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Management of early-stage non-small cell lung cancer with SABR

After completing this activity, the participant should be better able to:

- Identify the types of patients and lung lesions suitable for SBRT as a curative treatment
- Describe the benefits that SABR can offer over conventional radiation treatment in the management of early-stage NSCLC
- Describe the evolution of treatment leading to the use of SBRT for early-stage NSCLC

Introduction

Non-small cell lung cancer (NSCLC) has had the highest rate of cancer incidence and patient deaths in the U.S. for decades. Due to poor health/comorbidities, many patients are not able to receive the standard of care for early-stage disease, namely, surgical resection with lobectomy. As an alternative, some of these patients have been treated with standard fractionation radiation, traditionally to doses of 60-70 Gy over six to seven weeks, with limited durable tumor control. The inadequacy in treatment response has led radiation oncologists to consider other ways to treat these patients. Many have moved toward stereotactic body radiation therapy (SBRT)—also known as stereotactic ablative radiotherapy (SABR)—in treating early-stage primary NSCLC.

Origins of SABR use in the treatment of malignancies

The concept of using SABR/SBRT for the treatment of lung cancer can be traced back to the use of radiosurgery in the treatment of CNS malignancies in the 1940s and 1950s. Radiosurgery, a noninvasive treatment, is defined by the use of a single, high-dose fraction of radiation in the treatment of intracranial conditions. Dr. Lars Leksell of Sweden, along with physicist and radiobiologist Borje Larsson, were the first to implement the concept of delivering high doses of ionizing radiation to ablate neoplastic activity while limiting normal tissue side effects through the use of high-precision treatment targeting.[1] In early radiosurgery treatments, protons and gamma rays from a radioactive cobalt-60 source were used to irradiate patient lesions. To ensure precision and prevent movement, patients' skulls were immobilized and fiducial markers delineating a coordinate system were used. Thus, a high dose could be delivered safely and effectively.

Eventually, multiple linear accelerator and nonlinear accelerator systems were employed to deliver high doses of radiation in a limited number of treatments. For extracranial treatment, stereotactic body radiation therapy (SBRT) has been the term applied to the relatively complex process of high-dose precision treatment of neoplasms.[2,3]

The term stereotactic ablative radiotherapy (SABR) has been gaining traction recently because "ablative" more accurately describes how radiation affects the tumor tissue at large dose levels, leading to high local control rates and limited toxicity. The latter characteristic of SABR is predicated on the use of multiple imaging modalities—before, during, and after treatment—to ensure maximum tumor targeting and limited collateral effect on adjacent normal tissues. The term image-guided radiation therapy (IGRT) describes this use of imaging in target delineation, especially for treatments involving high doses per treatment such as SABR. Both the American Society for Radiation Oncology (ASTRO) and the American College of Radiology (ACR) have defined SABR to include all radiation therapy requiring very large doses per fraction.[4]

While treatment of CNS malignancies with radiosurgery has been standard, it is apparent that a leap in treatment paradigms has occurred with the use of SABR for early-stage NSCLC. The next section will discuss the indications, rationale, and methods of treating NSCLC with SABR.

SABR becomes possible for lung disease with improved technology

With the extremely high doses that can be used per fraction in SABR, normal tissue injury can have more profound consequences than in the setting of conventionally fractionated radiation. Several technological advances over the last 20 years have more closely approached the theory—and facilitated the acceptance—of SABR as a rational and safe treatment for lung tumors. Among these are tumor motion evaluation, patient immobilization, image guidance, and class solutions in radiation treatment planning.

It has been known for some time that lung tumors, especially those in the lower lobes of the lung, alter their positions in the thorax during the respiratory cycle as the diaphragm moves.[5-6]

The goal of SABR is to target disease while limiting normal lung parenchyma or critical structures from receiving any significant dose. With moving lung targets there is a risk of potentially missing the target at certain times of the respiratory cycle. With conventional radiation this would require treating larger volumes of normal lung parenchyma or thorax to compensate, but this approach cannot be implemented with the higher SBRT dose.

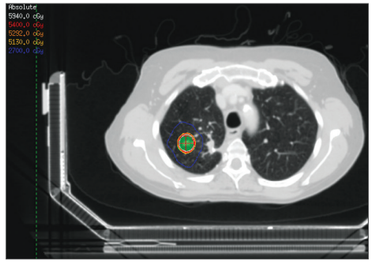

Figure 1. Axial computed tomography (CT) image of an early-stage NSCLC of the right lung. Isodose curves depict the tumor receiving the curative dose.

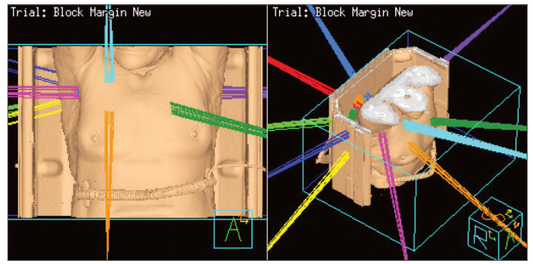

Figure 2. Skin rendering image set showing orientation and direction of SABR radiation beams entering the patient to converge on the tumor.

To counteract this problem, tumor motion tracking has become an intrinsic aspect of SABR treatment planning. Four-dimensional computed tomography (4D-CT) and fluoroscopy are utilized to assess the extent of tumor motion in all phases of the respiratory cycle. This information then allows the radiation team to account for motion when planning the fields of treatment with regard to margin on the moving target. To minimize the extra normal lung tissue added to the treatment field to ensure tumor coverage, strategies including abdominal compression, deep inspiration breath hold/respiratory gating, and tumor tracking with fiducials have been employed with varying degrees of success.[3,7-8]

Adequate patient immobilization is also a fundamental requirement of SABR treatment planning. The patient needs to be immobilized prior to each treatment to allow for reproducibility and consistency in target delineation over the one to five fractions normally given for SABR. Multiple types of immobilization systems are utilized nationally and internationally for lung SABR treatments, including vacuum cushions, stereotactic body frames, and thermal plastic restraints.

With the advent of computed tomography, then 4D-CT, magnetic resonance imaging (MRI), and positron emission tomography (PET) combined with CT over the last 20-25 years, radiation oncologists are more accurately able to define the site of lung disease. The margins placed around tumors to ensure coverage and treatment of malignancy have become smaller as imaging is more frequently used to identify tumor location with respect to normal tissues in the thorax (carina, chest wall, esophagus, trachea, spinal column, heart, and lung borders, among other anatomic considerations) and bony landmarks. Daily cone-beam CTs prior to treatment, between beam treatments, and after treatment allow us to evaluate the patient and tumor positioning and make real-time changes that promote tumor targeting and limiting of normal tissue collateral exposure.

Finally, with continued treatment of patients with SABR, practitioners have become adept at determining which beam arrangements are optimal to treat lung disease while avoiding normal tissue toxicities. It has become apparent that the use of more beams (10-12, on average) is able to achieve objectives set on covering the tumor while limiting dose to the heart, rest of lung, spinal cord, esophagus, brachial plexus, chest wall, etc. (Figs. 1-2).

Clinical indications for early-stage lung cancer treatment with SABR

In order to understand why radiation oncologists moved toward use of SABR in treating primary NSCLC, one has to appreciate the poor outcomes in controlling this disease with standard fractionated radiation therapy (more than five treatments). Generally, the median OS for medically inoperable patients treated with standard radiation is 1.5 years, with a five-year OS of approximately 20%. These outcomes are significantly improved compared to no treatment but fall well below the outcomes from surgery. SEER data has suggested that radiation (with doses ranging from 45 Gy to 66 Gy at 1.8 to 2 Gy per fraction) versus no treatment offers a five- to seven-month OS benefit.[16] Multiple institutions, including MD Anderson Cancer Center, Indiana University, and various European centers, by 2005 had published their own experiences with fractionated radiation for medically inoperable stage I and II NSCLCs in comparison to no treatment. Clearly, radiation is beneficial versus no treatment yet inferior to outcomes from surgery.

Hence there has been a push to escalate the radiation total dose as well as the dose per fraction in the hope of attaining better locoregional control. Studies from Memorial Sloan Kettering Cancer Center and the Radiation Therapy Oncology Group (RTOG) attempted to escalate the total dose with standard fractionation and found a survival benefit with final doses above 80 Gy.[19]

However, there was significantly increased acute and late pulmonary

toxicity with both higher total doses and slightly increased dose per fraction above 2 Gy, suggesting the need for treatment refinement.

From diminishing returns from higher total doses with limited fraction sizes, it became apparent that SABR may offer the benefits of improved local tumor control while avoiding normal tissue toxicity with adequate image guidance, tumor motion assessment, modern patient immobilization, and treatment planning. Indiana University conducted a series of studies over the last decade that set the stage for large, cooperative group trials that have since verified the standard use of SABR in medically inoperable, early-stage NSCLC patients.[20-21]

A phase I study for T1-T2 N0 NSCLC patients evaluated doses ranging from 24 Gy in 3 fractions to 72 Gy in 3 fractions to establish dose-limiting toxicity. No maximum tolerated dose (MTD) was reached for the T1 patients 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 with significant tumor control.

A phase II study, also at Indiana University, that built off the phase I study included 70 medically inoperable, clinical T1 N0 NSCLC patients treated with SABR to a dose of 60 Gy in 3 fractions and T2 N0 (greater than 7 cm) patients treated to 66 Gy in 3 fractions.[22-23]

With a median follow-up of 17 months, two-year local control (LC) was 95%, median OS was 2.7 years, and two-year OS was 55%. These numbers started approaching surgical outcomes for the same group of resectable patients. The study also showed, however, that patients with centrally located lesions (near the bronchial tree), had more than twice as many severe grade 3 toxicities as those with peripheral tumors (46% vs. 17%) and included six treatment-related deaths. Four of the six deaths were attributed to pneumonia, potentially as a result of reduced pulmonary toilet capabilities. On update at 50 months, three-year LC was still very high at 88% and OS appreciable at 42%. Of note, multiple other studies from institutions in the U.S., Japan, and Scandinavia have performed similar trials and reported similar local control and survival rates with comparable total doses and dose per fraction schema.[24-27]

As part of the continuing evaluation of SABR, the RTOG in 2002 undertook a phase II, multi-institutional study based on the Indiana data to assess in a robust manner the efficacy of stereotactic treatments of early-stage NSCLC.[28] Fifty-five patients with medically inoperable T1-T2 N0 NSCLC disease were included with a few more specific parameters: lesions < 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. The study's findings were ultimately published in the *Journal of the American Medical Association* and ended up being one of the most impactful papers of 2010.

Overall, with a median follow-up of 2.9 years, the three-year tumor control was 98% (with one marginal failure at the primary tumor site), the three-year local (tumor plus lobe) control was 91%, three-year locoregional control was 87%, three-year distant metastasis (DM) rate was 22%, and median OS was 48 months. There was limited toxicity, with no deaths from treatment. Eleven of 55 patients failed distantly, potentially as a consequence of initial understaging of their disease. Despite this distant failure rate, survival rates achieved with this treatment regimen compare very favorably with surgical patients. Disease-free and overall survival at three years were 48% and 56%, respectively.[28]

At this time, several studies nationally and internationally are trying to address a number of questions related to SABR for early-stage NSCLC. RTOG 0813, a phase I/II trial that has completed accrual of patients with centrally located tumors, is attempting to identify an MTD for these lesions using a five-fraction regimen starting at 50 Gy and extending to 60 Gy (12 Gy/fraction). RTOG 0618 is a phase II, multi-institutional study (accrual complete) that treated patients with SABR to a dose of 54 Gy in three fractions for NSCLC, early-stage operable lesions. Most critically, there are at least three studies set to open or already activated that compare SABR versus surgery head-to-head. A national phase III study supported by the Joint Lung Cancer Trialists' Coalition (JoLT-Ca) has just opened for accrual that will randomize high-risk, early-stage T1/T2 N0 (tumors less than or equal to 5 cm) NSCLC patients to either SABR (54 Gy in 3 fractions) or sublobar resection. "High-risk" refers to those patients who could potentially have excessive toxicity outcomes from a lobectomy and thus would receive only sublobar surgeries. Similar trials are expected to open at the U.S. VA Hospital System and in Europe.

Conclusion

In reviewing the literature, it is obvious that SABR should be the primary modality in the treatment of medically inoperable NSCLC patients because it offers outcomes approaching surgical equivalence. The natural extension of this finding is to assess SABR's outcomes versus surgery outcomes in patients at high risk of morbidity from lobar resections. Such studies are in the early stages of patient accrual. The roles for SABR continue to increase and should be maintained as an integral aspect of any academic or private practice treatment repertoire.

Puneeth Iyengar, M.D., Ph.D., is Assistant Professor of Radiation Oncology at UT Southwestern Medical Center.

Puneeth Iyengar, M.D., Ph.D.

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