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SABRTOOTH: A randomised controlled feasibility study of Stereotactic Ablative Radiotherapy (**SABR**) with surgery in pa**T**ients with peripheral stage I n**O**n-small cell lung cancer (NSCLC) c**O**nsidered **T**o be at **H**igher risk of complications from surgical resection

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Trial registration, funding and sponsor

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Competing interest statement

All authors declare: no support from any organisation for the submitted work, except for the declared funding support from YCR and RfPB; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

Abstract

Objectives

Stereotactic Ablative Radiotherapy (SABR) is a well-established treatment for medically inoperable peripheral stage I non-small cell lung cancer (NSCLC). Previous non-randomised 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 multi-centre, randomised controlled feasibility study targeting patients with peripheral stage I NSCLC considered to be at higher-risk of surgical complications. Fifty-four 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. Of 106 assessed as eligible (33.3%), 24 patients (22.6%) were randomised to SABR (n=14) or surgery (n=10). A key theme for non-participation was treatment preference with 43 (41%) preferring non-surgical treatment and 19(18%) preferring surgery. The average monthly recruitment rate was 1.7 patients against a target of 3. Fifteen patients underwent their allocated treatment, 12 SABR, 3 surgery.

Conclusions

We conclude that a phase III RCT randomising higher-risk patients between SABR and surgery is not feasible in the National Health Service (NHS). 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 non-surgical approach.

Introduction

Stage I non-small cell lung cancer (NSCLC) is curable, with surgery considered the standard of care for medically fit patients. Reported 5-year overall survival (OS) rates range from 53-89% for stage IA1-3 disease and 49-71% 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 co-morbidities. This is confirmed in the UK with data from the most recently published National Lung Cancer Audit (NLCA) 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' is stereotactic ablative radiotherapy (SABR). For medically inoperable peripherally located stage I NSCLC, SABR has been shown to have improved overall survival rates and 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 whilst others have favored surgery (5-8). A systematic review of studies published between 2006 and 2013 showed an equivalent 2-year OS between SABR and surgery (9) and similarly, a meta-analysis of articles published between 2000 and 2012 indicated no significant difference in OS between the two treatment strategies (10). Finally, a single-centre competing risk analysis has shown no difference in cancer-specific survival between SABR and surgery in unmatched patients (11)

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 co-morbidity, smoking history, and socio-economic 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 (NCT01336894) (12-14). 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 (13). 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 (14). 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, multi-centre, 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.

Full details of the study protocol have been published previously (15). Patients were identified by lung cancer teams through the multi-disciplinary 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) (16). Pre-treatment investigations were as reported previously (15). 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-hour telephone or web-based system centrally governed by the Clinical Trials Research Unit, University of Leeds (15).

Procedures

Treatment was aimed to start within 31 days of randomisation, in line with 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. Sub-lobar

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. Post-operative care was as per local unit protocols. Participants who were assessed as being unfit for surgery pre-operatively were treated according to local guidelines.

SABR treatment was based on the accepted guidelines of the UK SABR consortium (17) 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 NCRI Radiotherapy Trials Quality Assurance Team (RTTQA). 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 drop-out. Follow-up frequency and data collection was as previously reported (15) 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 (SCs) and unexpected serious complications (USCs) required reporting within 30 days of surgery or final SABR administration.

A qualitative sub-study 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.

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 endpoint analysis was based on the population of patients recruited during the formal monitoring period. 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 (ITT) population.

All analyses were performed in SAS version 9.4.

A Trial Steering Committee (TSC) met to review the safety and ethics of the study prior to opening to and during recruitment.

Results

Between 1 July 2015 and 31 January 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 patients were randomised (28.6%), 14 to SABR and ten to surgery from five UK centres (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 reason for patients not assessed as eligible, not approached or declining randomisation where known. The trial population was 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 age was 75 years (54-88) and the majority were female (n=14, 58.3%). All but one participant presented with one or more pre-existing condition. Surgical participants had a larger median tumour size (2.7 vs 1.9cm) and greater proportion of stage T2a tumours (70.0% vs 21.4%) compared to SABR.

Twenty-four patients were randomised over the whole recruitment period (14 SABR, 10 Surgery). With a median recruitment rate of 4 patients across the 5 recruiting centres (range: 1, 9). The formal assessment of the primary endpoint began 6 months after the start of recruitment and over the 13-month formal monitoring of recruitment period, 22 patients were randomised (12 SABR, 10 Surgery). 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 endpoint 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 surgery and two were deemed to be ineligible post-randomisation (Figure 1). All seven participants went on to receive radiotherapy (six SABR, one conventionally fractionated radiotherapy). In the SABR group, one participant was deemed ineligible post-randomisation and received radical radiotherapy; the final participant was lost to follow-up.

Median time from randomisation to start of treatment for the 3 surgery and 12 SABR participants was 38 days (range: 20 to 61) and 29 days (range: 19 to 48) 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 3 participants receiving 54 Gy in 3 fractions, 8 receiving 55Gy in 5 fractions, and 1 receiving 60Gy in 5 fractions. Median time between surgical operation date and date of discharge was 13 days (range: 4 to 15). Median time on study measured from randomisation to date of last follow-up, withdrawal or death was 9.2 months (range: 0.2 to 20.3), 11.8 months (range: 4.1 to 20.3) for SABR and 7.6 months (range: 0.2 to 12.7) for surgery.

Table 6 presents the compliance rates with the EQ-5D-5L and EQ-VAS questionnaires. Compliance rates for the QLQ-C30, QLQ-LC13 and Use of Resources questionnaires were similar and for returned questionnaires, the completion rates were high. The mean and standard deviation 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; 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% (5/21) of all the reported complications were CTCAE grade 3 compared to 8.7% (6/69) 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 four 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

Twelve 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; 2) patients making sense of their decision by talking to health care 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 ECOG 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 endpoints 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 (18). 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 (19).

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.

Consenting 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. 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 if clinician bias consciously or subconsciously influenced the patients and hampered patient's acceptance of randomisation. However, it is important to note that approximately 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, on-line 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 (SDM) 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. It is however recognised that incorporating SDM into daily clinical practice brings its own challenges (20) and requires skilled clinicians, a combination of interventions that support the patient, clinician and organisation and “buy-in” from the clinical team and organisation (21).

SABRTooth has shown that is it not feasible to randomise higher-risk stage I non-small cell lung cancer 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. Whilst 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.

Contributors

KNF, LMcP, WG, DRB, DSM, CFF, JH, JB, FC, PA, AS and MS conceived and designed the study. RN, CO and SB coordinated the study and collected and validated the study data. ME, RB, CFF, BN, JF, CP, MEJC, MK and JB recruited patients to the study. LMcP, JW, JB,

JH and PH analysed the data. All authors approved the final version of the publication. KNF and LMcP are responsible for the overall content of the article as guarantors.

The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Data sharing

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 Dr Kevin Franks [kevin.franks@nhs.net] in the first instance.

Transparency declaration

The joint first authors (KNF and LMcP) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; and that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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433 **Figure 1. CONSORT diagram**

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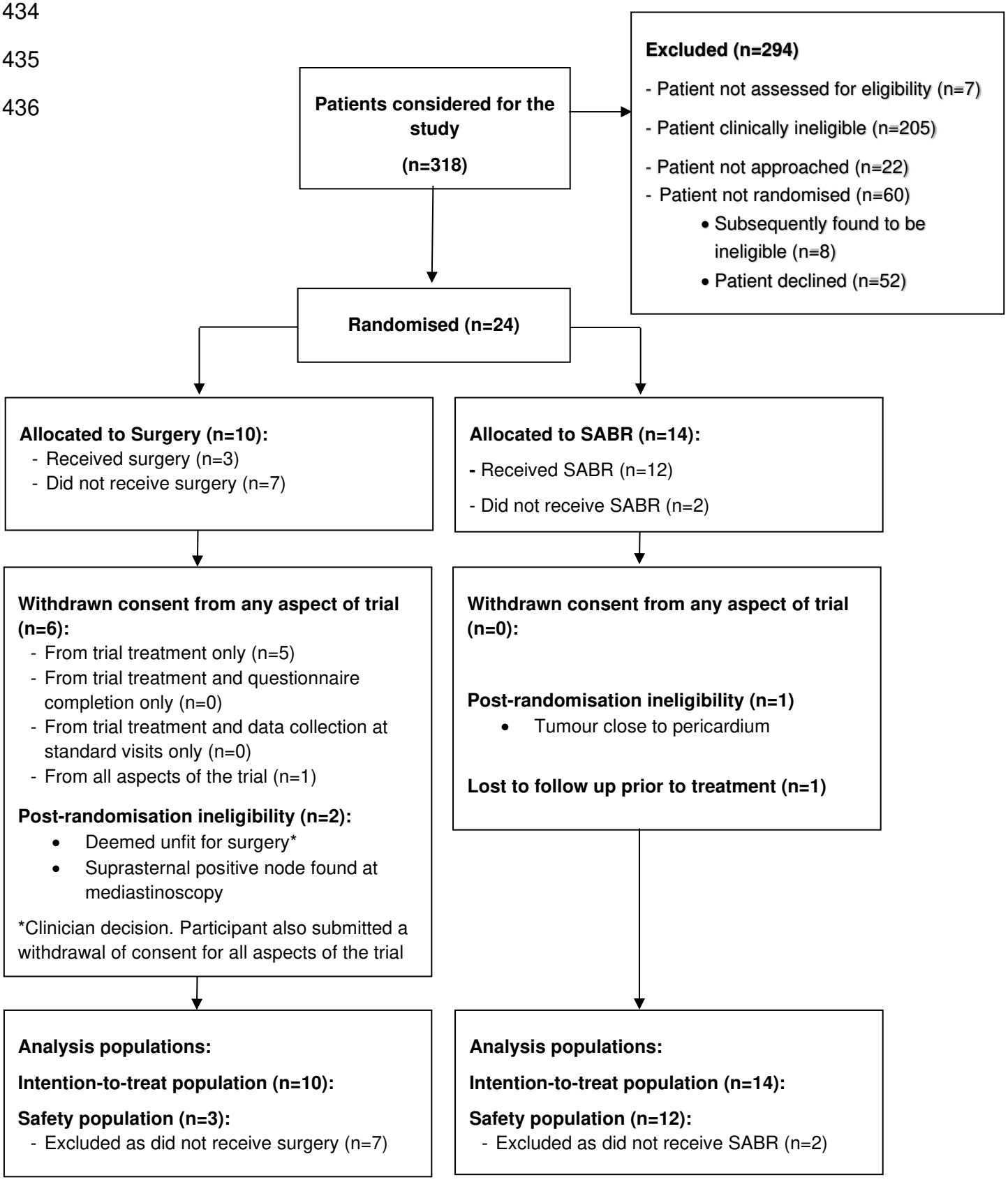
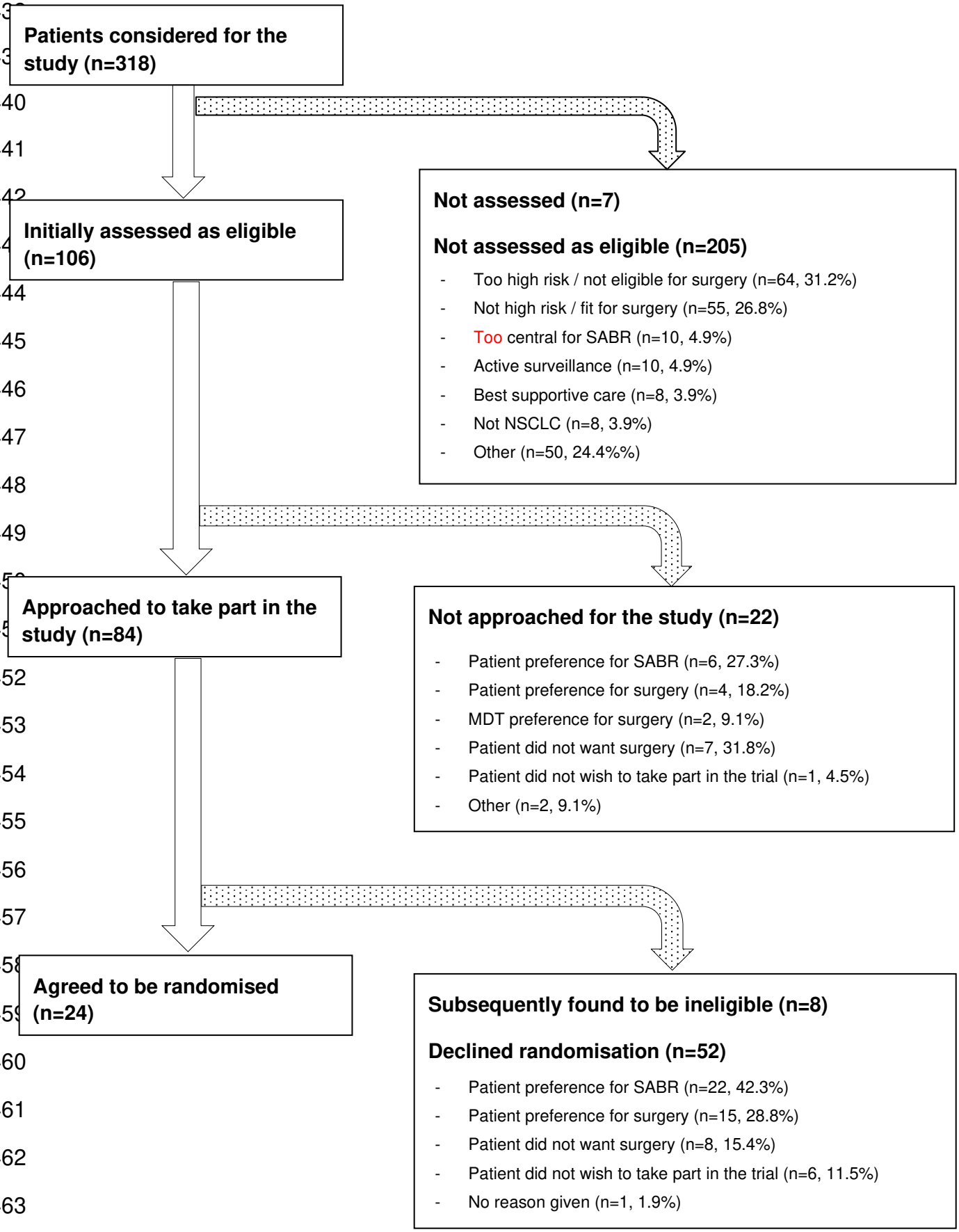


Figure 2. Flow of patients through the study screening process



464 **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 more than 2cm 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 >1cm in axial dimension must be sampled by mediastinoscopy, endo-bronchial 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 6. Female patients must satisfy the investigator that they are either not of childbearing potential or not pregnant (i.e.	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.

be willing to undergo a pregnancy test within 72hrs of surgery or day 1 of SABR treatment) 7. Able and willing to provide written informed consent.	

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466 **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 <u>Higher risk</u> of complications compared to group B *(Potentially eligible for SABRTooth)*	▪ CPEX – VO2 Max 10-15 L/kg/min ▪ ISWT – walk 250-400 metres ▪ 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 – <u>Lower risk</u> of complications	▪ CPEX- VO2 Max >15 L/kg/min, Anaerobic Threshold ▪ ISWT – walk > 400 metres and without significant desaturation ▪ Predicted post-operative FEV1 > 50% ▪ 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- VO2 Max <10 L/kg/min ▪ ISWT – walk < 250 metres and significant desaturation ▪ Pre-operative FEV1 < 30% ▪ Mortality Risk from Nottingham score > 20% at 90 days for lobectomy (Derived using the SABRTooth trial calculator provided). It is not	Not suitable for the trial

	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 cerebro-vascular event (e.g. within 3 months of planned surgery)	

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468 **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 non-participation 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 (OS) at the end of the study

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477 **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-memoir, 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 mid-way 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

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480 **Table 5. Baseline demographics and disease characteristics**

	Surgery (N=10)	SABR (n=14)	Total (N=24)
Gender			
Female	6 (60.0%)	8 (57.1%)	14 (58.3%)
Male	4 (40.0%)	6 (42.9%)	10 (41.7%)
Age			
Mean (s.d.)	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 (s.d.)	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 co-morbidity index			
Mean (s.d.)	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 (s.d.)	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)

	Surgery (N=10)	SABR (n=14)	Total (N=24)
Missing	0	1	1
Nottingham risk score (%)			
Mean (s.d.)	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

481 * Patient lost to follow-up before result confirmed

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483 **Table 6. EQ-5D-5L and EQ-VAS compliance rates**

Questionnaires Received	Surgery n (%)	SABR n (%)	Total n (%)
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%)**
Pre-treatment 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%)

Questionnaires Received	Surgery n (%)	SABR n (%)	Total n (%)
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%)**

Footnote: The denominator represents the number of expected questionnaires at each time point, excluding those participants who had died, withdrawn from QoL or did not reach that time point by the end of the follow-up period

493 **Table 7. Site perceived drivers and challenges to recruitment**

Recruitment Drivers	Recruitment Challenges
<u>Patient factors</u> • patients not having a treatment preference <u>Recruiter factors</u> • 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 <u>Site factors:</u> • clear channels of communication between the teams at site • having the study firmly embedded in the MDT	<u>Patient factors</u> • 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 <u>Recruiter factors</u> • 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 <u>Site factors</u> • 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

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Supplementary Material

1. Qualitative Research

2. Recruitment Pathways

3. SABRTooth Radiotherapy Guidelines