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Use of multiparametric MRI and PET-CT to evaluate radiological changes after lung stereotactic ablative radiotherapy (SABR) – SIMPLE AS (Surveillance Imaging with MRI and PET in Lung patiEnts After SABR) Study

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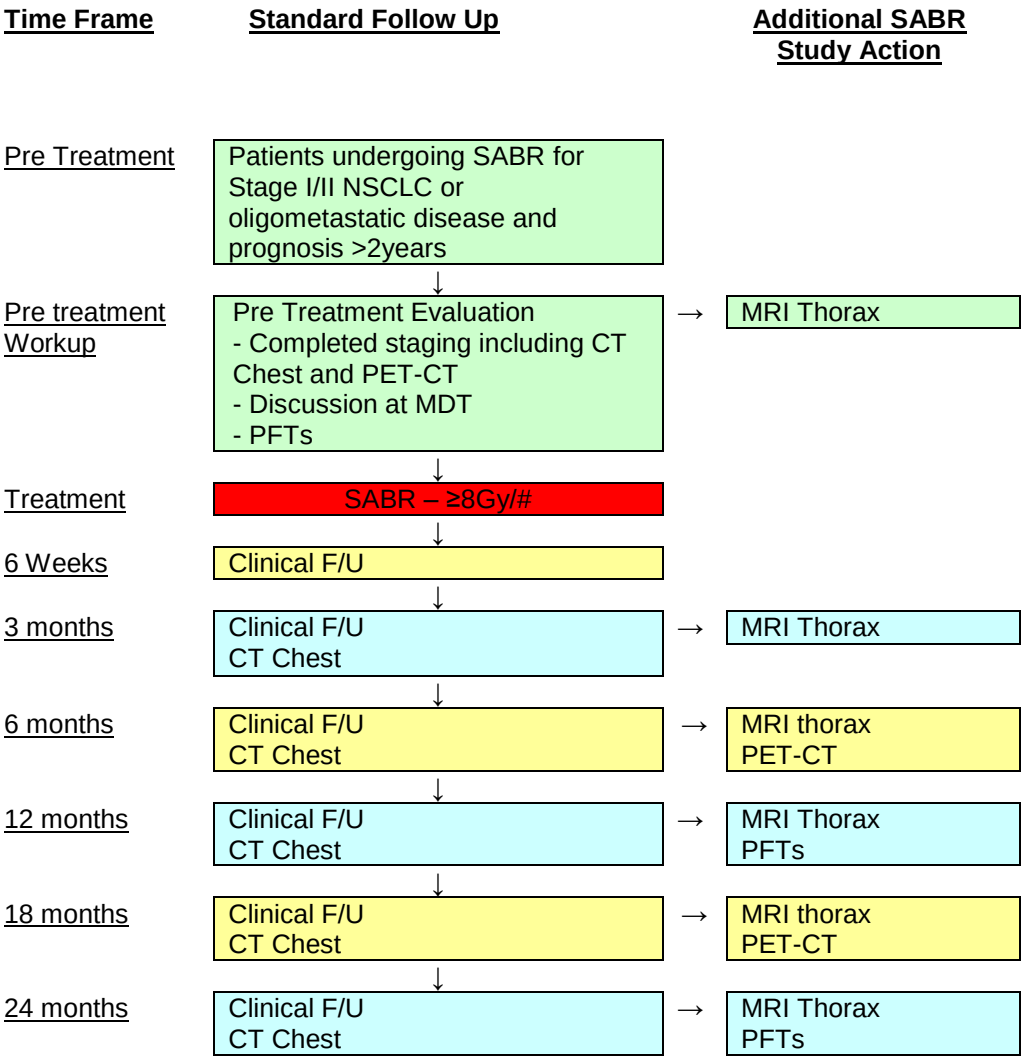
ABBREVIATIONS

ADC	Apparent Diffusion Coefficient
ADR	Adverse Drug Reaction
AE	Adverse Event
BED	Biologically Equivalent Dose
COPD	Chronic Obstructive Pulmonary Disease
CR	Complete Response
CRFs	Case Report Forms
CT	Computed Tomography
CTCAE	Common Terminology Criteria For Adverse Events
DCE	Dynamic Contrast Enhanced
DWI	Diffusion Weighted Imaging
FDG	Fluorodeoxyglucose
F/U	Follow Up
GGOs	Ground Glass Opacities
Gy	Gray
HASTE	Half-Fourier Acquisition Single Shot Turbo Spin Echo
LC	Local Control
LD	Longest Diameter
MDT	Multidisciplinary Team
MRI	Magnetic Resonance Imaging
MTV	Metabolic Tumour Volume
NPV	Negative Predictive Value
NSCLC	Non-Small Cell Lung Cancer
OS	Overall Survival
PD	Progressive Disease
PET-CT	Positron Emission Tomography-Computed Tomography
PETRA	Pointwise Encoding Time reduction with Radial Acquisition
PFTs	Pulmonary Function Tests
PI	Principal Investigator
PPV	Positive Predictive Value
PR	Partial Response
RECIST	Response Evaluation Criteria In Solid Tumours
ROC	Receiver Operator Characteristics
SABR	Stereotactic Ablative Body Radiotherapy
SAE	Serious Adverse Event
SD	Stable Disease
STIR	Short Tau Inversion Recovery
SUSAR	Suspected Unexpected Serious Adverse Reaction
SUV	Standardized Uptake Value
TLG	Total Lesional Glycolysis
Tx	Treatment
VIBE	Volumetric Interpolated Breath-hold Examination

1. Study Schema



2. SYNOPSIS

Background

Lung cancer is the 5th most common cancer in Australia and accounts for the highest number of cancer-related mortalities (1). Stereotactic ablative body radiotherapy (SABR) has recently emerged as a treatment option for patients who are medically inoperable or refusing surgery (2, 3). SABR is able to deliver a biologically equivalent dose (BED) in excess of 100 Gray (Gy), a considerable dose escalation from the 60-70Gy received with conventional radiation. Due to the higher BED administered with SABR, the tumour and normal tissue changes that occur in the months to years after treatment, are vastly different to the changes that occur after conventional radiotherapy. There is currently no consensus on the optimal follow up imaging protocol in patients post lung SABR (4).

Objectives

The primary objectives are to;

- Qualitatively and quantitatively assess post SABR tumour response on serial Magnetic Resonance Imaging (MRI), Positron Emission Tomography-Computed Tomography (PET-CT) and Computed Tomography (CT)
- Qualitatively and quantitatively assess post-SABR effects on normal tissues on serial MRI, PET-CT and CT

Secondary objectives are to;

- Assess the validity of the Dahele scale for post-SABR tumour changes seen on CT
- Develop a method for standardized synoptic reporting of post-SABR tumour changes on MRI and PET-CT and
- Develop a 'scoring system' for MRI and PET-CT based assessment post-SABR

Study Plan

This is a prospective cohort study with patients receiving radical radiotherapy at Liverpool, Campbelltown and Prince of Wales Hospitals. Patients with early stage Non-Small Cell Lung Cancer (NSCLC) or pulmonary oligometastatic disease will have the current standard workup prior to undergoing SABR, with the addition of a pre-treatment MRI. SABR will be delivered as per department guidelines. Treatment will not be altered as a result of this study. The post treatment surveillance of patients will be identical to current department standards with clinical review and CT scan of chest at 3, 6, 12, 18 and 24 months. In addition, patients will have MRI performed at 3, 6, 12, 18 and 24 months post SABR. A PET-CT will be performed 6 and 18 months post SABR. Pulmonary Function Tests (PFTs) will be performed at 12 and 24 months post SABR (See Study Schema).

3. RATIONALE / BACKGROUND

3.1 Introduction

Lung cancer is the 5th most common cancer in Australia and accounts for the highest number of cancer-related mortalities (1). The World Health Organization estimates that lung cancer accounted for 1.6 million of the 8.2 million cancer related deaths in 2012 (5). Though traditionally surgical resection has been the standard of care for patients with early stage NSCLC, many patients have comorbidities precluding surgery. SABR has recently emerged as a treatment option for patients who are medically inoperable or refusing surgery (2, 3).

The SABR technique allows for ablative doses of radiotherapy to be conformally delivered, with steep dose gradients. SABR is able to deliver a BED in excess of 100Gy, a considerable dose escalation from the 60-70Gy received with conventional radiation. The increasing availability and implementation of SABR over the last decade has coincided with greater image guidance and more conformal radiotherapy delivery systems. Although there have not been direct randomized trials comparing SABR to surgery, the local control rates are comparable to surgical series. Prospective phase II trials have reported excellent local control rates of in excess of 90% at three years with SABR for patients who are medically inoperable or refuse surgery (6, 7). There have been two randomised trials comparing SABR to conventional radiotherapy. The multi-institutional Trans-Tasman study, TROG CHISEL trial (NCT01014130) has recently completed accrual. The Scandavian SPACE trial reported only in abstract form has shown no difference in survival but less toxicity in the SABR arm (WCLC 2015).

The emergence of SABR as a viable treatment option has extended to pulmonary oligometastatic disease. A systematic review showed local control rates of pulmonary oligometastases to be approximately 78% at 2 years (8).

3.2 What is already known

Despite the excellent local control rates achieved with SABR, local recurrences do occur. With the rising implementation of SABR, the complexities of post treatment surveillance are likely to become an increasingly important issue. The difficulties of surveillance post SABR are exemplified by studies that have demonstrated only benign tissue in the resection of presumed recurrences (9). The majority of current guidelines are based on recommendations that were considered appropriate for conventional fractionation techniques. The post treatment changes in irradiated lung following SABR are vastly different to those in conventional fractionation, secondary to the higher biological doses delivered and the differing method of delivery. SABR treatment often involves multiple beams or arc therapy, delivering low doses of radiation to large amounts of lung.

A recent systematic review suggested it should comprise of surveillance CT scans at 3-6 months during the first year, then 6-12 months thereafter, with PET-CT scans performed only if suspicion of recurrence (10) (See Appendix 1). The authors also suggests an algorithm for investigation of recurrence, with PET-CT suggested if CT changes demonstrate high-risk features or enlargement of CT density and a Standardized Uptake Value (SUV) cut off of 5.0 to be considered as the trigger for potential biopsy. However, at present there is variance in practice worldwide, due to the paucity of evidence. In particular, other groups have not validated this algorithm (11).

3.2.1 CT imaging post SABR

Acute and late lung reactions post SABR

Previous authors have documented the changes that occur to lung tissue post SABR (10, 12, 13). Dahele reported that changes seen on CT within 6 months post SABR

can vary from no change, to patchy ground glass opacification, diffuse patchy opacification, patchy consolidation and diffuse consolidation (12) (See Appendix 2). The actuarial median time to acute changes was 17 weeks. In this same publication, late changes were characterized as no change, scar like fibrosis, mass like fibrosis or a modified conventional pattern. Attempts to validate this scoring system have demonstrated high inter-observer variability (11).

Recurrence post SABR

Secondary to the high rates of benign lung changes seen post SABR, the detection of recurrences is extremely challenging. The changes in the lung parenchyma secondary to radiation-induced damage are dynamic; making changes seen on sequential CT scans an unreliable indicator of disease status. Since SABR is a relatively new technique and local recurrence rates are low, there is a paucity of data on the topic of imaging changes for recurrence post SABR. Due to the highly conformal dose delivery during SABR and steep dose gradients, lung changes post SABR can often mimic recurrence. Fibrotic changes post SABR can often appear mass like, which can be difficult to distinguish from recurrence (14). Matsuo et al showed that mass like fibrosis occurred in 68% patients, with median time of 5 months post SABR (15). The *Response Evaluation Criteria In Solid Tumours (*RECIST) criteria using CT, therefore, is not a reliable indicator of recurrence in this population. Kato et al (2010) compared serial CT examinations in patients with recurrence to those without and concluded that local recurrence should be suspected on CT when there is a bulging margin, disappearance of air bronchograms, pleural effusion or increase in the abnormal opacity after 12 months (16). Huang and colleagues concluded that the presence of >3 high-risk features confers local recurrence (Appendix 3). While CT is the suggested first line imaging modality for patients having post SABR surveillance, its pitfalls and shortcomings are well noted.

3.2.2 PET-CT imaging post SABR

Acute changes on PET-CT post SABR

In the acute setting post SABR, a transient rise in SUV may occur, due to post radiotherapy inflammatory response (17, 18). For patients with low SUV prior to SABR, transient small rises can occur at the 2-week mark. Conversely, those with high SUV prior to SABR delivery may have small decreases in SUV. Lung injury following ablative radiation doses can commonly result in a metabolically active lesion, which may rise transiently immediately post-SABR.

Response assessment using PET-CT post SABR

In the setting of post SABR response assessment, the role of Fluorodeoxyglucose (FDG) PET-CT is less clear. In a prospective series by Henderson et al, 6 of 13 patients treated with SABR for stage 1 NSCLC were found to have SUV values of >3.5, twelve months following treatment, without any evidence of disease relapse (17). Zhang et al performed PET-CT scans at 1 month, 6 months and when clinically indicated on 128 patients post SABR for stage I lung cancer (19). They found that a SUV cut off of >5.0 had a 50% positive predictive value (PPV) and a 100% negative predictive value (NPV) for recurrence. Patients with SUV<5.0 are frequently found to have fibrotic tissue rather than recurrence. The authors recommended that if an SUV>5.0 is found in the area of primary post-SABR, a biopsy should be performed. Subjecting patients to a biopsy can be problematic, especially in the setting of a population often deemed unsuitable for surgery due to respiratory causes, commonly Chronic Obstructive Pulmonary Disease (COPD).

3.2.3 MRI imaging post SABR

Role of MRI in lung cancer

The current role of MRI in the context of lung cancer, both diagnostic and response assessment settings, is limited. Recent studies have suggested the superiority of

Diffusion Weighted Imaging (DWI) and Dynamic Contrast Enhanced (DCE) MRI over PET-CT in characterizing pulmonary nodules, with increased specificity (20, 21). Other studies have also suggested a potential role in TNM[1] staging, with scope for added value in detecting chest wall invasion or lymph node involvement using Short Tau Inversion Recovery (STIR) sequences. (22, 23).

Role of MRI in response assessment for lung cancer.
An advantage of this modality is the absence of additional radiation incurred through the scan. A study by Ohno et al (2003) showed the potential prognostic value of DCE MRI in terms of predicting local failure following chemo-radiotherapy for lung cancer (24). The same group later demonstrated the potential value of Apparent Diffusion Coefficient (ADC) in pre-treatment DWI MRI over SUV scores in PET-CT in predicting response to therapy (25). This predictive value has also been demonstrated in the setting of post-treatment response assessment, with a study showing a significant difference in survival depending on early ADC changes on DWI after chemo-RT for lung cancer. The study showed that patients treated with chemo-RT with early increase in ADC had a median survival of 24 months, and those with stable or decreased ADC had a median survival of 12 months (26). Chang et al also demonstrated the potential role of early ADC change on DWI MRI for assessing response in lung cancer post chemo-RT. All this research has been in the setting of conventional radiotherapy, and whether it can be extrapolated to patients receiving SABR is not yet known.

Role of MRI in response assessment post SABR for lung cancer
This is currently investigational, with an ongoing study being performed at Princess Margaret Hospital (Cho et al). This study hopes to recruit 30 patients, with one MRI scan performed greater than 1 year post treatment, with patients classified as suspicious for recurrence, equivocal or fibrosis. Otherwise to the best of our knowledge, no published series involving MRI in response assessment post SABR exists. DWI MRI has been shown in small prospective series to have some predictive value in Stage 1 NSCLC (27).

Role of MRI in assessing acute lung toxicity post SABR
There is a paucity of data using MRI to assess lung toxicity post conventional or stereotactic radiotherapy for lung cancer.

3.3 What is missing

Although recommendations exist for CT and PET-CT-based follow-up after SABR, better metrics are required for early detection of recurrence, to allow for salvage, and to avoid unnecessary investigations in patients with benign radiation-induced lung injury (4).

3.4 What the study is going to find out

This study will qualitatively and quantitatively assess MRI and PET-CT for the surveillance of patients with early stage NSCLC or pulmonary oligometastatic disease treated with SABR. Similarly, it will also qualitatively and quantitatively assess the changes that occur in normal tissues after delivery of SABR. We intend to assess the validity of current recommendations that utilise CT and PET-CT, and to explore whether or not MRI adds anything to current recommendations. It is possible that upon completion of this review, MRI becomes a recommended imaging modality in the surveillance of people treated with SABR.

3.5 How this is going to be achieved

[1] **TNM** Classification of Malignant Tumours

All patients who are enrolled in the study will receive the standard pre-treatment work-up, treatment and post treatment surveillance. In addition patients will be subjected to six additional MRIs and two additional PET-CTs. By performing standard work-up with additional MRIs and PET-CT, a direct comparison will be able to drawn between the imaging modalities of CT, PET-CT and MRI. This will best identify patients and/or circumstances where PET-CT and/or MRI are of additional value to the standard surveillance protocol currently recommended.

3.6 What impact will the study have

There is a paucity of data using MRI and PET-CT to assess lung toxicity post conventional or stereotactic radiotherapy for lung cancer. The role of MRI in post treatment surveillance is currently investigational, with an ongoing study being performed at Princess Margaret Hospital (Cho et al). The results of this study will represent one of the first studies investigating the value of MRI after delivery of SABR. We anticipate that this research study will offer tremendous insight into the role of MRI and PET-CT in post SABR surveillance.

4. AIMS/OBJECTIVES/HYPOTHESES

4.1 Primary Objectives

1. To qualitatively and quantitatively assess post SABR tumour response on serial MRI, PET-CT and CT
2. To qualitatively and quantitatively assess post-SABR effects on normal tissues on serial MRI, PET-CT and CT

4.2 Secondary Objectives

1. Assess validity of the Dahele scale for post-SABR tumour changes seen on CT
2. Develop a method for standardized synoptic reporting of post-SABR tumour changes on MRI and PET-CT
3. Develop a 'scoring system' for MRI and PET-CT based assessment post-SABR

4.3 Hypothesis

It is hypothesised that post treatment MRI and PET-CT offer more information on tumour control and late normal tissue toxicity than the current surveillance imaging recommendation of CT alone.

5. PARTICIPATING SITES

Liverpool Hospital
Elizabeth Street
Liverpool
Sydney 2170

Campbelltown Hospital
Therry Road
Campbelltown
Sydney 2560

Prince of Wales Hospital
High Street
Randwick
Sydney 2031

6. RESEARCH PLAN / STUDY DESIGN

6.1 Study Design and Methods

Study Population
36 patients aged over 18 years with Stage I/II NSCLC (and no involved nodes) or oligometastasis to the lung will be recruited for this study. Allowing for a 15% discontinuation rate, this will leave 30 patients for analysis. A consensus on diagnosis must be achieved, and treatment recommendation with SABR of greater than 8Gray per fraction. Patients will be screened to ensure they have no contraindication for an MRI scan.

Inclusion Criteria:

1. Patients undergoing SABR for Stage I/II NSCLC or lung oligometastases
2. Able to attend follow up for 2 years

Exclusion Criteria

1. Prognosis < 2 years
2. Patient refusal
3. Contraindication to MRI
4. Inability to give informed consent

Contraindication to Contrast
The presence of a contraindication to iodine contrast or Gadolinium contrast will not exclude patients from the study. Imaging will be performed without contrast

Prognosis of Patients likely enrolled in study
Previous studies and meta-analyses of patients treated with SABR have demonstrated the following points:

- 3year overall survival (OS) rates in early stage NSCLC of 42% (28)
- 3year local control (LC) rates in early stage NSCLC of 88% (29)
- Local, regional and distant recurrences occur early, median 14.9, 13.1 and 9.6 months respectively in early stage NSCLC (30)
- 2yr LC rates of 78% in oligometastatic pulmonary disease
- 2yr OS rates of 54% in oligometastatic pulmonary disease (8)

This data was utilised in the creation of the Radiation Safety Report.

6.2 Type of study

Prospective cohort study with patients recruited from Liverpool, Campbelltown and Prince of Wales Hospitals.

6.3 Pre treatment

As per standard workup for all patients with early stage NSCLC or pulmonary oligometastatic disease undergoing radiotherapy, participants in the study will need to have:

- Multidisciplinary team (MDT) consensus on diagnosis, either *Lung MDT* or *alternate site- specific MDT* in setting of lung oligometastases
- Complete staging including CT and PET-CT within 30 days prior to simulation
- Pulmonary function tests within 30 days prior to the commencement of treatment
- Informed consent

Additionally, as part of prospective study, patients will need to have:

- MRI +/- contrast if no contraindications

6.4 Treatment and Planning

As per departmental guidelines all patients must have stereotactic radiotherapy, with a dose ≥8Gy per fraction.

Data collected on treatment/planning will include:

- Dose
- Fractions
- Technique
- RT plan DICOM data

6.5 Follow up and Imaging schema

Follow up CT scan

CT scan of thorax with contrast if no contraindications. In the setting of renal impairment, renal physician advice or pre and post scan intravenous fluids may be given at discretion of treating radiation oncologist. Sequential CT scans will be performed at the same institution.

Dedicated SABR CT radiologist, primary investigators and treating radiation oncologist will review all CT scans and complete response assessment.

Where appropriate, all CT scans will be assessed and graded for:

RECIST criteria

- *Complete Response (CR)*: Disappearance of all target lesion
- *Partial Response (PR)*: At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD
- *Stable Disease (SD)*: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for Progressive Disease (PD), taking as reference the smallest sum LD since the treatment started
- *Progressive Disease (PD)*: At least a 20% increase in the sum of the largest diameter (LD) of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions

Acute lung changes are per DAHELE grading system
Acute occurring within first 6 months from treatment. Five categories of acute changes described by Dahele et al. (See *Appendix 2*)

- Diffuse consolidation
- Patchy consolidation
- Diffuse ground glass opacities (GGOs)
- Patchy GGO
- No evidence of increasing density

For patients undergoing treatment of more than one lesion, CT changes associated with each lesion will be scored separately. Any scans taken for reasons/concerns other than follow up surveillance (eg. Infection) will not be scored

Late lung changes are per DAHELE grading system
Late occurring more than 6 months after completion of treatment. Classified into one of four categories described by Dahele et al (See *Appendix 2*)

- Modified conventional patter of fibrosis
- Mass like fibrosis
- Scar like fibrosis
- No evidence of increasing density

A synoptic method of reporting CT scans post SABR will be developed including index of suspicion for recurrence or relapse – local and regional.

Follow up PET scan

PET-CT scan will be performed at Liverpool and Prince of Wales hospitals. All PETs will use 18F-FDG. PET assessment will include SUV measurement and other metrics to qualify any post SABR changes as likely benign or suspicious for malignancy

All PET scans will be assessed and graded for:

- Maximum SUV
- Metabolic Tumour Volume (MTV)
- Total Lesional Glycolysis (TLG)
- Change in maximum SUV
- Change in MTV and TLG
- Pulmonary nodules
- Nodes
- Nodal site by stations
- Nodal max SUV
- Distant metastasis
- Sites of Distant Metastases

Assessment of PET scans will be done by nuclear physicians across both sites for all PET scans. This will help minimise the inter-observer variability.

Follow up MRI scan

MRI scan will be performed at the various enrolled hospitals within the study or within the private radiology sector. Where possible, the treating clinician will endeavour to ensure that all an individual's MRIs are performed at the same facility. Gadolinium contrast will be delivered where there are no contraindications. Total estimate scan time is 45 minutes for each patient.

Follow up PFTs

Two additional pulmonary function tests will occur after the delivery of SABR. These tests will occur at twelve and 24 months, at no additional cost to the patient. These will be recorded in an electronic data form within the oncology information system.

Toxicity

During all clinical follow up appointments (6 weeks, 3 months, 6 months, 12 months, 18 months and 24 months post completion of SABR) the supervising clinician will be required to fill out an electronic or paper dataform to document patient status, disease status based on conventional imaging (CT) and scoring of toxicities based on Common Terminology Criteria for Adverse Events (CTCAE V4).

6.6 Expected duration of study

It is intended to recruit 36 patients, across all treatment sites over a 2 year period. After an anticipated 15% drop out rate, there will be 30 patients remaining. For all patients it is intended to complete two year follow up. This means the projected finishing time is February 2021.

6.7 In event of recurrence

In the event of suspected recurrence on clinical follow up or imaging, patients will be managed according to current institutional practice. Depending on treatment factors, patient factors and results of investigations, this may include further imaging and/or biopsy. This will be left to the discretion of treating radiation oncologist; however discussion in multidisciplinary setting is encouraged.

6.8 Data Collection

Prior to SABR:

Demographic information

Age
DOB
ECOG
Weight
Comorbidities
Current Smoker
- If yes, number of pack years

Ex smoker
- If yes, number of pack years

Diagnosis
Reason not surgical candidate
Sex

Clinical Information

Tumour size (x,y,z dimensions)
Stage (I or II for NSCLC, Stage IV for oligometastatic disease)
Biopsy (Y/N)
- Histological subtype

Date of diagnosis
Date of MDT discussion
Date of CT/PET-CT/MRI/PFTs
PFT results
- FEV1.0, % predicted
- FVC, % predicted
- DLCO, % predicted

Treatment Information:

Date of first treatment

Date of last treatment
Total dose
Number of fractions
Duration of treatment

Follow-up Information:

Date of Follow-up
Clinical Follow-Up
- Weight
- ECOG
- Examination
    - Local progression
    - Nodal progression
    - Distant progression

CTCAE (version 4.0)
- Cough
- Dyspnoea
- Pneumonitis
- Hypoxia
- Chest wall pain

PFTs
- FEV1.0
- FVC
- DLCO

Date of MRI (Dr Moses and PI)
- Primary tumour size (cm)
- New nodal disease (Y/N)
- New metastatic disease (Y/N)
- Suspicion for recurrence (Y/N)
- Qualitative assess rib, lung changes
- Sequences (qualitative information only)

Date of PET-CT (Dr Peter Lin, Dr Michael Lin, Dr Wegner Dr Ho-Shon and PI)
- Maximum SUV
- Metabolic Tumour Volume (MTV) (eg. SUV2.0)
- Total Lesional Glycolysis (TLG)
- Change in maximum SUV (compared to pre treatment PET-CT)
- Pulmonary nodules
- Nodes
- Nodal max SUV
- Distant metastasis
- Site of distant metastasis
- Suspicion for recurrence

Date of CT (Radiologist, Radiation Oncologist and PI)
- Primary tumour size (cm)
- Contrast given (Y/N)
- New nodal disease (Y/N)
- New metastatic disease (Y/N)
- New pleural effusion (Y/N)
- Suspicion for recurrence
- Overall Response (RECIST) (one of either)
    - Complete Response
    - Partial Response
    - Stable Disease
    - Progressive Disease
- Dahele Changes (one of either)
    - Modified conventional pattern of fibrosis
    - Mass like fibrosis

    - Scar like fibrosis
    - No evidence of increasing density
- Description (can be more than one)
    - Ground glass opacification (Y/N)
    - Fibrotic changes (Y/N)
    - Atelectasis (Y/N)

6.8.1 Table of assessments

Study Period	Pre-treatment baseline	Planning	Treatment	6 weeks post Tx	3 months	6 monthly FU
Week					3 months after end of RT	6, 12, 18 and 24 months post RT
Informed Consent [a]	X					
Eligibility Check	X					
Demographic Information	X					
Medical History	X					
Registration	X					
Staging CT Chest	X					
Staging PET-CT	X					
Discussion at MDT	X					
PFTs	X					X(12,24 only)
Planning Summary/Dosimetry		X				
Treatment Summary			X			
Clinical FU			X	X	X	X
CT Chest					X	X
MRI Thorax	X				X	X
PET-CT						X (6,18m only)
CTCAE Radiotherapy				X	X	X

6.9 Statistical analyses

Statistical analyses will be performed by using software SPSS and p-value <0.05 will be considered statistically significant. The majority of the information collected will be qualitative, as opposed to quantitative. This is an exploration of imaging post lung SABR, an area that has not been significantly researched. Receiver operator characteristics (ROC) will be used to obtain an optimal threshold for individual MRI and PET-CT parameters.

7. ETHICAL CONSIDERATIONS

7.1 Recruitment and selection of participants

Inclusion Criteria:

1. Patients undergoing SABR for Stage I/II NSCLC or lung oligometastases
2. Able to attend follow up for 2 years

Exclusion Criteria

1. Prognosis < 2 years
2. Patient refusal
3. Contraindication to MRI
4. Pregnant
5. Inability to give informed consent

7.2 Informed consent

All patients will receive an information sheet outlining the trial, their commitments and possible risks involved. Written informed consent will then be obtained prior to registration. Patients may leave the study at any time without compromising their treatment. The study will be submitted for the approval of the South Western Sydney Local Health District Human Research Ethics Committee. All information regarding trial participants will be treated with strict confidence. Data which identify any of the trial participants will not be revealed to anyone not directly involved in the clinical care of that participant. If a patient withdraws from the study, then the standard follow up will be resume and the information collected up until the time of withdrawal will be used for study purposes.

7.3 Confidentiality and Privacy

All information will be re-identifiable only. The Confidentiality and Privacy of patient information will be respected. All clinical, imaging and toxicity data will be available to the researchers during the research project. Information will be stored on Electronic Medical Records (EMR) which is password protected and in the study patient files located at the Ingham Institute at Liverpool. Patients treated at POWH will have information stored on the POWH EMR, and where required, information will be stored on patient files located at the Ingham Institute at Liverpool.

7.4 Data storage and Record retention

- All internal imaging will be stored on password protected research drive on Pinnacle and/or MIM. These images will be de-identified. Password protected hard drive will also be used for back up of images.
- PET-CT analysis for all patents will occur at both sites. PET-CTs will be anonymised and sent to alternate site for review, either electronically or via DVD.
- All external imaging will be stored securely in patient files within locked cabinets by the Radiation Oncology Clinical Trials team at the Ingham Institute, which accessed only via swipe access approval
- All patient data including tumour and treatment details, will be stored on password protected EMR.

- Consent forms will be stored on password protected EMR and in the patients study folder.
- A de-identified registration form and consent form will be submitted to the trial coordinating centre at Liverpool Hospital to allow registration of the participant.
- Planning, treatment, toxicity data and follow up information will be collected using paper and electronic Case Report Forms (CRFs) and all data will be deidentified and submitted to the trial coordinating centre located at Liverpool Hospital. It is the investigator's responsibility to retain study essential documents for at least 15 years after the completion of this clinical study at each trial site in accordance with ICH GCP Guidelines. All submitted trial data and information will be stored in the Radiation Oncology clinical trials office located at Liverpool Hospital, either on a password protected computer or in files kept in a locked room. Access to this information will be limited to the principal investigator (PI), research assistants and statistician as authorized by the delegation log.
- Data analysis will also be undertaken in conjunction with Dr Chiara Paganelli from the University of Politecnico di Milano, Italy on the de-identified MRI and CT datasets collected as part of this study. The datasets will be de-identified, original scans will remain at Liverpool Hospital (copies will be sent via University of New South Wales CloudShare) and the files will be password protected at all times.
- Anonymised MRI data will be sent to CSIRO to investigate the feasibility of MR only planning by Tony Young, Medical Physicist at Liverpool Hospital. To assess geometric distortion of MRI data, the baseline CT and MRI scans will be utilized by Investigator Amy Walker, Medical Physicist at Liverpool Hospital

7.5 Additional Radiation Exposure

Patients will be informed of the additional radiation exposure as a result of enrolling in this study (see Radiation Dosimetry Report). The risk of harm including a secondary malignancy from this additional exposure will be communicated with patients in both verbal and written communication. If a patient decides to withdraw at any time as a result of this added exposure, then they will be free to withdraw at any time without consequence.

8. SAFETY AND ADVERSE EVENTS

Standard toxicity data collection will occur in this study at each follow up appointment. Limited safety reporting is required for this study as the patients will receive standard of care treatment. Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (SADR) reporting will only be completed for serious events related to additional imaging for the study occurring up to 7 days after each research imaging investigation for MRIs and PET-CTs.

The following conditions are excluded from SAE reporting:

- Hospitalisations or death related to disease progression.
- Any planned hospitalisation.
- Elective hospitalisation for treatment of the underlying disease.
- Elective hospitalisation allowing a simplification of study treatment/study procedure or to facilitate administration of treatment i.e. Porta-Cath insertion.
- Elective hospitalisations for other procedures, e.g. screening colonoscopy, stent change, cardiac catheter, etc.
- Hospital admission for social reasons (i.e. carer unavailable to care for patient).

8.1 Reporting of Serious Adverse Events

Any SAE occurring in a study participant will be reported to the local HREC within 24-72 hours of knowledge of the SAE, in accordance with the safety reporting policy of the HREC. The HREC safety reporting form will be completed, signed and submitted by the investigator.

Investigators must conform to the SAE reporting timelines, formats and requirements of the various entities to which they are responsible, but at a minimum those events that must be reported are those that are:

- Related to study participation,
- Unexpected, and
- Serious or involve risks to subjects or others

The minimum necessary information to be provided at the time of the initial report includes:

- Study identifier
- Study Centre
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

8.2 Serious Unexpected Suspected Adverse Reaction (SUSARs)

All SUSARs occurring in a study participant will be reported to the local HREC in an expedited fashion (i.e. within 15 calendar days of first knowledge), or for fatal or life threatening events, an initial or full report within 7 calendar days and a follow-up report if necessary within the 15 calendar day timeframe. An investigator will complete, sign and submit the SUSAR report.

9. OUTCOMES AND SIGNIFICANCE

This study offers to improve the quality of surveillance imaging in the cohort of patients receiving lung SABR. This study involves the novel use of emerging technologies, and represents one of the first studies exploring the benefit of both MRI and PET-CT after lung SABR. This project aims to develop an optimal follow-up imaging schema for patients treated with SABR. If developed, this schema will serve to identify recurrences of pulmonary neoplasms earlier, and increase the chances of cure or local control in those patients receiving SABR. SABR is an emerging treatment option for early stage NSCLC and pulmonary oligometastatic disease, and any improvements in the surveillance post SABR benefit anyone who requires SABR in the future. By identifying recurrences earlier, salvage treatment options may offer greater benefit.

10.TIMELINES / MILESTONES

Timeline	Study goals	Descriptions
June 2015 to January 2017	1. Literature review 2. Finalise study protocol 3. Ethics approval/amendments 4. Physics statement for additional radiation exposure	1. Update literature review on the current role of MRI and PET-CT in the follow up of lung SABR patient 2. Finalise study protocol with co-investigators 3. Obtain NEAF ethics approval from participating hospitals 4. Any study where anticipated exposure of radiation is expected to be above "normal" requires a statement from qualified physicists.
February 2017– February 2019	1. Study 2. Adjustments	1. Recruitment of 36 patients. Analysis of images by PI, radiologist and treating specialist. Data analysis (including statistical analyses) 2. Review the study protocol and further improvement(s) as required. 3 monthly meeting with investigators for issues, concerns. Update interested parties of progress
February 2017 – February 2021	1. Complete follow up 2. Presentations	1. Completion of recruitment (expected completion of recruitment in October 2018). Minimum 24 months follow up for all recruited patients. 2. Conference presentations of interim results as appropriate. Manuscripts preparation and publications of interim results

11. PUBLICATION POLICY

It is intended that the completed data will be presented and published in an international conference and journal respectively. At time of writing there are no current restrictions or obligations in regards to this.

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13. APPENDICES

Appendix 1

Proposed follow up imaging algorithm (Huang et al, 2012) (10)

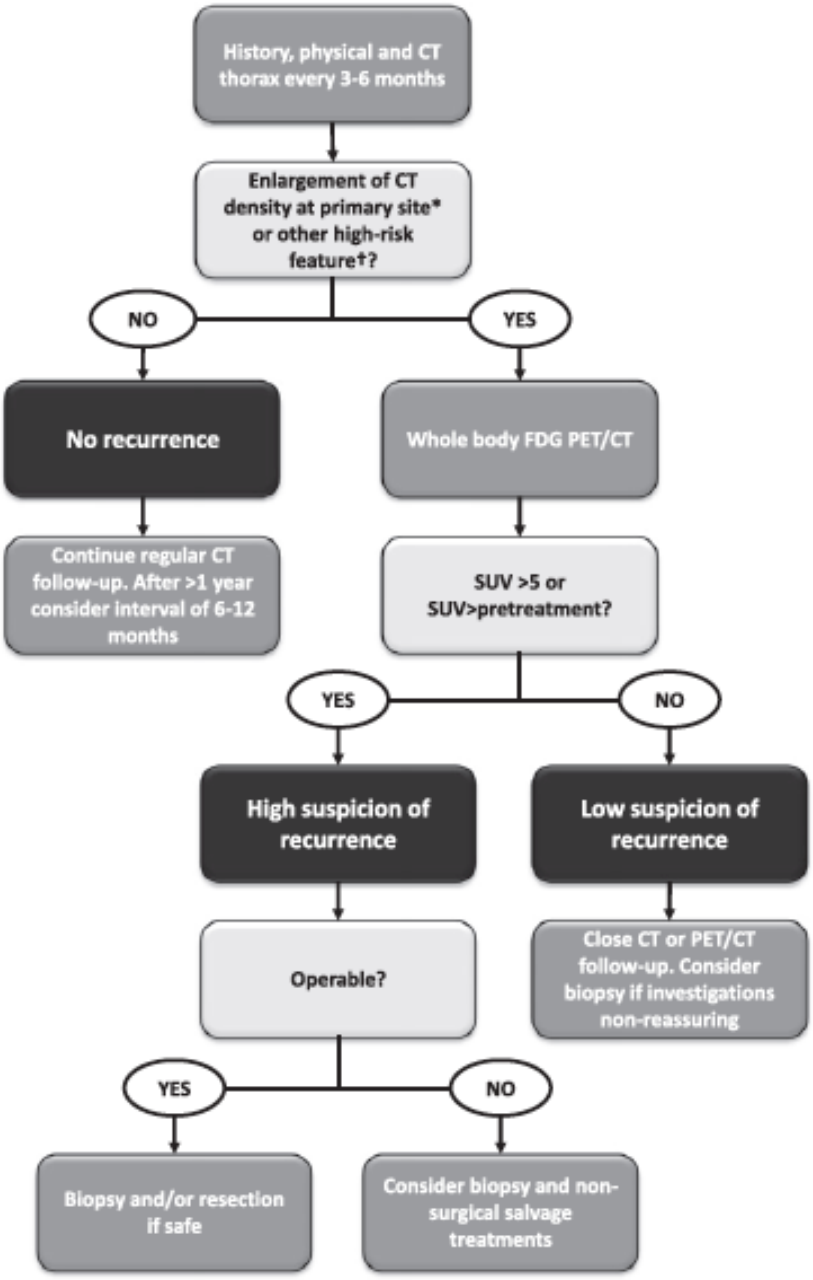

Fig. 2. Proposed algorithm for follow-up of patients post-SABR who are candidates for salvage treatment. *Enlargement of CT density: as described by RECIST 1.1 by an increase in the sum of the diameters (SOD) of the target lesion by at least 20% from baseline (i.e. post-SABR nadir size) and absolute increase in SOD of at least 5 mm [44]. †High-risk features: sequential enlargement on repeat CT, opacity enlargement after 12 months, bulging margin, disappearance of air bronchograms, linear margin disappearance, ipsilateral pleural effusion or lymph node enlargement. *Abbreviations:* Stereotactic ablative radiotherapy (SABR), computed tomography (CT), 18F-fluorodeoxyglucose positron emission tomography (FDG-PET), standardized uptake values (SUV).

Appendix 2

Post SBRT lung changes scoring system (Dahele et al, 2011) (12)

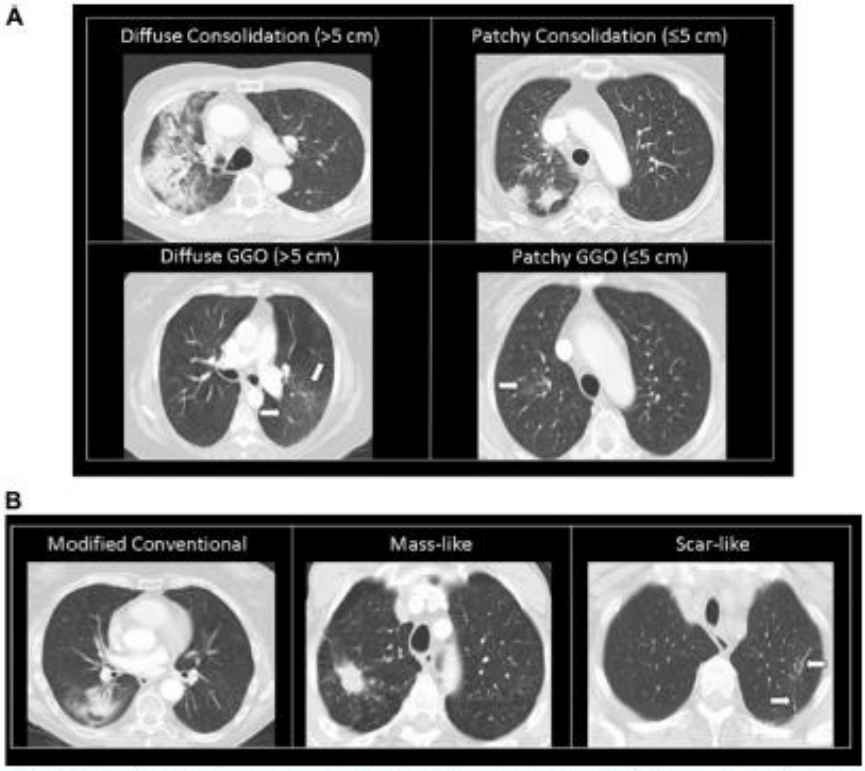

FIGURE 1. Classification of radiological changes after stereotactic body radiotherapy (SBRT). *A*, Acute radiological pneumonitis within 6 months of treatment. One category (no increasing density) not shown. *B*, Late radiological fibrosis after more than 6 months from the time of treatment. One category (no increasing density) not shown. GGO, ground glass opacity.

TABLE 2. Scoring System for Classifying Acute Radiological Changes After Stereotactic Body Radiotherapy (SBRT)[9]

Name	Description
Diffuse consolidation	Consolidation more than 5 cm in largest dimension. The involved region contains more consolidation than aerated lung
Patchy consolidation	Consolidation less than 5 cm in largest dimension and/or the involved region contains less consolidation than aerated lung
Diffuse GGO	More than 5 cm of GGO, (without consolidation). The involved region contains more GGO than normal lung
Patchy GGO	Less than 5 cm of GGO, (without consolidation), and/or the involved region contains less GGO than normal lung
No evidence of increased density	No new abnormalities. Includes patients with tumors that are stable, regressing or resolved, or fibrosis in the position of the original tumor that is not larger than the original tumor

GGO, ground glass opacity.

TABLE 3. Scoring System for Classifying Late Radiological Changes After Stereotactic Body Radiotherapy (SBRT)[10]

Name	Description
Modified conventional pattern	Consolidation, volume loss, and bronchiectasis similar to, but usually less extensive than, conventional radiation fibrosis. Larger than the original tumor size. Occasionally with associated GGO
Mass-like fibrosis	Well-circumscribed focal consolidation limited to area surrounding the tumor. The abnormality must be larger than the original tumor
Scar-like fibrosis	Linear opacity in the region of the tumor associated with volume loss
No evidence of increased density	No new abnormalities. Includes patients with tumors that are stable, regressing or resolved, or fibrosis in the position of the original tumor that is not larger than the original tumor

GGO, ground glass opacity.

Appendix 3

High Risk Features (HRFs) on CT post SABR as per Huang et al, 2012 (10)

Table 2. High-risk features for recurrence on CT. Data from reference (51).

High-risk feature	Sensitivity (%)	Specificity (%)
Enlarging opacity	92	67
Sequential enlargement	67	100
Enlargement after 12 months	100	83
Bulging margin	83	83
Linear margin disappearance	42	100
Loss air bronchogram	67	96
Cranio-caudal growth of ≥5 mm and ≥20%	92	83