Abstract

Stereotactic ablative radiotherapy (SABR), also known in older reports as stereotactic body radiation therapy, represents an evolving and expanding radiation treatment option for many forms of local malignancy, from primary tumors to metastatic and recurrent disease. It involves the precise delivery of higher doses of external-beam radiation per treatment over a shortened treatment course compared with traditional regimens. SABR has become the standard of care for patients with medically inoperable early-stage non–small cell lung cancer (NSCLC) and is becoming a more viable option for surgical candidates with early-stage primary NSCLCs who prefer noninvasive modalities of treatment. Although SABR is being used for the treatment of primary and metastatic disease in many sites of the body, such as the central nervous system, liver, pancreas, spine metastases, and isolated nodal disease in the mediastinum and abdomen, this article focuses on treatment of NSCLC in the thorax. Specifically, this review provides the rationale, evidence, and indications for treating early-stage lung cancers with SABR. (JNCCN 2012;10:1514–1520)

The concept of stereotactic ablative radiotherapy (SABR), known in older reports as stereotactic body radiation therapy (SBRT), for the treatment of lung cancer traces its roots back to the use of stereotactic radiosurgery in the treatment of central nervous system (CNS) malignancies from the 1940s through the 1960s. Although noninvasive, radiosurgery defined the use of single, high-dose fractions of radiation in the treatment of intracranial processes. Drs. Leksell and Larsson of Sweden used the concept that limited high doses of ionizing radiation could ablate neoplastic activity and still limit normal tissue side effects if the treatment was targeted with high precision. Early in radiosurgery, protons and gamma rays from a radioactive cobalt-60 source were used to irradiate lesions. To promote precise targeting of treatment, patients’ skulls were immobilized with a frame, and fiducial markers regulating a coordinate system were implemented. Thus, a large ablative dose could be delivered with high levels of precision, allowing a safe and effective therapy.

Ultimately, multiple linear accelerator and non-linear accelerator systems have been used to deliver high doses of radiation in limited treatments. For extracranial treatment, originally extracranial stereotactic radioablation, later coined stereotactic body radiation therapy, described the complex process of high-dose precision treatment of neoplastic events. The more recent term stereotactic ablative radiotherapy has been gaining traction, because the involvement of the term ablative may more accurately describe the radiobiologic and pathologic consequences of high dose-per-fraction treatment on cell division and tissue function. The capacity for SABR to deliver high doses to tumor while limiting adjacent normal tissue toxicity is predicated on the use of all available imaging modalities, before and during treatment, to ensure optimal disease delineation, precise targeting, and delivery of radiation dose. A term has been created, image-guided radiation therapy (IGRT), to describe the use of imaging for ensuring precision in radiation delivery to tumor, especially for treatments involving high doses per treatment, such as SABR. Both the American Society of Therapeutic Radiology and Oncology and the American College of Radiology have defined SABR to include all radiation therapy requiring very large doses per fraction. Therefore, each governing body has also created guidelines to ensure quality control in the setting of SABR, which requires adequate...
technology for target delineation, experience of radiation oncologists in understanding and implementing treatment with high doses, and support from radiation physicists, dosimetrists, and therapists.

Because of the inherent concern over normal tissue toxicity in the setting of fractionated radiotherapy, let alone SABR, anatomic considerations are paramount in deciding the practicality of using SABR for malignancy. As a regenerative and generally tolerable organ with known areas of high-dose radiation susceptibility, the liver has become a more applicable target for SABR. From the earliest days of radiosurgery, treatment of CNS malignancies has been standard. It has become apparent, however, that a leap in treatment paradigms has been evolving with the use of SABR for early-stage non–small cell lung cancer (NSCLC) in both the medially inoperable and borderline operable settings. This article provides a discussion of the indications, rationale, and methods of treating NSCLCs with SABR, and presents information that can be appreciated by the general medical community.

**Improved Technology Allows SABR for Early-Stage Lung Cancer**

With the extremely high doses that can be used per individual treatment in SABR, limiting normal tissue toxicity as a means of optimizing the therapeutic ratio becomes imperative. Normal tissue injury can have more profound consequences in the setting of SABR than fractionated radiation based on radiobiologic principles. Hence, technology has needed to catch up with theory for SABR to be a rational and safe treatment for lung tumors. Several technological advances over the past 20 years have facilitated the acceptance of SABR treatments in the thorax. Among them are tumor motion assessment and control, patient immobilization and positioning, target delineation and imaging guidance for precise radiation targeting, and class solutions in radiation treatment planning.

Lung tumors, especially those in the lower lobes of the lung, can have their positions in the thorax altered during the respiratory cycle with movement of the diaphragm.\(^6,7\) The goal of radiation treatment is to target only the disease areas while limiting the normal tissue parenchyma or critical structures that will receive any significant dose. This becomes more paramount with SABR because of the inherent high doses delivered with this technique over limited treatments. With moving lung targets, SABR has several potential limitations, including potentially missing the target at times of the respiratory cycle and having to therefore treat larger volumes of normal lung parenchyma or thorax to overcome this limitation. To counteract this problem, tumor motion tracking has become an intrinsic aspect of SABR treatment planning. Four-dimensional CT (4D-CT) and fluoroscopy are being used to assess the extent of tumor motion in various phases of the respiratory cycle. This information then allows the radiation team to better account for the motion and location of the malignancy at all times when planning the volumes of disease needing treatment and the fields of treatment. To minimize the extra normal lung tissue added to the treatment volume to ensure adequate coverage of the tumor as part of motion control, abdominal compression, deep inspiration breath-hold/respiratory gating, and tumor tracking with fiducials have been used with varying degrees of success.\(^4,8–10\) For the latter technique, radio-opaque seeds can be placed in the tumor by pulmonologists, interventional radiologists, or radiation oncologists to facilitate assessment of tumor motion.

Adequate patient immobilization and positioning are also fundamental requirements of SABR treatment planning and delivery. Limiting patient movement with immobilization during radiation planning sessions and all treatments allows for reproducibility and consistency in precise radiation delivery to the target over the 1 to 5 fractions normally given for SABR. Multiple immobilization systems are being used nationally and internationally for lung SABR treatments, including vacuum cushions and thermal plastic restraints. The authors’ group has been using both an evacuated vacuum molded cushion and a stereotactic body frame to immobilize and position patients with lung cancer. The stereotactic body frame uses a fiducial coordinate system that allows for equivalent patient positioning at each treatment, allowing optimization and reproducibility in targeting.

With the advent of CT, 4D-CT, MRI, and PET/CT, radiation oncologists are more accurately able to define the site and volumetric extent of lung cancers as part of target delineation, while sparing excessive normal tissue irradiation. Daily cone beam CTs before each SABR treatment allows clinicians to evaluate and make changes that promote precise
and near-real-time targeting of and radiation delivery to tumor as part of IGRT principles. The margins placed around the tumors to ensure coverage and adequate treatment of malignancy have become more controlled, because the field has incorporated daily image guidance before every SABR delivery.

Finally, with continued treatment of patients with SABR, radiation dosimetrists, physicists, and oncologists have become adept at determining which forward-planned optimal beam arrangements are necessary to treat NSCLC while minimizing normal tissue toxicities. It has become apparent that the use of more beams (11–13 on average, as shown in Figure 1A) can achieve objectives set on covering tumor and limiting dose to areas such as heart, remainder of lung, spinal cord, esophagus, brachial plexus, and chest wall. Noncoplanar beams are recommended to provide the most conformal treatment of tumor with a high dose, as is the occasional beam across the contralateral lung. Daily imaging, motion determination, and pretreatment PET/CT evaluation have helped delineate disease and increase the accuracy of SABR treatment planning. Conformal dose distributions with rapid fall-off to normal tissues, as shown in Figure 1B, allow large ablative dose effects to be localized within and near the tumor without significant loss of pulmonary function in most patients.

Clinical Indications for Lung Cancer SABR: Feasibility and Benefit

To understand why radiation oncologists moved toward the use of SABR in treating primary NSCLCs and metastatic disease to the lungs, the poor outcomes in controlling these disease states with fractionated radiation therapy (eg, 25–37 daily treatments) must be understood. Stage III and IV NSCLCs are not discussed in this review, because no indications exist to use SABR in their primary treatment, although the use of SABR for ablating oligometastatic disease is becoming more common.

For stage I and II NSCLC and isolated tumor metastases to the lungs, the standard approach to treatment has historically been surgical resection. For surgically resected stage I lesions, the 5-year overall survival (OS) rate is 60% to 70% in several series. Although not optimal, these outcomes are far better than those for patients with medically inoperable disease whose traditional recourse would have involved limited treatment because of poor performance status. Patients with medically inoperable early-stage NSCLC with no intervention have a short OS. Without surgery, radiation, or chemotherapy, median OS is approximately 1 year, and the 5-year OS rate is approximately 10%. The 5-year disease-specific survival rate for these patients is 10% to 25%, suggesting that, despite medical comorbidities, most will succumb to malignancy. Several registry and retrospective analyses and meta-analyses have verified a similar range of cause-specific survival for this cohort.

Patients with inoperable NSCLC who actually received some local treatment in the form of fractionated radiation therapy had significantly improved outcomes compared with patients who received no treatment, but these outcomes were much poorer than those of patients who underwent surgery. Generally, the median OS for these patients is 1.5 years, with a 5-year OS rate of approximately 20%. SEER data have suggested that radiation versus no treatment offers a 5- to 7-month OS benefit. These potential curative doses ranged from 45 to 66 Gy at 1.8 to 2 Gy per fraction. By 2005, several institutions had published their own experiences with fractionated radiation for medically inoperable stage I and II NSCLCs compared with no treatment. Clearly, radiation was beneficial versus no treatment but outcomes were inferior to those for patients who underwent surgery.

As a result, there was a push to escalate the radiation total dose and dose per fraction in the hopes of attaining better locoregional control, and potentially survival, with radiation therapy alone. Memorial Sloan-Kettering Cancer Center, among other centers, attempted to escalate total dose with standard fractionation and found that final doses greater than 80 Gy were associated with limited OS, on the order of 36% at 5 years. However, none of the dose-escalation studies ever reached a maximum tolerated dose (MTD), suggesting a need for alternate approaches. Trials comparing higher total doses with fractions of 2 Gy concurrent with chemotherapy are still ongoing for this group of patients with early-stage medically inoperable NSCLC.

Observations of diminishing returns from higher total doses with limited fraction sizes delivered conventionally showed that the use of SABR may offer the benefits of improved local tumor control while avoiding normal tissue toxicity, with adequate image guidance, tumor motion assessment, and modern pa-
Figure 1  (A) Multiple noncoplanar beam arrangements typical of stereotactic ablative radiotherapy. (B) Compact dose deposition with rapid falloff to normal tissue facilitates ablative dose delivery.

tient immobilization and treatment planning. SABR can deliver the same total dose as conventional radiation but in far fewer actual treatments, providing a theoretical and practical biologic tumor control benefit. With the technologic enhancements described earlier, although SABR offers a higher effective dose to tumors compared with standard fractionation, normal tissues could be equivalently protected, optimizing the therapeutic ratio. This rationale was displayed in the subsequent clinical trials.

Indiana University, therefore, conducted a series of studies over the past decade that paved the way for large, cooperative group trials that have verified the standard use of SABR in patients with medically inoperable early-stage NSCLC.21,22 A phase I study in patients with T1–T2,N0 NSCLC evaluated dose escalation ranging from 24 Gy in 3 fractions to 72 Gy in 3 fractions in terms of dose-limiting toxicity. The MTD was not reached in the patients with T1 tumors up to 60 Gy in 3 fractions or T2 tumors less than 5 cm up to 66 Gy in 3 fractions, effectively showing that these individuals could tolerate high doses of radiation in limited fractions quite well. The MTD was reached at 66 Gy in 3 fractions for T2 tumors greater than 5 cm. Furthermore, although 10 local failures occurred, only 1 was seen in a patient who received higher doses per fraction (>16 Gy).

A phase II study, also at Indiana University, built off the phase I study and included 70 patients with medically inoperable, clinical T1,N0 NSCLC treated with SABR to a dose of 60 Gy in 3 fractions and patients with T2,N0 NSCLC (>7 cm) treated to 66 Gy in 3 fractions.23,24 With a median follow-up of 17 months, the 2-year local control rate was 95%, median OS was 2.7 years, and 2-year OS rate was 55%. These numbers started approaching those for surgical outcomes for equivalent-staged patients. The study also showed, however, that patients with centrally located lesions (near the bronchial tree shown in Figure 2), had more than twice as many severe grade 3 toxicities (46% vs 17%) as peripheral tumors, and included 6 treatment-related deaths. Of these deaths, 4 were attributed to pneumonia, potentially as a result of reduced pulmonary toilet capabilities. At 50 months, the 3-year local control rate was still very high at 88% and the OS rate was appreciable at 42%. Multiple other studies from institutions in the United States, Japan, and Scandinavia have performed similar trials and reported similar local control and survival rates with several total dose and dose per fraction schemata.25–28

As part of the natural evolution of SABR evaluation in 2002, the RTOG undertook a multi-institutional phase II study based on the Indiana data to assess in a robust manner the efficacy of stereotactic treatments of early-stage NSCLC.29 Radiation quality assurance was a priority to ensure consistent SABR technique and use at the multiple institutions. Once again, 55 patients with medically inoperable T1–T2,N0 NSCLC were included, with a few more specific parameters: lesions larger than 5 cm and all patients treated with 60 Gy in 3 fractions without heterogeneity correction (equivalent to 54 Gy in 3 fractions with heterogeneity correction, which assumes the body has different parts with different
densities). No centrally located lesions within 2 cm of the bronchial tree were included, a lesson learned from the earlier phase II Indiana study. Forty-four patients had T1 lesions and the remaining 11 had T2 tumors. The study’s findings were published in the Journal of the American Medical Association and the report was one of the most impactful papers in 2010. Overall, with a median follow-up of 2.9 years, the 3-year tumor control rate was 98% (with 1 marginal failure at the primary tumor site), 3-year local (tumor plus lobe) control rate was 91%, 3-year locoregional control rate was 87%, 3-year distant metastasis rate was 22%, and median OS was 48 months. Limited toxicity was seen, with no deaths from treatment. Eleven of the patients experienced distant failure, potentially as a consequence of understaging up front. Despite this distant failure rate, survival rates achieved with this treatment regimen compare favorably with those of patients who underwent surgery. At 3 years, disease-free and OS rates were 48% and 56%, respectively. Furthermore, SABR is one of a limited set of well-established medical recourses for this patient population with poor performance status. High-dose fractionated radiation and radiofrequency ablation are other less-effective options if SABR is not compatible with a patient’s condition.

Results of all clinical trials suggest that SABR is well tolerated in patients with NSCLC who have peripheral lesions. Centrally located NSCLC lesions are still being evaluated for MTD delivered with SABR in ongoing RTOG studies. Known toxicities are associated with SABR for lung cancer. Increasingly well-understood dose constraints on normal tissue structures are being used by radiation oncologists as a means of limiting this toxicity. No definitive guidelines currently exist for using pulmonary function cutoffs to exclude patients from treatment as a way to limit toxicity. In the future, reviewing findings from all of the current SABR trials, forced expiratory volume in the first second of expiration (FEV₁) and diffusing capacity of carbon monoxide (DLCo) values may be found that predict for significantly higher SABR-related pulmonary toxicity. However, the original critical role for SABR was in the treatment of patients with NSCLC with terrible lung function. Hence, SABR may always be a treatment option for early-stage NSCLC in patients who cannot tolerate surgery despite the pulmonary values.

Low-grade resolving fatigue can be common in patients with lung cancer undergoing SABR. From the early Indiana University studies on medically inoperable patients with poor performance status, 10% had a 10% decline in at least one measured value of pulmonary function (eg, FEV₁, forced vital capacity, DLCo, P O₂). Most of these patients’ values eventually returned to baseline, however. DLCo and P O₂ were most commonly affected. One of 2 patients had dose-limiting grade 3 pneumonitis and one had grade 3 hypoxemia. Otherwise, this population of patients with poor lung function tolerated SABR very well. Dose-limiting toxicities, including death, were reported in the phase II study from Indiana University for centrally located lesions, leading to the current RTOG dose assessment study. With peripheral lesions in RTOG 0236, 28% of patients had grade 3/4 toxicity, primarily pulmonary or musculoskeletal (pain) in nature, with no deaths. Overall, SABR seems to be very well tolerated for most patients with NSCLC.

The Future of SABR for NSCLC

Currently, many studies nationally and internationally are trying to address several questions related to SABR for NSCLC. Several dose fractionation

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**Figure 2** In the Indiana University phase II trial using stereotactic ablative radiotherapy, patients with tumors touching or within the dotted line surrounding the central bronchial tree were more likely to experience high-grade toxicity with potent 3-fraction therapy than those with more peripheral tumors.
schemes are being used to identify an optimal total dose and dose per fraction. The limits of tumor size and location are also being investigated (ie, the use of SABR for larger tumors and those that are more centrally located). RTOG 0813, a phase I/II trial that has been accruing patients with centrally located tumors, is attempting to identify an MTD for these lesions using a 5-fraction regimen starting at 10-Gy each to a total dose of 50 Gy and extending to 12-Gy fractions to a total dose of 60 Gy. Furthermore, the RTOG initiated study 0915, another phase II evaluation assessing 2 different dose fractionation schedules in inoperable patients with peripheral stage I lesions, 34 Gy in 1 treatment versus 48 Gy in 4 treatments. The more effective of these regimens will be compared head-to-head with the RTOG historical standard to date: 54 Gy in 3 treatments.

SABR for medically inoperable early-stage lung cancer became a standard therapy in North America shortly after publication of the RTOG 0236 results. Ongoing randomized trials in Australia/New Zealand and several Scandinavian countries are comparing SABR with conventionally fractionated radiotherapy. Although randomized studies offer the highest level of evidence for a new therapy, large population cohort studies can also provide high-level evidence for its use. One such study was published in the Netherlands using national records relating to trends of treatment and outcomes over 3 eras for elderly patients with lung cancer. SABR was generally not available in the first era, partially penetrating treatment centers in the middle era, and widely available in the third. Survival improved from the first to the third era. The only factors that could explain the improvement were the increased likelihood that a medically inoperable patient would be treated rather than observed and the use of SABR. Survival among patients treated surgically or with conventional radiation did not change in the 3 eras, and increasing numbers of patients were treated with SABR. This begs the question of whether a patient selection difference exists between SABR and surgery for patients with early-stage NSCLC who may not be candidates for lobectomy. A study from William Beaumont Hospital showed improved local control with SBRT but worse OS compared with wedge resection because of potential in-built patient selection biases.

Consequently, it is apparent that SABR for patients with early-stage NSCLC may be effective enough to be used as a first-line therapy for individuals who even have borderline operable lesions. Four cooperative group studies are trying to determine whether SABR may be considered equivalent to surgeries less than lobectomy for stage I, T1,N0 or also T2,N0 NSCLCs. RTOG 0618 is a phase II, multi-institutional study that has completed accrual after treating patients with SABR to a dose of 54 Gy in 3 fractions, with heterogeneity correction for early-stage operable NSCLC lesions for which patients prefer radiation. A national ACOSOG/RTOG phase III study (Z4099/1021) just opened for accrual that will randomize patients with high-risk early-stage T1/T2,N0 (tumors ≤3 cm) NSCLC to either SABR (54 Gy in 3 fractions) or sublobar resections. Patients must be high-risk surgery candidates and therefore more apt to undergo sublobar resections traditionally. Approximately 420 patients will be enrolled to compare SABR and surgery in terms of disease control and survival.

Conclusions

In reviewing the literature, it has become obvious that SABR should be the primary modality in the treatment of patients with medically inoperable lung cancer, providing higher rates of survival, tumor control, and avoidance of toxicity compared with historical reports of conventional radiation or no treatment. As a consequence, the natural extension of these findings is to assess outcomes of SABR with surgery in patients at high risk of morbidity from surgery (ie, patients with high-risk operable disease). Such a study is in the early stages of patient accrual. Although its metastatic indications are outside the scope of this review, SABR can be used to treat limited numbers of lung metastases from multiple primaries, and also to treat isolated nodal or other metastases at distant subdiaphragmatic or intracranial sites. A future potential indication will be to use SABR with systemic agents in the treatment of limited-volume metastatic disease. These early-stage trials are also ongoing.

From primary therapy to coverage of oligometastatic disease, SABR is being used for a variety of disease states in oncology. The roles for SABR continue to increase and should be maintained as an integral
aspect of any academic or private practice treatment repertoire. To this point, peripheral T1 or T2 lesions up to 5 cm can be treated with 3- or 5-fraction SABR regimens, depending on proximity to the chest wall. For lesions centrally located, treatment with SBRT on trial is most acceptable. If not, 10 Gy times 5 is gaining favor as a safe standard of care. For lesions larger than 5 cm, fractionated radiation to 60 to 70 Gy at 2 Gy per fraction is considered appropriate.

References