

Review

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Sublobar resection in high-risk patients for lobectomy: current and future strategy

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Abstract

Surgical resection by lobectomy is the gold standard of therapy for early stage non-small cell lung cancer. However, not all patients are medically fit to undergo surgery. In patients considered high-risk for lobectomy, alternative strategies have been developed including radiofrequency ablation, cryoablation, microwave ablation, stereotactic radiation therapy, wedge resection, and segmentectomy. This work reviews the definition of high-risk, and the outcomes that have been associated with each treatment technique. Some technical points regarding wedge resection versus segmentectomy are noted. Future directions are discussed in the context of treatment for patients considered at high-risk for lobectomy.

Keywords: Non-small cell lung cancer, sublobar resection, surgical technique, high-risk patients

INTRODUCTION

This work is intended to review the current literature surrounding the definition of a patient with lung-cancer who is considered high-risk for lobectomy, discuss different treatment modalities and their outcomes for these patients, and note some potential future directions and their benefits to high-risk patients. PubMed and EMBASE were reviewed and works were included based on relevance. Previous work in this field has involved clinical trials to determine patients who are considered high-risk, their results with sublobar resection, radiofrequency ablation (RFA), cryoablation, microwave ablation (MWA), stereotactic body radiation therapy (SBRT), and comparisons of these alternative techniques against sublobar resection.



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Technical aspects of wedge resection and segmentectomy are discussed for high-risk patients, and future directions of lung cancer treatment that could specifically benefit high-risk patients are noted.

DEFINITION OF HIGH-RISK

One of the most used definitions for high-risk patients come from the American College of Surgeons Oncology Group (ACOSOG) Z4032 trial of stage I non-small cell lung cancer (NSCLC), with tumors ≤ 3 cm, that focused on clinical details to define high risk^[1]. Patients were considered high-risk for sublobar resection, or sublobar resection with brachytherapy, if their pulmonary function tests (PFTs) showed a Forced Expiratory Volume in 1 second (FEV₁) $\leq 50\%$ of predicted, or if their Diffusing Capacity for Carbon Monoxide (DLCO) was $\leq 50\%$ of predicted, or if they met two of the following criteria: age ≥ 75 years, FEV₁ 51%-60% predicted, DLCO 51%-60%, diagnosed with pulmonary hypertension (pulmonary artery systolic greater > 40 mmHg) as estimated by echocardiography or right heart catheterization, left ventricular ejection fraction $\leq 40\%$, resting or exercise arterial pO₂ ≤ 55 mmHg or SpO₂ $\leq 88\%$, pCO₂ > 45 mmHg, or Modified Medical Research Council Dyspnea Scale score ≥ 3 .

However, while ACOSOG Z4032 provides a precise definition, controversy still exists. Puri *et al.*^[2] reported the non-propensity score matched findings of their review of 1066 patients from the Washington University School of Medicine. They found that perioperative outcomes for the high-risk group by ACOSOG Z4032 were not different from normal-risk patients - respiratory failure, 4% (7/194) in high risk *vs.* 5% (41/872) in normal risk ($P = 0.70$); prolonged air leak of > 5 days, 8% (16/194) in high risk *vs.* 6% (54/872) in normal risk ($P = 0.36$); and 30 day/hospital mortality 1% (2/194) in high risk *vs.* 2% (14/872) in normal risk ($P = 0.75$). The most recent National Comprehensive Cancer Network NSCLC guidelines focus on a definition of high-risk that is aimed at risk of recurrence and leaves the definition of 'operative' high-risk unresolved^[3].

PERI-OPERATIVE OUTCOMES OF HIGH-RISK PATIENTS UNDERGOING SUBLOBAR

RESECTION

Fernando *et al.*^[4] reported perioperative outcomes for their high-risk patients in 2011. Three deaths (1.4%, 3/222), one in the sublobar resection group and two in the sublobar resection with brachytherapy group, occurred within 30 days. Three more deaths occurred by 90 days (2.7% 6/222), and four of the deaths within 90 days were attributed to the surgery performed. Kent *et al.*^[5] provided a further operative and pathologic analysis of this patient group in 2013. When segmentectomy ($n = 57$ patients) was compared to wedge resection ($n = 153$ patients), they found that segmentectomies had better margin size than wedge resections, median 1.5 cm (range 0.1-6.5 cm) *vs.* 0.8 cm (0-3.6 cm), $P = 0.0001$; greater number of lymph node stations sampled, median 3 (0-6) *vs.* 1 (0-6), $P < 0.0001$; and greater number of lymph nodes removed, median 4 (0-20) *vs.* 1 (0-23), $P < 0.0001$.

Sancheti *et al.*^[6] reported on their institution's experience with 'high-risk' patients defined by ACOSOG Z4032. The study focused on Stage I NSCLC and, in their sub-analysis of patients who underwent sublobar resection, reported shorter operative time in the high-risk group *vs.* standard risk group, median 89.0 min (range 64.0-110.0) *vs.* 112.5 min (74.0-145.5), $P = 0.04$; but longer length of stay, median 4 days (3-7) in the high risk group *vs.* median 3 days (2-5) in the standard risk group, $P = 0.003$. They found no statistical difference in total patient numbers with major morbidity, 12.3% (7/57) high risk group *vs.* 6.7% (4/40) standard risk group, $P = 0.39$; but, noted more patients with minor morbidity in the high-risk group, 43.9% (25/57) *vs.* 20% (12/60) in the standard risk group, $P = 0.02$. The 3-year survival from sublobar resection was worse for high risk patients than standard risk patients, 57% *vs.* 71%, but not statistically significant, $P = 0.15$.

Lastly, Puri *et al.*'s^[2] sub-analysis of their high-risk patients who underwent sublobar resection found no differences in perioperative outcomes between high-risk patients ($n = 72$) and normal-risk patients ($n = 112$). Atrial fibrillation was slightly more common in the high-risk group than normal-risk, 11% (8/72) vs. 6% (7/112), $P = 0.28$, but this was potentially due to low event rates in both groups. They did not report the sublobar resection group survival Kaplan-Meier curves, but noted on logistic regression analysis that ACOSOG Z4032 high-risk status was not associated with the risk of perioperative complications (data not provided in their manuscript)^[1,2].

THERAPEUTIC CHOICE FOR OPTIMAL LONG-TERM OUTCOMES OF HIGH-RISK PATIENTS

Since Ginsberg *et al.*'s^[7] 1995 report on the Lung Cancer Study Group's randomized control trial of lobectomy vs. limited resection for T1 NSCLC, lobectomy has remained the gold standard for resection of early stage lung cancer. However, the current NCCN guidelines state that anatomic pulmonary resection is the preferred method for the majority of patients with NSCLC^[3,7]. The NCCN guidelines further elaborate on sublobar resection as being appropriate in the setting of "poor pulmonary reserve or other major comorbidity that contraindicates lobectomy", while noting that SBRT is recommended for medically inoperable patients or patients who refuse surgery^[3]. As there is no clear definition for "high-risk" patients, the choice of therapy for high-risk patients remains the purview of the clinicians treating the patient. Ablation techniques, SBRT, and lobectomy continue to be options for high-risk patients, in addition to sublobar resection.

Multiple ablation techniques have been reported for lung cancer including RFA, microwave ablation, and cryoablation^[8-10]. In 2005, Fernando *et al.*^[8] reported RFA as an alternative for patients with peripheral lung cancer who are not surgical candidates. In their initial 18 patient series with 21 total tumors, they treated patients of all stages with a median tumor size of 1.8 cm (range 1.2-4.5 cm). In this broad patient set, they noted a mean progression-free survival of 16.8 months. In 2007, Simon *et al.*^[11] published their 153 patient series from 1998-2005 that reviewed the outcomes of patients treated with RFA who were refused surgery or were not deemed suitable as surgical candidates. The 5-year survival rate for stage I NSCLC was 27%, with local progression-free rate for tumors ≤ 3 cm equal to 47%, and for > 3 cm equal to 25%. A recent review of the National Cancer Database compared SBRT to RFA for stage I NSCLC (4,454 SBRT vs. 335 RFA patients)^[12]. RFA patients were noted to have more comorbidities than SBRT patients. They performed a propensity score matching and found no difference in the overall survival rate (OS) at 1-, 3-, and 5- years (31.9% SBRT vs. 27.1% RFA, $P = 0.835$).

MWA is another thermal ablation technique that uses high temperature to destroy tumors^[9]. Zhong *et al.*^[9] reported on 113 patients who underwent microwave ablation; 35 patients had early stage disease and 78 patients had late stage lung cancer. 10.6% (12/133) of all patients had a pneumothorax after the procedure, but no intraoperative or perioperative deaths were observed. At 3 years, they reported that the survival of the early stage group was 84.7%, in comparison to 71.7% in the advanced stage group, $P = 0.576$. Zhao *et al.*^[13] reported a longer-term follow-up (out to 5 years) of 34 early stage patients (T1a-T3N0M0). Pneumothorax was noted in 24 cases (59%) with 6 cases requiring chest tube insertion (15%). Their 5-year overall survival rate was 46.7%. Yuan *et al.*^[14] performed a meta-analysis of 53 studies to compare outcomes of RFA with MWA for primary lung cancer and pulmonary metastases. They found a pooled pneumothorax rate of 34.3% (95%CI: 25.9%-43.1%) in the RFA group vs. 33.9% (95%CI: 23.8%-44.8%) in the MWA group, $P = 0.957$. Severe pneumothorax that required intervention occurred in 12.3% of patients (95%CI: 6.8%-19.1%) in the RFA group and in 11.0% of patients (95%CI: 4.5%-19.7%) in the MWA group, $P = 0.797$. Based on the 8 studies for RFA and 6 studies for MWA, they found comparable median OS for the 2 groups, RFA 28.4 months (95%CI: 20.9-35.8) vs. MWA 24.4 months (95%CI: 16.9-31.8).

Cryoablation is the other common ablative technique and works by creating a freezing zone that first freezes the extracellular fluid and then the intracellular fluid, causing cellular and tissue destruction during multiple cycles with temperature ranges typically in the -20C to -40C range^[15,16]. For Stage I NSCLC, Yamauchi *et al.*^[17] reported a 3-year overall survival of 88% and a disease-free 3-year survival of 67%, while Moore *et al.*^[18] reported a 5-year overall survival of 67.8% ± 15.3, cancer-specific survival of 56.6% ± 16.5, and 5-year progression-free survival rate of 87.9% ± 9. Yamauchi reported pneumothorax in 28% cases (7/25) vs. Moore's report of 51.0% (24/45); and each reported 1 case requiring chest tube insertion. Zemlyak *et al.*^[19] performed a small retrospective, non-propensity matched comparison between sublobar resection ($n = 25$), radiofrequency ablation ($n = 12$) and percutaneous cryoablation ($n = 27$) and found that the 3-year overall survival was 87.1%, 87.5%, and 77%, respectively, $P > 0.05$. Additionally, the 3-year cancer-specific and cancer-free survival for sublobar resection, radiofrequency ablation, and percutaneous cryoablation groups was 90.6% and 60.8%, 87.5% and 50%, and 90.2% and 45.6%, respectively with $P > 0.05$ for intergroup comparisons of 3-year cancer specific survival and 3-year cancer free survival. They noted that the lack of significance was likely due to a small sample size.

The American Society of Radiation Oncology defines SBRT as ablation radiation doses in 1-5 fractions with high conformal techniques^[20]. They note in these consensus guidelines that stage I NSCLC patients with "high operative risk" should be offered SBRT as an alternative to sublobar resection, but the longer-term outcomes over 3 years are not well-established. Some of the longest survival data for SBRT comes from a follow-up of the North Central Cancer Trials Group N0927 randomized phase II study, comparing 34 Gy vs. 48 Gy SBRT for medically inoperable stage I peripheral NSCLC^[21-22]. They found that the 5-year overall survival in the 34 Gy and 48 Gy groups were 29.6% (95%CI: 16.2%-44.4%) and 41.1% (95%CI: 26.6%-55.1%) respectively. Progression-free survival at 5 years was 19.1% (95%CI: 8.5%-33.0%) and 33.3% (95%CI: 20.2%-47.0%) for the 34 Gy and 48 Gy groups respectively. A recent systematic review and pooled analysis compared RFA to SBRT, and found that SBRT has better 5 year local tumor control rate, 42% (95%CI: 30%-54%) RFA vs. 86% (95%CI: 85%-88%) SBRT $P < 0.001$; but similar OS, 32% (95%CI: 22%-43%) for RFA vs. 40% (95%CI: 36%-45%) for SBRT $P = 0.41$ ^[23]. In 2019, Ager *et al.*^[24] reviewed the National Cancer Database and compared 14,651 SBRT patients to 1141 patients who underwent some form of percutaneous local tumor ablation therapy (LTA). After propensity score matching, their Cox modeling found a hazard ratio of 0.83, 95%CI: 0.73-0.94, $P = 0.002$, showing improved survival for SBRT patients. Adjusted rates of OS at 5 years were 31.0% and 26.2% for SBRT and LTA, respectively. Chi *et al.*^[25] also reviewed the National Cancer Database and compared SBRT to multiple different forms of surgery for early stage lung cancer. They found that the 5-year overall survival for the resection groups ranged from 48.1% (wedge resection) to 64.6% (lobectomy), compared to 30.4% in the SBRT cohort, $P < 0.01$ for each resection type vs. SBRT. Their Cox model hazard ratios for wedge resection, segmentectomy, and lobectomy compared to SBRT demonstrated improved overall survival with surgery with values from 0.55 (wedge resection) to 0.40 (lobectomy), each P value < 0.01 .

In terms of surgical treatment, Jensik *et al.*^[26] were the first to propose segmentectomy as an appropriate alternative to lobectomy for small-sized lung cancers. Since then, the debate has continued with findings for and against this in randomized trials, large database studies, and meta-analysis reviews, with lobectomy continuing as the standard of care with allowances for sublobar resection of high-risk cases^[3,7,27,28]. Relatively few studies have focused on direct comparisons of surgical options in high-risk patients. Ijsseldijk *et al.*^[28] recently published a comprehensive systematic review and meta-analysis of 100 studies comparing SBRT, sublobar resection, and lobectomy. In this work, they found that lobar resection had a 5-year OS of 74% [0.69, 0.78], sublobar resection had a 70% OS [0.64, 0.77], and SBRT had a 46% OS [0.35, 0.57], with both surgical survivals statistically better compared to SBRT, both $P < 0.01$. Disease-free survival at 5 years in patients who had lobar resection was 76% [0.71, 0.82], sublobar resection was 71% [0.67, 0.76], and SBRT was 46% [0.35, 0.57], with both surgical survivals statistically better compared to SBRT, $P < 0.01$. However,

this work was not specified to include only high-risk patients. Hou *et al.*^[29] performed a specified meta-analysis directly comparing segmentectomy to sublobar resection for high-risk patients in 9 studies. They noted heterogeneous definitions for what qualified as high-risk, but most studies had followed Fernando *et al.*'s^[1] criteria from their 2011 work mentioned earlier in this review. For OS, Hou *et al.*^[29] included 7 studies, and on meta-analysis found that the hazard ratio for segmentectomy compared to wedge resection for stage I NSCLC was 0.80 in favor of improved OS with segmentectomy compared to wedge resection [95%CI: 0.68-0.93; $P = 0.004$]. On subgroup analysis, there was comparable OS for stage I tumors ≤ 2 cm; however, the hazard ratio favored improved OS with segmentectomy compared to wedge resection, 0.39 [95%CI: 0.15-1.02; $P = 0.06$]^[29]. Cancer-specific survival also favored segmentectomy over wedge resection, hazard ratio 0.42 [95%CI: 0.20-0.88; $P = 0.02$]. They were unable to fully assess disease-free survival as only 3 studies reported data that was usable for comparison.

Unfortunately, even with all this data, the best option for high-risk patients who can undergo limited resection, but not full lobectomy, remains unclear. Three randomized control trials are ongoing comparing lobectomy to sublobar resection for early stage NSCLC, ≤ 2 cm with N0 lymph node status^[30-32]. All three studies have reported their peri-operative safety results and found no substantial differences. Suzuki *et al.*^[30] noted a higher airleak rate in their 552 segmentectomy patients compared to their 554 lobectomy patients, 6.5% *vs.* 3.8%, $P = 0.04$. However, Altorki *et al.*'s^[31] report did not note an increased airleak in their sublobar resection group, 340 patients total, compared to their 357 lobectomy patients. This was despite including wedge resections and segmentectomies in their sublobar resection group; 201 wedge resection patients and 139 lobectomy patients^[31]. Stamatis *et al.*^[32] noted equal rates of prolonged air leak in their 53 segmentectomy patients compared to their 54 lobectomy patients. Until the long-term outcomes of these randomized control trials are evaluated, the choice of therapy should be determined by a multidisciplinary team. Surgical resection, when feasible and preferably segmentectomy, remains the recommended treatment if lobectomy is not possible^[3].

SUBLOBAR RESECTION TECHNICAL POINTS: WEDGE RESECTION VS SEGMENTECTOMY

Patient selection remains of paramount importance for surgical procedure choice. Wedge resection and segmentectomy are most appropriate for smaller, peripherally located lesions away from the hilum of the lung. Segmentectomy should be favored when possible given its respect for anatomic planes, but comes with a caveat. The target lesion must lie within the boundaries of one segment or group of segments. One of the authors has written extensively regarding this process and reported that patients with lesions under 2 cm that are resected with segmentectomy have no difference in outcomes compared to the patients treated with lobectomy^[33-35]. Segmentectomies are more technically challenging as the surgeon must create a fissure between segments and then dissect out and ligate the segmental vessels and bronchus. Wedge resection is performed without respect to anatomic planes or specific vessels, but can be useful when the target lesion is very small (1 cm or less), subpleural, or crosses segmental borders. Care should be taken to ensure that the margins from the edge of the tumor to the final staple line are appropriately wide to minimize recurrence and that adequate lymph nodes are removed to ensure accurate staging^[36-38].

FUTURE DIRECTIONS

Radiomics is a rapidly growing field in which radiographic images are used to determine features such as lesion shape, volume, texture, attenuation, and other factors that are not readily apparent or are too difficult for an individual radiologist to assess visually or qualitatively^[39]. Radiomics is being studied to predict histologic subtypes, specific mutations, and benefit of adjuvant chemotherapy after resection^[40-42]. Radiomics has already been used to predict OS in NSCLC; specifically, the recurrence of NSCLC after SBRT^[43-45]. Radiomics may even be able to predict survival based on resection type and offer high-risk patients more tailored care.

Another advancement lies in improved lesion targeting for NSCLC that is not located at the outermost periphery. Image-guided video-assisted thoracoscopic surgery (iVATS) is an emerging technology that is being developed to allow localization of non-palpable lesions^[44]. Early reports indicate excellent rates of localization using modifications of previously developed techniques with wires, microcoils, and indocyanine green with near-infrared imaging^[46-48]. These lesions are then removed with sublobar resections. Of note, the use of this technology requires a hybrid operating room equipped with a CT scanner, which is not available at all facilities. By being able to remove deeper lesions while still performing wedge resection or segmentectomy, iVATS offers high-risk patients another surgical option for lesions that previously may have required lobectomy.

CONCLUSION

In summary, high-risk patients remain a poorly defined group, with patients typically defined as those with some degree of poor pulmonary function and often other significant functional or medical limitations. In these patients, surgical resection is the gold standard relative to SBRT and ablative techniques. Segmentectomy should be performed rather than wedge resection when feasible, and when lobectomy is not an option. Future developments in radiomics and iVATS technique may help further refine the optimal treatment approaches for high-risk patients.

DECLARATIONS

Authors' contributions

Made substantial contributions to the conception and design of the study, performed data analysis and interpretation, data acquisition, as well as provided administrative, technical and material support: Dolan D, Swanson S

Availability of data and materials

Not applicable.

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None.

Conflicts of interest

Dr. Swanson reports receipt of honoraria from Covidien and Ethicon for speaking and consulting services.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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