A qualitative study of patients' attitudes to the risks and potential benefits of potential toxicities of radical re-irradiation for lung cancer

Short title: Lung cancer patients' attitudes to a second course of radiotherapy

This study will be performed according to the UK Policy Framework for Health and Social Care Research (2017) and WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI Ethical Principles for Medical Research Involving Human Subjects 1964 (as amended).

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CONTENTS

Synopsis	4
1. Introduction	5
1.1. Lung cancer and recurrence	
1.2. Current treatments for recurrent disease	
1.3. Current evidence for radical re-irradiation	
1.4. Need for a prospective trial of radical re-irradiation	
1.5. Patient acceptance of re-irradiation	
1.6. Patient attitude to risk of toxicity	
1.7. Relationship of symptoms from initial radiotherapy and willingness for re-treatment	
1.8. Choice of Quality of Life scoring system and need for a baseline comparator	
1.9. Rationale and summary	
2. Aims and Objectives	9
2.1. Aims	
2.2. Primary objectives	
2.3. Secondary objectives	
3. Methodology	10
3.1. Study design	
3.2. Inclusion and exclusion criteria	
3.3. Recruitment and sampling	
3.4. Consent	
3.5. Semi-structured interview	
3.6. End of study	
3.7. Potential risks and benefits	
3.8. Mitigation for SARS-CoV-2	
3.9. Data storage and retention	
4. Statistical considerations and method of analysis	14
4.1. Sample size	
4.2. Method of analysis	
5. Ethics	15
6. Finance and indemnity	16
7. Publications	17
8. References	18
Appendix A – Attitudes to Re-irradiation literature search	20
Appendix B – Consent form, Patient Information sheet, Interview structure	21

SYNOPSIS

Study Title:	A qualitative study of patients' attitudes to the risks and potential benefits of radical re-irradiation for lung cancer
Study Design:	Single centre, qualitative interviews
Study Objectives:	Primary Objective (1) Explore patients' feelings and concerns about having a second course of radiotherapy for recurrent lung cancer Secondary Objectives (1) Identify factors that patients consider when deciding on potential treatments in the setting of locally recurrent lung cancer (including effect of COVID-19 on treatment choice) (2) Investigate how patients' acceptance of side effects changes with the different projected outcomes of re-irradiation (3) Explore the relationship between the toxicities patients experienced during radiotherapy and their attitudes to a second course of radiotherapy (4) Investigate patients' awareness of surveillance imaging after radical treatment and willingness for scans
Study Population:	Patients treated in the West of Scotland Cancer Centre who have completed a course of radical radiotherapy to their thorax for lung cancer
Procedure:	• Consent patient during radiotherapy (at radiotherapy on-treatment review clinic) • Confirm consent and arrange interview at 4 weeks after completion of radiotherapy • Semi-structured interview at 5 weeks after completion of radiotherapy (by telephone or video consultation)
Outcome:	Identification of patients' concerns regarding re-irradiation to direct future clinical trial design

1. INTRODUCTION

1.1 Lung cancer and recurrence

Lung cancer is the most lethal malignancy in the UK, with over 45,000 people diagnosed each year, and over 39,000 deaths[1]. Of those suitable for radical treatment, it is estimated that approximately 45% of lung cancer patients (approximately 5,000 patients in the UK) will have radical radiotherapy to their chest as part of initial treatment[2]. However, there is a substantial risk of either: isolated recurrent thoracic disease (which occurs in 20-30% of patients with non-small cell lung cancer (NSCLC) treated with radiotherapy or chemoradiotherapy[3,4]) or; development of a second primary lung cancer (the risk of which is 14% over 10 years after initial treatment[5]). There are an estimated 800 patients per year in the UK who may be suitable for further radical treatment yet there are no clear treatment guidelines in this situation.

1.2. Current treatments for recurrent disease

For patients with recurrent disease or a metachronous lung primary, treatment options comprise systemic treatment, surgery, or thoracic re-irradiation. Each has risks and potential benefits.

Systemic therapies may be very effective for patients with EGFR mutated, ALK rearranged or PDL1 expressing tumours with disease control lasting for many months or years[6,7,8]. Unfortunately, this applies to a minority of patients: EGFR mutations and ALK re-arrangements are present in only 10% of NSCLC cases, and high PDL1 levels are seen in 24 to 28%. In patients without these molecular biomarkers, cytotoxic chemotherapy offers a median progression free survival of only 4 months[9]. With all systemic treatments, the patient is continually 'on treatment' and must attend hospital clinics regularly for assessment and blood tests, while experience multiple potential side effects that may be severe enough to cause hospitalisation, the risk of which is up to 68%[9] for patients receiving cytotoxic chemotherapy. In addition, systemic treatments (with the exception of immunotherapy) rarely offer long-term disease control.

Life extending options for localised disease recurrence are surgery or radical re-irradiation. For surgery, patients need to be fit enough to tolerate a major operation, which is often not the case due to the prevalence of cardiac and respiratory co-morbidities in this group. Radical re-irradiation can offer long-term disease control in selected patients and avoids the risks of surgery. Radiotherapy is generally completed within a few weeks (typically 2-6 weeks), and patients are monitored without treatment until their clinical condition changes, which could be many months or years. This compares well to systemic therapies, where patients would be on 2-4 weekly cycles of treatment until disease progression, with the continual risks of toxicity.

However, re-irradiation may cause severe toxicities in some patients. This is likely to be due to the cumulative dose received by the normal tissues surrounding the tumour. There is limited evidence to predict how normal tissues recover after an initial course of radiation. This means that it is unclear what the cumulative dose limits are for the organs at risk (OAR) in the thorax. Furthermore, some recurrent cancers may be resistant to radiotherapy, leading to concerns

about futility of treatment. Therefore, it is important to develop high quality prospective trials to determine the safety and efficacy of radical re-irradiation.

1.3. Current evidence for radical re-irradiation

Thoracic re-irradiation has been performed since 1963 with variable results and toxicities[10]. The benefits are good symptom control when given at palliative doses and long-term disease control in a minority of patients who are radically treated. There is currently a lack of high level evidence to inform clinicians of the safety and efficacy of radical re-irradiation, with only one prospective phase 1 study evaluating thoracic re-irradiation and several retrospective reviews[11].

The phase I study (Wu *et al.* 2003) evaluated radical dose, conventionally fractionated re-irradiation to recurrent lung cancers in 23 patients, who received a median dose of 66 Gray (Gy) at first treatment, and 51 Gy at re-irradiation. Median overall survival (OS) from re-irradiation was 14 months (range 2-37), with no acute grade 3 or greater toxicities recorded (RTOG grading). There was a 22% rate of grade 1-2 pneumonitis and 9% rate of grade 1-2 oesophagitis. There have been several retrospective reviews of re-irradiation using radical doses and conventional fractionation[12,13,14,15,16]. For radical dose re-irradiation, median OS in these reviews ranged from 7.1 to 13.5 months with 1 year local control rates of 57% to 66%. The radiotherapy techniques used in these studies are often outdated (e.g. 3D conformal radiotherapy) and have methodological flaws including inaccurate toxicity reporting since they are database reviews, rather than prospective trials.

1.4. Need for a prospective trial of radical re-irradiation

Local data from the Beatson West of Scotland Cancer Centre demonstrates that only 6.7% of the expected number of patients who may be eligible for re-irradiation receive this treatment. Reasons for the low uptake of this treatment include: limited prospective trial data demonstrating efficacy, concerns about safety, no clear guidance on surveillance post-radical radiotherapy leading variable detection of recurrence and patient refusal. A Canadian working group documented clinician's opinions on offering re-irradiation, with 35% declining to re-treat a standardized case[17]. As there clearly are different opinions on optimal treatment for patients with recurrent disease, a contemporary prospective clinical trial is warranted. The outcomes of this study would be robust data on safety, local control and overall survival. This will help develop treatment options for patients with recurrent disease. A recent survey of UK clinical oncologists demonstrates widespread enthusiasm for contemporary re-irradiation studies, with 76% of responders interested in further research on this topic[18].

1.5. Patient attitudes to re-irradiation

The key aim of this study is to elucidate patients' concerns about re-irradiation. This information is needed to firstly assess whether patients would accept re-irradiation as a treatment. Secondly, any barriers to participation identified in this qualitative study can be addressed in the clinical trial design. A literature search yielded no published data regarding patient acceptance or patient experience of re-irradiation for any tumour groups (see Appendix A). There could be many reasons why patients do not want to have re-irradiation

such as reluctance to undergo uncomfortable repeat investigations, issues regarding transport to the radiotherapy centre, side effects from the original treatment or anxiety about experimental treatment. Awareness of patients' concerns about re-irradiation is crucial to develop a feasible clinical trial.

1.6. Patients' consideration of alternative treatments in the locally recurrent setting

As previously mentioned, no guidelines exist for the treatment of locally recurrent lung cancer. The choices for patients include systemic treatment, radical radiotherapy or a watch and wait strategy in asymptomatic patients. How patients choose between these treatment options is important to explore because any randomization in a prospective trial will need both equipoise from the clinician, but also patient agreement that either treatment arm is appropriate. There are no published data on this topic. This discussion is particularly pertinent during the COVID-19 pandemic as patients and clinicians attempt to reduce the amount of hospital visits and treatments that could deplete the immune system. This interview study will identify what treatments patients would agree to, thereby improving the future trial design.

1.7. Relationship of symptoms from initial radiotherapy and willingness for re-treatment

Joseph *et al.*, when reporting a re-irradiation workshop, stated that patients who tolerated initial radiotherapy poorly were unsuitable for re-irradiation[17]. This refers to clinicians' concerns of causing severe toxicity with re-irradiation and may be a barrier to successful trial recruitment. Historically, re-irradiation has a significant risk of toxicity. The rates of severe toxicity may be lower using the newly published cumulative dose constraints, although these need validation. There are no prospective published data regarding whether patients who have toxicities are less likely to want further treatment. There is a need to identify if there is a relationship between the severity of patients' symptoms during initial treatment and their willingness for re-irradiation. This study will explore whether, despite toxicities from first the first radiotherapy course, patients still would consider aggressive re-treatment, and if so, what changes would they want to make their second course of radiotherapy more tolerable.

1.8. Patients' attitude to risk of toxicity

The safety of the prospective re-irradiation clinical trial depends in part on the use of cumulative dose constraints to the normal tissue OARs. The evidence for re-irradiation dose constraints is limited. In general, the higher the cumulative dose to an OAR, the greater the risk of toxicity. There is no published evidence describing patient's attitude to risk, and what toxicities they would accept for a given outcome.

In addition, new radiotherapy technology has become available to distribute the dose of radiotherapy across different OARs. The first iteration of this approach is intensity modulated radiotherapy (IMRT) which is now the standard of care for radiotherapy in many tumour sites. The benefit of this approach is to reduce the areas receiving a high dose of radiotherapy, but increase the area receiving a low dose bath. By reducing the OARs receiving the highest dose, the side effects patients develop are reduced.

One development of IMRT is multi-criteria optimisation (MCO). This uses a planning algorithm which generates multiple plans simultaneously. This allows the clinician to keep the tumour dose the same, but shift the dose from different OARs, to achieve the best plan. Recent work has demonstrated that using MCO in re-irradiation planning can reduce dose to the oesophagus significantly, at the cost of increasing the dose to the lungs[19]. The significance for the patient is that the clinician is reducing the risk of oesophagitis and swallowing difficulties, but increasing the risk of pneumonitis and breathlessness. There is no published evidence describing what side effects lung cancer patients would accept and, if they had to have a side-effect, which would they prefer. Further research into this will guide clinicians to make treatment planning decisions with patient input.

1.9. Attitudes to surveillance after radical radiotherapy

Any future prospective trial in recurrent lung cancer requires timely detection of local relapse. Recent guidelines have suggested surveillance CT scans every 6 months to detect recurrent disease, although the strength of evidence supporting these recommendations are weak. The majority of studies focus on the overall benefits that surveillance has on outcome and very few report on patient's quality of life. This interview study will explore patients' attitudes to surveillance scanning, and discuss the benefits and risks of either approach. Further information on this is important in the context of a re-irradiation trial as it is anticipated that surveillance CT scans will be a key method of identifying suitable trial patients.

1.10. Rationale and Summary

A prospective clinical trial to evaluate radical re-irradiation for lung cancer is urgently needed, as there are no contemporary robust trial data about this treatment. The results could have significant benefits for an under-served lung cancer population, by finding out which patients should receive re-irradiation, and how to deliver re-irradiation safely. However, to ensure that this interventional trial is designed appropriately and that it recruits well, it is necessary to interview patients who have already completed one course of radiotherapy. This group of patients have been chosen because they would be eligible for the re-irradiation clinical trial, and they have experienced radical lung radiotherapy and its side-effects.

The purpose of this qualitative study is to discover what the potential barriers to accepting re-irradiation are, explore patients' attitudes to alternative treatments for local recurrence, what side effects are most concerning, and acceptance of surveillance CT scans. To be able to explore fully patients' concerns and attitudes, semi-structured interviews will be conducted. The interviews will take place after patients have completed their first course of radiotherapy. The information learnt from these patients' experience will shape a future re-irradiation prospective trial protocol to ensure that it is both acceptable to patients and clinically relevant.

2. AIMS AND OBJECTIVES

2.1 Aims

The aim of this study is to explore patients' experience of radical radiotherapy for lung cancer and their attitudes to having a second treatment.

2.2. Primary Objectives

(1) Explore patients' feelings and concerns about having a second course of radiotherapy

2.3. *Secondary Objectives*

(1) Identify factors that patients consider when deciding on potential treatments in the setting of locally recurrent lung cancer (including effect of COVID-19 on treatment choice)
(2) Investigate how patients' acceptance of side effects changes with the different projected outcomes of re-irradiation
(3) Explore the relationship between the toxicities patients experienced during radiotherapy and their attitudes to a second course of radiotherapy
(4) Investigate patients' awareness of surveillance imaging after radical treatment and willingness for scans

3. METHODOLOGY

3.1. Study design

This is a qualitative interview study. The semi-structured qualitative interviews will take place after radiotherapy is completed and explore positive and negative aspects of that treatment, followed by discussion about concerns about re-irradiation, and risk of side-effects. Figure 1 provides an overview of the study design.

3.2. Inclusion and Exclusion Criteria

Patients must meet all of the following inclusion criteria to be considered for this study:

- Age 18 years old or above
- Pathological or radiological diagnosis of non-small cell lung cancer
- Undergoing radical radiotherapy to the thorax using the following fractionations (55 Gray in 20 fractions, 54 Gray in 36 fractions or any Stereotactic Ablative Body Radiotherapy (SABR) fractionation that delivers a biological effective dose of greater than $100Gy_{10}$) as part of their primary lung cancer treatment at time of study enrolment
- Patients receiving concurrent and/or adjuvant systemic therapies are permitted
- Radiotherapy is delivered in the Beatson West of Scotland Cancer Centre
- Signed, written informed consent
- Willing and able to complete study processes

Patients who meet any of the following exclusion criteria will not be enrolled on to the study:

- Not fluent in English

3.3. Recruitment and sampling

In order to ensure adequate representation of patients receiving systemic treatment and different types of radiotherapy (as their experience of treatment will vary considerably), four patients will be recruited from each of the following radiotherapy sub-types: SABR, Continuous hyperfractionated accelerated radiotherapy CHART, concurrent chemoradiotherapy and radiotherapy alone.

For patients undergoing SABR, they will be approached by a radiographer at their mould room appointment, where the aims of the study and the study procedures will be explained, and participant information sheet will be given to them. They will then have approximately 3 weeks to consider this information. When they return to have their radiotherapy, the radiographer will enquire if they wish to be involved in this study. If so, they will be seen by the researcher for consent on the same day.

Patients receiving CHART, concurrent chemoradiotherapy, or radiotherapy alone, will be recruited through the on-treatment review clinic. This clinic at the Beatson West of Scotland Cancer Centre is where patients having radical radiotherapy are monitored every week during their treatment. It is staffed by clinical nurse specialists and radiographers. They will pre-screen new patients attending their first/second on-treatment review clinic during the first

two weeks of radical radiotherapy. Patients who meet the inclusion criteria will be approached by the clinical nurse specialist/radiographer in the clinic. The aim of the study and the study rationale will be described and an information sheet will be given to the patients (see Appendix B).

3.4. Consent

When the patient returns to the Beatson for the on-treatment radiotherapy review in the following week (i.e. the second/third week of treatment), or in the first week of radiotherapy treatment for patients receiving SABR, the nurse specialist/radiographer will ask the patient if they would like to discuss the study with the researcher. If the patient agrees, the patient will meet the researcher and answer any questions. If the patient wishes to participate in the study, they will complete three consent forms with the researcher, one for the patient to keep, one for the site file and one for the medical notes. Consent will be re-confirmed at the pre-interview phone call and at the start of the interview. If the patient would like to conduct the interview using the NHS Anywhere virtual consultation platform, a web address will be given to the patient at this point.

3.5. Semi-structured interview

The patient and the researcher will arrange a mutually convenient time for the qualitative interview 4 weeks after completion of radiotherapy (+/- 5 days). On this pre-interview call, the patient will also re-confirm the consent to be involved in this study. If the patient wished to use the NHS Anywhere platform, then the web address will be also re-confirmed with them. Patients will also be invited to have a family member or friend nearby for the interview to offer support if needed. The interview will be performed after 5 weeks as it allows for most of the acute side effects of treatment to subside, but the patient would not have any idea of how effective the treatment has been, as this may bias their answers. The interview will be done either over the telephone or using the NHS Anywhere virtual consultation platform. The interview will be recorded. At the start of the interview, consent will also be re-confirmed. The structure of the interview is documented in Appendix B.

As some of the topics of the interview could be distressing, if at any point during the interview the patient becomes upset, the interview will be paused and the patient given time to recover. The interview can proceed again only once the patient agrees to do so, otherwise the interview will be permanently stopped. As the interview will be conducted over the telephone, if the patient needs further support and consents to it, the researcher will contact the patient's clinical team and request that they contact the patient to offer further care. In addition, the patient may have a member of family or a friend with them to assist them. The patient will also have a routine follow-up visit with their clinical team one week after the interview, where they may wish to discuss any issues which have arisen from the interview.

During the interview, if the patient describes any symptoms or issues that require medical attention the researcher may inform the patients' clinical team with the patients' consent. The recording of the interview will be anonymised, transcribed and stored securely on the NHS IT systems.

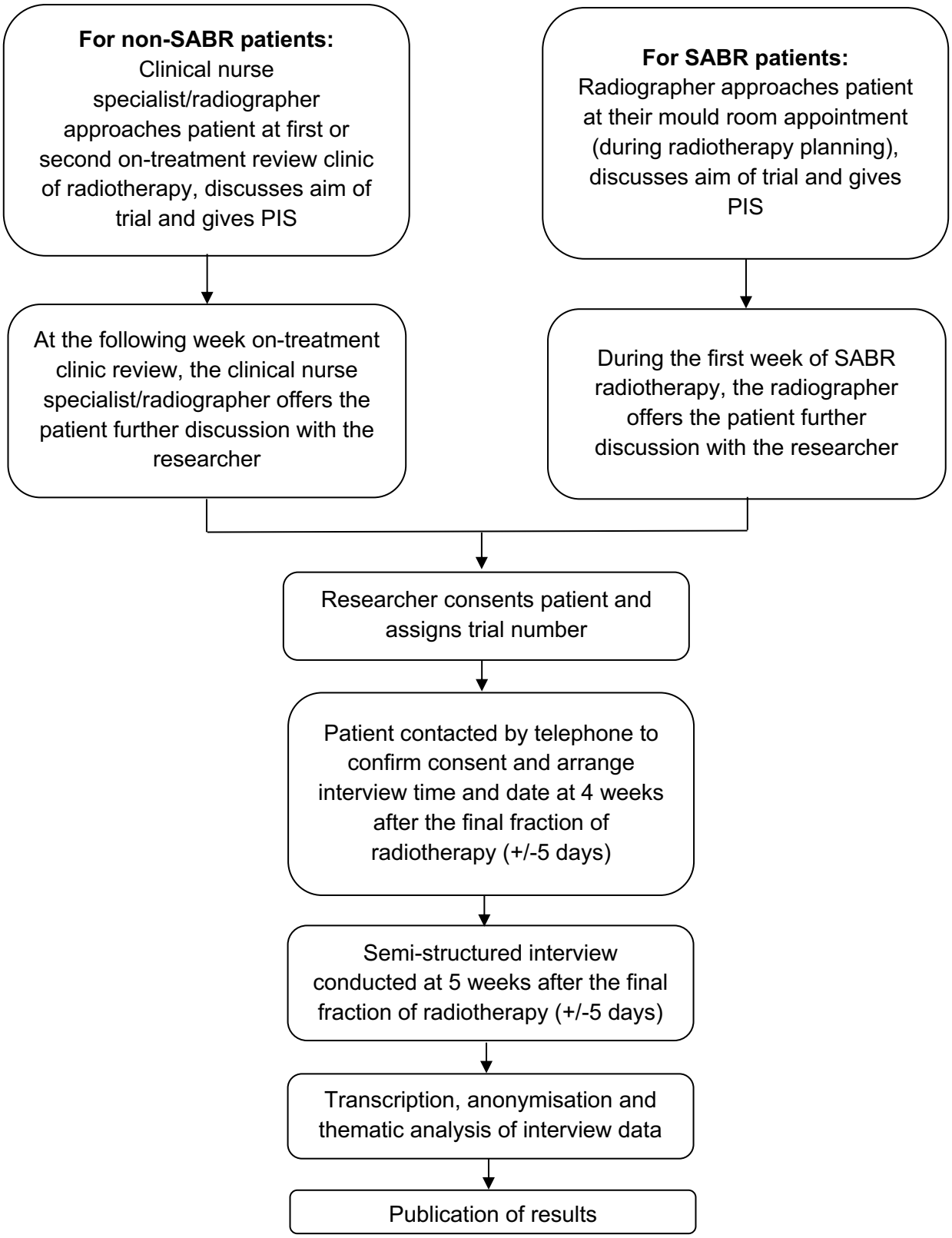

Figure 1. Study schema

3.6. End of study

The patient will have completed the study once the interview has ended. They will be given the option to be kept informed about the outcomes of the study and ongoing work. At any point, patients can withdraw from the study with no change to their medical treatment. Once the patient has left the study, they will be followed-up as per standard practice of their treating clinical oncologist.

3.7. Potential risks and benefits

The principal risk of this study is that any discussion of traumatic experiences such as being unwell or relapse after arduous treatment can cause significant psychological harm. The steps taken to mitigate this risk are to inform the patient from the outset of the topics that will be discussed in the interview in both the patient information sheet and in the consent process. If the patient becomes distressed in the interview, then the interview will be halted and further support offered (from the patient's regular clinical team, and, if the patient has agreed, a member of their family or a friend).

The patient will have no direct benefit from taking part in this study as this study does not involve any change in the medical care that the patient receives. However, the results from the study will help the design of a prospective trial of re-irradiation, and this will improve the safety of this treatment for future patients. Additionally, the results of these interviews may identify areas to improve the patient experience in patients having initial radiotherapy at the Beatson West of Scotland Cancer Centre.

3.8. Mitigation for SARS-CoV-2

The WHO declared a global pandemic in response to the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in early 2020. In order to limit patients' exposure to potential infectious contacts, this study will perform most of the study procedures over either the telephone or using secure remote consultation software. The patient will meet the researcher in person only once, when consent is being taken, at the same time as they are attending the on-treatment radiotherapy review clinic, thus reducing the need for additional visits to hospital.

3.9. Data storage and retention

The interviews will be recorded on to the Winscribe system (this is the system used for recording clinic dictations in the Beatson). The recordings will be password protected. They will be transcribed either by the researcher, or NHS clerical staff. The original recordings will be stored securely on the NHS IT system until the end of the study, as source data in case of audit. Once the trial is complete, the source recordings will be destroyed. The source recording will be transcribed and anonymised. The anonymised transcripts will be transferred to the University of Glasgow IT systems for analysis using NVivo software. Once analysis is complete, this study will be written for publication. The anonymised transcribed source data will be uploaded on to the Enlighten data repository curated by the University of Glasgow, where it will be kept for at least 10 years and will be accessible to other

researchers on application as per the University of Glasgow data protection policy. Anonymised data from this study may be used in other studies if appropriate.

4. STATISTICAL CONSIDERATIONS AND METHOD OF ANALYSIS

4.1 Sample Size

The estimated minimum target recruitment for this study is 16 patients, based on the likelihood that data saturation has been achieved[20]. If saturation has not been achieved, then the study will continue to recruit to a maximum of 30 patients.

4.2 Method of analysis

The anonymised transcripts will be uploaded to NVivo software, provided by the University of Glasgow. The interviews will then undergo thematic analysis to identify key attitudes to re-irradiation.

There is a quantative element to this study, where patients are asked to rate the severity of side effects from radiotherapy (describing their side effects as either mild/moderate or severe) and if they would consider a second course of radiotherapy. These will be analysed using descriptive statistics and Chi-squared testing.

5. ETHICS

Consent and ethics approval

All patients who participate in this study must have signed the written consent form (Appendix B). This study is subject to ethics approval from the West of Scotland Research Ethics Committee.

Confidentiality

Patients participating in this study will be given a trial number, which will be used on the interview recordings and transcripts. The original recordings will be stored securely on the NHS IT systems. The recordings will be transcribed and anonymised. Any identifiable patient information in the transcripts will be redacted. The source recordings will be retained until the end of the study, as source data in case of audit. Once the study is complete, the source records will be destroyed. All data will be stored on secure password protected NHS or University of Glasgow IT systems.

6. FINANCE AND INDEMNITY

Indemnity

No special insurance is in place regarding this study.

Sponsor

NHS Greater Glasgow and Clyde will act as the sponsor for this study.

Funding

This study is funded by a grant from the Beatson Cancer Charity and The University of Glasgow.

7. PUBLICATIONS

The results of this study will be part of the principal investigator's PhD thesis, but also written for publication, and disseminated at posters and presentations at relevant conferences. The study findings will also be sent to the patients (if they wish to receive updates).

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APPENDIX A

Literature review

We performed a literature search to identify if this information was available from published studies.

Search engine used: Medline, Google scholar

Search terms:

Re-irradiation AND (patient experience OR attitudes OR acceptance) = 43 papers (2 useful)
Sinfield et al. 2009
Joseph et al. 2010

Lung cancer AND radical radiotherapy AND patient experience = 360 papers (1 useful)
Langendijk et al. 2001

Lung cancer AND radical radiotherapy AND symptom control = 93 papers (1 useful)
Fairchild et al. 2008

Lung cancer AND (re-treatment OR re-irradiation OR "retreatment" OR "reirradiation") AND Patient experience = 36 papers (1 useful)
Shalini et al. 2019

Lung cancer AND (re-treatment OR re-irradiation OR "retreatment" OR "reirradiation") AND symptom control = 126 papers, 1 useful)
Kruser et al. 2014

Limits – English language

APPENDIX B

Copy of patient information sheet
Copy of consent form
Copy of semi-structured interview sheet