Current Treatment Options in Oncology
DOI 10.1007/s11864-010-0119-z

Lung Cancer

# Alternatives to Surgery for Early Stage Non-Small Cell Lung Cancer-Ready for Prime Time?

*Millie Das, MD*
*Mohamed H. K. Abdelmaksoud, MD, MS*
*Billy W. Loo Jr., MD, PhD**
*Nishita Kothary, MD*†

**Address**
**Department of Radiation Oncology, Stanford University and Cancer Center, 875 Blake Wilbur Drive, Stanford, CA 94305-5847, USA*
*E-mail: BWLoo@Stanford.edu*
†*Department of Radiology, Division of Interventional Radiology, Stanford University, 300 Pasteur Drive, H3652, Stanford, CA 94305-5642, USA.*
*E-mail: kothary@stanford.edu*



## Opinion statement

Surgery is the standard of care for early stage non-small cell lung cancer (NSCLC), with lobectomy being the most oncologically sound resection. Medically inoperable patients and high-risk surgical candidates require effective alternatives to surgery; even operable patients may opt for less invasive options if they are proven to achieve similar outcomes to surgery. Minimally invasive local treatment modalities including dose-intensified conformal radiation therapy, most notably stereotactic ablative radiotherapy (SABR; also known as stereotactic body radiation therapy), and thermal ablation methods such as radiofrequency ablation (RFA) and microwave ablation (MWA) are emerging as promising treatment options whose roles in the treatment of early stage lung cancer are being defined. Early clinical experience and a rapidly growing body of prospective clinical trials, primarily in medically inoperable patients, are demonstrating encouraging effectiveness and safety outcomes in some cases approaching historical results with surgery. Given the very poor prognosis of the medically inoperable patient population, these alternatives to surgery, particularly SABR, are starting to be considered appropriate first-line therapy in properly selected patients, and prospective cooperative group trials to evaluate and optimize RFA and SABR in specific patient subsets are being conducted. For operable patients, prospective multi-center and cooperative groups trials of SABR are ongoing or completed, and international randomized trials of SABR vs. surgery have been initiated. Thus, promising alternatives to surgery for early stage NSCLC are ready for prime time evaluation in the setting of clinical trials, and participation in ongoing trials for both operable and medically inoperable patients is strongly encouraged.

Published online: 25 June 2010

## Introduction

Lung cancer continues to be the leading cause of cancer death in the United States and worldwide. Since lung cancer continues to be diagnosed at advanced stages, the 5-year survival rate remains dismal at 15% [1]. However, when lung cancer is detected at an early stage, the outcome of patients is significantly improved, with 5-year survival rates ranging from 43% to 77% [2, 3]. Early stage (stage I) non-small-cell lung cancer (NSCLC) includes those T1 or T2 primary tumors with no evidence of hilar or mediastinal nodal disease (N0) or metastatic spread (M0) [2]. The standard of care for treatment of fit patients with stage I disease is surgical resection via lobectomy. When compared to nominally less invasive surgical procedures such as sublobar resection, lobectomy was found to be superior with a threefold lower loco-regional recurrence rate [4]. However, many patients are medically inoperable, or have excessive risk of surgical morbidity owing to comorbid conditions. In those patients unable or unwilling to undergo surgery, historically the primary treatment modality has been external beam radiotherapy. Conventional external beam radiotherapy for inoperable NSCLC has consisted of radiation doses of about 60 Gy or greater delivered in daily fractions over six or more weeks. However, the historical efficacy of conventional radiation therapy has been suboptimal, with crude local failure rates of 19–70% [5], and median overall survival improvement from 14 to 21 months compared to observation alone, but only 15% five-year survival [6]. More recently, substantial improvements in the technology of radiation therapy as well as other minimally invasive treatment techniques have led to promising treatment outcomes in some cases rivaling the historical results of surgery. Here we review the latest advances in dose-intensified conformal radiotherapy, including stereotactic ablative radiotherapy (SABR), radiofrequency ablation (RFA), and microwave ablation (MWA) as alternative treatment approaches in early stage disease.

## Conformal radiotherapy

- Three-dimensional conformal radiation therapy (3DCRT) refers to the use of multiple-shaped radiation beams to confine the high-dose radiation region better to a specified target and improve sparing of surrounding normal tissues [7]. In patients with stage I NSCLC who received conventional radiation doses (60–72 Gy) with 3DCRT, 2- to 3-year local control rates have remained discouraging at 43–55% [8, 9], indicating the need to intensify therapy. The addition of single agent chemotherapy to standard-dose 3DCRT for medically inoperable patients did not appear to improve outcomes significantly, though there was a trend toward modest survival improvement [9]. Radiation dose intensification has thus been studied as a means to improve the efficacy. Dose intensification can be accomplished by dose escalation (increasing the total radiation dose), acceleration (decreasing the overall treatment time), or a combination of the two. Studies of total dose escalation have demonstrated that when irradiation can be restricted to small volumes of lung tissue using 3DCRT, doses of up to 102.9 Gy could be delivered without excessive pulmonary toxicity [10, 11]. Although a strong dose–response relationship was apparent, even at the highest dose levels of over 80 Gy, local failure in the irradiated field remained a significant problem with 5-year local control rates of 49% (including some locally advanced tumors) [10] to 67% [11]. Additionally, to reach such high total doses with conventional daily fraction sizes requires up to nearly 10 weeks of overall treatment time. Subsequent studies have thus investigated alternate strategies for radiation dose intensification.
- Acceleration of the radiation course may be accomplished by using a higher frequency of treatments (i.e., two or more fractions per day) of slightly smaller than conventional dose per fraction (hyperfractionation), or by using a smaller total number of larger than conventional dose fractions (hypofractionation). Most of the more recent studies in

early stage lung cancer have focused on the latter approach. The Cancer and Leukemia Group B (CALGB) trial 39904 studied the use of 3DCRT with hypofractionation in patients with stage I (T1/T2 N0) NSCLC and poor pulmonary function. A total dose of 70 Gy was maintained while reducing the treatment from 29 to 17 daily fractions. The treatment was generally well tolerated and results were promising, with a median overall survival of 38.5 months and 92% local tumor control at 51 months of follow-up [12]. The National Cancer Institute of Canada Clinical Trials Group recently completed a phase II trial (NCIC BR.25) of accelerated 3DCRT (60 Gy in 4-Gy fractions) for early stage NSCLC and results are pending [13]. Additionally, in an attempt to reduce the risk of distant metastatic disease, CALGB is planning a phase II study of accelerated conformal radiotherapy and systemic chemotherapy in patients with early stage NSCLC.

## Stereotactic ablative radiotherapy

- At the extreme of radiation dose conformity and intensity is stereotactic ablative radiotherapy (SABR), also known as stereotactic body radiation therapy (SBRT). These large doses of radiation delivered in a small number of treatments (with most current protocols using five or fewer fractions) are ablative, destroying the function of underlying anatomy in addition to sterilizing the tumor, and thus require sophisticated techniques to ensure accurate delivery and minimize normal tissue injury (Fig. 1). Highly conformal dose distributions are accomplished using a large number of radiation beams, often with noncoplanar arrangements and/or computer optimized intensity modulation, and targeting smaller volumes of tissue is made possible

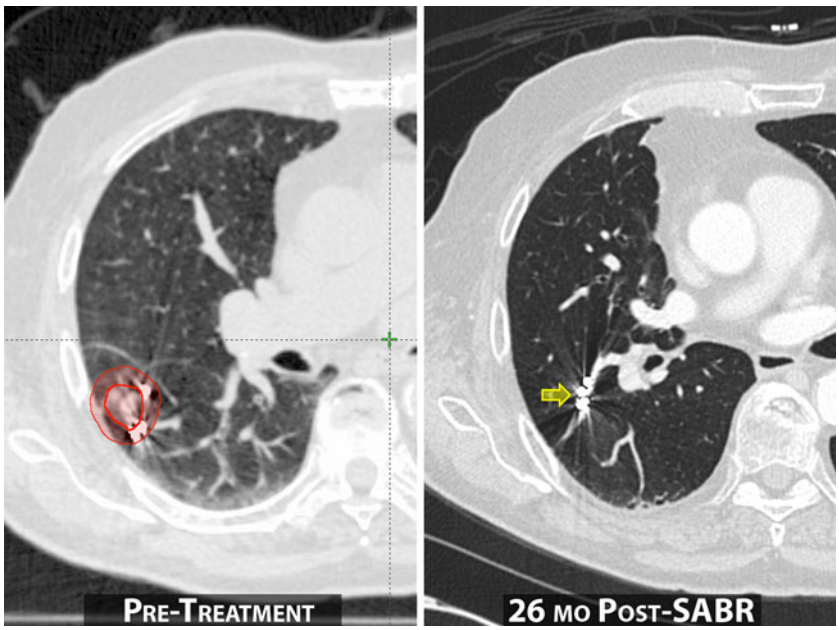


**Figure 1.** Peripherally located stage I NSCLC in a medically inoperable patient, treated with stereotactic ablative radiotherapy (SABR), using a dose of 50 Gy in four fractions. The tumor and surrounding target volume are outlined in *red*. Metallic fiducial markers implanted via CT-guided percutaneous needle placement at the time of biopsy facilitated image-guided dynamic tumor tracking with the radiation beam during treatment. There was a complete response with only minimal fibrosis surrounding the implanted markers (*arrow*), and no evidence of disease 26 months after treatment

by reducing uncertainty from positioning and breathing-induced motion by immobilization devices, image-guidance, and dynamic motion compensation methods. Importantly, the radiation schedules used in SABR cannot be compared with those used in conventional schemes simply by the total dose because the biological effect is highly sensitive to the large differences in fraction size. Conversion to biologically effective dose (BED), which takes into account the effect of fraction size, has been used to compare differing radiation schedules for lung cancer [14]. Modern SABR regimens use BED greater than 100 Gy, the dose range found to be associated with local control rates over 80–90% for early stage tumors [15, 16], whereas conventionally fractionated radiation regimens are typically in the BED range of 70–80 Gy.

## SABR for medically inoperable patients

- Since the first clinical study of SABR of lung and other tumors was initiated in 1991 [17], published reports of this treatment modality have increased exponentially and much has been learned about factors impacting both its efficacy and potential toxicities (Table 1). Most studies have been phase I or II trials in the medically inoperable patient population. The first published North American prospective phase I clinical trial of SABR for lung tumors and subsequent analyses found a critical impact of tumor volume on local control from single fraction therapy in the dose range of 15–30 Gy, with a promising one-year local control of over 90% for small tumor volumes under 12 mL [18–20]. Indiana University investigators conducted a pivotal series of phase I and II studies of SABR in a well-defined population of strictly medically inoperable patients with stage I NSCLC [21, 22]. These studies found a strong dose–response relationship, and that a dose of 60 Gy in three fractions, the most intensive regimen currently in use, is effective and safe for peripherally located tumors. They also identified central tumor location and large tumor size as risk factors for major toxicity with this very aggressive dose [23]. Local control at 3 years was 88% [22]. This was the basis for the recently reported Radiation Therapy Oncology Group (RTOG) 0236 trial, a multi-center prospective phase II study of SABR for peripherally located stage T1–T3 (chest wall invasion only, ≤5 cm in size) N0 M0 NSCLC in

**Table 1. Selected trials of SABR for early stage NSCLC**

| Trial | Number of patients | Stage | Median follow-up (months) | Dose & fractionation | Any toxicity ≥ grade 3, n (%) | Local control | Overall survival |
|---|---|---|---|---|---|---|---|
| Stanford University [19] | 32 (20 primary NSCLC) | T1-2 N0M0 | 18 | 15–30 Gy in one fraction | 4 (12.5) | 91% at 1 year for dose ≥25 Gy | 85% at 1 year |
| Indiana University [22] | 70 | T1-2 N0M0 | 50.2 | 60–66 Gy in three fractions | 11 (15.7) | 88.1% at 3 years | 42.7% at 3 years |
| RTOG 0236 [24•] | 55 | T1-2 N0M0 | 34.4 | 60 Gy in three fractions | 15 (27.2), no deaths | 98% at 3 years | 72% at 2 years, 56% at 3 years |
| VU University, Netherlands [25] | 206 | T1-2 N0M0 | 12 | 60 Gy in three, five, or eight fractions | 6 (3) | 97% at 1 years; 93% at 2 years | 64% at 2 years |

medically inoperable patients using the 60 Gy in three fractions regimen (equivalent to 54 Gy in three fractions when using more accurate dose calculation algorithms) [24•]. Among 55 evaluable patients with a median follow-up of 34 months, 3-year actuarial local control was 98%, and there were only two regional relapses. Median survival was 48 months, and distant metastasis was the primary mode of progression (11 patients). Of note, an extensive credentialing process assured the technical quality of the treatment and probably contributed to the excellent outcomes in a multi-institutional setting. Other investigators have found somewhat less intensive SABR regimens (e.g., 60 Gy in eight fractions or 50 Gy in four fractions) to have promising local control of 98–100% at 12–17 months, apparently without increased toxicity in centrally located tumors at least during early follow-up [25, 26]. In this frail population of patients, relevant questions are whether SABR induces declines in pulmonary function testing parameters or whether there is a threshold of pulmonary function below which SABR is contraindicated, but neither has been found consistently, supporting its use in even very impaired patients who nevertheless have a high risk of mortality from tumor progression [19, 27, 28].

## SABR for potentially operable patients

- A provocative question given the promising and in some cases mature results of SABR in medically inoperable patients is whether it may be effective enough to consider in patients who could undergo surgery. An analysis of a large multi-institutional experience in Japan found that in 257 patients with stage I NSCLC treated with various SABR regimens, 5-year local control was 84% when the BED was at least 100 Gy [16]. While most of these patients were medically inoperable, further analysis of a subgroup of 87 patients who were medically operable but elected non-surgical therapy and received a BED over 100 Gy revealed 5-year local control rates of 92% and 82% and 5-year overall survival of 76% and 64% for patients with stage IA and IB disease, respectively, with treatment-related morbidity rates of 1.4% for grade 3 radiation pneumonitis and 3.4% for rib fracture [29]. This essentially equals the historical results of some of the best thoracic surgical series yet with lower treatment-related mortality and morbidity [3, 30]. Following on these results, the Japanese Clinical Oncology Group (JCOG) has completed trial 0403, a prospective phase II study of SABR (48 Gy in four fractions) for stage IA NSCLC with accrual arms for operable and medically inoperable patients, and mature results will be presented later in 2010 [31].

## Challenges and potential pitfalls in SABR

- A common challenge after any local ablative therapy for early lung cancer including limited resection is distinguishing tumor persistence or recurrence from treatment-related changes in the lung parenchyma. Fibrosis and subclinical radiation pneumonitis are frequently observed after SABR and need to be distinguished from tumor recurrence on CT and FDG-PET imaging. Treated volumes can show 18F-FDG uptake for at least 12 months after SABR [32, 33]. Careful radiological follow-up is paramount in patients who are treated using

SABR because salvage surgery or mediastinal radiation therapy may be possible options in cases of local or regional recurrence [34]. Given the extreme radiation doses administered, normal organ toxicity is a major concern and much data on this have recently emerged in the literature. Already discussed above is tumor proximity to the central airways as a risk factor when using the most intensive dose regimens. Similarly, other complications have been described that might be anticipated based on tumor location, including symptomatic radiation pneumonitis [35], rib fracture and chest wall pain [36, 37], radiation dermatitis [38], and brachial plexopathy [39]. Each of these analyses has identified a strong relationship between the toxicity and the dose and volume of irradiation to the respective organs at risk, providing valuable information to guide the safe administration of SABR going forward. Thus, while SABR has been a well-tolerated and safe treatment modality overall, potential risks and complications clearly need to be addressed and studied in future trials.

## Ongoing multi-institutional and cooperative group clinical trials of SABR

- While SABR is beginning to emerge as a standard treatment option for medically inoperable early NSCLC given the limited alternatives, much remains to be learned about optimal dose regimens for given individuals, accounting for tumor size, location, and other patient factors. The results of multi-institutional and cooperative group studies will be the most informative and practice-changing (Table 2). For peripherally located tumors, the RTOG is conducting a randomized phase II trial (0915) to determine which of two regimens (34 Gy single fraction vs. 48 Gy in four fractions) to compare in a future phase III trial to the current standard of 54 Gy in three fractions set by RTOG 0236 [40]. For centrally located tumors, RTOG 0813 is a phase I/II dose escalation study to determine the maximum tolerated dose in five fractions, starting with a total dose of 50 Gy [41]. Both of these studies have recently opened.
- For patients who could undergo surgery, RTOG 0618 is a phase II study evaluating the 60 Gy in three fractions regimen for peripherally located tumors analogous to the RTOG 0236 study for medically inoperable patients [42]. Accrual to this study has been robust and completion is anticipated in 2010. Finally, there are already two open international randomized phase III trials, the STARS and ROSEL studies, comparing SABR vs. surgery in patients with operable stage I NSCLC [43, 44]. All of these trials will be critical for defining the appropriate role of SABR in the treatment of early stage NSCLC.

## Radiofrequency ablation

- Radiofrequency ablation (RFA) is a procedure in which high-frequency electrical currents are passed through an electrode creating heat that coagulates tissue surrounding the electrode. When performed percutaneously, RFA for lung tumors is most often done under the guidance of computed tomography (CT). Presently, it has been approved by the US Food and Drug Administration (FDA) for the treatment of primary and metastatic tumors in soft tissue that includes the lung and liver. Lung RFA is generally reserved for patients with poor cardiac or respiratory function who are not considered good

**Table 2. Ongoing prospective multi-center or cooperative group trials of SABR and RFA in stage I NSCLC**

| Trial | Title |
|---|---|
| RTOG 0915 | A Randomized Phase II Study Comparing 2 Stereotactic Body Radiation Therapy (SBRT) Schedules for Medically Inoperable Patients With Stage I Peripheral Non-Small Cell Lung Cancer |
| RTOG 0813 | Seamless Phase I/II Study of Stereotactic Lung Radiotherapy (SBRT) for Early Stage, Centrally Located, Non-Small Cell Lung Cancer (NSCLC) in Medically Inoperable Patients |
| RTOG 0618 | A Phase II Trial of Stereotactic Body Radiation Therapy (SBRT) in the Treatment of Patients With Operable Stage I/II Non-Small Cell Lung Cancer |
| STARS | Phase III Study to Compare CyberKnife® Stereotactic Radiotherapy With Surgical Resection in Stage I Non-small Cell Lung Cancer |
| ROSEL | A Randomized Clinical Trial of Surgery Versus Radiosurgery (Stereotactic Radiotherapy) in Patients With Stage IA NSCLC Who Are Fit to Undergo Primary Resection |
| ACOSOG Z4033 | A Pilot Study of Radiofrequency Ablation in High-Risk Patients With Stage IA Non-Small Cell Lung Cancer |

candidates for surgery, those with recurrent lung metastases, and those with local recurrence after radiation therapy [45]. RFA has the advantages that it is minimally invasive, with relatively low incidence of major morbidity or mortality, and that it can often be completed in a single session, usually not requiring a hospital stay. Contraindications to RFA include those that are patient related and those that are tumor related. Patient-related contraindications include an underlying bleeding diathesis, sepsis, respiratory infection, or infection at the site of puncture. While there are no absolute tumor-related contraindications for lung RFA, relative contraindications include tumor size greater than 4 cm and a distance of less than 1 cm to the hilum or large vessels due to the risk of airway or vascular injury [46]. The procedure is also felt to be best suited for patients with peripherally located lesions; centrally located tumors near large blood vessels are not ideally treated due to the "heat sink" effect where heat is dissipated by blood flow [47].

- Data regarding the efficacy of RFA for primary treatment of stage I NSCLC are limited given that most reports include patients with metastatic lung tumors from other primary sites, such as colon, and do not include long-term follow-up (Table 3). Overall, outcome appears to be dependent upon tumor size. In a study by Simon *et al.* [48•], 75 patients with stage I NSCLC were treated with RFA and followed for 5 years; the 5-year progression-free survival (PFS) was significantly higher in tumors less than 3 cm (47%) compared to larger tumors (25%). The RAPTURE multi-center trial evaluated RFA use in both metastatic and primary lung tumors less than 3.5 cm in size. Although only 13 patients with stage I NSCLC were included, 2-year overall survival was remarkably high at 75% [49•]. Two studies have specifically evaluated RFA in stage I NSCLC with encouraging results; these include a trial conducted by Hiraki *et al.* [50] that analyzed 19 patients with an overall survival of 74% at 3 years and a trial by Pennathur *et al.* [51] of 20 patients with an overall survival of 68% at 2 years. A recent retrospective review of 79 patients with primary NSCLC treated with RFA also showed that at a mean follow-up of 17 months, 57% of patients showed no evidence of recurrence; of the 43% of patients who did recur, the most common pattern of recurrence was local, with increasing tumor size and stage correlating

**Table 3. Selected trials of RFA in patients with inoperable stage I NSCLC**

| Trial | Number of patients with stage I NSCLC | Mean tumor diameter (cm) | Median follow-up (months) | Outcome |
|---|---|---|---|---|
| Simon *et al.* [48•] | 75 (IA, <3 cm: 56; IB, >3 cm: 19) | 2.7 | 20.5 | Progression-free survival: <3 cm: 83% at 1 year, 47% at 5 years >3 cm: 45% at 1 year, 25% at 5 years |
| Lencioni *et al.* [49•] | 13 (IA: 10; IB: 3) | 2.5 | 24 | Overall survival at 2 years: 75% cancer-specific survival at 2 years: 92% |
| Hiraki *et al.* [50] | 20 (IA: 14; IB: 6) | 2.4 | 21.8 | Progression: 35% (7/20) at 4.4–38.3 months |
| Pennathur *et al.* [51] | 19 (IA: 11; IB: 8) | 2.8 | 29 | Progression at 1 year: 42% (8/19) Overall survival at 1 year: 95% Median time to local progression: 27 months |

with an increased risk of recurrence [52]. There is an ongoing American College of Surgeons Oncology Group (ACOSOG) phase II trial (Z4033) [53] assessing the safety and efficacy of RFA in high-risk T1N0 patients with NSCLC. Additional prospective and comparative trials will further define the role of RFA as a treatment modality in early stage NSCLC (Table 2).

- The challenges associated with lung RFA include assessment of treatment response and the potential for complications. Often, there is an inflammatory response that can last up to 3 months, which can lead to the mass appearing initially larger and then decreasing slowly over time [54]. Overall mortality ranges from 0 to 5.6% after RFA to the lung [55]. Pneumothorax is the most frequent complication (although a chest-tube is rarely indicated), with reports ranging from 83% in earlier studies [56] to 9% in more recent studies [57]. Thermal injury to adjacent structures can result in pain and perforation, though this is extremely rare. Large central airways can be damaged and some studies require tumors to be located at least 1 cm from the trachea, main bronchi, esophagus, heart, and major blood vessels [58]. Other complications, such as fever, hemoptysis, pleural effusion, and pleuritic chest pain have also been described. Overall, the complications are usually mild and self-limited and RFA is felt to be a well-tolerated and safe procedure.

## Microwave ablation

- Like RFA, microwave ablation is a thermal energy ablative, minimally invasive procedure that is performed percutaneously. However, unlike RFA, MWA operates at frequencies of 900–2450 MHz and agitates water molecules via a 14.5-gauge microwave antenna [59]. Clinical experience with MWA for lung tumors remains limited at this time and no definitive statement can be made regarding its use given the significant heterogeneity of the studies that have evaluated MWA (including primary lung vs. metastatic lesions, the MWA method, location of the lesions, and intent for local control vs. palliation). The potential advantages of microwave over other thermal-based modalities are the larger volume and faster tissue heating with a given applicator. Moreover, in contrast to RFA, MWA does not rely on an electrical circuit and permits the use of multiple applicators to be applied simultaneously [60]. In a study of 28 tumors in 20 patients

who underwent MWA, Feng *et al.* [61] reported a response of 50% ablation or more in 13 (46.4%) nodules and a complete response in 3 (10.7%). There were no complications associated with MWA in this study. However, MWA can be associated with complications similar to those seen with RFA as discussed in the last section. In addition, abscess formation after MWA has been reported and the long-term complications remain unknown [62]. A more recent study by Wolf *et al.* [63] evaluated MWA of 82 lung tumors in 50 patients. At a median follow-up of 10 months, 26% of patients had residual disease at the ablation site and another 22% had recurrent disease distant from the ablation site. Overall, local control at 1 year was 67%, and overall survival was 55% and 45% at 2 and 3 years post-ablation respectively. Additional studies are warranted, with a closer analysis of patients with early stage disease, in order to determine whether MWA can be an effective treatment alternative in this subset of patients.

- The combination of thermal ablation with external beam radiation or SABR is another novel treatment approach for early stage NSCLC. The rationale for using a combination of methods is that thermal ablation is most effective in the center of the tumor (with higher chances of recurrence in the periphery owing to incomplete ablation), while external beam radiotherapy or SABR are likely to be more effective in the periphery of the tumor (and less effective in the center due to necrosis and anoxia). Grieco *et al.* [64] reported on 41 patients with stage I/II NSCLC who were treated with thermal ablation (using either RFA or MWA) followed by external beam radiotherapy. The overall survival rates were 97.6% at 6 months, 86.8% at 1 year, 70.4% at 2 years, and 57.1% at 3 years. The combination therapy was well tolerated with a low rate of complications and will need to be further evaluated in future studies.

## Conclusion

- Patients with inoperable stage I NSCLC were once considered to have little chance of long-term survival. Recent advances in radiation therapy, along with the development of other treatment alternatives, now offer these patients the possibility of improved outcomes. Additional results from prospective trials are needed in order to validate the safety and efficacy of the various treatment modalities. Certainly, SABR, RFA, and MWA show considerable promise in the treatment of early stage NSCLC and are ready for prime time evaluation in the setting of clinical trials already underway, including international randomized comparisons with surgery. Ultimately, the goal will be to have enough information to make more personalized treatment decisions based upon both patient and tumor characteristics that can allow for optimal therapeutic results, even in the most compromised patients. Participation in ongoing trials for both operable and medically inoperable patients is strongly encouraged.

# References and Recommended Reading

Papers of particular interest, published recently, has been highlighted as:
• Of importance
•• Of major importance

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ: **Cancer statistics, 2009.** *CA Cancer J Clin* 2009, **59(4):**225–249.

2. Goldstraw P, Crowley J, Chansky K, Giroux DJ, Groome PA, Rami-Porta R, Postmus PE, Rusch V, Sobin LInternational Association for the Study of Lung Cancer

International Staging Committee; Participating Institutions.: **The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours.** *J Thorac Oncol* 2007 **2(8):**706–714.

3. Asamura H, Goya T, Koshiishi Y, Sohara Y, Eguchi K, Mori M, Nakanishi Y, Tsuchiya R, Shimokata K, Inoue H, Nukiwa T, *et al.*: **A Japanese Lung Cancer Registry study: prognosis of 13,010 resected lung cancers.** *J Thorac Oncol* 2008, **3(1):**46–52.
4. Ginsberg RJ, Rubinstein LV: **Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group.** *Ann Thorac Surg* 1995, **60(3):**615–622 discussion 622–613.
5. Qiao X, Tullgren O, Lax I, Sirzén F, Lewensohn R: **The role of radiotherapy in treatment of stage I non-small cell lung cancer.** *Lung Cancer* 2003, **41(1):**1–11.
6. Wisnivesky JP, Bonomi M, Henschke C, Iannuzzi M, McGinn T: **Radiation therapy for the treatment of unresected stage I–II non-small cell lung cancer.** *Chest* 2005, **128(3):**1461–1467.
7. Armstrong JG, Burman C, Leibel S, Fontenla D, Kutcher G, Zelefsky M, Fuks Z: **Three-dimensional conformal radiation therapy may improve the therapeutic ratio of high dose radiation therapy for lung cancer.** *Int J Radiat Oncol Biol Phys* 1993, **26(4):**685–689.
8. Lagerwaard FJ, Senan S, van Meerbeeck JP, Graveland WJ: **Has 3-D conformal radiotherapy (3D CRT) improved the local tumour control for stage I non-small cell lung cancer?** *Radiother Oncol* 2002, **63(2):**151–157.
9. Campeau M-P, Herschtal A, Wheeler G, Mac Manus M, Wirth A, Michael M, Hogg A, Drummond E, Ball D: **Local control and survival following concomitant chemoradiotherapy in inoperable stage I non-small-cell lung cancer.** *Int J Radiat Oncol Biol Phys* 2009, **74(5):**1371–1375.
10. Kong F-M, Ten Haken RK, Schipper MJ, Sullivan MA, Chen M, Lopez C, Kalemkerian GP, Hayman JA: **High-dose radiation improved local tumor control and overall survival in patients with inoperable/unresectable non-small-cell lung cancer: long-term results of a radiation dose escalation study.** *Int J Radiat Oncol Biol Phys* 2005, **63(2):**324–333.
11. Sura S, Yorke E, Jackson A, Rosenzweig KE: **High-dose radiotherapy for the treatment of inoperable non-small cell lung cancer.** *Cancer J* 2007, **13(4):**238–242.
12. Bogart JA, Hodgson L, Seagren SL, Blackstock AW, Wang X, Lenox R, Turrisi AT III, Reilly J, Gajra A, Vokes EE, Green MR: **Phase I study of accelerated conformal radiotherapy for stage I non-small-cell lung cancer in patients with pulmonary dysfunction: CALGB 39904.** *J Clin Oncol* 2010, **28(2):**202–206.
13. **Radiation therapy in treating patients with stage I or stage II non-small cell lung cancer that cannot be removed by surgery (NCIC BR.25)**: http://clinicaltrials.gov/ct2/show/study/NCT00346320. Accessed March 12, 2010.
14. Fowler JF, Tome WA, Fenwick JD, Mehta MP: **A challenge to traditional radiation oncology.** *Int J Radiat Oncol Biol Phys* 2004, **60(4):**1241–1256.
15. Wulf J, Baier K, Mueller G, Flentje MP: **Dose–response in stereotactic irradiation of lung tumors.** *Radiother Oncol J Eur Soc Therap Radiol Oncol* 2005, **77(1):**83–87.
16. Onishi H, Shirato H, Nagata Y, Hiraoka M, Fujino M, Gomi K, Niibe Y, Karasawa K, Hayakawa K, Takai Y, Kimura T, *et al.*: **Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer: updated results of 257 patients in a Japanese multi-institutional study.** *J Thorac Oncol* 2007, **2(7 Suppl 3):**S94–S100.
17. Blomgren H, Lax I, Näslund I, Svanström R: **Stereotactic high dose fraction radiation therapy of extracranial tumors using an accelerator. Clinical experience of the first thirty-one patients.** *Acta Oncol* 1995, **34(6):**861–870.
18. Whyte RI, Crownover R, Murphy MJ, Martin DP, Rice TW, Decamp MM, Rodebaugh R, Weinhous MS, Le Q-T: **Stereotactic radiosurgery for lung tumors: preliminary report of a phase I trial.** *Ann Thorac Surg* 2003, **75(4):**1097–1101.
19. Le Q-T, Loo BW, Ho A, Cotrutz C, Koong AC, Wakelee H, Kee ST, Constantinescu D, Whyte RI, Donington J: **Results of a phase I dose-escalation study using single-fraction stereotactic radiotherapy for lung tumors.** *J Thorac Oncol* 2006, **1(8):**802–809.
20. Loo BW, Shen J, Quinlan-Davidson S, Filion E, Dieterich S, Maxim PG, Wakelee HA, Whyte RI, Le Q: **Tumor size is a critical determinant of local control in single fraction stereotactic radiotherapy of pulmonary tumors.** *Int J Radiat Oncol* 2008, **72(1):**S467–S468.
21. McGarry RC, Papiez L, Williams M, Whitford T, Timmerman RD: **Stereotactic body radiation therapy of early-stage non-small-cell lung carcinoma: phase I study.** *Int J Radiat Oncol Biol Phys* 2005, **63(4):**1010–1015.
22. Fakiris AJ, McGarry RC, Yiannoutsos CT, Papiez L, Williams M, Henderson MA, Timmerman R: **Stereotactic body radiation therapy for early-stage non-small-cell lung carcinoma: four-year results of a prospective phase II study.** *Int J Radiat Oncol Biol Phys* 2009, **75(3):**677–682.
23. Timmerman R, McGarry R, Yiannoutsos C, Papiez L, Tudor K, DeLuca J, Ewing M, Abdulrahman R, DesRosiers C, Williams M, Fletcher J: **Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer.** *J Clin Oncol* 2006, **24(30):**4833–4839.
24. • Timmerman R, Paulus R, Galvin J, Michalski J, Straube W, Bradley J, Fakiris AJ, Bezjak A, Videtic G, Choy H: **Stereotactic body radiation therapy for medically inoperable early-stage lung cancer patients: analysis of RTOG 0236.** *Int J Radiat Oncol Biol Phys* 2009, **75(31):**S3.

This is the first reported cooperative group trial of SABR for early stage NSCLC with mature (3 years) follow-up, demonstrating excellent (98%) local control and survival for a strictly medically inoperable patient population.

25. Lagerwaard FJ, Haasbeek CJA, Smit EF, Slotman BJ, Senan S: **Outcomes of risk-adapted fractionated stereotactic radiotherapy for stage I non-small-cell lung cancer.** *Int J Radiat Oncol Biol Phys* 2008, **70(3):**685–692.
26. Chang JY, Balter PA, Dong L, Yang Q, Liao Z, Jeter M, Bucci MK, McAleer MF, Mehran RJ, Roth JA, Komaki R: **Stereotactic body radiation therapy in centrally and superiorly located stage I or isolated recurrent non-small-cell lung cancer.** *Int J Radiat Oncol Biol Phys* 2008, **72(4):**967–971.
27. Henderson M, McGarry R, Yiannoutsos C, Fakiris A, Hoopes D, Williams M, Timmerman R: **Baseline pulmonary function as a predictor for survival and decline in pulmonary function over time in patients undergoing stereotactic body radiotherapy for the treatment of stage I non-small-cell lung cancer.** *Int J Radiat Oncol Biol Phys* 2008, **72(2):**404–409.
28. Stephans KL, Djemil T, Reddy CA, Gajdos SM, Kolar M, Machuzak M, Mazzone P, Videtic GMM: **Comprehensive analysis of pulmonary function test (PFT) changes after stereotactic body radiotherapy (SBRT) for stage I lung cancer in medically inoperable patients.** *J Thorac Oncol* 2009, **4(7):**838–844.
29. Onishi H, Nagata Y, Shirato H, Arimoto T, Gomi K, Karasawa K, Hayakawa K, Takai Y, Ouchi A, Takeda A: **Stereotactic body radiotherapy (SBRT, BED ≥** 100 Gy) for operable stage I non-small cell lung cancer: is SBRT comparable to surgery? *Int J Radiat Oncol Biol Phys* 2007, **69(3, Suppl 1):**S86–S87.
30. Allen MS, Darling GE, Pechet TTV, Mitchell JD, Herndon JE, Landreneau RJ, Inculet RI, Jones DR, Meyers BF, Harpole DH, Putnam JB, *et al.*: **Morbidity and mortality of major pulmonary resections in patients with early-stage lung cancer: initial results of the randomized, prospective ACOSOG Z0030 trial.** *Ann Thorac Surg* 2006, **81(3):**1013–1019 discussion 1019–1020.
31. **A phase II study of stereotactic body radiation therapy in patients with T1N0M0 non-small cell lung cancer (JCOG 0403)**: http://clinicaltrials.gov/ct2/show/NCT00238875. Accessed March 12, 2010.
32. Bradley J: **Radiographic response and clinical toxicity following SBRT for stage I lung cancer.** *J Thorac Oncol* 2007, **2(7 Suppl 3):**S118–S124.
33. Henderson M, Hoopes D, Fletcher J, Lin P, Tann M, Yiannoutsos C, Williams M, Fakiris A, McGarry R, Timmerman R: **A pilot trial of serial 18f-fluorodeoxyglucose positron emission tomography in patients with medically inoperable stage I non-small-cell lung cancer treated with hypofractionated stereotactic body radiotherapy.** *Int J Radiat Oncol Biol Phys* 2010, **76(3):**789–795.
34. Haasbeek CJ, Senan S, Smit EF, Paul MA, Slotman BJ, Lagerwaard FJ: **Critical review of nonsurgical treatment options for stage I non-small cell lung cancer.** *Oncologist* 2008, **13(3):**309–319.
35. Yamashita H, Nakagawa K, Nakamura N, Koyanagi H, Tago M, Igaki H, Shiraishi K, Sasano N, Ohtomo K: **Exceptionally high incidence of symptomatic grade 2–5 radiation pneumonitis after stereotactic radiation therapy for lung tumors.** *Radiat Oncol* 2007, **2:**21.
36. Pettersson N, Nyman J, Johansson K: **Radiation-induced rib fractures after hypofractionated stereotactic body radiation therapy of non-small cell lung cancer: a dose– and volume–response analysis.** *Radiother Oncol J Eur Soc Therap Radiol Oncol* 2009, **91(3):**360–368.
37. Dunlap NE, Cai J, Biedermann GB, Yang W, Benedict SH, Sheng K, Schefter TE, Kavanagh BD, Larner JM: **Chest wall volume receiving >30 Gy predicts risk of severe pain and/or rib fracture after lung stereotactic body radiotherapy.** *Int J Radiat Oncol Biol Phys* 2010, **76(3):**796–801.
38. Hoppe BS, Laser B, Kowalski AV, Fontenla SC, Pena-Greenberg E, Yorke ED, Lovelock DM, Hunt MA, Rosenzweig KE: **Acute skin toxicity following stereotactic body radiation therapy for stage I non-small-cell lung cancer: who's at risk?** *Int J Radiat Oncol Biol Phys* 2008, **72(5):**1283–1286.
39. Forquer J, Fakiris A, Timmerman R, Lo S, Perkins S, McGarry R, Johnstone P: **Brachial plexopathy from stereotactic body radiotherapy in early-stage NSCLC: dose-limiting toxicity in apical tumor sites.** *Radiother Oncol* 2009, **93(3):**408–413.
40. **Radiation therapy in treating patients with stage I non-small cell lung cancer (RTOG 0915)**: http://clinicaltrials.gov/ct2/show/NCT00960999. Accessed March 12, 2010.
41. **Stereotactic body radiation therapy in treating patients with stage I non-small cell lung cancer (RTOG 0813)**: http://clinicaltrials.gov/ct2/show/NCT00750269. Accessed March 12, 2010.
42. **Stereotactic body radiation therapy in treating patients with stage I or stage II non-small cell lung cancer that can be removed by surgery (RTOG 0618)**: http://clinicaltrials.gov/ct2/show/NCT00551369. Accessed March 12, 2010.
43. **International randomized study to compare cyberknife stereotactic radiotherapy with surgical resection in stage I non-small cell lung cancer (STARS)**: http://clinicaltrials.gov/ct2/show/NCT00840749. Accessed March 12, 2010.
44. **Trial of either surgery or stereotactic radiotherapy for early stage (IA) lung cancer (ROSEL)**: http://clinicaltrials.gov/ct2/show/NCT00687986. Accessed March 12, 2010.
45. Gillams AR, Lees WR: **Radiofrequency ablation of lung metastases: factors influencing success.** *Eur Radiol* 2008, **18(4):**672–677.
46. Gomez FM, Palussiere J, Santos E, Tourdias T, Cornelis F, Saiz V, Montes H, Eker O: **Radiofrequency thermocoagulation of lung tumours. Where we are, where we are headed.** *Clin Transl Oncol* 2009, **11(1):**28–34.
47. Goldberg SN, Hahn PF, Tanabe KK, Mueller PR, Schima W, Athanasoulis CA, Compton CC, Solbiati L, Gazelle GS: **Percutaneous radiofrequency tissue ablation: does perfusion-mediated tissue cooling limit coagulation necrosis?** *J Vasc Interv Radiol* 1998, **9(1 Pt 1):**101–111.
48.• Simon CJ, Dupuy DE, DiPetrillo TA, Safran HP, Grieco CA, Ng T, Mayo-Smith WW: **Pulmonary**

**radiofrequency ablation: long-term safety and efficacy in 153 patients.** *Radiology* 2007, **243(1):** 268–275.

This is a retrospective study evaluating the outcome of 153 patients with inoperable primary or metastatic lung tumors who were treated with RFA.

49.• Lencioni R, Crocetti L, Cioni R, Suh R, Glenn D, Regge D, Helmberger T, Gillams AR, Frilling A, Ambrogi M, Bartolozzi C, *et al.*: **Response to radiofrequency ablation of pulmonary tumours: a prospective, intention-to-treat, multicentre clinical trial (the RAPTURE study).** *Lancet Oncol* 2008, **9(7):**621–628.

This is the first large, multicenter, intention-to-treat prospective clinical trial testing the safety and efficacy of RFA in the treatment of both primary and metastatic lung tumors.

50. Hiraki T, Gobara H, Iishi T, Sano Y, Iguchi T, Fujiwara H, Tajiri N, Sakurai J, Date H, Mimura H, Kanazawa S: **Percutaneous radiofrequency ablation for clinical stage I non-small cell lung cancer: results in 20 nonsurgical candidates.** *J Thorac Cardiovasc Surg* 2007, **134(5):**1306–1312.
51. Pennathur A, Luketich JD, Abbas G, Chen M, Fernando HC, Gooding WE, Schuchert MJ, Gilbert S, Christie NA, Landreneau RJ: **Radiofrequency ablation for the treatment of stage I non-small cell lung cancer in high-risk patients.** *J Thorac Cardiovasc Surg* 2007, **134(4):**857–864.
52. Beland MD, Wasser EJ, Mayo-Smith WW, Dupuy DE: **Primary non-small cell lung cancer: review of frequency, location, and time of recurrence after radiofrequency ablation.** *Radiology* 2010, **254(1):**301–307.
53. **Radiofrequency ablation in treating patients with stage I non-small cell lung cancer (ACOSOG Z4033)**: http://clinicaltrials.gov/ct2/show/study/NCT00109876. Accessed March 12, 2010.
54. Abbas G, Pennathur A, Landreneau RJ, Luketich JD: **Radiofrequency and microwave ablation of lung tumors.** *J Surg Oncol* 2009, **100(8):**645–650.
55. de Baere T, Palussiere J, Auperin A, Hakime A, Abdel-Rehim M, Kind M, Dromain C, Ravaud A, Tebboune N, Boige V, Malka D, *et al.*: **Midterm local efficacy and survival after radiofrequency ablation of lung tumors with minimum follow-up of 1 year: prospective evaluation.** *Radiology* 2006, **240(2):**587–596.
56. Suh RD, Wallace AB, Sheehan RE, Heinze SB, Goldin JG: **Unresectable pulmonary malignancies: CT-guided percutaneous radiofrequency ablation—preliminary results.** *Radiology* 2003, **229(3):**821–829.
57. Belfiore G, Moggio G, Tedeschi E, Greco M, Cioffi R, Cincotti F, Rossi R: **CT-guided radiofrequency ablation: a potential complementary therapy for patients with unresectable primary lung cancer—a preliminary report of 33 patients.** *AJR Am J Roentgenol* 2004, **183(4):**1003–1011.
58. Ambrogi MC, Lucchi M, Dini P, Melfi F, Fontanini G, Faviana P, Fanucchi O, Mussi A: **Percutaneous radiofrequency ablation of lung tumours: results in the mid-term.** *Eur J Cardiothorac Surg* 2006, **30(1):**177–183.
59. Simon CJ, Dupuy DE: **Current role of image-guided ablative therapies in lung cancer.** *Expert Rev Anticancer Ther* 2005, **5(4):**657–666.
60. Dupuy DE: **Microwave ablation compared with radiofrequency ablation in lung tissue-is microwave not just for popcorn anymore?** *Radiology* 2009, **251(3):**617–618.
61. Feng W, Liu W, Li C, Li Z, Li R, Liu F, Zhai B, Shi J, Shi G: **Percutaneous microwave coagulation therapy for lung cancer.** *Zhonghua Zhong Liu Za Zhi* 2002, **24(4):**388–390.
62. Padda S, Kothary N, Donington J, Cannon W, Loo BW Jr., Kee S, Wakelee H: **Complications of ablative therapies in lung cancer.** *Clin Lung Cancer* 2008, **9(2):**122–126.
63. Wolf FJ, Grand DJ, Machan JT, Dipetrillo TA, Mayo-Smith WW, Dupuy DE: **Microwave ablation of lung malignancies: effectiveness, CT findings, and safety in 50 patients.** *Radiology* 2008, **247(3):** 871–879.
64. Grieco CA, Simon CJ, Mayo-Smith WW, DiPetrillo TA, Ready NE, Dupuy DE: **Percutaneous image-guided thermal ablation and radiation therapy: outcomes of combined treatment for 41 patients with inoperable stage I/II non-small-cell lung cancer.** *J Vasc Interv Radiol* 2006, **17(7):**1117–1124.