Critical Review of Nonsurgical Treatment Options for Stage I Non-Small Cell Lung Cancer

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:
1. Discuss the current results obtained with primary resection in stage I NSCLC.
2. Describe clinical outcomes with nonsurgical techniques such as stereotactic radiation therapy and radiofrequency ablation.
3. Identify potential advantages and drawbacks of these nonsurgical techniques.
4. Assess which patients would benefit most from these techniques.

ABSTRACT

Surgery has traditionally been regarded as the treatment of choice for patients with stage I non-small cell lung cancer. However, the morbidity and mortality associated with surgery in elderly patients with considerable comorbidity remains of concern, as are the poor 5-year survival rates. Until recently, conventional radiation therapy was the only alternative curative treatment option for patients who were unfit for surgery, but with lower local control rates that were inferior to those with surgery. However, a growing body of clinical data on outcomes with newer nonsurgical treatment options such as stereotactic radiation therapy (SRT) and radiofrequency ablation (RFA) is now available.

SRT is a noninvasive method showing a 2-year local control rate in excess of 85% in both T1 and T2 tumors after three to eight fractions of high-precision radiotherapy. Despite the use of very high radiation doses, high-grade toxicity is limited to approximately 5% of patients. Percutaneous RFA is an invasive method showing 2-year local control rates of approximately 64% in smaller tumors, but results are poorer in lesions ≥3 cm. Compared with SRT, a higher procedure-related morbidity and mortality rate has been reported, mainly caused by pneumothorax and hemorrhage. Although data from randomized trials of conventional radiotherapy versus SRT or RFA are not available, the use of SRT is becoming widespread.
for patients who are unfit for surgery. Reported 2-year local control rates after SRT are comparable with those achieved with surgery, and prospective randomized trials comparing surgery with SRT in patients who are fit to undergo surgery are now being planned. The Oncologist 2008;13:309–319

**Introduction**

Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related mortality worldwide, with over 1 million deaths every year [1]. Only about 20% of patients present with stage I disease (tumor–node–metastasis [TNM] stage T1–2N0M0) [2], but even after complete surgical excision, the 5-year survival rate is <70% as a result of tumor recurrence, noncancer-related mortality, and second malignancies [3–5]. Large differences in outcome are observed within stage I after surgery, with 5-year overall survival rates ranging from 77% for small T1 tumors to 35% for large T2 tumors [6].

Surgery is the current standard of care for patients with stage I NSCLC [7], but can be associated with significant morbidity and even mortality, particularly because patients suffering from lung cancer are often elderly with high comorbidity rates [8]. Age itself is an independent predictor of postsurgical survival in NSCLC patients, even after adjustment for significant covariates [9]. A wait-and-see policy is inappropriate in patients who are unfit for surgery because the 5-year overall survival rate in untreated stage I NSCLC patients is in the range of 6%–14% [10, 11], with a 5-year disease specific survival rate of only 23% for T1 tumors [11]. Given a median survival duration of 9–14 months, it is recommended that surgical resection or other ablative therapies not be delayed for even small lung tumors. Newer nonsurgical treatments with high cure rates will clearly have a major impact on outcomes in patients at high risk for surgical morbidity. This review highlights the drawbacks of surgery as a treatment option (Table 1) and critically reviews new developments in nonsurgical treatments for stage I NSCLC.

**Surgery**

**Mortality**

Surgery is associated with a 30-day postoperative mortality rate in the range of 1%–5% for lobectomy and up to 10% after right-sided pneumonectomy (Table 2). A study in the U.S. revealed that survival was superior for patients undergoing resection at hospitals where many procedures were performed, compared with survival in centers performing a smaller number of lung-resection procedures [12]. Recent studies reported lower mortality rates after surgery for lung cancer, a finding that may reflect improved perioperative patient care. For example, the American College of Surgeons Oncology Group Z0030 trial reported an overall operative mortality rate of only 1.4% for lobectomy and 4% for pneumonectomy. Nevertheless, 38% of patients developed major complications, with the most common being atrial arrhythmias, prolonged air leaks, and prolonged chest tube drainage. Such complications are significant as they prolong hospitalization and have a major adverse impact on patients [13]. Similarly, a retrospective multicenter series from Japan by Wada et al. [14] on 7,000 resections showed a 1.3% mortality rate overall and a 3.2% mortality rate after pneumonectomy.

**Postsurgical Recurrences**

The International Association for the Study of Lung Cancer Lung Cancer Staging Project analyzed a large international database and reported 5-year survival rates of 77% and 71% after radical excision of pT1N0 tumors ≤2 cm (pT1a; n = 1,816 patients) and tumors 2–3 cm, respectively (pT1b; n = 1,653 patients) [6]. The corresponding 5-year survival rates for pathologically staged T2N0 tumors measuring 3–5 cm (pT2a; n = 2,822), 5–7 cm (pT2b; n = 825), and >7 cm (pT2c; n = 364) were 58%, 49%, and 35% (p < .0001), respectively. When examining survival rates according to clinical stage instead of pathological stage, the 5-year survival rates were as low as 53% for T1a and 26% for T2c tumors. Between 20% and 30% of patients develop recurrence after surgery for stage I NSCLC, despite preoperative staging using fluorodeoxyglucose positron emission tomography (FDG-PET) scans [15]. Most recurrences develop at

Table 1. Why are alternatives to surgery needed in stage I non-small cell lung cancer?

<table>
<thead>
<tr>
<th>Reason</th>
</tr>
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<tbody>
<tr>
<td>Significant morbidity and mortality are associated with surgery</td>
</tr>
<tr>
<td>Limited resections (e.g., lobectomy or segmentectomy) are not always possible</td>
</tr>
<tr>
<td>Quality of life deteriorates after surgery</td>
</tr>
<tr>
<td>There is poor long-term survival (30% rate of recurrence and second primary tumors)</td>
</tr>
<tr>
<td>Surgery impairs the fitness of patients, limiting curative treatment options in the case of second tumors</td>
</tr>
<tr>
<td>Toxicity is greater in elderly patients</td>
</tr>
</tbody>
</table>
distant sites, including pulmonary, brain, bone, and adrenal gland metastasis. Locoregional recurrences occurred in 12% of patients in the series of Martin-Ucar et al. [16] after a median follow-up of 4 years following lobectomy. Comparable results were reported by Martini et al. [3] in 598 patients who were followed up for a median of 7.6 years. The majority (20%) developed systemic recurrences; locoregional disease manifested in 7% [3]. Sixty percent of all recurrences developed within 2 years, and only 9% developed after 5 years.

After surgical resection, second primary lung tumors are reported to occur at a rate of 1%–2% per patient-year [3]. The cumulative risk for second lung tumors and other smoking-related cancer increases and reaches 15%–20% at 8 years after resection [3, 17]. In cases where initial surgical treatment has led to a reduction in quality of life (QoL) or pulmonary reserve, a patient’s ability to undergo curative treatment for a second tumor may be restricted. A previous tumor at any site is an independent prognostic factor that increases the probability of death by 1.5 times at 5 years, independent of other comorbidities, TNM classification, and age [18].

### Extent of Resection

Although lobectomy is considered the standard surgical procedure in stage I lung cancer, 5%–15% of patients require a bilobectomy and 5%–15% require a pneumonectomy [13, 19, 20]. If extensive surgery is required for a central tumor, a sleeve resection is preferred over a pneumonectomy because of better postoperative pulmonary function [21]. In frail patients who may not be able to tolerate lobectomy, a more limited procedure, that is, a segmentectomy or wedge resection, is used, although data regarding local control are inconsistent [3, 22–24]. One report suggested that local recurrences may be more frequent after limited resection in tumors >3 cm [25]. A randomized trial by the Lung Cancer Study Group suggested that a threefold higher local failure rate occurred in patients who underwent limited resection versus lobectomy, but reanalysis of the data revealed no significant differences in overall survival [22, 26]. Similarly, a recent meta-analysis on the published literature reported comparable survival rates with both limited resection and lobectomy for stage I lung cancer, but advised caution in interpretation of the results because interstudy heterogeneity was detected [27].

A procedure that may reduce the morbidity associated with open thoracotomy, especially postoperative pain, is the use of video-assisted thoracoscopic surgery (VATS) [28]. VATS and open thoracotomy have been compared in small studies, where the procedure was reported not to have detrimental effects on local control or overall survival [29–31]. Although VATS has been in use since the 1990s, this procedure was only performed in 10% of patients included in a recent large multi-institutional study [13]. The safety and efficacy of VATS remain to be confirmed in larger randomized trials [32].

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### Table 2. Thirty-day postsurgical mortality for early-stage lung cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>n of patients</th>
<th>Pneumonectomy (%)</th>
<th>Right pneumonectomy (%)</th>
<th>Left pneumonectomy (%)</th>
<th>Bilobectomy (%)</th>
<th>Lobectomy (%)</th>
<th>Wedge (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birim et al. [19]</td>
<td>269</td>
<td>7.5</td>
<td>–</td>
<td>0</td>
<td>3.8</td>
<td>1.9</td>
<td>0</td>
<td>3.3</td>
</tr>
<tr>
<td>Damhuis et al. [42]</td>
<td>6,109</td>
<td>3.8 &lt;60 yrs</td>
<td>9.5</td>
<td>6.0</td>
<td>2.9</td>
<td>2.9</td>
<td>–</td>
<td>4.2</td>
</tr>
<tr>
<td>Allen et al. [13]</td>
<td>1,023</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>1</td>
<td>3</td>
<td>1.4</td>
</tr>
<tr>
<td>Thomas et al. [89]</td>
<td>515</td>
<td>6.2</td>
<td>11.9</td>
<td>0</td>
<td>5.3</td>
<td>2.3</td>
<td>0</td>
<td>2.9</td>
</tr>
<tr>
<td>Little et al. [40]a</td>
<td>11,668</td>
<td>8.5</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>4.5</td>
<td>4.9</td>
<td>5.2</td>
</tr>
<tr>
<td>Ludwig et al. [90]</td>
<td>310</td>
<td>4.6</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>4.6</td>
</tr>
<tr>
<td>Harpole et al. [91]b</td>
<td>3,516</td>
<td>11.5</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>4.0</td>
<td>–</td>
<td>5.2</td>
</tr>
</tbody>
</table>

*P<0.05 compared with lobectomy.

*aPatients with non–stage I tumors are also included.

bPatients with non–stage I tumors and patients with benign disease (<10%) are also included.
QoL After Surgery
Surgery is associated with loss of pulmonary function and exercise capacity in the range of 10%–40%, depending on the extent of the resection and time elapsed since surgery [33–35]. Respiratory symptoms and pain are important factors resulting in the frequent deterioration in QoL after surgery [36, 37]. Post-thoracotomy pain is a frequent symptom, persisting for >4 years in approximately 30% of patients [38], and 5% of patients experience severe and disabling post-thoracotomy pain syndromes [39]. In the planned randomized trials of surgery versus noninvasive techniques, QoL will have to be one of the major study endpoints, because the morbidity and mortality associated with surgery, and subsequent deterioration in QoL, are the most important reasons to search for less invasive treatment alternatives.

Greater Toxicity in Elderly Patients
Approximately 45% of the patients presenting with lung cancer are aged ≥70 years at the time of diagnosis [40]. Although advanced age is not an absolute contraindication for surgery, significant comorbidity is observed in approximately 70% of lung cancer patients in the age group ≥70 years [8]. Frequent comorbidities, such as cardiovascular disease and severe chronic obstructive pulmonary disease, result in higher perioperative morbidity and mortality rates after open thoracotomy in older patients [41]. The postoperative mortality rate is only 1.7% in patients <60 years of age and 9.4% in octogenarians [42]. More limited resections have been recommended in frail elderly patients, because any increase in local recurrences in elderly patients may be balanced by less surgical morbidity and mortality [41]. Analysis of the Surveillance, Epidemiology, and End Results database revealed no differences in long-term survival between lobectomies and limited resections in patients ≥70 years old [9].

Even with the problems stated above and the absence of randomized clinical trials to support its use, the role of surgery as a standard treatment is supported by observational data showing higher local control and survival rates than with conventionally fractionated radiation therapy [7, 43]. However, the benefits and especially the toxicity of surgery need to be weighed constantly against those of new, less invasive treatment approaches, especially in elderly patients at high risk for surgical morbidity (Table 3).

| Table 3. Which patients are at high risk for surgical morbidity? |
|-----------------|-----------------|
| Preoperative assessment [92] | |
| pCO₂ >45 mmHg | |
| pO₂ <50 mmHg | |
| Predicted postoperative FEV₁ <0.7 l or <40% of the reference value | |
| Age >70 yrs | |
| Poor exercise tolerance, tested by | |
| Stair climbing <2 stairs | |
| Timed walking tests | |
| Exercise testing with gas analysis (VO₂ max <15) [93] | |
| Preoperative DLCO <40% of predicted [94] | |
| Preoperative FEV₁ <70% [95] | |
| Cardiac problems (LVEF <40%, arrhythmia, MI within 6 months) | |
| Obesity | |

Abbreviations: DLCO, diffusion capacity of the lung for carbon monoxide; FEV₁, forced expiratory volume in 1 second; LVEF, left ventricular ejection fraction; MI, myocardial infarction; pCO₂, partial pressure of carbon dioxide; pO₂, partial pressure of oxygen; VO₂ max, maximal oxygen consumption in ml·kg⁻¹·min⁻¹).

New Noninvasive or Minimally Invasive Techniques
Stereotactic Radiation Therapy
Stereotactic radiation therapy (SRT) was first developed in the 1950s for the treatment of intracranial lesions. Technological developments in planning and treatment delivery of radiation therapy in the last decade have led to the application of this technique to extracranial sites including the thorax and abdomen. SRT is a form of high-precision radiotherapy delivery characterized by (a) reproducible immobilization to avoid patient movement during treatment sessions; (b) measures to account for tumor motion during imaging, treatment planning, and radiation delivery; (c) use of dose distributions tightly covering the tumor, with rapid dose falloff in surrounding normal tissues in order to reduce toxicity; and (d) most importantly, the use of extremely...
high doses of radiation usually delivered in three to eight treatment fractions within a 2-week period [45].

The radiation schedules used in SRT cannot be simply compared with those used in conventional schemes by comparing total dose, because the dose per fraction is not identical. However, the relative efficacy of radiotherapy fractionation schemes can be predicted and compared by calculating the biologically effective dose (BED) [46]. Conventionally fractionated schedules typically use doses with a BED of 70–80 Gy. Modern SRT schedules use dose schedules equivalent to a BED \(\geq 100\) Gy, resulting in superior tumor kill. Several fractionation schedules are undergoing evaluation, and a frequently used schedule for peripheral lung tumors is three fractions of 20 Gy, equivalent to a BED as high as 180 Gy [47].

The results and toxicity of SRT reported by studies in which at least 40 patients with stage I NSCLC were included are summarized in Table 4. Typical local control rates with schedules using a BED \(>100\) Gy are approximately 90%. The largest series were reported from Japan [48, 49], Scandinavia [50], the U.S. [47], and the Netherlands [51], comprising experience in over 750 patients. The largest series was published by Onishi et al. [49] and retrospectively described the results of 257 patients treated in 14 institutions in Japan [52], using a number of different treatment doses and delivery approaches. At a median follow-up of 38 months (range, 2–128 months), the local recurrence rate was 8.4% in patients who were treated to a BED \(\geq 100\) Gy. As with radiofrequency ablation (RFA), most reports on outcomes with SRT have been in patients who are unfit to undergo surgery, and include only a minority of patients who refused surgery. This introduces a large selection bias compared with surgery, rendering overall survival less suitable for comparison. This Japanese study, however, also included nearly 100 patients who refused surgery, and the 5-year overall survival rate of 70.8% observed after a

<table>
<thead>
<tr>
<th>Study</th>
<th>n of patients</th>
<th>Schedule</th>
<th>BEDa</th>
<th>Median follow-up (months)</th>
<th>Actuarial local control</th>
<th>Complications</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baumann et al. [50]</td>
<td>138</td>
<td>30–48 Gy in 2–4 fractions</td>
<td>60–120 Gy</td>
<td>33</td>
<td>3-yr, 85%</td>
<td>Atelectasis grade &gt;2, 2%; pneumonitis grade &gt;2, 1%; rib fracture, 4%</td>
<td>Multicenter with variety of dose schedules</td>
</tr>
<tr>
<td>Lagerwaard et al. [51]</td>
<td>197</td>
<td>3 \times 20 Gy; 5 \times 12 Gy</td>
<td>180 Gy; 132 Gy</td>
<td>12</td>
<td>2-yr, 94%</td>
<td>Pneumonitis grade &gt;2, 3%; rib fracture, 2%</td>
<td></td>
</tr>
<tr>
<td>Nagata et al. [48]</td>
<td>45</td>
<td>4 \times 12 Gy</td>
<td>106 Gy</td>
<td>30</td>
<td>2-yr, 98%</td>
<td>Pneumonitis grade &gt;2, 0%</td>
<td></td>
</tr>
<tr>
<td>Nyman et al. [96]</td>
<td>45</td>
<td>3 \times 15 Gy</td>
<td>113 Gy</td>
<td>43</td>
<td>80%b</td>
<td>Pneumonitis grade &gt;2, 0%; rib fracture, 4%</td>
<td></td>
</tr>
<tr>
<td>Onishi et al. [52]</td>
<td>257</td>
<td>18–75 Gy in 1–22 fractions</td>
<td>Variety</td>
<td>38</td>
<td>5-yr BED (\geq 100), 84%; 5-yr BED (&lt;100), 37%</td>
<td>Pneumonitis grade &gt;2, 5%</td>
<td>All observed health problems qualified as radiation toxicity</td>
</tr>
<tr>
<td>Timmerman et al. [55]</td>
<td>70</td>
<td>3 \times 20 Gy; 3 \times 22 Gy</td>
<td>180 Gy; 211 Gy</td>
<td>18</td>
<td>2-yr, 96%</td>
<td>Pericardial effusion grade V, 1%; bleeding grade V, 1%; bacterial pneumonia grade V, 6%</td>
<td></td>
</tr>
<tr>
<td>Uematsu et al. [97]</td>
<td>50</td>
<td>50–60 Gy in 5–10 fractions</td>
<td>Variety</td>
<td>36</td>
<td>94%b</td>
<td>Pneumonitis grade &gt;2, 0%; rib fracture, 4%</td>
<td>In some patients SRT was given after conventional radiation treatment</td>
</tr>
<tr>
<td>Xia et al. [98]</td>
<td>43</td>
<td>5 \times 10 Gy</td>
<td>100 Gy</td>
<td>27</td>
<td>3-yr, 95%</td>
<td>Pneumonitis grade &gt;2, 2%</td>
<td>25 stage I and 18 stage II primary lung</td>
</tr>
</tbody>
</table>

Includes series with \(\geq 40\) patients with stage I NSCLC.

aBED = \(D(1 + d/(\alpha/\beta))\), where \(D\) is total dose, \(d\) is dose per fraction, and the \(\alpha/\beta\) ratio is assumed to be 10 for tumor tissue.

bCrude local control.

Abbreviations: BED, biologically effective dose; NSCLC, non-small cell lung cancer; SRT, stereotactic radiation therapy.
BED of 100 Gy among those patients is at least equivalent to the outcome after surgery [6, 24, 53]. More than 350 patients have undergone SRT at the VUmc University Medical Center since 2003. The results of the first 197 patients with a total of 210 primary lung tumors for local control and toxicity were recently reported by Lagerwaard et al. [51]. All patients were treated to a BED >100 Gy in three to eight fractions. The median follow-up time was 12 months (range, 3–44 months). Local relapse was observed in six patients, resulting in an actuarial 2-year local control rate of 94%, with no significant difference in local control between T1 and T2 tumors.

Response evaluation after SRT can be difficult because fibrosis and subclinical radiation pneumonitis are frequently observed, and establishing local control requires careful radiological follow-up. FDG-PET is of limited value in distinguishing fibrosis from tumor recurrence because treated volumes can show $^{18}$F-FDG uptake for at least 12 months after treatment [54]. Careful radiological follow-up of patients is paramount in patients who are treated using SRT, because salvage surgery or mediastinal radiation therapy might still be possible in cases of local or regional recurrence.

**Toxicity of SRT**

Reported long-term toxicities exceeding grade II (National Cancer Institute – Common Toxicity Criteria version 3) are limited to <10% of patients, and were mainly observed with large or centrally located tumors [47, 55]. In the series by Onishi et al. [49], pulmonary complications exceeding grade 2 were observed in 14 patients only (5.4%). Timmerman et al. [55] reported the need for caution when a BED of 180–210 Gy was administered for centrally located tumors adjacent to the mediastinum. In the patients treated by Lagerwaard et al. [51], using a “risk-adapted” approach with the BED limited to 105 Gy for central tumors, early toxicity was mild, with fatigue (32%), nausea (10%), and chest pain (8%) as the most frequently encountered acute side effects. Late toxicity was uncommon, with radiation pneumonitis exceeding grade 2 in six patients only (3%). Rib fractures and chronic pain syndromes located at the chest wall were observed in three patients each. Other authors have shown that a BED >100 Gy is sufficient to achieve local control [56], thereby justifying the continued treatment of central tumors at lower SRT doses.

As postsurgical deterioration in QoL is of concern, special attention has been paid to post-SRT changes in QoL measured using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (QLQ)-C30 and QLQ-LC13 Lung Cancer Modules [57]. Early analysis of these data indicates that the high local control rates achieved by the high radiation doses in SRT are not accompanied by changes in QoL. Serial measurements of pulmonary function after SRT show no significant decreases in total lung capacity, vital capacity, or forced expiratory volume in 1 second [58, 59]. These findings are also relevant with regard to the treatment of second primary lung tumors or late recurrences.

**RFA**

RFA is a well-established modality in the treatment of unresectable liver tumors, in both primary malignancies and metastases [60]. Recently, several authors have evaluated RFA for the treatment of small primary lung tumors and lung metastases in patients who are medically inoperable [61]. During RFA, a radiowave-emitting probe is inserted into the tumor under computed tomography (CT) guidance and is used to heat the tumor to 90–100°C, resulting in focal coagulation necrosis. Most published reports on RFA for lung lesions have described the techniques used and short-term complications, but data on long-term local control are mainly limited to patients with metastatic lesions, and are not widely available for patients with stage I NSCLC. RFA is generally not recommended for centrally located tumors, although experience is increasing [62]. Positioning the RFA electrode in small apical lung tumors, in posteriorly located tumors close to the diaphragm, and in tumors in the proximity of the scapula is technically difficult [63]. The local control rate using RFA appears comparable with that using conventionally fractionated radiation therapy, but varies widely depending on the tumor size (Table 5). In the largest reported series, which evaluated 153 patients, local control at 2 years ranged from 25% for T2 tumors to 64% for T1 tumors [64]. In one series of selected patients with small tumors, local control up to 93% at 18 months was reported, but this series included mostly patients with pulmonary metastasis and only nine patients with a primary stage I lung tumor [65].

**Toxicity of RFA**

The most frequent complication of RFA is pneumothorax, which requires chest tube insertion in 10%–20% of patients. The largest reported series, by Simon et al. [64], observed an overall 30-day mortality rate of 3.9%, with a procedure-specific mortality rate of 2.6%. Similar morbidity rates were reported by other authors [65–67], and a short period of hospitalization is required in approximately 10% of patients because of pneumo- or hemothorax, hemothysis, bronchopleural fistulas, or abscess formation. The data currently available suggest that the toxicity profile of RFA is not unfavorable in comparison with the complications of limited surgery in high-risk patients. A significant new de-
development is an alert issued by the U.S. Food and Drug Administration (FDA) on mortality observed with the use of RFA for lung lesions [68]. It was pointed out that RFA equipment has not been cleared by the FDA for this indication, and the FDA recommended that this treatment not be used outside clinical trials until more clinical safety data are available.

**FUTURE DEVELOPMENTS**

**Staging and Screening in Early-Stage NSCLC**

The number of patients with early-stage NSCLC is expected to increase as a result of screening programs, technological advances in imaging including FDG-PET/CT, and the more widespread use of CT scans for various other indications. No survival benefit has yet been proven for the use of screening CT scans in populations at high risk for lung cancer, but randomized trials, like the National Lung Screening Trial and the NELSON Trial, are still ongoing [69]. Superior staging techniques like FDG-PET can improve identification of true early-stage disease by excluding patients with otherwise occult metastatic disease [70].

A diagnosis of lung cancer is not always histologically established before surgery, even when using a full clinical workup including bronchoscopic and CT-guided biopsy. Use of CT screening in Japan has led to an increase in the number of patients in whom no histopathological confirmation was obtained before surgery, from 30% to 50% [71]. The authors attributed this finding to the increased prevalence of smaller CT-detected tumors, which are less accessible by needle biopsy. Consequently, pathology in excised lesions revealed the presence of benign disease in 13% of cases. The likelihood of inadvertently treating benign disease can be reduced by applying the Swenson criteria (age, smoking history, previous cancer, tumor diameter, spiculation, and tumor location [72]), combined with the results of FDG-PET [73], in order to estimate the probability of malignancy. Although the chance of treating benign disease is likely to be <5% when including FDG-PET in the pretreatment workup [74], a cytological or histological diagnosis is still recommended, where possible, for both surgical and nonsurgical treatment.

The ability to predict the likelihood of malignancy may be further increased in the future by using cytopathology combined with gene-expression profiling in normal lower airway cells obtained at bronchoscopy, with a reported 95% sensitivity and a 95% negative predictive value for lung cancer [75]. Advances in proteomics might also bring a

### Table 5. Results of RFA in the treatment of stage I NSCLC or metastasis

<table>
<thead>
<tr>
<th>Study</th>
<th>n of patients</th>
<th>Tumors (n)</th>
<th>Median follow-up (months)</th>
<th>Actuarial 2-year local control (%)</th>
<th>Complications</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simon et al. [64]</td>
<td>153</td>
<td>189</td>
<td>21</td>
<td>≤3 cm, 64; &gt;3 cm, 25</td>
<td>Pneumothorax, 28%; chest tube, 10%; hemoptysis, 3%; infection, 2%; mortality&lt; 3%</td>
<td>116 primary lung; 73 metastasis</td>
</tr>
<tr>
<td>Sakurai et al. [99]a</td>
<td>–</td>
<td>581</td>
<td>–</td>
<td>–</td>
<td>Pneumothorax, 55%; chest tube, 18%</td>
<td>–</td>
</tr>
<tr>
<td>Hiraki et al. [100]a</td>
<td>128</td>
<td>342</td>
<td>12</td>
<td>60</td>
<td>–</td>
<td>25 primary lung; 317 metastasis</td>
</tr>
<tr>
<td>Yan et al. [67]</td>
<td>55</td>
<td>–</td>
<td>24</td>
<td>Overall, 56; ≤3 cm, 75; &gt;3 cm, 18</td>
<td>Pneumothorax, 29%; chest tube 16%</td>
<td>All patients, colorectal metastasis</td>
</tr>
<tr>
<td>De Baere et al. [65]</td>
<td>60</td>
<td>100</td>
<td>&gt;12</td>
<td>93b</td>
<td>Pneumothorax, 54%; chest tube, 9%; hemoptysis, 10%; infection, 6%</td>
<td>9 patients primary lung; 51 patients metastasis</td>
</tr>
<tr>
<td>Yamagami et al. [101]</td>
<td>41</td>
<td>129</td>
<td>–</td>
<td>–</td>
<td>Pneumothorax, 30%; chest tube, 4%</td>
<td>4 patients primary lung; 37 metastasis</td>
</tr>
<tr>
<td>Kang et al. [102]</td>
<td>50</td>
<td>120</td>
<td>–</td>
<td>–</td>
<td>Pneumothorax, 18%; hemothorax, 2%</td>
<td>23 patients primary lung; 27 patients metastasis</td>
</tr>
</tbody>
</table>

Includes series with 40 patients, including patients with metastasis.

aOverlapping (same institution) patient series.

b18 months.

cProcedure-specific 30-day mortality rate.

Abbreviations: NSCLC, non-small cell lung cancer; RFA, radiofrequency ablation.
clinically usable diagnostic tool, analyzing protein expression levels in blood or other tissue samples [76]. The use of bronchoscopy in screening, especially in combination with endobronchial optical spectroscopy or autofluorescence, will increase the incidence of early-stage endobronchial disease [77, 78]. This could be a valuable development, because extensive surgical resection can often be prevented in these patients by the use of local endobronchial treatment modalities, including photodynamic therapy, brachytherapy, electrocautery, cryotherapy, and neodymium-doped yttrium aluminum garnet laser, which are increasingly used not only for palliation of late obstructing cancers but also for primary treatment of early-stage endobronchial disease [79–81].

**Adjuvant Chemotherapy**

Up to 50% of patients with stage IB NSCLC eventually develop disease recurrence despite initial local treatment with curative intent. Cisplatin-based chemotherapy was shown in a meta-analysis to produce a survival benefit in patients with stage II and higher disease [82]. However, no significant survival advantage was seen in stage IB disease, and a disadvantage for chemotherapy was observed in patients with stage IA disease. A method for the selection of patients with stage IB or even stage IA disease who could potentially benefit from adjuvant treatment could be a valuable development. Efforts are being made to estimate the likelihood of relapse based on genetic profiling, and initial findings show that genetic profiling might be a better predictor of disease recurrence and survival than classic clinical staging [83, 84]. An additional method to estimate the probability of disease recurrence might be the use of FDG-PET, because the level of FDG uptake in the primary lung tumor appears to be predictive of disease-free survival [85]. An alternative way to increase the therapeutic gain of adjuvant therapy is not to predict the likelihood of disease relapse, but to predict the likelihood of drug resistance, for example, by the measurement of excision repair cross-complementation group 1 (ERCC1) gene expression. ERCC1 encodes for a protein needed in the repair of DNA damage caused by platinum-based chemotherapy such as cisplatin, carboplatin, and oxaliplatin. Only ERCC1-negative patients might benefit from platinum-based chemotherapy [86].

Selecting patients with a combination of a high probability of disease recurrence and a high probability of drug sensitivity might show a benefit of adjuvant chemotherapy even in early-stage disease.

**Planning Clinical Trials of New Techniques Versus Surgery**

Although the median follow-up duration is relatively short, the available data on SRT suggest that local control using SRT might be equivalent to that with surgery, with a superior toxicity profile. Phase II and III trials are in preparation in the U.S., The Netherlands, and Japan. The formal staging of NSCLC in the upcoming TNM update will remain unchanged for early-stage disease [6, 87, 88], but treatment strategies may evolve to take into account the different prognostic subgroups of stage I disease.

Some issues that need to be accounted for in the design of these studies are (a) sufficiently long follow-up in order to establish locoregional control and survival as well as late treatment toxicity, including QoL measurements and lung function testing, because less treatment toxicity is the main reason to test alternatives to surgery; (b) differences in the approach to mediastinal lymph nodes (no treatment during SRT compared with mediastinal lymph node dissection in the surgery arm), thus introducing differences in regional failure as a possible study endpoint; (c) long-term frequent radiological follow-up for patients treated using SRT in order to distinguish radiation-induced fibrosis from local recurrences, and for the evaluation of regional control, especially as patients might be eligible for salvage treatment; and (d) the inclusion of patients without histopathological proof of malignancy.

As about half of patients are operated upon without histological proof [71], many patients with smaller tumors may be excluded from these trials if histological proof was mandatory. In selected populations where the incidence of atypical infections is unlikely, a combination of clinical and radiological tumor characteristics, combined with the use of FDG-PET, can reduce the likelihood of treating benign disease to <5% [73, 74]. In such cases, an option would be to include patients without a cyto- or histopathological diagnosis in randomized studies as long as careful monitoring of the surgical patients does not show an unacceptable percentage of benign disease.

**Conclusions**

The current standard of care for patients with stage I NSCLC is an anatomical surgical resection that achieves local control in most patients, but which is associated with a risk for significant morbidity. New minimally invasive or noninvasive treatment options, including SRT and RFA, have been explored as alternatives in patients who are unfit for surgery. Local control with SRT even appears to be comparable with that achieved with surgery, but with far lower complication rates. In view of the toxicity and mortality observed after RFA, the safety of this treatment for lung tumors requires further evaluation before use outside clinical trials. A potential drawback of SRT is that it is not yet widely available, as well-trained
staff and modern image-guided linear accelerators are required to deliver this treatment.

Randomized trials comparing SRT with the operable patient group are eagerly awaited. Until such time that these data become available, SRT should be strongly considered as a treatment option in all patients who are at high risk for surgical morbidity.

REFERENCES


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101  Haasbeek, Senan, Smit et al.