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Stereotactic ablative body radiotherapy (SABR) for primary and secondary lung tumours

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Abstract

Stereotactic ablative body radiotherapy (SABR) represents a technological breakthrough in radiotherapy technique, with proven benefits to patients in terms of improved tumour control and overall survival. The key components of SABR are described. The current evidence base for SABR for the treatment of primary and secondary lung tumours is appraised, and key ongoing trials are identified.

Keywords: *Stereotactic ablative body radiotherapy; lung; cancer; radiosurgery.*

Introduction

Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related mortality worldwide, with over 1 million deaths every year[1]. Most patients with primary NSCLC present with advanced disease. Only about 20% of patients present with stage I disease (T1-2N0M0); these are the patients who can benefit from stereotactic ablative body radiotherapy (SABR). SABR delivered to stage I primary lung cancers achieves excellent local control rates. Given these excellent control rates, and the possibility of long-term survival in selected patients with solid tumours and limited metastases, there has been increasing interest in the use of SABR for secondary metastases to the lung. The primary tumour types that are most appropriate for this treatment approach include sarcoma, colorectal cancer and germ cell tumours[2]. This article discusses SABR, a technological breakthrough in radiotherapy, for the treatment of primary and secondary lung tumours.

SABR: definition

Stereotactic radiotherapy was first developed in the 1950s for the treatment of intracranial tumours. Technological advances in radiotherapy planning, treatment delivery, and tumour tracking have led to the application of this technique to extracranial sites including the thorax and abdomen (now termed SABR). SABR is a form of high-precision radiotherapy characterized by: reproducible immobilization to avoid patient movement during radiation delivery; measures to account for tumour motion during treatment planning and radiation delivery; dose distributions tightly covering the tumour, with steep dose gradients away from the tumour into surrounding normal tissues in order to minimize toxicity; and, most importantly, the use of extremely high ablative doses of radiation, usually delivered in 3–8 treatment fractions within a 2-week period[3].

Lung SABR

Reproducible immobilization

Patients to be treated with SABR must be securely immobilized in a reproducible treatment position. Immobilization for lung stereotactic body radiation therapy (SBRT) treatments is often achieved with the use of a vacuum-formed personalized immobilization device (VacBag). Patients can also be immobilized with body

frames and diaphragmatic pressure to reduce breathing movement.

As with all radiotherapy techniques, patient positioning is extremely important. A treatment position must be selected that the patient can comfortably maintain for the duration of treatment (can be 60–90 min). Consideration should also be given to arm position to allow the optimum range of beam angles to treat the tumour without passing through unnecessary non-target tissue.

Motion management

Irrespective of the SABR system being used, it is imperative that intrafraction and interfraction tumour motion is accurately evaluated and accounted for in order to avoid a geographical miss of the target. Lung tumours are subject to respiratory motion, and therefore motion management is crucial. Tightening of expansion margins around the target in order to increase dose to the target, and reduce normal tissue dose, make this vital.

Some SABR systems are capable of gated delivery. This means that radiation delivery is only triggered at certain predefined phases of the respiratory cycle. The advantage of gated delivery (versus delivery of radiotherapy throughout the respiratory cycle) is that the volume of irradiated normal lung can be reduced with gating of treatment.

A frameless robotic radiosurgery system has been developed that incorporates a compact 6 MV x-band linear accelerator mounted onto a robotic arm that can track and adapt to the respiratory motion of a lung tumour target. A predictive respiratory model is constructed prior to each treatment fraction. This is constructed by (1) paired diagnostic radiographs of lung tumour implanted fiducials at discrete points of time in the respiratory cycle and (2) chest wall mounted optical markers monitored in real time by a camera system. The radiographs are taken by ceiling-mounted perpendicular oblique X-ray sources. The model (which is continuously updated during treatment delivery) allows treatment delivery via the robotic arm to be synchronized with the respiratory motion of the lung tumour target, obviating the need for gating. Tracking of the target is another way of reducing the volume of irradiated lung as the expansion margins, which are normally large to account for respiratory motion, can be significantly reduced.

The fiducials that are approved for the tracking described above are gold seeds. A range of dimensions are available. Fiducials can be implanted percutaneously with computed tomography (CT) guidance, or via bronchoscopy. Certain well-selected lung tumours with key characteristics (axial dimension >1.5 cm, peripheral, tumour not obstructed by spine in live radiographs), can sometimes be tracked without the need for fiducials with the X-Sight Lung system. This tracks the tumour target by detecting the contrast of the tumour mass against surrounding lung, having compared this to the expected tumour location from data on the radiotherapy planning CT.

SABR systems that do not incorporate gating or tracking techniques require carefully applied individualized margins to be applied to the CT-visualized tumour volume to account for organ motion and set-up error. It is critical to incorporate four-dimensional (4D) treatment planning in order to truly individualize margins. A 4D CT scan set consists of a series of three-dimensional (3D) CT image sets acquired at different respiratory phases. After acquisition, the images are sorted into different phases of the respiratory cycle. A typical sorting signal is the movement of a real-time position management system (Varian) block mounted on the patient's abdominal wall, which acts as a surrogate for respiratory motion. The detailed knowledge of tumour motion captured in the 4D CT can be used to allow the application of optimum individualized margins, usually after the creation of a maximum intensity projection (MIP) set through all respiratory phases.

Highly conformal treatment plans

Prior to the recent development of SBRT for treatment of localized lung cancer, patients were treated with conformal radiotherapy. Patients would undergo a planning CT scan, the CT images would be sent to a 3D workstation to allow visualization and manipulation of the CT data for treatment localization[4]. The visible tumour (termed gross tumour volume, or GTV) would be outlined on CT. As a standard 3D CT represents only a snapshot of tumour position, margins are applied to encompass the (possible) full range of motion of the tumour. Typical margins would be 1 cm axially and 1.5 cm in the superior and inferior planes. These margins also incorporate set-up error, where the patient, despite careful positioning, may not be set up exactly as they were at planning CT. The resultant volume is called a planning target volume, or PTV. The dosimetrist would work to achieve the desired 3D dose distribution by trying a variety of configurations of beam angles, wedges and beam weightings until a suitable solution is reached. This approach is termed forward planning.

The SABR treatment delivery systems are integrated with sophisticated treatment planning systems, which have fusion capability with positron emission tomography (PET) scans. PET fusion has been shown to improve the accuracy of target volume outlining[5,6]. Studies have demonstrated a change in the PTV contouring in approximately 30% of cases of NSCLC, which may have important consequences for both toxicity and tumour control. PET fusion may allow smaller volumes to be outlined (especially likely in cases of atelectasis), and this would allow smaller volumes of normal lung to be irradiated, which should improve the toxicity profile of the treatment[7]. Alternatively, PET may increase the outlined tumour volumes (due to findings of PET-positive lymph nodes, especially within the hilar or mediastinal nodal stations), which is likely to have a positive impact on tumour control[8].

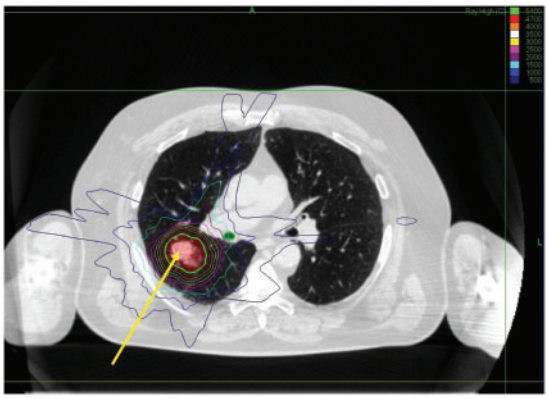

Figure 1 **A typical SABR plan. The arrow points to a gold seed fiducial (1 mm × 5 mm). This was placed percutaneously via an 18 gauge needle under CT guidance. The PTV target is shaded red. The thick green line is the prescription isodose line. This patient's tumour was treated with 54 Gy. The plan shows a sharp fall off in dose away from the target. The coloured isodose lines refer to doses in cGy.**

Optimum patient positioning and immobilization, target localization, and importantly, sophisticated image guidance, gating and tracking techniques during treatment delivery are crucial components of the SABR process. As a result of these improvements in radiotherapy technique, the GTV to PTV margins can be safely reduced. Typical margins for SABR in practice are 0.5 cm axially and 1 cm in the superior/inferior direction (RTOG 0236), although other international studies have accepted margins of 3–5 mm (ROSEL study).

Planning to tighter margins (in SABR vs 3D conformal radiotherapy) clearly offers clinical gains in terms of reducing the volume of irradiated lung, and consequential acute and late toxicity, and allows for dose escalation to the target.

In addition, SABR systems are integrated with sophisticated treatment planning systems that have inverse planning capability. This approach requires the physicist/oncologist to specify dose-volume constraints and/or dose limits to tumour target, as well as nearby organs at risk (OARs). These constraints drive the planning software algorithms to satisfy the constraints as near as possible. Inverse planning tends to be the preferred planning technique for complex targets requiring multiple beams[9]. The sophisticated planning systems, as always guided by physicists, are able to generate highly conformal plans, with a sharp dose gradient away from the target. In addition, the ability to deliver non-coplanar (off axis), non-isocentric beams with some SABR systems, can also help to achieve optimum conformality. A typical SABR plan with excellent conformality is shown in Fig. 1.

There are, however, caveats to this approach. Given the tight GTV to PTV margins applied, accurate target delineation is critical. Close collaboration with radiology colleagues during target localization is critically important.

High dose radiation

In practice, it is primarily the tolerance radiation dose of surrounding OARs that limits the dose that can be safely delivered to tumour targets by conventionally fractionated conformal radiotherapy. There is a dose–response relationship with radical radiotherapy[10].

The improvements to radiotherapy technique, which are a critical part of SABR in practice, have allowed the irradiation of OARs to be minimized (without compromising tumour coverage), and therefore dose escalation to tumour is now possible. Given the dose–response relationship, this has allowed tumour control to be significantly improved (for an equivalent level of toxicity).

Typical radical radiotherapy regimes for stage I lung cancer, prior to SABR, consisted of total doses of 55–74 Gy in 20–37 daily fractions of 2–2.75 Gy over a period os 4–7.5 weeks. Typical SABR regimes now deliver a dose of 54–60 Gy in 3–5 fractions of 12–20 Gy per fraction for peripheral tumours.

The radiation schedules used in SABR cannot be directly compared with those used in conventional radiotherapy, because the dose per fraction is not identical. To compare the relative efficacy of the different fractionation schedules, the biologically effective dose (BED) must be calculated[11]. Conventionally, fractionated schedules delivering 2 Gy per fraction (e.g. 64 Gy in 32 fractions or 70 Gy in 35 fractions) typically have a BED of 70–80 Gy. In contrast, modern SABR schedules use doses equivalent to a BED >100 Gy, resulting in superior tumour cell kill[12]. A frequently used schedule for peripheral lung tumours is 20 Gy × 3 fractions, which delivers a BED as high as 180 Gy[13]. The delivery of such high doses of radiotherapy per fraction (hypofractionation) means that the irradiated tumour cells (as well as any normal body cells irradiated to the prescribed dose) cannot possibly repair DNA strand breaks, and vascular collapse and tumour necrosis ensues. The prescribed dose is considered ablative[14].

Primary lung cancer

Most patients with primary NSCLC present with advanced disease. Only about 20% present with stage I disease (T1-2N0M0), and even those undergoing complete surgical resection have a 5-year survival rate of <70%[15–17].

Surgery is currently the standard of care for patients with stage I NSCLC[18]. Surgery, however, carries a significant mortality rate, with a 30-day post-operative mortality rate of 1–5% for lobectomy[19]. Surgery is also associated with morbidity such as loss of lung function

and exercise capacity (10–40%)[20–22] and prolonged post-thoracotomy pain (30%)[23].

Traditionally, patients with stage I NSCLC who were deemed medically inoperable, or who declined surgery, were offered radical radiotherapy (treating to a total dose of 55–74 Gy in 20–37 daily fractions of 2–2.75 Gy, over a period of 4–7.5 weeks). The results for conventional radiotherapy have, however, been inferior to surgery (possibly partly due to selection bias), with 2- and 5-year recurrence-free survival rates of 29% and 7%, respectively[24].

Given the significant morbidity and mortality of surgery for this patient group, and the disappointing disease-control rates from conventional radiotherapy, it is important to develop more effective, well-tolerated radiotherapy techniques. SABR offers excellent disease-control rates, and is a well-tolerated treatment, for carefully selected patients. The published results of SABR for primary lung cancer are critically reviewed.

Statement of search strategies

A search for the published results of SABR for lung cancer was carried out using PubMed. The following terms were searched for in all fields: "stereotactic body radiotherapy", "stereotactic body radiation therapy", "stereotactic radiosurgery", "radiosurgery", and "CyberKnife" and "lung OR pulmonary OR thoracic". Appropriate publications were selected from the lists generated, and additional publications were found through a manual search of the references contained in these papers. Searches were carried out in May 2012.

Evidence for SABR in primary lung cancer

The key SABR trials for primary lung cancer are summarized in Table 1. When selecting papers for inclusion, preference was given to studies with histological confirmation, prospective studies, and studies with a reasonable length of follow-up.

Indiana University undertook a phase I, dose-escalation study of 47 medically inoperable patients with stage 1 NSCLC. The starting dose was 3×8 Gy. The maximum tolerated dose (MTD) for T2 tumours >5 cm was reached at 66 Gy in 3 fractions. MTD was not reached for T1 tumours. Of 10 patients who recurred locally, 9 patients received doses <16 Gy per fraction. This was an early indication of the importance of BED in tumour control for lung cancer[13].

The same institution went on to treat 70 medically inoperable patients with stage 1 lung cancer in a prospective phase II study. Histological confirmation was obtained. The study included both central and peripheral (>2 cm in all directions from the proximal bronchial tree) tumours. The treatment dose delivered was 60–66 Gy in 3 fractions. At a median follow-up of 50 months, the 3-year local control rate was 88.1% and the 3-year overall survival rate was 42.7%. Toxicity analysis showed that tumour location is an important consideration. The grade 3–5 toxicity rate in peripheral tumours was 10.8%, but for central tumours this rate was as high as 27.3%[25].

The toxicity experienced in those treated with central tumours led to this group being excluded from the next prospective phase II study, the RTOG 0236. This landmark trial was a multicentre study conducted in the United States. The 55 evaluable patients had biopsy-proven stage I NSCLC; all patients treated had peripheral tumours <5 cm, and were medically inoperable. Treatment dose was 54 Gy in 3 fractions. At a median follow-up of 34.4 months, the 3-year local control rate was 97.6%, and the 3-year overall survival rate was 55.8%. Crucially, the toxicity was more favourable than for the previous study in which these dose levels were first piloted. The grade 3 toxicity rate was 12.7%, the grade 4 toxicity rate was 3.6%, and there was no grade 5 toxicity. This trial therefore showed an excellent local control rate (97.6% at 3 years) with acceptable toxicity[26].

The largest published series of SABR for primary lung cancer is a retrospective series of 257 patients from 14 Japanese institutions. This was a mixed group of patients with stage I lung cancer with surgically resectable disease. The patients had SABR because either they were medically inoperable or they declined surgery. The patients had either central or peripheral tumours. The dose-fractionation regimes used were highly variable: 30–84 Gy in 1–14 fractions. When analysing those patients treated with fractionation regimes with a BED of >100 Gy, the 5-year actuarial local control rate was 84%, and the 5-year overall survival rate was 71%. Toxicity was acceptable[27]. Patients who decline surgery by choice (as opposed to those who are medically inoperable) tend to have less co-morbidities and a superior performance status, which may explain the improved overall survival rates in this cohort of patients compared with the RTOG 0236 study.

Onishi et al.[27] compared 5-year overall survival data for their SABR-treated patients (72% for stage IA disease and 66% for stage IB disease) with the results of published surgical series (61–72% for stage IA disease and 40–50% for stage IB disease). The overall survival rates for SABR in stage I patients, therefore, compares favourably with the rates following surgical resection[27–30].

Shibamoto et al.[31] published a prospective, multicentre Japanese study stratifying 180 patients to dose-fractionation regimes (44–52 Gy in 4 fractions) according to tumour size. All patients had histologically confirmed stage I NSCLC <5 cm. One hundred and twenty patients were medically inoperable, while 60 operable patients had declined surgery due to patient choice. Local control rate at 3 years was 85%. Overall survival at 3 years was 69% overall (74% for operable patients and 59% for medically inoperable patients) and 52% at 5 years overall.

Table 1 **Published series of SABR for early stage primary NSCLC**

Reference	Publication date	Publication type	Status	No. of patients	Tumour location	Dose	Median follow-up (months)	Local control	Overall survival	Grade 3+ toxicity
McGarry et al.[13]	2005	Single-centre phase 1	Medically inoperable	47	Peripheral or central	24 Gy in 3 fractions escalating to 72 Gy/3 fractions	15	79% at median 15 months	Not reported	11% lung, 2% pericardial, 2% dermatitis
Fakiris et al.[25]	2009	Single centre phase II	Medically inoperable	70	Peripheral or central	60–66 Gy in 3 fractions	50	3 years 88.1%	3 years 42.7%	10.8% peripheral, 27.3% central
Timmerman et al.[26]	2010	Multi-centre phase II (RTOG 0236)	Medically inoperable	55	Peripheral only	54 Gy in 3 fractions	34.4	3 years 97.6%	3 years 55.8%	12.7% grade 3, 3.6% grade 4, no grade 5
Onishi et al.[27]	2007	Multi-centre retrospective series	Medically inoperable or declined surgery	257	Peripheral or central	30–84 Gy in 1–14 fractions	38	5 years 84% for BED >100 Gy	5 years 71% for BED >100 Gy	5.4% lung, 1% oesophagitis, 1.2% dermatitis
Shibamoto et al.[31]	2012	Multi-centre prospective series	Medically inoperable or declined surgery	180	Peripheral or central	44–52 Gy in 4 fractions	36	3 years 85%	5 years 52%	13.3% grade 2+ pneumonitis, 0.6% grade 3 pleural effusion
Nagata et al.[32]	2010	Multi-centre phase II (JCOG 0403)	Medically inoperable or declined surgery	65	Peripheral or central	48 Gy in 4 fractions	45.4	3 years local progression free survival 68.5%	3 years 76%	7.7% lung, 1.5% chest pain
Baumann et al.[33]	2006	Multi-centre retrospective series	Medically inoperable	138	Peripheral or central	30–48 Gy in 2–4 fractions	33	33 months 88%	3 years 55%	10%
Baumann et al.[34]	2009	Multi-centre phase II	Medically inoperable or declined surgery	57	Peripheral only	45 Gy in 3 fractions	35	3 years 93%	3 years 60%	26% grade, 3 2% grade 4
Lagerwaard et al.[35]	2008	Multi-centre retrospective series	Medically inoperable or declined surgery	206	Peripheral or central	60 Gy in 3–8 fractions, according to tumour location	12	1 year 97%	2 years 64%	3% pneumonitis, 1.9% rib fractures, 1.5% chest pain
Andratschke et al.[36]	2011	Single centre retrospective series	Medically inoperable	92	Peripheral or central	24–45 Gy in 3–5 fractions	21	5 years 83%	3 years 38%, 5 years 17%	11.9% lung, 3.3% rib fracture, 1% fatigue

The JCOG 0403 study[32] was a multicentre, prospective phase II study of 65 resectable NSCLC patients with histological confirmation. The patients were treated with 48 Gy in 4 fractions. Local progression-free survival was 68.5% at 3 years, and the overall survival rate was 76% at the same time point.

A number of important series have been published from European centres. A multicentre retrospective series of 138 patients from the Nordic countries was published by Baumann et al.[33]. The patients were medically inoperable. They were treated with 30–48 Gy in 2–4 fractions. The local control rate at 33 months was 88% and the 3-year overall survival rate was 55%. A more recent prospective multicentre phase II study from the same institutions and published by the same author, treated 57 patients with 45 Gy in 3 fractions[34]. The local control rate was 93% at 3 years and the overall survival rate at 3 years was 60%. The prospective study reported an acute grade 3 toxicity rate of 26%, primarily dyspnoea and chest wall pain. Only 1 patient had late grade 4 toxicity (dyspnoea); this patient had had prior radiotherapy to a contralateral lung primary.

A Dutch group[35] and a German group[36] have also published important series. The Dutch group treated both central and peripheral tumours ($n = 206$) with a risk-adapted fractionation regime of 60 Gy in 3–8 fractions depending on tumour location. The local control rate was 97% at 1 year and the overall survival rate was 64% at 2 years. The risk-adapted strategy appeared to have a favourable toxicity profile with a grade 3+ pneumonitis rate of only 3%; rib fractures occurred in 2%. The German group also treated both peripheral and central tumours to a lower total dose of 24–45 Gy in 3–5 fractions. Five-year local control data are reported at 83% and the 3-year overall survival rate was 38%. There was a grade 3+ lung toxicity rate of 12% and rib fractures occurred in 3.3%.

Table 1 summarizes these key studies of SABR for primary lung cancer. The studies have analysed outcome data from over 1000 patients treated with this technique. Local control rates at 3 years vary between 88% and 97.6%. Overall survival at 3 years is 38–76%.

Zhang et al.[37] performed a meta-analysis on 2587 patients across 34 studies to evaluate the optimal BED for SABR for stage I NSCLC. The delivered BED was divided into quartiles (83.2 Gy = low, 83.2–106 = medium, 106–146 = medium-to-high, and >146=high). There was a statistically significant overall survival benefit at 2 years for those receiving medium to medium-to-high BED regimes.

In the United Kingdom, the data for SABR for stage I NSCLC was reviewed by the National Radiotherapy Implementation Group (NRIG). Their report published in 2010 concluded that the data for this group of patients is sufficiently robust for SBRT to be recommended as an alternative to surgery in those patients unfit, or unwilling, to undergo surgery[38].

It is hoped that the outcome of further clinical trials will inform our decision-making for treatment decisions:

- The RTOG 0618 phase II study of operable stage I/II patients treated with 54 Gy in 3 fractions to peripheral tumours has now completed accrual. The RTOG 0915 randomized phase II study comparing two different SABR schedules (34 Gy in 1 fraction vs 48 Gy in 4 fractions) for medically inoperable stage I peripheral NSCLC patients has also completed accrual. Results of both studies are awaited.
- The RTOG 0813 phase I/II dose escalation study (escalating 50–60 Gy in 5 fractions), which aims to determine the safe and effective dose for central lung tumours in medically inoperable patients, is recruiting well.
- The ROSEL study in Europe for stage I NSCLC patients randomised to surgery or SABR, but sadly the study has been terminated due to poor recruitment.
- The STARS phase 3 study randomizes stage I NSCLC patients to either surgery or SABR. Recruitment is ongoing.

Evidence for SABR for secondary lung metastases

Localized primary cancer is usually treated with curative intent with local treatments such as surgery and/or radiotherapy often in combination with a systemic therapy component for the elimination of micrometastatic disease. In contrast, patients with distant metastasis are usually treated with palliative intent with systemic therapy such as chemotherapy or hormone treatment.

More recently, however, the existence of a status intermedius between widespread metastatic disease and local, organ-confined disease has been hypothesized; this state has been called oligometastatic disease[39]. Local therapies have been trialled in this group of patients in recent years, in the hope that the oligometastases seen on scans (usually defined as <5 in number) are the only remaining disease. This would make the local treatment potentially curative. Alternatively, the Norton–Simon hypothesis suggests that reducing tumour burden by local treatment may increase the efficacy of subsequent systemic therapy[40].

Prior to the development of SABR the local treatments used for oligometastases in the lung were surgery or radiofrequency ablation. The International Registry of Lung Metastases records 5206 cases of lung metastatectomy. The 5-year overall survival rate for the series was 36% in completely resected cases, with a 15-year survival rate of 22%, supporting the possibility of long-term survival in this group of patients with oligometastatic disease[41], especially from a colorectal primary.

Table 2 **Published studies of SABR for lung metastases**

Reference	Publication year	Publication type	Tumour location	Number of patients/ targets	No of metastases per patient	Primary cancer	Dose/ fractionation	Median follow-up (months)	Local control	Overall survival	Grade 3+ toxicity
Schefter et al.[42]	2006	Single-centre phase I	Peripheral or central	12/21	1–3	Colorectal 33%, lung 17%, kidney 17%, sarcoma 17%	48–60 Gy in 3 fractions	21	Not reported	At median 21 months:33%	None. Grade 1–2 oesophagitis 25%
Rusthoven et al.[43]	2009	Multi-centre phase I/II	Peripheral only	38/63	1–3	Colorectal 24%, sarcoma 18%, kidney 18%, lung 13%	60 Gy in 3 fractions	15.4	2 years 96%	2 years 39%	7.9% grade 3. No grade 4
Yoon et al.[44]	2006	Single-centre prospective	Peripheral or central	53/80	1–3	Lung 28%, liver 22%, colorectal 19%, head and neck 11%	30–48 Gy in 3–4 fractions	14	At median 14 months 70–100%	2 years 51%	None
Brown et al.[45]	2008	Single-centre retrospective	Peripheral or central	35/69	2–8	Lung 22%, kidney 18%, sarcoma 15%, head and neck 10%	5–60 Gy in 1–4 fractions	18	At median 18 months 71%	At median 18 months 77%	1 patient grade 4 pneumonitis
Okunieff et al.[46]	2006	Single-centre phase II	Peripheral or central	50/125	1–5	Colorectal 29%, breast 20%, lung 16%	48–57 Gy in 3–10 fractions	18.7	3 years 91%	3 years 25% for BED 100 Gy	None
Norihisa et al.[47]	2008	Single-centre retrospective	Peripheral or central	34/43	1–2	Lung 38%, colorectal 18%, head and neck 10%	48–60 Gy in 4–5 fractions	27	2 years 90%	2 years 84%	1 patient grade 3
Dhakal et al.[49]	2012	Single-centre retrospective	Peripheral or central	15/74	1–16	Soft tissue sarcoma	50 Gy in 5 fractions preferred	Not reported	3 years 82%	Median 2.1 years	None

Given the excellent local control rates achieved with SABR to primary lung cancers, together with the possibility of long-term survival that is possible in some patients with oligometastases, there has been increasing interest in the use of SABR for oligometastases to the lung.

Studies investigating SABR for the treatment of lung metastases tended to include patients who had often received multiple previous chemotherapy, i.e. they were often heavily pretreated. A selection of important publications on SABR for lung metastases are displayed in Table 2.

The University of Colorado carried out a phase I clinical trial to determine the MTD for SABR of lung metastases; there was to be a seamless transition to a subsequent phase II trial. Twelve patients with 1–3 lung metastases were treated in the phase I study with a starting dose of 48 Gy in 3 fractions increasing to a predefined upper dose limit of 60 Gy in 3 fractions[42]. Extrathoracic disease was permitted. There were no cases of dose-limiting toxicity, so the phase II study proceeded with a treatment dose of 60 Gy in 3 fractions. Taking the phase I/II study group as a whole, 38 patients had 63 lung metastases treated. At a median follow-up of 15.4 months, the 2-year local control rate was 96%, with a 2-year overall survival rate of 39%. Most patients (63%) progressed distantly at a median of 4 months after SABR, which explains the disappointing overall survival rate in the context of excellent local control. The grade 3 toxicity rate was acceptable at 7.9%. There was no grade 4 toxicity[43].

Yoon et al.[44] conducted a single-centre prospective study of primary NSCLC and lung metastasis patients. Fifty-three patients had lung metastases (1–3 lesions). All patients had a PET scan to confirm their staging. The starting dose was 30 Gy in 3 fractions; this was escalated to 48 Gy in 4 fractions (BED = 105.6). In keeping with the data for primary NSCLC, this study showed a dose–response relationship. At a median follow-up of 14 months, those treated with 30 Gy in 3 fractions had a local control rate of 70%, those treated with 40 Gy in 4 fractions had a 77% local control rate, and those treated with 48 Gy in 4 fractions had a 100% local control rate. There was no reported grade 3+ toxicity.

Brown et al.[45] published the treatment outcomes of a retrospective series of 35 patients with lung metastases (up to 8 lung metastases were treated per patient). Dose/fractionation was highly variable, prescribed dose was 5–60 Gy in 1–4 fractions (according to the number of metastases for treatment and the tolerance of OARs). At a median follow-up of 18 months, the local control rate was 71%, with an overall survival rate of 77%. One patient with 2 adjacent lung metastases experienced grade 4 pneumonitis.

Okunieff et al.[46] treated 49 evaluable patients with a total of 125 lung metastases. Each patient had up to 5 metastases. Thirty of these patients were treated with curative intent to a preferred dose of 50 Gy in 5 fractions (BED 100 Gy). The local control rate for all lesions at 3 years was 91%, with an overall survival at 3 years in those treated with curative intent of 25%. There was no reported grade 3+ toxicity.

Norihisa et al.[47] treated 35 patients with 1–2 lung metastases. The starting dose of 48 Gy in 4 fractions was escalated to 60 Gy in 5 fractions achieving a 2-year local control rate of 90%, and a 2-year overall survival rate of 84%. One patient acquired a bacterial chest infection after treatment and was reported to have grade 3 lung toxicity.

In terms of primary malignancies, several groups have reported prolonged survival with surgical resection of lung metastases from soft tissue sarcoma, such that this approach is now considered the standard of care in well-selected patients[48]. A retrospective series from the University of Rochester reviewed the records of 15 patients with soft tissue sarcoma lung metastases that were considered inoperable, and who therefore received SABR. The median number of metastases treated per patient was 4 (range 1–16) per patient. The preferred dose/fractionation was 50 Gy in 5 fractions. The 3-year local control rate was 82%, with a median survival of 2.1 years. There was no grade 3 toxicity[49].

Table 2 summarizes these key studies of SABR for lung metastases. The studies have analysed outcome data from 475 targets in 237 patients. Overall, SABR in this patient population is well tolerated with a grade 3+ toxicity rate of only 4%. The most promising treatment outcomes in terms of local control and overall survival seem to be achieved with regimes prescribing a BED of >100 Gy[50]. Local control at 3 years is 39–84%, and overall survival at 2 years is 39–84%.

Comparison with surgical data is difficult in the absence of randomized trials; the patients treated in the above trials were invariably medically inoperable, which has an impact on overall survival rates. However, the results for SABR are encouraging, and this non-invasive approach is a valid alternative to surgery or radiofrequency ablation in medically inoperable patients, or those declining surgery.

Summary

The recent advances in radiotherapy described in this review have enabled the safe delivery of SABR regimes, which deliver a high dose per fraction and a high BED. These high-BED regimes achieve excellent rates of tumour control. Although surgery remains the standard of care for operable patients with stage 1 NSCLC, SABR is now a realistic option for medically inoperable patients. SABR offers superior local control and overall survival rates to conventional radiotherapy, with acceptable toxicity. The results of key studies are eagerly awaited to further inform treatment decisions and refine the dose/fractionation.

Conflict of interest

The authors have no conflicts of interest to disclose.

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