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Stereotactic body radiation therapy in stage I inoperable lung cancer: from palliative to curative options

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Summary

Surgery has historically been the standard of care for operable stage I non-small cell lung cancer (NSCLC). However, nearly one-quarter of patients with stage I NSCLC will not undergo surgery because of medical comorbidity or other factors. Stereotactic ablative radiotherapy (SABR) is the new standard of care for these patients. SABR offers high local tumour control rates rivalling the historical results of surgery and is generally well tolerated by patients with both peripheral and centrally located tumours. This article reviews the history of SABR for stage I NSCLC, summarises the currently available data on efficacy and toxicity, and describes some of the currently controversial aspects of this treatment.

Key words: *stereotactic body radiation; lung cancer; stage I; SABR; SBRT; local control; toxicity*

Introduction

Non-small cell lung cancer (NSCLC) accounts for around 85% of all lung cancers [1]. The preferred treatment of stage I NSCLC is lobectomy with systematic mediastinal lymph node evaluation [1]. However, nearly 25% of patients with stage I NSCLC will not undergo surgery, usually because of poor lung function, frailty, comorbitidies or patient refusal [2]. For these patients there are various treatment options including, usually, conventional fractionated radiotherapy, but also chemotherapy, targeted therapy, radiofrequency ablation, cryotherapy and observation. Historically, the efficacy of conventional fractionated radiotherapy has been suboptimal, with local failure rates of 40% [3], and an improvement in median survival time compared with observation alone from 14 to 21 months, but only a 15% 5-year lung cancer-specific survival rate [2]. Recently, substantial advances in the technology of radiation therapy have led to promising treatment outcomes, in some cases rivaling the historical results with surgery [4]. Indeed, local control rates of up to 92% have been reported in the literature [4]. This article reviews the history of stereotactic ablative radiotherapy (SABR) for stage I NSCLC, summarises the currently available data on efficacy and toxicity, and describes some of the current controversial aspects of this treatment.

Rationale for stereotactic ablative radiotherapy for lung tumours

Stereotactic ablative radiotherapy (SABR) is a form of high-precision radiotherapy that was originally developed in the 1950s in order to accurately treat small intracranial lesions with high biological doses of radiation. Technological developments in image guidance, planning and delivery of radiation therapy in the last decade have led to the application of this technique to extracranial sites, including the thorax and abdomen [5]. Typically, SABR is delivered using in-room imaging (IGRT: image guided radiation therapy) and 4D motion accommodation, to ensure accurate dose delivery [6]. SABR delivery is characterised by: (1.) reproducible and secure immobilisation to avoid patient movement during long treatment sessions; (2.) rigorous accounting for organ motion; (3.) use of dose distributions tightly covering the tumour by use of multiple (e.g. ≥10) or large-angle arcing small aperture fields, with rapid dose falloff in surrounding normal tissues in order to reduce toxicity; and (4.) most importantly, an ablative dose in three to eight treatment fractions within a 2-week period delivered to the patient with subcentimeter accuracy [7].

Radiobiological aspects of SABR

The most widely accepted means of describing the relationship between radiation dose and cell survival for conventionally fractionated radiotherapy is the linear-quadratic formula [8]. Some have suggested that it is not applicable to higher daily doses or smaller fraction numbers, and that it overestimates the biological effect of large-dose fractions [9, 10]. A few modifications have been proposed in order to correct modelled SABR dose-response curves, such as utilisation of the older multitarget model [11] or modification of the existing linear-quadratic model by incorporation of aspects of the lethal-potentially lethal model [12]. This question has not been answered definitively and more research is needed to model better high dose-fractional treatments [13]. These include different radiobiological effects of SABR, such as vascular and stromal effects that are not seen with CFRT [14, 15], normal tissue effects, preservation of the immune response [16, 17], and the combination of effective mechanisms with targeted drugs.

Another important aspect of SABR dose delivery relates to the duration of the treatment session. Several authors have argued that treatments sessions exceeding half an hour might be associated with a clinically significant loss in cytotoxicity [18, 19].

Immobilisation and target reproducibility

Stable and reproducible patient positioning is essential. This can be achieved with two systems:

– ''Frame'' systems: first reported by Lax and colleagues [20], they provide both immobilisation and a fiducial system that can approximate initial target localisation independently of other image guidance systems (room lasers and cone-beam computed tomography (CT)), which is then enhanced and adjusted by means of image-guided systems [20, 21]. These systems often integrate a mechanical tool for reducing breathing mobility, such as abdominal compression.

– ''Frameless'' systems: rely on the combination of markers and image-guided systems (planar or volumetric imaging and/or real-time tumour tracking) to relocate a reference position within the patient [22–24].

Both approaches provide similar reliability. Many recent studies suggest the use of new image-guided systems currently available in conjunction with SABR may improve the accuracy and precision of radiation delivery while potentially obviating the need for stereotactic body frames [23, 24].

The other important factor which has to be addressed is breathing mobility. Because lung tumours can move up to 5 cm (especially for tumours near the diaphragm) [25, 26], it is important that a method exists either to limit this motion or to track the tumour and gate treatment delivery. There are three general techniques to control tumour motion:

(1.) Reduction of tumour motion (dampening): abdominal compression with an attached plate that is pressed against the abdomen to reduce diaphragmatic excursions [20, 24].

(2.) Administration of radiation within a particular portion of the patient's breathing cycle (expiration or inspiration) (gating): utilises respiratory cycle monitoring combined with a surrogate to trigger delivery of radiation during a specific segment of the respiratory cycle [27].

(3.) Tracking the tumour position (chasing): moving the radiation beam path to follow the motion of the tumour [28].

Regardless of motion control equipment, careful assurance of high accuracy and reproducibility is essential for precise treatment delivery.

Target definition

The gross tumour volume (GTV) is typically defined on CT in lung windowing. The use of FDG PET-CT (FDG: 2-deoxy-[18F] fluoro-2-D-glucose; PET: positron emission tomography) information in radiotherapy planning allows better target volume definition, and reduces interobserver variability [29]. Typically in SABR, the GTV is equal to the clinical target volume (CTV) as no prophylactic treatment is allowed, keeping the volume of normal tissues exposed to high doses to a minimum [30]. The treatment dose used might be high enough to treat possible extension, through falloff of dose around the GTV. An internal target volume (ITV) can also be delineated based on the volume needed to encompass tumour motion. The margin from CTV to PTV (planning target volume), which includes setup uncertainty, will depend on the method of immobilisation, the assessment of tumour motion, and the methods for setup and geometric verification [6, 31]. However, because of similar geometric requirements with different methods for SABR, a relatively narrow range of margins between CTV and PTV is currently used in clinical practice. Margins generally used are 10 mm and 5 mm in the in the cranial-caudal plane and transversal plane, respectively [20, 24, 30, 32]. Normal tissues or organs at risk that must be contoured include both lungs, heart, trachea and proximal bronchi, distal bronchial tree, spinal canal, oesophagus, and brachial plexus.

Treatment planning

SABR is characterised by a very steep dose falloff on the margin of the target volume. This requires the use of multiple shaped beams (usually 10–15) or large angle arc rotations [33–35]. Use of noncoplanar beams is encouraged to avoid overlap of dose at points of entrance and exit [36]. Prescription isodose conformality to the target volume is generally assessed with a conformality index, which is the ratio of the prescription isodose volume to the PTV. Dose deposited outside the PTV increases this ratio. This ratio should be kept below 1.2 [37, 38]. Typical PTV coverage should be 95% to 100% with 99% of the PTV covered by 90% of the prescription dose [37, 38]. Any areas receiving greater than 105% of the prescription dose, commonly referred to as high-dose spillage, are generally confined to the PTV [37, 38]. In many centres, prescription lines covering the PTV will typically be the 60% to 90% line, usually 80% (rather than 95%–100%); however, higher isodoses

(hotspots) must be manipulated to occur within the target and not in adjacent normal tissue [39–41]. Dose distribution of an SABR plan should satisfy three major criteria: conformal high dose, compact intermediate dose and respect of normal tissue dose-volume constraints. Reducing high-dose spillage outside the intended treatment volume is critical for preventing normal tissue toxicity in organs at risk [37, 38]. Dose-volume relationships in the setting of SABR are still ambiguous. These constraints are frequently modified on the basis of patient outcome data in ongoing multicentre trials evaluating SABR [42]. The dose constraints for the organs at risk (including the spinal cord, oesophagus, ispsilateral brachial plexus, heart, trachea, and ipsilateral bronchus and whole lung) under the Radiation Therapy Oncology Group (RTOG) protocol 0236 [32] are shown in table 1.

Current results of SABR for medically inoperable stage I NSCLC

Local control

Despite the use of a wide range of equipment, techniques and fractionation schemes, nearly all published series of SABR for medically inoperable stage I NSCLC report 85% to 95% local control rates (summarised in table 2) [30, 32, 39, 43–46].

One of the first prospective trials was initiated by Indiana University. This was a dose-escalation phase I study in patients with stage I medically inoperable NSCLC to assess toxicity and local control rates [30]. Forty-seven patients were treated with SABR escalating from a starting dose of 24 Gy over three fractions (3 x 8 Gy fractions) up to 72 Gy in three fractions (3 x 24 Gy fractions). Patients were stratified into three dose escalation groups based on T stage and tumour size. The maximum tolerated dose (MTD) was 66 Gy (3 x 22 Gy fractions) for T2 tumours larger than 5 cm (T2 >5 cm) and was not reached for T1 tumours at 60 Gy (3 x 20 Gy fractions) or T2 tumours less than 5 cm (T2 <5 cm) at 66 Gy (3 x 22 Gy fractions). At a median follow up of 15.2 months, local failure had occurred in ten patients, in nine at doses of 16 Gy or less and only one at higher doses [29]. The same team conducted a phase II trial that further evaluated efficacy and safety of SABR in this patient population [39]. Doses established in the phase I trial were used to treat 70 patients. With a median follow up of 50.2 months, 3-year local control and survival rates were 88.1% and 42.7%, respectively [39]. Similarly, updated results from a phase II trial of SABR for medically inoperable stage I NSCLC in Scandinavia using 45 Gy in three fractions showed 3-year local control and overall survival rates of 92% and 60%, respectively, in 57 patients with a median follow-up of 35 months [43].

Most recently, Timmerman et al. presented mature results of the RTOG trial 0236 [32]. A total of 59 patients with peripherally located medically inoperable stage I NSCLC were accrued and 55 were evaluable (44 with T1 and 11 with T2 tumours). The prescribed dose was 54 Gy in three fractions of 18 Gy. The 3-year tumour control rate was 97.6% at a median follow-up of 34.4 months. Only one patient had a primary tumour failure [32]. In this same context another recent prospective phase II trial was conducted at the University of Torino. This trial included 62 patients with stage I NSCLC (43 with T1 and 19 with T2 disease) treated with SABR. The radiation dose was three fractions of 15 Gy each (45 Gy). At a median follow-up of 28 months, the 3-year local control and overall survival rates were 87.8% and 57.1%, respectively, with 8 out of 20 noncancer related deaths [44]. Lagerwaard et al. from the Netherlands evaluated outcomes of ‘‘risk-adapted’’ SABR in 206 patients with stage I NSCLC of whom 81% were medically inoperable. The decision process for the fractionation schemes was customised on the basis of tumour size and location [42]. Local control was greater than 90% [45]. No randomised comparison between conventionally fractionated radiotherapy and SABR for early NSCLC is available, but a recent meta-analysis of observational studies revealed significantly superior 5-year overall survival with SABR as opposed to conformal radiotherapy (42% vs 20%) [47]. Due to the large differences in both reported local control rates and the number of fractions, randomisation in such a trial will prove challenging. In countries such as the United States [48], Japan [49] and The Netherlands [50], SABR gained wide acceptance for this indication.

Patterns of failure

After conventional radiotherapy, the locoregional recurrence rate in early stage NSCLC may be as high as 70% [3]. In contrast, distant metastases constitute the major problem after SABR, a finding similar to that seen after surgery [32, 43, 45, 51–53].

RTOG 0236 reported only one patient with primary tumour site failure (including marginal failure), with a 3-year primary tumour control rate of 98%. Failure beyond the involved lobe occurred in three other patients, giving a 3-year local control rate of 91%. Regional failure within hilar or mediastinal lymph nodes was quite low (two patients), despite nonsurgical staging, giving a 3-year locoregional control rate of 87% [32]. Eleven patients failed in distant sites, frequently within 1 year after SABR [32]. In a recent sys-

Table 1: Organ tolerance dose limits for Radiation Therapy Oncology Group study 0236[a] [32].

Organ	Volume	Dose (Gy)
Spinal cord	Any point	18 Gy
Oesophagus	Any point	27 Gy
Ipsilateral brachial plexus	Any point	24 Gy (8 Gy / fraction)
Heart	Any point	30 Gy (10 Gy / fraction)
Trachea and ipsilateral bronchus	Any point	30 Gy (10 Gy / fraction)
Whole lung (right and left)	<10% of volume	20 Gy[b]

[a] Exceeding organ limits by more than 2.5% constituted a “minor” protocol violation. Exceeding these organ limits by more than 5% constituted a “major” protocol violation.
[b] Also known as V20 or volume of total lung getting 20 Gy or more.

tematic review of SABR for NSCLC studies, the main pattern of failure after lung SABR was distant metastasis. This occurred in 11% to 29% of patients in studies with ≥30 months of follow-up, but also in over 50% of patients in some series [53]. Nodal recurrences occurred in approximately 10% of patients in most studies (range 0%–23%) [53]. Recurrences were associated with increased tumour size [53].

One hypothesis to explain the low rates of regional recurrence after SABR might be that there was sufficient dose falloff, related to the high biological dose radiotherapy, to the regional nodes, and thus tumour cells in these nodes may be sterilised [40]. Low regional recurrence rates can also be explained by immune activity. Lee et al. demonstrated that SABR substantially increases T-cell responses in the draining lymphatic tissues in mice, leading to strong anticancer cytotoxic activity; this effect is not seen after standard low-dose conventionally fractionated radiotherapy [16]. Because the risk of distant failure is significantly higher for T2 tumours, some authors have advocated investigating the role of neoadjuvant chemotherapy in these patients [43, 53]. The general failure pattern after SABR underlines the importance of accurate lymph node staging before therapy. PET/CT is the best noninvasive imaging technique for the accurate determination of nodal status in these patients, who are usually medically unfit for surgical staging or not willing to undergo surgery [54]. The present series included few patients without PET staging whose outcome was not significantly inferior to PET/CT staged patients [55].

Toxicity

Published reports of SABR for lung cancer describe a very low acute and late toxicity rate compared with conventional radiation techniques in medically impaired patients, with rates for grade 3 or higher toxicity being typically less than 4% [13, 32, 45, 56]. These low rates of toxicity are presumably due to both the precision of treatment delivery and the structural physiology of lung tissue [57]. However, the real risk of late toxicity may be underestimated, as long-term follow-up has been limited owing to the relatively high noncancer-related mortality in patients who are usually medically unfit. In addition, symptoms of pulmonary toxicity may be masked by exacerbations of coexisting chronic obstructive pulmonary disease (COPD) and pneumonias.

Only a few investigators have carefully followed clinical toxicity after SABR. The most commonly reported toxicities are radiation pneumonitis, oesophagitis, skin reactions, chest wall pain and general malaise such as fatigue [58]. In general, the common side-effects are mild to moderate (grade 1 to 2) and transient. The reported rate of grade ≥3 late toxicity was less than 10% in most studies [4, 45, 51–60]. Most of the accumulated grade 5 events have occurred when patients received high-dose SBRT to centrally located tumours adjacent to mediastinal organs [39, 51, 61, 62].

Table 2: Summary of the results of the prospective trials of stereotactic ablative radiotherapy for early stage non-small cell lung cancer.

Trial	Number of patients	Stage	Median follow-up (months)	Dose and fractionation	Any toxicity ≥ grade 3. n (%)	Local control	Overall survival
Le QT et al. [61]	32 (20 primary NSCLC)	T1–2 N0 M0	18	15-30 Gy in 1 x	4 (12.5)	91% at 1 year for dose ≥25 Gy	85% at 1 year
Fakiris AJ Et al. [39] Phase II	70	T1–2 N0 M0	50.2	60-66 Gy in 3 x	11 (15.7)	88.1% at 3 years	42.7% at 3 years
Timmerman R (RTOG 0236) [32] Phase II	55	T1–2 N0 M0	34.4	60 Gy in 3 x	9 (16.3), no deaths	97.6% at 3 years	55.8% at 3 years
Lagerwaard Fj et al. [45]	206	T1–2 N0 M0	12	60 Gy in 3 x, 5 x or 8 x	6 (3)	93% at 2 years	64% at 2 years
Nagata Y et al. [84]	45	T1–2 N0 M0	30	48 Gy in 4 x	0 (0)	98% at 2 years	82% at 3 years
Koto M et al. [46] Phase II	31	T1–2 N0 M0	32	45 Gy in 3 x, or 60 Gy in 8 x	1 (3)	T1: 77.9% at 2 years T2: 40.0% at 2 years	71.7% at 3 years
Xia T et al. [85]	43	T1–2 N0 M0 (25 patients) T1–2 N1 M0	27	50 Gy in 5 x	1 (2.3)	96% at 3 years	91% at 3 years
Taremi M et al. [86]	108	T1–2 N0 M0	19.1	48 Gy in 4 x or 54–60 Gy in 3 x or 50–60 Gy in 8–10 x	Acute: 4 (3.7) Late: 12 (11.1)	82% at 4 years	30% at 4 years
Bral S et al. [64]	40	T1–3 N0 M0	16	60 Gy in 3 or 4 x	8 (20)	84% at 2 years	52% at 2 years
Grills IS et al. [40]	124 (SBRT: 58, Surgery: 69)	T1–2 N0 M0	30	48 Gy in 4 x or 60 Gy in 5 x	6 (10.9)	7.2% at 2.5 years	72% at 2.5 years
Ricardi U et al. [44] Phase II	62	T1–2 N0 M0	28	45 Gy in 3 x	2 (3.2)	87.8% at 3 years	57.1% at 3 years
Baumann P et al. [43] Phase II	57	T1–2 N0 M0	35	45 Gy in 3 x	17 (29.8)	92% at 3 years	60% at 3 years
Timmerman R et al. [87] Phase II	70	T1–2 N0 M0	17.5	60-66 Gy in 3 x	14 (20)	95% at 2 years	54.7% at 2 years

x = fraction(s)

As a result of the severe toxicity reported for central tumours in the study at Indiana University [39] and other trials, all central lesions have been excluded from RTOG 0236 [32]. An RTOG clinical study (RTOG 0813, NCT00750269) is evaluating the use of different SABR regimens to treat tumours located within the zone of the proximal bronchial tree [63]. A risk-adapted approach has been studied at VU University Medical Centre and the SABR regimen varies according to tumour location [45]. Three fractionation schemes were applied; three fractions of 20 Gy (for T1 tumours), five fractions of 12 Gy (for T1 tumours with broad contact with the thoracic wall, or T2 tumours) or eight fractions of 7.5 Gy (for tumours adjacent to the heart, hilus or mediastinum). This approach has yielded acceptable treatment-related toxicity in 206 patients [45].

Another prospective phase II, risk-adapted, SABR trial was reported by Bral and colleagues from Belgium [64]. This study included 40 patients with stage T1–3N0M0 NSCLC up to 6 cm in size, located both in the periphery (n = 23) as well as in the central zone (n = 17), as defined by the RTOG 0236 study [32, 64]. Peripheral tumours received 60 Gy in three fractions and central tumours received 60 Gy in four fractions. With a median follow-up of 16 months, the lung-toxicity-free survival estimate at 2 years was 74%, and was related to the location (central vs peripheral) and the size of the target volume. The 2-year local progression-free survival (LPFS) and overall survival were 84% and 52%, respectively. The LPFS was significantly correlated with the initial tumour stage (T1 vs T2, p = 0.006). The dose reduction for central tumours did not increase the risk of local failure. The authors concluded that the adapted schedule did not lower the incidence of lung toxicity for peripheral or central lesions (13.0% vs 29.4%), but it had an impact on the severity of the toxicity. The pulmonary toxicity was location-dependent even at low doses [64].

In addition to central tumour location, factors associated with severe toxicity include fraction size [64, 65], and prior treatment (radiotherapy or chemotherapy) [60]. For apical tumours, when SABR is used there may be an increased risk of injury to the brachial plexus. In a series of 36 patients with apical lesions treated with SABR at a median dose of 57 Gy in three fractions, seven patients developed grade 2, 3 or 4 brachial plexopathy [66]. These authors felt that the tolerance of the major trunks of the brachial plexus was around 26 Gy for a three-fraction regimen [66].

For peripheral lung tumours, chest-wall toxicity may be manifested as rib fractures or pain [67, 68]. The incidence of chest wall toxicity was illustrated by a series of 347 treated lesions, which included 203 on the chest wall. Both chest-wall pain and rib fractures were more frequent when chest-wall lesions, as compared with nonchest-wall lesions were irradiated (16% vs 3% and 8% vs 1%, respectively) [67]. Nevertheless, chest-wall toxicity after SABR occurs less frequently than post-thoracotomy pain syndromes, which can manifest in about 50% of surgical patients and may persist up to 5 years after treatment (in up to 30% of patients), although the more widespread use of video-assisted thoracic surgery appears to have reduced this complication [69, 70].

SABR is an emerging treatment option in lung cancer without long-term follow up. Constraints that are currently being used in prospective trials are often based on a small number of cases where the toxicity was observed, theoretical equations and computer simulations. To ensure the best possible understanding of the limits of safety of SBRT as clinical practice evolves, it is of great importance that the adverse radiation effects in individual clinical series be adequately reported.

SABR for high-risk groups

SABR is an effective and safe treatment modality for high surgical risk patients with early-stage NSCLC. Such high-risk patients include elderly patients with low performance status and severe comorbidity (e.g. severe COPD), and patients who have previously undergone lung resection or thoracic irradiation [71].

Elderly patients are less likely to undergo surgery because of comorbidities, functional deficits, poor performance status and patient preference [50]. SABR studies did not exclude these patients. The median age in these studies ranged from 71 to 76 years, with three studies recruiting patients in their 90s [59, 72, 73]. Despite this population of elderly patients with comorbidities deemed unsuitable for surgery, SABR was found to be well tolerated with local control rates comparable to surgery. The most important side effect from SABR is pneumonitis, although rates of grade 2 or more pneumonitis were typically less than 5%. A potential limitation of SABR in the elderly is the duration of each fraction, which can typically exceed 30 minutes. Some elderly patients, particularly those with significant comorbidities, might find immobilisation on a treatment table for this length of time intolerable. Volumetric intensity-modulated arc therapy is currently being developed for use in SABR to allow a considerably shorter delivery time [74].

SABR was not shown to impair pulmonary function, although patients with severe COPD constituted more than one-third of treated individuals [43, 75, 76]. Data from a single-institution cohort and a systematic literature review produced a 1-year actuarial survival of 79% to 95% and 3-year survival of 43% to 70% for SABR. Surgically treated patients had an actuarial survival of 45% to 86% at 1 year and 31% to 66% at 3 years. No patient died within 30 days after SABR, whereas 10% of patients died after surgery [77].

SABR has also been applied safely for recurrent or second lung cancers in patients who have undergone previous pneumonectomy or prior irradiation to the thorax [75, 78]. These factors take on increased importance if oncological outcomes between SABR and surgery are equivalent. This has prompted a cooperative group-sponsored prospective randomised trial comparing the two treatments in high-risk patients that has recently started accruing (American College of Surgeons Oncology Group Z4099 / RTOG 1021) [79].

SABR for operable early-stage NSCLC

Although there has been no direct comparison with surgery, the results from observational studies suggest that the results with SABR for stage I NSCLC are similar to those

of surgery. Onishi et al. have reported the largest series (257 patients, 158 inoperable and 99 operable) and the longest follow-up, with a 5-year overall survival of 47%, a local failure rate of 13.5% and a regional failure rate of 8.2% [59]. These authors make favourable comparisons with groups of patients treated with standard surgery [59]. Others have reported local failure rates ranging from 3% to 16% [30, 43, 45, 56]. Crabtree et al. compared short-term outcomes with SABR and surgical resection for clinical stage I NSCLC. Matched-patient analyses revealed no differences between the groups in terms of overall survival, disease-specific survival or local control. No treatment-related deaths occurred as a consequence of SABR. In the surgery group, the operative mortality rate was 3.2% (15/462) patients [56]. Grills et al. from William Beaumont Hospital compared patients with stage I NSCLC who had received treatment with either SABR or wedge resection, and reported that rates of freedom from any failure, causes-specific survival, distant metastasis, and local, regional, and locoregional recurrence did not differ significantly after a 30-month median follow-up, but the overall survival rate was significantly higher in the surgery patients than in those patients who had received SABR. No treatment-related deaths were observed as a consequence of either treatment [40]. As with the results of Onishi et al. and Crabtree et al., these results are provocative. However, again, these studies are retrospective and uncontrolled, and subject to many biases confounding interpretation.

These findings further underscore the importance of the awaited international phase III trial conducted by the MD Anderson Cancer Center (STARS trial, NCT00840749). In this trial, 1,030 patients with T1 or T2 (<4 cm) NSCLC will be randomly assigned to surgery or SABR (15 Gy x 4 fractions or 20 Gy x 3 fractions for central and peripheral lesions, respectively). The primary endpoint is 3-year overall survival [80]. A second European phase III trial (ROSEL trial, NCT00687986) was terminated because of poor patient recruitment [81]. Other trials such as RTOG 0618 [82] and JCOG 0403 (NCT00238875) [83], recently closed to accrual, might shed furtherlight on this issue (table 3).

Conclusion

In summary, new technical refinements in delivery of SABR have led to a widespread use of this technique. At the present time SABR is firmly established as a standard-of-care therapy for patients with early-stage inoperable lung cancer. Although recent guidelines for the planning and the execution of SABR for lung cancer have been published [31], there is still much room for improvement. The role of SABR in operable patients remains to be defined by randomised trials (table 3).

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Table 3: Ongoing prospective trials of stereotactic ablative radiotherapy in lung cancer.

Trial	Title
Operable	
RTOG 0618 [82]	A Phase II Trial of Stereotactic Body Radiation Therapy (SBRT) in the Treatment of Patients With Operable Stage I/II Non-Small Cell Lung Cancer
JCOG 403 [83]	A phase II study of stereotactic body radiation therapy in patients with T1N0M0 non-small cell lung cancer
STARS [80]	Phase III Study to Compare CyberKnife Stereotactic Radiotherapy With Surgical Resection in Stage I Non-small Cell Lung Cancer
Inoperable	
TROG 09.02 [88]	A randomised phase III trial of highly conformal hypofractionated image guided ("stereotactic") radiotherapy (HypoRT) versus conventionally fractionated radiotherapy (ConRT) for inoperable early stage I non-small cell lung cancer (CHISEL).
RTOG 0915 [89]	A Randomized Phase II Study Comparing 2 Stereotactic Body Radiation Therapy (SBRT) Schedules for Medically Inoperable Patients With Stage I Peripheral Non-Small Cell Lung Cancer
RTOG 0813 [90]	Seamless Phase I/II Study of Stereotactic Lung Radiotherapy (SBRT) for Early Stage, Centrally Located, Non-Small Cell Lung Cancer (NSCLC) in Medically Inoperable Patients
SPACE [91]	Stereotactic precision and conventional radiotherapy evaluation. A multicenter randomized phase II study of stereotactic hypofractionated radiotherapy with body frame versus conventionally fractionated radiotherapy for stage I medically inoperable non-small cell lung cancer

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