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Early View

Original article

SABRTOOTH: A randomised controlled feasibility study of Stereotactic Ablative Radiotherapy (SABR) with surgery in paTients with peripheral stage I nOn-small cell lung cancer (NSCLC) cOnsidered To be at Higher risk of complications from surgical resection

Kevin N. Franks, Lucy McParland, Joanne Webster, David R. Baldwin, David Sebag-Montefiore, Matthew Evison, Richard Booton, Corinne Faivre-Finn, Babu Naidu, Jonathan Ferguson, Clive Peedell, Matthew E.J. Callister, Martyn Kennedy, Jenny Hewison, Janine Bestall, Walter M. Gregory, Peter Hall, Fiona Collinson, Catherine Olivier, Rachel Naylor, Sue Bell, Peter Allen, Andrew Sloss, Michael Snee

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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

Author list and emails

Kevin N Franks[1,2*$], kevin.franks@nhs.net

Lucy McParland[3*], lucymcparland@hotmail.co.uk

Joanne Webster[3], J.C.Webster@leeds.ac.uk

David R Baldwin[4], David.Baldwin@nuh.nhs.uk

David Sebag-Montefiore[1,2,3], D.SebagMontefiore@leeds.ac.uk

Matthew Evison MD[5], m.evison@nhs.net

Richard Booton[5], richard.booton@mft.nhs.uk

Corinne Faivre-Finn[6], Corinne.Finn@christie.nhs.uk

Babu Naidu[7], b.naidu@bham.ac.uk

Jonathan Ferguson[8], jonathan.ferguson@nhs.net

Clive Peedell[8], clive.peedell@stees.nhs.uk

Matthew EJ Callister[9], matthew.callister@nhs.net

Martyn Kennedy[9], martyn.kennedy@nhs.net

Jenny Hewison[10], J.Hewison@leeds.ac.uk

Janine Bestall[10], J.Bestall@leeds.ac.uk

Walter M Gregory[3], W.M.Gregory@leeds.ac.uk

Peter Hall[11], p.s.hall@ed.ac.uk

Fiona Collinson[3], F.J.Collinson@leeds.ac.uk

Catherine Olivier[3], C.M.Olivier@leeds.ac.uk

Rachel Naylor[3], R.Naylor@leeds.ac.uk

Sue Bell[3], S.E.Bell@leeds.ac.uk

Peter Allen[12], pallen278@icloud.com

Andrew Sloss[12], andy@51055.com

Michael Snee[1], m.snee@nhs.net

*Joint first authors

[$]Corresponding author

Corresponding author contact information:

Dr Kevin N Franks

Level 4, Bexley Wing

Leeds Cancer Centre

St James's University Hospital

Beckett Street

Leeds

UK

LS9 7TF

Email: kevin.franks@nhs.net

Phone: 0113 206 7854

Affiliations

[1] Leeds Cancer Centre, St James's University Hospital, Leeds

[2] Leeds Institute of Medical Research, University of Leeds, Leeds

[3] Clinical Trials Research Unit, Leeds Institute of Clinical Trials Research, University of Leeds, Leeds

[4] Nottingham University Hospitals, Nottingham

[5] Manchester University Hospitals NHS Foundation Trust & University of Manchester

[6] University of Manchester and The Christie NHS Foundation Trust, Manchester

[7] Institute of Inflammation and Ageing, College of Medical and Dental Sciences, University of Birmingham.

[8] The James Cook University Hospital, Middlesbrough

[9] Department of Respiratory Medicine, Leeds Teaching Hospitals, Leeds

[10] Leeds Institute of Health Sciences, University of Leeds, Leeds

[11] Western General Hospital, University of Edinburgh, Edinburgh

[12] Patient and Public Involvement Representative, UK

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.

Tables and Figures

Figure 1. CONSORT diagram

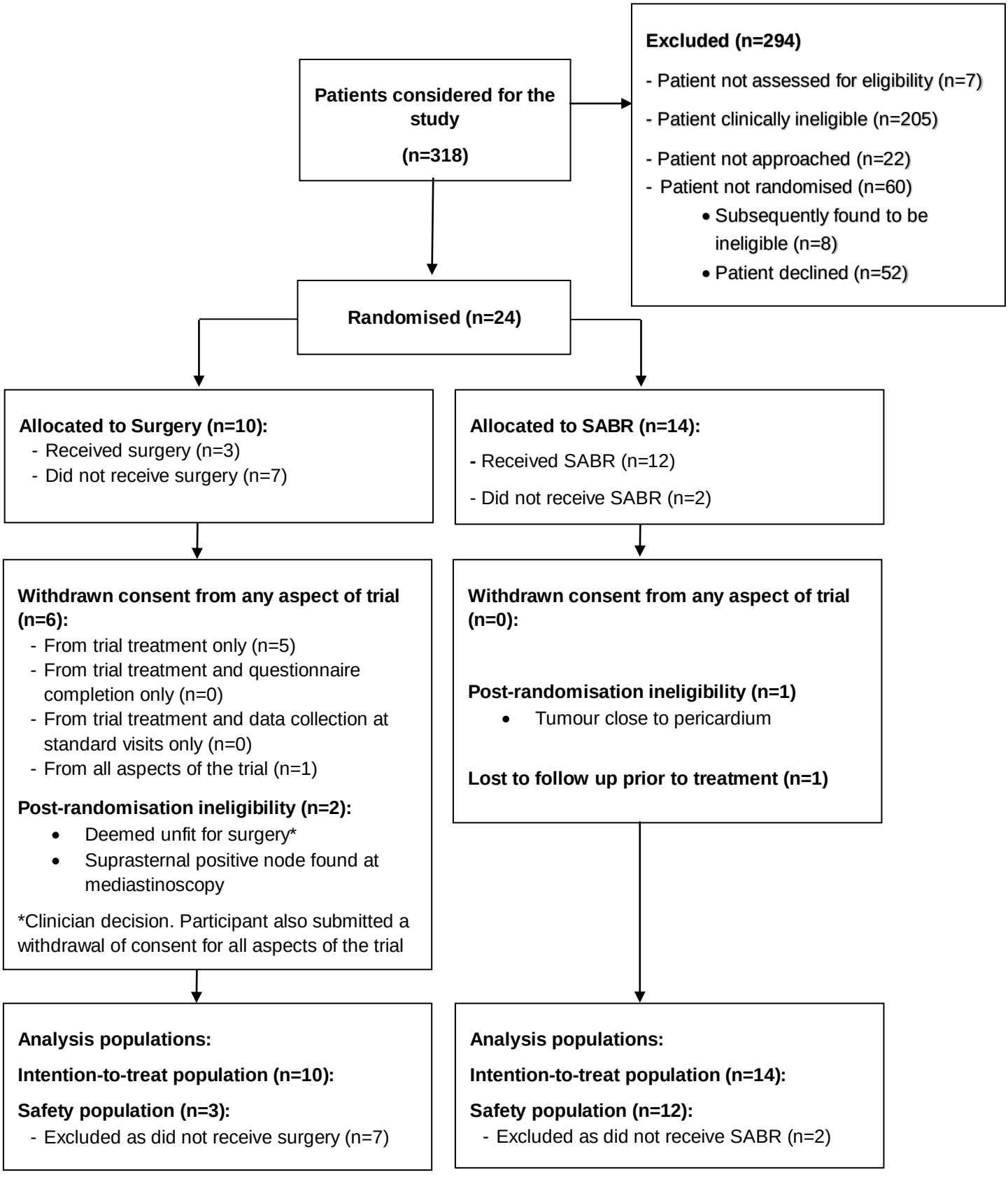

Figure 2. Flow of patients through the study screening process

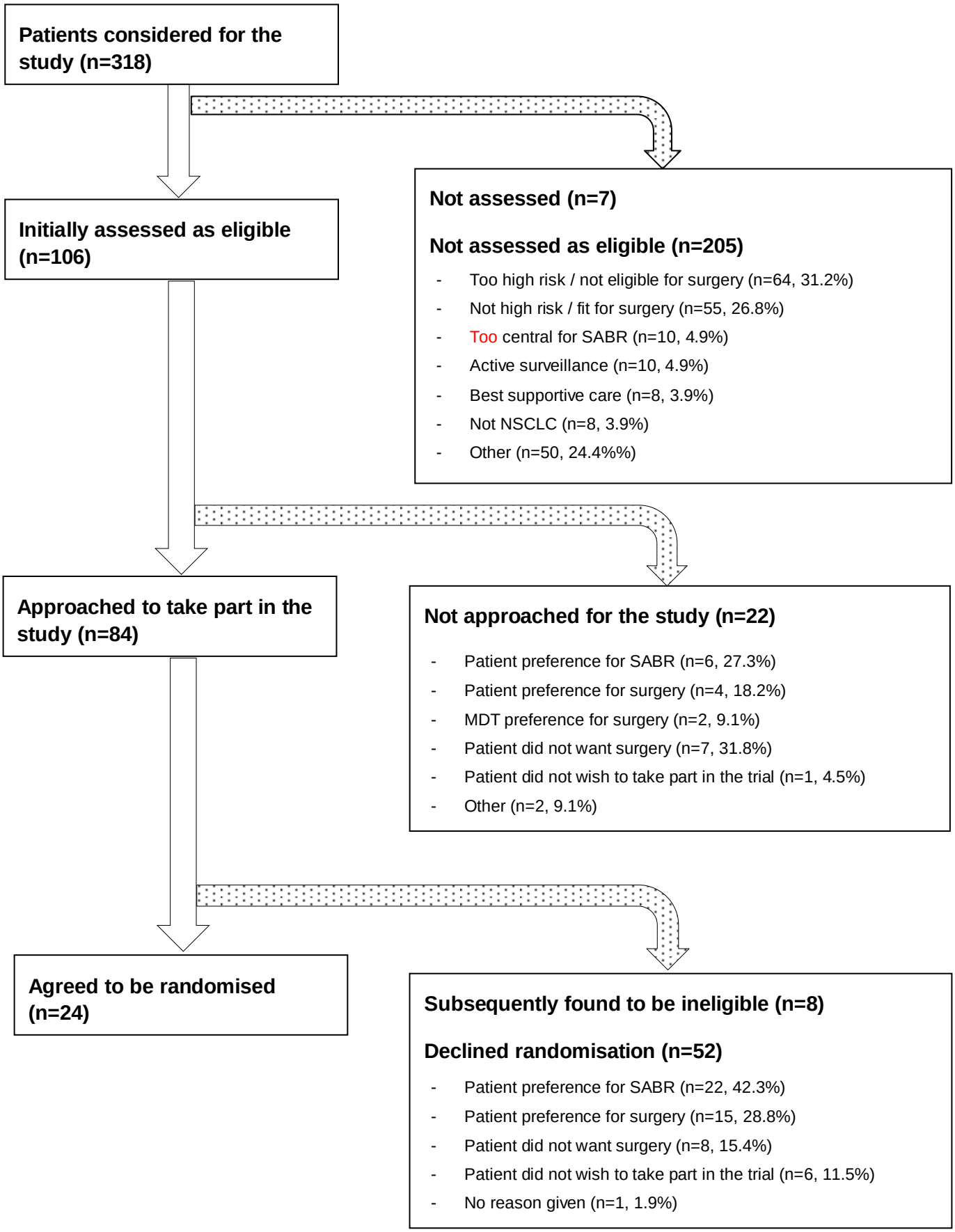

Table 1. Eligibility criteria

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. be willing to undergo a pregnancy test within 72hrs of	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.

surgery or day 1 of SABR treatment) 7. Able and willing to provide written informed consent.	

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 – 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 – Lower risk 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 anticipated that patients will need a pneumonectomy in this group of peripheral	Not suitable for the trial

	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)	

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

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

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

* Patient lost to follow-up before result confirmed

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%)
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)			

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

Table 7. Site perceived drivers and challenges to recruitment

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

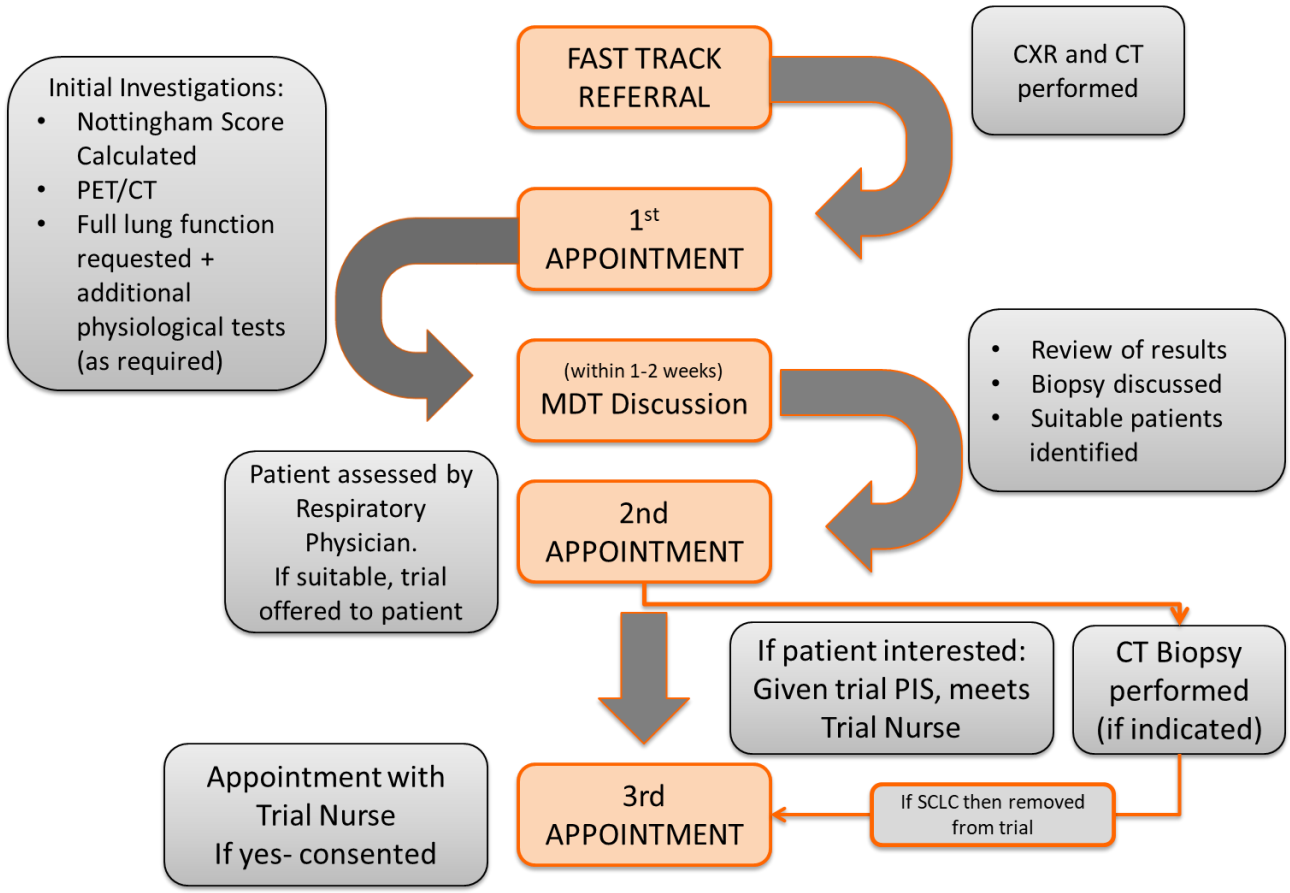
Supplementary Material

1. 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. Overall patients were happy with the way the study was presented to them. Patients described having a clear preference for surgery or SABR and wanted to make their own decision about treatment. Health professionals and people in the patient's network could influence decision-making. Patients suggested that a randomised option would be suitable for people unable to make a decision or for those who lived alone and hence had no one with whom they could discuss their treatment options. Some patients found decision-making difficult, and taking part in the trial was sometimes seen as a third option, adding another layer of complexity to decision making.

Those with a preference for SABR had previous knowledge or experience of SABR. SABR was often chosen by patients who had other multi-morbidities or a poor experience of surgery. Patients who preferred surgery tended to have had previous good experiences or were willing to accept the short-term risks associated with surgery for the chance to discover whether their lymph glands were affected and if the disease had progressed.

2. Recruitment Pathways



3. SABRTooth Radiotherapy Guidelines

A study to determine the feasibility and acceptability of conducting a phase III randomised controlled trial comparing 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.

Radiotherapy Guidelines

THIS DOCUMENT SHOULD BE READ IN CONJUNCTION WITH THE SABRTooth PROTOCOL

Sponsor: **Leeds Teaching Hospitals NHS Trust [MO14/11248]**
Funded by: **National Institute for Health Research (NIHR)**
Research for Patient Benefit (RfPB) [PB-PG-0613-31114]

Amendments to RT Guidelines

Version 1.0 - original version

Contents

Foreword

This document describes the QA processes for the SABRTooth trial. When used in conjunction with the main trial protocol it provides all the information necessary for entering patients into the trial.

This document should not be used as a guide for the treatment of patients outside of the **SABRTooth** trial.

Every care has been taken in drafting these guidelines but corrections or amendments may be necessary. These will be circulated to Investigators in the trial, but centres entering patients for the first time are advised to contact the SABRTooth RTTQA physicist to confirm they have the most recent and approved version.

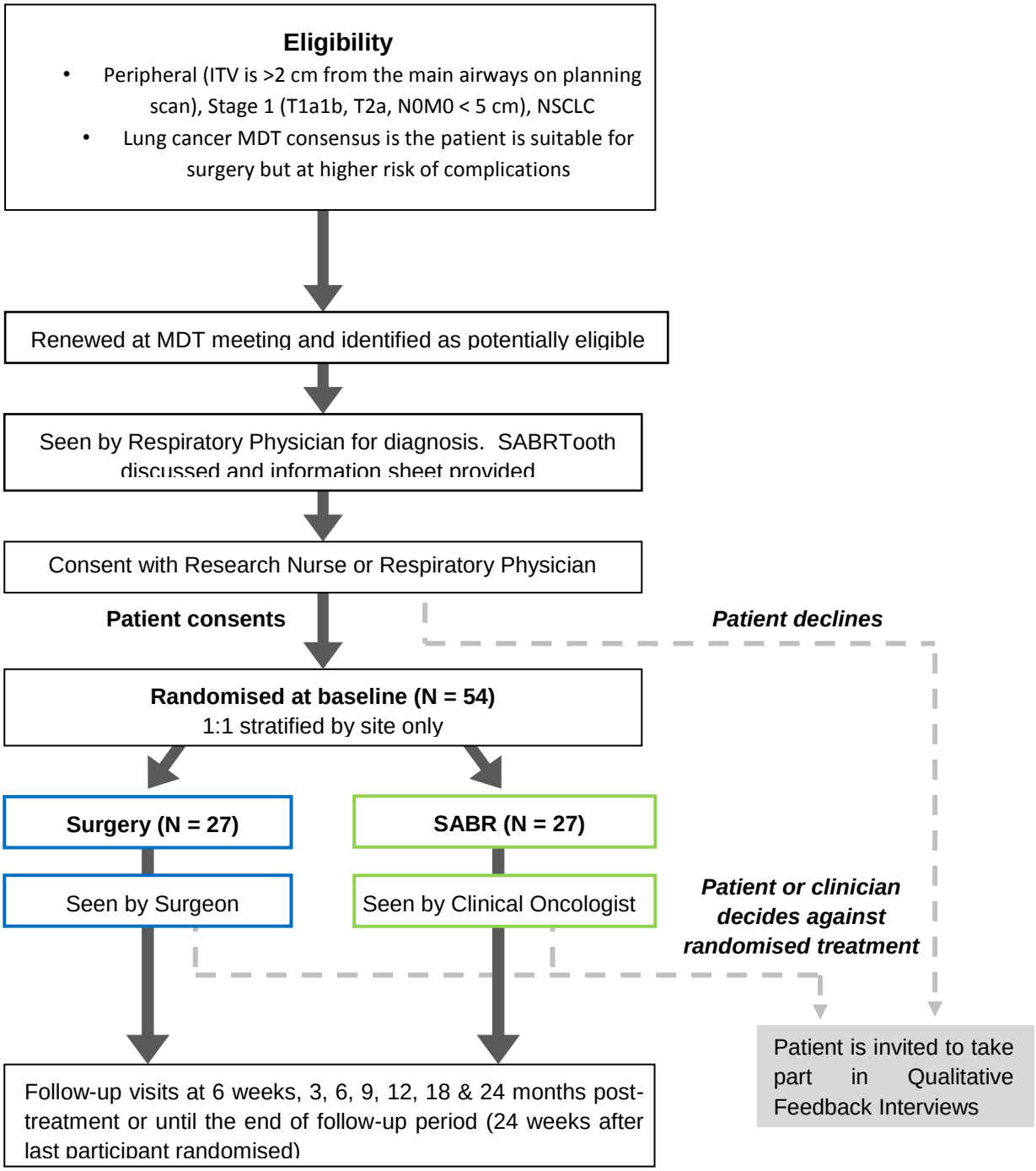
If you have any queries in regards to this please contact the RTTQA group. For contact details please refer to the 'Contact Details' section.

Trial Summary

Title	A study to determine the feasibility and acceptability of conducting a Phase III randomised controlled trial comparing 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.
Acronym	SABRTooth
Background	Lung Cancer survival rates in the UK are inferior to other European and North American countries. Optimising therapy for all stages of the disease is therefore a high priority. Stage I non-small cell lung cancer (NSCLC) is curable and surgery is considered the standard of care for fit, good performance status patients, with 5 year overall survival (OS) of around 60%. However, a high proportion of patients with Stage I NSCLC are elderly and/or have medical co-morbidities. Despite guidelines, variation exists in clinical practice with a wide range in UK surgical resection rates by region (8-25%). The optimal treatment for patients who are at higher risk of surgical complications (mortality and morbidity) is unknown. SABR may be an equally appropriate treatment but this needs to be formally assessed.
Design	The SABRTooth trial is a UK multi-centre, two-group individually randomised controlled feasibility study targeted at patients with peripheral Stage I non-small cell lung cancer considered at higher risk from surgery. In total, 54 patients are planned to be recruited into the study over a 21 month period from 4 tertiary treatment sites and 2 smaller referral sites. Due to the different treatment modalities in the two arms it is not feasible to blind patients or clinicians.
Objectives	This study aims to determine the feasibility and acceptability of performing a large-scale definitive randomised Phase III trial comparing surgery with stereotactic ablative radiotherapy (SABR) for patients with peripheral Stage I non-small cell lung cancer (NSCLC) at higher risk from surgery in the UK.

Endpoints	Primary endpoint: - Recruitment rate/month over months 7-21 Secondary endpoints: - Number of patients screened/month and identified as eligible/month - Proportion of patients undergoing their allocated treatment procedure - Reasons for non-participation of eligible patients - Reasons for participants not undergoing their allocated treatment procedure - Proportion of QoL questionnaires returned and completed (i.e. EQ-5D™, EQ-VAS™, QLQ-C30, QLQ-LC30, Resource Use and Societal economic questionnaire) at each data collection timepoint - EQ-5D utility scores and standard deviation estimates Exploratory endpoints: - - Qualitative assessment of patient acceptability of the trial - Descriptive assessment of participant recruitment pathway across the 6 recruiting trial sites. - Descriptive assessment of the decision making in recruiting site MDTs in identification of higher risk patients and use of available tools to aid this decision making including the predictive score - 30/90/180 day mortality rates
Population	54 patients with peripheral Stage I non-small cell lung cancer considered at higher risk from surgery recruited from 6 UK trial sites.
Randomisation	Participants will be randomised on a 1:1 basis to undergo either surgical resection or SABR. Stratified permuted block randomisation will be used to ensure treatment groups are well balanced for recruiting trial site.
Duration	21 months of recruitment followed by 6 months of additional follow-up.
Evaluation of outcome measures	Follow-up frequency will be in line with current NHS practice, with data collected at routine follow up visits at 6 weeks, 3m, 6m, 9m, 12m, 18m and 24m post-treatment (or until 6 months after the final participant has been randomised). Minimal clinical data and patient reported questionnaire data will also be collected at 15m and 21m post-treatment. Overall survival data will be captured again at the end of the study for all participants via the National Cancer Data Repository (NCDR)
Eligibility	Please refer to the SABRTooth Protocol

Trial Schema



Contact Details

Chief Investigator: Dr Kevin Franks Consultant Clinical Oncologist St James's Institute of Oncology Leeds Teaching Hospital NHS Trust Tel: 0113 206 7854 Email: kevin.franks@nhs.net	**Trial Management** Catherine Lowe Senior Trial Manager Clinical Trials Research Unit University of Leeds Tel: 0113 343 1672 Email: sabrtooth@leeds.ac.uk
Clinical Advisor Professor David Sebag-Montefiore Professor of Clinical Oncology University of Leeds and Leeds Cancer Centre Tel: 0113 2068586 Email: d.sebagmontefiore@leeds.ac.uk	**Clinical Advisor** Mr Babu Naidu Thoratic Surgeon University of Birmingham Tel: 0121 371 3228 Email: b.naidu@bham.ac.uk
Clinical Advisor Professor David Baldwin Respiratory Physician Nottingham University Hospitals NHS Trust Tel: 0115 9691169 Email: David.Baldwin@nuh.nhs.uk	**Clinical Advisor** Dr Michael Snee Consultant Clinical Oncologist Leeds Teaching Hospital NHS Trust Tel: 0113 2067614 Email: Michael.Snee@leedsth.nhs.uk
Radiotherapy Physics Advisor: John Lilley Lead Treatment Planning and R&D Physicist St James's Institute of Oncology Leeds Teaching Hospital NHS Trust Tel: 0113 206 7617 Email: johnlilley@nhs.net	

Radiotherapy Trials Quality Assurance Group RTTQA

RTTQA Physicist	Rushil Patel Lead SABR Physicist RTTQA Mount Vernon Cancer Centre Tel: 01923844714 Email: rpatel1@nhs.net
RTTQA Physicist Cover	David Eaton Lead Physicist RTTQA Mount Vernon Cancer Centre Tel: 01923844714 Email: david.eaton@nhs.net

For further details regarding RTTQA:

Visit www.rttrialsqa.org.uk

Elizabeth Miles (Mount Vernon Hospital): Elizabeth.miles@nhs.net

Radiotherapy QA Programme

The trial QA programme run by the NCRI National Radiotherapy Trials Quality Assurance Group (RTTQA) consists of two stages: pre-trial and on-trial QA. An overview of the RTTQA credentialing process, along with the documentation, is given on the RT Trials QA website (www.rttrials.org.uk)

Pre-trial QA

Each centre must complete Pre-trial QA before the centre is accepted to recruit patients for the trial. Pre-trial QA consists of completion of:

- **Facility questionnaire**: general and trial specific questions on equipment, software and techniques to be used for the trial. The Facility Questionnaire should be updated by each centre if any local changes are made to the approved technique.

- **Dummy run**: QA of the outlining and planning technique will be performed by each centre sending three patients (one for each dose fractionation regimen) that are eligible for the trial for review. Adherence to the protocol will be assessed. See Appendix 2 for details)

- The **National SABR Consortium Lung Audit** or equivalent independent audit that has taken place at the centre within 3 years of entering the trial. Evidence of independent audit should be provided as part of the pre-trial QA. Please discuss with RTTQA if this is not possible.

Streamlining of QA process: Every effort has been made to streamline the amount of QA required to enter the trial. Please contact RTTQA if you have any concerns about the QA programme.

On-trial QA

On-trial QA is performed on clinical patients who have been recruited into the trial and consists of:

- **Prospective review** of first recruited patient of each dose fractionation type from all centres. These reviews assess protocol compliance of outlining and treatment planning and must be completed before the patient commences treatment.

- **Data collection** by the QA centre from all patients treated in the trial. For each patient, this includes: clinical history (including report of relevant imaging), 4DCT images (all phases and any 3D datasets), contours, plan and total dose cubes along with a completed plan assessment form (**PAF**). All data must be appropriately anonymised.

SABR Treatment Planning and Delivery

Introduction to SABR

Stereotactic ablative body radiotherapy (SABR) refers to the precise irradiation of an image-defined extra-cranial lesion with the use of high radiation dose in a small number of fractions. Centres entering patients into SABRTooth must already have a Lung SABR treatment pathway in place which complies with the UK SABR Consortium Guidelines.

Pre-treatment image acquisition

Pre-treatment image acquisition must follow the UK SABR Consortium guidelines

Patient positioning

As per local institution. Aim is to produce a reproducible, comfortable and stable position that the patient can tolerate for up 45 min. Please refer to the UK SABR Consortium Guidelines and the National Radiotherapy Implementation Group Report Image Guided Radiotherapy (IGRT) Guidance for implementation and use for further guidance.

Treatment set-up should be by reference to tattoos on reproducibly stable areas of skin, and to bony anatomical landmarks. The tattoos should be applied at the time of planning scan acquisition.

Image acquisition

Motion management (for tumour motion >1cm) should follow the UK SABR Consortium Guidance. Planning with a 4DCT scan is highly recommended (particularly if motion is >1cm). For centres without 4DCT, repeated helical CT scans (e.g. free-breathing, exhale and inhale) or slow CT can be used to generate an ITV. Details of the pre-treatment imaging technique must be included in the completed SABRTooth Facility Questionnaire.

IV contrast should be used unless there is contra-indication.

Slice thickness: contiguous axial slices of ≤3mm

Scan limits: To include the whole of the chest according to UK SABR Consortium Guidelines.

Outlining

The outlining definitions for SABRTooth are based on the UK SABR Consortium Guidelines. The structures that must be delineated are outlined in the table below. Please note the following information:

Gross Tumour Volume (GTV) is defined as the radiologically visible tumour in the lung, contoured using lung settings. Mediastinal windows may be suitable for defining tumours proximal to the chest wall. Where available, and deemed useful information from PET/CT should be incorporated into delineating the GTV.

- All tumour and critical organ contours should be reviewed by a consultant radiologist if there are any concerns with delineation.
- There may be occasions where PTV coverage may need to be compromised in order to meet organs at risk constraints. Some centres may edit the PTV back from the relevant OAR as part of the optimisation technique. If this is needed, **the original PTV must be left unedited** and a second PlanPTV structure created with the necessary clipping applied to the structure only.
- Please follow the nomenclature outlined below when submitting contours to RTTQA

Target definition	
Nomenclature	**For 4DCT Planned Patients**
GTV_{Mid}	Radiologically identified tumour on Mid-ventilation 4DCT dataset
GTV_{Exh}	Radiologically identified tumour on Maximum Exhale 4DCT dataset
GTV_{Inh}	Radiologically identified tumour on Maximum Inhale 4DCT dataset
CTV	No expansion for microscopic disease is used in SBRT i.e. GTV= CTV.
ITV	ITV encompasses either the GTV_{Mid},GTV_{Exh},GTV_{Inh} and any additional tumour seen or full tumour extent on maximum intensity projection. If a MIP is used, GTVs do not need to be contoured.
PTV_XXXX	*ITV* + 5 mm. The margins from CTV to PTV will depend on the method of immobilisation, the assessment of tumour motion and methods for on treatment set-up verification/repositioning used at each centre. XXXX to be replaced by the prescription dose in cGy
	For patients where 4DCT is inadequate for planning or motion assessment, a single free breathing helical CT should be acquired and the below population base margins are applied according to RTOG 0236.
GTV	Radiologically identified tumour on the free-breathing helical dataset.
CTV	No expansion for microscopic disease is used in SBRT i.e GTV= CTV.
PTV_*XXXX*	GTV + 1.0cm Cranio/Caudal and 0.5cm Ant/Post and Lateral. XXXX

	to be replaced by the prescription dose in cGy
Organs at risk delineation	
Lungs	Both the right and left lungs should be contoured as one structure using pulmonary windows. All inflated and collapsed lung should be included. However, GTV and trachea/ipsilateral bronchus as defined above should not be included. The V20 will be calculated using both lung volumes minus the GTV.
Trachea	The trachea will be contoured using lung and mediastinal windows on CT to correspond to the mucosal, submucosa and cartilage rings and airway channels associated with these structures. Contouring of the proximal trachea should begin at least 10cm superior to the extent of the PTV or 5cm superior to the carina (whichever is more superior) and continue inferiorly to the superior aspect of the proximal bronchial tree.
Bronchus	The proximal bronchial tree will be contoured using lung and mediastinal windows on CT to correspond to the mucosal, submucosa and cartilage rings and airway channels associated with these structures. The proximal bronchial tree will include the most inferior 2cm of distal trachea and the proximal airways on both sides. The following airways will be included according to standard anatomical relationships: the distal 2cm of trachea, the carina, the right and left mainstem bronchi, the right and left upper lobe bronchi, the intermedius bronchus, the right middle lobe bronchus, the lingular bronchus, and the right and left lower lobe bronchi. Contouring of the lobar bronchi will end immediately at the site of a segmental bifurcation.
Airways_2cm	In addition, as a guide to the ineligibility requirements for not enrolling patients with tumours in the zone of the proximal bronchial tree, an artificial structure 2cm larger in all directions from the proximal bronchial tree should be created. If the GTV on the planning dataset (or GTV on helical CT) falls within this artificial structure, contact SABRTooth QA team
SpinalCord	The spinal cord will be contoured based on the bony limits of the spinal canal. The spinal cord should be contoured starting at least 10cm above the superior extent of the PTV and continuing on every CT slice to at least 10cm below the inferior extent of the PTV.
Oesophagus	The oesophagus will be contoured using mediastinal windowing on CT to correspond to the mucosal, submucosa, and all muscular layers out to the fatty adventitia. The oesophagus should be contoured starting at least 10cm above the superior extent of the PTV and continuing on every CT slice to at least 10cm below the inferior extent of the PTV.
Pericardium	The heart will be contoured along with the pericardial sac. The

	superior aspect (or base) for purposes of contouring will begin at the level of the inferior aspect of the aortic arch (aortopulmonary window) and extend inferiorly to the apex of the heart.
Ipsilateral_BrachialPlexus	The defined ipsilateral brachial plexus originates from the spinal nerves exiting the neuroforamina on the involved side from around C5 to T2. However, for the purposes of this protocol only the major trunks of the brachial plexus will be contoured using the subclavian and axillary vessels as a surrogate for identifying the location of the brachial plexus. This neurovascular complex will be contoured starting proximally at the bifurcation of the brachiocephalic trunk into the jugular/subclavian veins (or carotid/ subclavian arteries) and following along the route of the subclavian vein to the axillary vein ending after the neurovascular structures cross the 2nd rib.
Additional OARs	For lower lobe tumours it may be necessary to contour the stomach/small bowel and/or liver **PARTICULARLY** if non-coplanar beams are used in the treatment plan. Please contact RTTQA if these OARs are close to local tolerances
Additional planning structures	
Body	The body contour should also be contoured.
Skin	Skin should be created from the outer most 5mm of the body contour. Doses should not exceed stated tolerances
PlanPTV	As described above, this structure should be created if the PTV needs to be edited as part of the optimisation process to ensure PTV doses are reported consistently using the unedited PTV.
Planning Volumes	Additional structures can be used for IMRT optimisation. These should be clearly differentiated from the trial structures e.g. by labelling zzPTV+2cm, zzcontrast

Treatment Planning and Delivery

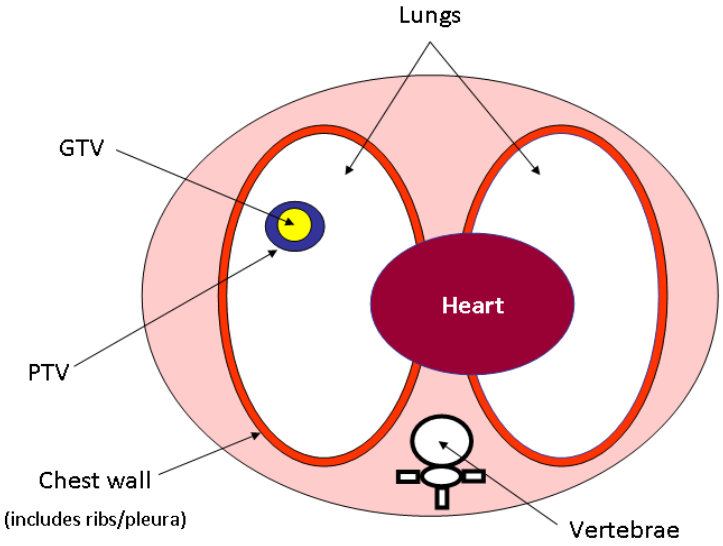
Treatment Type	Centres may use 3D conformal, IMRT or VMAT RT planning for SABRTooth patient. The chosen technique must be detailed in the completed SABRTooth Facility Questionnaire.
Isocentre Position	As per local protocol. Recommend use of midline isocentre for CBCT verification
Beam selection	For 3DP conformal plans, typically at least seven beams will be needed to achieve adequate target coverage using SABR whilst sparing critical structures, including skin surface. Plans may be non-coplanar if

	necessary. Beams energies above 10MV should not be used, Flattening Filter Free beams are allowed to be used.
Dose Calculation	Inhomogeneity correction must be applied. The use of modern 'type-b' superposition-convolution algorithms (e.g. Pinnacle and Oncentra Master Plan collapsed cone algorithms, or the Eclipse AAA algorithm) or Monte Carlo is required as these algorithms calculate lung and tumour doses more accurately than older 'type-a' algorithms. Analysis of the dose-volume histogram (DVH) for the PTV and critical normal structures forms the basis for selecting a particular treatment plan. It is therefore recommended that plans be calculated on a fine dose grid, with a separation no greater than 2.5mm, to ensure the accuracy of the DVH calculations.
Dose Prescription	Prescribed so that the prescription dose is covering 95% the PTV

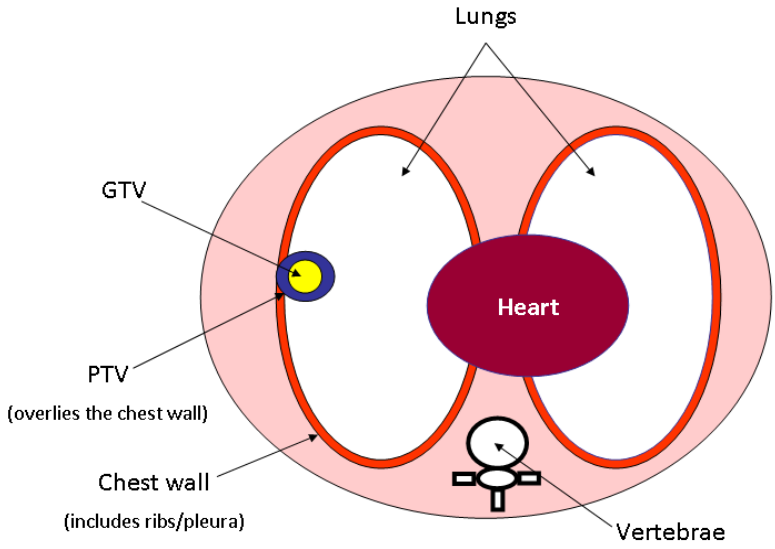
Dose Fractionation

Dose will be delivered in a single phase based on the accepted guidelines of the UK SABR consortium, with 3 dose fractionation schedules based on the location of the tumour

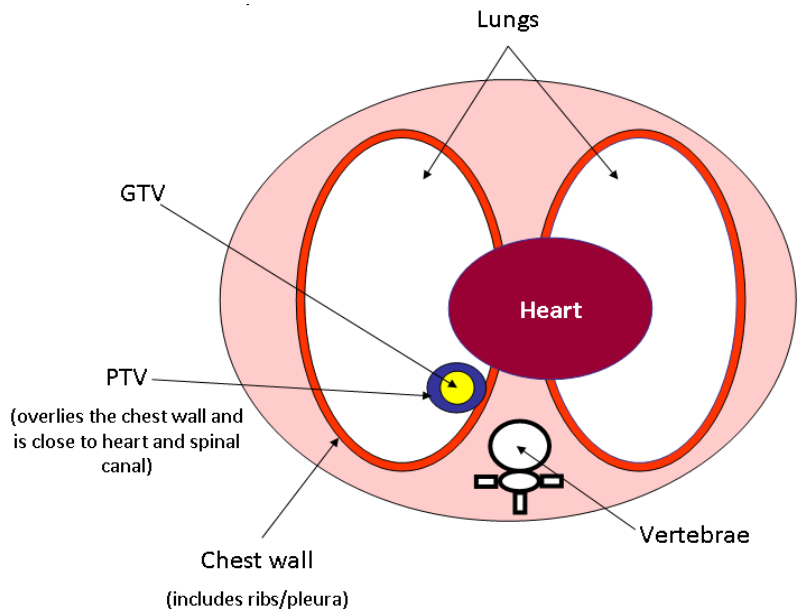
1. tumour whose planning target volume (PTV) does not abuts the chest wall or mediastinal structures: **54Gy** in three fractions (18Gy/fraction)



2. For tumours whose planning target volume touches or extents into the ribs/ pleural: **55Gy** in five fractions (11Gy/fraction) or **60Gy** in five fractions (12Gy/fraction)



3. For tumours where the dose constraints for an organ at risk cannot be met **60Gy** in eight fractions (7.5Gy/fraction)



Planning Aims

Target volume dose planning aims are in line with those described in the (UK SABR Consortium)

- Dose prescription should be chosen such that D95%(PTV) ≥ 100% of the prescribed dose (e.g. 54Gy for the 3 fraction schedule), and D99%(PTV) ≥ 90% of the prescribed dose.
- D_{max}(PTV) should ideally be ≥110% of the prescribed dose and ≤140%. However D_{max}(PTV) between 105-110% and 140-145% may be accepted in some cases.

Plans must also meet the dose conformity requirements described in Table 1 according to PTV volume. These are also in line with those described in the UK SABR Consortium Guidelines [1]

Plans must also meet the organs at risk dose objectives outlined in Table 2. Please discuss with the SABRTooth Team if you feel your centre will have problems meeting these constraints.

The appropriate Plan Assessment Form (PAF) should be completed for each patient according to dose fractionation. This includes those values requested for dose reporting purposes only. PAFs are available for the RTTQA website www.rttrialsqa.org.uk.

Table 1: Dose Conformity Requirements:

(a) For 54Gy in 3 fractions

PTV Volume (cc)	**R100**		**R50**		**D_{max} (>2cm from PTV)$^{+}$**		**Lung-GTV* V20 (%)**	
	optimal	mandatory	optimal	mandatory	optimal	mandatory	optimal	mandatory
<20	<1.25	1.25-1.40	<12	12-14	<35.1Gy	35.1-40.5Gy	<5	5-8
20.1-40	<1.15	1.15-1.25	<9	9-11	<37.8Gy	37.8-43.2Gy	<6	6-10
>40.1-60	<1.10	1.10-1.20	<6	6-8	<37.8Gy	37.8-43.2Gy	<10	10-15
60.1-90	<1.10	1.10-1.20	<5	5-7	<37.8Gy	37.8-43.2Gy	<10	10-15
>90.1	<1.10	1.10-1.20	<4.5	4.5-6.5	<37.8Gy	37.8-43.2Gy	<10	10-15

(b) For 55Gy in 5 and 60Gy in 8 fractions

PTV Volume (cc)	**R100**		**R50**		**D_{max} (>2cm from PTV)$^{+}$**		**Lung-GTV* V20 (%)**	
	optimal	mandatory	optimal	mandatory	optimal	mandatory	optimal	mandatory
<20	<1.25	1.25-1.40	<12	12-14	<35.8Gy	35.8-41.3Gy	<5	5-8
20.1-40	<1.15	1.15-1.25	<9	9-11	<38.5Gy	38.5-44.0Gy	<6	6-10
>40.1-60	<1.10	1.10-1.20	<6	6-8	<38.5Gy	38.5-44.0Gy	<10	10-15
60.1-90	<1.10	1.10-1.20	<5	5-7	<38.5Gy	38.5-44.0Gy	<10	10-15
>90.1	<1.10	1.10-1.20	<4.5	4.5-6.5	<38.5Gy	38.5-44.0Gy	<10	10-15

where:

R100 = Vol(100%)/Vol(PTV) = ratio of prescription isodose (e.g. 54Gy, 55Gy, or 60Gy) volume to the PTV volume

R50 = Vol(50%)/Vol(PTV) = ratio of 50% prescription isodose (e.g. 27Gy, 27.5Gy, or 30Gy) volume to the PTV volume

$^{+}$ **D_{max} (>2cm from PTV) =** maximum point dose at least 2cm from the PTV in any direction

***Lung-GTV V20** = percentage of Lung-GTV (as defined above) receiving >20Gy

Table 2**: OAR Dose Constraints**

Organ	**Volume**	**Three Fraction Regime (54Gy in 3#)**		**Five Fraction Regime (55Gy in 5#)**		**8 Fraction Regime (60Gy in 8#)**	
		Optimal	**Mandatory**	**Optimal**	**Mandatory**	**Optimal**	**Mandatory**
SpinalCord	0.01 cm^3	18 Gy	18-22 Gy	25 Gy	25-28 Gy	25 Gy	25-28 Gy
Oesophagus	0.1 cm^3	24 Gy	24-27 Gy	27 Gy	27-28.5Gy	27 Gy	27-28.5Gy
Ipsilateral_Brachial Plexus	0.1 cm^3	24 Gy	24-26 Gy	27 Gy	27-29 Gy	27Gy	27-29Gy
Heart	0.1 cm^3	24 Gy	24-26 Gy	27 Gy	27-29 Gy	50Gy	50-60Gy
Trachea, Ipsilateral Bronchus	0.1 cm^3	30 Gy	30-32 Gy	32 Gy	32-35 Gy	32 Gy	32-35 Gy
Lungs-GTV*	V20	<10%	N/A	<10%	N/A	<10%	N/A
	V12.5	<15%	N/A	<15%	N/A	<15%	N/A
Liver **		V15<700ccV V21<33% V15<50%	N/A	V15<700cc V30<60% Mean<20Gy	N/A	V27<30% V24<50%	N/A
Chest Wall***	30 0.01	30Gy 37Gy	N/A	32Gy 39Gy	N/A	32-35Gy 39Gy	N/A

* Lung-GTV as defined above

** Liver -valid only if >1000cc of liver imaged

*** Chest wall -optional constraint and local institution to decide whether to try and achieve this

Plan Approval

The RT plan must be reviewed in a radiotherapy MDT or by another consultant who signs the treatment card before treatment. This is essential to try and avoid re-planning patients, especially when the tumour is close to a critical OAR

Plan Checking and Patient Specific QA

All treatment plans should undergo local checking and patient-specific QA procedures. Details of these procedures should be provided in the Facility Questionnaire.

Monitor units should be checked by measurement for a minimum of one dose point in an appropriate homogeneous region of the high dose volume. Independent calculation programs may be used in place of measurements, provided the centre has a previous high level of experience in measurement QA and has a system in place for verifying errors found by the independent calculation.

Fluences may be verified either individually per beam (i.e. each gantry orientation) or at representative planes for all beams together, with measurements being made through at least PTV and spinal cord. Appropriate film / ion chamber or diode arrays / EPID should be used in conjunction with software to compare with the isodoses from the TPS. At least a dose difference measurement or gamma index is required.

Centres with sufficient experience that no longer routinely check fluences for every patient will be accepted.

Replanning

Local procedures should be followed for rescanning and replanning patients. Data associated with any replans of SABRTooth patients during radiotherapy treatment must also be submitted to the SABRTooth QA team (i.e. rescan CTs, structures, plan, dose cube and plan assessment form). This data will not be subject to prospective review given the

time pressures of replans. However they may be reviewed retrospectively at the QA team's discretion. Data from replans is important for long-term trial analysis, as with any treatment plan data, when any protocol deviations may be related to treatment outcome. Please note the plan assessment form includes a section where replan details can be annotated.*

Radiotherapy Delivery

Lung SABR should be delivered according to the National Radiotherapy Implementation Group Report Image Guided Radiotherapy (IGRT) Guidance for implementation and use.

Centres using gated treatments should discuss their technique with the SABRTooth team prior to using in the trial

Treatment Verification

Once the treatment plan has been generated, it is recommended that centres conduct a 'trial set up' session (day-zero), prior to starting treatment, in order to confirm that all the beams are deliverable, that the patient can maintain the treatment position, to verify the patient setup procedure and, if the technology is available, use respiratory-correlation to assess margin adequacy.

It is suggested that centres verify patient setup before and, if possible, during treatment using a procedure that can validate the position of the tumour relative to the patient anatomy for online image matching and correction. Volumetric imaging with cone beam CT, CT on rails or megavoltage CT is highly recommended as bony landmarks are not a reliable surrogate and cannot detect changes in internal anatomy. Daily online imaging matching to the target or fiducial is mandatory, using the no action level protocol. Multiple images during the treatment fraction should be considered to verify any shift or if the treatment exceeds 30 minutes.

Radiotherapy Schedule

Protocols for booking patients and gaps in treatment should follow the latest SABR Consortium guidelines.

Case Reviews and Trial Data Collection

Case Reviews

To ensure a short response time for patients requiring prospective review, please notify the SABRTooth QA physicist when a patient has been identified so that we can be ready to review volume delineation and subsequently the radiotherapy plan.

Please send the outlining (CTs and structures) as soon as it has been completed along with a case history to rpatel1@nhs.net . This should be submitted as soon as possible so that it can be reviewed prior to the start of planning. The plan data (structures, plan, dose and plan assessment form) should be submitted as soon as possible following satisfactory outline review and in good time prior to the patient's RT start date.

Please allow time for amendments and re-review as necessary and for any local patient-specific QA.

When each of the first patients of each dose fractionation have been recruited and reviewed, the SABRTooth QA team will discuss the need for further outlining and/or planning review based on the centre's performance on the initial reviews. RTTQA reserves the right to ask for additional case reviews and spot-checks on any SABRTooth patient.

Data Collection

Data for all patients treated in the trial should be submitted to the QA centre (this applies to both case reviews, non-case review patients and any replans). Please send, in DICOM format

- CT images
- Contours, ensuring all CTVs, PTVs and OARs are present and correctly named using the trial nomenclature
- Plan
- Dose cube (total dose)
- Completed plan assessment form (please fill in electronically)
- Clinical history and stage / tumour classification and relevant imaging reports

All data should be transferred to the QA centre via the NHS secure server. This can be accessed via: https://nww.sft.nhs.uk/sft/upload1 . Its use requires an NHS.net email account. Please send QA submissions to rpatel1@nhs.net

Data Anonymisation

All data sent to the QA centre must be anonymised prior to being sent; data that has not been anonymised will not be accepted. Please refer to the RTTQA website for further guidance.

It is suggested that the trial number and initials be used to identify the patient. It may be of use to keep your own list of names and ID's as well.

Bibliography

Consortium, U. S. (n.d.). *UK SABR Consortium Guidelines.*

ROSEL Study. (n.d.).

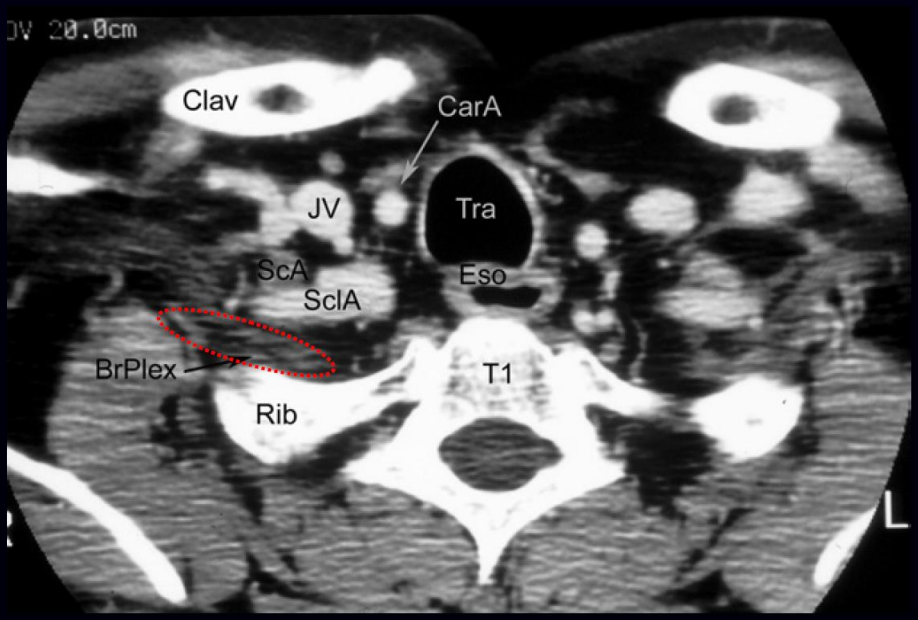
IGRT Guidance https://www.sor.org/sites/default/files/document-versions/National%20Radiotherapy%20Implementation%20Group%20Report%20IGRT%20Final.pdf

Brachial Plexus

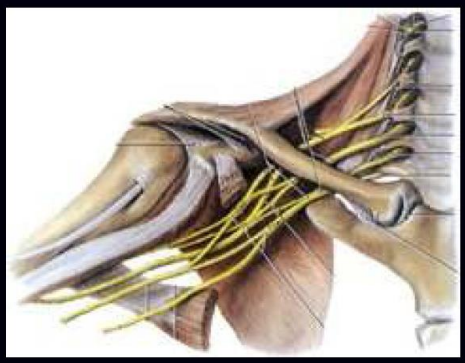
..for the purposes of this protocol only the major trunks of the brachial plexus will be contoured using the subclavian and axillary vessels as a surrogate for identifying the location of the brachial plexus.

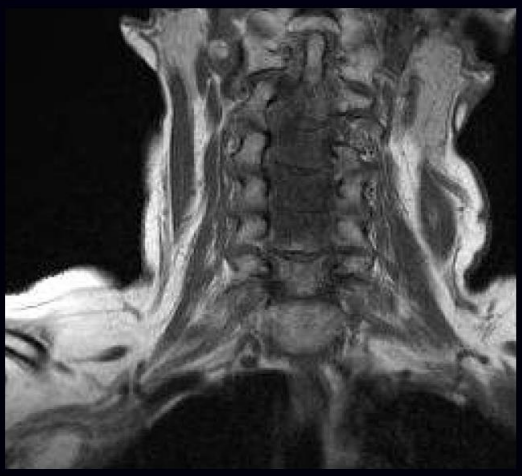
- This neurovascular complex will be contoured starting proximally at the bifurcation of the brachiocephalic trunk into the jugular/subclavian veins (or carotid/subclavian arteries) and following along the route of the subclavian vein to the axillary vein ending after the neurovascular structures cross the 2nd rib.

Level of T1

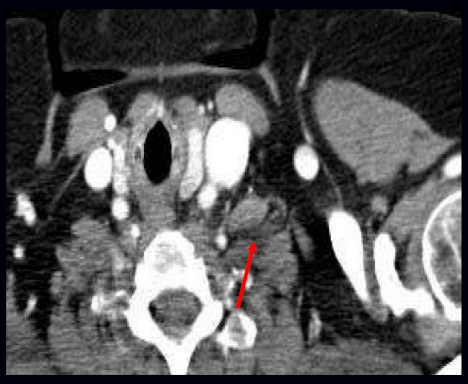


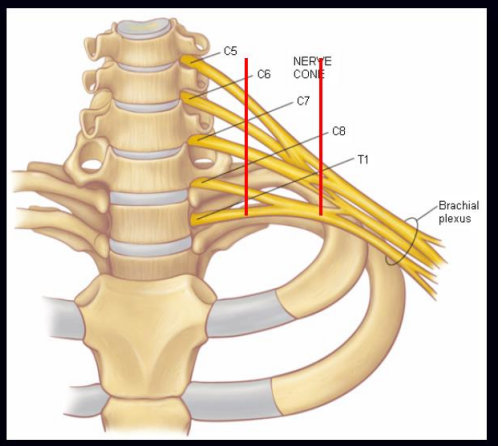
The anterior rami of the spinal nerves of C5, 6, 7, 8, and T1 form the roots of the brachial plexus.



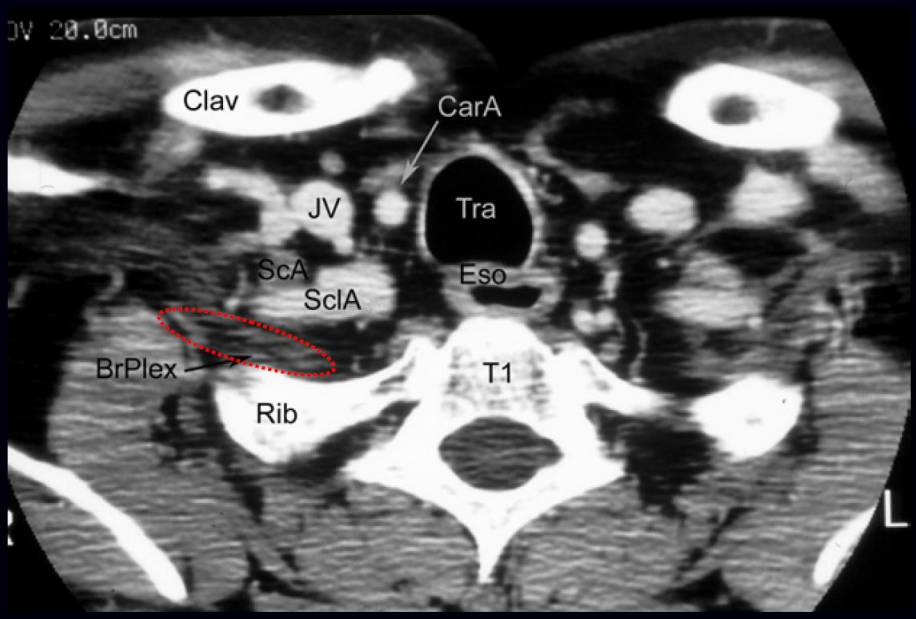


The 3 trunks of the brachial plexus pass between the anterior and middle scalene muscles

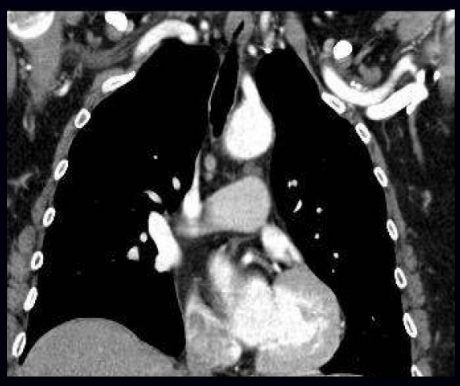


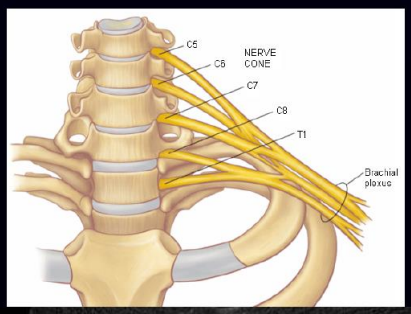


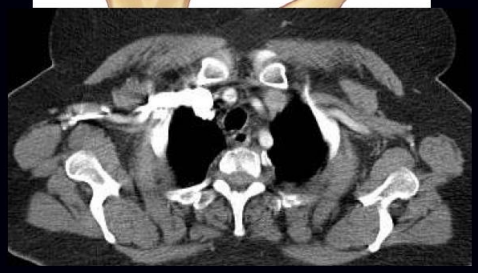
Level of T1



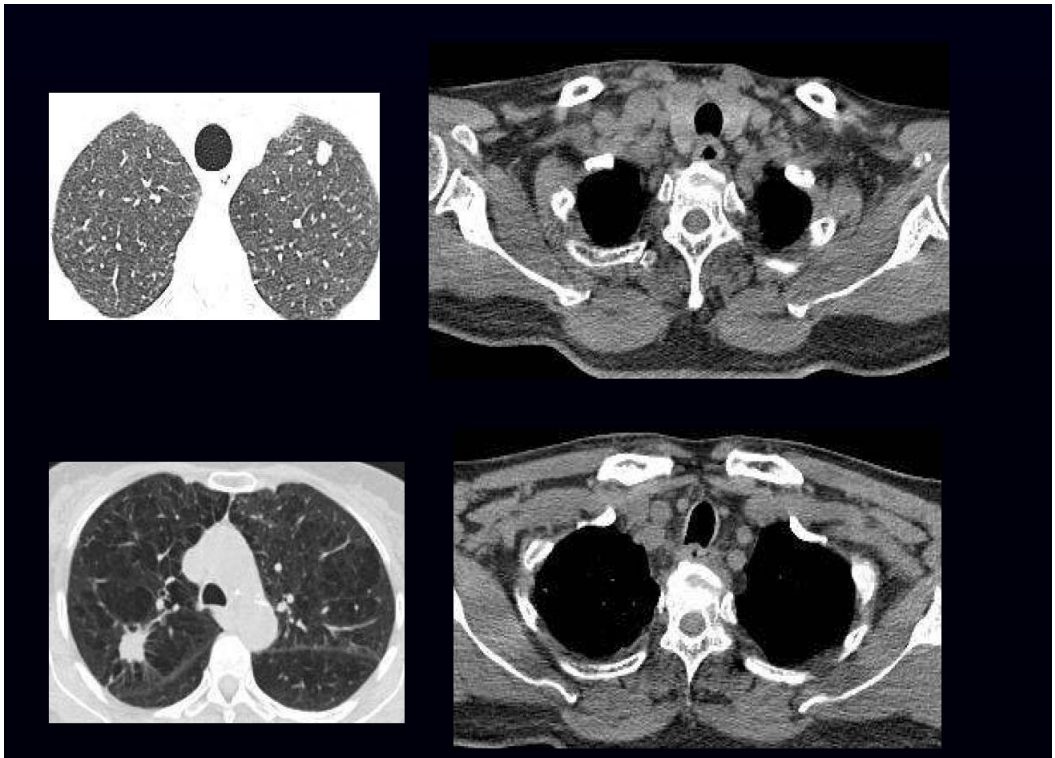
The cords are named the lateral, posterior, and medial cord, according to their relationship to the axillary artery. The cords pass over the first rib close to the apex of the lung and continue under the clavicle immediately posterior to the subclavian artery.





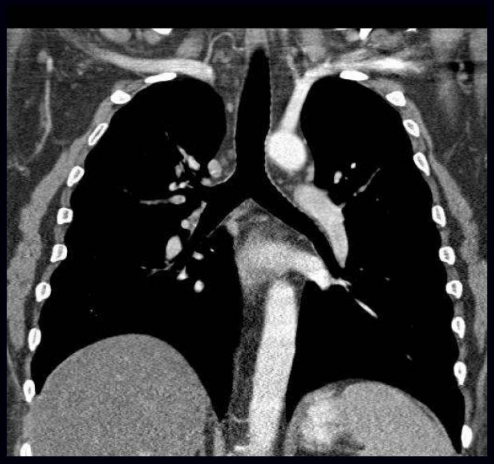


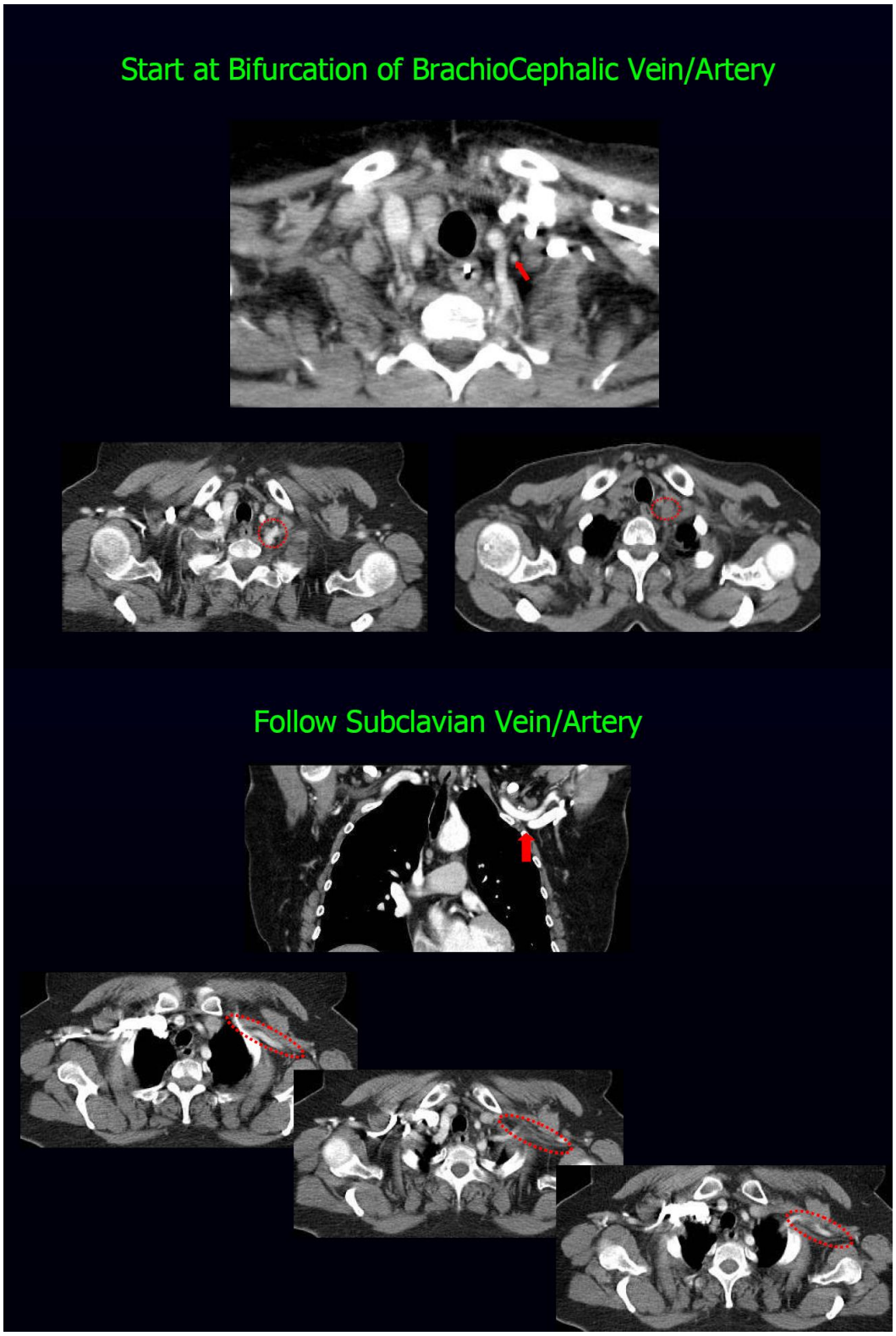
The connective tissue of the prevertebral fascia and the anterior and middle scalenes envelops the brachial plexus as well as the subclavian and axillary artery in a neurovascular "sheath".



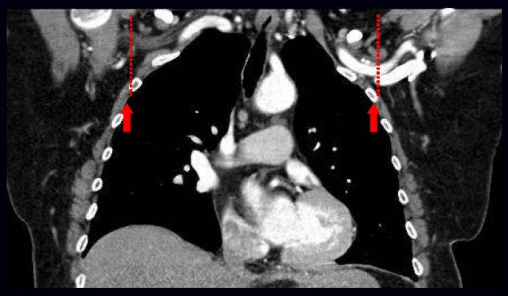
In Practice……

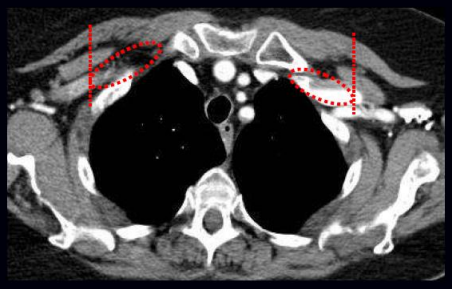
- Start at Bifurcation of BrachioCephalic Vein/Artery
- Follow Subclavian Vein/Artery
- End when vessels cross Second Rib

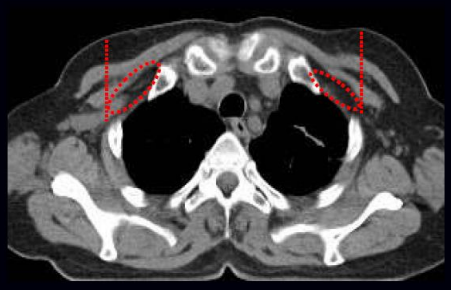



Start at Bifurcation of BrachioCephalic Vein/Artery
Follow Subclavian Vein/Artery

End when vessels cross Second Rib





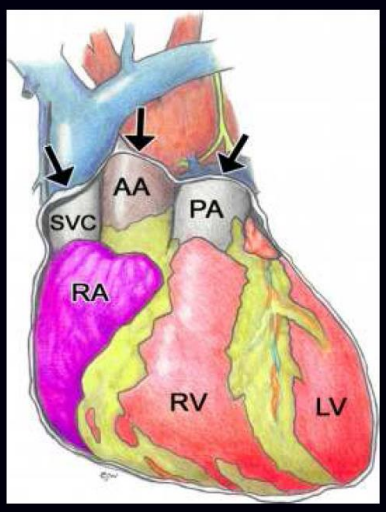


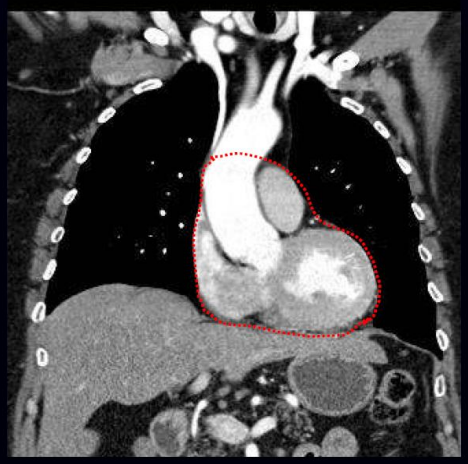
Heart / Pericardium

The heart is contoured along with the pericardial sac

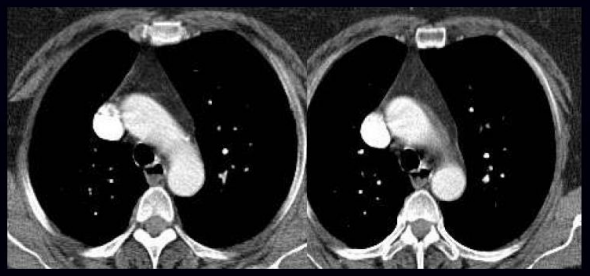
The superior aspect (or base) for purposes of contouring will begin at the level of the inferior aspect of the aortic arch (aortopulmonary window) and extend inferiorly to the apex of the heart.

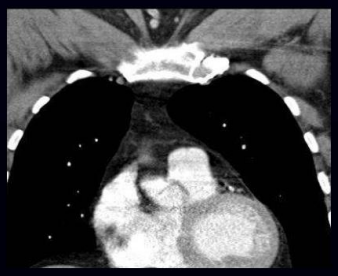
The pericardium is a 2-layered sac that surrounds the heart and extends superiorly to cover the main pulmonary artery, ascending aorta, and SVC

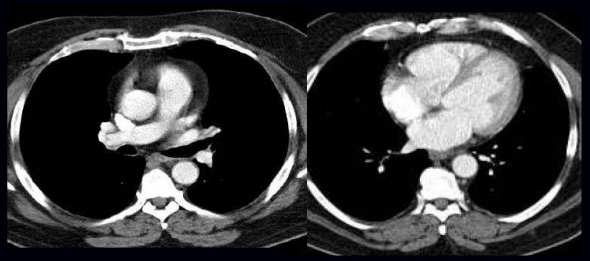


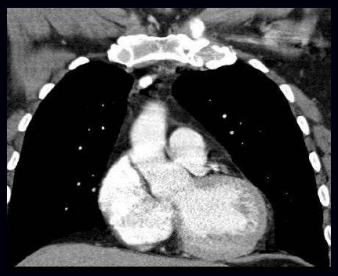


Normal Pericardium

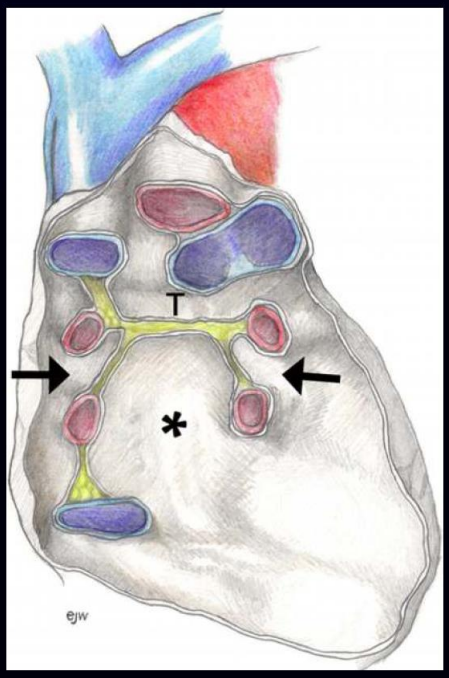




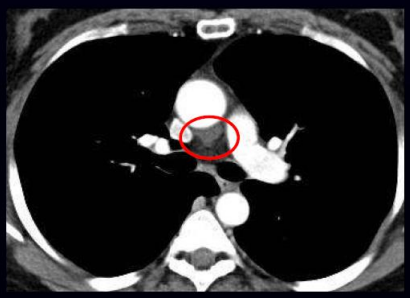


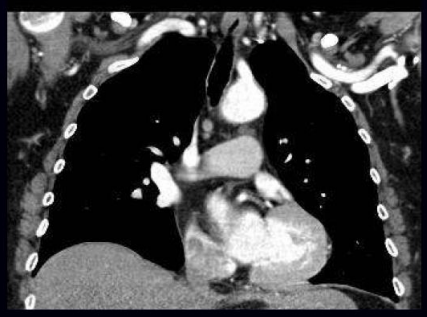


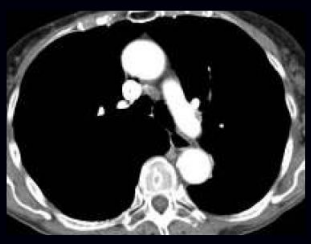
- The visceral pericardium adheres to the heart and great vessels.
- It forms recesses and sinuses, which can be visible at cross-sectional imaging if they contain enough fluid, even in the absence of pericardial effusion.
- Knowledge of the location of these recesses and sinuses will prevent mistaking them for enlarged lymph nodes or other masses

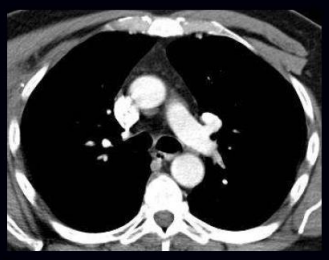


The transverse sinus(pericardial recess) lies posterior to the ascending aorta and main pulmonary artery, just above the left atrium.

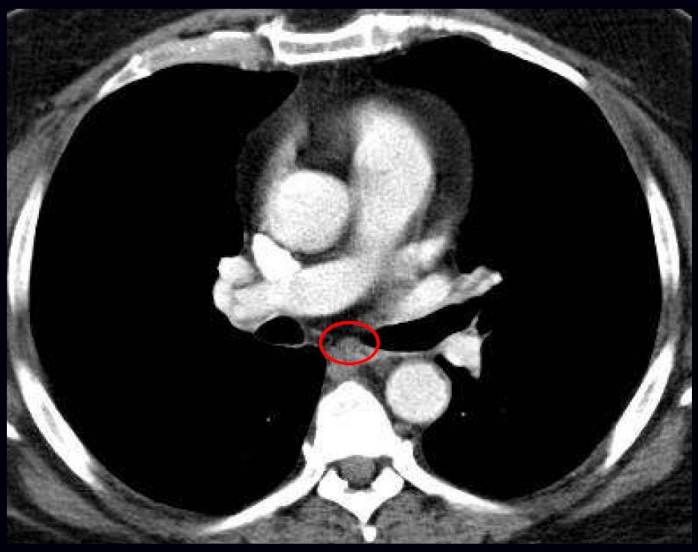








The oblique sinus is the posterior extension of the pericardium and lies posterior to the left atrium and anterior to the oesophagus.



Appendix 2: Dummy Run Instructions

Aim: to ensure patients can be outlined and planned according to SABRTooth protocol using the current patient pathway at each centre

Task:

RTTQA and the SABRTooth team require submission of 3 example patients from each centre that:

- Satisfy the SABRTooth eligibility criteria (section 7 of the SABRTooth protocol): please refer to appendix 1 below.
- Satisfy the planning criteria described in the SABRTooth Radiotherapy Guidelines.
- Include a patient from each dose fractionation criterion (54Gy in 3#, 55Gy in 5# and 60Gy in 8#) as defined by the SABRTooth protocol

A clinical history must be included with each submission,

The three cases should be appropriately anonymised and sent via the NHS England Secure File Transfer Service (https://nww.sft.nhs.uk) to rpatel1@nhs.net for review by the SABRTooth team.

Once the treatment plans have been accepted by the QA team, the accepted plans must undergo patient specific QA, and the QA data sent to the QA team. This should be obtained by following the standard local procedure. No extra forms are included for this data as all centres will have created their own documentation. This is required for completion of the planning exercise. It is recommended that this is carried out once the plans have been accepted to avoid the centre carrying out QA unnecessarily.