SABRTooth: a randomised controlled feasibility study of stereotactic ablative radiotherapy (SABR) with surgery in patients with peripheral stage I nonsmall cell lung cancer considered to be at higher risk of complications from surgical resection

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Despite recruiting at a higher rate than previous studies, SABRTooth showed that a large UK RCT was not feasible. Patients found it challenging to accept randomisation between surgery and SABR due to their preferences. Alternative study designs are needed. https://bit.ly/2XtlVo6

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ABSTRACT

Objectives: Stereotactic ablative radiotherapy (SABR) is a well-established treatment for medically inoperable peripheral stage I nonsmall cell lung cancer (NSCLC). Previous nonrandomised evidence supports SABR as an alternative to surgery, but high-quality randomised controlled trial (RCT) evidence is lacking. The SABRTooth study aimed to establish whether a UK phase III RCT was feasible.

Design and methods: SABRTooth was a UK multicentre randomised controlled feasibility study targeting patients with peripheral stage I NSCLC considered to be at higher risk of surgical complications. 54 patients were planned to be randomised 1:1 to SABR or surgery. The primary outcome was monthly average recruitment rates.

Results: Between July 2015 and January 2017, 318 patients were considered for the study and 205 (64.5%) were deemed ineligible. Out of 106 (33.3%) assessed as eligible, 24 (22.6%) patients were randomised to SABR (n=14) or surgery (n=10). A key theme for nonparticipation was treatment preference, with 43 (41%) preferring nonsurgical treatment and 19 (18%) preferring surgery. The average monthly recruitment rate was 1.7 patients against a target of three. 15 patients underwent their allocated treatment: SABR n=12, surgery n=3.

Conclusions: We conclude that a phase III RCT randomising higher risk patients between SABR and surgery is not feasible in the National Health Service. Patients have pre-existing treatment preferences, which was a barrier to recruitment. A significant proportion of patients randomised to the surgical group declined and chose SABR. SABR remains an alternative to surgery and novel study approaches are needed to define which patients benefit from a nonsurgical approach.

Introduction

Stage I nonsmall cell lung cancer (NSCLC) is curable, with surgery considered the standard of care for medically fit patients. Reported 5-year overall survival rates range from 53% to 89% for stage IA1–3 disease and from 49% to 71% for stage IB disease [1]. However, a significant proportion of patients with stage I NSCLC are not suitable for surgery because of their age and/or poor fitness, often related to a patient's significant medical comorbidities. This is confirmed in the UK with data from the most recently published National Lung Cancer Audit where only 60.6% of stage I–II patients with a performance status of 0–2 underwent surgery [2]. This confirms that a significant proportion of patients are deemed to be at higher risk of surgical complications, including death.

An alternative approach to treating these "higher risk" patients is stereotactic ablative radiotherapy (SABR). For medically inoperable peripherally located stage I NSCLC, SABR has been shown to have improved overall survival rates, better local control [3] and better quality of life [4] when compared with conventional fractionated radical radiotherapy. Propensity-matched retrospective series of SABR in operable patients suggest that SABR may be an alternative to surgery, while others have favoured surgery [5–8]. A systematic review of studies published between 2006 and 2013 showed an equivalent 2-year overall survival between SABR and surgery [9], and similarly, a meta-analysis of articles published between 2000 and 2012 indicated no significant difference in overall survival between the two treatment strategies [1]. Finally, a single-centre competing risk analysis has shown no difference in cancer-specific survival between SABR and surgery in unmatched patients [10].

However, all these analyses are limited due to the quality of the retrospective data and, even with propensity matching, case selection and other significant factors (*e.g.* specific comorbidity, smoking history and socioeconomic factors) cannot be accounted for fully. Randomised trials for medically operable patients have been attempted in the past and closed prematurely due to failure to recruit (ROSEL (NCT00687986), STARS (NCT00840749) and ACOSOG-RTOG (American College of Surgeons Oncology Group–Radiation Therapy Oncology Group) (NCT01336894)) [11–13]. A pooled analysis of the STARS and ROSEL trials suggested that SABR was better tolerated and may lead to better OS than surgery for operable stage I NSCLC. This pooled analysis provoked significant debate in the lung cancer community and the consensus was that a larger RCT was required to validate these results [12]. Researchers involved in the ACOSOG-RTOG trial recommended that such a study would require commitment by investigators when discussing the trial with patients and close collaboration between surgeons and radiation oncologists [13]. Ultimately, clinician and patient acceptability of a challenging randomisation between SABR and surgery is key to the successful conduct of such trial.

The main challenge when trying to compare two very different treatment modalities with differing toxicity and treatment-related mortality profiles is to achieve equipoise amongst clinicians and patients. The aim of the SABRTooth study was to determine the feasibility and acceptability of conducting a large definitive phase III RCT comparing surgery with SABR in patients with stage I NSCLC deemed to be at a higher risk of surgical complications.

Material and methods

Study design and participants

The SABRTooth study was a UK-based, multicentre, open-label, parallel-group randomised controlled feasibility study in patients with peripheral stage I NSCLC considered to be at higher risk of complications from surgical resection.

In total, 54 patients were planned to be recruited to provide evidence that when recruitment rates were scaled up, a large definitive phase III RCT would be possible. Recruitment was from four established thoracic surgical centres and one selected larger referral unit.

Ethical approval was granted by Yorkshire and The Humber – Leeds West Research Ethics Committee (ref: 14/YH/1162). All patients provided written informed consent.

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TABLE 1 Eligibility criteria

Inclusion criteria	Exclusion criteria
1) Histological and/or clinical and radiological diagnosis of NSCLC. 2) Primary tumour characteristics: i) Peripherally located tumour as defined in the RTOG 0236 study and UK SABR Consortium guidelines. This states that the tumour must be >2 cm in axial diameter from a major airway="no fly zone". This includes the trachea, carina, right and left main bronchus and extends to the bifurcation of the right upper, right middle, right lower, left upper and left lower lobe bronchioles. ii) Maximal axial diameter of ⩽5 cm measured on lung windows on computed tomography. 3) No evidence of hilar or mediastinal lymph nodes involvement. Any hilar or mediastinal lymph nodes that are either PET-positive or >1 cm in axial dimension must be sampled by mediastinoscopy, endobronchial ultrasound or oesophageal endoscopic ultrasound and demonstrate negative cytology and/or pathology. 4) Local lung cancer MDT consensus opinion that patient is considered suitable for either surgical resection or SABR treatment and to be at higher risk of complications from surgical resection. 5) Age ⩾18 years. 6) Female patients must satisfy the investigator that they are either not of childbearing potential or not pregnant (*i.e.* be willing to undergo a pregnancy test within 72 h of surgery or day 1 of SABR treatment). 7) Able and willing to provide written informed consent.	1) Previous radiotherapy within the planned treatment volume. 2) History of clinically significant diffuse interstitial lung disease. 3) Any history of concurrent or previous invasive malignancy that, in the opinion of the investigator, could impact on trial outcomes. 4) Clinical or radiological evidence of metastatic spread. 5) History of psychiatric or addictive disorder or other medical condition that, in the opinion of the investigator, would preclude the patient from meeting the trial requirements. 6) Previous systemic therapies, including targeted and experimental treatments, for their current lung cancer diagnosis.

NSCLC: non-small cell lung cancer; RTOG: Radiation Therapy Oncology Group; SABR: stereotactic ablative radiotherapy; PET: positron emission tomography; MDT: multidisciplinary team.

Full details of the study protocol have been published previously [14]. Patients were identified by lung cancer teams through the multidisciplinary team (MDT) meetings, after assessment of eligibility. The core eligibility criteria did not change during the study (table 1). Guidance for defining patients at a higher risk from surgical complications from a lobectomy was based on national and international standard criteria (*e.g.* lung function, performance status, fitness assessment), Thoracoscore and the "Nottingham" nomogram (table 2) [15]. Pre-treatment investigations were as reported previously [14]. All data/scores were recorded prospectively, but ultimately, the final decision on patient eligibility rested with the local MDT.

Randomisation and masking

Patients were randomised (1:1) to surgery or SABR using a 24-h telephone or web-based system centrally governed by the Clinical Trials Research Unit, University of Leeds [14].

Procedures

Treatment was aimed to start within 31 days of randomisation, in line with National Health Service (NHS) guidelines.

The aim of surgery was a R0 resection; both thoracotomy and video assisted thoracoscopic surgery (VATS) were acceptable. The recommended procedure was an anatomical resection, ideally by lobectomy or an anatomical segmentectomy if not suitable for lobectomy. Sublobar or wedge resection was acceptable if an anatomical resection was not deemed possible by the treating surgeon. Sampling of at least three lobe-specific N2 nodal stations was recommended, though for wedge resections lymph node sampling was not mandated, as, due to patient factors, the duration of the anaesthetic may need to be minimised.

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This study is registered with ClinicalTrials.gov as NCT02629458. The study data can be made available *via* a controlled access approach (https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-015-0604-6) upon reasonable request. Requests for data access should be directed to the corresponding author in the first instance.

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TABLE 2 Definition of "higher risk" for surgery

We have suggested the below criteria for all groups to assist patient selection. However, as there are other individual contributing factors the final decision on whether the patient is suitable for the trial will rest with the local MDT		
Group A		
Suitable for surgery, but at higher risk of complications compared to group B (potentially eligible for SABRTooth)	CPEX: V'_{O_2}max 10–15 L·kg^{-1}·min^{-1} ISWT: walk 250–400 m Mortality risk from Nottingham score −6–20% at 90 days (derived using the SABRTooth trial calculator provided)	The patient can be approached for the trial if they meet one or more of these criteria
Group B		
Suitable for surgery, lower risk of complications	CPEX: V'_{O_2}max >15 L·kg^{-1}·min^{-1}, anaerobic threshold ISWT: walk >400 m and without significant desaturation Post-operative FEV_1 >50% predicted Mortality risk from Nottingham score <6% at 90 days for lobectomy (derived using the SABRTooth trial calculator provided). It is not anticipated that patients will need a pneumonectomy in this group of peripheral cancers	Not suitable for the trial
Group C		
Unsuitable for surgery as predicted risk of complications too high	CPEX: V'_{O_2}max <10 L·kg^{-1}·min^{-1} ISWT: walk <250 m and significant desaturation Pre-operative FEV_1 <30% predicted Mortality risk from Nottingham score >20% at 90 days for lobectomy (derived using the SABRTooth trial calculator provided). It is not anticipated that patients will need a pneumonectomy in this group of peripheral cancers Reduced ejection fraction (*e.g.* <40%) or evidence of ongoing myocardial ischaemia Recent cerebrovascular event (*e.g.* within 3 months of planned surgery)	Not suitable for the trial

MDT: multidisciplinary team; CPEX: cardiopulmonary exercise testing; V'_{O_2}max: maximal oxygen uptake; ISWT: incremental shuttle walk test; FEV_1: forced expiratory volume in 1 s.

Postoperative care was as per local unit protocols. Participants who were assessed as being unfit for surgery preoperatively were treated according to local guidelines.

SABR treatment was based on the accepted guidelines of the UK SABR consortium [16] for peripherally located stage I NSCLC, with three dose schedules based on the location of the tumour (supplementary material). Where participants were unable to receive their allocated treatment, *e.g.* if a SABR plan didn't meet planning objectives, radical radiotherapy or surgery would be considered according to local guidelines. Radiotherapy quality assurance was provided by the National Cancer Research Institute Radiotherapy Trials Quality Assurance Team. Details of the trial radiotherapy quality assurance are contained in the supplementary material: SABRTooth Radiotherapy Guidelines.

Treatment-related complications were treated as per local guidelines.

Data collection

All patients considered for the study were "tracked" up until the point of randomisation to establish reasons for dropout. Follow-up frequency and data collection was as previously reported [14] and in line with current NHS practice.

Complications, defined as any untoward medical event that has a causal relationship to the study or administration of any procedures, were collected from the end of surgery or final SABR administration until the end of the follow-up period. Serious complications and unexpected serious complications required reporting within 30 days of surgery or final SABR administration.

A qualitative substudy explored in up to 15 patients, their acceptability of the study. Eligible patients who declined study participation, or participants who were randomised but did not take up their treatment allocation were invited to take part in a feedback interview to identify reasons for their choices.

Intended recruitment pathways were captured *via* site-specific visits prior to the start of recruitment. A follow-up questionnaire captured changes to intended recruitment pathways, tools/criteria used to identify eligible patients and factors perceived to be a driver or challenge to recruitment.

TABLE 3 Secondary and exploratory objectives

Secondary objectives
To determine the number of patients screened and identified as eligible
To assess the uptake of allocated treatment procedure
To assess reasons for nonparticipation of eligible patients and participants not undergoing their allocated treatment procedure
To assess the feasibility of collecting QoL and Use of Resources data and determine the optimal frequency of data collection
To obtain EQ-5D utility estimates to inform the sample size calculations for a future phase III trial
Exploratory objectives
To qualitatively explore in a cohort of patients their acceptability of the study
To explore participant recruitment pathways at both treatment centres and referral units
To explore the use of available tools in defining patients at a higher risk from surgical resection
To monitor the 30-/90-/180-day mortality rates and overall survival at the end of the study

QoL: quality of life; EQ-5D: EuroQol five-dimension instrument.

Outcomes

The primary objective of the study was to quantitatively assess recruitment rates, *i.e.* patients providing consent for randomisation into the study, regardless of uptake of their randomised treatment procedure. An average rate of three patients per month across the five centres was needed over a formal monitoring period to demonstrate that a phase III trial would be feasible in the UK. The formal monitoring of recruitment period began 6 months after the start of recruitment (allowing for a run-in period for site set-up) for 13 months. Table 3 details the secondary and exploratory objectives.

Recruitment strategies

Significant efforts were made during study development to optimise recruitment. During the study, aspects of the recruitment strategy were modified based on feedback received from sites and patients. Aspects of these approaches are detailed in table 4.

Statistical analysis

The final analysis took place after the final participant had been followed-up for 6 months. Analyses involved descriptive and summary statistics and no formal hypothesis testing was conducted. The primary end-point analysis was based on the population of patients recruited during the formal monitoring period.

TABLE 4 Strategies to optimise recruitment

During study development
Establishing an MDT group and conducting study workshops to develop the grant application and design the protocol. The MDT group comprised clinical oncologists, surgeons, chest physicians, patient and public representatives, statisticians and trial managers
Establishing recruitment pathways which reflected the well-established referral pathways for cancer patients in the NHS whereby all cancer patients' cases are discussed in an MDT meeting before a treatment decision is made, allowing all suitable patients to be screened
Hosting a launch meeting to achieve and maximise "buy-in" from the surgeons, respiratory physicians and oncologists from each participating site before the study opened. Patient representatives provided guidance on how to approach patients with "mock" consultations
Ensuring the study was introduced to patients, and suitable patients were consented, by the research nurse and/or respiratory physician before meeting a surgeon and/or oncologist to reduce any clinician bias when describing the equipoise between the two treatments
During recruitment
Developing recruitment aids for the research nurses and clinicians, including a one-page MDT summary sheet to aid identification of potential patients, a more detailed eligibility aide-mémoire, a flip-chart to aid discussions of the treatments and randomisation process with patients and recruitment training videos of mock consultations
Developing recruitment aids for patients with the focus of describing the equipoise between the two treatments. Including a patient video describing the study and a shorter two-page participant information leaflet and publicity posters for clinic waiting areas
Conducting multiple study workshops/training days for the research nurses and patient and public representatives throughout the study and additional meetings/presentations at the British Thoracic Oncology Group annual conference (2016, 2017)
Site visits midway through the study by the chief investigator and trial manager to observe lung MDT meetings, meet local the local team and provide refresher training on study processes
Regular email updates on study progress *via* newsletters
Hosting video calls with sites to identify any challenges to recruitment and share "best practices" and "tips" for recruitment

MDT: multidisciplinary team; NHS: National Health Service.

The treatment and safety data are presented for the safety population, *i.e.* participants who received at least one dose of radiotherapy or who underwent surgery. The screening data is presented for the screening population, *i.e.* patients who were screened for entry into the study. All further analyses were carried out using the intention-to-treat population.

All analyses were performed in SAS version 9.4 (SAS, Cary, NC, USA).

A trial steering committee met to review the safety and ethics of the study prior to opening to and during recruitment.

Results

Between July 1, 2015 and January 31, 2017, 318 patients were considered for the study. 106 (33.3%) were initially assessed as eligible and 84 (79.2%) were approached to take part. In total, 24 (28.6%) patients were randomised from five UK centres, 14 to SABR and 10 to surgery (figure 1). The last date of patient follow-up was in July 2017.

Figure 2 presents the flow of patients through the screening process and reasons for patients not assessed as eligible, not approached or declining randomisation where known. The trial population was

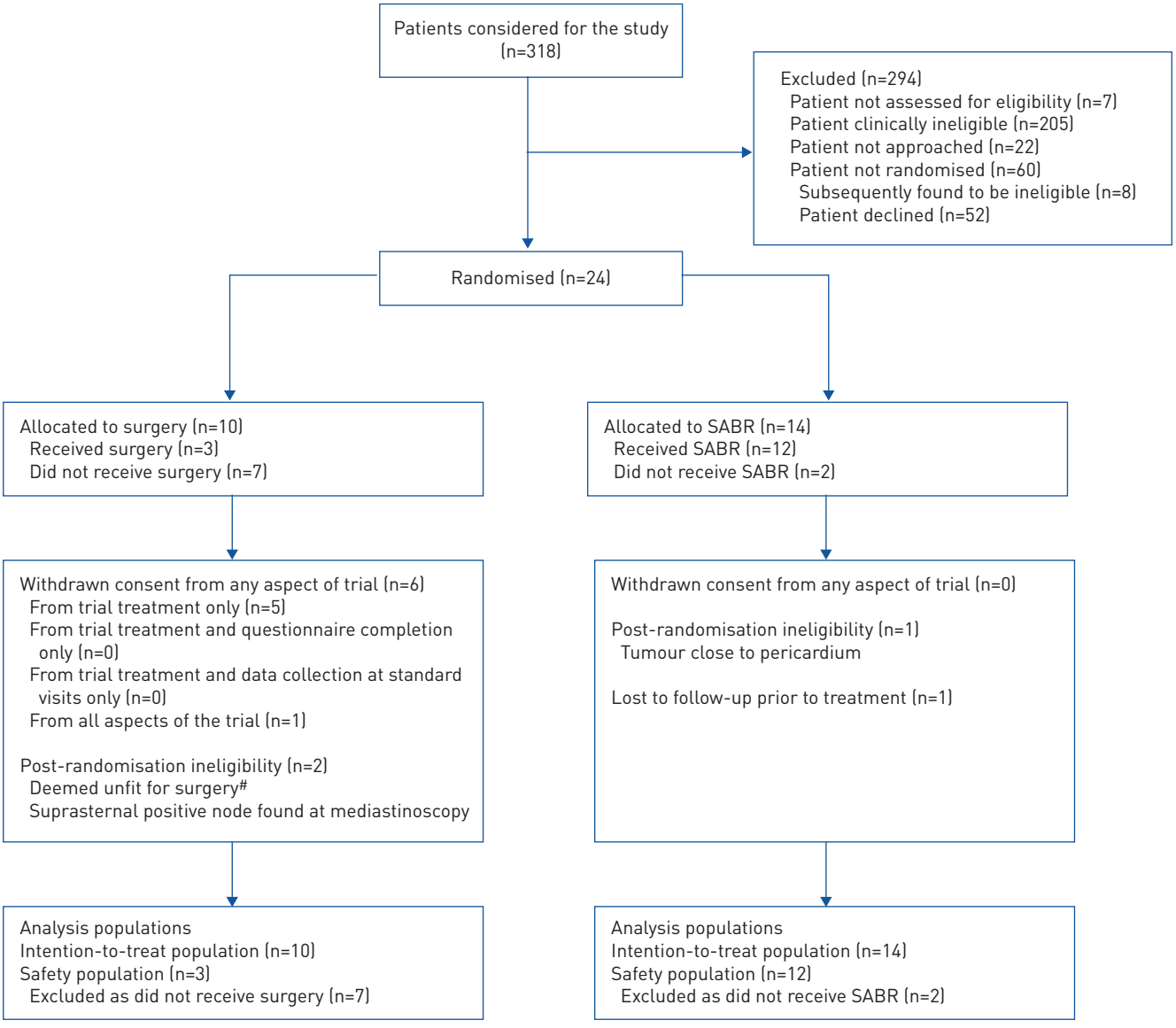

FIGURE 1 Consolidated Standards of Reporting Trials diagram. SABR: stereotactic ablative radiotherapy. #: clinician's decision; participant submitted a withdrawal of consent for all aspects of the trial.

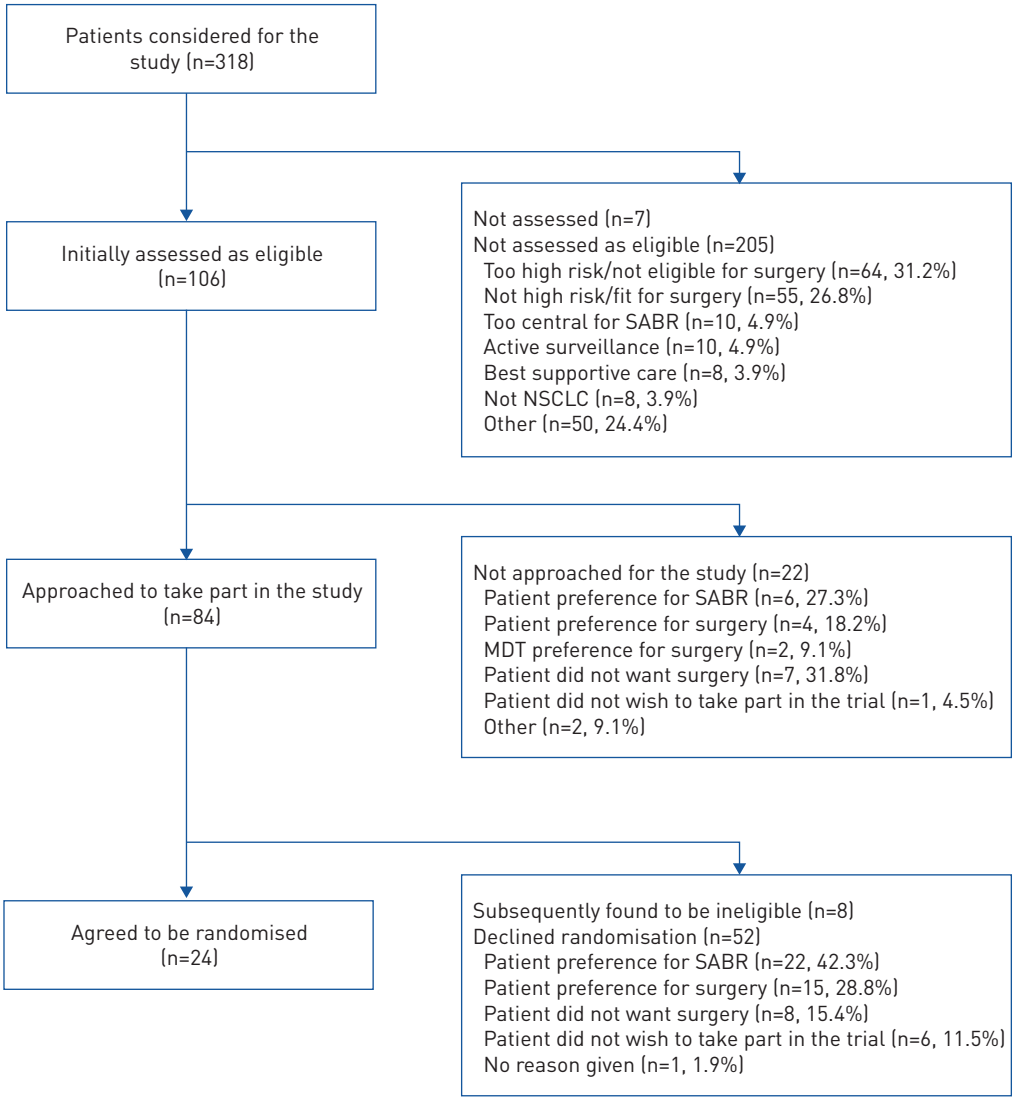

FIGURE 2 Flow of patients through the study screening process. SABR: stereotactic ablative radiotherapy; NSCLC: non-small cell lung cancer.

representative of the general lung population with stage I NSCLC. Of the 84 patients initially assessed as eligible and approached for the study, 52 (61.9%) declined randomisation with 42.3% (n=22) preferring SABR and 28.8% (n=15) for surgery; eight patients did not want surgery, six did not wish to enter a trial and one patient did not specify a reason.

Table 5 presents the baseline demographic and disease-related characteristics of the randomised study population. The median (range) age was 75 (54–88) years and the majority of patients were female (n=14, 58.3%). All but one participant presented with one or more pre-existing conditions. Surgical participants had a larger median tumour size (2.7 *versus* 1.9 cm) and greater proportion of stage T2a tumours (70.0% *versus* 21.4%) compared to SABR.

24 patients were randomised over the whole recruitment period (SABR n=14, surgery n=10), with a median (range) recruitment rate of four (1–9) patients across the five recruiting centres. The formal assessment of the primary end-point began 6 months after the start of recruitment and over the 13-month formal monitoring of recruitment period, 22 patients were randomised (SABR n=12, surgery n=10). There was an average recruitment rate of 1.7 patients per month, falling short of the required three patients per month to meet the primary end-point and demonstrate feasibility of recruitment. All five recruiting sites recruited to the study.

Of the 24 participants randomised, 62.5% (n=15) underwent their allocated treatment procedure; 30.0% (n=3) of participants randomised to surgery compared to 85.7% (n=12) randomised to SABR (figure 1). Of the seven participants not undergoing surgery, all were tumour stage T2a. Five did not wish to have

TABLE 5 Baseline demographics and disease characteristics

	Surgery	SABR	Total
Patients	10	14	24
Sex			
Female	6 (60.0)	8 (57.1)	14 (58.3)
Male	4 (40.0)	6 (42.9)	10 (41.7)
Age years			
Mean±SD	71.9±6.06	76.0±11.46	74.3±9.63
Median (range)	73.5 (63.0–79.0)	79.0 (54.0–88.0)	75.0 (54.0–88.0)
Missing	0	0	0
Pre-existing conditions			
Yes	9 (90.0)	14 (100)	23 (95.8)
No	1 (10.0)	0 (0.0)	1 (4.2)
Cancer type			
Adenocarcinoma	5 (83.3)	6 (75.0)	11 (78.6)
Squamous cell cancer	1 (16.7)	1 (12.5)	2 (14.3)
Unknown[#]	0 (0.0)	1 (12.5)	1 (7.1)
ECOG performance status			
0	4 (40.0)	2 (14.3)	6 (25.0)
1	4 (40.0)	10 (71.4)	14 (58.3)
2	2 (20.0)	2 (14.3)	4 (16.7)
Tumour stage			
T1a	1 (10.0)	8 (57.1)	9 (37.5)
T1b	2 (20.0)	3 (21.4)	5 (20.8)
T2a	7 (70.0)	3 (21.4)	10 (41.7)
Tumour size cm			
Mean±SD	2.5±0.84	2.1±0.78	2.3±0.82
Median (range)	2.7 (0.7–3.5)	1.9 (1.2–4.3)	2.2 (0.7–4.3)
Missing	0	0	0
Charlson comorbidity index			
Mean±SD	3.7±1.83	3.9±3.15	3.8±2.63
Median (range)	4.0 (1.0–6.0)	3.5 (1.0–13.0)	4.0 (1.0–13.0)
Missing	0	0	0
Thoracoscore %			
Mean±SD	3.2±2.81	3.0±1.31	3.1±2.05
Median (range)	2.0 (0.1–9.6)	3.0 (0.6–4.7)	3.0 (0.1–9.6)
Missing	0	1	1
Nottingham risk score %			
Mean±SD	6.2±3.58	6.3±2.82	6.3±3.08
Median (range)	6.8 (2.0–10.9)	5.8 (2.7–12.7)	6.0 (2.0–12.7)
Missing	0	0	0

Data are presented as n or n (%), unless otherwise stated. SABR: stereotactic ablative radiotherapy; ECOG: Eastern Cooperative Oncology Group. [#]: patient lost to follow-up before result confirmed.

surgery and two were deemed to be ineligible post-randomisation (figure 1). All seven participants went on to receive radiotherapy (SABR n=6, conventionally fractionated radiotherapy n=1). In the SABR group, one participant was deemed ineligible post-randomisation and received radical radiotherapy; the final participant was lost to follow-up.

Median (range) time from randomisation to start of treatment for the three surgery and 12 SABR participants was 38 (20–61) days and 29 (19–48) days, respectively. All participants who underwent protocol treatment received it as planned. The surgical procedure undertaken was either VATS (n=2) or open (n=1). SABR dose fractionation was as per the UK SABR Consortium guidelines with three participants receiving 54 Gy in three fractions, eight receiving 55 Gy in five fractions and one receiving 60 Gy in five fractions. Median (range) time between surgical operation date and date of discharge was 13 (4–15) days. Median (range) time on study measured from randomisation to date of last follow-up, withdrawal or death was 9.2 (0.2–20.3) months, 11.8 (4.1–20.3) months for SABR and 7.6 (0.2–12.7) months for surgery.

Table 6 presents the compliance rates with the EuroQol-5D-5L and -VAS questionnaires. Compliance rates for the Quality of Life Questionnaire (QLQ)-C30, QLQ-LC13 and Use of Resources questionnaires were

TABLE 6 EuroQol-5D-5L and -VAS compliance rates

	Surgery	SABR	Total
Baseline questionnaire			
Yes	10 (100.0)	14 (100.0)	24 (100.0)
No	0 (0.0)	0 (0.0)	0 (0.0)
Total	10 (100)	14 (100)	24 (100)
Pretreatment questionnaire			
Yes	5 (50.0)	13 (92.9)	18 (75.0)
No	5 (50.0)	1 (7.1)	6 (25.0)
Total	10 (100)	14 (100)	24 (100)
6 week (clinic visit)			
Yes	6 (75.0)	13 (92.9)	19 (86.4)
No	2 (25.0)	1 (7.1)	3 (13.6)
Total	8 (100)	14 (100)	22 (100)
3 month (clinic visit)			
Yes	5 (62.5)	12 (85.7)	17 (77.3)
No	3 (37.5)	2 (14.3)	5 (22.7)
Total	8 (100)	14 (100)	22 (100)
6 month (clinic visit)			
Yes	3 (42.9)	10 (83.3)	13 (68.4)
No	4 (57.1)	2 (16.7)	6 (31.6)
Total	7 (100)	12 (100)	19 (100)
9 month (clinic visit)			
Yes	0 (0.0)	8 (88.9)	8 (50.0)
No	7 (100.0)	1 (11.1)	8 (50.0)
Total	7 (100)	9 (100)	16 (100)
12 month (clinic visit)			
Yes	1 (25.0)	5 (83.3)	6 (60.0)
No	3 (75.0)	1 (16.7)	4 (40.0)
Total	4 (100)	6 (100)	10 (100)
15 month (postal)			
Yes	0 (0.0)	2 (66.7)	2 (40.0)
No	2 (100.0)	1 (33.3)	3 (60.0)
Total	2 (100)	3 (100)	5 (100)
18 month (clinic visit)			
Yes	n/a	1 (50.0)	1 (50.0)
No	n/a	1 (50.0)	1 (50.0)
Total	0	2 (100)	2 (100)

Data are presented as n (%). The denominator represents the number of expected questionnaires at each time point, excluding those participants who had died, withdrawn from quality of life assessment or did not reach that time point by the end of the follow-up period. SABR: stereotactic ablative radiotherapy.

similar and for returned questionnaires, the completion rates were high. The mean±SD of the EQ-5D utility scores (where scores could be derived) for surgery and SABR respectively were 0.8±0.22 (n=10) and 0.8±0.09 (n=14) at baseline; 0.9±0.14 (n=5) and 0.8±0.11 (n=13) pre-treatment; 0.7±0.35 (n=7) and 0.8±0.11 (n=13) at 6 weeks; 0.7±0.34 (n=6) and 0.7±0.20 (n=12) at 3 months; and 0.7±0.45 (n=4) and 0.7±0.17 (n=10) at 6 months. Beyond this, data are limited in the surgical group. Summaries of the QLQ-C30, QLQ-LC13 and Use of Resources questionnaires are available on request.

In the surgical group, 23.8% (five out of 21) of all the reported complications were Common Terminology Criteria for Adverse Events grade 3 compared to 8.7% (six out of 69) of events in the SABR group. All complications were attributed to protocol treatment and were expected.

At the time of final analysis there were three participant deaths. One occurred 4 days post-surgery due to a post-operative bronchopneumonia in a patient with ischaemic heart disease. Two participants in the SABR group died 326 and 405 days post-treatment due to progressive lung cancer and unrelated septicaemia.

Qualitative research

12 patients took part in the qualitative interviews; nine who had declined participation and three who declined to take up their randomised allocation to surgery. These patients had a clear preference for surgery or SABR. Further details are provided in the supplementary material, but key themes included

1) the complexity of decision making when choosing between different treatments alongside the decision to take part in a trial; and 2) patients making sense of their decision by talking to healthcare professionals, family and friends, or using their own prior experience or knowledge of the treatment.

Recruitment pathways were similar between sites as presented in the supplementary material. However, strategies for introducing and discussing the study with patients were adapted in each centre. Mentioning the study earlier in the patient pathway was found to be helpful and did not overburden patients with information. Table 7 presents a summary of the perceived challenges to recruitment, and factors believed to encourage recruitment from a site perspective.

The assessment criteria and tools used to identify suitable study patients varied between sites. MDT opinion and Eastern Cooperative Oncology Group performance status were always used.

Discussion

The SABRTooth feasibility study failed to achieve the predefined recruitment target of an average of three patients per month during the 13-month formal monitoring period; demonstrating that a larger phase III RCT of SABR *versus* surgery is not possible in the UK. Despite the lower than anticipated recruitment, a great deal of insight was obtained about running a trial in this context in the UK.

Multiple secondary end-points were studied to evaluate the most optimal study design and explore reasons for participation/non-participation. Adaptation and learning were built into the trial, employing strategies that had been successful in other randomised trials between surgery and non-surgical treatments [17]. The recruitment strategy was modified throughout the study based on feedback from sites and through greater understanding the complexity of the conversations between patients and clinicians when discussing this trial. Alternative approaches to randomisation were also considered, including the pre-randomisation model employed in the STABLE-MATES trial (NCT02468024). It was felt that there was insufficient evidence and concerns around the methodological robustness of this design to support this change during the recruitment period of SABRTooth [18].

TABLE 7 Site-perceived drivers and challenges to recruitment

	Recruitment drivers	Recruitment challenges
Patient factors	Patients not having a treatment preference	Patients having a treatment preference: Often influenced by their awareness of their illness and comorbidities, preconceived ideas about the risk/benefits of surgery/SABR, previous treatment experiences (be it themselves or friends/relatives) Patients did not like having the decision removed from them, and were not used to clinicians having uncertainty about the best treatment options
Recruiter factors	Introducing the study as early as possible Providing patients with appropriate level of information Equipoise and effectiveness of both treatments being clearly explained to the patients so they that felt comfortable with the concept of randomisation The strategy for discussion of the study with the patient, including the terminology used, *e.g.* "early-stage lung cancer" and "cure" were seen as being important Follow-up calls to help patients consolidate their thinking about the study and address any concerns	Patients being overloaded with information potentially making their decision harder Ethical issues around "challenging" patient preferences and difficulties in challenging the MDTs opinions Lack of equipoise of research nurses/other team members, which may be conveyed unconsciously to patients Difficulty in defining "higher risk" and patients towards to the lower end of the scale but still eligible often being sent towards surgery Pool of eligible patients not being as big as expected Resection rates published on a national audit, which may lead to a push for surgery
Site factors	Clear channels of communication between the teams at site Having the study firmly embedded in the MDT	Clerical issues, meaning patients were referred straight to surgery Time pressures of MDT discussions to discuss and identify all potentially suitable patients Staffing levels and additional time pressures on staff to identify and discuss the study with patients which require longer appointments

SABR: stereotactic ablative radiotherapy; MDT: multidisciplinary team.

The reasons for the SABRTooth study failing to recruit are complex and reflect both pre-existing patient and clinician preferences, as detailed in table 7.

Obtaining consent and randomising patients prior to meeting the treating surgeon or oncologist by a research lung research nurse and/or respiratory physician was intended to remove treating clinician bias, but may also have contributed to the high surgical dropout rate. Education and training were provided before and during the SABRTooth study to the research nurses and respiratory physicians to try and optimise the explanation of the trial and facilitate consent. Given the relatively small numbers of researchers and patients it was not possible to assess whether clinician bias consciously or subconsciously influenced the patients and hampered patient's acceptance of randomisation. However, it is important to note that ~70% of the patients who were considered eligible but declined the study had a preference for non-surgical treatments and were predominantly older with significant comorbidities.

Targeting higher risk patients reduced the number of potential eligible patients, but reflected patients for where there is most clinician equipoise between surgery or SABR. Approached patients found the study information to be clear and well-presented which often prompted more in-depth conversation with clinicians regarding their treatment options. Therefore, all approached patients would have been aware they were higher risk for surgery and been more aware of all the treatment options, particularly the option of a non-surgical approach. This may have influenced the patient's equipoise as patients had a clear preference for one of the treatment options when asked. Patients were clear that this was personal decision which they wanted to make for themselves, often after talking to health professionals, family or friends.

In an era of increasing availability of information of treatment options, through formal literature, online information and patient forums, patients are, and will continue to be better informed of their treatment options. The SABRTooth study has shown that the majority of eligible patients, when given further information on both options, have a treatment preference for a non-surgical approach, both in the screened population and for those patients randomised to surgery.

We need to involve patients in the treatment decision-making process and a shared decision-making approach is of growing interest in oncology studies. This is particularly relevant when the treatment options are preference-sensitive, *i.e.* when there are multiple suitable treatment options. However, it is recognised that incorporating a shared decision-making into daily clinical practice brings its own challenges [19] and requires skilled clinicians, a combination of interventions that support the patient, clinician and organisation and "buy-in" from the clinical team and organisation [20].

SABRTooth has shown that is it not feasible to randomise higher-risk stage I NSCLC patients to surgery or SABR in the NHS. However, there are ongoing RCTs in similar populations (at the time of publication) which include the VALOR (NCT02984761 and STABLE-MATES (NCT02468024) studies, which are open to recruitment in North America and may answer this important research question.

Further work is required to address the issues raised in the SABRTooth study. While a randomised trial might be feasible where there are sufficient resources to address the equipoise of all involved, the extent to which this could be applied in routine clinical practice would be limited. Thus, randomising between SABR and surgery is challenging within the NHS, particularly when focusing on a well-informed selected older population with comorbidities. Despite RCTs being considered a gold standard framework for evaluating clinical trials, they are not always suitable to answer every question. Alternative strategies are needed to provide the evidence to assist policy makers, practitioners and patients to decide the most appropriate treatment. Future studies for high-risk patients with stage I/II NSCLC may benefit from non-randomised designs that take account of the decision-making and preferences of the patients and clinicians as part of shared decision-making.

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