perform a needle biopsy to define the histologic type.

5.3.4.2 Outcomes and Treatment Approach—Surgical resection in patients with contralateral pulmonary tumor nodules appears to result in good 5-year survival (Fig 8). In these reported series there were no differences whether the nodules were of the same

FIGURE 8. [Section 5.3.4.1, 5.3.4.2] Additional contralateral tumor nodules.

Study	No. of patients	% Resected	% pN2	% 5-year Survival		
				All	Same histol	diff histol
SEER[163]	5,382	6	53	**3**	-	-
CCR[161]	1,148	8	-	**2-6**[a]	-	-
IASLC[160]	362	2	-	**3**	-	-

Inclusion criteria were studies of ≥20 patients with a primary lung cancer and an additional contralateral nodule from December 1989-April 2012. See Figure 6 legend for expansion of abbreviations.
[a]Range of estimated 5-y survival for various histologic types.

or different histology. It is difficult to correlate these data with the current stage classification rules or with the IASLC database. It would appear that the lesions of different histology should be viewed as synchronous primary lung cancers, and in fact, perhaps many of the lesions of the same histologic type should be as well. In contrast, series in which few patients underwent resection reported very poor survival.

5.3.4.3 Recommendations

5.3.4.3.1. In patients with a contralateral lobe tumor nodule(s), it is suggested that evaluation of extrathoracic metastases (eg, PET and brain MRI/CT) and invasive evaluation to rule out mediastinal node involvement should be carried out (Grade 2C)**.**

Remark: Such involvement rules out curative-intent treatment.

5.3.4.3.2. In patients with NSCLC and a contralateral lobe tumor nodule(s) (and no mediastinal or distant metastases), resection of each lesion is suggested, provided the patient has adequate pulmonary reserve (Grade 2C)**.**

5.4 Multifocal Lung Cancer

5.4.1 Definition: Multifocal disease is well recognized for bronchioloalveolar carcinoma (BAC).[175-177] However, the large majority of these cancers are adenocarcinomas and not pure BAC.[178] Because the term *BAC* is used in different ways, its use has been abandoned.[127] The relationship of newly defined histologic entities (ie, adenocarcinoma in situ, minimally invasive adenocarcinoma, lepidic predominant adenocarcinoma) are not fully understood, but many studies suggested that lesions may slowly transform along this spectrum of increasing invasiveness.[127,176,177,179-186]

Although the term *BAC* has been retired, patients are still seen with multiple foci of such tumors. MFLC may be increasing in frequency, particularly in Asia, or it may just be better appreciated because of an increase in the use of CT imaging. A better understanding of these tumors is hampered by lack of a clear definition. These tumors are variably included among patients with multiple distant metastases, synchronous SPLCs, and additional nodules.

The approach used here is to define such patients according to clinical features as opposed to pathologic features, which generally are not available until after treatment (ie, resection) has been carried out. We define MFLCs as multiple lesions arising from ground glass opacities (GGOs), which may develop a solid component.[116,176,178,181,187] There may be a limited number or multiple lesions.[178] We include patients with a GGO lesion suspected or proven to be malignant and other small GGO lesions that are more likely adenomatous alveolar hyperplasia (AAH) than an invasive carcinoma because data suggest that AAH is a precursor to such tumors.[186,177,179-184,188,189] Including such patients also satisfies the need for a clinically applicable definition. At the other end of the spectrum are patients with an infiltrative pattern of disease either confined to a particular area (segment or lobe) or appearing diffusely in the lung parenchyma (also called pneumonic type of adenocarcinoma).[116,190,191] These conditions should also be included among multifocal cancers.

Most studies reporting on patients with multiple tumor nodules specifically excluded what was formerly known as BAC because of the well-recognized propensity for multifocal disease and because of the excellent long-term survival after resection of such lesions.[192,193] It seems inappropriate to think of GGO lesions that histologically have only a small invasive component as multiple metastases that represent spread from a primary site. In fact, it is often difficult to identify a dominant primary site. Because these patients often have multiple lesions, it is also less appealing to consider these lesions as synchronous primary cancers and group them together with patients with two traditional lung cancers (ie, solid, spiculated masses). Finally, given our level of understanding of a complex process, speculating about a possible mechanism of spread (ie, hematogenous, lymphatic, aerogenous) is unlikely to provide a solid basis for classification or to help to guide treatment.[194] Therefore, we believe that it is best to consider multiple GGO lesions that are suspected to be malignant as a separate entity. Having a definition allows for the study of these tumors and comparison with other situations, which is not possible if they are grouped together with other types of multiple foci of cancer (eg, solid nodules, spiculated synchronous primary cancers). However, it is acknowledged that further study is needed to better characterize and understand these tumors. Data demonstrating that multifocal GGO lesions are much more common in women and nonsmokers than solitary GGO lesions

also support the consideration of these conditions as a separate entity.[195,196]

There appears to be a decreased propensity for nodal or systemic spread and an increased propensity for additional pulmonary foci.[116,176,181,187,196] This is also consistent with the observation that most of these lesions turn out to be adenocarcinoma in situ, minimally invasive adenocarcinoma, or lepidic predominant adenocarcinomas, which have been found to exhibit fewer metastases.[197,198]

The ACCP panel suggests that the T(m) designation be used for patients with MFLC[150] (see the staging article in these guidelines[10]). The decreased propensity for nodal or systemic spread makes it more appropriate to use a nomenclature that acknowledges multiple tumors in the T designation but maintains a composite N and M designation that applies to all the multiple tumors in aggregate.

5.4.2 Patient Evaluation: A decreased propensity for metastatic spread suggests a decreased need for mediastinal and distant staging prior to definitive treatment. The well-known high false-negative rate (about 90%) of PET scan for GGO also argues indirectly that PET imaging is unlikely to be helpful in patients with MFLC.[199,200] A careful clinical evaluation and nodal assessment at the time of resection should be done. However, at this point, this entity is still poorly defined and not completely understood; therefore, whenever there is any suspicion, it seems prudent to err on the side of more-extensive staging investigations (eg, invasive mediastinal staging).

5.4.3 Outcomes and Treatment Approach: There is a growing body of data that demonstrates excellent survival after resection of small solitary GGO lesions.[149] Furthermore, data support that sublobar resection of single lesions presenting as a GGO is adequate.

Much fewer data have been published on the outcome of patients with multiple cancers presenting as GGO lesions (ie, multifocal cancers). A survival of 100% and a very low recurrence rate after resection of MFLC have been reported,[195,196] and good survival is demonstrated by the articles identified in our systematic literature search (Fig 9).[178,201-203]

It is reasonable to suggest that limited resection of MFLCs should be performed. This is supported by the good outcomes of limited resection for single GGO lesions (see Howington et al[149] in the ACCP Lung Cancer Guidelines), the perception of a decreased propensity for nodal and systemic metastases, an increased propensity to develop new pulmonary foci of cancer, and the need to preserve lung parenchyma when patients present with multiple lesions. The good survival that is reported after resection argues for an aggressive, curative-intent approach rather than palliative treatment. The role of adjuvant chemotherapy or radiotherapy is not defined, although rationale for this is poor if the propensity for nodal and distant metastases is low. It is reasonable to consider adjuvant therapy as outlined for other patients with NSCLC if N1 or N2 involvement is found, but not if pN0 status is demonstrated for multifocal cancer (although no direct data are available that address this).

Often, patients with MFLC also have lesions not believed to be malignant (ie, <10 mm pure GGO lesions, which are AAH in the majority). We suggest that these patients be approached according to the data available for isolated lesions with the same characteristics.[94] Lesions that are sufficiently suspicious of being malignant should prompt treatment, whereas those that are not should continue to be observed. Only a few studies have addressed this clinical situation specifically. There appears to be no greater risk of malignancy in the small GGO lesions in patients with lung cancer vs those without.[178]

5.4.4 Recommendations

5.4.4.1. In patients with multiple lesions that are at least partially ground glass and are suspected

FIGURE 9. [Section 5.4.3] Multifocal lung cancer.

First Author	No. of patients	Median F/U (mo)	% pN2	% Surg Treated	% Multifocal	CT appearance (% GGO)			% BAC Histology		% 5-y Survival
						Solid	Mixed	Pure	Mixed	Pure	
Casali[201]	40	48	-	100	15	-	-	-	-	100	64
Ebright[202]	100	86	-	100	29	-	-	-	53	47	74
Carretta[137]	26	82	-	100	55	71	26	7	10	40	92
Nakata[180]	31	28	6	100	84	28	43	29	69[a]	31	93
Mun[203]	29	46	0	100	93	0	100	0	29[b]	71	100
Roberts[192]	14	60	0	100	100	-	-	-	14	57	64
Kim[178]	23	40	0	44	100	0	100	0	26[b]	69	100
Average									34	59	**84**

Inclusion criteria were studies involving multifocal lung cancer and ≥ 10 patients from December 1989-April 2012.
AAH = adenomatous alveolar hyperplasia; BAC = bronchioloalveolar carcinoma; GGO = ground glass opacity.
[a]Includes adenocarcinoma.
[b]Includes AAH.

to be malignant, it is suggested that these are classified as MFLC (Grade 2C)**.**

5.4.4.2. In patients with suspected or proven MFLC who have a negative clinical evaluation and normal mediastinum by CT, it is suggested that distant and mediastinal staging are not routinely necessary (Grade 2C)**.**

5.4.4.3. In patients with suspected or proven MFLC, it is suggested that curative-intent treatment should be pursued (Grade 2C)**.**

5.4.4.4. In patients with suspected or proven MFLC, it is suggested that sublobar resection of all lesions suspected of being malignant be performed, if feasible (Grade 2C)**.**

6.0 Isolated Brain Metastasis

6.1 Patient Selection and Workup

Approximately 25% of patients with stage IV NSCLC have a brain metastasis. The median survival of patients with a brain metastasis is about 2 months when treated with steroids alone, and 3 to 6 months when treated with whole-brain radiotherapy (WBRT).[204,205] These time frames probably apply more to symptomatic brain metastases and less to small, incidentally discovered, asymptomatic lesions. 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. Such treatment of these patients is discussed By Simoff et al,[206] "Symptom Management in Patients With Lung Cancer" the ACCP Lung Cancer Guidelines.

Approximately 10% of patients with stage IV adenocarcinoma have an excellent performance status and the brain is the only site of metastatic disease.[19] 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 group and this treatment approach are the focus of this section.

Aggressive curative-intent treatment of a brain metastasis may involve either surgical resection of the metastasis or ablation of the metastasis by radiosurgery. Treatment decisions are based on prognostic factors to maximize neurologic function and survival while avoiding unnecessary therapies.[204] Alternatively, WBRT is given for palliative intent or prophylactically to prevent or delay the appearance of further brain metastases. SRS involves a precisely focused beam of radiation with a steep falloff of the dose outside the target area. Although no randomized trial of surgery vs radiosurgery has ever been completed, comparison of the results of these techniques in patients treated palliatively suggests that they provide similar survival, local control, morbidity, and mortality.[207,208] A Cochrane review also found equivalent outcomes.[209] A number of technical issues often favor one of these treatments over the other, and therefore, they are best viewed as complementary modalities. In this section, we considered these 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 turns up negative results. 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) or remain completely controlled (metachronous presentation). Involvement of mediastinal nodes portends a worse prognosis.[8,210-217] Therefore, it appears reasonable to perform invasive mediastinal staging prior to selecting patients for resection of the brain metastasis and the primary lung lesions.

Most studies suggested that adenocarcinoma histology is associated with a higher likelihood of brain metastases,[213,214,217,218] with some exceptions.[204,219,220] The number of brain metastases may not matter as long as the number is small (three or fewer) and they can all be completely resected (as has been demonstrated by several retrospective studies in patients treated for palliation).[208,221] The outlook may be better for patients who are younger, female, have a metachronous presentation, have a good performance status, or have a lower T stage.[214,217,218,220,222] The outlook may also be better in patients with supratentorial lesions and those with a brain metastasis <3 cm in diameter.[220] 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.

6.2 Treatment Outcomes

Survival statistics of patients with a brain metastasis who were treated with curative intent are presented in Figure 10.[217,223-230] Long-term (5-year) survival after definitive treatment of an isolated brain metastasis and a primary lung cancer is about 15%. This is corroborated by two recent reviews.[77,204] The local tumor control at 1 year is 80% to 90%, with a median survival of 6 to 12 months; two-thirds of the cases involved a metachronous presentation.[204,205,208] The operative mortality averages 2% for surgical resection. SRS allows for the treatment of brain metastases in almost any location, including the brainstem.

FIGURE 10. [Section 6.2] Isolated brain metastases.

First Author	No. of patients	% Survival	
		2-year	5-year
Synchronous Presentation			
Bonnette[214]	103	28	11
Wronski[220]	86	14	8
Hu[223]	84	16	7
Xu[224]	64	20	13
Nakagawa[225]	60	10	-
Mordant[226]	57	-	13
Girard[217]	51	42	-
Flannery[228]	42	34	21
Flannery[229]	39	11	8
Louie[220]	35	22	-
Arrieta[230]	30	60	-
Granone[213]	30	47	14
Billing[215]	28	54	21
Average		**30**	**13**
Metachronous Presentation			
Wronski[220]	145	29	17
Moazami[222]	91	10	6
Furak[210]	45	-	16
Flannery[228]	33	59	13
Mussi[229]	30	47	19
Nakagawa[225]	28	11	-
Average		**31**	**13**

Inclusion criteria were studies of ≥20 patients reporting specific data for synchronous or metachronous brain metastases and curative-intent treatment from December 1989-April 2012.

Administration of WBRT after resection or SRS for an isolated brain metastasis is widely practiced, although this is not well supported by data. The only randomized study[231] found no difference in survival. Conflicting results have been reported by multivariate analyses,[220,232,233] a case-matched study,[22] and retrospective comparison studies.[217,234] Most of these studies included many patients with other metastases in whom definitive treatment of the brain metastasis was a palliative procedure.

Studies of the effect of adjuvant WBRT on the rate of recurrent brain metastases have shown conflicting results. The only randomized study found the rate of brain recurrences to be significantly lower (18% vs 70%, $P < .001$) after WBRT.[191] Other studies found either no difference[214,235-238] or significantly lower brain relapse rates with WBRT.[232,239] Most of these studies included many patients with other metastatic sites. There are no data regarding the role of adjuvant chemotherapy in patients who have undergone curative resection of a brain metastasis, but given the data supporting adjuvant chemotherapy for resected stage II and IIIA tumors, it is reasonable to give it for stage IV as well in patients with a good performance status.

6.3 Recommendations

6.3.1. In patients with an isolated brain metastasis from NSCLC being considered for curative treatment, invasive mediastinal staging and extrathoracic imaging (either whole-body PET or abdominal CT plus bone scan) are suggested (Grade 2C)**.**

Remark: Involvement of mediastinal nodes and/or metastatic disease represents a contraindication to curative-intent treatment.

6.3.2. 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 1C)**.**

6.3.3. 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 1C)**.**

6.3.4. In patients who have undergone a curative resection of an isolated brain metastasis, adjuvant WBRT is suggested (Grade 2B)**.**

Remark: Adjuvant chemotherapy is reasonable in patients with a good performance status with the goal of decreasing the incidence of brain recurrences, although no studies have specifically addressed this.

6.3.5. In patients who have undergone a curative resection of an isolated brain metastasis, adjuvant chemotherapy is suggested (Grade 2B)**.**

Remarks: Adjuvant chemotherapy is reasonable in patients with a good performance status, although no studies have specifically addressed this.

7.0 Isolated Adrenal Metastasis

7.1 Patient Selection and Treatment Results

Highly selected patients have been reported who have undergone resection of an adrenal metastasis from NSCLC with curative intent, with an overall 5-year survival of about 25% (Fig 11).[240-244] Survival after resection of the primary cancer and the adrenal metastasis appears to be good primarily in patients without nodal involvement.[246,247] Other factors, such as the histologic type and ipsilateral vs contralateral location, do not have prognostic value in

FIGURE 11. [Section 7.1] Adrenal metastasectomy.

First Author	No. of patients	% Lung Cancer	% 5-y Survival of Lung Cancer Patients	Positive Prognostic Factors
Tanvetyanon[245]	110	100	25	None
Pham[246]	78	100	40	Negative intrathoracic nodes
Porte[247]	43	100	12	None
Mercier[240]	23	100	23	DFI > 6 months
Raz[241]	20	100	34	Ipsilateral metastasis, N2 negative
Lucchi[242]	14	100	36	None
Strong[243]	94	39	29	None
Wade[244]	47	30	26	None
Average			**27**	

Inclusion criteria were patients with adrenal metastasis undergoing curative-intent surgical therapy reported in publications with ≥10 patients with lung cancer from December 1989-April 2012. DFI = disease-free interval from lung resection.

the limited number of reported patients who underwent this treatment.[245-249] Patients with synchronous tumors were younger than patients with metachronous tumors, but their 5-year survival was similar (26% vs 25%). The perioperative complication rates were low, but most patients ultimately died of progression of their disease.

7.2 Recommendations

7.2.1. In patients with an isolated adrenal metastasis from NSCLC 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 suggested (Grade 2C)**.**

Remark: Involvement of mediastinal nodes and/or other sites of distant metastases represent a contraindication to resection.

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

7.2.3. In patients with no other sites of metastases and a previously completely resected primary NSCLC (*metachronous* presentation), resection of an isolated adrenal metastasis is recommended (Grade 1C)**.**

7.2.4. In patients who have undergone a curative resection of an isolated adrenal metastasis, adjuvant chemotherapy is suggested (Grade 2B)**.**

Remark: Adjuvant chemotherapy is reasonable in patients with a good performance status, although no studies have specifically addressed this.

8.0 General Series of Surgery in Patients With Isolated Distant Metastases

Several series reported on surgical therapy of isolated metastatic disease from lung cancer, with 5-year survival ranging from 32% to 86%.[250-252] The structures involved include extrathoracic lymph nodes, bones, kidneys, GI organs, and soft tissue, including muscle and skin.

One prospective study was reported.[253] Eligible patients had solitary synchronous (identified at the same time as the primary lung cancer) metastatic disease from NSCLC and were to receive both preoperative and postoperative chemotherapy. Only 23 patients were enrolled, and 20 received definitive therapy for metastatic disease, 13 underwent complete resection of the primary lung tumor, and only 10 underwent complete resection of both the metastatic and the primary focus. The median survival was 11 months for the entire cohort (5-year survival was not reported). This study included many patients with N2 disease, which is a poor prognostic feature.[253] No clear recommendations can be made regarding isolated distant metastases other than those involving the brain or adrenal gland.

9.0 Summary

The available data for patients with Pancoast tumors (T3,4 N0,1) suggest that the best survival is achieved by preoperative chemoradiotherapy followed by surgical resection. Preoperative radiotherapy followed by surgical resection is a reasonable alternative. Involvement of subclavian vessels, the vertebral column, or mediastinal lymph nodes is associated with reduced survival after resection. At the time of resection, it is important to carry out a complete resection, including a lobectomy. There are no data on how

patients with unresectable, yet still potentially curable Pancoast tumors should be treated. However, extrapolation from the data for non-Pancoast stage III NSCLC suggests that definitive 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 central T4 NSCLC have N2,3 or M1 involvement, surgical resection should be pursued in highly selected patients with T4 N0, 1 M0 tumors. The survival of such patients in whom a complete resection was achieved appears to be better than after treatment with chemoradiotherapy alone. However, the operative mortality is relatively high, and patients must be carefully staged, selected, and treated in a center with experience. In patients with complete (R0) resection and an absence of N2 mediastinal lymph nodes, long-term survival is possible. Preoperative chemoradiotherapy may also be beneficial, and planned circulatory bypass may facilitate a safe operation.

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. Patients with a lung cancer and an additional malignant nodule are difficult to categorize, and the current stage classification rules are ambiguous. Such patients should be evaluated by an experienced multidisciplinary team to determine whether the additional lesion represents an SPLC or an additional tumor nodule corresponding to the dominant cancer. If the lesion is within the same lobe as the lung cancer, 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 ($T3_{Satell}$ lesion). If a second lesion in another lobe is suspected of being malignant, it is difficult to define whether this represents a synchronous SPLC vs a manifestation of systemic disease. The patient should undergo a thorough investigation for evidence of metastatic disease before making a decision about 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 survival is lower 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 SPLC. This is particularly important if the histologic type is the same as the primary cancer and if the interval between cancers has been < 4 years. A new cancer appearing in < 2 years should be assumed to be a recurrence or metastasis unless it is clearly of a different histologic type. Although some cancers appearing between 2 and 4 years after the first primary lung cancer may be SPLC, caution should be used when the interval has been < 4 years. Resection of an early stage SPLC should be undertaken, although the prognosis is not as good as that for an early stage single primary lung cancer.

Multifocal cancer arising from GGOs, formerly recognized under the rubric of BAC, also require multidisciplinary team evaluation. Each lesion should be evaluated individually whether intervention is required, and if so, limited surgical resection appears to yield good results.

Patients who have previously undergone complete resection of a primary lung 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 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).

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Additional information: The supplement tables can be found in the "Supplemental Materials" area of the online article.

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