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Review

Management of early-stage non-small cell lung cancer using stereotactic ablative radiotherapy: Controversies, insights, and changing horizons ☆

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ABSTRACT

The use of stereotactic ablative radiotherapy (SABR) for early-stage non-small cell lung cancer is growing rapidly, particularly since it has become the recommended therapy for unfit patients in current European and North American guidelines. As three randomized trials comparing surgery and SABR closed prematurely because of poor accrual, clinicians are faced with a dilemma in individual patient decision-making. Radiation oncologists, in particular, should be aware of the data from comparative effectiveness studies that suggest similar survival outcomes irrespective of local treatment modality. The necessity of obtaining a pathological diagnosis, particularly in frail patients prior to treatment remains a challenge, and this topic was addressed in recent European recommendations. Awareness of the high incidence of a second primary lung cancer in survivors, as well as other competing causes of mortality, is needed. The challenges in distinguishing focal scarring from recurrence after SABR also need to be appreciated by multidisciplinary tumor boards. With a shift in focus toward patient-centered decision-making, clinicians will need to be aware of these new developments and communicate effectively with patients, to ensure that treatment decisions are reflective of patient preferences. Priorities for additional research in the area are proposed.

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Lung cancer is a leading cause of cancer-related death worldwide [1,2], and incident cases are expected to rise in the near future owing to an aging population [3]. Although the majority of patients present with locally advanced or metastatic disease, the incidence of early-stage non-small cell lung cancer (ES-NSCLC) is expected to increase, due to a wider use of thoracic CT scans in general medical practice [4,5], along with the implementation of formal CT screening, which has been shown to lead to earlier detection of early-stage cancers [6,7]. Although surgery is currently considered the standard of care for ES-NSCLC, elderly patients (i.e., $\geqslant$65 years) commonly present with multiple comorbidities [8]. The willingness to operate on such patients is variable [9], largely due to higher risks of morbidity and mortality [10,11]. Elderly patients with ES-NSCLC pose a particular epidemiologic and public health challenge as they are both less likely to receive guideline recommended treatments [12], and less likely to participate in, or to be eligible for, clinical trials [13].

Historically, elderly patients were often not treated (Fig. 1). There are several reasons for this, including the fact that conventionally fractionated radiotherapy delivered using techniques available prior to 2000, was considered to offer marginal gains with the inconvenience of daily treatment over several weeks [14]. Conversely, stereotactic ablative radiotherapy (SABR), which is defined as the accurate and precise delivery of high doses of radiation over a few treatment fractions, is less cumbersome for patients and is associated with excellent local control [15]. Radiation doses that are biologically equivalent to 100 Gy_{10} or more are required in lung SABR to achieve high local control rates [16,17]. These doses are in excess of what is practical using conventionally fractionated treatment schemes with standard techniques. Currently, the optimal SABR dose is unknown, although a meta-analysis suggests that highest (>146 Gy_{10}) BED fractionations may have lower OS than medium–high (106–146 Gy_{10}) fractionations [18]. In population studies, the increasing use of SABR for ES-NSCLC is associated with an overall survival benefit when compared to no treatment or conventional radiotherapy [11,19]. The growing use of SABR for thoracic malignancies worldwide is

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reflected by patterns of care studies from Europe [20,21], North America [22–24], and Asia [25].

In this review, we will discuss evolving trends in patient selection/outcomes, challenges faced in diagnostic management, the importance of quality assurance, and the challenges facing survivors following this treatment modality.

Optimizing patient selection and outcomes

Comparative effectiveness research (CER)

CER refers to the generation of evidence that compares the benefits and harms of interventions designed to address the prevention, diagnosis, treatment or follow-up of a clinical condition [26]. CER assists all healthcare stakeholders in healthcare in making informed decisions to improve outcomes at the individual and population levels. The contrasting merits between randomized control trials (RCTs), the gold standard in CER, and observational studies have recently been highlighted as they pertain to specific challenges in oncology such as rising costs and rapidly evolving technology [27,28]. The challenges of performing RCTs, even when there is a good clinical question, have been clearly illustrated in lung SABR. Three phase III RCTs (ROSEL, STARS, RTOG 1021) comparing SABR with either lobectomy or sublobar resection were launched between 2008 and 2011, but all 3 failed to accrue [29]. Nonetheless, development of their protocols provided the radiation oncology community with valuable standards in quality-assurance and credentialing for the broader implementation of lung SABR [30].

In the absence of RCT data, other forms of CER are crucial in guiding decision making [31]. Table 1 summarizes relevant CER studies using propensity-score matching, match-pair analysis, Markov modeling, cost-effectiveness and meta-analytic methodologies. In general, the main conclusion from the CER studies is that there is clinical equipoise when comparing SABR and surgery, especially in the face of competing risks of death associated with advanced age and increased comorbidities. It is important to note that studies employing matching technique designs are, by definition, unable to entirely eliminate measured confounders, and potential imbalances can exist due to unmeasured factors [32].

Despite the challenges faced by RCTs comparing SABR and other modalities for ES-NSCLC, randomized comparisons have been possible in some cases. For example, the stereotactic precision and conventional radiotherapy evaluation (SPACE) trial randomized 102 ES-NSCLC patients to either SABR (66 Gy in 3 fractions at the isocenter and 45 Gy at the periphery, over 1 week) versus conventional radiotherapy (relatively homogeneous 70 Gy in 35 fractions over 7 weeks) [33]. The use of larger margins around the target (20 mm versus 5–10 mm) was required in the conventional arm. The results have been presented only in abstract form with limited follow-up, however, local control did not differ between the two modalities. The conventional treatment was associated with a higher risk of grade 1–2 toxicity (increased rates of esophagitis and pneumonitis). SPACE suggests that although high rates of local control may be achieved with long courses of conventional RT, the therapeutic ratio is better with SABR when compared with conventional radiotherapy using large margins. Accrual to a similarly designed RCT (CHISEL, Clinicaltrials.gov, NCT01014130) is ongoing; however, unlike SPACE, CHISEL employs smaller margins and cone beam CT setup in the conventional RT arm.

In view of the rising healthcare costs, economic evaluations of SABR in lung cancer deserve mention [34–36]. Cost-effectiveness analyses (CEA) have consistently demonstrated that while lobectomy appears to be preferred over SABR for operable ES-NSCLC, SABR is cost-effective when compared to sublobar resection [37–39]. For medically inoperable patients, SABR dominates (less costly, improved survival) conventional radiotherapy, a finding that is generalizable to different healthcare payer models [39–42].

Developments in surgery

In recent years, much attention has been paid toward reducing the toxicity of surgery in ES-NSCLC, and recent prospective RCTs such as the ACOSOG Z0030 [43] and Z0032 [44] report low mortality rates. However, the vast majority of patients are treated outside of trials, where survival is likely to be poorer, and results from specialized surgical databases may not be generalizable to broad clinical practice [15,45]. For example, a recent SEER-Medicare analysis revealed a national rate of in-hospital postoperative complications exceeding 50% among patients older than 65 years, with a 30-day mortality of 4.2% [46]. Both the 30-day and 90-day mortality were lower at teaching hospitals, with 90-day mortality being 5.4% (teaching) versus 7.8% (non-teaching) ($p = 0.001$).

Lobectomy is considered the current treatment of choice in patients with adequate lung function [47]. More limited resections, such as a segmentectomy (i.e., macroscopic removal of the tumor with the division of vessels and bronchi within an anatomical segment) and wedge resection, may be associated with increased local recurrences for tumors measuring more than 2 cm. The optimal

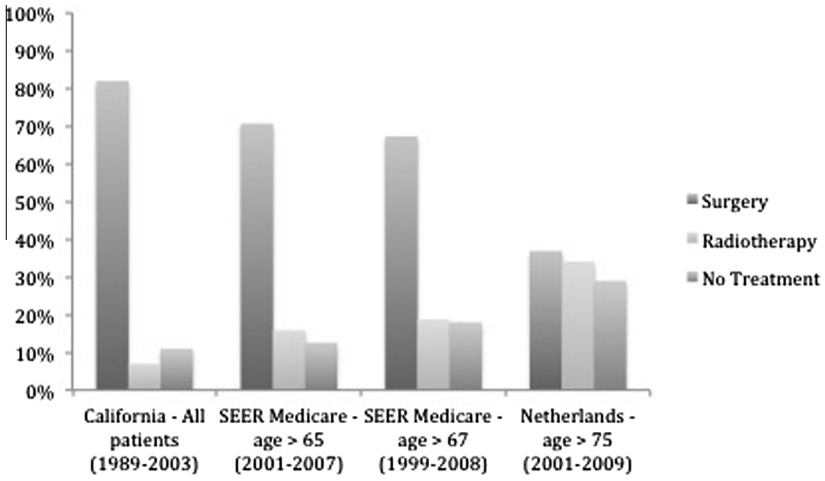

Fig. 1. Depiction of population trends of decreased surgical utilization, and increased proportion of untreated patients, with increasing age. The median overall survival of untreated patients in these studies ranged from 6.6 to approximately 12 months [11,123–125].

Table 1
CER studies comparing surgery versus SABR in stage I NSCLC.

Study	Study design	Number of patients	Surgical procedure	Overall survival		Conclusions/comments
				Surgery	SABR	
Crabtree [126]	Propensity-score matching	Unmatched: surgery = 458, SABR = 151 matched: 112/ group	(Bi) lobectomy, 78% sublobar, 19% pneumonectomy, 4%	78%, 3 yrs 68%, 3 yrs	47%, 3 yrs 52%, 3 yrs	Although surgical resection seems to result in better OS versus SABR, matching these patients remains challenging
Matsuo [127]	Propensity-score matching	Unmatched: surgery = 65, SABR = 115 matched: 53/ group	Sublobar resection	56%, 5 yrs	40%, 5 yrs	SABR is an alternative to sublobar resection in high-risk patients who cannot tolerate lobectomy due to comorbidities
Shirvani [128]	SEER population, propensity-score matching	Unmatched: surgery = 8711, SABR = 382 matched: 251/ group	Lobectomy, 83% sublobar, 17%	Lobectomy vs. SABR, HR 1.01 (SA: 1.16–1.28)		Lobectomy is preferred for older adults fit for surgery. SABR is promising as it offers a lower risk of periprocedural death
Solda [83]	Systematic review	Weighted average of surgical patients from IASLC database vs. reviewed SABR studies		68%, 2 yrs	70%, 2 yrs	Results favor direct comparison of surgery and SABR for operable localized NSCLC
Varlotto [125]	Match-pair and propensity scoring	Unmatched: surgery = 180, SABR = 137 matched: 89/ group	Lobectomy, 73% wedge, 27%	69%, 3 yrs 86%, 3 yrs	41%, 3 yrs 42%, 3 yrs	On manual matching, wedge and lobectomy had significantly improved OS over SABR, differences disappeared when adjusting for propensity score
Verstegen [129]	Propensity-score matching	Unmatched: 86 surgery, 527 SABR matched: 64/ group	VATS lobectomy	77%, 3 yrs	80%, 3 yrs	No significant difference in OS supports the need to compare the two treatments in a randomized control trial
Grills [130]	Retrospective	Surgery = 69 SABR = 55	Wedge resection	87%, 30 m	72%, 30 m	OS was improved after surgery. SABR patients tended to be older with more comorbidities
Louie [94]	Markov model	Lobectomy and SABR outcomes modeled from various sources		At 5 yrs, surgery 2–3% benefit in OS		Large patient numbers would be required to detect small differences in OS
Shah [37]	Markov model	Lobectomy, wedge resection and SABR outcomes modeled from various sources		Not reported, model validated based on recurrence patterns		SABR is the dominant strategy compared to wedge resection. In patients eligible for lobectomy, surgery is most cost-effective
Zheng [131]	Meta-analysis	Forty SABR studies (n = 4850) and 23 surgery studies (n = 7071)		~80%, 3 yrs	57%, 3 yrs	When adjusting for potential operability in SABR patients, no difference found in OS

yrs = year, m = months, OS = overall survival, SA = sensitivity analyses.

surgical techniques for lesions measuring 2 cm or smaller, are the subject of ongoing RCTs. The use of video-assisted thoracoscopic surgery (VATS) is increasing, but the available RCTs have not been sufficiently powered to detect important differences between the thoracoscopic and open techniques in either overall or disease-free survival [47]. This is despite the fact that fewer hilar and mediastinal lymph nodes are generally sampled during a VATS procedure, than with open thoracotomy [48,49].

Proponents of surgery, even for patients with ES-NSCLC who are at high risk for surgery, have strongly argued that the improved diagnosis of occult nodal disease, and subsequent administration of chemotherapy to such patients, will lead to survival benefits [50]. However, even in patients who fulfilled the criteria of being at high risk and who were treated in the ACOSOG Z0032 trial, 31% underwent no nodal evaluation [51]. In tumors detected by a CT-screening program, all of which were treated by general thoracic surgeons at specialized centers, a mediastinal nodal resection was performed in only 55% of patients who underwent a sublobar resection [52]. The fact that differences in nodal harvesting do not influence survival in this study, as well as population studies [49], suggests that the purported benefits of a surgical procedure should be scrutinized carefully, particularly in view of the competing non-cancer causes of mortality in those who underwent a sublobar resection in the I-ELCAP study. Similarly, more than half of all high-risk patients with ES-NSCLC who were treated in ACOSOG Z0032 had intercurrent deaths due to non-cancer causes [44].

The majority of RCTs, including the largest (ACOSOG Z0030) that addressed this issue, have failed to demonstrate a survival benefit of a mediastinal lymph node dissection (MLND) as opposed to nodal sampling [43]. Fig. 2 provides a schematic on the relative merits of the number needed to treat (NNT) and number needed to harm (NNH) when considering the potential advantage of surgery to provide information that can be used to guide decision-making on adjuvant systemic therapy. This calculation exercise is based on the assumption that approximately 15% of clinical ES-NSCLC patients are upstaged with nodal disease at the time of surgery, despite negative pre-operative mediastinal staging [48,49], an estimate that may need to be reconsidered when more data are forthcoming from the use of minimally invasive modalities to stage the mediastinum such as endobronchial and endoscopic ultrasound needle aspirations (EBUS and EUS, respectively) in SABR patients [53]. As the ultimate survival impact of improved staging for NSCLC patients eligible for SABR is unknown, clinical trials evaluating the use of pre-treatment EBUS and EUS are underway (Clinicaltrials.gov, NCT01786590).

Who benefits from adjuvant systemic therapy?

The rates and patterns of failure following SABR for ES-NSCLC have been reported to be broadly similar to those after surgery, with the predominant pattern being distant metastases in approximately 20% of cases [54,55]. To help guide the identification of

patients who may benefit from systemic therapy after SABR, models have been developed to predict for systemic disease, with a higher pretreatment FDG-PET maximum standardized uptake value (SUV_{max}) and larger tumor size (T2) often cited [56–58]. In one such model, image-based biomarkers were studied in 117 patients with ES-NSCLC, and it was postulated that tumor size, contact with the mediastinal pleura, and SUV_{max} could be used to construct a prognostic index for patients at highest risk for developing metastases [59]. For patients with distant failure, biomarker targets such as epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) rearrangement have paved the way for tyrosine kinase inhibitors (e.g., gefitinib/erlotinib, and crizotinib, respectively) as first line treatments in the metastatic setting [60]. Currently, the role of targeted agents following SABR for ES-NSCLC is unclear. It has been reported that caution should be employed when SABR and VEGF-modulating drugs are used in the same patient, even when separated by 2–3 months or more, since this has been reported to be associated with an increase in esophageal fistulae [61] and grade 3–5 bowel ulceration or perforation (in the abdominal SABR setting) [62]. Interstitial lung disease and fatal pneumonitis have been reported when an epidermal growth factor receptor inhibitor was used with lung SABR, despite acceptable dosimetry [63]. More safety data are required in order to establish safety of combined use of targeted systemic agents and SABR.

Central tumors

In centrally located ES-NSCLC, more extensive surgical resections such as pneumonectomy or broncho-angioplastic procedures may be required in order to achieve a radical excision. Irrespective of the type of surgery performed, rates of perioperative mortality and surgical complications are approximately 5% and 25%, respectively [64]. SABR has been used as an alternative in this context, with mixed results in early years. The Radiation Therapy Oncology Group (RTOG) 0236 trial excluded tumor within a 2 cm radius of the trachea and bronchial tree (the so-called "no fly zone"), as results from a phase 2 trial demonstrated that such patients had a 2-year freedom from grade 3 to 5 toxicity rate of only 54% [65,66]. Since then, non-randomized data have shown that other, more protracted hypofractionated schemes are well tolerated, as such protracted schedules reduce the risk of late toxicity by using a lower dose per fraction. A recent systematic review of treatment of central tumors, based on mostly retrospective data, found an overall treatment-related mortality rate of 2.7%, with grade $\geqslant 3$ toxicity occurring in less than 9% of cases [64]. Life-threatening toxicities included severe bronchial stenosis, hemoptysis, and fistulae [67]. However, with a BED less that 210 Gy_3, which corresponds to a dose of approximately 60 Gy in 8 fractions, the treatment mortality rate was 1%. The review concluded that post SABR survival in ES-NSCLC is not affected by tumor location (provided that adequate doses can be delivered to the target), that prescription doses in excess of 100 Gy_{10} are required to achieve local control rates greater than 85%, and that treatment related mortality can be reduced by 75% when biological normal tissue doses are 210 Gy_3 or less.

In patients for whom dose constraints for standard SABR fractionation schedules are unable to be met, such as those with large tumor size, or significant overlap of the PTV with the esophagus or large airways, alternative hypofractionated schemes have been described. For example, one report described use of a strategy of 70 Gy in 10 fractions when constraints for a 50 Gy in 4 fraction central tumor protocol were exceeded [68]. Ultimately, these and other studies may help guide clinical management as results from the RTOG 0813 phase 1/2 dose escalation study for SABR in central lesions are awaited.

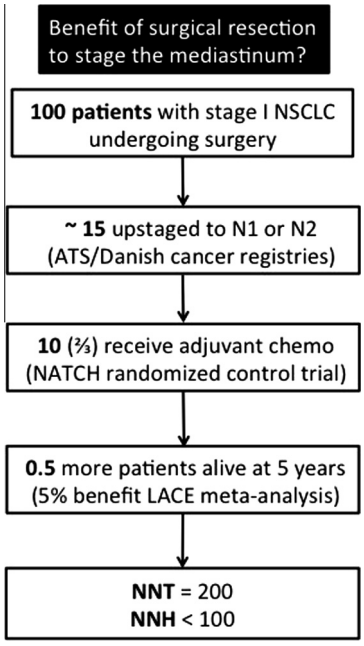

Fig. 2. Schematic demonstrating the number needed to treat (NNT) when considering surgery to guide adjuvant chemotherapy decision-making for stage I NSCLC at 5 years [48,49,132,133]. Conversely, number needed to harm (NNH) when considering a post-operative mortality rate of at least 1%, is 100 or less [10].

Diagnostic management

Need for pre-treatment pathology prior to SABR

A pathological confirmation of malignancy is generally preferred prior to the initiation of any curative-intent therapy for ES-NSCLC [47]. In practice, the reported rates of histological confirmation of malignancy prior to SABR for ES-NSCLC are variable, ranging from 35% to 100% (Table 2). A population study found that patient age and co-morbidity predicted for the likelihood of not having a pathological diagnosis in lung cancer [69]. Many candidates for SABR have co-morbidities including compromised pulmonary and cardiac function, that may heighten the risks associated with transthoracic biopsy, or repeated biopsy if the initial attempt is inconclusive [70,71].

Models to predict the probability of malignancy using clinical, CT [72], and FDG-PET features [73] of a solitary pulmonary nodule (SPN) have been developed. The term SPN has been defined as a single, well-circumscribed, radiographic opacity that measures up to 3 cm in diameter, and is surrounded completely by aerated lung [72]. Caution should be employed, however, if such models have not been validated for specific geographic regions of practice [74]. Use of FDG-PET may perform poorly when used for a clinical diagnosis of stage I NSCLC, in areas where granulomatous disease and other infectious etiologies are endemic [73]. In an American population-based analysis, the rate of benign diagnosis after surgery for suspected lung cancer ranged from 1.3% to 25.0% [74]. Increasing rates in the pathologic diagnosis of benign disease is correlated with the growing use of video-assisted thoracoscopic surgery (VATS) [47], and is not without toxicity. In a review of surgical patients in the Dutch–Belgian randomized lung cancer screening trial (NELSON), the rate of major and minor post-operative complications in cases that ultimately proved to be benign were 17% and 21%, respectively [75]. These results demonstrate a need for regular audit of surgery and pathology results both at the institutional and regional/national geographic levels.

A likelihood of malignancy threshold of 85% has been suggested prior to treatment of a SPN without pathologic confirmation of malignancy (Table 3) [76]. A similar estimate was derived using a decision analytic model, where strategies of surveillance, performing SABR in a PET-avid SPN in the absence of pathology, and performing a biopsy in a PET-avid SPN prior to SABR, were evaluated using existing data on performance of diagnostic tests, toxicity/complication rates, and recurrence/survival outcomes [77]. This study determined that a PET-directed SABR strategy (without prior biopsy) could be warranted above a point estimate of malignancy of 85%, a finding that was highly sensitive to the diagnostic performance of biopsy, as well as the ability of subsequent CT follow-up surveillance to appropriately detect false negative SPNs to allow for treatment thereafter. One caveat to the use of PET-directed management strategies is that there is a need for standardization of FDG-PET methodology, as variability in imaging protocols will result in heterogeneity of reported SUVs [78].

Quality assurance and generalizability

Technologic advances and rigorous quality assurance programs have improved the ability of radiation oncologists to confidently deliver large hypofractionated doses in SABR with accuracy and precision [79]. Incremental advances include: the use of 4D-CT (time-based correlation of respiratory motion with CT images) to account for tumor motion during the breathing cycle, verification of tumor position prior to treatment with image guidance (e.g., cone beam CTs or fiducial-based strategies), and more accurate dosimetry when employing algorithms that account for different tissue inhomogeneities.

Proper radiation planning, prescription and delivery are key to achieving optimal outcomes. The use of less accurate radiotherapy planning algorithms was found to be associated with more local failures [80], a finding recapitulated in the preliminary results of two prospective multicentre studies in potentially operable patients from Japan that reported local failure rates of 14% at 3 years [81]. Furthermore, optimal prescriptions require coverage of the entire tumor volume with a high dose, and failure to achieve high enough doses at the periphery of the tumor is associated with higher recurrence risks [47,82].

Several commercial platforms are available to deliver SABR. While differences in treatment capabilities exist in the various lung SABR delivery platforms, a systematic review found no differences in overall survival for ES-NSCLC when using different technologies [83]. Published guidelines in both North America [84–86] and the European Union [47,87] have supported institutional credentialing procedures, standardization of normal tissue tolerances, and increased discourse on the use of SABR in a multidisciplinary setting.

Survivorship

The utility of surveillance following curative lung cancer resection has previously been questioned, as historically, only 1–4% of recurrences undergo salvage resection [88]. Survivorship in lung cancer, however, extends beyond the detection of salvageable recurrences. Investigators from Memorial Sloan Kettering Cancer Center (MSKCC) have proposed a thoracic survivorship model that considers risk of second primary lung cancer (SPLC), quality of life (QoL), preventative care (such as routine screening for other malignancies), and the management of comorbid conditions that require active management [89]. As the MKSCC model was mostly comprised of surgical patients, we highlight survivorship challenges following lung SABR here.

QoL

A systematic review of QoL following surgery for lung cancer found that dyspnea, fatigue and decreases in physical functioning can persist for at least 2 years following treatment [90]. Changes in pulmonary function (PF) after SABR appear to be correlated with pretreatment PF: those with the worst pretreatment PF tend to improve, while those with the best pretreatment PF have modest losses [91,92]. The few reports describing QoL following SABR for lung cancer have limited follow-up and are largely comprised of patients who are less fit at baseline. In general, these reports describe minimal clinically meaningful changes [93]. Although hypothesis generating, modeling studies have postulated that potential survival benefits of lobectomy, when compared to SABR for medically operable ES-NSCLC patients, may be mitigated by QoL considerations [94].

Second primary lung cancer (SPLC)

Survivors of lung cancer are at risk of developing a second primary lung cancer (SPLC) at a rate of approximately 3% per year [95], a risk that is highest in the first year and persists even after a decade [96]. In both the MKSCC model and in a RCT comparing chest X-ray and minimal dose CT surveillance, a high proportion of SPLC cases were detected in asymptomatic individuals [97]. SPLCs are also prevalent in survivors of other smoking-related primary malignancies such as head and neck and esophageal cancers; in the former, they account for over 50% of non-head and neck cancer-related deaths [98]. On the basis of current evidence, SABR also appears to be a valid first-line alternative to surgery in medically

Table 2
Studies demonstrating the variable rates of pathologic confirmation worldwide prior to SABR in ES-NSCLC.

Reference	Study type	Number of patients	Region	% Biopsy	Overall survival
Haasbeek [11]	Population registry	1570	Netherlands	72	50% (2 yrs)
Ricardi [21]	Retrospective	196	Italy	100	68% (3 yrs)
Guckenberger [20]	Retrospective	591	Central Europe	85	47% (3 yrs)
Grills [134]	Retrospective	505	United States	87–95	48% (3 yrs)
			Canada	72	
			Netherlands	41	
			Germany	70	
Onishi [135]	Retrospective	2278	Japan	73	91% (2 yrs)
Senthi [55]	Retrospective	676	Amsterdam	35	41 mo (md)
Baumann [136]	Prospective	57	Sweden	67	60% (3 yrs)
			Denmark		
			Norway		
Timmerman [65]	Prospective	55	North America	100	56% (3 yrs)

yrs = years, mo = months, md = median.

Table 3
Studies addressing likelihood of malignancy threshold recommendations to inform the appropriate use of SABR for ES-NSCLC in the absence of pathologic confirmation.

Reference	Study type	Recommended threshold (%)	Comments
American College of Chest Physicians [72]	Consensus-based guideline	65	No distinction between surgery and non-surgical treatment modalities
International Association for the Study of Lung Cancer [137]	Consensus-based guideline	85	Indirectly addressed, as the number of resections for benign disease should be less than 15% in a CT-screened population
Senan [76]	Expert opinion	85	Suggests combining volume-doubling time with a predictive model to establish risk of malignancy
Louie [77]	Decision analysis	85	Threshold sensitive to the uncertainty in diagnostic performance of biopsy and the ability to reliably detect false negatives on surveillance

operable patients with SPLC, particularly as QoL considerations become more important during the survivorship period.

In patients previously treated with pneumonectomy for lung cancer, and who developed a subsequent malignancy in their remaining lung, the operative mortality and complication rates are as high as 8% and 40%, respectively [99]. The limited experience using SABR for such patients is encouraging with no reports of treatment-related mortality in the available literature [100,101]. Finally, when comparing outcomes of SPLC using SABR with first primary lung cancer, there do not appear to be any differences in efficacy in overall survival or recurrence [102].

Ground glass opacities (GGOs)

Early invasive lung adenocarcinomas can present with in-situ, multi-focal lesions that appear as regions of GGOs [103]. Management of GGOs is currently evolving, as some data suggest that a sublobar resection may be adequate [104], while others suggest that the indolent nature of pure GGO lesions may justify an active surveillance approach until a solid component develops [105]. Compared to other NSCLC subtypes treated with SABR, adenocarcinoma in situ (formerly termed bronchoalveolar carcinoma) appears to have similar patterns of failure [106]. However, one caveat in the use of SABR for GGO-predominant lesions is the risk for underdosing the target volume due to a loss of electronic disequilibrium. In one study, the delivered dose to a subcentimeter peripherally-located GGO surrounded by low-density emphysematous lung was estimated to be more than 20% less than the calculated dose using a less advanced treatment planning algorithm [107].

Distinguishing fibrosis versus recurrence

Radiation-induced lung injury following lung SABR can manifest as CT-density changes in up to 90% of cases at 2 years after treatment [108]. As these changes can occasionally mimic recurrence, traditional metrics to assess tumor response following definitive RT such as the Response Evaluation Criteria in Solid Tumors (RECIST) criteria may result in misdiagnosis of fibrosis as a recurrence, which may lead to unnecessary diagnostic and therapeutic procedures [109]. Further confounding the ability to properly diagnose a local recurrence, benign lung injury may result in FDG-avidity following SABR [110] and these changes can persist for up to a year. Although SUV_{max} values as high as 7 have been reported in the setting of benign lung injury following SABR [111], a systematic review suggests that an SUV_{max} value above 5 is highly suggestive of recurrence [112]. High-risk features (HRFs) on serial CT scan suggestive of recurrence include: enlarging opacity, sequential enlargement, enlargement after 12 months, bulging margin, linear margin disappearance, loss air bronchogram, and cranio-caudal growth. Employing a minimum cut-off of $\geqslant 3$ of these HRFs has been demonstrated to have high sensitivity and

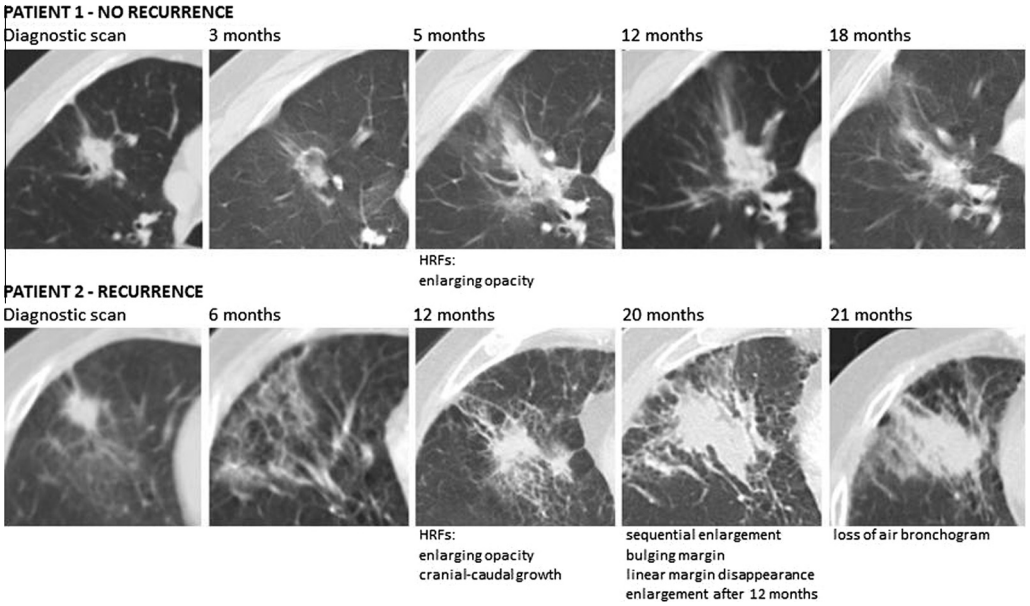

Fig. 3. Use of high-risk features (HRFs) on CT to diagnose recurrence. In patient 1, a 5 month follow-up CT shows an enlarging opacity, with additional scans showing fibrosis with no additional HRFs. No evidence of local recurrence. In patient 2, diffuse consolidation is demonstrated at 6 months. Additional HRFs are demonstrated after 12 months. The patient was diagnosed with a local recurrence at 21 months and underwent salvage lobectomy shortly after.

Table 4
Priority areas for research on the use of SABR for ES-NSCLC.

Patient selection
• If a RCT is not feasible in medically operable ES-NSCLC patients, investigate the role of SABR through CER using detailed prospective registration of comorbidity and toxicity data
• Establish the risks and benefits of SABR in CT-screened ES-NSCLC lung cancer patients
• Develop robust prediction models for distant metastasis risk in order to guide adjuvant treatment
• Establish the safety and appropriate administration of adjuvant systemic therapy
• Identify patients in whom SABR should not be offered, due to high risk of early mortality from competing causes
Quality assurance
• Monitor outcomes of SABR in community practice, as well as salvage surgery due to misclassification of benign fibrosis
• Establish optimal SABR doses for central tumors
• Determine safe dose-toxicity criteria for critical normal organs
Diagnostic management
• Establish the role of biopsy in the FDG-PET era in different global populations
• Determine the role of EBUS/EUS for staging subgroups of FDG-PET staged patients
Survivorship
• Explore the safety and role of surgical or re-SABR salvage

CER = comparative effectiveness research, SDM = shared decision making, EBUS = endobronchial ultrasound, EUS = endoscopic ultrasound.

specificity (greater than 90%) of recurrence, with a recommendation to proceed to biopsy or salvage treatment (Fig. 3) [113]. With the increasing using of lung SABR, distinguishing fibrosis from recurrence is a research priority for survivorship, as salvage treatment by surgery [114–116] or repeat SABR [117] while feasible, are not without toxicity.

The European Society of Medical Oncology consensus conference on lung cancer recommended 6 monthly CT scans for 3 years for patients who are suitable for salvage treatment, followed by annual CT scans thereafter [118]. Frequency of follow-up may be decreased and tailored for individuals who are not candidates for salvage treatment. The role of surveillance using FDG-PET has not been clearly defined, though its selective use is recommended when recurrence after SABR is suspected based on serial CT imaging. As FDG-PET is associated with a high incidence of false positive findings in this setting, biopsy should be sought whenever possible.

Shared decision making

In situations where there is clinical equipoise between treatment modalities, shared decision-making (SDM) has been encouraged to try and align medical management with a patient's preference and values [119]. SDM is a process in which patients and physicians discuss the current evidence on different treatment options and mutually arrive at a clinical management plan [120]. Achieving this often requires the input of a multidisciplinary team, and currently these initiatives vary in practice from ad hoc to routine. In healthcare systems where implementing such a policy for all patients is not feasible, focusing efforts on high-risk surgical patients would afford the highest value [121]. For instance, risks such as poorer QoL and higher 30- and 90-day post-treatment mortality after surgery in ES-NSCLC [10] may be particularly relevant for older patients who are more likely to have significant co-morbidities [122]. Conversely, while SABR may be considered attractive as an outpatient procedure with rare treatment-related mortality, for those desiring certainty, the development of benign CT changes during follow-up that mimic recurrence may be a source of anxiety.

Conclusions

SABR is now established as the preferred treatment option for medically inoperable patients with peripherally located ES-NSCLC. Although RCTs in medically operable/borderline operable patients, designed to compare surgery and SABR have been unable to accrue, non-randomized comparative effectiveness analysis argues for clinical equipoise between these treatments. Comparative effectiveness research will be instrumental in guiding decision-making for other emerging indications and addressing unanswered questions related to the use of SABR in ES-NSCLC (Table 4).

Conflict of interest

Drs. Senan and Dahele have received honoraria and travel support from Varian Medical Systems. Dr. Dahele has received honoraria and travel support from BrainLAB AG. Drs. Senan and Palma hold a non-commercial patent for the use of advance imaging feature analysis to assess for response after radiotherapy. The VU University Medical Center has a research agreement with Varian Medical Systems.

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