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EARLY-STAGE NON–SMALL-CELL LUNG CANCER

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Summary of Literature Review

Introduction/Background

Lung cancer is the most common malignancy worldwide, with more than one million cases diagnosed yearly [1]. In the United States, 2012 cancer statistics estimated 226,160 new cases and 160,340 deaths due to lung cancer, making it the leading cause of cancer mortality in both men and women [2]. Almost 85% of lung cancers are non–small-cell (NSCLC) in histology [3]. Approximately 15%–20% of NSCLC patients present with localized, node-negative disease (“early stage”) [2]. Recently, the International Association for the Study of Lung Cancer issued a new staging manual that included changes to the lung cancer staging system [4]. These changes included greater emphasis on primary tumor size as a prognostic factor, resulting in further stratification of T1 and T2 tumors and reclassification of tumors larger than 7 cm as T3. Additionally, although tumors <5 cm remained stage I, tumors between 5 and 7 cm are now grouped into stage IIA. For the purposes of this review, however, early-stage tumors will follow the definitions within the American Joint Committee on Cancer (AJCC) staging manual, sixth edition [5], since relevant research and current practice have been largely based on those criteria. For patients deemed fit for an operation who have a clinical diagnosis of stage I NSCLC, surgical intervention has historically been the gold standard.

Assessment of Patient Operability

Baseline pulmonary function will help determine a patient’s suitability for resection [6]. The potential decline in lung function will vary with the extent of the resection; pneumonectomy causes the greatest decline in pulmonary function values [including forced expiratory volume in one second (FEV1), forced vital capacity, and maximum oxygen consumption], whereas lobectomy causes less decline than pneumonectomy. FEV1 declines less with a segmentectomy than with a lobectomy [7]. Pulmonary function may recover in 3–6 months after a lobectomy and from 6 months to indefinitely to recover after a pneumonectomy [8,9]. Current evidence suggests that surgery should not be withheld on the basis of age alone in patients who otherwise have acceptable pulmonary functions testing [6]. Two sets of guidelines for preoperative evaluation of the lung resection candidate, one from the British Thoracic Society and Society of Cardiothoracic Surgeons of Great Britain and Ireland Working Party [10], and the second by the American College of Chest Physicians, have been published and should be referred to for the algorithms provided to assess the lung cancer patient [11]. Most objective assessment criteria in these guidelines are similar and include the premise that individuals with lung cancer should be assessed by a multidisciplinary team to determine their suitability for lung resection. Surgical outcomes, in fact, appear related to expertise, and patients are best assessed by a thoracic surgical oncologist who devotes a significant portion of his/her practice to treating lung cancer [12]. Lastly, patients are best managed in health care centers with expertise in major pulmonary resection because surgical experience and hospital volume to significantly impact morbidity and mortality [13,14].

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Management of the Medically Operable Lung Cancer

Standard Approach

In patients with a clinical diagnosis of stage I NSCLC and who are deemed appropriate for resection, surgical resection, usually via lobectomy, with mediastinal lymph node sampling or dissection remains the standard of care and is based essentially on historical experience and empirical data as reported in the literature [15]. Lobectomy is generally the preferred treatment as warranted by tumor location, with pneumonectomy generally reserved for central tumors in which sleeve lobectomy would not allow for adequate margins [15]. Surgical mortality is low in most modern reports. For patients undergoing comprehensive preoperative assessment, the risk of surgical mortality should be ≤4% for lobectomy and ≤9% for pneumonectomy [10]. In patients with stage I NSCLC who are considered appropriate candidates for thoracoscopic anatomic lung resection (lobectomy or segmentectomy), there is increasing use of video-assisted thoracoscopic surgery (VATS) by surgeons experienced in these techniques, and this approach may be an acceptable alternative to open thoracotomy in select cases [16]. A systemic review and meta-analysis of randomized and nonrandomized patients undergoing VATS for early-stage NSCLC revealed no significant difference between VATS and open lobectomy in the rate of postoperative complications, mortality, or locoregional recurrence but did suggest a lower rate of systemic recurrence (P = .03) and 5-year mortality rate with VATS (P = .04) [17]. (See Variant 1.)

In patients undergoing major resection for stage I NSCLC, intraoperative comprehensive mediastinal lymph node sampling or dissection is generally recommended for accurate pathologic staging. Of interest, a Cochrane-pooled analysis of randomized trials has shown survival is superior in patients undergoing complete mediastinal lymph node dissection compared with those having lymph node sampling [18]. On the other hand the trial ACOSOG Z0030 has analyzed the survival impact after lung resection of lymph node dissection versus lymph node sampling. Preliminary analysis has found no difference in operative mortality based on lymph node procedure [19]. In a recent review of more than 13,000 early-stage lung cancers treated with resection from 1990 to 2000 and classified as pathologic stage I NSCLC by the AJCC staging manual, sixth edition, the 5-year overall survival (OS) rate for stage IA and IB disease was 71%–77% and 35%–58%, respectively [20].

Limited Resection

For patients whose cardiopulmonary function precludes major pulmonary resection, alternative surgical strategies have been described. For select patients with chronic obstructive pulmonary disease [emphysema], favorable results for combined lung volume reduction surgery with curative-intent lung cancer resection have been reported [21]. Limited parenchymal resections such as wedge resection and segmentectomy also have been advocated for compromised patients. Cancer and Leukemia Group B (CALGB) 9335, a prospective trial evaluating the feasibility of VATS-based wedge resection in high-risk patients with clinical T1N0M0 NSCLC [22], found overall high operative failure rates (29%) and also noted the need to convert some study patients (17%) to conventional thoracotomy. Critically, limited resection may not offer equivalent oncologic outcomes compared with major pulmonary resection in high-risk patients. The Lung Cancer Study Group carried out a prospective randomized trial comparing lobectomy with limited resection in 247 patients with peripheral clinical stage IA NSCLC [23]. This study found that locoregional recurrence was tripled (18% versus 6%) in the limited resection group compared with lobectomy, and a statistical trend suggested that OS and disease-specific survival was impaired by limited resection. This study established lobectomy as the standard of care for the medically operable patient with early-stage disease.

External Beam Radiotherapy or Brachytherapy After Limited Resection

Postoperative external beam radiotherapy (EBRT) has been employed to improve local control after limited resections in high-risk patients with mixed results: some series suggest feasibility and safety, but others note challenges in defining the postoperative target [22,24]. The use of intraoperative brachytherapy (ie, the physical placement of radioactive iodine seeds in the surgical bed) in the setting of limited resections has been more frequently used to overcome the higher failure rates associated with limited resections while limiting potential toxicity from EBRT. Some published series report brachytherapy as well tolerated with satisfactory local control rates and limited radiation-associated toxicity [25]. However, others note significant surgical- and brachytherapy-related complications with this combined approach [26]. The American College of Surgeons Oncology Group trial Z4032 recently completed a phase III trial comparing wedge resection with or without brachytherapy for stage I NSCLC patients at a high risk for major pulmonary resection [27]. The results of this study should serve as a benchmark for the efficacy and toxicity of adjuvant brachytherapy after limited resection.

Adjuvant Radiotherapy After Standard Surgical Resection

There is no established role for adjuvant radiotherapy (RT) after standard surgical resection of early-stage disease. In 1998, the Post Operative Radiation Therapy (PORT) trials group completed a large meta-analysis involving data from 9 randomized trials and reported on pooled outcomes from patients treated with or without adjuvant RT after resection for stage I to III NSCLC [28]. This report revealed a 24% reduction in local recurrence but an absolute increase in mortality of 7% at 2 years when using adjuvant radiation, which on subset analysis was restricted to patients with stage I or II NSCLC. In contrast, a randomized single institution trial published in 2002 specifically addressed the role of adjuvant RT in resected stage I NSCLC and found a decrease in local recurrence from 23% to 2% in the patients receiving adjuvant RT to the bronchial stump and hilum, and without an associated survival detriment [29]. This study has not been replicated. Lastly, a subgroup analysis of the ANITA trial, a phase III study of the survival benefit of adjuvant Navelbine® in resected stage I, II, and IIIA NSCLC patients, looked at the impact of PORT administered in a nonrandomized fashion and found no support for the use of PORT in patients with N0 disease [30].

Adjuvant Chemotherapy After Standard Surgical Resection

In general, there are no prospective randomized data to support the routine use of adjuvant cisplatin-based chemotherapy for patients with resected stage I NSCLC. Although large, contemporary randomized trials [31-35] of adjuvant cisplatin-based chemotherapy versus observation in resected stage I-III NSCLC have been published, none of the studies found improvement in OS in the subset of patients with stage I disease. In a meta-analysis of individual patient data from the 4,584 patients enrolled on these 5 trials [36], although an absolute 5-year OS benefit of 5.4% (hazard ratio (HR) of 0.89, 95% confidence interval [CI], 0.82 to 0.96), and a statistically significant interaction between chemotherapy effect and stage for OS survival was observed (P = .04), for patients with stage IA disease (n=347) the HR favored observation, suggesting a potential detrimental effect to chemotherapy (HR of 1.41, 95% CI, 0.96 to 2.09). For patients with stage IB (n=1371) there was a trend towards a beneficial effect of chemotherapy that did not reach statistical significance (HR of 0.93, 95% CI, 078 to 1.10). For patients with resected stage II/III disease, a statistically significant benefit for adjuvant cisplatin-based chemotherapy was seen. CALGB 9633 trial randomized patients with resected stage IB NSCLC to 4 cycles of adjuvant carboplatin and paclitaxel or observation. Final results of this study suggested no survival benefit related to the addition of chemotherapy after an interim analysis had suggested a possible early improvement [37]. That said, an unplanned, retrospective subset analysis suggested that patients with ≥4-cm tumors (n=196) may obtain a small survival benefit with adjuvant carboplatin and paclitaxel, but this finding remains controversial [38]. (See Variant 2.) In Japan, the drug tegafur-uracil (UFT) has been tested in the adjuvant setting in a number of randomized trials. A meta-analysis of 6 trials comparing surgery alone versus surgery followed by adjuvant UFT confirmed the survival benefit of this drug in resected early-stage lung cancer [39]. UFT is not available outside Japan.

Management of the Medically Inoperable Patients

About 20% to 30% of patients with potentially resectable but medically inoperable early-stage NSCLC are not offered surgery because of the increased risk from their medical comorbidities, of which impaired pulmonary function is the most common [40]. For compromised patients, observation alone leads to unacceptable outcomes; lung cancer was shown to be cause of death in 53% of 75 stage I medically inoperable patients not receiving definitive therapy in a study by McGarry et al [41]. Treatment options frequently offered to this population include limited surgical resection [7] (see above) or conventional RT (see below); however, outcomes appear inferior to lobectomy.

Conventional Radiotherapy in the Medically Inoperable Patient

For medically inoperable early-stage NSCLC patients offered EBRT alone using conventional techniques as primary management, lung cancer results have been consistently inferior to the surgical results reported for operable patients. In a review of 18 studies published from 1988 to 2000 on conventional RT for stage I NSCLC, where the median RT dose was 60 Gy in 30 fractions, local recurrence was the most common cause of failure, ranging up to 70% [42]. A similar report [43] on clinical stage I NSCLC treated with RT alone using modern techniques and staging, with a median RT dose of 64 Gy, overall and progression-free survival rates at 5 years were 48% and 28%, respectively. In that study, 49% of patients had local failure as part of their relapse pattern.

Additionally, accelerated conformal radiation therapy has been investigated for early-stage NSCLC. In a CALGB study, the nominal dose of radiation therapy was kept at 70 Gy, while the number of fractions was reduced from

29 to 17, and the dose per fraction was increased from 2.41 Gy to 4.11 Gy. Out of 39 patients treated, local relapse was observed in 3, and the treatment was well tolerated [44].

Stereotactic Body Radiotherapy

Stereotactic body radiotherapy (SBRT), also known as stereotactic ablative radiotherapy, involves RT delivery using very high doses per fraction; rapid dose drop-off in the surrounding normal tissues; RT delivery over few sessions; administration only to small (ie, <5 cm) discrete targets without regional micrometastatic spread (ie, without nodal involvement); and applicable to organs whose functional structures could support focal ablation of physiologic units without compromising overall functionality (eg, liver, lung) [45]. Over the past decade, a range of publications have now described stereotactic approaches to the management of early-stage lung cancer, with a range of technological approaches and dose regimens ranging from as many as 10 fractions to as few as a single fraction [45-59]. In summary, results from these retrospective and prospective reports demonstrate a consistent theme: the suggestion of excellent outstanding local control with SBRT for stage I patients with nearly all series reporting 85% to 98.5% control rates. Of interest, there appears to be an SBRT dose-response relationship for lung cancer since local failure rates appear to rise when the treatment dose is less than a certain biological threshold: using radiobiological parameters, SBRT doses are felt to require a biologically equivalent dose of at least equivalent 100 Gy_{10} [51] to achieve similar control rates. With positron emission tomography (PET)-based staging primarily employed in most SBRT series, mediastinal or hilar nodal failures appear to be rare, ranging from 0% to 10%. Distant failure remains the predominant pattern of failure for patients treated with SBRT, at the rate of 15% to 30% of stage I patients treated with SBRT. The Radiation Therapy Oncology Group® (RTOG®) initiated a prospective phase I/II trial (RTOG 0236) in medically inoperable peripherally located early-stage NSCLC measuring ≤5 cm utilizing a regimen of 60 Gy (54 Gy with heterogeneity correction) in 3 fractions over 8 to 14 days. The study went on to enroll 59 patients over a multi-institutional setting and closed in October 2006. Study results have recently been published and were remarkable for a 3-year primary tumor control rate of 97.6%, a local-regional control rate of 87.2%, and a median OS of 48.1 months with no treatment-related deaths reported [55]. (See Variant 3.)

Regarding the concept of heterogeneity correction as noted above for the SBRT total dose [ie, 60 Gy (54 Gy with heterogeneity correction)], tissue heterogeneity in the vicinity of the lung has implications on the accuracy of the dose distributions. Dose that would have normally been deposited in the tumor is carried away into the surrounding lung tissue, resulting in potential underdosage of the tumor. The literature is replete with articles demonstrating the need for accurate, "heterogeneity-corrected" dose algorithms in lung cancer planning [60,61]. Consequently, the RTOG has adopted the requirement that algorithms employing heterogeneity corrections be used for treatment planning for both early and locally advanced stage lung cancer [62-64]. To mitigate inaccuracies with dose calculations, it is strongly recommended that algorithms employing accurate heterogeneity correction techniques be used for lung cancer treatment planning. Pencil-beam-type algorithms should be avoided [65].

There has consistently been remarkably little toxicity reported with SBRT used in medically inoperable early-stage lung cancer patients, with grade 3 or higher rates typically less than 4% [45-57]. The major exception to the low rates of SBRT toxicity was reported by Timmerman et al following their experience of treating "central" lung tumors, defined as lying within 2 cm of the tracheobronchial tree, in the setting of phase II series using a dose schedule that ultimately provided the basis for RTOG 0236 (60 Gy [54 Gy with heterogeneity correction] in 3 fractions) [47,53]. In that phase II experience, 54% of patients with "central" tumors had were free from severe toxicity for 2 years. In contrast, central lesions have routinely been safely treated with slightly lower total doses and dose per fraction (such as 50 Gy in 4–5 fractions) with similar local control and toxicity as seen in treatment of "peripheral" lesions to higher doses [66,67] when normal tissue tolerances were respected. (See Variant 4.) In spite of the high baseline prevalence of pulmonary comorbidities in patients treated with lung SBRT, the incidence of symptomatic radiation pneumonitis is very low, ranging from 0% to 5% in reported series [45,46,49-52,55,56]. Recent reports have highlighted chest wall pain or rib fracture as an increasingly noted delayed side effect, though symptoms are typically mild to moderate. Chest wall symptoms are reported in 5% to 15% of patients with peripheral lesions and appear to be related to treatment dose, fractionation, and beam arrangement [52,68-70].

Given that lung cancer patients treated with SBRT generally have significant medical comorbidities, approaches to staging and workup are frequently intended to be noninvasive and minimally harmful. Although pathologic confirmation of malignancy by biopsy is the gold standard, this is not readily achievable in some patients due to medical contraindications. For those nonbiopsied patients, treatment is then offered on the basis of a clinical diagnosis of cancer; ie, based only on radiographic criteria such as serial computed tomography (CT) chest scans showing a growing lesion and an accompanying fluorine-18-2-fluoro-2-deoxy-D-glucose PET scan either demonstrating high (standardized uptake value [SUV] >5) metabolic activity on a single scan, or progression of intermediate activity over serial scans. Nonbiopsied patients treated with SBRT may represent up to 30% of some practices; studies to date suggest reassuringly that such patients have outcomes similar to the biopsy-proven cases [52]. (See Variant 5.) Similarly, mediastinoscopy is rarely carried out in these patients. CT-based, and more recently PET-based, staging has been used to characterize and clinically define the mediastinal lymph nodes.

Radiofrequency Ablation

Radiofrequency ablation (RFA) has been described as a treatment option for medically inoperable early-stage lung cancer. RFA involves placing an electrode within the tumor tissue, which will generate heat from radiofrequency energy, leading to tumor destruction and necrosis around the electrode. A number of retrospective series involving varied patient populations have been published on the use of RFA to treat lung malignancies [71-75]. Complete radiographic responses achieved with RFA are reported in 38% to 93% of tumors [72,75]. Primary tumor relapse rates after RFA range from 8% to 43% [6]. Two-year cancer-specific survival after RFA ranges from 57% to 93% and overall 3-year survival rates range from 15% to 46% [6]. Smaller tumor size, metastases, and an ablation zone 4 times the tumor diameter may predict complete response [71,72]. Pneumothorax has been reported in subjects as an adverse event, with some patients requiring catheter or chest tube insertion [72].

The American College of Chest Physicians (ACCP) and Society of Thoracic Surgeons (STS) discuss this modality in their 2012 consensus statement on the management of the high-risk lung cancer patient [6]. Per the ACCP/STS report, the reduced primary control seen with RFA makes it a reasonable treatment option only for those high-risk patients with peripheral lesions who are not candidates for SBRT or sublobar resection or have failed prior SBRT. The risks and benefits of RFA in a medically compromised population remain to be defined, and prospective comparisons with potentially less morbid treatments such as SBRT are not yet published.

Summary

- Patients with early-stage lung cancer are best cared for by a multidisciplinary team with expertise in thoracic malignancies.
- For medically operable early-stage lung cancer patients, major pulmonary resection and appropriate nodal dissection remain the gold standard for cure of stage I NSCLC.
- Routine use of adjuvant RT and/or chemotherapy for resected stage I lung cancer patients is not recommended, however carefully selected patients with high-risk features may be considered for such treatments.
- For patients who present with significant surgical risks or who have significant competing comorbidities, attempting cure must be balanced by minimizing treatment toxicities. Developments in surgery (eg, limited resection with or without intraoperative brachytherapy); radiation therapy (eg, SBRT) and interventional radiology (eg, RFA) offer potential means of achieving this balance.
- With excellent local control and minimal side effects, lung SBRT is emerging as standard treatment for medically inoperable stage I NSCLC, particularly for peripherally located lesions.
- Ongoing studies are defining the role of SBRT for high-risk or fully operable early-stage NSCLC and the optimal SBRT dose and fractionation in different clinical situations (such as central lesions).
- The role of RFA needs to be further defined.

Supporting Documents

- ACR Appropriateness Criteria® Overview
- Evidence Table

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Clinical Condition: **Early-Stage Non–Small-Cell Lung Cancer**

Variant 1: **70-year-old man, former smoker with 2-cm peripheral right upper lobe (RUL) adenocarcinoma; PET shows hypermetabolic uptake at RUL lesion but is otherwise negative; mediastinoscopy negative; FEV1 60% predicted; Karnofsky Performance Scale (KPS) 90.**

Treatment	Rating	Comments
Major Pulmonary Resection		
Lobectomy + nodal dissection/sampling	9	
Pneumonectomy + nodal dissection/sampling	1	
VATS (with major or sublobar resection)	9	
Limited resection (wedge/segmentectomy)	3	
Systemic Therapy		
Adjuvant chemotherapy	1	
Adjuvant biologics	1	
Chemotherapy only	1	
Radiotherapy		
Definitive external beam radiotherapy (1.8–2 Gy/fraction)	3	
Definitive hypofractionated radiotherapy (2.5–6 Gy/fraction)	3	
Adjuvant fractionated radiotherapy (1.8–2 Gy/fraction)	1	
SBRT	5	Surgery is the gold standard treatment. SBRT clinical trials are underway. When thinking of this procedure, consider comorbidities and patient factors.
RFA	1	
Observation	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: **Early-Stage Non–Small-Cell Lung Cancer**

Variant 2 **68-year-old woman with 4.2-cm left upper lobe (LUL) adenocarcinoma on CT-guided biopsy; PET shows hypermetabolic uptake at lingular lesion but is otherwise negative; FEV1 70% predicted; KPS 70; concurrent rheumatoid arthritis under control.**

Treatment	Rating	Comments
Major Pulmonary Resection		
Lobectomy + nodal dissection/sampling	8	
Pneumonectomy + nodal dissection/sampling	2	
VATS (with major or sublobar resection)	7	
Limited resection (wedge/segmentectomy)	3	
Systemic Therapy		
Adjuvant chemotherapy	5	
Adjuvant biologics	1	
Chemotherapy only	1	
Radiotherapy		
Definitive external beam radiotherapy (1.8-2 Gy/fraction)	3	
Definitive hypofractionated radiotherapy (2.5-6 Gy/fraction)	3	
Adjuvant fractionated radiotherapy (1.8-2 Gy/fraction)	2	
SBRT	6	
RFA	1	
Observation	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: **Early-Stage Non–Small-Cell Lung Cancer**

Variant 3 **73-year-old woman with COPD, on stable 2 L oxygen by nasal prongs, new 1-cm LUL lesion on chest radiograph after upper respiratory tract infection treated successfully with antibiotics; PET shows hypermetabolic uptake at LUL lesion with SUV 5 but is otherwise negative; bronchoscopy washings positive for adenocarcinoma; FEV1 40%; DLCO 45% predicted; KPS 70.**

Treatment	Rating	Comments
Major Pulmonary Resection		
Lobectomy + nodal dissection/sampling	1	
Pneumonectomy + nodal dissection/sampling	1	
VATS (with major or sublobar resection)	2	
Limited resection (wedge/segmentectomy)	3	
Systemic Therapy		
Adjuvant chemotherapy	1	
Adjuvant biologics	1	
Chemotherapy only	1	
Radiotherapy		
Definitive external beam radiotherapy (1.8–2 Gy/fraction)	3	
Definitive hypofractionated radiotherapy (2.5–6 Gy/fraction)	6	
Adjuvant fractionated radiotherapy (1.8–2 Gy/fraction)	1	
SBRT	9	
RFA	4	
Observation	2	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: **Early-Stage Non–Small-Cell Lung Cancer**

Variant 4: **83-year-old man with 3-cm right infrahilar adenocarcinoma; PET shows hypermetabolic uptake at right lesion with SUV 10 but is otherwise negative; FEV1 40% predicted; KPS 70.**

Treatment	Rating	Comments
Major Pulmonary Resection		
Lobectomy + nodal dissection/sampling	2	
Pneumonectomy + nodal dissection/sampling	1	
VATS (with major or sublobar resection)	2	
Limited resection (wedge/segmentectomy)	1	
Systemic Therapy		
Adjuvant chemotherapy	1	
Adjuvant biologics	1	
Chemotherapy only	1	
Radiotherapy		
Definitive external beam radiotherapy (1.8–2 Gy/fraction)	5	
Definitive hypofractionated radiotherapy (2.5–6 Gy/fraction)	6	
Adjuvant fractionated radiotherapy (1.8–2 Gy/fraction)	1	
SBRT	8	
RFA	2	
Observation	2	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: **Early-Stage Non–Small-Cell Lung Cancer**

Variant 5 **70-year-old man with new 2-cm RUL PET-avid lesion with SUV 5 but otherwise negative. The pulmonologist's assessment is that the lesion is too peripheral to sample and that a CT biopsy would be unsafe, which was confirmed by an experienced interventional radiologist. FEV1 50%/DLCO 50% predicted; KPS 70, wears supplemental O^2 at night.**

Treatment	Rating	Comments
Major Pulmonary Resection		
Lobectomy + nodal dissection/sampling	3	
Pneumonectomy + nodal dissection/sampling	1	
VATS (with major or sublobar resection)	4	
Limited resection (wedge/segmentectomy)	5	
Systemic Therapy		
Adjuvant chemotherapy	1	
Adjuvant biologics	1	
Chemotherapy only	1	
Radiotherapy		
Definitive external beam radiotherapy (1.8–2 Gy/fraction)	3	
Definitive hypofractionated radiotherapy (2.5–6 Gy/fraction)	5	
Adjuvant fractionated radiotherapy (1.8–2 Gy/fraction)	1	
SBRT	7	
RFA	2	
Observation	1	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		