CHEST Evidence-Based Medicine

American College of Chest Physicians and Society of Thoracic Surgeons Consensus Statement for Evaluation and Management for High-Risk Patients With Stage I Non-small Cell Lung Cancer

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Background: **The standard treatment of stage I non-small cell lung cancer (NSCLC) is lobectomy with systematic mediastinal lymph node evaluation. Unfortunately, up to 25% of patients with stage I NSCLC are not candidates for lobectomy because of severe medical comorbidity.**
Methods: **A panel of experts was convened through the Thoracic Oncology Network of the American College of Chest Physicians and the Workforce on Evidence-Based Surgery of the Society of Thoracic Surgeons. Following a literature review, the panel developed 13 suggestions for evaluation and treatment through iterative discussion and debate until unanimous agreement was achieved.**
Results: **Pretreatment evaluation should focus primarily on measures of cardiopulmonary physiology, as respiratory failure represents the greatest interventional risk. Alternative treatment options to lobectomy for high-risk patients include sublobar resection with or without brachytherapy, stereotactic body radiation therapy, and radiofrequency ablation. Each is associated with decreased procedural morbidity and mortality but increased risk for involved lobe and regional recurrence compared with lobectomy, but direct comparisons between modalities are lacking.**
Conclusions: **Therapeutic options for the treatment of high-risk patients are evolving quickly. Improved radiographic staging and the diagnosis of smaller and more indolent tumors push the risk-benefit decision toward parenchymal-sparing or nonoperative therapies in high-risk patients. Unbiased assessment of treatment options requires uniform reporting of treatment populations and outcomes in clinical series, which has been lacking to date.** ***CHEST 2012; 142(6):1620–1635***

Abbreviations: ACCP = American College of Chest Physicians; ACOSOG = American College of Surgeons Oncology Group; BED = biologic equivalent dose; CALGB = Cancer and Leukemia Group B; CFRT = conventionally fractionated radiation therapy; DLCO = diffusing capacity of lung for carbon monoxide; IPF = idiopathic pulmonary fibrosis; LCSG = Lung Cancer Study Group; NSCLC = non-small cell lung cancer; pHTN = pulmonary hypertension; PICO = population, intervention, comparison, and outcome; ppo = predicted postoperative; $p\dot{V}O_2$ = peak oxygen consumption with exercise; RFA = radiofrequency ablation; RTOG = Radiation Therapy Oncology Group; SBRT = stereotactic body radiation therapy; STS = Society of Thoracic Surgeons

EXECUTIVE SUMMARY

The standard treatment of stage I non-small cell lung cancer (NSCLC) is lobectomy with systematic mediastinal lymph node evaluation. Unfortunately, up to 25% of patients with stage I NSCLC are not lobectomy candidates because of severe medical comorbidity. Despite high competitive mortality from underlying lung disease, the mortality related to untreated NSCLC cannot

be ignored except in patients who are severely debilitated by their comorbidity, with limited life expectancy. A multidisciplinary consensus panel was assembled through the Workforce on Evidence-Based Surgery of the Society of Thoracic Surgeons (STS) and the Thoracic Oncology Network of the American College of Chest Physicians to address treatment of high-risk patients with stage I NSCLC. The management suggestions were unanimously agreed upon by the consensus panel and represent expert opinions based on available literature.

Respiratory failure and pulmonary complications represent the most significant risks following lung resection, and preprocedural risk assessment is based primarily on pulmonary function. Currently available treatment techniques for high-risk patients with stage I NSCLC include sublobar resection with or without brachytherapy, stereotactic body radiotherapy (SBRT), and radiofrequency ablation (RFA). Each of these modalities has historically been associated with decreased procedural morbidity and mortality but increased involved lobe and regional recurrence when compared with lobectomy. Improvements in radiographic staging and the detection of smaller and more indolent tumors push risk/benefit decisions toward parenchymal sparing or nonoperative therapies in this population. Unbiased assessment of treatment options for high-risk patients requires uniform reporting of comorbidities and outcomes in clinical series, which has been lacking to date.

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Medical Assessment

1. **FEV_1 accurately predicts morbidity and mortality following major lung resection. Assessment of FEV_1, including calculation of estimated postoperative value, prior to resection is suggested as a means for assessing risk.**
2. **Diffusing capacity of lung for carbon monoxide (DLCO) accurately predicts morbidity and mortality following major lung resection. Assessment of DLCO, including calculation of estimated postoperative value, prior to resection is strongly suggested as a means for assessing risk.**
3. **Peak oxygen consumption with exercise accurately predicts morbidity and mortality following major lung resection. The predictive ability is strongest in patients with impaired FEV_1 or DLCO. Assessment of peak oxygen consumption with exercise prior to major lung resection in patients with impaired FEV_1 or DLCO is suggested as a means for assessing risk.**

Relevant Outcome Measures

4. **Health-related functional status and quality-of-life assessment are important and underreported for the treatment of high-risk patients with stage I NSCLC and suggested for inclusion in clinical decisions.**

Sublobar Resection

5. **Segmentectomy or extended wedge resection with margins >1 cm or equal to the tumor diameter with hilar and mediastinal nodal evaluation is suggested as a safe and effective alternative to lobectomy in high-risk patients with stage I NSCLC.**
6. **In patients with stage I NSCLC >75 years of age, segmentectomy or extended wedge resection is suggested as an effective and potentially beneficial alternative to lobectomy.**
7. **Anatomic segmentectomy is preferred when possible to wedge resection in patients who undergo sublobar resection for stage I NSCLC.**
8. **Adjuvant intraoperative brachytherapy should be considered in conjunction with sublobar resection to reduce involved lobe recurrence.**

Radiation Therapy

9. **Conventionally fractionated radiation therapy with definitive intent and sufficient dose intensity is a reasonable treatment**

option for high-risk stage I NSCLC, but, for tumors < 5 cm, where normal tissue dose constraints can be respected, SBRT is preferred over conventionally fractionated radiation therapy for definitive treatment of high-risk stage I NSCLC.

10. **A modified SBRT treatment schedule is suggested for tumors within 2 cm of the proximal bronchial tree to decrease treatment-related toxicity.**

Percutaneous Ablative Therapy

11. **RFA is a reasonable treatment option in high-risk patients with stage I NSCLC with peripheral lesions < 3 cm, but reduced primary tumor control limits enthusiasm for its use to those patients who are not candidates for SBRT or sublobar resection.**
12. **When RFA is used for tumors > 3 cm, combination with radiation therapy is suggested, but there is no consensus on sequence of therapy.**
13. **RFA is not suggested for lesions adjacent to major bronchovascular structures or the esophagus.**

Introduction

Recommended treatment of stage I non-small cell lung cancer (NSCLC) is complete resection of the primary tumor by lobectomy and associated lymphatics. Operative mortality rates for lobectomy are currently 1% to 5%,[1-3] but patients with underlying lung disease have inherent increased risk. Although no single test can determine the safety of resection, much is known about the relative risks. Numerous variables have been examined as predictors of morbidity and mortality after lung resection, but controversy continues. What constitutes prohibitive risk in a lethal disease such as NSCLC remains a matter of judgment, and clinicians must weigh risks, benefits, and patients' preferences when making treatment recommendations.

Lobectomy with systematic mediastinal node evaluation has been the accepted standard treatment of early-stage NSCLC since the 1940s. The morbidity and mortality of lobectomy has changed over time and will likely continue to decrease with evolving techniques. Sublobar resection has been performed for patients with stage I NSCLC with poor pulmonary reserve for many decades, and nonsurgical treatment options have recently arisen, including stereotactic body radiotherapy (SBRT) and percutaneous ablative therapy (radiofrequency ablation [RFA], cryoablation, and microwave ablation). These treatments appear to decrease the risk of respiratory failure, disability, and death, but have limited evidence of efficacy compared with lobectomy.

Up to 25% of patients with clinical stage I NSCLC have limited pulmonary reserve,[4] representing nearly 10,000 individuals each year in the United States. Patients with untreated stage I NSCLC have a median survival of only 18 months.[5] Despite high competitive mortality from severe underlying lung disease, the mortality related to untreated NSCLC cannot be ignored in most patients. This project is an expert consensus opinion with regard to the evaluation and treatment of high-risk patients with stage I NSCLC to assist clinicians in tailoring treatment decisions.

Materials and Methods

Task forces were independently assembled through the Workforce on Evidence-Based Surgery of the Society of Thoracic Surgeons (STS) and the Thoracic Oncology Network of the American College of Chest Physicians (ACCP) to address high-risk patients with stage I NSCLC, because of commonality of interest, efforts were combined and a multidisciplinary writing committee was assembled. Relevant population, intervention, comparison, and outcome (PICO) questions were formulated and provided to an independent evidence-based investigator in January 2010. In addition, targeted searches were run in the OVID version of MEDLINE in February 2010 and limited to publication since 1995,

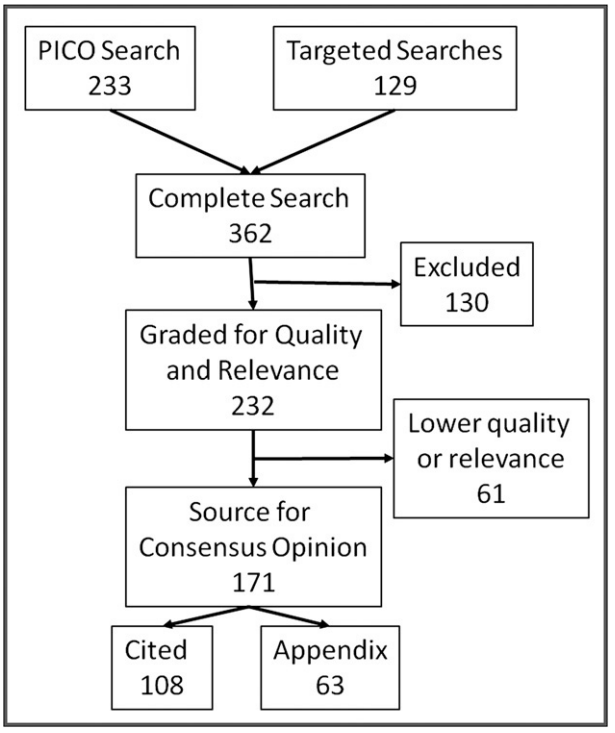

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram of records included in evaluation. The primary reasons for exclusion were data not relevant to the topic, data not specific to stage I non-small cell lung cancer, data limited to the treatment of adenocarcinoma in situ, duplicate data, or descriptive data without outcomes. PICO = population, intervention, comparison, and outcome.

English language, and human subjects. Abstracts were reviewed by at least two authors and excluded if duplicative, not targeted to stage I NSCLC, or limited to adenocarcinoma in situ. Data were extracted and graded on quality[6] and relevance to subject (Fig 1, e-Appendix 1). Limited data quality made a consensus statement more appropriate than clinical guidelines.

All data reference the sixth edition of the American Joint Committee on Cancer lung cancer staging system.[7] The reporting of local recurrence was unified by reviewing recurrence definitions from each trial and placing into one of three categories defined in Table 1.

The consensus panel conferred by conference call, e-mail, and semiannually at national meetings. Agreements were achieved through iterative discussion and debate. Management suggestions were unanimously agreed upon (perfect consensus) prior to approval by the Workforce on Evidence-Based Surgery and Executive Committee of the STS and the Thoracic Oncology Network, the Council of Networks, and the Board of Regents of the ACCP. Suggestions are based on expert opinion and should not be used for performance measurements or competency purposes.

Results

Medical Assessment

Morbidity following lobectomy via thoracotomy is not trivial, with a 30% to 40% incidence of postoperative complications and 1% to 5% operative mortality rate.[1-3] Although morbidity is high, many complications do not contribute meaningfully to risk/benefit decisions, such as urinary tract infections, whereas others, including respiratory failure, can significantly impact survival and quality of life. Respiratory failure remains the leading cause of morbidity and mortality after lobectomy. Patients with advanced lung disease have decreased survival defined by the severity of their disease. In patients with COPD, $FEV_1 < 35\%$ predicts approximately 10% mortality per year (50% 5-year survival).[8-11] Careful medical assessment is imperative to identify appropriate therapy in this population.

The majority of research on preoperative evaluation for major lung resection focuses on pulmonary assessment. The quality of evidence is moderate and comes from retrospective analyses of single-institution prospective databases, which are biased by patient selection. Recent reports from very large, prospective clinical databases (containing physiologic information) and administrative databases (generally without physiologic information) increase the quality of evidence but can still be affected by selection bias.

Treatment-related risk is linked to pulmonary function and numerous other factors. Patients with better lung function going into a procedure are more likely to do well afterward. Early studies relied primarily on baseline measurements for assessing risk, which do not account for the volume or relative contribution of affected parenchyma. Postoperative estimated values of lung function have largely supplanted earlier methods of assessing risk. A variety of techniques are used to assess regional function, including segment method, radionuclide scanning, and quantitative CT scanning.[12-15] The accuracy of postoperative function estimates is influenced by the extent and distribution of emphysema, region of resection, patient's fitness, and perioperative preparation.[16] Current data on prediction of outcomes are based on thoracotomy. Recent publications suggest that morbidity rates may be lower in patients undergoing video-assisted thoracoscopic surgery resection,[10,17] and pulmonary function parameters may not accurately predict complications following video-assisted thoracoscopic surgery lobectomy.[8]

There is general agreement that the risk of complications is increased in patients with pulmonary hypertension (pHTN) and idiopathic pulmonary fibrosis (IPF). Overall, patients with IPF have substantially shortened life expectancy and increased risk for mortality and pulmonary complications following resection.[18,19] The effects of pHTN on interventional outcomes are less well known. It is unclear whether elevated resting mean pulmonary arterial pressure is predictive of morbidity or mortality.[20] Because of the paucity of data regarding IPF and pHTN, suggestions for physiologic evaluation focus on the effects of COPD on outcomes.

FEV_1: Postoperative FEV_1 drops precipitously within 24 h of resection, with 30% to 50% decrease from

Table 1—*Suggested Common Terminology Describing Tumor Recurrence*

Typical Terminology	Refined Terminology	Definition
Local control	Primary tumor control	No residual tumor within primary targeted tumor < 2 cm from primary tumor or resection line
	Involved lobe control	No tumor in treated lobe > 2 cm from primary tumor or staple line
Regional control	Nonprimary lobe control	No tumor within another ipsilateral lobe
	Hilar node control	No tumor in ipsilateral hilar nodes
	Ipsilateral mediastinal control	No tumor in ipsilateral mediastinal nodes
Distant control	Distant nodal control	No tumor in ipsilateral supraclavicular or contralateral mediastinal lymph nodes
	Distant metastatic control	No tumor deposits characteristic of NSCLC in contralateral lung or other sites

NSCLC = non-small cell lung cancer.

preoperative values and 10% to 30% decrease below estimated postoperative predicted (ppo) values.[16,21,22] A minimum of 3 to 6 months are required to return to 80% to 90% of preoperative values.[16,21-24] The decline in FEV_1 6 weeks after lobectomy is smaller in patients with COPD (0%-8%) than without (16%-20%).[16,25]

Large observational studies indicate that decreasing FEV_1 (% predicted or ppo) is associated with increased risk for pulmonary and cardiovascular complications, ICU readmission, and prolonged hospitalization.[26,27] The OR of complications developing is about 0.1 per 10 percentage point decrease in FEV_1.[27,28] However, FEV_1 accounts for only a portion of the risk for morbidity, which is mostly due to other undefined factors. A statistical relationship between mortality and spirometry is more difficult to demonstrate due to selection bias in large observational databases and low incidence of operative mortality. One study identified decreasing FEV_1 in association with increased risk of mortality after lobectomy.[29] It is impossible to identify an absolute cutoff value that consistently differentiates normal from high risk, or high from prohibitive risk, because of numerous other factors, including tumor location and contribution of effected segments. However, ppo values $< 40\%$ are useful in identifying patients at increased risk in whom individual consideration is warranted.[30,31]

Diffusion Capacity: Postoperative diffusion capacity of lung for carbon monoxide (DLCO) decreases 25% to 30% in the immediate postoperative period and returns to 80% to 90% of preoperative values > 2 months after lobectomy.[16,23] Decreasing DLCO is associated with increased postoperative morbidity and ICU readmission.[26,28,32,33] Similar to FEV_1, the relative risk of complications increases 10% to 20% per each 10-point decrease in DLCO.[26-28] Decreasing DLCO is also associated with an increased risk of operative mortality; the relative risk of mortality increasing 20% to 35% per 10-point decrease in DLCO.[27,28] Identifying an absolute cutoff that reliably differentiates acceptable from unacceptable risk is inappropriate, but ppo values $< 40\%$ are useful in identifying higher risk patients.[30-32]

FEV_1 and DLCO have only modest correlation with each other. DLCO can be low in the absence of COPD.[27,32] DLCO is a strong predictor of postoperative outcomes in patients with normal spirometry and useful in assessing risk in patients without COPD.[26,28,32] Accurate risk assessment necessitates DLCO measurement, but it is absent in $> 40\%$ of patients in the United States who undergo major lung resection.[26,29]

Exercise Testing: Peak oxygen consumption with exercise ($p\dot{V}O_2$) decreases after lobectomy and returns to 85% to 100% of preoperative > 2 months after

Table 2—*Comparison of Morbidity, Mortality, Local/Regional Recurrence, and Survival Between Lobectomy and Sublobar Resection*

		Lobectomy					Sublobar Resection				
Study	Study Design	No.	Morbidity, %	Mortality, %	Regional Recurrence, %	5-y Survival, %	No.	Morbidity, %	Mortality, %	Regional Recurrence, %	5-y Survival, %
LCSG[52]/1995	Prosp, randomized	122	N/R	1.6	6.4	65	125	N/R	0.8	17	44
Landreneau et al[53]/1997	Prosp, nonrandomized	117	31	3.3	9	68	102	21	0	19.6	58
Koike et al[58]/2003	Prosp, nonrandomized	159	N/R	N/R	1.3	90.1	74	N/R	N/R	2.7	89.1
Martin-Ucar et al[59]/2005	Retrospective, case matched	17	17.6	5.8	12	64	17	17.6	5.8	0	70
Okada et al[54]/2006	Prosp, nonrandomized	305	6.6	N/R	4.9[a]	89.1	262	7.3	0.4	6.9	89.6
Schuchert et al[57]/2007	Retrospective	246	32.4	3.3	4.9	80	182	33.7	1.1	7.7	83

LCSG = Lung Cancer Study Group; N/R = not reported; prosp = prospective.
[a]Local, not further defined.

lobectomy.[12,21,23,24] Impairment of $p\dot{V}O_2$ is associated with increased postoperative morbidity, particularly cardiopulmonary complications. A moderate-sized observational study demonstrated a relative risk of cardiopulmonary complications of 15% per unit decrease in $p\dot{V}O_2$.[34] $p\dot{V}O_2$ has been used to determine if individuals with unacceptable lung function by other measures might tolerate resection.[35,36] Measurement of $p\dot{V}O_2$ does not add to risk stratification if FEV_1 and DLCO are normal, but in patients with preoperative FEV_1 or DLCO $<80\%$, decreasing $p\dot{V}O_2$ is associated with increased operative risk. However, in patients with ppo FEV_1 or ppo DLCO or both $<40\%$, major resection was well tolerated if $p\dot{V}O_2$ was >10 mL/kg/min.[34] Other methods of exercise testing have been studied as predictors of operative risk for patients with lung cancer. Stair climbing, shuttle walking, exercise oximetry, and the 6-min walk test each variably predict resection risk.[12,37-40]

Summary: There are algorithms for defining risk for lung resection,[31,41] which provide general cutoffs to trigger additional assessments and suggest cutoffs that differentiate high- from prohibitive-risk patients. However, surgical and anesthetic techniques are continually improving, so current guidelines require continual revision. Identification of patients who are at excess risk from lobectomy remains a clinical decision.

Relevant Outcome Measures

The most commonly reported outcomes after NSCLC resection are hospital morbidity and mortality.[1-3] Other meaningful outcomes include length of hospitalization, discharge disposition, readmission, return to work, neurocognitive function, breathlessness, pain, cost, and quality of life. Expanding measured outcomes beyond short-term morbidity and mortality, to include health-related functional status, quality of life, and patient satisfaction, is essential when evaluating invasive treatments in frail populations. Relative to patients with other cancers, patients with NSCLC have worse performance status regardless of extent of disease.[42] Although physicians focus on morbidity and mortality, patients will tolerate "high-burden" therapy if it results in a return to current health. Patients want to avoid permanent functional or cognitive impairment.[43]

Health-related functional status reported via the Short Form-36 is worse in patients who have undergone pulmonary resection than in age- and sex-matched control subjects.[44] Postresection health-related functional status is worse than preoperative status in parameters related to physical capability, social functioning, pain, and mental health.[44,45] Preoperative dyspnea and decreased DLCO negatively affect postoperative quality of life.[44] Increasing extent of resection is consistently linked to worse physical capability, energy, and pain.[45]

Very few series of sublobar resection, SBRT, and RFA report on health-related functional status or quality of life. van der Voort and colleagues[46] noted no functional decline and improved emotional status following SBRT in patients with medically inoperable NSCLC. Radiofrequency Ablation of Pulmonary Tumors Response Evaluation (RAPTURE), a multiinstitutional RFA study in high-risk patients, reported no deterioration of Short Form-12 (physical and mental components of Short Form-36) or Functional Assessment of Cancer Therapy-Lung scores.[47] Further assessments of functional health status are essential to adequately assess treatment options in high-risk populations.

Sublobar Resection

Early experience with sublobar resection for stage I NSCLC revealed comparable morbidity, reduced mortality,[48,49] and preserved pulmonary function compared with lobectomy.[50,51] Enthusiasm waned when the Lung Cancer Study Group (LCSG) demonstrated an increase in regional recurrence (17.2% vs 6.4%) following sublobar resection compared with lobectomy.[52] This represents the only prospective, randomized comparison of lobectomy and sublobar resection for NSCLC and established lobectomy as the surgical standard for early-stage NSCLC. A substantial body of literature has emerged over the last decade resurrecting

Table 3—*Recurrence and Survival for Sublobar Resection With Brachytherapy for High-Risk Stage I NSCLC*

			Local/Regional Failure (%)		Overall Survival (%)	
Study/Year	No.	Resection Type	Resection Alone	Sublobar Resection + Brachytherapy	Resection Alone	Sublobar Resection + Brachytherapy
Lee et al[72]/2003	33	31 wedge 2 segment 1 lobe	N/A	6 (primary tumor)	N/A	47 (5 y)
Santos et al[73]/2003	203	N/R	18.6 (involved lobe)	2.0 (involved lobe)	60 (4 y)	67 (4 y)
Fernando et al[66]/2005	124	51 wedge 73 segment	17.2 (involved lobe)	3.3 (involved lobe)	N/R	N/R
Birdas et al[71]/2006	41	14 wedge 27 segment	N/A	4.8 (regional)	N/A	54 (4 y)

Lobe = lobectomy; N/A = not applicable; segment = segmentectomy; wedge = wedge resection. See Table 1 and 2 legends for expansion of other abbreviations.

interest in sublobar resection. Single-institution series consistently demonstrate equivalent regional recurrence and survival for anatomic segmentectomy compared with lobectomy for small node-negative tumors (Table 2).[53-59]

Increasing age is associated with increased risk following lung resection.[60,61] A study from the Surveillance, Epidemiology, and End Results (SEER) program found that lobectomy carried no survival benefit in patients >75 years old.[62] Kilic and colleagues[63] reported reduced morbidity and mortality for patients with stage I NSCLC >75 years old who underwent segmentectomy compared with lobectomy, with no difference in regional recurrence (6% vs 4%) or survival (49.8% vs 45.5%).

Tumor size is important in the evaluation of parenchymal-sparing treatments. Several reports document equivalent disease-free survival when comparing lobectomy and segmentectomy for tumors ≤2 cm.[64-66] A review of 1,272 patients found no difference in disease-free survival between lobectomy and segmentectomy for tumors ≤2 cm.[65] A prospective, randomized, multi-institutional study is being conducted by Cancer and Leukemia Group B (CALGB 140503)[67] evaluating sublobar resection for stage I NSCLC ≤2 cm, with significant implications for high-risk patients.

Sublobar resections can be performed by anatomic segmentectomy or wedge resection. Interestingly, in the LCSG trial, segmentectomy carried a decreased risk of involved lobe recurrence compared with wedge resection,[52] more closely approximating recurrence and survival following lobectomy. The superiority of segmentectomy as compared with wedge has been demonstrated in multiple series[65,68] and is supported by a 2008 evidence-based review.[69] A strict definition for adequate margins in sublobar resections remains unresolved, but the involved lobe and regional recurrence decrease with margin distance >1 cm or greater than the maximum tumor diameter.[63,68,70]

Adjuvant Brachytherapy: Intraoperative brachytherapy is used to decrease involved lobe and regional recurrence associated with sublobar resection. Single-institution series report regional failures of 2% to 6% (Table 3).[66,71-73] The American College of Surgeons Oncology Group (ACOSOG) completed accrual on a prospective randomized trial (Z4032)[74] comparing sublobar resection with or without intraoperative brachytherapy for high-risk stage I NSCLC.[75] After 90 days, postoperative pulmonary function was similar in both arms, and mortality for all patients was 2.7%. Lower lobe tumor location was the only factor associated with drop in $FEV_{1.}$[76] Recurrence data are maturing.

Summary: For high-risk patients with stage I NSCLC, anatomic segmentectomy or wide wedge resection is suggested as a parenchymal-sparing alternative to lobectomy. Adjuvant intraoperative brachytherapy appears safe and reduces involved lobe recurrence. Prospective, randomized studies (CALGB 140503 and ACOSOG Z4032)[67,74] will better delineate the usefulness of sublobar resection in NSCLC.

Conventionally Fractionated Radiation Therapy

Comparisons of conventionally fractionated radiation therapy (CFRT) vs observation in patients with early-stage NSCLC and severe COPD indicate that CFRT can be curative and provides modest prolongation of survival.[77,78] A review of 18 studies using CFRT alone for NSCLC[79] included 1,562 patients with medically inoperable stage I NSCLC and reported 34% overall survival and 39% cancer-specific survival at 3 years. Primary tumor relapse was 40% and was the predominant reason for treatment failure. Modern CFRT techniques and dose intensification have improved outcomes, but 5-year regional control and overall survival remain suboptimal (Table 4).[80-82]

Table 4—*Impact of Modern Radiation Therapy Technique and Treatment Intensification in Clinical Stage I NSCLC*

Study	Population	No.	Treatment Dose	Outcome	
				Overall Survival	Local/Regional Control
Fang et al[82]	MDACC	111	2D RT, median dose 64 Gy, range 20-74 Gy	10% (5 y)	34% (5 y) (regional)
		85	3D RT, median dose 66 Gy, range 45-90.3 Gy	36% (5 y)	70% (5 y) (regional)
Chen et al[81]	University of Michigan	16	RT 63-84 Gy	27 mo, median	14.3 mo, median (regional)
		12	RT 92.4-102.9 Gy	33 mo, median	19.3 mo, median (regional)
Campeau et al[80]	Peter MacCallum Cancer Centre	34	RT 55-60 Gy	33% (2 y)	55% (2 y) (local, not further defined)
		39	RT 60 Gy + chemotherapy	57% (2 y)	66% (2 y) (local, not further defined)

2D = two dimensional; 3D = three dimensional; MDACC = MD Anderson Cancer Center; RT = radiation therapy. See Table 1 and 2 legends for expansion of other abbreviations.

Table 5—*Multiinstitutional Retrospective and Prospective Single Institution Studies Evaluating SBRT for Clinical Stage I NSCLC*

Study	No. (% Medically Inoperable)	Median Tumor Size (max)	% Biopsied	Nominal Dose	BED, Gy	Median F/U, mo	2-y Primary Tumor Control	2-y Overall Survival	2-y Cancer-Specific Survival	Toxicity ≥ Grade 3
Multicenter retrospective studies										
Bauman et al[83]	138 (96)	3.7 cm, (9 cm)		30-48 Gy/2-4 fx	75-120	33	85% (3 y)	26% (5 y)	66% (3 y) 40% (5 y)	10%
Onishi et al[89]	257 (61)	2.8 cm, (5.8 cm)		30-84 Gy/1-14 fx	57.6-180	38	84% (5 y) (BED ≥ 100) 36% (5 y) (BED < 100)	57% (3 y) 47% (5 y)	77% (3 y) 73% (5 y)	4%
Prospective single-institution studies										
McGarry et al[88]	47 (100)	8.5 mL (mean T1) 50.5 mL (mean T2)	100	24-72 Gy/3 fx	43- 245	NR	78%	N/R	N/R	15%
Yoon et al[92]	21 (76)	< 5 cm	100	30 Gy/3 fx or 40-48 Gy/4 fx	60-106	13	81% (100% at 48 Gy)	51%	86%	0%
Xia et al[91]	25 (100)	N/R	100	50 Gy/10 fx	75	NR	96% (3 y)	91% (3 y)	N/R	4%
Le et al[87]	22 (82)	3.7 cm, (6.2 cm)	100	15-30 Gy/1 fx	37.5-120	27.8	T1: 100% ≤ 20 Gy: 50% > 20 Gy: 87%	46%	62%	13.5%
Collins et al[84]	15 (100)	2 cm, (3.5 cm)	100	45-60 Gy/3 fx	112-180	12	100% (crude)	87%	N/R	6.5%
Koto et al[86]	31 (65)	2.5 cm (4.8 cm)	100	45 Gy/3 fx or 60 Gy/8 fx	112-105	32	T1: 78% T2: 40% (3 y)	72% (3 y)	83% (3 y)	6.5%
Fakiris et al[85]	70 (100)	16.7 mL (212 mL)	100	T1-60 Gy/3 fx T2-66 Gy/3 fx	180-211.2	50.2	88% (3 y)	43% (3 y)	82% (3 y)	15.7%, 27% central, 10% peripheral
Ricardi et al[90]	62 (90)	N/R (< 5 cm)	65	45 Gy/3 fx	112.5	28	93%	69%	79%	3%

BED = biologically effective dose; F/U = follow up; fx = fraction; max = maximum reported tumor size; SBRT = stereotactic body radiation therapy. See Table 1 and 2 legends for expansion of other abbreviations.

Stereotactic Body Radiation Therapy

SBRT refers to highly precise and accurate delivery of very conformal and dose-intensive radiation to small-volume targets. Synonymous terms include stereotactic ablative body radiotherapy and stereotactic radiosurgery. It represents more aggressive dose intensification than can be safely achieved with CFRT methods. SBRT requires careful dose distribution and accurate delivery to ensure target coverage despite smaller margins.

Most early SBRT trials in patients with medically inoperable stage I NSCLC were dose-finding studies (Table 5).[83-92] Larger phase 2 studies have replicated outcomes of early retrospective series (Table 6).[93,94] The recent Radiation Therapy Oncology Group trial, (RTOG 0236)[95] was limited to a homogeneous population with stage I NSCLC treated in a uniform fashion with 60 Gy in three fractions.[94] All patients had biopsy confirmation of NSCLC and staging with CT and PET scanning and were deemed medically inoperable by an experienced thoracic surgeon or pulmonologist. Indicators defining inoperability included $FEV_1 < 40\%$; ppo $FEV_1 < 30\%$; $D_{LCO} < 40\%$; hypoxemia or hypercapnia; pHTN; diabetes with end-organ damage; or severe cerebral, cardiovascular, peripheral vascular disease, or chronic heart disease. Primary tumor control of 98%, regional control of 87%, and overall survival of 56% at 3 years were achieved and represent the best outcomes for SBRT in a high-risk population. RTOG 0618[96] used the same treatment regimen but was limited to patients deemed high risk but operable by a thoracic surgeon or pulmonologist; accrual is completed and the results are pending.

These studies demonstrate a dose-response relationship favoring more intensive regimens and higher rates of primary tumor progression with larger tumors. Regimens with biologically equivalent dose (BED) >100 Gy consistently result in $>90\%$ primary tumor control for T1 tumors and overall survival $>50\%$. These results are superior to those historically observed with CFRT. A recent meta-analysis indicated overall survival improvement with SBRT compared with CFRT.[97]

Toxicity: Most trials report no significant change in pulmonary function parameters following SBRT. Treatment-related toxicities tend to increase with dose, although high-grade toxicities are uncommon and treatment-related deaths are rare. Toxicities include injury to lung, chest wall, brachial plexus, skin, and central thoracic structures, and fatigue. Organ volume, prior thoracic radiation, and radiosensitizing chemotherapy increase the risks of toxicity. An Indiana University study reported excessive toxicity for tumors

Table 6—*Prospective Multicenter/Cooperative Group Studies Evaluating SBRT for Clinical Stage I NSCLC*

Study	Study Group	No. (% Medically Inoperable)	% Biopsied	Median Tumor Size (max)	Nominal Dose	BED, Gy	Median F/U, mo	3-y Primary Tumor Control, %	3-y Overall Survival, %	3-y Cancer-Specific Survival, %	Toxicity ≥ Grade 3, %
Bauman et al[93]	Nordic Study Group	57 (93)	67	16 mL, (51 mL)	45 Gy/3 fx	112.5	35	92	60	88	30
Timmerman et al[94]	RTOG 0236	55 (100)	100	N/R (<5 cm)	60 Gy/3 fx	180	38.7	98	56	N/R	27

BED = biologically effective dose; RTOG = Radiation Therapy Oncology Group. See Table 1, 2, and 5 legends for expansion of other abbreviations.

Table 7—*Primary Tumor Control and Survival Following RFA for Clinical Stage I NSCLC*

Study	No.	System	Median Tumor Size (max), cm	Median F/U, mo	Primary Tumor Control, %	Overall Survival, %	Cancer-Specific Survival, %
Lee et al[104]	10	Covidien	4.1 (6)	14	60 (1 y)	80 (1 y)	100 (1 y)
Pennathur et al[105]	19	AngioDynamics	2.6 (3.8)	29	58 (2 y)	68 (2 y)	N/R
Hiraki et al[111]	20	Covidien/Boston Scientific Corp	2.4 (6)	21.8	63 (3 y)	74 (3 y)	83 (3 y)
Hsie et al[102]	12	Boston Scientific Corp	N/R	30	92 (3 y)	50 (3 y)	N/R
Beland et al[100]	69	Covidien	2.5 (5)	16	62 (2 y)	N/R	30 (3 y)
Lanuti et al[103]	31	Covidien	2 (4.4)	17	68.5 (3 y)	47 (3 y)	39 (3 y)
Lencioni et al[79]	13	AngioDynamics	1.5 (3.4)	24	87.5 (2 y)	75 (2 y)	92 (2 y)
Fernando et al[107]	9	Boston Scientific Corp	2.5 (4.5)	14	66 (2 y)	N/R	N/R

RFA = radiofrequency ablation. See Table 1, 2, and 5 legends for expansion of other abbreviations.

within 2 cm of the proximal bronchial tree (46%) compared with peripheral tumors (17%).[98] Higher central toxicity rates are not consistently observed with less intense SBRT regimens, and most protocols account for tumor location.

Summary: For high-risk patients with stage I NSCLC, definitive radiation therapy is an appropriate treatment option with curative potential. There is sufficient nonrandomized evidence to suggest SBRT over CFRT on the basis of superior survival, local control, and improved patient convenience. SBRT requires specialized equipment and technical expertise. The ACOSOG and RTOG (Z0499/1021)[99] are sponsoring a randomized comparison of SBRT and sublobar resection for high-risk patients with stage I NSCLC, which should help define use of these technologies.

Ablative Therapies

RFA is the most studied ablative technology for NSCLC. There are no randomized trials comparing RFA with other local therapies (ie, SBRT or surgery). There is accumulating experience indicating the feasibility of RFA for medically unresectable stage I NSCLC,[47,100-107] but the literature on efficacy and long-term outcome remains sparse. There are three competing US Food and Drug Administration-approved technologies for RFA in soft tissues: AngioDynamics, Covidien (Valley Laboratory Division), and Boston Scientific. The efficacy of different RFA systems has not been formally compared, and there is no consensus regarding superiority. RFA in lesions >3 cm or within 1 cm of hilar structures must be cautiously evaluated because of risk for incomplete ablation and damage to bronchovascular structures.[108]

The level of evidence with regard to RFA and local and regional control is low. Many studies include both primary and metastatic lesions, making it difficult to quantify the effect for NSCLC. Eight studies report specifically on outcomes after RFA for stage I NSCLC.[100,102-105,109-111] The primary tumor relapse rate ranges from 8% to 43% (Table 7).[100,102-105,107,111] Primary tumor recurrence after RFA for tumors <3 cm is 22% to 25%[112] and >50% for tumors >3 cm.[101,102,111] Primary tumor relapse rates improve to 8% to 12% when CFRT is added.[101,110]

Cancer-specific survival is the most important parameter in high-risk populations but is not always reported. Two-year cancer-specific survival after RFA ranges from 57% to 93%.[47,103,111] Overall 1-, 2-, and 3-year survival rates are 63% to 85%, 55% to 65%, and 15% to 46% (Table 7).[113] ACOSOG Z4033,[114] the only prospective, multi-institutional trial evaluating uniform RFA treatment in patients with high-risk, stage I

Table 8—*Toxicity Related to RFA Treatment of Clinical Stage I NSCLC*

Study	No.	System	Median Tumor Size (max), cm	Toxicity, %		
				Pneumothorax	CT Scan Placement	Effusion
Lee et al[104]	10	Covidien	4.1 (6)	35	7	7
Belfiore et al[109]	33	Covidien/AngioDynamics	3.5 (6)	9	0	9
Pennathur et al[105]	19	AngioDynamics	2.6 (3.8)	63	63	N/R
Dupuy et al[110]	24	Covidien + 66-Gy CFRT	3.5 (7.5)	29	12	N/R
Hiraki et al[111]	20	Covidien /Boston Scientific Corp	2.4 (6)	57	5	17
Hsie et al[102]	12	Boston Scientific Corp	N/R	25	25	N/R
Lanuti et al[103]	31	Covidien	2 (4.4)	13	8	21

CFRT = conventionally fractionated radiation therapy. See Table 1 and 7 legends for expansion of abbreviations.

NSCLC, has completed accrual and survival data are maturing.[115]

Toxicity: Several publications demonstrate no significant loss in lung function after pulmonary RFA.[14,103,116] Morbidity ranges from 15% to 55%.[102-104,109-111] The most prominent complications are pneumothorax (16%-54%) and pleural effusion (19%), which are grade 2 adverse events (Table 8). Other complications include alveolar hemorrhage, bronchopleural fistula,

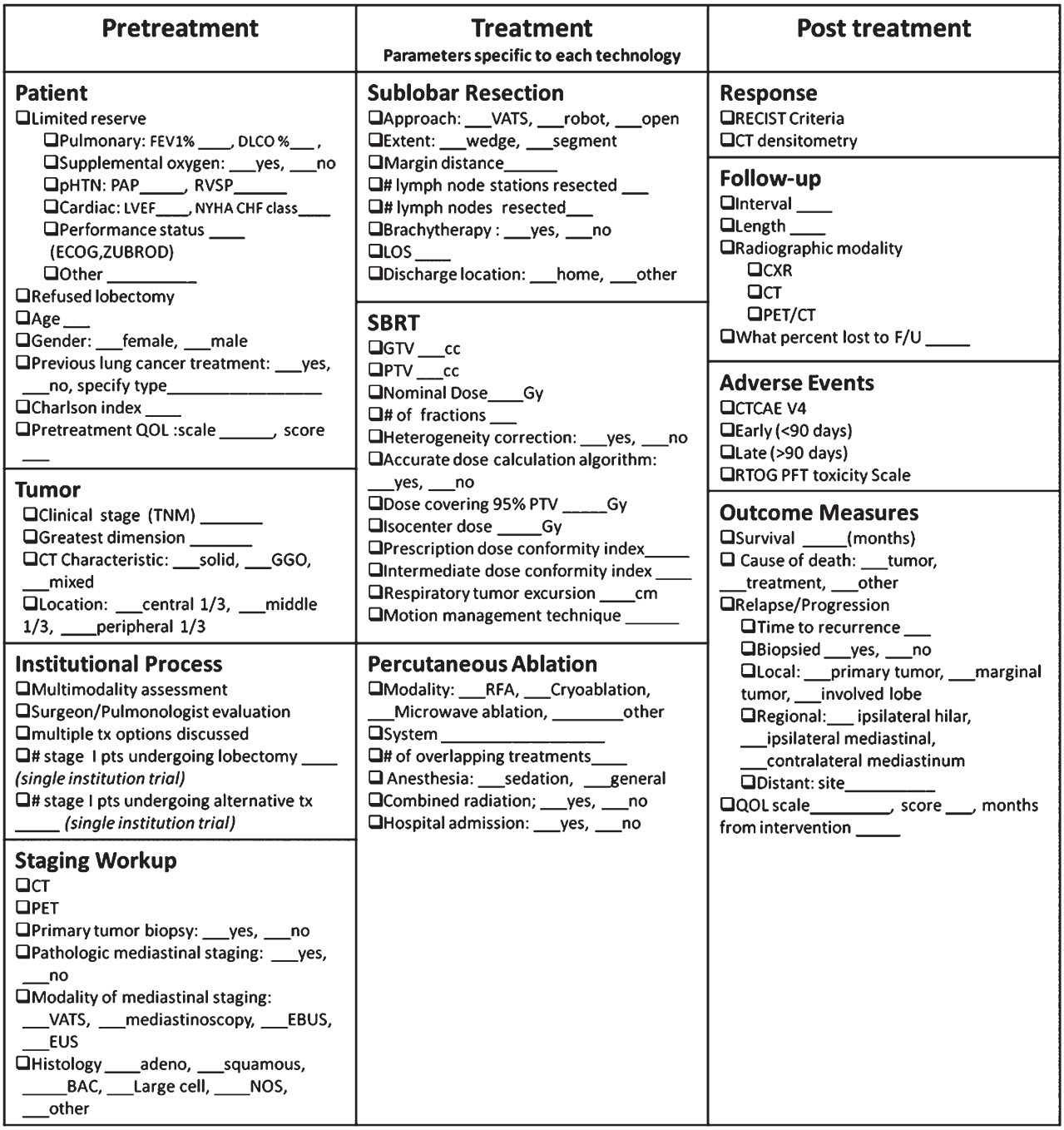

FIGURE 2. Suggestions for minimal reporting in clinical trials evaluating treatment strategies for high-risk stage I non-small cell lung cancer. adeno = adenocarcinoma; BAC = adenocarcinoma in situ; CHF = congestive heart failure; CTCAE V4 = common terminology criteria for adverse events, version 4; CXR = chest radiograph; DLCO = diffusing capacity of lung for carbon monoxide; EBUS = endobronchial ultrasound; ECOG = Eastern Cooperative Oncology Group; EUS = endoscopic ultrasound; F/U = follow up; GGO = ground glass opacity; GTV = gross tumor volume; LOS = length of stay; LVEF = left ventricular ejection fraction; NOS = not otherwise specified; NYHA = New York Heart Association; PAP = pulmonary artery pressure; PFT = pulmonary function test; pHTN = pulmonary hypertension; PTV = planning treatment volume; QOL = quality of life; RECIST = response evaluation criteria in solid tumors; RFA = radio frequency ablation; RTOG = Radiation Therapy Oncology Group; RVSP = right ventricular systolic pressure; SBRT = stereotactic body radiotherapy; segment = segmentectomy; VATS = video-assisted thoracic surgery; wedge = wedge resection.

massive hemoptysis, hemothorax, neuropathy, and pneumonia.[103,113] Most complications are of low severity and self-limited. Procedure-related mortality is $<1\%$; however, RFA in pneumonectomy patients was associated with death in two series.[106,117]

Summary: For high-risk patients with stage I NSCLC, RFA is a safe treatment option that can be used as a single modality for tumors ≤ 3 cm. Primary tumor control is better with smaller tumors, approximating 90% for tumors <2 cm. Toxicity appears to be decreased compared with SBRT and sublobar resection, but reduced primary tumor control limits enthusiasm for RFA to those patients who are not candidates for those treatments or prefer single-session outpatient intervention.

Discussion

The tendency for early metastasis from NSCLC makes treatment with localized therapies challenging. SBRT, RFA, and sublobar resection have been associated with increased risk for involved lobe and regional recurrence compared with lobectomy. Improvements in radiographic staging and detection of earlier and more indolent cancers tip the risk/benefit balance for high-risk stage I NSCLC toward less radical interventions. Evidence suggests that in well-staged and properly selected patients, sublobar resection and SBRT provide a curative option with decreased risk of toxicity and death.

The biggest hurdle in evaluating therapeutic options for high-risk patients is lack of uniformity in the reporting among trials. The majority of evidence is retrospective or from single-institution evaluations. Some consistency in reporting exists within a given modality but almost none across modalities. A common language and criteria for evaluation are needed going forward. Simply stating a patient is medically unfit for lobectomy is inadequate; medical disability needs to be qualified and quantified to allow comparisons between trials. Outcomes must include early and late toxicity, relapse location, and quality-of-life assessment. Suggested minimal reporting information is outlined in Figure 2. Validated reporting criteria exist for each parameter but are rarely completely reported.

Summary

There are now several treatment options available for high-risk patients with stage I NSCLC. A multidisciplinary approach is essential for the management of individual high-risk patients with NSCLC, and a similar approach is required on an organizational level to further define the appropriate use of each modality.

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Additional information: The e-Appendix can be found in the "Supplemental Materials" area of the online article.

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