Review Article

Practical considerations of lung stereotactic ablative radiotherapy in the developing world

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Abstract: Lung cancer is the most common cause of cancer-related death in the world with a disproportionally high burden of disease in low- and middle-income countries (LMICs). Stereotactic ablative radiotherapy (SABR) is the standard of care treatment for inoperable patients with early-stage non-small cell lung cancer (ES-NSCLC) and is currently being evaluated in several randomized control trials in the operable patient setting. SABR for ES-NSCLC has been widely implemented throughout high-income countries (HICs), yet its implementation in LMICs, where the burden of disease is highest, has been limited. The purpose of this report is to provide a practical outline for practitioners to implement SABR for ES-NSCLC while addressing potential barriers that may arise in LMICs. We ultimately aim to describe the essential infrastructure, patient selection, human resources, technical requirements, radiation therapy (RT) planning, RT delivery, patient follow up, quality assurance (QA), and cost considerations required to effectively and safely deliver SABR for ES-NSCLC.

Keywords: Lung neoplasm; stereotactic ablative radiotherapy (SABR); global oncology; radiotherapy

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Introduction

Lung cancer is the most common cause of cancer-related mortality worldwide with World Health Organization GLOBOCAN estimates of 2.09 million new cases and 1.76 million deaths in 2018 (1). A disproportionate burden of lung cancer is in low- and middle-income countries (LMICs), and the disparity of lung cancer incidence and mortality between LMICs and high-income countries (HICs) is only expected to rise over the next decade (2). Worldwide, approximately 85% of lung cancer diagnoses are non-small cell lung cancer (NSCLC) (3), an estimated 8–18% of which present as stage I disease (4,5). Early-stage NSCLC (ES-NSCLC) is a curable disease, and historically the gold standard treatment for ES-NSCLC has been lobectomy and mediastinal lymph node evaluation for operable patients. However, up to 30% of patients are not surgical candidates while others may refuse surgery (6,7). For these patients, high dose radiotherapy is currently the

only remaining curative option.

Conventionally fractionated radiotherapy (CFRT) for ES-NSCLC involves long treatment courses over 6 to 7 weeks. Local failure is the most common site of progression for CFRT in ES-NSCLC with local control as low as 30% in some series (8). Stereotactic ablative radiotherapy (SABR) is fundamentally different from CFRT, delivering image-guided ablative radiation doses in a limited number of fractions with more stringent precision and accuracy.

SABR can provide excellent local control (LC) in ES-NSCLC with most 3-year LC rates reported between 80% and 97.5% (9-12). SABR seems to be particularly effective when a biologic equivalent dose (BED) ≥100 (alpha/beta ratio =10) is achieved, which is much higher when compared to CFRT (13). In the randomized setting, SABR has also been shown to have significantly less grade 3 or higher toxicities compared to CFRT, including less pneumonitis, esophagitis, chest pain, dyspnea, and cough with the added benefit of shorter treatment courses and less patient travel (14). There is also growing retrospective data showing that SABR has comparable outcomes, both in LC and overall survival (OS), compared to surgery in operable patients (9,15,16) with several actively accruing randomized control trials around the world (17-20).

Since the first reports of SABR for ES-NSCLC in the 1990s, utilization in HICs has sharply risen, particularly over the past 10–15 years (21). There are many high-quality guidelines from national and international bodies in HICs on SABR, both in general and specific to ES-NSCLC (11,22-27). In LMICs however, where the burden of lung cancer is greatest, SABR is not routinely available (28). In this review, we aim to describe the practical barriers and necessary components to deliver SABR for ES-NSCLC in LMICs.

Infrastructure and health care system

National level

Radiotherapy services overall, including SABR, require planning on the national level, otherwise they may be inaccessible to the majority of patients in a given country (29). Even in many HICs, socioeconomic differences may lead to disparities in adequate treatment for lung cancer, including SABR (30,31). SABR is a powerful, non-invasive tool against ES-NSCLC that serves as a valuable and robust addition to an already established system of cancer care, which is a prerequisite to its meaningful use.

Policies and guidelines aiming to improve the quality of care for patients and improve clinical effectiveness by implementation of evidence-based care in daily practice are needed and must be supported by national academic bodies. A framework for designing and implementing a comprehensive SABR program requires proper infrastructure including technology, personal requirements, and continuous education. In addition, it is important to discuss and promote a sustainable plan at a national level that will help drive the SABR program success.

Human resources training programs need to be in place throughout the whole national territory comprising not only radiation oncology and physics residency programs, but also specific training for therapists, dosimetrists, and nurses. Continuing education programs have to be offered to keep these professionals updated on constantly evolving practices, such as SABR. For all these activities, national standards shall be well defined and aligned with international recommendations, including periodic evaluations.

SABR requires a unique infrastructure regarding materials and technologies, as it will be discussed next. In this context, national programs can be created to facilitate technology adoption by offering incentives to foreign companies or local distributors. In addition, it is advisable to create proper conditions for local companies and local start-ups to develop more cost-effective products and solutions at least for the lower complexity goods, such as immobilization devices.

Local/institutional level

On a local and institutional level, successful implementation and maintenance of a lung SABR program require a multidisciplinary healthcare team. Radiation oncologists need to engage all necessary stakeholders in the initiation of SABR program, which includes, but is not limited to, institutional leadership, pulmonologists, thoracic surgeons, pathologists, and radiologists. The system needs to have the capacity for complete and timely patient staging, which includes tissue diagnosis and lymph node sampling via endobronchial ultrasound or mediastinoscopy when indicated (25). Eligible and or potentially eligible patients should be evaluated and discussed in multidisciplinary tumor boards for optimal treatment recommendations. The healthcare system should also have the computed tomography (CT) capacity for upfront staging of patients, and routine radiographic follow up required after completion of SABR (see “Follow up” section below).

Fluorodeoxyglucose (FDG) positron emission tomography (PET) is encouraged for initial staging and can be helpful in follow up to distinguish local recurrence from fibrosis after SABR (See "Follow up" section below).

Department of radiation oncology level—human resources

Within the radiation oncology department, effective and safe delivery of SABR requires institutional expertise in 3D techniques and an investment of time and resources from an integrated team including radiation oncologists, physicists, therapists, dosimetrists, management, and clinical support staff. In particular, SABR requires a high level of medical physics involvement during each step of the process including simulation, image guidance, stereotactic localization system commissioning, small-field measurements, treatment planning and maintenance of a systematic quality assurance (QA) program (22). The International Atomic Energy Agency (IAEA) recommends one radiation physicist per center for up to 400 patients treated annually (32), but taking into account the complexity of SABR, additional physics support is needed for a given patient load; a helpful resource in estimating physics workforce for a SABR program is "*The Abt study of medical physicist work values for radiation oncology physics services: round IV*" (33). Departmental investment in staff education on SABR planning and delivery is critical both for initiation and maintenance of an effective program. Examples of possible educational opportunities include internal SABR didactic rounds, vendor-led training, external observerships at experienced institutions in SABR for ES-NSCLC (11) and experts' consultancy. Overall, technical and clinical expertise takes time and experience to develop and an integrated and specialized team is essential. One approach, as described by Dahele *et al.* on the early lung SABR experience at Princess Margaret Hospital, is to have regular multidisciplinary rounds dedicated exclusively to SABR cases (34). Finally, strategies to mitigate brain drain of human resources are important to maintaining a SABR program in LMICs (35).

While many of these features at the national, local, and department levels may seem out of reach for many LMICs, there are examples of successful expansion of radiotherapy services including in India, Bangladesh, and Zimbabwe (36). There is also a precedent for implementation of SABR programs, particularly in middle-income countries, with excellent outcomes (37). Perhaps most notable among these is from Brazil, where Abreu *et al.* reported a single institution experience from Hospital Sirio-Libanes in Sao Paulo (38). In their series, 54 patients who were non-surgical candidates or declined surgery, received SABR for biopsy-proven ES-NSCLC. Median dose was 54 Gy in 3 fractions prescribed to the periphery of the tumor consistent with the Radiation Therapy Oncology Group (39) 0618 study (9). Two-year LC and OS was 89.1% and 80.0%, respectively. Both of these rates are comparable to other published experienced from HICs for inoperable ES-NSCLC treated with SABR, demonstrating the feasibility of SABR in LMICs if the adequate national, regional, and institutional resources are in place (10,12,14,40,41).

Patients

Incidence of early-stage NSCLC

Technical expertise and clinical outcomes using SABR for the treatment of ES-NSCLC have been shown to improve with institutional experience (42) and at high volume centers (40). The European Society for Radiotherapy and Oncology (ESTRO) ACROP Consensus Guidelines recommend 12 to 50 and UK-SABR Consortium recommend 25 patients per year as a minimum (11,43). As such, obtaining data to estimate the number of patients that an institution in an LMIC could reasonably treat may help determine if the investment of resources to initiate and to maintain a lung SABR program would be worthwhile. Due to overall poor population registry data in LMICs, it is difficult to estimate the percentage of patients with NSCLC who present as early-stage and would be amenable to SABR. We anticipate that, with overall less access to care in LMICs compared to HICs, a smaller number of patients would be presenting with ES-NSCLC. Limited data Available online Brazil estimates that 8.8% of their patients with NSCLC are early-stage at time of diagnosis, compared to 18% in the United States (4,5). CT screening protocols may be able to diagnose more early-stage cancers in high-risk patient populations and have been attempted around the world including in at least two LMICs (Brazil and Korea) (44). There are many inherent challenges to CT screening in most LMICs such as limited imaging, clinical workup, and pathology capacity to handle a large screening program. There is a high false positive rate of pulmonary nodules detected from CT screening, which may be even higher in areas of endemic infectious granulomatous disease as in most of Latin America. In the end, despite a lower rate

of ES-NSCLC compared to HICs, the overall high burden of disease in LMICs suggests that the incidence of ES-NSCLC, and therefore the number of potentially curable patients with SABR, is quite high.

Patient selection

Per ESTRO ACROP Consensus guidelines for SABR in ES-NSCLC, all patients should be discussed in a multidisciplinary setting and patients should have a maximum ECOG performance status of 3 and a life expectancy of at least 1 year (11). A thorough history and physical evaluation should always be performed at initial encounter including, but not limited to, inquiry of prior RT, history of interstitial lung disease, and contraindications to RT. Tobacco use and exposures should be investigated, and smoking cessation counseling offered accordingly. A diagnostic CT with IV contrast of the chest and upper abdomen including adrenal glands is recommended, with consideration of PET/CT also. Pulmonary function tests, if not previously done, should be obtained (45). Tumor size and location must be carefully assessed.

Criteria for "operability" are highly variable depending on the center and the surgical team evaluating a patient (46). Common variables evaluated beyond performance status and co-morbidities include forced expiratory volume in 1 second (FEV1), diffusing capacity of the lung for carbon monoxide (DLCO), and the arterial partial pressure of oxygen (PO_2) and carbon dioxide (PCO_2) (9). Ultimately, thoracic surgeons in the setting of multidisciplinary evaluation and discussion should determine operability. One additional consideration is the use of video-assisted thoracotomy (47) *vs.* open thoracotomy (OT) for lobectomy. VATS has been widely implemented including in many LMICs. In a randomized control trial, VATS was associated with reduced post-operative hospitalization, reduced chest pain, and improved quality of life compared to OT (48). Additionally, a 2013 meta-analysis reported improved 5-year OS for patients with stage I NSCLC with use of VATS compared to OT (49). While there may be circumstances in which OT is preferred, the routine use of OT at an institution may shift the risk to benefit ratio toward the use of SABR for many patients.

SABR has become the standard of care for inoperable ES-NSCLC (45), and its implementation can have a dramatic impact on the survival of this patient population. In a population-based study in the Netherlands spanning from 2001 to 2009, the introduction of SABR was associated with a 7% overall mortality reduction in patients 75 years or older diagnosed with stage I NSCLC going untreated, and the 2-year OS improved from 35.8% to 52.5% (50). Moreover, in elderly patients with COPD, a Markov model predicted a 5-year OS benefit of 9.0% *vs.* 2.8% without treatment (51). Overall, even for patients of advanced age with significant co-morbidities, quality SABR may lead to a survival benefit. This is a patient population that historically was unlikely to receive treatment, and without availability of SABR, continues to receive no treatment or inferior treatments today throughout most LMICs.

Histologic confirmation

A biopsy should be performed to confirm the diagnosis of NSCLC when possible. PET/CT can assist in differentiating cancer from benign disease, with a negative predictive value up to 95% in one series evaluating mediastinal lymph nodes in patients with T1 category NSCLC (52). Models using PET/CT to predict the probability of malignancy of a solitary pulmonary nodule exist, but need validation for different geographical regions (53). The specificity of PET/CT drops substantially in areas of endemic lung disease from 77% (95% CI, 73–80%) to approximately 61% (95% CI, 49–72%) (54). In patients who cannot safely tolerate a biopsy, have a non-diagnostic biopsy, or refuse a biopsy, ASTRO Consensus Guidelines recommend that if a multidisciplinary consensus agrees the lesion is consistent with a malignant lung tumor, SABR without a biopsy can be considered (27).

Tumor characteristics: histology

Historically, there was concern using SABR for lung adenocarcinoma or adenocarcinoma *in situ* (formerly bronchoalveolar) because of a pattern of microscopic spread that may not be adequately covered (34). However, recent series suggest that LC with SABR for ES-NSCLC is better for adenocarcinoma compared to squamous cell carcinoma (SCC) (55,56). For instance, Hörner-Rieber *et al.* reported that among 126 consecutive patients with ES-NSCLC treated with SABR, LC for SCC was 81% compared to 96% and 100% LC for "high-risk" and "non-high-risk" adenocarcinoma with a median follow up of 22 months (P=0.026) (55). If SCC received an EQD2 ≥150 Gy at planning target volume (PTV) isocenter, then no significant difference in LC was seen between the histologic subtypes (P=0.355). In summary, there may be a role for risk-adapted radiation prescriptions based on histology, but for now,

the dose prescription is not routinely changed based on histology alone.

Tumor characteristics: location

The primary distinction in location for ES-NSCLC is whether the tumor is in the peripheral or central lung. Central tumors are generally defined as within a 2-cm radius of the main tracheobronchial tree. This definition originates from an early phase II study conducted at the University of Texas Southwestern Medical Center that treated ES-NSCLC with 60–66 Gy in 3 fractions without heterogeneity corrections (HCs), and found an 11-fold increased risk of severe (grade 3–5) toxicity for those with centrally-located tumors as defined above (P<0.04) (57). Since this early report published in 2006, more fractionated approaches have yielded better outcomes for central tumors. For instance, RTOG 0813 was a seamless phase I/II study that treated T1–T2 category central tumors with a 5-fraction schedule over 1.5–2 weeks with a dose of 10–12 Gy per fraction. A preliminary report demonstrates that 60 Gy in 5 fractions (n=33) resulted in a 2-year LC and OS of 87.7% and 72.7% and 7.2% rate of grade 3–5 toxicity (58). Other more fractionated approaches (48–60 Gy in 6–7.5 Gy per fraction) from Japan and the Netherlands have also yielded reasonable outcomes (59). OS seems to be equivalent between those with peripheral and central ES-NSCLC; however, the proximity of central tumors to additional OARs results in different toxicity profiles and requires different approaches in fractionation (59).

A concept of ultra-central tumors has emerged with variable definitions in the literature. It generally includes tumors where the PTV overlaps with the central bronchial tree, esophagus, or pulmonary artery (60). These represent a patient population at high risk for severe treatment-related toxicity, and are likely poor candidates for SABR at an institution without significant experience and expertise. There is evidence supporting even more fractionated approaches such as 60 Gy in 8–15 fractions, however, this is an area of active investigation (60,61). Patient with ultra-central tumors should only be treated in very experienced center or enrolled in prospective studies. Ultra-central tumors are currently being investigated by the Canadian Pulmonary Radiotherapy Investigators Group [stereotactic body radiotherapy for ultra-central NSCLC: a safety and efficacy trial (ClinicalTrials.gov Identifier: NCT03306680)].

One additional consideration is for tumors with broad abutment or invasion of the chest wall. While prospective evidence is lacking, generally these are not contraindications to SABR but 3-fraction regiments should be avoided and chest wall and/or rib dose constraints met if possible, to minimize risk of treatment-related morbidity (see "Planning: dose fractionation" below for further discussion).

Tumor characteristics: size

Most prospective data for SABR in ES-NSCLC are for tumors 5 cm in diameter or smaller (34). However, SABR for tumors greater than 5 cm has been shown to be both safe and efficacious (62,63). For instance, Woody *et al.* reported that 40 patients with a median tumor size of 5.6 cm (range, 5.1–10.0 cm) who received 50 Gy in 5 fractions, at 18 months follow-up, resulted in a LC rate of 91.2%, OS of 59.7%, and grade 3 toxicity or greater rate of only 7.5% (62). Instead of using a strict centimeter limit for tumor diameter, one should let the organs at risk (OARs) determine whether a tumor can be safely treated with SABR. If a tumor is too large to spare OARs, then a hypofractionated non-SABR approach may be more reasonable, such as 60 Gy in 15 fractions. This practical approach has been implemented in several institutions and is topic of a current randomized control trial (RCT) in Canada evaluating SABR *vs.* hypofractionated RT (NCT01968941) (41,64).

Tumor characteristics: number of lesions

Retrospective evidence supports equivalent local control and toxicity for both synchronous and metachronous primary lung lesions compared to solitary lesions treated with SABR (65,66). The 2017 ASTRO Evidence-Based Guidelines support the use of SABR in these settings with emphasis on multidisciplinary evaluation and decision-making. In the synchronous setting, biopsy to help distinguish lung primary *vs.* multifocal metastatic disease, and in the metachronous setting distinguishing between a new primary *vs.* recurrent disease, are essential treatment decision considerations. In both circumstances, complete staging of the patient, if curative treatment is intended, is required including PET/CT, brain MRI, and mediastinal lymph node evaluation before proceeding with surgical resection, SABR, or an alternative definitive RT approach (27).

Treatment simulation

Patients should undergo a planning CT scan in the treatment position with precise visualization of targets

for delineation and assessment of target motion. The size of targets, particularly small ones, can be overestimated with large CT scan slice thicknesses (67), and therefore a maximum of 2–3 mm slice thickness is recommended (25). CT scans should include the entire lungs, typically extending from the cricoid cartilage superiorly to the second lumbar vertebra inferiorly (25). If non-coplanar beams are utilized, then the CT scan should extend further (approximately 15 cm inferiorly and superiorly of the target) to assure accurate dosimetry (68), including at least a portion of the patient head (lower jaw) to help choose beam paths and avoid gantry collision. The tumor should be well visualized, and IV contrast may be helpful in contouring central tumors near the mediastinum or atelectasis.

Patient positioning

Time of delivery for each fraction of SABR can take significantly longer than CFRT, especially if using static beam delivery, and time of treatment has been associated with increased patient motion (69). Patient comfort, position stability, and reproducibility are essential to reduce inter- and intra-fractional motion, which is more likely to occur with these relatively longer treatments. Patient positioning ideally is supine with arms raised above head in a comfortable, stable, and reproducible manner. Various devices can be utilized to facilitate this, including alpha-cradle, body frame, wing board, and an integrated arm and knee support system. Interestingly, in a study by Shah *et al*., treatment delivery time, DLCO, and diaphragmatic excursion were independent predictors of intra-fractional tumor motion but not the type of immobilization device (70). This suggests that if patients are properly positioned with pre-treatment cone-beam CT (CBCT), any of the previously listed devices may be acceptable.

For patients who cannot tolerate arms-up position, safe and effective SABR may still be feasible with one or both arms down. Since beam entry angles become more limited when arms are down, volumetric modulated arc therapy (VMAT) is favored over static delivery techniques to utilize available angles optimally. VMAT has been shown to have only minor differences in dosimetry with plans generated with arms down compared to with arms up (71). Analgesics and anxiolytics can be considered to help with patient comfort as needed. They may not be frequently required if using VMAT because of a significant decrease in treatment delivery time compared to non-coplanar static intensity modulated beams, which requires couch rotations and generally more monitor units to deliver the same prescribed dose (72).

CT imaging techniques and assessment of tumor motion

All patients receiving lung SABR require assessment of patient-specific tumor motion (22). There are multiple techniques to assess tumor motion including fluoroscopy, "slow-CT", acquisition of multiple helical CTs at maximum inspiration and expiration, and 4-dimensional CT (4D-CT) (73). While a detailed review of each of these techniques is beyond the scope of this manuscript, the overlying message is that 4D-CT reduces the likelihood of systematic error and it is the gold standard for SABR planning. On latest guidelines, 4D-CT is recommended by NRG Oncology (74) and considered a minimum requirement to deliver lung SABR per ESTRO ACROP Consensus Guidelines (11).

However, in the context of LMICs, the access to such technology may be very limited and alternate methods can be considered since most of the original—and successful—lung SABR trials did not apply such 4D-CT technology (9,58,75). Also, ESTRO ACROP Consensus Guidelines specified that 4D-CT was considered mandatory by a borderline agreement between 50% of the participant institutions, while the others considered approaches such as slow CT or repeated 3D-CTs as sufficient as well.

One potential problem with 4D-CT is that irregular breathing during acquisition can lead to artifacts. Slow CTs can be combined with fast breath-hold inspiration and expiration 3D-CTs to estimate the ITV, but this may lead to either over or under-estimation of tumor motion, being dependent on patient compliance as well. Therefore, regardless of the available method of motion evaluation, detailed review of the images should be performed at the time of acquisition during CT simulation.

For patients with large (>10 mm) tumor motion, compensation strategies exist to decrease it, most notable of which is abdominal compression. Abdominal compression theoretically decreases tumor motion by decreasing diaphragmatic excursion. It can be particularly useful for lower lobe lesions, with Bouilhol *et al*. reporting a mean reduction in tumor motion amplitude of 3.5 mm for lower lobe tumors and only 0.8 mm for tumors in the middle and upper lobes (76). In a minority of patients with large tumor motion, it may be reasonable to treat using alternative strategies for motion compensation including respiratory gating, breath hold or active breathing control (ABC) (73).

In general, these techniques lead to longer treatment times, which is associated with increased intra-fractional movement. Also, they may compromise patient comfort or turn the process even more dependent on patient's compliance, thus introducing new sources of uncertainties and errors to the process. Finally, these strategies require additional hardware, software, and training to assure reproducibility. Overall, any motion compensation strategy needs to be evaluated and implemented with great care.

Delineation of targets and OARs

Gross tumor volume (GTV) and clinical target volume CTV)

When using 4D-CT, typically the GTV is contoured either on each phase or, more to improve efficiency, on a subset of the available phases (usually maximum expiration and inspiration phases), and then propagated (manually or automatically) onto the intermediate phases using the RT planning software. Soft tissue windowing alone can lead to underestimation of the actual tumor volume for parenchymal lesions, and therefore the lung window is typically favored (77). Soft tissue windowing may still be needed to help distinguish tumor from mediastinal structures or smaller vessels. EORTC Guidelines for high precision lung RT recommend W =1,600 and L =600 for parenchymal lesions and W =400 and L =20 for mediastinum, which approximates the pre-set lung and soft tissue windowing available in most RT planning software (25). Intra-venous contrast can be helpful in delineating the GTV when abutting adjacent structures, such as the mediastinum and chest wall. PET-CT can be fused to the simulation 4D-CT, and therefore incorporated into the GTV, but this technique requires caution. PET has overall poor spatial resolution and can have significant blurring of the tumor due to respiratory motion during image acquisition. There may also be inaccuracies in the PET and 4D-CT coregistration.

Some centers will expand the GTV to create a CTV, however, consistent with RTOG 0915, we do not recommend routine expansion of the GTV to create a CTV in lung SABR (12).

Internal target volume (ITV)

As described above, 4D-CT is considered to be the gold standard for delivery of lung SABR. Once the GTV has been delineated on all 4D-CT phases, and inclusion of the tumor has been verified, each GTV instance can be accumulated (summed) into a new structure, which is considered as the ITV. It should be noted that there are other techniques for creating an ITV. For instance, the ITV using a maximum intensity projection (MIP) image set has been shown to be comparable in both phase- and amplitude-sorted 4D-CT approaches, and is often faster to contour (78). However, MIP may underestimate the ITV for large tumors (>3.5 cm diameter), those located next to the diaphragm, at the border of the mediastinum, chest wall or any other structure with density higher than lung tissue and, finally, for tumors that have large motion amplitude (>1 cm). Therefore, defining ITV on MIP alone is not our favored approach (79).

Alternatively, when using slow CT combined with inspiration and expiration breath hold 3D-CTs, the ITV can be generated by the summation of the GTVs delineated on the three sets. It is important to note when contouring at the slow CT that the windowing has to be adjusted in order to exacerbate the blurring produced by tumor motion.

PTV

With the use of daily image guided radiotherapy (IGRT), a 5-mm ITV to PTV expansion is recommended when using a 4D-CT ITV technique, and a 5-mm radial and a 10-mm superior-inferior expansion is recommended if using breath hold techniques or gating (12). When defining the superior-inferior expansion, the margin has to be a multiple of the slice thickness (e.g., if slice thickness is 2 or 3 mm, the expansion has to be 6 mm, while it may become 4 mm if 5 mm is used).

There are several strategies on how to manage PTVs that overlap with OARs, which is particularly common with central and, by definition, always present with ultra-central tumors. The PTV margin is for setup uncertainty and motion, which in principle should not be compromised. Therefore, PTV and OAR overlap will exist, but the hot spots are strictly limited within the OARs to minimize the risk of toxicity (see "Treatment planning" below for details).

OARs

In addition to OARs usually included in thoracic CFRT (spinal cord, esophagus, heart, bilateral lungs, and brachial plexus for upper lobe lesions), SABR requires delineation

Table 1 Common SABR dose fractionation schedules for ES-NSCLC

Tumor location	Number of fractions					
	3 fractions (11)		4 fractions (11)		5 fractions (57)	
	Dose	BED (α/β =10)	Dose	BED (α/β =10)	Dose	BED (α/β =10)
Peripheral	54	151.2	–	–	–	–
If broad-based chest wall contact	45	112.5	48	105.6	–	–
Central	–	–	–	–	50	100.0
	–	–	–	–	60	132.0

All doses are prescribed to the periphery of the PTV with HCs. 3-fraction (fx) schedules for central tumors should never be used. BED (α/β =10) should generally be ≥100 and ≤180 balancing likelihood of local control *vs.* treatment-related toxicity. BED, biologic equivalent dose.

of additional OARs that may not typically be contoured for conventionally fractionated or palliative RT courses. These include the proximal trachea, proximal bronchial tree, great vessels, skin rind, ribs, and chest wall. Particularly for lower lung tumors or if non-coplanar beams are used, OARs such as the stomach, spleen, liver, and small bowel may need to be contoured, as severe toxicity can rarely be seen (80). Circumferential irradiation of the esophagus, trachea, and large bronchi should be avoided due to the increased risk of severe toxicity (12). The most precise and accurate image set to use to delineate OARs when using 4D-CT is on a mid-position or average intensity projection (AIP) image set because this reflects the mean position of the organs during the CT scan. A less robust but still acceptable alternative is to contour OARs on the end-expiratory phase of the 4D-CT. This may be reasonable because OARs spend the most time proportionately in this phase, and volumetric lung constraints are the most conservative when the lung volume is smallest as it is at the end expiratory phase (34). Naturally, if a breath-hold technique is utilized, then all target and OARs would be delineated on the breath hold CT. RTOG has an openly available onlineas that outlines many of the OARs for thoracic RT (81).

There is evidence of an institutional learning curve when it comes to OAR and target volume delineation, and therefore a standardized, institutional protocol for peer review is warranted before proceeding with treatment planning (82).

Treatment planning

Dosimetry

A grid size of 2 mm and type B dose calculation are mandatory for lung SABR (11). Less sophisticated dose calculation algorithms, such as pencil beam not only lead to less accurate and precise dosimetry but are also associated with worse local control (83). Use of HCs is required on more recent RTOG trials and is recommended (12,84). It is essential when adopting dose fractionation schedules for an institution to keep in mind the HC method and to avoid the use of fractionation schedules from prior studies that did not use HC.

A minimum of 7 non-opposing static beams of approximately equal weighting are recommended, generally a few of which are non-coplanar. VMAT should include a cumulative minimum of 340 degrees of arc rotation.

Dose and fractionation

There are many acceptable dose fractionation schemes (see *Table 1* for commonly used schedules) with evidence for better local control with a BED ≥100 Gy (α/β =10) (13). A 2013 review by Senthi *et al.* on SABR for centrally-located ES-NSCLC concluded that BED (α/β = 10) ≤210 Gy decreased the risk of treatment-related mortality by 75%; however, other retrospective reports suggest increased toxicity with only modest LC benefit at even lower BEDs (59,85). In general, we recommend a BED (α/β =10) between 100–180 Gy. For central tumors, 3-fraction dose schedules have been associated with high rates of severe toxicity and should be avoided (57,59). SABR to lesions with broad-based contact with the chest wall can lead to chest wall toxicity such as pain and/or rib fracture, and 3-fraction dose schedules should also be avoided in these patients (*Table 1*).

There are many ways to prescribe the dose, and it is important to remember that the underlying principle of SABR dosimetry is not dose homogeneity but rather rapid dose falloff. As such, we recommend prescribing to the

Table 2 Dose constraints for OARs in 3-, 4-, and 5-fraction SABR for ES-NSCLC

OARs	3 Fractions (22)		4 fractions (12)		5 fractions (22)	
	Volume (cc)	Dose (Gy)	Volume (cc)	Dose (Gy)	Volume (cc)	Dose (Gy)
Spinal cord	<1.2	12.3	<1.2	13.6	<1.2	14.5
	<0.35	18	<0.35	20.8	<0.35	23
	Max	21.9	Max	26	Max	30
Esophagus	<5	17.7	<5	18.8	<5	19.5
	Max	25.2	Max	30	Max	35
Brachial plexus	<3	20.4	<3	23.6	<3	27
	Max	24	Max	27.2	Max	30.5
Heart/pericardium	<15	24	<15	28	<15	32
	Max	30	Max	34	Max	38
Great vessels	<10	39	<10	43	<10	47
	Max	45	Max	49	Max	53
Trachea and large bronchus	<4	15	<4	15.6	<4	16.5
	Max	30	Max	34.8	Max	40
Bronchus-smaller airways	<0.5	18.9	–	–	<0.5	21
	Max	23.1	–	–	Max	33
Ribs	<30	30	–	–	–	–
	<1	28.8	<1	32	<1	35
	Max	36.9	Max	40	Max	43
Chest wall	–	–	70	<16 (25)	–	–
	–	–	2	<43 (25)	–	–
Skin	<10	30	<10	33.2	<10	36.5
	Max	33	Max	36	Max	39.5
Stomach	<10	16.5	<10	17.6	<10	18
	Max	22.2	Max	27.2	Max	32
Lung (bilateral)	<1,500	11.6	<1,500	11.6	<1,500	12.5
	<1,000	12.4	<1,000	12.4	<1,000	13.5

AAPM Report of TG101 (22), RTOG 0915 (12), EORTC (25) Recommendations for high-dose, high precision radiotherapy for lung cancer.

60–90% isodose line to the periphery of the PTV with 100% corresponding to the maximum dose as per RTOG 0915 protocol (12).

Plan assessment

Dose constraints for OARs (see *Table 2* for commonly used dose constraints) should be strictly followed to avoid unacceptable toxicity. One possible exception is when a tumor abutting or invading the chest wall or ribs makes coverage of the PTV and meeting these OAR dose constraints challenging. Exceeding these dose constraints may increase the risk of chest wall toxicity (rib fracture, pain, or others), and patients should be consented on this risk; however, the morbidity that comes from not adequately controlling the tumor is of more significant concern. The

principle of not allowing doses >105% of the prescribed dose in OARs, including chest wall and ribs, should be applied to all circumstances. For central tumors, the same challenge of adequately covering the PTV and meeting OAR dose constraints also occurs, and due to risk of severe toxicity including death, the OAR dose constraints should take precedence and more fractionated approaches may be needed to deliver RT safely.

In addition to PTV coverage and OAR dose constraints, there are parameters assessing conformality and low dose spillage that should be assessed to evaluate a SABR plan quality objectively. Conformity index (CI) (the volume receiving the prescription dose divided by PTV) should generally be <1.2. Low dose spillage can be assessed with the $D_{2\ cm}$ (the maximum dose 2 cm from the PTV) and the gradient index $R_{50\%}$ (volume encompassed by the 50% isodose line divided by the volume of the PTV). Of note, a CI <1.2 may not be possible with small tumors (approximately <2.5 cm in an axial plane or smaller) and tables exist with acceptable $D_{2\ cm}$ and $R_{50\%}$ based on tumor size (12).

Treatment plans should be presented for peer review before treatment initiation. Rieber *et al.* found that institutional experience was the main prognostic factor for LC in lungs lesions treated with SABR (42). Alternative ideas for external review to mitigate the lack of institutional experience inherent with a new SABR program may be partnerships with experienced institutions, or the use of remote contour and plan review.

Treatment delivery

SABR is most often delivered utilizing a specialized stereotactic RT delivery system or a traditional linear accelerator with online volumetric imaging (such as CBCT). Traditional linear accelerators may sometimes be adapted with ancillary features for more accurate RT delivery such as micro-multi-leaf collimators (23). The most practical delivery unit for initiation of a lung SABR program is likely the traditional linear accelerator with online volumetric imaging, as this allows treatment of patients with both stereotactic and CFRT. The most common SABR treatment schedules are either daily or every other day with overall comparable outcomes. As Dahele *et al.* describe, there are less often utilized weekly treatment schedules with reasonable results, and in the setting of machine downtime or missed treatments, these less frequent delivery schedules can be considered (34,86).

Institutions using SABR should have written protocols in place including steps to assure safe treatment delivery. A verification simulation where patient setup using image-guidance and gantry and couch positions without actual treatment delivery is recommended to assure treatment can be completed in its entirety without complication. Online volumetric image-guidance is required before every treatment, and CBCT is strongly encouraged. Written action levels should be selected for patient re-positioning. It is recommended that the radiation oncologist be present to approve patient alignment after CBCT is completed and before treatment is initiated. The American Association of Physicists in Medicine (AAPM) Task-Group 101 (TG-101) recommends that a physicist be present throughout the first fraction of SABR and should either be present at the console or be readily available for each subsequent fraction (22). Especially early in an institution's experience with SABR, a repeat CBCT after each fraction to assess changes in patient positioning during treatment may be helpful to assure reliable patient immobilization. A suggested flowchart for SABR for ES-NSCLC is presented in *Figure 1*.

Another desirable control for lung SABR procedures is to monitor the patient respiration throughout treatment using skin surface monitors (e.g., cameras tracking reflective markers on the torso, optical surface monitors, or strain gages), breathing monitors (e.g., spirometers or thermistors), or tracking implanted markers (e.g., fiducials or transponders). Such monitors can be used not only for gating but also to inform therapists of breathing irregularities, allowing them to intervene in the treatment if necessary (74).

Quality assurance (QA)

Initiation and maintenance of a robust QA program are essential for safe delivery of SABR. There are various safety protocols Available online multiple governing bodies that can provide detailed guidance on the technical aspects of QA (22-24,87-89). In a practical sense, SABR requires more stringent QA than CFRT (90) (see *Table 3* for modified ESTRO-ACROP Mandatory Components). Beyond the technical aspects of QA, an integrated team with excellent physician leadership and a just culture with all stakeholders active in patient safety is needed (91). Peer review of contours and plans should be performed, and this ideally is completed in a multidisciplinary setting with radiation oncologists, physicists, dosimetrists, and therapists present.

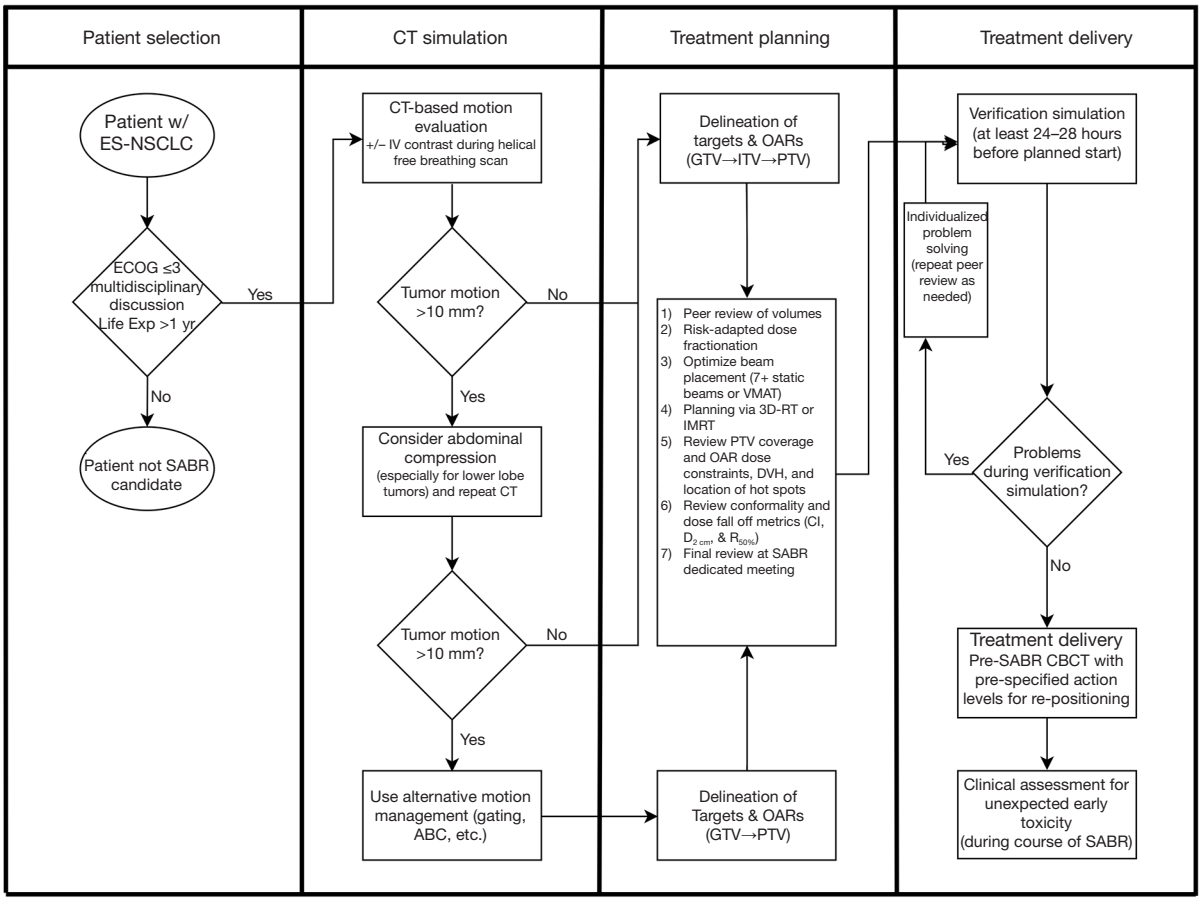

Figure 1 SABR for ES-NSCLC flowchart. ES-NSCLC, early-stage non-small cell lung cancer; SABR, stereotactic ablative radiotherapy.

Follow up

Standardized clinical and radiographic follow up is recommended for all patients. A comprehensive assessment of toxicity and systematic recording, including severity, is essential for institutional feedback on a SABR program. Late symptoms such as rib fracture, chest wall pain, and partial lung collapse, which are exceedingly uncommon after conventionally fractionated RT, can occur after SABR. Structured follow-up for assessment of clinical outcomes is needed, and publications of results from SABR programs in LMICs are encouraged. The National Comprehensive Cancer Network (NCCN) Guidelines from the United States recommend a history & physical and chest CT with (or without) contrast every 3–6 months for the first 3 years after SABR, then every 6 months for 2 additional years, before transitioning to low-dose non-contrast chest CT annually (45).

SABR-induced lung changes are significantly different from lung changes after conventionally fractionated RT, and distinguishing focal lung fibrosis secondary to SABR from tumor recurrence can be challenging. High-risk CT features that have been associated with recurrence, such as sequential enlarging opacity, loss of air bronchogram, loss of linear margins, and, particularly if only co-planar beams were utilized, cranio-caudal growth can all be seen post-SABR even when a local recurrence is not present (92). Local FDG-avidity on PET may rise temporarily after SABR as a consequence of the treatment itself, but ultimately can be helpful in distinguishing fibrosis from local recurrence with one review article suggesting high-risk CT features with an SUV ≥5 as being highly suggestive of recurrence (93). While local recurrences are rare after SABR, early assessment is essential as potentially curative salvage therapy, such as resection, may still be possible. With that said, over-use of invasive procedures has been reported after SABR for what ultimately are benign

Table 3 Adapted ESTRO-ACROP Guidelines for mandatory (minimum) components to deliver SABR for ES-NSCLC (11), and Right column reflects our opinion on additional recommendations

SBRT workflow	Minimum requirements	Commentary
Equipment	• C-arm linear accelerator (linac) with volumetric in-room image guidance; • CT based tumor motion evaluation strategy	Most practical approach for a new SABR program is to treat on conventional c-arm linac. 4D-CT and MLC <10 mm for best practice
Staff, teaching, and credentialing	• Written departmental protocols; • Multi-disciplinary project team for SBRT implementation and application; • Structured follow-up for clinical outcome assessment	Consider external partnerships or remote chart rounds with experienced centers
Patient selection	• Discussion in interdisciplinary tumor board; • Maximum ECOG Performance Status 3; • Minimum life expectancy of 1 year	Biopsy strongly preferred (please see "Patients: histologic confirmation" section)
Treatment planning	• 3D conformal treatment planning; • Type B algorithms for HCs; • ITV based motion management strategy	IMRT preferred over forward planning; dynamic IMRT (VMAT) is preferred over static beam arrangements due mainly to faster treatment times
Dose prescription	• Risk-adapted fractionation schemes for peripheral and central tumors, and for tumors with broad chest wall contact	Institutional protocols should standardize risk-adapted fractionations
Image guidance	• Daily pre-treatment volumetric image-guidance	Daily CBCT is the preferred image-guidance
Follow-up	• Follow-up according to published guidelines; • FDG-PET imaging in case of suspected local recurrence	Systematic follow up with recording of outcomes and toxicities including severity. Publication of outcomes from LMICs encouraged
Quality assurance	• Intensified QA (mechanical accuracy of 1.25 mm and a dosimetric accuracy of 3% in lung phantom inside the treatment field); • Small field dosimetry detectors for commissioning • End-to-end testing in a lung phantom • QA of in-room image-guidance systems and of the 4D-CT scanner • Weekly checks of the alignment of the IGRT system with the MV treatment beam • Measurement based patient specific QA for IMRT and VMAT plans	End-to-end testing in 4D lung phantom is considered best practice

ES-NSCLC, early-stage non-small cell lung cancer; CT, computed tomography; 4D-CT, 4-dimensional CT; SABR, stereotactic ablative radiotherapy; MLC, multileaf collimator; VMAT, volumetric modulated arc therapy; CBCT, cone-beam CT; HC, heterogeneity correction; FDG, fluorodeoxyglucose; PET, positron emission tomography; QA, quality assurance; IGRT, image guided radiotherapy; IMRT, intensity modulated radiotherapy.

changes from RT (53). Information on dose distribution can be helpful, emphasizing the importance of active participation of the treating radiation oncologist in SABR patient follow up. The complexity of radiographic follow up requires active radiation oncologist participation and multidisciplinary management of local and regional disease can still yield clinical outcomes similar to those patients without recurrence (94).

Cost

While we have referred to HICs and LMICs collectively, there is a considerable diversity among the nations that represent these groups and a detailed discussion on the

cost-effectiveness of and reimbursement models for SABR in each nation is beyond the scope of this report. Overall, funding is necessary, and unless a compensating method of reimbursement is recognized and implemented, the desired level of SABR provision will be impaired (95). There is data suggesting SABR for ES-NSCLC is cost-effective from a payer perspective in HICs, such as Canada (96) and the United States (97), respectively. What is logical and well-discussed by Lievens *et al.* is that the over- or under-financing of a specific treatment such as SABR, may overly limit or promote its use (98). However, there is little data on the topic of SABR compensation or cost-effectiveness from the payer or provider perspective in LMICs. Many countries may compensate based on a number of fractions without adequately taking into account the increased resources needed to deliver SABR. This could bring concerns about decreased reimbursement if SABR is implemented. Development of institutional expertise is dependent on human resource continuity, and lack of adequate funding for fair compensation may contribute to brain drain, thus jeopardizing sustainability (35). Education on the many advantages of SABR and advocacy for fair compensation and inclusion in universal healthcare coverage is needed on national levels in many LMICs.

Conclusions

SABR is the standard of care for inoperable patients with ES-NSCLC. It has been widely implemented throughout HICs over the past 15 years and has been shown to improve survival in this population both at institutional and national levels. In LMICs where the burden of lung cancer is greatest, SABR is not readily available. However, with adequate infrastructure, financial investment in technology and human resources, and systematic, written protocol-based implementation, SABR can be delivered effectively and safely in LMICs.

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Footnote

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