



## Advances and controversies in the management of early stage non-small cell lung cancer

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### Abstract

Complete resection continues to be the gold standard for the treatment of early-stage lung cancer. The landmark Lung Cancer Study Group trial in 1995 estab-

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lished lobectomy as the minimum intervention necessary for the management of early-stage non-small cell lung cancer, as it was associated with lower recurrence and metastasis rates than sublobar resection and lower postoperative morbidity and mortality than pneumonectomy. There is a growing tendency to perform sublobar resection in selected cases, as, depending on factors such as tumor size, histologic subtype, lymph node involvement, and resection margins, it can produce similar oncological results to lobectomy. Alternative treatments such as stereotactic body radiotherapy and radiofrequency ablation can also produce good outcomes in inoperable patients or patients who refuse surgery.

**Key Words:** Video-assisted thoracoscopic surgery; Sublobar resection; Radiofrequency ablation; Stereotactic radiosurgery; Early stage; Lung cancer

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**Core Tip:** Complete resection continues to be the gold standard for the treatment of early-stage lung cancer. Lobectomy remains the gold standard for the treatment of early-stage non-small cell lung cancer, but there is a growing tendency to perform sublobar resection in selected cases. Alternative treatments such as stereotactic body radiotherapy and radiofrequency ablation can also produce good outcomes in inoperable patients or patients who refuse surgery.

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## INTRODUCTION

Complete resection continues to be the gold standard for the treatment of early-stage lung cancer. The landmark Lung Cancer Study Group trial in 1995 established lobectomy as the minimum intervention necessary for the management of early-stage non-small cell lung cancer (NSCLC), as it was associated with lower recurrence and metastasis rates than sublobar resection and lower postoperative morbidity and mortality than pneumonectomy[1]. The development of lung-sparing techniques (e.g., sleeve resection with vascular and/or bronchial reconstruction) has reduced the number of pneumonectomies performed and with this the risk of adverse outcomes, as the proportion of pneumonectomies is a quality indicator in thoracic surgery[2].

While lobectomy remains the gold standard for the treatment of early-stage NSCLC, there is a growing tendency to perform sublobar resection in selected cases, as, depending on factors such as tumor size, histologic subtype, lymph node involvement, and resection margins, it can produce similar oncological results to lobectomy[3]. Two randomized clinical trials comparing lobectomy and sublobar resection are currently underway: The United States Cancer and Leukemia Group B trial (CALGB 140503)[4] and the Japanese JCOG0802/WJOG4607L trial[5]. The results so far have shown no significant differences in postoperative morbidity or mortality, but as discussed in greater detail below, data on survival and pulmonary function are pending.

The use of minimally invasive techniques for the surgical treatment of early-stage NSCLC has increased in recent years. Video-assisted thoracoscopic surgery (VATS) is the current procedure of choice for most resections in this setting. A recent nationwide cohort study conducted in Spain reported that over 50% of recent anatomic lung resections had been performed by VATS[6]. The main advantages of VATS compared with open surgery are decreased postoperative pain, fewer postoperative complications, and in some cases even, better oncological outcomes. There are, however, substantial geographic variations in the use of VATS.

Advances in VATS techniques and the design of specific surgical material have led to a progressive reduction in the number of incisions required. Most thoracic surgeons now use between one and three incisions and describe similar oncological results[6,7]. Subxiphoid VATS is another minimally invasive technique associated with good outcomes when performed by teams with extensive experience in VATS; it has been linked to a lower incidence of postoperative neuropathic pain[8].

The increasing adoption of VATS has favored its use in more locoregionally advanced lung cancers. Data from large series of angio-bronchoplastic or extended lung resections performed by experienced thoracic surgeons show similar outcomes to thoracotomy[9].

Good outcomes have also been described with robotic-assisted thoracoscopic surgery in the setting of anatomic resections, although the cost-effectiveness of the technique is not so clear[10].

As we discuss below, alternative treatments such as stereotactic body radiotherapy (SBRT) and radiofrequency ablation (RFA) can also produce good outcomes in inoperable patients or patients who refuse surgery.

## ROLE OF SUBLOBAR RESECTION IN LUNG CANCER

Anatomic sublobar resections have produced comparable oncological results to lobectomy in the treatment of tumors < 2 cm without nodal involvement or distant metastasis[11]. These favorable results have led to an increased use of segmentectomy, which, depending on tumor stage and resection margins, can produce similar oncological results to lobectomy in selected patients[12].

Anatomic segmentectomy is oncologically more valuable than atypical (wedge) resection in early-stage cancer as it permits the performance of hilar and mediastinal lymph node dissection[13].

Its main advantage, however, is its parenchyma-sparing effect, which results in better postoperative respiratory function than lobectomy. In view of the above, anatomic sublobar resection can be considered an appropriate treatment for patients with compromised respiratory function unable to tolerate standard lobectomy. Patients considered to be at high operative risk include patients with FEV<sub>1</sub> < 50% or DLCO < 50% and elderly patients with impaired lung function, pulmonary hypertension, and poor left ventricular function[14,15].

Compared with lobectomy, VATS sublobar resection has been linked to shorter hospital stays and drainage times, a lower incidence of supraventricular arrhythmia, and fewer postoperative respiratory complications[11].

In certain cases, anatomic segmentectomy involves a higher risk of air leakage when electrocautery is used for intersegmental plane dissection (as reported by several Japanese groups)[5,13]. Air leakage is not common when absorbable sutures are used, which is the case in most lung resections.

The only randomized prospective trial to compare lobectomy and sublobar resection in T1N0M0 lung cancer (the Lung Cancer Study Group trial) concluded that patients treated with sublobar resection had a higher risk of locoregional recurrence and death[1]. It should be noted, however, that these results were published in 1995 and that lung tumors are now diagnosed earlier.

Several retrospective studies published since 2000 have reported good oncological outcomes in patients with small peripheral tumors (stage I and < 2 cm) treated with segmentectomy[13,16-19].

As mentioned, the ongoing CALGB[4] and Japanese[5] trials have not detected any differences between lobectomy and sublobar resection for postoperative morbidity or mortality, but survival and pulmonary function outcomes are not yet available[4,13,20].

Thus, it remains to be determined whether segmentectomy is a valid alternative to lobectomy for the treatment of early-stage NSCLC in patients fit for both procedures[4,5].

## POSTRESECTION ADJUVANT THERAPY IN NSCLC

Thirty percent of lung cancer patients have early-stage disease when diagnosed. The standard treatment is surgery, followed or not by chemotherapy with or without radiotherapy.

Data from retrospective series show that less invasive surgical procedures result in fewer complications, allowing earlier initiation of chemotherapy, but do not appear to have an impact on overall survival (OS).

Postoperative radiotherapy in stage I and II NSCLC is indicated for patients with positive margins. According to the recent results of the phase III LUNG ART trial, postoperative radiotherapy did not have any beneficial effects in patients with pathologic mediastinal involvement (N2), in addition, it induced high levels of toxicity. Chemotherapy, however, was associated with a 5.4% increase in OS at 5 years, regardless of age [hazard ratio (HR) = 0.89]. Chemotherapy is indicated for resected stage II and IIIA NSCLC[21], but its use in stage I disease is more controversial. The standard treatment is four cycles of doublet cisplatin-based chemotherapy. The only clinical trial to investigate the use of carboplatin in this setting reported negative results[22]. Survival outcomes, however, are poor, mainly because of high rates of distant recurrence. Five-year OS rates range from 73% for stage IB disease to 65% for stage IIA disease, 56% for stage IIB disease, and 41% for stage IIIA disease[23]. It is therefore important to continue to explore new treatments and prognostic and predictive biomarkers.

Attempts to improve treatment outcomes with the addition of antiangiogenics[24] or vaccine-based therapy[25] have been unsuccessful. The potential benefits of immunotherapy are being investigated, as good results have been reported for adjuvant immunotherapy in more advanced stages of disease and other types of tumor [26]. Ongoing trials include PEARLS (pembrolizumab), BR31 (durvalumab), ANVIL (nivolumab), Impower 010 (atezolizumab), and Canopy-A (canakinumab). No results, however, are available yet. Immunotherapy, both alone and combined with chemotherapy, has shown promising results in the neoadjuvant setting. Chemoimmunotherapy has significantly improved complete and major pathological responses in NSCLC (by approximately 36% and 65%, respectively) and has also led to downstaging in over 70% of patients[26,27]. It remains to be determined whether immunotherapy is more effective as a neoadjuvant or adjuvant treatment[28].

Agents targeting driver mutations are being investigated in multiple trials, but results are still pending. We do have results from the ADAURA trial, where patients with completely resected *EGFR* mutation-positive NSCLC, regardless of whether or not they had received prior chemotherapy, were randomized to receive osimertinib [a third-generation tyrosine-kinase inhibitor (TKI)] or placebo for 3 years. The progression-free survival (PFS) outcomes for patients with stage II and IIIA disease in the osimertinib group were unprecedented, with an HR for disease recurrence or death of 0.17. In addition, the benefits were observed in all the subgroup analyses. The adverse events were to be expected based on the experience with this drug. Osimertinib was also associated with a reduction in brain recurrences (HR = 0.18)[29]. These results were sufficient for the United States Food and Drug Administration to approve osimertinib as an adjuvant treatment for NSCLC with *EGFR* mutations. Recent results from another trial showed that icotinib, a first-generation TKI, improved PFS (HR = 0.36) in patients with resected stages II and IIA disease; results on OS have not been published yet[30]. Nonetheless, in the CTONG trial of adjuvant treatment with gefitinib, the improvement observed for PFS was not carried over to OS, reflecting previous findings for other targeted therapies. It remains to be seen whether osimertinib will achieve a survival benefit in the ADAURA trial.

Little has been reported on the use of biomarkers in this setting, as they were not a requirement in most of the trials conducted to date. Thus, the potential values of *BRCA1* and of *ERCC1* and thymidylate synthase were not validated in the respective SCAT and ITACA trials. Contradictory results have been reported for the prognostic value of PDL-1 expression and tumor mutational burden[31-33]. Nonetheless, next-generation sequencing is a promising strategy for the detection of residual disease after surgery[34,35]. A recent meta-analysis showed that residual molecular disease detected by circulating tumor DNA analysis after complete resection was associated with a higher risk of recurrence and death.

Despite the available evidence, treatment should always be individualized, with careful assessment of risks and benefits, particularly in the current scenario of COVID-19[36].

## SBRT IN EARLY-STAGE LUNG CANCER

SBRT is a high-precision technique that delivers high doses of radiation over a short period of time[37]. Conceptually derived from cranial stereotactic radiosurgery, it is

now used in multiple anatomic locations. It is the treatment of choice for early-stage lung cancer in medically inoperable patients or patients who refuse surgery, with a 5-year local control rate of 90%[38]. It improves survival in older patients and reduces the number of untreated patients. When SBRT is not feasible, hypofractionated radiotherapy is preferred to conventionally fractionated schedules[39]. Acute toxicity is rare in SBRT, and includes mild fatigue 1-2 wk after treatment; quality of life is rarely affected[40]. The risk of severe toxicity is low[41], and the most common adverse effect is decreased lung capacity. SBRT can be highly toxic in patients with a history of interstitial lung disease and its use should be assessed by a multidisciplinary committee. Late adverse effects include pain, rib fractures, dyspnea, and ventricular tachycardia[38]. Other effects are esophagitis, epithelitis, and brachial plexopathy. Complications are largely influenced by tumor location and size, radiation dose and target volume[42]. Pathological confirmation is not always possible, and some authors have suggested that up to 16% of lung nodules may be benign[4].

SBRT has certain technical characteristics that need to be taken into account when planning and administering treatment. Four-dimensional computed tomography (CT) is recommended for preoperative simulation, and multiple beams or arcs should be used for planning purposes as they help limit toxicity[43].

Dose schedules for peripheral tumors vary, but mostly consist of 3-8 fractions of 7.5-20 Gy each; results for a dose of 54 Gy in 3 fractions include a 3-year local control rate of 91%, a 3-year disseminated failure rate of 22%[44], a 5-year local control rate of 80%, and a 5-year local control rate of 31%[41]. A phase II trial comparing 30 Gy in 1 fraction and 60 Gy in 3 fractions showed 2-year survival rates of 71% and 61%, respectively, with no differences in toxicity[45]. On comparing 34 Gy in 1 fraction and 48 Gy in 4 fractions, Nagata *et al*[46] found OS rates of 61% and 78%, respectively, and no differences in survival, primary tumor control, or toxicity. In their meta-analysis of 34 observational studies involving 2597 patients, Zhang *et al*[47] determined that the most beneficial dose regimens were those that achieved a biologically equivalent dose of 83.3-146 Gy[47].

Centrally located tumors are tumors located within 2 cm, in any direction, of a critical mediastinal structure, such as the bronchial tree, esophagus, heart, brachial plexus, major vessels, spinal cord, phrenic nerve, and recurrent laryngeal nerve. SBRT is not suitable for ultracentral tumors, but hypofractionated schedules consisting of 6-15 fractions could be considered[48]. Risk-adapted schedules have achieved high local control rates and limited toxicity. Evidence to date shows a 5-year OS rate of 50% and a local control rate of 93%[49,50]. A systematic review of SBRT efficacy and toxicity in centrally located NSCLC showed similar local control and survival rates to those achieved in peripheral tumors.

Three randomized clinical trials have compared SBRT and surgery, although they had problems with accrual. A pooled analysis of the STARS and ROSEL trials showed comparable 3-year recurrence-free survival. Results from the ACOSOG Z4099 trial have not been reported. In the RTOG 0813 trial, 100 medically inoperable patients with central tumors were treated with 50-60 Gy in 5 fractions on alternating days. This resulted in 2-year local control, OS, and PFS rates of 88%, 70%, and 53%, respectively; 15 patients experienced grade 3 or higher toxicity (grade 3, 10 patients; grade 4, one patient; and grade 5, four patients). The standard treatment for patients with operable tumors is surgery, lobectomy, and mediastinal lymph node dissection. The RTOG 0236 [41] and 0915[47] trials showed a 3-year OS rate of 56% over a median follow-up of 4 years and a 5-year OS rate of 40%. The local control and 3-year survival rates were 87.3% and 59.9%, respectively. High recurrence rates, however, were observed in the SBRT group during follow-up[51,52]. Results from the VALOR, SABRTooth, RTOG 3502, and STABLE-MATES trials are pending (Table 1).

When used to treat multiple synchronous tumors *vs* solitary tumors, SBRT offers similar local control and toxicity rates and worse survival rates[53]. The role of SBRT is being investigated in T3-4N0M0 tumors with schedules of 8-10 Gy per fraction in 8-10 fractions. Two-year local control rates of 68%-73.2% have been described[54-56].

A recent study demonstrated that SBRT after contralateral pneumonectomy was safe. Arifin *et al*[57] analyzed 59 studies with a mean follow-up of 25.4 mo and found a mean 1-year OS rate of 80.6%, a 2-year local control rate of 89.4%, and a grade  $\geq 3$  rate of 13.2%.

## RFA IN EARLY-STAGE NSCLC

RFA is a minimally invasive CT-guided procedure originally approved for use in liver



**Table 1 Studies analyzing surgery and stereotactic body radiotherapy in non-small cell lung cancer**

Ref.	Type	Surgery-RT, No.	Surgery-RT, Local failure	Surgery-RT, PFS	Surgery-RT, OS	Surgery-RT, Toxicity	LoE
Grills <i>et al</i> [74], 2010	R	69 wedge resection; 58 SBRT; Unfit for lobectomy	20%-4% ( $P = 0.07$ )	65% <i>vs</i> 77% ( $P = 0.37$ )	87% <i>vs</i> 72% ( $P = 0.01$ )	Readmission 10%; Pneumonitis 2%; Fracture 11%	3
Varlotto <i>et al</i> [75], 2013	R	48 sublobar resection +132 lobectomy; 137 SBRT	At 5 yr 18.8% lobectomy <i>vs</i> SBRT 12.2% ( $P = 0.382$ ); Resection 7.1%	No differences ( $P = 0.378$ )	At 5 yr lobectomy <i>vs</i> SBRT 33.7%; Resection 86.3% ( $P = 0.04$ , $P = 0.003$ )		3
Versteegen <i>et al</i> [76], 2013	R	64 VATS; 64 SBRT; 54% inoperable	At 3 yr 3.1% <i>vs</i> 1.6% ( $P = 0.04$ )	79.7% <i>vs</i> 75%	76.9% <i>vs</i> 90.8% ( $P = 0.83$ )	23.4% <i>vs</i> 6.3% $G \geq 3$ ( $P = 0.03$ )	3
Matsuo <i>et al</i> [77], 2014	R	53 sublobar resection; 53 SBRT	At 5 yr 14.1% <i>vs</i> 28.3% ( $P = 0.059$ )		55.6% <i>vs</i> 40.4% ( $P = 0.124$ )		3
Zheng <i>et al</i> [78], 2014	MA	11921; 7071 surgery; 4850 SBRT	At 1 yr 93% lobectomy <i>vs</i> 91.5% sublobar resection <i>vs</i> 96.3% SBRT. At 3 yr 85% <i>vs</i> 78.4% <i>vs</i> 87.8%. At 5 yr 80% <i>vs</i> 63.4% <i>vs</i> 83.9% ( $P = 0.45$ )	At 1 yr 93.5% lobectomy <i>vs</i> 90.3% sublobar resection <i>vs</i> 87.1% SBRT. At 3 yr 82.9% <i>vs</i> 82.1% <i>vs</i> 65.8%. At 5 yr 74.8% <i>vs</i> 71.2% <i>vs</i> 65.8% ( $P = 0.46$ )	At 1 yr 92.5% lobectomy <i>vs</i> 93.2% sublobar resection <i>vs</i> 83.4% SBRT. At 3 yr 77.9% <i>vs</i> 80.7% <i>vs</i> 56.6%. At 5 yr 66.1% <i>vs</i> 71.7% <i>vs</i> 41.2% HR = 0.52, 95%CI: 0.2-1.36 for lobectomy and HR = 0.49, 95%CI: 0.19-1.3 for sublobar resection		1
Yu <i>et al</i> [79], 2015	R	1078; 711 surgery; 367 SBRT			At 2 yr 77.7% <i>vs</i> 59.9% ( $P = 0.01$ )	Acute 54.9% <i>vs</i> 7.9% ( $P < 0.001$ ). Chronic 73.9% <i>vs</i> 69.7% ( $P = 0.31$ )	3
Rosen <i>et al</i> [80], 2016	R	1781 lobectomy; 1781 SBRT			At 5 yr 59% <i>vs</i> 29%; 58% <i>vs</i> 40% for patients who refused surgery ( $P = 0.010$ )		3
Ma <i>et al</i> [81], 2016 (adjusted for operable patients)	MA	6969; 3436 VATS; 4433 SBRT		No differences ( $P = 0.378$ )	No differences HR = 2.02, 95%CI: 0.45-3.07 ( $P = 0.36$ )		2
Deng <i>et al</i> [82], 2017	MA	13598	No differences ( $P = 0.453$ )		At 3 yr 68.1% <i>vs</i> 47.7% ( $P < 0.001$ )		1
Grills <i>et al</i> [74], 2010	P. III	222 Lobectomy; 254 SBRT	At 5 yr 5% <i>vs</i> 8% ( $P = 0.388$ )	At 5 yr 72% <i>vs</i> 53% ( $P = 0.018$ )	At 5 yr 78% <i>vs</i> 61% ( $P = 0.006$ )		1
Ackerson <i>et al</i> [83], 2018	R	151 surgery; 70 SBRT	At 3 yr 10% <i>vs</i> 15% ( $P = 0.71$ )	42% <i>vs</i> 29% ( $P = 0.004$ )	At 3 yr 63% <i>vs</i> 35% ( $P < 0.001$ )	23%-17%	3
Tamura <i>et al</i> [84], 2019	R	141 surgery; 106 SBRT	Higher for SBRT ( $P = 0.0082$ )	At 5 yr 69.7%-50.2% ( $P = 0.036$ )	At 5 yr 69.7% <i>vs</i> 50.2% ( $P = 0.036$ )	8.6% surgery; SBRT $G \geq 2$ 7.5%	3

G: Grade; LoE: Level of evidence; MA: Meta-analysis; P: Phase; OS: Overall survival; RT: Radiotherapy; VATS: Video-assisted thoracoscopic surgery.

tumors. It is a percutaneous technique that consists of applying an alternating current (420-500 kHz) to the tumor tissue, resulting in high temperatures ( $> 70^{\circ}\text{C}$ ) that cause tissue necrosis and protein denaturation[58].

Because air is a poor conductor of electricity and a good thermal insulator, the lung is theoretically an ideal site for the application of RFA as the surrounding parenchyma is barely affected[59]. The use of RFA to treat lung tumors was first described by Dupuy *et al*[60] in 2000.

The main advantages of RFA over surgery are that it is minimally invasive (percutaneous technique performed with local anesthesia), can be administered on an outpatient basis or under 24-h hospitalization, and does not require thoracotomy[59].

The use of RFA is limited to the treatment of lesions  $< 3$  cm located in the outer two-thirds of the lung parenchyma. Tumor size affects the homogeneity of the temperature distribution within the lesion. Tumors  $> 3$  cm require the use of several overlapping electrical fields to achieve a high enough temperature, and this increases the risk of complications. As with surgery, a margin of healthy parenchymal tissue must be included in the radiofrequency field, but this is difficult to achieve because of the

thermal insulation effect mentioned above[61-63].

Central lesions carry a higher risk of complications due to their proximity to the bronchial tree, esophagus, and heart. RFA may be less effective when applied to tumors located close to blood vessels with a diameter > 0.3 cm due to what is known as a “heat sink” effect (a cooling effect caused by the constant renewal of blood within the vessel)[59].

The main adverse effects associated with RFA are pneumothorax [the most common complication (11%-67%) following removal of the electrode from the parenchyma], pleural effusion (related to the increase in pleural temperature), hemoptysis, and more rarely, infections, bronchial fistula, and nerve or cardiac injuries.

In a recent meta-analysis comparing RFA and sublobar resection, Chen *et al*[59] analyzed four retrospective studies involving 309 patients: 155 treated with RFA and 154 with sublobar resection. The patients who underwent sublobar resection had significantly higher 1- and 3-year OS and PFS rates (97% *vs* 91% for 1-year OS, 67% *vs* 52% for 3-year OS, 91% *vs* 81% for 1-year PFS, and 67% *vs* 48% for 3-year PFS). Patients in the RFA group had more complications, but they were milder than those seen in the sublobar resection group.

In their prospective phase II trial of 42 patients with inoperable early-stage lung cancer, Palussière *et al*[64] concluded that RFA was a well-tolerated technique with 1- and 3-year local control rates of 84.38% and 81.25%, respectively, and comparable OS rates to those achieved with SBRT. Good tolerability has also been described by other authors[65], including Li *et al*[61] in their meta-analysis of 1989 patients.

Few studies have compared local treatments (RFA and SBRT), and the little evidence that exists is based on unbalanced, retrospective data. Randomized prospective studies are needed. Authors who have compared RFA and SBRT, however, agree that SBRT should be the technique of choice for inoperable early-stage cancer because of its favorable safety profile and greater survival benefits. RFA, in turn, should be reserved for small tumors not located near vessels or mediastinal structures[66-68].

At the molecular level, hypoxia-inducible factor-1 $\alpha$  has been proposed as an independent prognostic marker in the setting of RFA, as high levels have been linked to an increased risk of mortality[69].

In conclusion, RFA may be useful for treating inoperable early-stage lung cancer, in particular tumors < 3 cm located far from the mediastinum and vessels with a diameter > 0.3 cm[70,71]. The poorer outcomes reported for RFA compared with sublobar resection may be due to the lack of randomized, prospective studies comparing the two treatments, as studies to date have included patients who are unfit for surgery, that is older, more frail patients with more comorbidities and as a result a worse prognosis[72,73].

## CONCLUSION

Complete resection continues to be the gold standard for the treatment of early-stage lung cancer. Lobectomy remains the gold standard for the treatment of early-stage NSCLC, but there is a growing tendency to perform sublobar resection in selected cases. Alternative treatments such as SBRT and RFA can also produce good outcomes in inoperable patients or patients who refuse surgery.

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