Title: Extracting greater data from standard CT imaging in Non-Small Cell Lung Cancer

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Doctor of Medicine
Declaration of originality

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Summary

Lung cancer is the leading cause of cancer death worldwide. Patients with lung cancer have a very poor outcome compared to other common cancers. The aim of this project is to identify whether CT data accumulated by patients with Non-Small Cell Lung Cancer (NSCLC) provide an untapped resource that can improve their quality of care, by generating more information from existing imaging. Extracting additional data from imaging is termed radiomics. One way of extracting this data is using mathematical descriptions of an image or regions of interest within an image. This type of assessment is termed Textural Analysis (TA).

The experimental work described in this thesis uses a second order TA technique to analyse CT (Computer Tomography) imaging data from patients with NSCLC. The software developed as part of this project uses a voxel by voxel analysis of CT imaging, by comparing grey levels using grey level co-occurrence matrices (GLCMs).

Three approaches (themes 1-3) were explored. The first approach shows that TA can help differentiate between tumour and Radiation Induced Lung Injury (RILI) after Stereotactic Ablative Body Radiotherapy (SABR) in early stage lung cancer. The second approach suggests that assessing muscle loss on diagnostic imaging can help predict outcome in advanced NSCLC. The third and final approach uses TA to generate a functional assessment of lung function. TA is able to differentiate between patients who are fit or unfit for radical radiotherapy, based on TA of lung tissue on CT imaging, rather than formal lung function tests.

TA technique described in this thesis is a novel intervention in gaining functional data from CT imaging. It is particularly attractive as the analysis is generated from routine oncological imaging. As a result these tools have the potential to be cost effective and could be integrated into a standard radiology workflow.
<table>
<thead>
<tr>
<th>Glossary</th>
<th>Description</th>
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<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>CBCT</td>
<td>Cone Beam Computer Tomography Scan</td>
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<tr>
<td>CERR</td>
<td>Computational Environment for Radiotherapy Research, software.</td>
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<tr>
<td>CT</td>
<td>Computer Tomography</td>
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<tr>
<td>CTE</td>
<td>Commissioning through evaluation</td>
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<tr>
<td>CVSSP</td>
<td>Centre for Vision, Speech and Signal Processing, Univ of Surrey</td>
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<tr>
<td>EBRT</td>
<td>External Beam Radiotherapy</td>
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<tr>
<td>Entropy</td>
<td>A texture analysis marker, which is a measure of disorder</td>
</tr>
<tr>
<td>Filter</td>
<td>Is the size of the window the software uses to analyse each voxel</td>
</tr>
<tr>
<td>Gy</td>
<td>Gray, unit of radiotherapy dose</td>
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<tr>
<td>GTV</td>
<td>Gross Tumour Volume</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard Ratio</td>
</tr>
<tr>
<td>IMRT</td>
<td>Intensity Modulated Radiotherapy</td>
</tr>
<tr>
<td>ITV</td>
<td>Internal Target Volume</td>
</tr>
<tr>
<td>LMQ</td>
<td>Lloyd Max Quantiser, method of quantisation in which the specific values at which the levels are chosen to minimise the difference between the quantised image and the original image.</td>
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<td>NSCLC</td>
<td>Non-Small Cell Lung Cancer</td>
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<td>PD-L1</td>
<td>Programmed Death Ligand 1</td>
</tr>
<tr>
<td>PET-CT scan</td>
<td>Positron Emission Tomography-Computer Tomography Scan</td>
</tr>
<tr>
<td>PTV</td>
<td>Planning Target Volume</td>
</tr>
<tr>
<td>Quantisation</td>
<td>Dividing a continuous variable into a pre-set number of discrete levels</td>
</tr>
<tr>
<td>ROI</td>
<td>Region of interest</td>
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<tr>
<td>RILI</td>
<td>Radiation induced lung injury</td>
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<tr>
<td>RSCH</td>
<td>Royal Surrey County Hospital</td>
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<tr>
<td>SABR</td>
<td>Stereotactic Ablative Radiotherapy</td>
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<tr>
<td>TKI</td>
<td>Tyrosine Kinase Inhibitor</td>
</tr>
<tr>
<td>VMAT</td>
<td>Volumetric Modulated Arc Therapy</td>
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Summary of publications (full versions in appendix 1)

Prizes and oral presentations:

1. 1<sup>st</sup> prize for best poster at Post-graduate Conference, University of Surrey, 2017

2. Oral presentation shortlisted for Royal College of Radiology Ross Prize at National Cancer Research Institute Conference, 2017

3. Finalist 3 minute thesis competition, University of Surrey, 2017

4. Runner up, audit poster competition, Royal Surrey County Hospital, 2017

5. British Thoracic Radiation Oncology Group poster runner up prize, 2018

6. Oral presentation at medisens medical imaging conference, 2018

Doctor of medicine

Publication: Clinical Applications of textural analysis in Non-Small Cell Lung cancer, Phillips et al. British Journal of Radiology. Accepted for publication, in press


4. Alobaidli, South, McQuaid, Scuffham, Phillips et al. A dose painting study based on CT intra-tumoral heterogeneity vs FDG PET uptake in NSCLC. Radiotherapy & Oncology. 2017. S1 S841


Poster: 1. Wang, Donovan, Nisbet, South, Alobaidli, Ezhil, Phillips et al. Robustness of texture as a biomarker in radiomics applications. ESTRO 2017

**Stereotactic Radiotherapy Clinical Research Fellow**

**Publication:** Benefits of Stereotactic Radiotherapy Fellowships to Clinical Oncology Trainees, Phillips et al. Letter in Clinical Oncology, 2016 28(12)e221

**Abstracts:**

**Posters:**

2. Phillips et al. Predicting lung function and fitness for radiotherapy from a CT scan. University of Surrey Post Graduate Conference. Winner of best poster prize 2017

3. Stereotactic Ablative Body Radiotherapy (SABR) for oligometastatic cancer. Royal Surrey County Hospital audit day, 2017

Figure 1, thesis structure. TA = Textural analysis. SABR = Stereotactic Ablative Body Radiotherapy, NSCLC = Non-Small Cell Lung Cancer, TEXAS trial = TExtural Analysis Stereotactic radiotherapy trial, DAIL trial = Dietetic Assessment and Intervention in Lung cancer trial, TEAL trial = TExtural Analysis and Lung function trial.
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1.1 Project aim

The aim of this project is to identify whether CT data accumulated in a patient’s Non-Small Cell Lung Cancer (NSCLC) journey offers an untapped resource that can improve their quality of care, by generating more information from existing imaging. This could lead to greater information concerning the patient and their cancer, their prognosis and patient fitness. Furthermore it could reduce the number of tests that may be required and explore whether imaging biomarkers could help predict treatment risk and outcome. These tools would be cost effective as the investigations would already be complete and additional analysis could be integrated into a standard radiology workflow. The relationship between different parts of the project are illustrated in figure 1.

Figure 1, a diagrammatic representation of this thesis showing the 3 main themes of the project, understanding more about responses to SABR, predicting lung function and identifying sarcopenia.
1.2 Background to lung cancer:

1.2.1 Who gets lung cancer?

Lung cancer is the second most common form of cancer diagnosed in the UK in both men and women. Over 43,000 cases are diagnosed in the UK each year with over 35,000 deaths annually. Five year and ten year survival rates are 10% and 5% respectively (UK, 2015). It is the most common cancer diagnosis worldwide, and is the leading cause of cancer mortality (Ferlay et al., 2015). Lung cancer would be a rare disease were it not for smoking, which causes 80-90% of cases (Alberg and Nonemaker, 2008).

Lung cancer occurs in a vulnerable population. It is more common in older patients. More than 80% of new cases of lung cancer are diagnosed in the over 60s. More than 40% are diagnosed in men and women over 75 years. The number of cases of lung cancer in patients aged over 60 years old is rising (Foundation, 2017), particularly in those aged 81 or older, where cases have risen by nearly 1.5 times from 446 per 100,000 in 2004 to 666 per 100,000 in 2012.

Lung cancer is a disease of poverty (Li et al., 2015, Cooley and Jennings-Dozier, 1998, Gadgeel and Kalemkerian, 2003, Gadgeel et al., 2001) and risk of lung cancer is inversely proportional to socio-economic status. Lower socio-economic status is also associated with a higher prevalence of smoking, greater use of cigarettes that have a higher tar content or no filter and lower smoking cessation rates (Gadgeel and Kalemkerian, 2003) (Gadgeel et al., 2001). As well as greater active smoking behaviour, this population is more likely to be exposed to other risk factors such as higher passive smoking rates, occupational exposure, less healthy diets and occupational/environmental carcinogens (Cooley and Jennings-Dozier, 1998). The UK is a case in point, where it is estimated there would be 9,900 fewer cases of lung cancer if those worst off had the same incidence of lung cancer as the most affluent section of society (taskforce, 2015).

As the majority of lung cancers are associated with tobacco exposure, these patients are more likely to have multiple co-morbidities also caused by smoking. However, 20% of patients dying from lung cancer are not smoking related. Non-smoking related lung cancer is still in the top 10 causes of cancer related mortality in the USA. Exposure to tobacco is associated with numerous co-morbidities including Ischemic Heart Disease (IHD), Chronic Obstructive
Pulmonary Disease (COPD) and other primary cancers such as bladder cancer. Recent research suggests that nearly a fifth of patients (18%) have 4 or more co-morbidities (Gould et al., 2017). As well as occurring in a vulnerable, less fit population, lung cancer is difficult to diagnose in the early stage of the disease. Approximately half of patients present with advanced disease (Gould et al., 2017, UK, 2015), this has been confirmed in local audit data collated as part of the introductory work for this project (Ezhil, 2016).

Non-Small Cell Lung Cancer (NSCLC) is the most common pathological sub type of lung cancer, as a result, this project focuses on NSCLC.

1.2.2 Treatment outcomes

Table 1 shows stage at presentation and 5 year survival for lung cancer and breast cancer. It shows that the most common presentation with lung cancer is stage IV metastatic disease, whereas patients with breast cancer commonly present with localised (stage I and II disease). Figure 2 shows the 5 year survival for the 3 most common cancers diagnosed in the UK; breast, prostate and lung cancer.

<table>
<thead>
<tr>
<th></th>
<th>Stage at presentation lung cancer (%)</th>
<th>Stage at presentation breast cancer (%)</th>
<th>5 year survival lung cancer (%)</th>
<th>5 year survival breast cancer (%)</th>
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<tbody>
<tr>
<td>Stage I</td>
<td>15</td>
<td>40</td>
<td>35</td>
<td>100</td>
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<tr>
<td>Stage II</td>
<td>7</td>
<td>36</td>
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<td>Stage III</td>
<td>19</td>
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<tr>
<td>Unknown</td>
<td>10</td>
<td>11</td>
<td>10</td>
<td>85</td>
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</table>

*Table 1, stage at presentation and survival data for lung cancer in England, adapted from CRUK cancer statistics (UK, 2015)*

When lung cancer is compared to breast cancer (leading cancer diagnosed in women in the UK) and prostate cancer (leading cancer diagnosed in men in the UK), it shows how poor the outcomes are for lung cancer.
1.3 Improving outcomes for patients with Non-Small Cell Lung Cancer (NSCLC)

Lung cancer outcomes are poor and have the potential for improvement. In the longer term, increased rates of smoking cessation and control of tobacco are likely to have a big impact on incidence rates of lung cancer.

In terms of improving early diagnosis of lung cancer, low dose CT screening of high risk individuals has been shown to improve lung cancer mortality in data from the Lung Screening Trial in the USA (Aberle et al., 2011). Feasibility projects have been completed in the UK, including the UK Lung Cancer Screening Trial (Field et al., 2016a, Field et al., 2016b). However, at present, there is not a national screening programme in the UK for lung cancer.

Current lung cancer treatment is broadly divided into radical treatment: aiming to get rid of the cancer or provide long term control and palliative treatment: aiming to control the cancer and improve overall survival.

Figure 2, comparing 5 y overall survival (OS) for 3 most common cancers diagnosed in the UK.
### 1.3.1 Radical treatment

For early stage NSCLC (T1-2N0-1M0), treatment often involves a single modality, either surgical resection (with adjuvant chemotherapy in tumours greater than 4cm or the presence of regional lymph node metastases) or radiotherapy alone. Radiotherapy delivers high dose x-rays with high precision. For smaller (often peripheral) lung tumours a specific radiotherapy technique called Stereotactic Ablative Body Radiotherapy (SABR) can be used in preference to standard radiotherapy. It is also suitable for patients not medically fit for radical fractionated radiotherapy or surgery (Nanda et al., 2015, Palma et al., 2012, Palma et al., 2010, Palma et al., 2011). For locally advanced NSCLC (T1-4N2M0) radiotherapy is often combined with systemic chemotherapy, either sequentially or concurrently.

### 1.3.2 Palliative treatment

Before starting systemic drug treatment, early referral to palliative care and symptom management improves length of overall survival in patients with advanced (incurable) lung cancer (Temel et al., 2010). The majority of NSCLC tumours are either squamous cell carcinomas or adenocarcinomas. At present radical treatment is not significantly altered by NSCLC sub-type. However, palliative treatment can be significantly altered by presence or absence of specific markers, specifically the presence of PDL-1 in all NSCLC and the presence of EGFR mutations and ALK rearrangements in non-squamous cancers. Systemic therapy is at present the backbone of treatment in advanced NSCLC, for patients that are sufficiently fit to tolerate treatment (Zappa and Mousa, 2016). The most commonly used treatments are cytotoxic chemotherapy, immunotherapy (Reck et al., 2016) and targeted therapies such as tyrosine kinase inhibitors (TKIs). TKIs are first line treatment for patients with non-squamous tumours with a genetic alteration such as an ALK rearrangement or EGFR mutation (Solomon et al., 2014) (Yang et al., 2017).

Both immunotherapy and TKIs are given continuously and over a longer period when compared to chemotherapy. Patients are more likely to have more imaging with a prolonged treatment. Response assessment is more complex with immunotherapy, instead of simply categorising the outcome of treatment as a response, stable disease or progression, patients can undergo other reactions, such as the development of new lesions followed by a delayed response or a differential response (Wolchok et al., 2009). These different response patterns
may then affect the outcome. Multi-modality treatment is becoming increasingly common. For example treatment could include a combination of chemotherapy, radiotherapy and surgery in radical treatment, as well as chemotherapy with local treatment such as SABR in advanced disease. Recent data has shown that chemotherapy followed by SABR improves progression free survival from 3.9 months to 11.9 months, when compared to chemotherapy followed by further maintenance treatment in metachronous oligometastatic NSCLC (Gomez et al., 2016). This increasing complexity of treatment means that interpreting imaging is more complex, therefore tools to aid image interpretation are attractive.

1.4 Advanced analysis of CT images

Patients undergo regular cross-sectional imaging to diagnose, stage, assess response and in many cases undertake surveillance after treatment for lung cancer. This leads to a pool of imaging data that potentially has significant value beyond accurate staging of the patient. The most frequently used cross sectional imaging is a Computer Tomography (CT) scan. CT scans are relatively inexpensive, easily accessible and quick. A great deal of expertise exists in interpreting them.

In a CT scan attenuation of x-rays is measured and used to determine the appearance of different tissues by differing electron density. Water is given a value of 0, air -1000, soft tissue 100-300 and bone 700-3000. A series of cross sectional images (tomograms) are built up to give a complete scan. Composite images in coronal and sagittal planes can be created from the original axial images.

The use of imaging as a pool of mineable data is termed radiomics (Gillies et al., 2016). Advanced image analysis has the potential to facilitate the extraction of large amounts of data from an image. It is being investigated in multiple types of cancer (Prestwich et al., 2015). One method of extracting extra data from an image is using Textural Analysis (TA). This uses mathematical descriptions of a region of interest to compare between different areas in the same image or between images.

Different imaging modalities are used to investigate and assess patients with lung cancer. TA can be used in different imaging modalities. CT scans are the most widely used imaging tool in managing lung cancer. Other imaging modalities, particularly [(18)F]-2-fluoro-2-deoxy-D-
glucose positron emission tomography/computed tomography (FDG PET-CT) are useful in providing more accurate staging of patients with lung cancer. For example PET-CT can greatly aid the identification of malignant lung nodules with a sensitivity of 95% and specificity of 82% (Cronin et al., 2008). It is also useful in assessing treatment response and identifying tumour recurrence. FDG PET-CT super-imposes a functional assessment of tumour metabolism over a CT scan, which provides anatomical imaging. PET-CT is less widely available and considerably more expensive than standard CT imaging. Value-based care provides incentives to maximise information from standard investigations. Patients with lung cancer have a significant amount of imaging available that is potentially underused.

The majority of published work has focused on the analysis of the tumour as the region of interest (Phillips et al., 2017). A range of techniques have been used to help characterise a range of clinical questions including: risk of malignancy of lung nodules, likely histological subtype of lung cancer and treatment response. The available published literature is discussed in detail in chapter 3. This chapter is a revised version of a published review article prepared by the author in the course of this study (see appendix 1).

As well as focusing on the tumour, TA could be used to assess other tissues in the body. This could then be related to patient function. Table 1. Shows different ways that advanced CT analysis is being further investigated for non-malignant tissues.

From the sources identified in table 2, it is possible to gain greater information from a CT scan regarding patient ‘health’ or ‘fitness’ as well as greater information about a disease state. This thesis will present the results of research into this area. Firstly in patients with small primary lung tumours, in understanding the effects of Stereotactic Ablative Body Radiotherapy (SABR) on the lung and seeing if it is possible to predict acute inflammation after SABR (Huang et al., 2012), secondly in helping to predict patient fitness in 2 ways: showing that it is possible to predict lung fitness from a CT scan; and that measuring muscle mass can predict overall survival in NSCLC. These will be explored as 3 separate themes, however, they are united by the aim of gaining greater information from a patient’s CT scan.
<table>
<thead>
<tr>
<th>Type of assessment</th>
<th>Type of tissue</th>
<th>Example</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perfusion</td>
<td>Blood vessels-angiography</td>
<td>CT angiography of pulmonary arteries is a standard investigation for pulmonary embolus. CT cardiac angiography is a newer technique, it is being investigated as an extra source of data including in oncology patients.</td>
<td>(Girinsky et al., 2014, Group, 2003)</td>
</tr>
<tr>
<td>Pathological tissue density</td>
<td>Heart</td>
<td>Cardiac calcium scoring can predict the risk of coronary artery disease. CT can potentially predict cardiac function.</td>
<td>(Pathan and Negishi, 2016, Rahaghi et al., 2017)</td>
</tr>
<tr>
<td></td>
<td>Lung</td>
<td>Analysis of lung density has shown it is possible to differentiate benign lung diseases such as COPD and lung fibrosis from normal lung tissue.</td>
<td>(Sorensen et al., 2012, Park et al., 2016)</td>
</tr>
<tr>
<td></td>
<td>Liver</td>
<td>TA can be used to assess liver fibrosis</td>
<td>(Daginawala et al., 2016)</td>
</tr>
<tr>
<td>Biometrics</td>
<td>Muscle</td>
<td>Assessment of Sarcopenia (muscle loss) has been made in several types of cancer including gastric, renal cell, endometrial, pancreatic and bladder cancer surgery</td>
<td>(Zhuang et al., 2016, Peyton et al., 2016, Kuroki et al., 2015, Smith et al., 2014, Pecorelli et al., 2016)</td>
</tr>
</tbody>
</table>

Table 2: Previous studies that have investigated advanced CT analysis of non-malignant tissue.

1.5 The potential benefits of getting more information from a CT scan

In a resource-limited health setting, it is important to get as much value from investigations as possible. Despite being a source of significant data, CT scans are often only used to stage the patient or assess the response to treatment by measuring a lesion seen on an image.
Although the prevalence of smoking is decreasing, in the interim the incidence of lung cancer is increasing in the short term, particularly in older patients, as these patients were exposed to tobacco, before public health interventions such as a smoke free working environment were in place.

In a frail population it is important to gain as much value from non-invasive investigations as possible. A single test such as a CT scan, which can assess patient fitness as well as staging the cancer is an attractive option.

This thesis targets three main themes in extrapolating greater information from CT scans, one related to treatment response and two related to patient fitness. Assessing patients receiving SABR is the first major theme (theme 1). To understand the nature of the clinical problem a project was conducted in collaboration with Public Health England (PHE) to assess treatment of all stage 1 primary lung tumours diagnosed in 2015 in England. These results are discussed in chapter 2. Chapter 3 describes the background of TA in NSCLC. Chapter 4 is a technology assessment of the parameters of this TA tool, in terms of the variables in the image, variables in the TA tool and the potential for advanced analysis of the texture maps. Chapter 5 describes the initial analysis of the data generated from the TA of lung imaging from patients receiving SABR for NSCLC. Chapter 6 describes an initial study aiming to differentiate between tumour and Radiation Induced Lung Injury (RILI) after SABR.

The second theme is investigating the relationship between unintentional weight loss and outcome in patients with Non-Small Cell Lung Cancer. Chapter 7 discusses the initial retrospective work evaluating whether it is possible to predict the outcome based on weight loss or the presence of sarcopenia. It then goes on to discuss the results of an early analysis of the first cohort of patients entered into the DAIL (Dietetic Assessment and Intervention in Lung cancer) trial. Chapter 8 discusses the third theme, which is showing how TA of a segment of a radiotherapy planning CT scan can differentiate between those who are fit or are not fit for radiotherapy. Chapter 9 brings together the results and provides an overall summary and conclusion of the work. A list of publications and presentations arising from this work are listed in Appendix 1.

The novel research questions that this dissertation therefore aims to address may be listed as follows:
1. Can a methodology be generated in order to analyse a whole lung and identify the
tumour within it using advanced image analysis?

2. Is it possible to differentiate between early tumour recurrence and radiation induced
lung injury after stereotactic radiotherapy to primary lung tumours using texture
analysis?

3. Can texture analysis differentiate between individuals who are fit and unfit for radical
radiotherapy from imaging data generated from a radiotherapy planning CT scan?

4. Is it possible to understand the relationship between malnutrition, sarcopenia,
cachexia and changes in muscle appearance in advanced NSCLC?
References


Theme 1: CT Texture Analysis after SABR for Non-Small Cell Lung Cancer

Chapter 2: Identification of patients with stage 1 Non-Small Cell Lung Cancer as an appropriate cohort for the further investigation of texture analysis.

2.1 Background

As previously discussed lung cancer is the second commonest cancer diagnosed in men and women in the UK and has a very poor prognosis, with 10% of patients living 5 years and 5% living 10 years after diagnosis. It is the commonest cause of cancer mortality in the UK and worldwide. 80% of patients with lung cancer have Non-Small Cell Lung Cancer (NSCLC) and 20% of these present with early stage disease (UK, 2015). Other lung cancers such as Small Cell Lung Cancer rarely present with early stage disease. Therefore this chapter focuses on the patients with stage 1 NSCLC. The most common treatment options are surgical resection or radical radiotherapy. There is no current data on how frequently SABR (Stereotactic Ablative Body Radiotherapy) is used to treat stage 1 lung cancer. This chapter focuses on addressing this point.

The aim of theme 1 of the thesis is to identify whether or not texture analysis (TA) is useful in identifying the presence of tumour after SABR for primary lung cancer. At present there are no statistics on how commonly SABR is used to treat early lung tumours in England. This project was developed and carried out in collaboration with the National Cancer Registration and Analysis Service (NCRAS) at Public Health England. This was the first project combining a unique set of databases that includes all patients diagnosed with cancer in England and all radiotherapy treatments delivered to patients in England. At that point in time, it was difficult to establish who received SABR, as SABR did not have a specific code. This chapter describes the development of the methodology used to identify patients with lung cancer who received SABR, followed by presentation of the results and subsequent discussion.

From initial discussions with analysts from NCRAS it would be difficult to identify the absence of a treatment. Clinical data supports the use of SABR for stage 1 (T1a, T1b, T2a N0 M0) NSCLC. At this point in the process it was felt it would be easier to include all patients with stage 1 NSCLC and identify the different treatment options. The use of the national Radiotherapy
Dataset (RTDS) would allow radiotherapy treatments to be sub-divided into SABR and other non-SABR treatments, something that was not previously possible. Analysing treatment of all patients with stage 1 NSCLC would provide a cohort of patients who received radiotherapy, which could then be further analysed.

2.1.1 Poor survival in lung cancer

When compared to other common cancers, lung cancer survival is often very poor (Allemani et al., 2015), for example when comparing outcomes for 6 developed countries, 5 year survival for breast cancer is significantly higher (81-88.5%) than lung cancer (8.7-15.1%) (Coleman et al., 2011). Lung cancer survival rates in England are lower than in other developed countries such as Canada (8.7% vs 15.1%). This difference in outcome has been difficult to close over time, it is suggested that the difference is greater in older patients (taskforce, 2015). The Independent Cancer Task Force Report, ‘Achieving World Class Cancer Outcomes: A strategy for England 2015-2020’, has concluded that reasons for this include patients with lung cancer presenting at a more advanced stage and differences in treatment. One of the conclusions of this report was the need for greater access to cutting edge radiotherapy treatment, such as Stereotactic Ablative Body Radiotherapy (SABR). This would allow more patients to receive a radical treatment, when surgery is not suitable.

Standard first line treatment for early stage NSCLC would be surgical excision in the form of a lobectomy (Ginsberg and Rubinstein, 1995). However, surgery is not suitable for all patients: some may be medically inoperable, surgery may not be technically feasible or the patient may opt not wish to pursue surgical treatment. SABR is an established alternative treatment, which delivers high dose, accurate radiotherapy to treat a small target volume in fewer doses than standard radical radiotherapy.

SABR has shown a significant Overall Survival (OS) benefit from 10 months to 29 months (p=<0.001) when compared to Best supportive care (Nanda et al., 2015), and it has improved OS in patients aged over 75 years old (Palma et al., 2010). SABR has also been shown to be an effective treatment in patients with severe Chronic Obstructive Pulmonary Disease (COPD) as less lung is irradiated (Palma et al., 2012) compared to conventional radiotherapy. SABR has fewer side effects than radical radiotherapy and potentially has a survival benefit (Nyman
et al., 2016, Ball et al., 2017). An analysis of 273 patients receiving lung SABR for medically
inoperable early stage NSCLC treated in England, showed a median OS of 27.3 months, with
a 3 year local control rate of 95.7% (Murray et al., 2016a). As well as being effective, SABR is
well tolerated and more convenient. SABR does not cause a statistically or clinically significant
deterioration in Health Related Quality of Life Measures (Lagerwaard et al., 2012), and fewer
visits are required for treatment compared to fractionated radiotherapy. SABR has been
traditionally used to treat peripheral tumours, however by increasing the number of fractions
in which the treatment is delivered and respecting normal tissue constraints, toxicity does not
increase (Chang et al., 2014, Senthi et al., 2013). Patients undergoing surgery would routinely
undergo pathological staging of local lymph nodes, with the potential to upstage the tumour.
Adjuvant chemotherapy can provide a 5% OS benefit at 5 years among patients with a larger
than expected tumour or the presence of local and regional lymph node metastases (Pignon
et al., 2008). However, realistically the potential benefit of adjuvant chemotherapy in this
cohort would be very small (Louie et al., 2015).

The hypothesis within this work is therefore that fit patients would receive surgical resection
of their primary tumour in the form of lobectomy, whereas less fit patients are more likely to
receive SABR. In terms of comparing the 2 modalities of treatment in operable patients, the
only published randomised trial data comparing SABR with lobectomy is based on a pooled
analysis of two trials that did not complete recruitment (Chang et al., 2015), and non-
randomised evidence is limited (Mahmood et al., 2013). Therefore, I aimed to understand
the treatment of patients with stage 1 NSCLC tumours using national databases in
collaboration with Public Health England, aiming to provide further evidence on the use of,
and survival after, SABR in England. The benefit of using a large clinical dataset such as RTDS
is it can describe the actual clinical care being delivered to patients across a large geographical
region. As a result, it includes sufficient patients that broad conclusions about oncological
care can be drawn.
2.2 Materials and Methods

2.2.1 Difficulties in identifying the absence of the delivery of SABR

Data from national datasets (RTDS) and Hospital Episode Statistics (HES) were combined with cancer registration data extracted from PHE’s Cancer Analysis System (CAS) to identify patients with T1-T2a N0 M0 primary NSCLC.

The Radiotherapy Dataset (RTDS) is a data standard that requires all NHS Acute Trust providers of radiotherapy services in England to collect and submit standardised data monthly against a nationally defined dataset. The purpose of the standard is to collect consistent and comparable data across all NHS Acute Trust providers of radiotherapy services in order to provide intelligence for service planning, commissioning, clinical practice and research and the operational provision of radiotherapy services. Data collection began in 2009 and Public Health England (PHE) assumed responsibility for the dataset in 2016. Its aim is to provide a comprehensive database of radiotherapy treatments delivered by acute trusts providing radiotherapy in England.

Treatments performed 1 month before and 3 months after the date of diagnosis were included. These dates were chosen to only include treatments delivered in a timely manner. Surgery was recorded in both the cancer registration and inpatient (Admitted Patient Care, APC) Hospital Episode Statistic (HES) dataset. A patient was identified as receiving surgery if they had a record for a procedure defined by the major resection tumour OPCS list within 3 months from diagnosis. The list of procedures included in this list can be seen in table 1. The datasets were linked together by NHS number.

Radiotherapy treatment was divided into three groups: SABR, radical radiotherapy and palliative radiotherapy. At the time of data collection, lung SABR did not have a specific code within RTDS.
<table>
<thead>
<tr>
<th>Surgical code</th>
<th>Surgical procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>E391</td>
<td>Open excision lesion trachea</td>
</tr>
<tr>
<td>E398</td>
<td>Other specified partial excision trachea</td>
</tr>
<tr>
<td>E399</td>
<td>Unspecified partial excision trachea</td>
</tr>
<tr>
<td>E441</td>
<td>Excision carina</td>
</tr>
<tr>
<td>E461</td>
<td>Sleeve resection bronchus &amp; anastomosis HFQ</td>
</tr>
<tr>
<td>E541</td>
<td>Total pneumonectomy</td>
</tr>
<tr>
<td>E542</td>
<td>Bilobectomy lung</td>
</tr>
<tr>
<td>E543</td>
<td>Lobectomy lung</td>
</tr>
<tr>
<td>E544</td>
<td>Excision segment lung</td>
</tr>
<tr>
<td>E545</td>
<td>Partial lobectomy lung NEC</td>
</tr>
<tr>
<td>E548</td>
<td>Other specified excision lung</td>
</tr>
<tr>
<td>E549</td>
<td>Unspecified excision lung</td>
</tr>
<tr>
<td>E552</td>
<td>Open excision lesion lung</td>
</tr>
<tr>
<td>E559</td>
<td>Unspecified open extirpation lesion lung</td>
</tr>
<tr>
<td>T013</td>
<td>Excision lesion chest wall</td>
</tr>
<tr>
<td>T023</td>
<td>Insertion prosthesis into chest wall NEC</td>
</tr>
</tbody>
</table>

*Table 1: Major resection surgical procedures included in the cohort as ‘radical surgery’*

### 2.2.2 Methodological development for SABR patients

An initial data set of patients treated in 2014 was investigated to see if it was possible to identify those patients receiving SABR based on dose and fractionation. UK SABR consortium guidelines suggest 3 different dose/fractionations for lung: 54Gy in 3 fractions for tumours not near the chest wall or the central chest, 55Gy in 5 fractions where PTV would overlap with chest wall and 60Gy in 8 fractions for tumours near central structures. As the SABR consortium guidelines were new, other potential dose/fractionation combinations were possible, for example 70Gy in 10 fractions (Chang et al., 2014).

The first method was to identify patients who had received a dose consistent with consortium guidelines. A retrospective cohort analysis identified 555 patients who had received radiotherapy for lung cancer in 10 or fewer fractions. Of these 140 patients had received 55Gy in 5 fractions, 30 patients had received 54Gy in 3 fractions and 21 patients had received 60Gy in 8 fractions. These 3 treatment schedules made up 191 of 555 patients in the cohort (34%).

Sub analysis of this revealed that 67% of the cohort (373 of 555 patients) received their treatment in 5 fractions. 370 patients had received more than 50Gy in 5 fractions and 365 received 55Gy in 5 fractions or higher. This generated the hypothesis that the prescribed dose
was not being recorded, instead a maximum point dose was being recorded. Radiotherapy plans for SABR treatments have a higher dose in the centre of the treatment volume, which can be up to 140% of the prescribed dose. For example, if a patient receiving a prescribed dose of 55Gy in 5 fractions who had a maximum dose of 140% delivered in the centre, that maximum dose would be 77Gy. When this was checked by Public Health England, it was felt to be the cause of the range of doses seen in this analysis. Although recording data in this way has now been edited, the data was collected retrospectively and needed to take account of the maximum dose being recorded instead of the prescribed dose.

As using only consortium guideline doses to identify patients receiving lung SABR was insufficiently broad it was decided to define SABR as 48 Gy or more delivered in 8 or fewer fractions. As well as taking account of treatments where a point dose was recorded, it would also take account of any patients receiving 48Gy in 4 fractions, which was a common dose/fractionation used in other countries such as Japan and USA (Murray et al., 2016b). It would also include patients receiving 50Gy in 8 fractions, for central tumours or tumours close to the heart, which was a recognised alternative to 60Gy in 8 fractions.

Radical radiotherapy was defined as 50Gy or more delivered in more than 10 fractions; this included standard fractionation and patients receiving hyperfractionated radiotherapy (Saunders et al., 1999). Palliative radiotherapy was defined as 50Gy or less in 15 or fewer fractions. Any patients who received more than one category of radiotherapy during the assessment period were excluded (less than 0.5% of the radiotherapy cohort). Patients receiving concurrent radiotherapy to a different primary tumour were included in this cohort.

Patients identified as ‘no treatment recorded’ did not receive either radiotherapy, chemotherapy or major surgical treatment within the time period 1 month before and 3 months after the date of diagnosis. They may have received a minor surgical procedure, or less common treatment.

2.3 Results

2.3.1 Results for the whole cohort

In total 5,826 patients with stage 1 NSCLC tumours were identified. Of these, 72% had a histological diagnosis and 28% (1,629) did not have a tissue diagnosis recorded. The commonest tissue type was adenocarcinoma (2,419 cases, 42%), the next largest cohort were
those with an unspecified or unrecorded tissue diagnosis (1,629, 28%) followed by squamous cell carcinomas (1129, 19%). The upper lobes were the commonest anatomical site, with 59% of tumours situated there. 47% of those identified were female and 53% male. The mean ages of patients who received radiotherapy and no recorded treatment were similar (76.1 years vs 76.9 years); patients receiving chemotherapy were slightly younger and surgical patients were younger still (mean age 70.6 years and 68.6 years respectively).

Table 2 includes the patient and tumour characteristics and treatments. The most common treatment for stage 1 NSCLC was surgical resection, with nearly half of patients (45%, 2802 cases) undergoing surgery. The next largest group of patients was the 32% (1878 cases) who did not have a treatment documented, reasons for this are discussed in section 2.4.3. The third largest group was those receiving radiotherapy.
Figure 1: Percentage of stage 1 tumours treated with SABR by Strategic Clinical Network. Error bars are 95% confidence intervals.
15% of patients (877 cases) received radiotherapy. Of the radiotherapy cohort, 514 (59%) had SABR, 248 (28%) had radical radiotherapy and 115 (13%) had palliative radiotherapy. The rates of SABR, radical and palliative radiotherapy by strategic clinical network are summarised in Figure 1.

<table>
<thead>
<tr>
<th></th>
<th>No tx</th>
<th>SABR</th>
<th>Radical RT</th>
<th>Pall RT</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>total</td>
<td>total</td>
<td>%</td>
<td>total</td>
<td>%</td>
</tr>
<tr>
<td><strong>Stage</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1a</td>
<td>2,179</td>
<td>695</td>
<td>32%</td>
<td>223</td>
<td>10%</td>
</tr>
<tr>
<td>T1b</td>
<td>1,381</td>
<td>448</td>
<td>32%</td>
<td>147</td>
<td>11%</td>
</tr>
<tr>
<td>T2a</td>
<td>2,266</td>
<td>735</td>
<td>32%</td>
<td>144</td>
<td>6%</td>
</tr>
<tr>
<td><strong>Mean age</strong></td>
<td></td>
<td>-</td>
<td>76.9</td>
<td>-</td>
<td>75.7</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2,754</td>
<td>905</td>
<td>33%</td>
<td>236</td>
<td>9%</td>
</tr>
<tr>
<td>Female</td>
<td>3,072</td>
<td>973</td>
<td>32%</td>
<td>278</td>
<td>9%</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adeno</td>
<td>2,419</td>
<td>327</td>
<td>14%</td>
<td>145</td>
<td>6%</td>
</tr>
<tr>
<td>Carcinoid</td>
<td>346</td>
<td>60</td>
<td>17%</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>Large cell</td>
<td>67</td>
<td>10</td>
<td>15%</td>
<td>1</td>
<td>1%</td>
</tr>
<tr>
<td>Non-small cell</td>
<td>237</td>
<td>82</td>
<td>35%</td>
<td>45</td>
<td>19%</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Squamous</td>
<td>1,128</td>
<td>200</td>
<td>18%</td>
<td>83</td>
<td>7%</td>
</tr>
<tr>
<td>Unspecified</td>
<td>1,629</td>
<td>1,19</td>
<td>74%</td>
<td>240</td>
<td>15%</td>
</tr>
</tbody>
</table>

Table 2: Patient characteristics of cohort of stage 1 primary lung tumours diagnosed in 2015 in England. No tx = No treatment recorded within 3 months of diagnosis, SABR = Stereotactic Ablative Body Radiotherapy, Radical RT= Radical Radiotherapy, Pall RT= Palliative Radiotherapy and Surgery = Radical surgical resection of tumour.

Patients (83 cases) received chemotherapy as a single modality first treatment within the search period (1 month before to 3 months after diagnosis). As the search period only
included 3 months after diagnosis, if it took more than 3 months to deliver the first day of the first chemotherapy treatment, any subsequent treatments would not have been recorded. Figure 1 shows the differing SABR rates by Strategic Clinical Network (SCN), these vary from just under 5% in Wessex to nearly 15% in Yorkshire and the Humber. The 3 highest SABR rates are in Northern England, North West/South London and Yorkshire. The rate of SABR treatment does not obviously correlate to the geographic size of the SCN or the population within it.

A small number of patients (186 cases, 3%) received multi-modality treatment within the search period. The most common multi-modality treatment was surgery followed by chemotherapy. 107 of 186 patient receiving multi-modality treatment received this combination. This data suggests a very small number of patients (4% of the total surgical cohort) were upstaged and fit enough to receive chemotherapy.

### 2.3.2 SABR cohort

514 patients received SABR treatment at 24 radiotherapy centres.

<table>
<thead>
<tr>
<th>Treatment Type</th>
<th>Alive at 6 months</th>
<th>Alive at 12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>SABR only</td>
<td>97%</td>
<td>87%</td>
</tr>
<tr>
<td>Radical only</td>
<td>94%</td>
<td>82%</td>
</tr>
<tr>
<td>Palliative only</td>
<td>82%</td>
<td>67%</td>
</tr>
<tr>
<td>Surgery only</td>
<td>98%</td>
<td>95%</td>
</tr>
<tr>
<td>Chemotherapy only</td>
<td>94%</td>
<td>72%</td>
</tr>
<tr>
<td>Chemo and Surgery</td>
<td>98%</td>
<td>91%</td>
</tr>
</tbody>
</table>

*Table 3: OS by treatment modality*
<table>
<thead>
<tr>
<th>Treatment Type</th>
<th>Mean travel time (minutes)</th>
<th>Median travel time (minutes)</th>
<th>Min travel time (minutes)</th>
<th>Max travel time (minutes)</th>
<th>Inter quartile range</th>
<th>Standard deviation</th>
<th>No. of pts travelling 45 mins or less (%)</th>
<th>No. of patients travelling &gt; 45 mins (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SABR</td>
<td>39</td>
<td>30</td>
<td>1</td>
<td>379</td>
<td>29</td>
<td>37</td>
<td>378 (74)</td>
<td>136 (26)</td>
</tr>
<tr>
<td>Radical</td>
<td>29</td>
<td>28</td>
<td>3</td>
<td>89</td>
<td>21</td>
<td>16</td>
<td>218 (88)</td>
<td>30 (12)</td>
</tr>
<tr>
<td>Palliative</td>
<td>29</td>
<td>25</td>
<td>2</td>
<td>91</td>
<td>24</td>
<td>18</td>
<td>101 (88)</td>
<td>14 (12)</td>
</tr>
</tbody>
</table>

*Table 4. Travelling time to receive radiotherapy*

The mean travelling time (illustrated in table 4) was slightly higher for patients travelling to attend a SABR treatment, compared to radical or palliative radiotherapy. The differences in median travelling time were less marked.

### 2.4 Discussion

#### 2.4.1 Discussion of treatment of whole cohort

The aim of this project was to understand the use and accessibility of SABR for primary lung tumours in England. This task is made more complex by the fact that referrals to surgical centres and radiotherapy centres do not overlap and the treatments may be delivered in different Strategic Clinical Networks, both to each other and to the referring hospital.

From the results, it is clear that the most common treatment is surgical resection. It also has the best OS at 12 months: 95% of patients receiving a surgical resection were alive 1 year later. It is important to bear in mind that the surgical cohort is likely to be fitter than those undergoing alternative treatment. SABR is a recognised treatment for stage 1 NSCLC and was delivered to 9% of patients (13% of those who received active treatment). With more radiotherapy sites being commissioned to deliver SABR for primary lung tumours, it is likely that the proportion of patients in this cohort receiving SABR number may increase over time.

In terms of the patient population treated, the surgical cohort were 10 years younger on average than the SABR cohort. The mean ages of those receiving best supportive care and radiotherapy were similar.
98% of patients undergoing surgery had a histological diagnosis recorded; however, 2% did not, suggesting that there is likely to be a small cohort of patients whose data is incomplete. In the cohort overall, 28% of patients did not have a documented biopsy to prove the presence of NSCLC lung cancer. This equates with similar rates of microscopic examination confirmed lung cancer seen in other studies including data from the UK, where the rate of biopsy seen in patients with stage I-IV NSCLC was 26% (Walters et al., 2013). It is recognised practice that a significant proportion of patients with likely early stage lung cancer do not undergo biopsy before receiving SABR, principally because of concerns regarding a pneumothorax in patients who often have severe COPD. Previous data suggests a pneumothorax can occur in 15% of patients undergoing CT guided biopsy (Wiener et al., 2011, Vansteenkiste et al., 2014). Where no biopsy is obtained, international guidelines suggest that there should be 85% certainty or higher of a likely primary tumour before SABR is delivered (Vansteenkiste et al., 2014). Of the cohort receiving SABR, 53% had a documented tissue diagnosis. It would be expected that a higher proportion of patients undergoing SABR would be treated without histological confirmation of NSCLC compared to other treatment modalities. In a comparable cohort of 676 Dutch patients receiving SABR, histological confirmation was obtained in 35% of patients (Senthi et al., 2012). However, it is important to note that in the Dutch SABR cohort the proportion of adenocarcinomas and squamous cell carcinomas (SCCs) were equivalent, whereas in the English cohort adenocarcinomas outnumbered SCCs approximately 2:1. Traditionally, adenocarcinomas tend to be more peripheral tumours, whereas SCCs are more central. The predominance of adenocarcinomas may suggest that more peripheral tumours are being treated. The risk of significant toxicity in treating peripheral lung tumours with SABR is small. Treating more central tumours has a higher risk of airway collapse and haemorrhage (Senthi et al., 2013). The different proportions of tissues types may suggest that lower risk peripheral tumours are being more commonly treated with SABR; however, it may be related simply to the rise in the proportion of adenocarcinomas being diagnosed (Song et al., 2017).
Patients receiving SABR had to travel for longer to receive their treatment than those receiving fractionated radical radiotherapy or palliative radiotherapy. This data is likely to be skewed by a small number of patients travelling for a long time to receive SABR treatment.

2.4.2 Surgical cohort
Surgery was the most common treatment delivered for stage 1 NSCLC. 99% of patients had a documented histological subtype of lung cancer documented suggesting this data set is near complete. Surgery had the highest one year survival rate. It is unsurprising that surgery is the most common treatment for stage 1 NSCLC, particularly if accessing radiotherapy is difficult. Surgery avoids the needs for multiple visits to a radiotherapy department.

2.4.3 Cohort receiving no documented treatment
There is a large cohort of patients that do not have a documented standard treatment within 3 months of diagnosis. This could suggest that incidental tumours are found on imaging performed for other purposes, or that patients are not sufficiently fit for treatment, however over a third (36%) of those without a documented treatment had biopsy proven NSCLC, with
sufficient histological material to categorise the sub type of NSCLC. As these were early stage tumours it is likely that a malignant diagnosis would have had to be confirmed by CT guided biopsy or bronchoscopy. The early stage nature of these tumours means patients would not have been able to undergo less invasive diagnostic investigations such as a lymph node biopsy or aspiration of a pleural effusion, which are available for diagnosing more advanced disease. If patients were able to undergo an invasive biopsy, why did such a significant proportion not receive further treatment?

In terms of SABR it is well tolerated in older, less fit patients with co-morbidities. One reason for this could be the availability of SABR. It would be interesting to explore whether, with a wider availability of SABR, more patients would have received treatment and potentially fewer patients would have received no treatment, particularly if increased provision meant they would have had to travel less far. Fewer patients were able to access SABR within 45 minutes travelling time, compared to those receiving palliative or fractionated radical radiotherapy (74% vs 88% vs 88%). The Independent Cancer Taskforce have set out in ‘Achieving World Class Cancer Outcomes: 2015-2020’ the importance in aiming to improve older patients’ cancer outcomes. Cancer registry data from the SEER database in the USA has shown that SABR improves OS when compared to best supportive care (29 months vs 10 months) and improves outcomes in older patients (Nanda et al., 2015, Palma et al., 2011). It is also known that older patients with high co-morbidity scoring do worse after surgical resection of an early lung cancer (Wang et al., 2007). If more patients underwent SABR this would potentially improve the survival of the cohort as a whole.

There may have been more than one cancer diagnosed in some of these patients. Figure 2 shows that patients receiving chemotherapy alone or palliative radiotherapy had a worse outcome than those receiving no documented treatment. As these were early stage lung tumours, which were unlikely to be symptomatic it maybe that a different malignancy is being treated with chemotherapy or palliative radiotherapy. A concurrent malignancy would not have been identified using this methodology.

The major limitation of this data set is the need for performance status and co-morbidity scoring. It is likely that this would explain why patients had neither a biopsy nor treatment for a stage 1 tumour. This was not available at the time of analysis.
### 2.5 Summary of findings

This data suggests that SABR is an established treatment for early stage lung tumours, however, with the increase in the use of medical imaging, an ageing population and the potential for CT screening for lung cancer, the number of early stage tumours that are both detected and treated are likely to increase. More than 80% of new cases of lung cancer are diagnosed in the over 60s and more than 40% are diagnosed in those over 75 years. The number of cases of lung cancer in over 60’s is rising, particularly in those aged 81 or older, where cases have risen by nearly 1.5 times from 446 per 100,000 in 2004 to 666 per 100,000 in 2012. Many of these tumours are likely to occur in less fit individuals, which precludes surgery. SABR has the potential to be a very useful tool in this cohort and needs to be widely available. In England SABR is centrally commissioned by NHS England. This provides an opportunity to ensure that all patients have access to SABR without a prohibitive travelling time. It is vital that in a population of patients who are less likely to be fit, more likely to be older and have multiple co-morbidities they can access treatment locally to them.

The number of patients treated with SABR has the potential to increase. As discussed previously there appears to be a population of patients who are sufficiently well to have a biopsy proven diagnosis of NSCLC, but have not had timely treatment. It may be that for these patients SABR treatment is difficult to access. As patients not receiving a documented treatment make up 36% of the cohort, it is likely that improving cancer treatment rates in this cohort would have a significant benefit on survival rates of the cohort as a whole. An analysis by Palma et al. has shown that in a cohort of elderly patients with early stage NSCLC, as SABR became a more established treatment, the use of radiotherapy has increased, overall survival has increased and the proportion of patients receiving no treatment has decreased (Palma et al., 2010).

At present only a small number of projects have used RTDS to investigate patterns of radiotherapy treatment for cancer. The first published study looked at the use of radiotherapy in rectal cancer (Morris et al., 2016). This methodology provides a way of identifying large cohorts of well characterised patients receiving radiotherapy and is particularly useful in identifying patients having radiotherapy as a single modality treatment (Phillips et al., 2018).
As follow up time from treatment increases, OS will become a more relevant indicator. The use of RTDS will be a very helpful tool in understanding prescription patterns, OS and access to radiotherapy. This has the potential to provide a large dataset for further research.

In identifying access issues this data set may identify regions of England that need better provision of SABR. Follow up of this cohort over a longer time period will also provide real world outcome data to compare to clinical trials.

2.6 Future work: the appropriateness of Textural Analysis in patients receiving SABR for NSCLC

Investigating the use of texture analysis in patients receiving SABR is appropriate because: it has the potential to be cost effective; it can be completed on existing imaging; can potentially be used to help define malignancy or recurrence when a patient cannot have a biopsy; and the use of SABR is likely to increase.

The next chapter (chapter 3) focuses on different methods of TA to establish the context of TA in lung cancer. Chapters 4-6 establish and investigate a specific method of TA in patients who have received SABR for NSCLC.
References


Radiotherapy (SABR) in Patients with Medically Inoperable Peripheral Early Stage Lung Cancer: Outcomes for the First UK SABR Cohort. Clin Oncol (R Coll Radiol), 28, 4-12.


Theme 1: CT Texture Analysis after SABR for Non-Small Cell Lung Cancer

Chapter 3: Literature review of Clinical Applications of texture analysis in Non-Small Cell Lung cancer (NSCLC)

3.1 Background

The work generated for this thesis, described in chapter 2 has shown that surgery is the commonest treatment for Non-Small Cell Lung Cancer for stage 1 tumours in England. The second commonest active treatment is Stereotactic Ablative Body Radiotherapy. It showed that there was also a pool of patients who did not receive active treatment, which require further investigation.

The aim of theme 1 of this thesis is to see if it is possible to differentiate between tumour and radiation-induced lung injury (RILI) after SABR (Stereotactic Ablative Body Radiotherapy), however, it is important to put this work in context, by reviewing previously published literature regarding TA being used in NSCLC. In terms of developing a novel TA tool, reviewing the literature will help to understand previous approaches to TA and the clinical questions that have been investigated. Previously published TA has been undertaken at different time points of diagnosis and treatment for Non-Small Cell Lung Cancer. Previously published data can be categorised into pre-treatment TA and assessing treatment response. Pre-treatment TA has several potential roles, in aiding diagnosis of lung nodules and assessing their malignant potential, predicting treatment response and prognostication for a tumour. This can be performed on differing imaging modalities including CT and PET-CT.

When a patient has been diagnosed with lung cancer, during their treatment pathway they often undergo regular cross-sectional imaging to diagnose, stage, assess response and undertake surveillance after treatment, which leads to a pool of imaging data that potentially has significant value beyond accurate staging of the patient. Computed tomography (CT) is a central tool in managing lung cancer. It is relatively inexpensive, quick and widely available. [(18)F]-2-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (FDG PET-CT) superimposes a functional assessment of tumour metabolism. FDG PET-CT can greatly aid the identification of malignant lung nodules with a sensitivity of 95% and specificity of 82% (Cronin et al., 2008), but is less widely available and considerably more expensive.
Value-based care provides incentives to maximise information from standard investigations. Radiomics aims to extract and analyse large amounts of advanced quantitative data from medical imaging (Gillies et al., 2016). Textural Analysis (TA) is a subtype of radiomics, an example of an agnostic, rather than semantic, approach within this field, based on mathematical derivations rather than prior clinical concepts (Materka, 1998).

TA can be used on existing data sets with no further dedicated or specialist imaging required. A considerable body of literature has accumulated in this field. TA has the potential to differentiate between benign and malignant lung nodules (Devan et al., 2014, Dilger et al., 2015a, Froz et al., 2017, Lin et al., 2013, Hwang et al., 2015, Padma and Sukanesh, 2013a, Pires et al., 2013, Sun et al., 2013, Orozco et al., 2015, Son et al., 2014) prognosticate outcome(Ganeshan et al., 2010, Emaminejad et al., 2015, Hawkins et al., 2014a, Coroller et al., 2015, Fried et al., 2014, Grove et al., 2015, Song et al., 2016a, Kang et al., 2015, Cirujeda et al., 2016, Hunter et al., 2016, Fave et al., 2016, Parmar et al., 2015a, Kohutek et al., 2014), aid improved radiotherapy planning (Wu et al., 2016), predicting radiotherapy side effects(Cunliffe et al., 2013) and give a greater understanding of response assessment (Mattonen et al., 2014, Mattonen et al., 2015, Mattonen et al., 2016, Moore et al., 2015, Knollmann et al., 2014, Cook et al., 2015, van Gool et al., 2016, Ravanelli et al., 2013, Chong et al., 2014, Petrulli et al., 2015). The aim of this review is to explain how different TA methods have been investigated in non-small cell lung cancer, (NSCLC), and to describe their current applicability and future potential(Depeursinge et al., 2015).

3.2 Methods

In order to identify appropriate studies, 3 different search engines were interrogated, these were: Pubmed, Medline and Web of Science. I devised a search strategy in collaboration with the subject specific librarian at the University of Surrey library. I used the search terms “textural analysis”, “texture analysis” and “radiomics” with MeSH terms “lung neoplasms”, “non-small cell lung cancer” and “small cell lung cancer” to identify appropriate papers, abstracts and conference proceedings. The search period was limited to a period between January 2010 and December 2016. 341 references were identified, which were filtered using
the terms oncology, and English. Papers discussing other primary cancers and duplicates were excluded. This left 104 papers, all of which are included in this literature review.

3.3 Background to textural analysis (TA)

TA uses a range of mathematically calculated features to describe an image or region of an image. Often TA is used to describe a suspected or known tumour. The complexity of the analysis depends on the feature being described. Although different textural features have been generated from a wide range of sources, they can be broadly divided into three categories: first-order (least complex), second-order and higher-order (most complex). Different sub-categories of TA are summarised in table 1. First-order features are often calculated as a single figure describing the texture of the whole volume being analysed. Second-order features describe the relationship between 2 points, such as 2 pixels or voxels within the same image. Higher-order features describe the relationship between a pixel and more than one other pixel, i.e. a minimum of three points in space.

First-order textural features use a range of basic statistical methods to express a single measure, including: energy, kurtosis, maximum and minimum intensity, average intensity (median and mean), range of intensities, skewness, standard deviation, uniformity, entropy (irregularity of intensity value distribution) and variance. Standard deviation, variance and mean absolute deviation express how the range of intensities are distributed. Skewness measures how much histogram asymmetry there is around the mean. Kurtosis measures the sharpness of the histogram. Randomness can be computed using uniformity and entropy. Entropy is a measure of disorder. The higher the entropy the greater the disorder or heterogeneity. The lower the entropy, the higher the homogeneity. First order features do not take account of any spatial relationship between different points in an image. Much of the published TA work, particularly related to lung nodules focuses on first order features of TA (Jacobs et al., 2015, Park et al., 2011, Elizabeth et al., 2012a, Dennie et al., 2016, Han et al., 2015, Lee et al., 2014b).
<table>
<thead>
<tr>
<th>Feature</th>
<th>Name of feature</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>First order</td>
<td>Mean</td>
<td>Average intensity of values of an image</td>
</tr>
<tr>
<td></td>
<td>Variance</td>
<td>Spread or variation around the mean</td>
</tr>
<tr>
<td></td>
<td>Skewness</td>
<td>Symmetry of intensity values in an image. Skewness = 0 if histogram is symmetrical</td>
</tr>
<tr>
<td></td>
<td>Kurtosis</td>
<td>Indication of histogram flatness, Leptokurtic curves are steeper and platykurtic curves are flatter/less peaked</td>
</tr>
<tr>
<td></td>
<td>Energy</td>
<td>Uniformity of intensity values</td>
</tr>
<tr>
<td>Second order</td>
<td>Contrasts</td>
<td>Measures amount of local variation in intensity values</td>
</tr>
<tr>
<td>local</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Angular second moment</td>
<td>Measures homogeneity of intensity value distribution in an image</td>
</tr>
<tr>
<td></td>
<td>Homogeneity</td>
<td>Measures the homogeneity of the intensity values of the pixel pair</td>
</tr>
<tr>
<td></td>
<td>Correlation</td>
<td>Measures the linear dependencies of intensity values in an image</td>
</tr>
<tr>
<td></td>
<td>Entropy</td>
<td>Measure of randomness of intensity values in an image</td>
</tr>
<tr>
<td></td>
<td>Sum of 1st order features</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Higher order</td>
<td>Complexity</td>
<td>Measures amount of information in texture</td>
</tr>
<tr>
<td>(local)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Busyness</td>
<td>Measures the rate of change in intensity values</td>
</tr>
<tr>
<td></td>
<td>Contrast</td>
<td>Measures the variation of intensity values in an image</td>
</tr>
<tr>
<td></td>
<td>Coarseness</td>
<td>Measures the density of edges in an image</td>
</tr>
<tr>
<td></td>
<td>Texture Strength</td>
<td>Measures how definable (distinguishable) primitive texture is</td>
</tr>
<tr>
<td>High order</td>
<td>Grey-level non-uniformity</td>
<td>Represents the similarity of intensity values in an image</td>
</tr>
<tr>
<td>(regional)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Run length non-uniformity</td>
<td>Measures the run length similarity</td>
</tr>
<tr>
<td></td>
<td>Run percentage</td>
<td>Ratio of total number of runs to the total number of possible runs, measuring the homogeneity of runs. For images with most linear structure, the value of run percentage is lowest.</td>
</tr>
</tbody>
</table>

*Table 1: Categories of texture analysis. Adapted from Alobaidli et al. (Alobaidli et al., 2014)*
Second-order textural features describe a relationship between two points within the same region of interest. It can describe the three-dimensional size and shape and a range of values within a tumour.

By deriving a region of interest, measurements can be taken of variations across the tumour volume, including entropy, compactness, sphericity, surface area, and surface to volume ratio. Describing higher-order textural features is more complex than first or second-order features, as it involves identifying the relationship between 3 or more points.

TA often requires complex interpretation. It is common to compare clinical interpretation with clinical interpretation combined with TA. The impact of TA can be assessed by various tools including Receiver Operating Characteristic Area under the Curve (ROC-AUC) and Concordance Index (CI). ROC-AUC is an explanation of the ‘usefulness’ of a test assessing sensitivity and specificity, assuming a test can be defined in a binary way, i.e. ‘positive’ or ‘negative’. ROC-AUC gives a test four outcomes: true negative, true positive, false negative and false positive. The ROC-AUC analyses the true positive rate against the false positive rate, deriving values between 0.5-1.0. 0.5 shows a poor test as true positives = false positives, 1 is a perfect test with no false positives. Generally 0.6-0.7 = poor test, 0.7-0.8= a fair test, 0.8-0.9= a good test, >0.9= an excellent test. A second measure is CI, which measures how well a prognostic test distinguishes individuals from a population with or without a particular outcome. Values range from 0.5 (no discrimination) to 1.0 (perfect discrimination) (Tripepi et al., 2010). To be significant a CI measurement should exclude 0.5 from its confidence interval.

3.4 Pre-treatment textural analysis (TA)

A wide range of studies have used TA to attempt to define different aspects of lung lesions seen on pre-treatment imaging. TA has been used to differentiate benign or minimally invasive lesions from malignant tissue (particularly lung nodules) using CT (Devan et al., 2014, Dilger et al., 2015b, Froz et al., 2017, Lin et al., 2013, Hwang et al., 2015, Padma and Sukanesh, 2013b, Pires et al., 2013, Sun et al., 2013, Orozco et al., 2015, Son et al., 2014), FDG PET-CT (Orlhac et al., 2015) ultrasound (Nguyen et al., 2015), and different types of tumour histology (Basu, 2012, Wu, 2016, Chae et al., 2014), to aid assessment of the tumour and aid treatment decisions. These features can be combined to predict the likelihood of a nodule being malignant.
TA has also been employed to help classify histological subtypes. An automatic classifier of squamous cell and adenocarcinoma helped aid tissue classification (Wang and Yu, 2013) and TA of nucleus features has been shown to predict early recurrence of NSCLC (Wang et al., 2016).

3.4.1 Lung nodules

TA has been used to differentiate between different tissues and determine the risk of malignancy of small pulmonary nodules. Pulmonary nodules are focal opacities appearing on imaging that are defined as less than 3 cm in axial diameter; they can be solid, semi-solid or non-solid in appearance (Callister et al., 2015). CT density [measured in Hounsfield units (HU)] and morphology can be used to assess pulmonary nodules. Solid cancer, non-solid lepidic adenocarcinoma, blood and inactive fibrous tissue all have different HU measurements (Sieren et al., 2011). However, it is still difficult to predict with certainty the pathology of small lung lesions, because up to 39% of lung nodules with a benign CT morphological appearance can be malignant (Erasmus et al., 2000).

As the use of medical imaging increases, more lung nodules are likely to be identified. Lung cancer screening using low dose CT has a relative risk reduction of 20% for lung cancer specific survival, when compared to chest radiography in a high risk population. In each of the 3 years of screening, identification of a nodule occurred in 27.3%, 27.9% and 16.8% of the trial population in years 1-3 respectively. Individuals in whom a nodule was identified in years 1 and 2 were not automatically excluded from continuing with screening, but more than 95% of these nodules would be benign (Aberle et al., 2011). TA may aid risk stratification of these lung nodules. This has significant potential to improve the predictive value of screening and reduce the morbidities rendered by biopsy and surgical resection.

As stated, lung nodules can be broadly divided into solid, semi-solid and non-solid. Several studies have aimed to help classify lung nodules into broad categories before further analysis (Jacobs et al., 2015, Mukhopadhyay, 2016). Ground glass nodules (GGNs) are non-solid and can be difficult to extract from an image accurately (Park et al., 2011, Li et al., 2016). Three studies suggest TA can convincingly determine malignant from non-malignant nodules. The first study capitalised on potential differences in heterogeneity between the nodule edge and
centre. The difference was much greater in malignant nodules when compared to inflammatory nodules with ROC AUC of 0.836 (Suo et al., 2016). In a second study computer aided diagnosis of whether a lesion was benign or malignant achieved 94% accuracy in correctly identifying all non-cancerous lesions as benign using a single image slice (Elizabeth et al., 2012b).

In a cohort of 55 patients, CT TA improved specificity from 38.5% to 100% when compared to a FDG PET-CT-CT in differentiating primary lung tumours from granulomatous lung lesions (Dennie et al., 2016). Sensitivity was similar in both groups (75% using 5 TA features vs 79 with FDG PET-CT %). High entropy (high level of disorder) was more common in primary NSCLCs. Interestingly in this study, using a combination of 3 textural features generated from a contrast enhanced CT scan rather than a non-contrast CT scan reduced the sensitivity from 88% to 38%. The reason for this is not clear, but the presence of contrast may obscure the texture of the region of interest. Contrast could potentially act as a marker of vascularity, but as this study suggests, it could obscure textural information. The effect of contrast is not necessarily binary, as the results using contrast could depend on contrast related factors such as: speed of infusion, contrast agent used, amount of infusion given; image related factors such as delay between contrast and image acquisition and patient related factors such as cardiac output and body habitus. These factors may require standardisation so that is does not unduly influence the TA.

A combination of GGN and solid nodule have a higher malignant potential than GGO or solid nodules (62.5-89.6%)(Lee et al., 2014a, McWilliams et al., 2013), although at least half (49-70%) of these Partial Solid Ground Glass Nodules (PSNs) disappear within 3 months. Analysis was performed aiming to identify textural features that may predict persistent vs transient PSNs. When textural features were combined with clinical and CT features, differentiating performance significantly increased from 79% to 92.9% (p<0.05). As with the previous study Wang et al showed that TA can improve diagnostic certainty. In contrast to the previous study, this study analysed the whole tumour, instead of a single image slice. This technique improved sensitivity and specificity from 0.82 and 0.47 to 0.95 and 0.71 respectively (Wang et al., 2014). 3D TA has also been used to differentiate between pre malignant adenocarcinomas and early invasive adenocarcinomas (Chae et al., 2014). It is not currently clear how large a region of interest needs to be analysed. There are 3 possible approaches, 2D analysis of a single slice,
2D analysis of multiple slices or 3D analysis of the whole region of interest. If a single slice of an image identifying a lung nodule is being used, pragmatically the image showing the largest axial cross section of lesion is often chosen, but cross-sectional area does not definitely correlate with the greatest amount of extractable information. Han et al showed that 2D textural features generated on multiple slices from 3D data was better than generating it from a single 2D slice, although 3D data did not improve on multiple 2D slices, it can potentially analyse extra features not available in a 2D analysis. 2D analysis on a single plane on a single slice would not detect differences in other planes, for example if the axial plane was used, data regarding the coronal or sagittal plane of the tumour could not be generated. Analysing multiple 2D slices may help identify the most representative 2D slice, but does not overcome the limitations regarding information in 3D.

FDG PET-CT is another type of imaging used to assess lung nodules. In many institutions worldwide FDG PET-CT is less available than CT, but is a very useful tool in identifying malignant lung nodules, with a sensitivity of 95% and specificity of 82% (Cronin et al., 2008). Tracer uptake can be heterogeneous within a tumour because of areas of necrosis, differences in blood flow, cellular activity, micro-vessel density or hypoxia. Whilst this review focuses on the exploitable TA features of standard CT scans, where PET-CT data sets are available, additional value can be extracted from these scans. Fractal analysis is a TA modality that has been studied in this setting.

Fractal analysis is an example of higher order texture analysis. Fractals can be described as self-similar structures. The whole structure is made of up smaller repeating sub units that are identical to the overall structure, irrespective of the degree of magnification. A more fractal image or structure displays these properties. A less fractal structure does not display self similarity and would be regarded as more ordered as the structure/scale can be determined. Fractal analysis evaluates the spatial pattern of irregular objects, as a result morphological complexity and spatial heterogeneity can be given a specific value. Fractal analysis can take several forms giving different textural features: fractal dimension is a measure of how an object fills space, fractal abundance is a measure of the volume of space filled and lacunarity is a measure of heterogeneity of the structure inside an object (Sanghera et al., 2012). As
these different forms of fractal analysis can be given a specific value, repeating this analysis could potentially give an agreement value or threshold can that be user independent.

Morphological fractal dimension and density fractal dimension can be generated from CT and PET images of pulmonary images. Combining morphological fractal dimensions and FDG PET-CT or density fractal dimensions improves diagnostic accuracy to above 90% when comparing benign nodules with a primary NSCLC (Miwa et al., 2014) using FDG-PET alone.

MRI is not routinely used to assess lung tumours before treatment. However a small single institution series suggests that entropy derived from dynamic contrast enhanced MRI may predict progression free survival (PFS) (Yoon et al., 2016).

3.4.2 Pre-treatment textural analysis (TA) of primary lung tumours using CT

TA has been shown to have potential as an imaging biomarker to identify the histological subtype of NSCLC. Although many of these studies are relatively small, CT TA radio-genomics is a rapidly expanding field. CT TA has helped to differentiate KRAS oncogene mutated tumours from pan-wild type tumours (Weiss et al., 2014), EGFR (Epidermal Growth Factor Receptor) mutant tumours from wild type tumours (Ozkan et al., 2015, Rizzo et al., 2016), EGFR mutated tumours from ALK (Anaplastic Lymphoma Kinase) rearranged tumours (Caramella et al., 2015), lepidic adenocarcinomas from non-lepidic adenocarcinomas (Wang et al., 2015) and ALK rearranged tumours from un-rearranged tumours (Bluthgen et al., 2015, Yoon et al., 2015). Work in progress has identified a correlation between kurtosis (a first-order textural feature) in NSCLC and the expression of a gene coding for a protein that regulates mucin production, Mucin5AC. The expression of this gene is considered a marker of the activation of the MAP kinase signalling pathway. Increased presence of mucin produces lower attenuation with x-rays than soft tissue. This begins to demonstrate the potential for radio-pathologic correlation through advanced imaging analysis (Miles, 2016).

Conventional predictors of outcome in NSCLC include TNM staging, AJCC stage, age, sex, histology, co-morbidities and performance status. The use of a biomarker from CT imaging to prognosticate patients’ outcomes, risk of distant metastases and overall survival is attractive. CT texture features have been correlated with PET-CT SUVmax, tumour staging and degree of
tumour hypoxia (Ganeshan and Miles, 2013, Ganeshan et al., 2010). A combination of TA features have been identified that predict recurrence in surgical patients (Emaminejad et al., 2015) and overall survival in patients with adenocarcinoma (Hawkins et al., 2014b).

TA can assess many different features and this presents a challengingly large experimental space. In 98 patients with stage I-III NSCLC receiving radical radiotherapy, the 15 most predictive textural features were chosen from over 600 features, from pre-treatment CT scans (Coroller et al., 2015). Risk of distant metastases were divided into high risk and low risk with a CI of 0.62. Use of simple radiomic features were able to predict risk of distant metastases in a discovery and validation set of patients. In a similar study in stage 3 patients, receiving chemo-radiotherapy, textural features extracted from the Gross Tumour Volume (GTV), patients could be divided into high and low risk based on traditional prognostic factors such as staging and features from TA(Fried et al., 2014), with a CI of 0.89 and 0.91 for overall survival and loco regional control respectively. Grove et al showed that morphologically similar tumours could be divided into better and worse prognosis groups and validated this at a separate institution, using convexity and central tumour entropy. More irregular tumours conferred a worse prognosis (Grove et al., 2015).

TA in combination with machine learning has been shown to predict recurrence with a high degree of accuracy (CI 0.81)(Depeursinge et al., 2015) and overall survival (Song et al., 2016b), using the pre-treatment image of a single CT slice of 101 patients who underwent resection of stage I primary lung adenocarcinoma. The TA used a second-order feature called Riesz wavelets, which were chosen to differentiate between solid component and ground glass opacities (GGO). SVM (Support Vector Machine, a form of machine learning) has been used to classify high risk and low risk lesions, as well as risk of recurrence (Kang et al., 2015, Cirujeda et al., 2016). The benefit is that SVM can separate non-linear data; it can separate data into 2 groups that are not obviously distinct when plotted, when methods such as logistic regression are less useful. The more round the tumour (spherical disproportionality) and the greater the tumour heterogeneity, the less likely the response, in patients undergoing neo-adjuvant chemo-radiotherapy for NSCLC. The strength of this study was that treatment effect was assessed by pathological assessment of the surgically resected specimen. In a separate study
CT TA measures were able to predict tumour shrinkage after radical radiotherapy (Hunter et al., 2016).

A range of TA studies have been performed with broadly similar methodology. A patient cohort with a known outcome measure is identified. A single slice or whole tumour is segmented out from the rest of the scan. A range of first, second and higher order textural features can then be extracted. In many cases a large number of TA features can be calculated. Features are chosen that correlate with outcome. The difficulty is that different TA features are significant in different studies, using different methods of analysis. An association between TA features and outcome could be statistically significant by chance, especially if very large numbers of parameters are analysed. Some TA features are dependent on pre-processing of the image before TA is performed, whereas others are independent (Fave et al., 2016), which means the independent features were more likely to be robust, as they are not prone to variations in pre-processing. These concerns limit the reproducibility of many studies and their applicability as a practical clinical tool. Large robust data sets may help to overcome some of these limitations. For example, Palmar et al were able to analyse lung tumours and head and neck tumours in 878 patients with training and validation sets for both tumour types. In this study radiomic parameters were correlated with stage and prognosis (Parmar et al., 2015b). Reproducibility is a key element in using such a biomarker more widely.

TA can potentially increase the accuracy of nodal staging as lymph nodes can be auto-mapped and identified (Liu et al., 2016). TA has been shown to predict whether a lymph node is malignant or not in biopsy proven nodes, with a sensitivity of 81% and specificity of 80% (AUC= 0.87, p<0.0001). This was achieved using a combination of three textural features: entropy, GLNU (Grey Level Non Uniformity) and RLNU (Run Length Non Uniformity) with three features of shape, which assessed the degree to which a lymph node was circular. Using this combination 84% of malignant nodes and 71% of benign nodes were correctly classified on a non-contrast CT (Bayanati et al., 2015). However, only half the patients (22 of 43 patients) received a staging PET-CT scan. PET imaging shows a small improvement in diagnostic efficacy when compared to measuring nodal dimensions alone. A published study using commercially available software called TexRAD has shown that it is possible to differentiate malignant nodes from benign nodes with a low sensitivity of 53%, but much improved specificity of 97%,
with an ROC AUC of 83% (Andersen et al., 2016). TA based on endobronchial ultrasound has been shown to differentiate between benign and malignant nodes using fractal dimension (Nguyen et al., 2015).

### 3.4.3 Pre-treatment textural analysis (TA) of primary lung tumours using PET-CT

FDG PET-CT is used as standard to stage patients potentially suitable for radical treatment for NSCLC. It is becoming increasingly used in managing treatment in NSCLC. Using simple PET metrics such as mean and maximum SUV would not be defined as TA, but analysing tracer uptake can identify heterogeneity across the tumour.

Extracting texture features is dependent on the size and FDG uptake seen on FDG PET-CT imaging (Brooks and Grigsby, 2015, Chicklore et al., 2013, Hatt et al., 2015). FDG-PET texture features have been found to be prognostic (Pyka et al., 2015, Cheng et al., 2016, Fried et al., 2016, Desseroit et al., 2016a, Fried et al., 2014, Win et al., 2013) and provides more accurate prognostication than CT TA alone (Desseroit et al., 2015, Lovinfosse et al., 2016). Simple measures such as SUVmax and Metabolically Active Tumour Volume have been associated with overall survival (OS) after radiotherapy and response rates after palliative chemotherapy in metastatic lung cancer (Borst et al., 2005, Lee et al., 2006, Hatt et al., 2015, Hayano et al., 2016). In one study these metabolic measures have also been found to correlate with 1st order textural features (van Gómez López et al., 2014), however additional work has suggested that only second order features correlate with overall survival (Park et al., 2015). FDG PET-CT-CT has high test-retest and high inter observer stability. In contrast Cook et al showed that FDG PET parameters (such as SUVmax) did not predict outcome (Cook et al., 2013). FDG PET-CT studies have also been shown to aid the diagnosis of mediastinal lymph nodes (Gao et al., 2015). (Leijenaar et al., 2013). Although FDG is the commonest tracer used in clinical practice, other tracers such as F-fluoromisonidazole (F-MISO), a marker of tumour hypoxia, are available. F-MISO uptake can vary across tumours and therefore it is possible to assess tracer uptake heterogeneity and to use TA to generate textural features (Schwartz et al., 2017, Grkovich et al., 2015). FDG images take 15-20 minutes to acquire. As a result tumour movement caused by respiration during image acquisition appears to affect some, but not all, textural measures (Yip et al., 2014), for example busyness (a measure of intensity change between a voxel and those around it) was 20% higher in the 4D scan, suggesting that as...
possibly expected blurring means these measures are sensitive to motion. Fried et al identified that a combination of histogram features, co-occurrence matrices (using 2D relationships), shape and volume correlated with OS and loco regional control, but was not externally validated. Further studies have shown that SUVmax and mean, total lesional glycolysis (TLG) and metabolic tumour volume correlated positively with entropy. Energy and contrast had an inverse relationship (Lopez et al., 2014) and that the FDG PET and CT heterogeneity assessments can separately predict OS.

In a pilot study, Wu et al segmented sub-regions of tumour based on similarity of appearance, using CT and FDG PET-CT (Wu et al., 2016). Each tumour was over-segmented into multiple super pixels using K clustering of the FDG PET and CT images. The volume of the metabolically active sub-region predicted overall survival in this patient cohort, with a CI 0.67 and Hazard Ratio of 2.79 (log rank p=0.004). These regions appear to be robust against a degree of mis-registration, but the PET data does not appear to account for tumour movement. In supporting the use of TA in radiotherapy planning, some CT texture features are robust enough to be identified on linear accelerator based cone beam CT scans from on-treatment imaging during radiotherapy (Fave et al., 2015). Image quality and the ability to quantify an image is likely to improve as cone beam CT technology quality improves and optimisation of cone beam CT scan protocols becomes routine (Davies et al 2016).

The majority of these studies are retrospective. Many studies also use a lot of clinical data alongside to stratify outcome, adding in TA then slightly improves prediction of outcome compared to clinical data alone, rather than the tumour textural features alone predicting outcome. These studies are heterogeneous. They utilise different standards, measurements, equipment and techniques. For this reason it is difficult to achieve accurate reproducibility. Some studies have heterogeneous cohorts receiving different treatment, either combining tumours that received radiotherapy alone with chemo-radiotherapy or different radiotherapy schedules. Accurate localisation and segmentation of tumours on CT imaging is easier to overcome using appropriate windowing, than differences on FDG PET-CT, particularly if 3D PET is used. Some studies have specifically looked at reproducibility and this is an important area of further research (Hunter et al., 2013, Balagurunathan et al., 2014). At present it is unlikely that TA assessment is sufficiently robust to act as a biomarker.
3.5 Assessing treatment response using TA

Follow-up CT and PET-CT scans both provide additional opportunities for assessment of treatment response beyond simple visual interpretation. SUV intensity on FDG PET-CT imaging may give a faster response than decrease in tumour volume (Hicks, 2009). Early prediction of response to chemo-radiotherapy has been made using PET heterogeneity. In a study by Dong et al, patients undergoing a non-treatment FDG PET-CT scan (after receiving approximately 2/3 of total radiation dose), certain textural features indicated response to treatment with a higher sensitivity (92 vs 73%) and specificity (84 vs 80%) than baseline PET features (Dong et al., 2016).

In advanced NSCLC tumours neither volumetric measurements on CT nor RECIST criteria predicted OS (Knollmann et al., 2014). PET SUVmax has been associated with response to chemotherapy and TKIs (Cook et al., 2015, van Gool et al., 2016), but not with overall survival (Lee et al., 2006, Ravanelli et al., 2013). TA could identify response of adenocarcinomas in the metastatic setting, but could not identify response in non-adenocarcinomas.(Ravanelli et al., 2013). Different textural features have been identified in assessing response to chemo-radiotherapy (found tumour volume, mass, kurtosis, and skewness) or an EGFR tyrosine kinase inhibitor (heterogeneity) (Chong et al., 2014). 11-Cerlotinib PET requires further investigation, but has been shown to potentially identify TKI responders and non-responders in a murine model (Petrulli et al., 2015). Kurtosis after neoadjuvant chemotherapy and intensity variability after tyrosine kinase Inhibitor therapy have been shown to independently predict pathological response(Chong et al., 2014). Having a predictor of response is useful as non-responders could potentially avoid a toxic treatment, which would not benefit them and reduce costs of futile therapy.

Texture analysis has been used in a range of situations in NSCLC. The majority of data has been generated from either CT or PET-CT imaging. It has the potential to be used to gain greater data from diagnostic imaging. This could be in terms of: diagnostic certainty of an indeterminate lung nodule, predicting clinical outcome or assessing treatment response. The limitation of much of this work is that it is limited to a single methodology or institution. It is difficult to apply this more widely unless there are textural techniques robust to different scanners, settings or interpretation. The rest of this chapter discusses textural analysis applied
to the specific diagnostic challenge of differentiating between tumour and radiation induced lung injury after hypofractionated radical radiotherapy for primary lung tumours.

3.6 Defining the problem: differentiating between tumour and Radiation-Induced Lung Injury (RILI) after Stereotactic Ablative Body Radiotherapy (SABR)

SABR describes a battery of methods that facilitate the highly targeted delivery of a high dose of radiotherapy in fewer, larger doses to an early stage lung tumour. The centre of the tumour often receives 2 or 3 times the biological equivalent dose compared to standard radiotherapy.

3.6.1 Patterns of lung injury after SABR

Identifying early recurrence after radical radiotherapy can be complex, particularly after Stereotactic Ablative Body Radiotherapy (SABR) (Huang et al., 2012). Patients are commonly followed up using CT imaging. Post treatment changes after SABR are often dynamic for a year or more (Huang et al., 2012).

As the dose distribution for SABR is different to fractionated radical lung radiotherapy, it is unsurprising that the post-treatment changes seen on CT imaging are different (Trovo et al., 2010, Bibault et al., 2013). Lung injury is broadly divided into: early lung injury, commonly defined as occurring at between 1 and 6 months after treatment; a fibrotic reaction occurs between 12 and 24 months. These early changes can include new areas of consolidation, ground glass opacification, appearance of lung nodules and the development of a new pleural effusion. These changes occur with or without the presence of vascular and bronchial lung markings. Pulmonary fibrosis can resemble an interstitial pneumonia, fibrotic changes which develop at 12-24 months include decrease in lung volume, linear scarring, septal thickening, opacities and possible bronchiectasis. As SABR is delivered either as a continuous arc or with multiple beams, it is more difficult to differentiate between irradiated and unirradiated lung tissue.

Several studies have described changes to lung tissue after SABR and identified potential high risk features for recurrence, the difficulty being that these changes can occur in benign lung injury (Dahele et al., 2011, Nguyen and Palma, 2016, Nguyen et al., 2017). Bibault et al divided lung injury induced by SABR into 5 different patterns, these are: diffuse condensation, diffuse
ground glass opacity, patchy heterogeneous condensation with ground glass opacity, a mosaic of ground glass opacity and no reaction (Bibault et al., 2013). Diffuse condensation sees an increase in the attenuation of the lung parenchyma, which hides the vessels and bronchial walls. These changes fill the treated volume of lung. Ground glass opacity is defined as an area of increased density in the lung parenchyma, but does not obscure the bronchial and vascular markings seen in the lung.

The 5 patterns of RILI are essentially one of, or a combination of, no reaction, GGO or solid consolidation.

### 3.6.2 SABR and TA

The lung reaction makes differentiating between tumour and RILI difficult after SABR. TA has a role in pre-treatment and post treatment assessment. Pre-treatment textural features can improve prediction of outcome, compared to SUVmax alone (Kohutek et al., 2014). Compared to other treatment response assessments, the evidence base for using radiomics and textural features in SABR response assessment is relatively advanced. Treatment-related toxicity is also amenable to assessment by TA. The texture of regions of lung injury were compared with recurrence from CT imaging, by comparing areas of ground glass opacity and consolidation. These analyses showed recurrences were denser and had different textural features when compared to areas of RILI, this could also aid in identifying an early response (Mattonen et al., 2014, Mattonen et al., 2015, Mattonen et al., 2016).

Part of the reason that TA of CT images is attractive, is that FDG PET-CT has a limited role in identifying early tumour recurrence after SABR. This is partly because acute lung injury and inflammation can be PET avid. The 2 more proven markers of PET recurrence are FDG PET SUV >5 or a SUV value higher than the tumour on the diagnostic FDG PET-CT (Huang et al., 2012). Radiomic features have been extracted, which predict early recurrence and are able to improve sensitivity when compared to physician assessment (AUC 0.85, false negative rate 23% vs 99%) (Mattonen et al., 2016). Another study has suggested that perfusion characteristics of RILI and recurrence are different, with the areas of recurrence exhibiting changes in perfusion termed as wash-in and wash out phenomenon, not seen in areas of RILI (Moore et al., 2015). Lung CT TA changes can be identified in patients receiving radical
radiotherapy to the oesophagus, this technique not only identified patients who did, and did not, develop radiation pneumonitis, it also quantified it (Cunliffe et al., 2015). It achieved this by comparing randomly generated regions of interest in both pre and post treatment imaging.

3.7 TA in context

The use of TA and radiomics is rapidly evolving. It is attractive as it uses existing imaging data to gain greater information about a tumour or disease state. There has been sufficient work to establish that certain textural features can act as biomarkers. Indeed tumour kurtosis and entropy are entering real-world clinical evaluation as markers of poor prognosis (Miles, 2016). However to become more widespread a range of obstacles require attention. It is important to consider standardisation of each step in the process including: acquisition, segmentation (ideally auto-segmentation), analysis and interpretation of the data. TA techniques often require an expert to accurately delineate the tumour. TA requires a significant degree of computing power to generate the analysis, it is not currently integrated into current assessment of imaging in diagnosis and response assessment and TA potentially makes workflow with a radiology department more complex.

Some of these challenges can be overcome. For example, extracting textural features automatically reduces or eliminates inter-observer error (Tixier et al., 2014), using an automated technique to delineate tumour volume is more robust than manual delineation (Parmar et al., 2014) and commercialisation and user interface optimisation may facilitate the incorporation of TA into radiology department workflows. Many studies have analysed the primary tumour and so at present are more likely to be useful for pre-treatment prognostication, rather than post treatment assessment.

To gain the full benefit of textural features, identification and classification of features need to be sufficiently robust to overcome variables such as patient factors (including positioning, respiration phase and motion management and effects or lack of IV contrast), acquisition and processing variables such as image acquisition power, image slice thickness, image reconstruction algorithms, use of segmentation software and operator variability in tumour delineation. Some texture features are reproducible, while others are highly variable and do not generate the same results with repeat testing (Desseroit et al., 2016b, Orlhac et al., 2014). To minimise these variables and identify the changes related to tumours alone many studies
standardise their image acquisition process (Balagurunathan et al., 2014). Useful biomarkers need to overcome these features or have to be standardised to ensure accurate interpretation of this information.

TA of routine imaging is likely to have a range of uses in the future both within and outside of oncology. With more robust measures of texture it may be helpful in differentiating between benign and malignant lesions, identifying sub-types of malignancy. It will aid surgical and radiotherapy planning and hopefully provide more accurate response assessment. Response assessment is becoming more important as treatment becomes increasingly complex. Standard RECIST size criteria are not adequate for assessing response in immunotherapy as standard RECIST criteria underestimate benefit (Hodi et al., 2016). Texture could potentially have a role in assessing how a lesion changes rather than just using size assessment. Assessing response after stereotactic radiotherapy is difficult because of the localised radiotherapy change induced by the treatment. Differentiating between inflammation and tumour is difficult, particularly if a biopsy is inconclusive.

Outside of oncology TA has already been used to assess hepatic and pulmonary fibrosis (Alemzadeh et al., 2015) and to see if different lung pathologies can be diagnosed on imaging alone. It can potentially have a role in differentiating tissue anywhere in the body, potentially preventing the need for more invasive tests.

For these reasons being able to extract more information for standard imaging is an attractive way of getting more ‘value’ from investigations and is likely to be more routinely introduced into clinical practice in the coming years. In the context of this thesis the majority of published TA studies use a first order method. In much of the published work a biological hypothesis behind the texture comparisons is not obvious.

The aim of the work set out in this thesis is to develop a more complex TA tool, with the goal of analysing a whole lung and identifying sub-regions within it, to attempt to differentiate between tumour and post radiation lung injury after SABR. This work is described in chapters 4-6 of this thesis. The same tool has also been applied to see if it is possible to make a
functional assessment using anatomical data generated from a CT scan. The literature behind assessing lung function and sarcopenia is discussed in those specific chapters.

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THEME 1: CT Texture Analysis after SABR for Non Small Cell Lung Cancer

Chapter 4: Summary of Development of a method for operator independent tumour recognition using GLCM bases textural analysis of a whole lung, generated from Computer Tomography data

4.1 Background

The aim of the work presented in this thesis, was to understand whether advanced image analysis in the form of texture analysis (TA) could be used to differentiate between a tumour and radiation induced lung injury (RILI) after SABR for primary lung cancer, which may be very difficult to do by assessing the appearance of post treatment images (Huang et al., 2012, Huang et al., 2015, Bibault et al., 2013, Nguyen et al., 2017, Ronden et al., 2018). This would be achieved by identifying a methodology that required limited assumptions regarding the spatial characteristics of the tissue, as well as being able to potentially analyse the whole lung and differentiate between tissues. By analysing more lung using an analysis that could take account of spatial variations, more complex interactions could be investigated, identified and understood. As well as understanding the spatial variations, analysing large volumes of lung tissue overcomes the difficulty in identifying the tumour bed after treatment. After SABR there can a lot of benign post treatment related lung injury, termed RILI (radiation induced lung injury), this can make it difficult to identify the precise tumour bed in post treatment imaging. Analysing large volumes of lung overcomes this.

Choice of software

TA can be undertaken using commercial software, such as TexRAD (TexRAD Ltd, Cambridge, UK). When using TexRAD the user identifies a region of interest on a single slice of a CT scan. This undergoes first order TA and the region of interest generates a single number to representing the whole region, for example skewness or kurtosis. This analysis can then be applied to clinical outcome, for example comparing patients with tumours that have relapsed early vs never relapsed to see if the texture measures are different.

TexRAD was considered unsuitable for this project for a number of reasons. Firstly with a first order, single slice analysis, it would not be possible to take account of inhomogeneity both within a tumour and an area of RILI and between tumour and RILI. The analysis needed to
take account of sub regions within the lung as both a tumour and RILI could exist concurrently. Secondly, by not capturing all of the data regarding either tumour or RILI, it is more difficult to identify any patterns within tumour and RILI, which would allow the different ROIs (Regions of Interest) within the lung to be easily differentiated. This would not be possible with TexRAD. TexRAD is very user dependent and would require the user to have sufficient knowledge to identify the abnormality or region of interest.

TexRAD was unable to compare sub-regions within a region of interest without repeatedly re-drawing contours. Also as the source code was not available, it was more difficult to be sure of the exact method of analysis, as well as the fact the source code could not be manipulated to provide a more flexible TA tool. These limitations meant TexRAD was not suitable to pursue this project.

As TexRAD was not thought to be suitable, alternative software that could use second order TA was investigated. FiniteRT is software used for TA, it was developed in a collaboration between the University of Surrey and the Royal Surrey County Hospital (Alobaidli, 2017). Before the work described in this thesis, finiteRT had been limited to analysing tumours. It was used to investigate and correlate intra-tumoural heterogeneity on CT imaging with FDG-PET avidity, within the Gross Tumour Volume (GTV) of primary lung cancers, which were to be treated with radical radiotherapy (Alobaidli et al., 2017). This means that the previous study by Alobaidli et al focused on the analysis of the GTV as the region of interest. The region of interest was extracted from single phase non-contrast images from the CT component of the PET-CT scan. Previous work did not have to contend with variables such as would need to have been taken account of, if larger post treatment ROIs were to be analysed.

In order to develop as user independent a process as possible, the work outlined in this thesis had to take account of many more variables, when compared to the previous project e.g. the effect of IV contrast. New variables included understanding the effect of altering software parameters and the region of interest that was to be analysed. This summary covers the initial work on expanding the region of interest from the tumour to the whole lung, the work is laid out in more detail in appendix 4. The author devised and led the development of this methodology and process, which required active participation in developing the software as well as investigating the effects of different variables.
It became obvious that this tool had the potential to have wider applications in analysing CT data, other than in analysing post treatment response, such as analysing non-malignant tissue. Two examples of this are explored in themes 2 (muscle analysis) and 3 (lung parenchyma analysis) of this thesis.

FiniteRT was chosen as software to pursue differentiating between tumour and RILI after SABR, principally because it can take account of spatial relationships between sub-regions of a texture plot. The final workflow can be seen in figure 1.

FiniteRT uses a second order feature of TA called grey level co-occurrence matrices (GLCM), to create a map of heterogeneity. Essentially, the software divides the region of interest into voxels, before making a voxel by voxel comparison, assessing its similarity or dissimilarity to the 26 voxels immediately next to it in 3D space. The larger the structure the longer it takes the software to process the information. For comparison analysing a tumour volume would take several minutes and analysing an entire lung would take several hours. Each time a variable within the software is changed, the analysis needs to be re-run.

The software characterises the image using the GLCM to identify how often pairs of pixels with a specific value appear as a function of the position of the voxel in space. FiniteRT assigns the voxel an entropy score. Entropy is a measure of disorder, the higher the entropy score, the more dissimilar a voxel is to voxels around it. The calculation used to measure entropy is shown below. Inversely, a low entropy score means a voxel is similar (more uniform) to the voxels around it.

$$
Entropy = - \sum_{i=1}^{N} \sum_{j=1}^{N} P(i,j) \log P(i,j)
$$

(Alobaidli, 2017)

Where $P(i,j)$ is the probability that a voxel of intensity $i$ has a voxel of intensity $j$ immediately adjacent to it and the sum over $i$ and $j$ is over all intensity values in the image.

The aim of the project was to differentiate between tumour and RILI. As in-house software, the system had a range of parameters whose values need to be chosen. It was important to understand how altering these variables might maximise the differences between tumour and RILI. Firstly the size of the filter can be varied. The filter kernel/size is the size of the window
the software uses to analyse the GLCM. The software also sets the number of levels the data is divided or digitised into, which are the quantisation levels. The software makes a comparison between voxels by comparing data already divided into new quantisation levels, rather than by comparing the original values of the voxels in Hounsfield units, this reduces the calculation time and reduces the grey levels within the scan to a manageable number of levels. The initial version of software calculated the quantisation levels for each analysis using a Lloyd Max Quantiser (LMQ). Quantisation is described as the process of dividing up a continuous, or semi-continuous, range of values into a smaller range by group pixels with similar intensities. This means that similar HU values were often grouped together. A new value would then be given to each sub-region. The LMQ optimises the widths and values of the quantised bins to give the smallest RMS error from the original values (see equation below). The function to be minimised to achieve this was:

$$\epsilon = \sum_{i=1}^{L} \int_{t_i}^{t_{i+1}} (x - r_i)^2 p_x(x) dx$$

(Alobaidli, 2017)

Where: \(x\) is the original (unquantised) value, \(r_i\) is the value this is quantised to for the \(i\)th output level, \(p\) is the probability distribution of the original data, \(t\) is the value at which the quantised intensity transitions from one output level to another and \(L\) is the number of output levels.

This method of quantisation assigns thresholds based on the range of values within a region of interest. If the contents of ROIs are different, then the spread and quantity of specific density values are different, and the absolute density values at which the algorithm defines the quantisation levels will be different. For example if there are 2 ROI’s, one contains just lung tissue and one contains lung and bone, the actual values at which the quantisation levels are set are likely to be different. This type of quantisation has been termed individualised quantisation.

It is also possible to standardise the quantisation levels, so that 2 or more structures are analysed using identical quantisation values for quantising the data. The comparison of two or more regions of interest using identical quantisation levels has been termed uniform
quantisation. The initial version of finiteRT used individualised quantisation. As more work was completed it became apparent that uniform quantisation would be more useful. Previous data has suggested that there are 2 methods to define quantisation levels, one by dividing the range of values into equally spaced levels (bins) where the bin size varies for each image and the second standardises the quantisation by maintaining a constant intensity resolution. The second method, which is comparable to uniform quantisation is more robust to intra- and inter-image assessment (Leijenaar et al., 2015). As part of this project finiteRT was developed so that it could use either uniform or individualised quantisation.
Figure 1: summary of workflow to identify the tumour within the elephant plot using finiteRT
FiniteRT needed to take account of many variables, which could affect the analysis of large ROIs. Understanding how the texture maps and entropy scoring changed when the variables were altered had two benefits. Firstly in understanding which variables alter the outcome of the TA and secondly, which variables could have helped maximise the ability to identify the tumour.

Figure 2. Overview of development of Texture Analysis methodology using finiteRT. Summarised in chapter 4, presented in more detail in appendix 3.

These variables were divided into 2 groups, those image related and those analysis related. The analysis related variables related to understanding the effects of these variables in finiteRT on the results of the TA (e.g. number of quantisation levels), the image related variables related to variables that might affect the pre-TA captured image e.g. presence or absence of IV contrast. An overview is given in figure 1.
The ROI analysed, filter size and number of quantisation levels analysed were TA variables, the first group as identified above. Exploring the effect of altering these variables formed the first part of the experimental work summarised in this chapter (section 4.2 & appendix 4).

The second category of variables that may influence the analysis were the imaging variables. These were thought to include use of multi-phase radiotherapy planning scans, regions of interest containing tissues other than tumour or larger than the tumour, effects of intravenous contrast, breathing phase of the scan or the ability to interpret post treatment imaging. This work summarises the process of developing a model to understand the variables necessary to process and interpret a texture map of a whole lung, both before and after Stereotactic Ablative Body Radiotherapy (SABR).

4.2 Defining the experimental space 1: Preliminary work on software related variables

Early experimental work focused on understanding the effects of the software variables. The three software variables were the choice of ROI, size of filter and number of quantisation levels.

The major principle of identifying the tumour, was that it had a central low entropy region appearing in black, surrounded by a rim of higher entropy voxels, appearing in grey or white as seen in figure 3b). Altering the size of the ROI and the filter size did not compromise the ability to see the low entropy region of tumour, whereas increasing the number of quantisation levels did affect this region, as more quantisation levels, perhaps expectedly, meant more heterogeneity. Simply increasing the size of the ROI, consequently increasing the proportion of lung vs tumour within the ROI, altered the absolute values of the quantisation levels. Altering the filter size gave a more blurred image as filter size increased.
Figure 3. a) shows PET avid region of an FDG PET-CT scan, which represents tumour. b) shows this region as a texture map, with heterogeneous and homogeneous images. c) shows the same region of interest in terms of PET avidity.

As these variables did affect the outcome of the analysis, even if only subtly, it was decided at this point to standardise these variables, by fixing the number of quantisation levels, the filter size and as far as possible, the ROI. 8 quantisation levels and a 5mm filter size were chosen for further work for two reasons, firstly these settings had previously been used to identify the homogeneous region of the tumour (Alobaidli et al., 2017). Secondly and most importantly, using 8 levels of quantisation appeared to maintain the central homogeneous region of the tumour more robustly than 16 or 32 levels. Although this decision was revisited at a later date, when much larger ROIs were analysed, the principle of maintaining intratumoral homogeneity remained a central feature in the subsequent analysis, so the tumour centre could be easily identified.

4.3 Defining the experimental space 2: Preliminary work on image related variables

The next set of experiments investigated the imaging variables of the scans being analysed. The phase of the CT and the presence or absence of contrast appeared to affect the image, but did not affect the core aim of identifying the black central homogeneous region of the tumour.
Reviewing texture maps after SABR treatment suggested that the central region of homogeneity became less obvious after a successful treatment. This developed the hypothesis that a difference between tumour and RILI could possibly be identified.

From the work outlined in appendix and discussed in this summary it can be concluded that all of the variables affect the appearance of the texture map, but mostly in subtle ways. In combination these could have a profound effect on the ability to compare similar structures between patients. The aim of this preliminary work was to understand, which variables were important. Perhaps unsurprisingly, all the identified variables were important, however although these factors influence the analysis, they do not appear to affect the architecture of the texture map and its appearance is grossly unchanged. In conclusion the appearance of the texture map generated from the analysis did not appear to risk the loss of the central homogenous region of the tumour. To maximise the accuracy of future analysis further work aimed at standardising the analysis needed to be completed, to minimise the effect of as many independent variables as possible.

At this point it was felt that any future analysis would need to fix the filter size and number of quantisation levels and consider exploring uniform quantisation. Analysis would also aim to use scans with IV contrast in an identified breathing phase.

It was felt that fixing the quantisation levels using uniform values would mean that differences in the texture maps were likely to be due to the tumour, not changes in software parameters. It offered two other benefits. Firstly, it would also allow the entropy (disorder) scores generated from the analysed structures to be directly compared between scans and between patients. Secondly, fixing quantisation levels means the quantisation levels are not determined by the content of the texture map. For example, by fixing the quantisation levels it does not matter whether a dense structure, such as bone or muscle, is inadvertently included in a ROI, which should only include lung and tumour. In a clinical context it reduces the need for specialist knowledge to volume a region of interest and minimises the effects of any errors in generating a region of interest.

Going forward from this point, it was felt that further analyses should aim to include either large sections of lung or if possible the whole lung. Generating a contour of the lung requires less specialist knowledge than identifying the tumour bed (particularly in post treatment
imaging) and ensures that all post treatment inflammation would be included. To date all work had been completed on the GTV plus a margin of lung. If further analysis were to include large sections of lung tissue, then this would lead to a more complex analysis of the texture map, as the appearance of normal tissue as well as abnormal tissue would need to be accounted for. The texture analysis would also take a lot longer to process using finiteRT.

4.4 Calibrating the texture map analysis

The next step was to generate texture maps from large ROIs for large parts of the lung, or the whole lung. These analyses were completed using uniform quantisation using pre-determined levels, which allow more accurate comparisons to be made between regions of interest.

Different analysis approaches were taken, including combining the texture map using entropy scores with the density data from the original CT scan, as a 2 dimensional feature plot. The author then wanted to see if an alternative visual presentation of the analysis would allow easy detection of the dense low entropy region, which was thought to correspond to tumour. As the low entropy region appeared in black, on a suitably windowed texture map, so that white was low entropy and increased density was white, potentially meant it was possible to easily identify dense regions with a low entropy score as the same colour. Although visually interesting, combining entropy scores and density did not add more information. Experimental work aimed to identify whether different tumours had similar combined entropy/density scores, as well as seeing if different organs had different combined scores. In summary this required artificial manipulation of the texture data and this was felt to introduce a possible source of error, as the way in which they were combined, could be easily manipulated.

4.5 The ‘elephant plot’ An expression of combined CT and texture data as a hypothesis generating tool

From the previous work described in more detail in appendix 4, it appeared that adding more complexity to the analysis did not obviously help differentiate between tumour and other structures. Each analysed voxel had 3 pieces of information: a density score, an entropy score and its position in space within the CT scan. The more complex analyses did not use these pieces of data to the greatest advantage.
As a result the data was plotted for with a density score on the x axis and the entropy score on the y axis. This was initially plotted for a whole lung containing tumour and as a separate analysis, the whole contra-lateral lung that did not contain tumour. These can be seen in figure 4. The data plot labelled a) shows the lung containing tumour and the data plot labelled b) shows the contra-lateral lung, which does not contain tumour.

Figure 4: An ‘elephant plot’, a data plot of density (x axis) vs entropy score (y axis) for each data point from a whole lung segmented from a radiotherapy planning CT scan. a) is the lung ipsilateral to the tumour, b) is the contra-lateral lung. The absence of the ‘trunk’ of the elephant in b) suggests that this maybe a useful tool to identify the presence of tumour in a lung. X axis = density, Y axis = entropy score.

In this example the tumour makes up approximately 1% of the lung volume and it corresponds to the ‘trunk’ of the elephant. The presence of tumour is very easy to identify when comparing figure 4 a) and b). At this point it was felt that the elephant plot may be a useful tool in determining the presence of tumour in a lung, following SABR for primary lung cancer. Chapter 5 explores the initial analysis using the elephant plot.

The elephant plot illustrated in figure 4 shows how data points were distributed when a whole lung was identified and analysed. From the initial project concept the aim was to keep the ROI as simple as possible to identify. As a step on from identifying the whole lung, a whole scan was processed using both the LMQ quantisation method and the uniform quantisation, which is discussed in chapter 5.
The use and analysis of the elephant plot is discussed in more detail in chapters 5 and 6, however from the development of the methodology, it appears that the elephant plot is an experimental space, in which hypotheses can then be generated and tested.
References

ALOBAIDLI, S. 2017. Functional imaging and texture analysis in radiotherapy planning. PhD, University of Surrey.


**Theme 1: CT Texture Analysis after SABR for Non Small Cell Lung Cancer**

**Chapter 5: Preliminary Analysis of the texture maps, understanding the ‘elephant plot’**

**5.1 Preliminary analysis of the texture maps**

**5.1.1 Experiment 12 Does plotting the texture map as a 2D and 3D feature plot (the ‘elephant plot’) aid the analysis of tumour on pre-treatment imaging?**

**Aim:** As previously discussed in chapter 4 the elephant plot was a tool that could potentially help identify tumour within lung tissue. The author wanted to identify whether using a more advanced analysis method might help separate the data points relating to tumour from other data points more clearly. K mean clustering is a method to do this, it groups data around a pre-determined set number of clusters using means. K mean clustering aims to cluster unlabelled data, it is a form of unsupervised learning, i.e. data that is not in categories, such as all the voxels within a texture map. This means that groups/clusters are not pre-determined and are clustered by features of the data, for example the ideal would be for the k mean clustering to separate tumour from the rest of the data points within the texture map. The clusters form around a ‘centroid’, using a set of feature values, which define the clusters/groups. The process of generating the Kmean plot is outlined in figure 1.

The aim of this experiment was to see whether different clusters would obviously correspond to different tissues, particularly to see whether the tumour could be clustered separately to the rest of the lung.

It was hypothesised at this point that if this was possible, it would be easier to identify the larger tumours using K mean clustering, compared to smaller tumour, as larger tumours have more data points and potentially could be more easily separated from the rest of data.

**Experiment 12 Methods:** Large sections of lung involving at least 5cm above and below the tumour were analysed using finiteRT. In most cases this involved approximately 2/3 of the whole lung ipsilateral to the tumour. The aim was to group the data into 4 clusters. Texture analysis was performed on both the large section of lung and the primary tumour using 8 quantisation levels and a 5x5mm filter.

The data was then plotted using a 3D plot, using entropy, density and a combined metric of density and entropy.
Figure 1: An ‘elephant plot’, a data plot of density (x axis) vs entropy score (y axis) for each data point from a large section of lung segmented from a radiotherapy planning CT scan using 4 cluster K mean clustering (coloured red, blue, cyan and magenta). The tumour appears at the tip of the elephant plot in the high density low entropy region, highlighted by the blue oval. The magenta cluster in the highlighted region of a) separates tumour from other tissues. This does not occur in figure 1a) or b). Left side of diagram shows process of producing plot.

\[ f_{k\text{-means}} = \sum_{j \in [k]} \sum_{i \in S_j} \| x_i - \mu_j \|^2. \]

Kmeans function (Lloyd's algorithm) run in MATLAB. Where \( S_j \) = sets of points, to which \( u_j \) is the closest centre.
**Experiment 12 Results and Discussion:** In this experiment, 10 large sections of the lung of 10 patients with primary lung tumours were volumed and analysed. The region of interest included lung and primary tumour. This data was made up of a large number of data points, each representing a voxel, which had a density and an entropy score. K mean clustering is a method used to attempt to group uncategorised data. Figure 1 shows 3 examples using K mean clustering the texture map into 4 clusters. Of the 3 examples only the analysis in figure 1c) clusters the tumour separately to the rest of the data.

When reviewing the results of all 10 patients, it was noticed that in patients 9 and 6, that there wasn’t a low entropy high density region visible on the texture plot. Generating the hypothesis that for tumours to have a low entropy tip of the elephant trunk, the have to be above a minimum size. The size of the tumour in these 10 patients also suggested that the tumour was clustered differently, either not at all, with lung tissue or independently. Table 1 shows the different size of tumour volume and how they were clustered. In patients 6 and 9 (tumour volume 1.7 and 3.1 cm$^3$), there was not obvious low entropy high entropy region, so there was no tumour cluster. In patients 1, 3 and 4 (range of tumour size 9.4cm$^3$ to 13.1cm$^3$) the tumour was clustered with lung tissue, which has a similarly low entropy, but very different density.

In the 5 patients with the largest tumours in patients 5, 8, 2, 7 and 10 (tumour volume ranged from 26.5cm$^3$ to 83.6cm$^3$) the tumour was clustered separately, as seen in image c) figure 1. The k-mean clustering divided the data, but did not reveal any previously unsuspected conclusions about the elephant plot. The tip of the trunk that correlates with high density and low entropy as a different cluster did identify this as the region of the elephant plot that relates to tumour, but did not separate it in any additional way. As shown in figure 1, it did not consistently cluster the data points relating to tumour separately. 4 clusters were chosen as it was hoped that this would provide a workable number of clusters.

To confirm that anatomical position of the tumour and the other clusters, the regions clustered in the K mean clustering were then replotted using the scan co-ordinates. Figure 2 shows the results of 2 experiments. The same scan was analysed and has then undergone K mean clustering. The difference between the upper and lower images are the number of quantisation levels used in the analysis. In figure 2a) the tumour region is clustered with the low density low entropy region representing lung in their original position. The red cluster is
plotted as the tumour and within the lung parenchyma. In figure 2b) the number of quantisation levels is increased from 8 to 16. This has 2 effects, firstly the low density lung tissue (seen in red in image b) is clustered together and can be seen to be separate from the tumour. At this point it was felt that using K mean clustering could help identify the tumour, although, this did not occur in all cases, as a result it was used as an analysis technique for the next experiment.

<table>
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<th></th>
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<td>Pt 10</td>
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<td>Yes</td>
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</tbody>
</table>

*Table 1: table showing the tumour volumes and a tumour cluster appeared and comparing whether it was clustered alone, or in the same group as a low density lung region.*
Figure 2: Feature space plot of K mean clustered data from a large section of lung tissue using the spatial co-ordinates from original CT image. The upper image labelled a) relates to an elephant plot clustered into 4 clusters. The upper image was created using a filter size of 5 x 5mm and 8 quantisation levels. The lower image b) uses 16 quantisation levels with the same filter size. Plot a) shows that the magenta cluster corresponds to both tumour and low density lung. Plot b) shows that increasing the number of quantisation levels helps to isolate the tumour seen as magenta region.
5.1.2 Experiment 13 Does using a 3D feature plot aid the analysis of post treatment Radiation Induced Lung Injury (RILI) on post treatment scans?

**Aim:** Experiment 12 showed that it is possible to cluster the tumour region separately from the rest of the lung. The aim of experiment 13 is to see whether the clusters in a post treatment scan correspond to obvious anatomical areas in a patient who hasn’t recurred after radiotherapy.

**Experiment 13 Methods:** To repeat experiment 12 for pt 5 who hasn’t recurred on post treatment scans using a 5x5mm filter and both 8 and 16 quantisation levels, using a third metric, which was combined entropy and density. The texture map was inverted by subtracting the most positive value from zero. The entropy value was multiplied by 100 (as ITK-SNAP could not calculate decimal places. The resulting inverted entropy value was multiplied by the density in Hounsfield units.

**Experiment 13 Results and discussion:**

As in experiment 12, the aim of using K mean clustering was to see if an advanced analysis technique aided interpretation of the elephant plot. This experiment used a 3D ‘elephant plot’ to assess the data. The 3rd metric was a combination of density and entropy for each data point.

Figure 3 shows a 3D elephant plot of the lung containing tumour, after the patient has received SABR. The red region in the middle image of figure 3 correlates with the opacity within the lung seen in the right hand CT image in figure 3.

Figure 4 and 5 compare the changes in the 3D elephant plot before and after SABR. The major changes are that the cluster consistent with tumour, in the top right hand corner of the plot, becomes elongated, secondly the thin peak representing the rim of the tumour regresses away from zero entropy.

Figures 4 used 8 quantisation levels, figure 5 used 16 quantisation levels. The major difference between 8 and 16 quantisation levels is that the tumour is separated from the rest of the plot when 16 levels are used. In both the 8 and 16 level analyses the plot has the same morphological appearance after treatment. The tumour becomes more elongated and smeared. The tip of peak of the upper plot in figure 4 and figure 5 represent the heterogeneic
tumour rim. This rim increases in entropy and the peak representing the tumour rim regresses from the zero entropy line. At this point it suggests that only tumour had a region of zero entropy as this disappeared after treatment.

Figure 3: K mean clustering of post treatment scan, comparing K mean clustered plot and a plot using initial CT scan co-ordinates. On the left, central image shows the K mean clustering plotted using the original CT scan voxel co-ordinates. The right most image show the original CT image, the orange contour is the analysed region of interest.
Figure 4: comparing results of K mean clustering of a large section of lung ipsilateral to a primary lung tumour before and after SABR analysed using 8 quantisation levels

The K mean plots in experiment 12 and experiment 13 appeared to show a pre-treatment cluster consistent with tumour that was separated in space from the rest of the plot. Figure 18 in appendix 4 illustrates the morphology of the tumour, it shows a central region with an intensity value in the region of 4000 and the rim of the tumour with a negative intensity value of approximately -4000. This is also illustrated in the plots seen in figures 19-23 in appendix 4.

Although this analysis was promising, on reviewing the method of map inversion, it was realised that the inversion was not consistent and was dependent on the presence of the central zero entropy region seen in the centre of larger tumours. The method took the region of interest and set the central tumour homogeneity at 0. Then the maximum value of heterogeneity was identified and the whole map was subtracted from this. This meant there
were negative values. This method caused an aberration that the tumour should have been an extension of the heterogeneous tumour rim (seen in upper image in both fig 4 and 5) rather than in a separate position in the plot. This meant the separation was artificial and not a true result. When the whole texture map was inverted, rather than assigning specific values, the cluster was not separate. When the map was inverted so that all structures were inverted consistently the combined metric of density and entropy scoring did not appear to give any further information.

Figure 5: Comparing results of K mean clustering of a large section of lung ipsilateral to a primary lung tumour before and after SABR analysed using 16 quantisation levels.

At this point 2 important conclusions were made that would inform all future work. Firstly that as it was possible to volume large sections of lung, an effort should be made to volume the whole lung. Secondly that a 2D plot of density and entropy should form the basis of future analysis. The aim of this project was to keep the analysis as simple as possible. A third axis using a combined metric of density and entropy was subject to manipulation and it was not possible to identify a fair and consistent way of combining entropy and density. K mean
clustering did not add any further information. It had helped in dividing up the feature plot so that visually it was easier to look at different parts of the plot, but did not add further information. As a result it was felt that future plots should not be clustered.

At this point it had been technically feasible to generate texture maps for large volumes of lung tissue. Generating a texture map for the whole lung had several advantages. Existing radiotherapy planning software is able to auto-contour lungs. Generating an accurate lung contour requires less specialist knowledge, compared to identifying a region of interest within a lung. Lung tumours often move geographical position after SABR. By including the whole lung, the whole tumour bed and treated area would be included in the analysis irrespective of the position of the tumour bed.

The process of RILI after SABR is not well understood. Some patients develop significant opacification on lung imaging after SABR, whilst others develop very little change. By analysing the whole lung, this process may provide a method of tracking and understanding lung injury after SABR.

Including the whole lung is likely to make for more reproducible results and potentially makes it easier to compare different patients. The negative effects of analysing the whole lung, increases the potential ‘noise’ from confounders, such as other anatomical structures e.g. bone/rib and contrast. For an analytic approach using texture to succeed, it would need to be as simple as possible, in terms of minimising the number of steps of human interaction. A more automatic and independent process is likely to be easier to introduce in a standard radiology workflow, rather than one that requires an assessment by a radiologist at multiple points in time. Using the whole lung makes generating the region of interest simple and would require little specialist knowledge. Outlining and/or checking a region of interest could be done with minimal training, then automated analysis could be completed and the results could be interpreted at a single time point.
5.1.3 Experiment 14: Texture analysis of whole lung using varying numbers of quantisation levels.

**Aim:** The scans that had generated the structures analysed to date were revisited. A protocol was written to extend the large sections of lung to include the whole lung. The aim was to keep the localisation of the whole lung consistent between patients and between scans of the same patient. It was not clear whether it was possible to volume and analyse an entire lung. The second part of the experiment was to analyse the lung volumes using different quantisation levels to see the effect on the data plot.

**Experiment 14 Method:** Broadly the lung volume aimed to exclude the left and right main bronchus, lobar bronchi, hilum and any large blood vessels. The guidelines were created as part of the TEXAS trial protocol, which can be seen in appendix 2.

The whole lung was auto-contoured using eclipse radiotherapy planning software. The AVIP phase of the 4DCT scan was used for the volume. This volume was the edited back to avoid the trachea and 2 divisions of the bronchial tree, consistent with the structure volumed as an organ at risk in standard SABR planning for lung tumours. Using lung windows any liver was edited out of the volume.

**Experiment 14 Results and Discussion:** This analysis was initially performed on 4 patients, 2 who had recurred and 2 who were recurrence free. The combination of density and entropy score appeared to give a plot as seen in figure 6. Figure 6 shows how the pre-treatment plot changes after SABR. It also shows the effect of increasing the number of quantisation levels on these plots. Plots using 16 and 32 quantisation levels appeared to have a narrower curve, particularly in the high HU/low entropy region, which would correlate with tumour. In curve c) in figure 6 the use of 32 quantisation levels means the loss of the zero entropy high density region. This would potentially make it more difficult to identify the tumour within the data plot. As a result, 16 quantisation levels were chosen for future analysis, this was a compromise between the benefits of a greater spread of data than 8 levels and maintaining the zero tumour homogeneity previously identified in fig. 6, which was lost when using 32 levels.
Figure 6: Understanding how the appearance of the elephant plot is altered by increasing the number of quantisation levels used in the texture analysis. All these analyses are performed on the same region of interest from the same patient. a)-c) plots of density (x axis) vs entropy (y axis) on a pre-treatment CT scan. d)-f) plots of HU vs entropy on a post treatment scan. a) and d) have 8 quantised levels, b) and e) have 16 quantised levels, c) and f) have 32 quantised levels. Colours represent automatic clustering as clusters 1-4.
5.1.4 Experiment 15: generating texture analyses for whole lungs pre and post treatment

**Aim:** The aim of this experiment was to see if it was possible to generate texture maps for the whole lung, for both pre-treatment scans and post treatment scans.

**Methods:** The previous method explained in experiment 1 was used to segment a whole lung from the tumour, using guidelines from experiment 14. The analysis of each lung took several hours and successful analysis required some technical limitations to be overcome, to allow sufficient time for the analysis to be complete. Using the results from experiment 14, 16 quantisation levels were chosen and a 5x5mm filter was used. 3 different patients were chosen, who had not recurred after a successful SABR treatment, these 3 patients all had available planning scans and post treatment scans at 3, 6, 12 and 18-20 months post treatment.

**Results and Discussion:** Figure 7 shows that the plots of the whole lung ipsilateral to tumour for patients who received SABR for an early stage lung tumour, who had a successful treatment and the tumour did not recur. As a result these maps track the changes of RILI in the successful treatment of lung tumours, as the acute inflammation settles and becomes fibrosis. It shows that it is possible to plot the whole lung. It was felt that after this experiment, the K mean clustering did not add any further information to the 2D plots, as this analysis technique did not cluster the tumour separately from other tissues. As a result it was not used in further work and as per figure 7, all future plots were plotted in a single colour.

The major observation is at the curved peak to the right of the plot (the elephants trunk) in each patient in fig 7 is dynamic over time. This suggests it changes as the acute lung injury develops, then subsides, and is then followed by the development of fibrosis. Figure 7 generates the hypothesis that TA can potentially track these changes over time. From this work and experiment 12, it was felt the high density and low entropy region was likely to be tumour. However, it had not been proved conclusively. The current work meant that a region of interest could be identified on a CT scan, analysed and plotted, but a region of interest on the elephant plot could not be used to identify a region of interest in the scan. Two tools were developed, initially a region of interest analysis using a single point of interest, which is discussed in experiment 16. This tool was then used to generate a more complex region of interest analysis tool, which included multiple points. This tool is discussed in experiment 17.
Figure 7: Comparison of planning scan and post treatment scans for 3 patients whose tumour did not recur after SABR. X axis= density, Y axis= entropy. Plan= radiotherapy planning scan. 3, 6, 12 and 18-20 months= time after treatment
5.1.5 **Experiment 16: Single point region of interest analysis**

**Aim:** The aim of this project was to see how single points in the texture map relate to different points in the plot of the texture map.

**Experiment 16 Method:** Software was written to identify a specific point in the texture plot. The point was selected and then exported into matlab. This point was then replotted into the texture map in a different colour. Any point could be chosen within the texture plot. A variable was created for this point and it was transposed back into the texture map or original image using the original scan co-ordinates. The texture map was re-drawn with the single data point highlighted (an example of this can be seen in figure 8). The chosen data point could then be saved as a variable.

**Experiment 16 Results and Discussion:**

![Figure 8](image)

*Figure 8: Localising data points related to tumour using original CT scan spatial co-ordinates. 3 points extracted and plotted back in the texture map using the scan co-ordinates.*

Figure 8 shows 3 points from the high density, low entropy region of the texture analysis data plot. All 3 are in the tumour. Figure 9 shows the sub-analysis of a different region, which appears to relate to the edge of the liver.
Figure 9, Localising data points related to liver edge using original CT scan spatial co-ordinates. Texture analysis data plot, with 3 points extracted and plotted back in the texture map using the scan co-ordinates.

Figure 8 and 9 suggest that this tool is helpful as it can generate hypotheses. It suggests that the high density, low entropy region of the texture analysis plot is consistent with the tumour, however unless all data points in the plot are included, it is difficult to prove this conclusively.
Experiment 17: Multiple point region of interest analysis

**Aim:** This experiment aimed to investigate the regions of interest of the texture analysis data plot from the AVIP (Average Intensity Projection) phase of the pre-treatment radiotherapy planning CT scan of the ipsilateral lung to a primary lung tumour. The hypothesis for this experiment was that the majority of tumours contain a low entropy region, meaning the tumour is likely to be in the low entropy high density region of the texture analysis data plot.

**Methods:** 15 patients who received SABR had the lung containing tumour segmented from the AVIP phase of the 4DCT scan. This was then analysed. The region of interest tool was then set to plot all points with a density of 900-1200 and an entropy score of 2 or less. This region was then converted into a Niftii file and overlaid with a Niftii file of the texture map of the whole lung in ITK-SNAP (Yushkevich et al., 2006).

**Results and Discussion:** Image c) in figure 10 shows how the sub-region of the texture plot overlaps with the low entropy region of the tumour. The original CT image and texture map can be seen in a) and b) respectively. Figure 10 also shows the region of the data plot, which was analysed and overlaid with the original texture map. Image c) shows that the sub region identified in red overlaps neatly with the original texture map.

Figure 11 shows this comparison extended to 15 primary lung tumours overlap of the sub region (density 900-1200 and entropy 2 or less, seen in red). In 13 of 15 tumours this region overlaps with the tumour. This was a pictorial, rather than numerical analysis, but shows convincingly that the tumour sub region of the entire data plot can be predicted in the majority of tumours. What is not shown in figure 29, is that in some of the data plots other structures were included in the sub-region of the data plot, which were analysed. These were consistently larger blood vessels containing IV contrast.

The results of this experiment are shown in figure 10. It shows that the central homogeneous region of the tumour consistently overlaps with the structure generated by segmenting the tip of the high density low entropy tip of the texture analysis data plot, as described in the methods of experiment 17.
Figure 10: Overlaying the tip of the trunk in the elephant plot with the original texture map of the whole lung for 1 patient before treatment. Image a) shows the original CT image containing a primary lung tumour, image b) illustrates the texture map generated from the CT data. Image c) shows a red region representing the sub region of the texture map including data points with an entropy score of 2 or less and a density score of 900-1200 overlaid over the texture map. The data plots show the sub-region that was analysed.
Figure 11: Overlaying the tip of the trunk in the elephant plot with the original texture map of the whole lung for 15 patients from the AVIP phase of 4DCT planning scan before SABR treatment. The tip of trunk defined as points included with a density score of 900-1200 and entropy score of 2 or less, region of texture analysis data plot with texture map for 10 primary lung tumours treated with SABR. The images were generated by overlaying 2 texture maps, one from the whole texture map in white and the second in red as the sub-region of interest. The 7th image did not contain data points within the sub-region as appears much brighter than the other images.
5.1.7 Experiment 18: Understanding use of different phases of pre-treatment analyses

**Aim:** From previous experiments it was determined that it was possible to produce a texture analysis data plot for an entire lung. Experiment 17 showed it was possible to identify the tumour within the data plot. However, as the size of the analysed area had increased significantly since earlier experimental work, it was not clear what effect different phases of the 4DCT had on the texture analysis of an entire lung, as experiment 4 had only focused on the GTV. This was investigated to understand what effect movement had on the appearance of the pre-treatment elephant plot.

Radiotherapy planning of lung tumours uses a multi-phase 4 dimensional CT scan. When a patient is scanned, the patient completes a breathing cycle for every 2cm scanned. The patient is breathing comfortably during the scan, they are not aiming to maximally inspire and expire. The scan software generates 10 phases, CT0, CT10, CT20 etc. to CT90. CT0 is end inspiration and CT50 is end expiration. Between CT0 to CT50 the patient is breathing out and between CT50 and CT0 the patient is breathing in. Two composite volumes are generated. The AVIP (Average Intensity Projection) is the average image, the MIP (Maximum Intensity Projection) is the maximum density experienced during the breathing cycle within each voxel. Standard practice is to outline all structures on the AVIP, but take account of tumour motion on the MIP. It is important to understand how different phases affect the texture plot of the whole lung so that any confounding variables can be adjusted for. Patients undergo different scans in different breathing phases. The CT of the PET-CT is a single image series performed with the patient in free breathing, for planning the CT is performed with multiple phases and most diagnostic and post treatment scans are performed in inspiration breath hold.

**Experiment 18 Methods:** A single patient was used for this analysis. The radiotherapy planning structures had been drawn on the CT AVIP in Eclipse (Varian Medical Systems, Palo Alto). Eclipse contains a tool, which can auto-generate a structure from one phase of the 4DCT to other phases. A lung contour ipsilateral to the tumour and contra-lateral to the tumour was created for all phases of a scan of a single patient. These images were extracted and each volume was run twice, firstly standardised to itself using individualised quantisation and secondly standardised to the quantisation levels for the GTV for this patient (i.e. uniform quantisation).
Experiment 18 Results and discussion:

Figure 12 shows the comparison all phases of the 4D CT for the contra-lateral lung. The most unexpected observation is that all phases except the AVIP have an obvious high density low entropy region in the contra-lateral lung. In the ipsilateral plots seen in figure 13, all plots including the AVIP have a high density low entropy region. The other observation is that for phases CT20-40 and CT60-90, they all have a split high density low entropy region. This is seen in both the plots containing tumour and the plots not containing tumour. This raises the suspicion that the double plot is an effect of movement.

Figure 12: Elephant plots from textural analysis of a whole lung contra-lateral to the tumour generated from all phases of a 4DCT. Analysis included 10 4DCT phases and 2 composite volumes for the contra-lung of a patient having a radiotherapy planning 4DCT for SABR. None of the analysed structures contained tumour.

The elephant plots seen in figure 12 did not have standardised axes. The highest density point in the structure defines the X axis, this changes the relative shape of the data plots to each other making it difficult to compare different data plots. The high density low entropy region is an artefact due to how the structures for the different phases were generated. Eclipse has an auto-contouring tool that propagated the structure from the AVIP to the other phases. In these phases the structures were not reproduced faithfully, they included high density pixels related to rib and chest wall.
Figure 13: Elephant plots from textural analysis of a whole lung ipsilateral to the tumour generated from all phases of a 4DCT. 10 phases and 2 composite volumes for the ipsilateral-lung of a patient having a radiotherapy planning 4DCT for SABR. All of the analysed structures contained tumour.

The region of interest tool was used to transpose the data points of selected plots back into the original texture map using the co-ordinates of the original image. The results are seen in figure 14. The same definition as experiment 17 to analyse the high density low entropy region, i.e. density score of 900-1200 and entropy score of 2 or less. Figure 14 shows that the region of analysis from the high density low entropy region consistently overlaps with the position of the tumour in the original texture map, irrespective of the phase of the 4DCT used in the analysis.
Figure 14: Overlap of region of interest from data plot (density score 900-1200 and entropy score of 2 or less) with texture map from analysis of whole lung ipsilateral to tumour. a)= CT0, b)=CT20, c)=CT50, d)=CTAVIP and e)=CTMIP

As part of this experiment, it was noted the contents of the analysed structures were similar. What was not clear was whether FiniteRT would set similar quantisation level boundaries for similar structures. Optimal quantisation sets the levels based on the data in the structure being analysed. The values of the quantisation levels were compared between the CT0 of ipsilateral lung and contra-lateral lung, as well as to the quantisation levels of the GTV. The results can be seen in figure 15. As the tumour makes up a small amount of the total lung, it was not clear whether the presence of tumour in the lung volume would affect quantisation.
Figure 15: morphology of the elephant plots and quantisation levels for similar Regions of Interest. a) + b) standardised to self = individualised quantisation using LMQ. c) standardised to GTV = uniform quantisation using quantisation levels from GTV texture analysis.

Figure 15 shows that the individualised quantisation levels for the lung containing tumour and not containing tumour are broadly similar, but are different to the uniform quantisation levels set by the GTV. As a result this variability suggests that the values of the quantisation levels should be fixed to compare different structures. As the aim is to identify the presence of tumour, it was felt it would be reasonable to use tumour quantisation values to pre-dispose the plot to be able to identify tumour rather than other structures.
5.1.8 Experiment 19: Does uniform quantisation of texture maps affect data plot morphology?

**Aim:** The aim was to understand the effects of using individualised and uniform quantisation levels, to see if standardising the quantisation of data allows comparison of different analysed volumes. This experiment used the data plots from experiment 18, to understand the effects of optimised quantisation vs uniform quantisation.

**Experiment 19 Methods:** This experiment was made up of 2 parts. Firstly repeating the texture analysis as per experiment 18, however, in experiment 18 the quantisation levels were used individualised quantisation using the LMQ. In experiment 19, all structures to be analysed were standardised to the GTV of the same patient using uniform quantisation. The second part of the experiment was to take 2 lung structures containing tumour and standardise the quantisation to the tumour of the same patient and swap them, to standardise to the tumour of the other patient and compare the results.

**Experiment 19 Results and Discussion:**

*Figure 16: comparing individualised quantisation standardised to each structure versus uniform quantisation using the GTV Textural analysis to set quantisation levels. Blue circle identifies a difference in plot morphology.*
Figure 16 takes 3 plots from the lung ipsilateral to the tumour, standardised to itself in the upper row and to the GTV in the lower row. It shows that there are subtle morphological differences between the plots, highlighted in CT20 between the 2 standardisations.

Figure 17: Illustrating that altering the quantisation levels changes the appearance of the elephant plot. The top 2 data plots a) and b) show pt 3 and pt 18’s whole lung standardised to the tumour from the same patient. Plot c) shows pt 3 standardised to the GTV of pt 18, plot d) shows pt 18 standardised to the GTV of pt 3. The lower row shows the absolute values for the 16 quantisation levels of GTV for pt 3 and pt 18.

Figure 17 shows that quantisation affects both the appearance of the texture map and the entropy scoring of the individual data points, although it doesn’t affect the density of a data point. In the lower part of figure 17, it shows that the quantisation levels are set at different levels. For example, if 2 adjacent voxels had a density level of 240 and 379, they would both be in the same quantisation level based on the values from the GTV of pt 18, but would be 4 levels apart using the values set by the GTV of patient 3.

These changes in scoring show that the absolute values selected by the quantisation levels are important. This affects any comparison between different patients. The outcome of
experiment 19 was to aim to understand the effect of uniform quantisation levels, which would be optimal for identifying the GTV/tumour within a texture plot.
5.1.9 Experiment 20: Generating uniform quantisation levels for further analysis.

**Aim:** The aim is to generate uniform quantisation for lung tumours, which could be used for all future work.

**Methods:** 16 primary lung tumours were analysed used by the original finiteRT code. The GTV of each tumour was extracted from AVIP phase of the 4D radiotherapy planning scan. This allowed the software to select individualised quantisation levels for each tumour. The standardisations used for this experiment would then be used for all further work. As 16 quantisation levels gave a greater spread of data than 8 levels, but was more likely to maintain the central homogeneous region of most tumours, this experiment used 16 quantisation levels and a filter size of 5 x 5mm. A mean was then generated for each level and fitted to a line of best fit.

**Results:**
Table 2: Shows raw data for 16 quantisation levels for 16 different primary lung tumours.

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Density scores for each quantisation level.

Table 2: Shows raw data for 16 quantisation levels for 16 different primary lung tumours.
Figure 18: plotting the actual means of 16 quantisation levels (generated from textural analysis of 16 primary lung tumours) against a line of best fit.

Discussion:

Figure 18 shows the line of best fit plotted against the means of the 16 quantisation levels. As they are very similar a standard uniform quantisation file was created for further analysis. This would ensure that all future analyses would use the same quantisation, as a result, this would allow for comparisons between ROIs, both at different time points for the same patient and between patients. It would meant that the contents of the ROI did not affect the quantisation.
5.1.10 Experiment 21: Understanding differences in phases of a 4DCT using uniform quantisation.

**Aim:** In experiment 18, all phases of a 4DCT were examined. It was obvious that there were differences in the phases. The aim of this experiment was to understand the differences in phases of the 4DCT when the structures were analysed with uniform quantisation. I wanted to understand what effect tumour movement may have on the elephant plot. Because the 4DCT is divided into phases, I felt this was a predictable way of investigating this, although this was less likely to affect post treatment imaging, as most images are taken as a single phase in inspiration breath hold (if the patient can tolerate it).

**Method:** The following phases were chosen: CT0 (end inspiration), CT20 (mid-expiration), CT50 (end expiration) and CT70 (mid inspiration) were chosen, as well as both composite volumes (CTAVIP and CTMIP).

**Results and Discussion:** Figure 19 aids hypothesis generation. The most obvious finding is that all of the texture plots have a high entropy low density region except the AVIP of the contra-lateral lung in patients 5 and 8. The data plot for patient 17 has a much thinner high density low entropy region in the contra-lateral lung when compared to the ipsilateral lung containing tumour. The obvious difference between the ipsilateral and contra-lateral plots in the AVIP phase for patients 5 and 8 suggest it would be relatively simple to detect whether or not there is tumour in the plot, but this does not explain why there is a high density low entropy region visible in all phases of the 4DCT of the contra-lateral lung, i.e. in the lung that does not contain tumour.
Table 1: Comparison of CT0, CT20, CT50, CT70, CTAVIP and CTMIP between ipsilateral lung containing tumour and contra-lateral lung, for 3 patients (pt5, pt 8 and pt 17) using uniform quantisation levels.

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*Figure 19: comparison of CT0, CT20, CT50, CT70, CTAVIP and CTMIP between ipsilateral lung containing tumour and contra-lateral lung, for 3 patients (pt5, pt 8 and pt 17) using uniform quantisation levels.*
The second finding is the shape of the high density high entropy region. The AVIP plots are ‘averages’ based on phases CT0-CT90. For phases CT0, CT20, CT50 and CT70 there is a visible extra region, which is not visible in the AVIP plots, this is most obvious in patient 8. This is illustrated in figure 21. The region of interest analysis shows this section relates to rib being included in the volume. The volumes for this experiment were generated using an auto-contouring tool in eclipse from the AVIP volume. In patient 8, there appeared to be more movement and therefore the amount of rib moving in and out of the volume would be greater. As it is different parts of the rib, this is ‘smoothed’ out in the AVIP data plot.
Figure 21: region of interest analysis of high density low entropy region of CTO for contralateral (image a) and ipsilateral lung (image b). The high density low entropy region in plot a) relates to contrast in a hilar blood vessel. In plot b) the same region of interest in the data plot relates to both a central blood vessel and the tumour.
Figure 22: Region of interest analysis of high entropy high density region of ipsilateral lung to tumour of CTO for pt 8. The CT and texture map appearance can be seen and show that the high density high entropy region relates to rib being included in the volume.

The choice of the AVIP for further analysis, is beneficial because it includes all planning information and the contoured structures. Secondly that from examining pt 5, 8 and 17, the AVIP excludes the high density low entropy region for 2 of the 3 patients analysed in the contralateral lung, which are seen in all other phases of the 4DCT analysed and illustrated in figure 18. The high density low entropy region in the AVIP phase of the contra-lateral lung to tumour for patient 17, is less obvious than for the ipsilateral lung from the same scan. Figure 20 shows that this is related to IV contrast.
This difference in morphology between the AVIP and other series is likely to be related to 2 factors, firstly the auto-contoured structures are generated from the AVIP. It appears that rib being included in the lung volume is an artefact of the auto-contouring algorithm. The movement in different phases of the 4DCT means that different areas of rib and contrast appear in different geographical regions in different phases, meaning they do not appear as an average structure in AVIP.

![Figure 23: comparing anatomical position of high density voxels from different phases of the same slice of a 4DCT in the lung contra-lateral to tumour, in patient 5. a) = CT0, b) = CT20, c) = CT50, d) = CTMIP.](image)

Figure 23 shows 4 different phases of the 4DCT, which contained a high density low entropy region on the data plot. CT0 shows a large blood vessel with contrast, CT20 and CT 50 shows the same blood vessel has been excluded from the volume by the auto-contouring algorithm in eclipse. CT20 shows some high density, low entropy data points on the rim of the medial side of the lung. These are not visible on CT0 or CT50. The areas of uptake are different in different phases of the original 4DCT. The CTMIP is a composite image, showing maximal movement and as a result shows uptake at both the rim of the lung and contrast related overlap in the large blood vessel.

The AVIP phase of the contra-lateral lung does not have a high density low entropy region in the data plot. As the AVIP is a composite of the phases, it takes an average of all the phases, it appears that as the anatomical position of the high density low entropy region is different in each phase, this region of the plot gets smoothed out. As a result it is not visible in the AVIP.
The advantage of the absence of the high density low entropy region in the contra-lung suggests it could help guide whether or not there is tumour in a lung. To see if this was a consistent finding more AVIP phases were compared in the next experiment.
5.1.11 Experiment 22: Does excluding more of the hilum in the initial volume analysed in a texture plot reduce contrast as a confounder?

**Aim:** The aim of this experiment was to see if removing the hilum from the region of interest would reduce contrast being a confounder in the high density low entropy region of the texture analysis data plot. This was chosen as a way of reducing the chance of large hilar vessels being included in the region of interest as both the bronchial tree and an airway avoidance structure are standard volumes generated in a radiotherapy plan. This structure would also be relatively simple to auto-contour. This approach maintains the aim that the region of interest should be kept very simple and require as little as possible specialist knowledge.

**Methods:** The analysis of the AVIP of both lungs was undertaken, using the same method as in experiment 21. 2 examples of the elephant plot were chosen for this experiment.

In the contra-lateral plots with a high density low entropy region, these correspond to IV contrast. Contrast acts as a confounder for tumour. Figure 19 shows this in pt 17.

![Figure 24: shows a diagram and CT image of the airway avoidance structure, which forms the ‘no fly zone’ for treating lung tumours with SABR. Adapted from SABR consortium guidelines](image)

It is standard practice to treat tumours 2cm or more from the bronchial tree. This is calculated by contouring a volume for the bronchial tree that includes all of the left and right main bronchi and the lobar bronchi. A margin of 2cm is added to this contour to create an airway avoidance structure, an example of this can be seen in figure 24 (Consortium, 2015). Standard
practice would be to not treat tumours within the airway avoidance structure. This structure would contain large vessels disseminating from the hilum. By excluding this volume the aim would be to remove large vessels containing tumour from the whole lung, whilst keeping the tumour within the lung/region of interest.

Figure 25 shows the bronchial tree and the edited volume.

![Diagram of lung volumes used to exclude hilum from texture analysis of whole lung. Blue = bronchial tree, magenta = volume excluding tumour and bronchial tree + 1cm and cyan = volume excluding tumour and bronchial tree + 2cm.](image)

For 8 patients who had never recurred after SABR, the whole lung volume was edited to create 4 structures. Firstly the lung was edited to avoid bronchial tree + 1cm and + 2cm and exclude the tumour (seen in figure 25). Two further volumes were then generated from each structure, including the tumour and excluding the bronchial tree +1cm and +2cm. This process was repeated for each patient.

The total list of volumes generated and analysed for each patient were as follows; whole lung, whole lung minus tumour, tumour, whole lung excluding bronchial tree +1cm, whole lung excluding bronchial tumour +2cm, whole lung excluding bronchial tree +1cm and tumour and finally, whole lung excluding bronchial tree + 2cm and tumour.
Results and Discussion:

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Figure 26: Summary of whether excluding the bronchial tree aids interpretation of the elephant plot. A comparison of data plots from the whole lung (planning CT) containing tumour, tumour alone, lung-tumour, then lung-tumour and exclusion of hilar structures from the ROI with a 1cm and 2 cm margin. Excluding the bronchial tree + 2cm does not alter the appearance of the elephant plot.

Figure 26 shows 2 examples of the results for this experiment. It shows the data plot for the whole lung that contains tumour from the planning CT for pt’s 5 and 6.

Figure 27: region of interest analysis for high density low entropy region of lung-minus tumour with bronchial tree +2cm excluded from the whole lung volume.

When the tumour is excluded (lung-tumour) from the plot for pt 5, the high density low entropy region disappears, however, this is not the case in patient 6, figure 27 shows that the
residual high density low entropy region is related to the edge of liver inadvertently being included in the lung volume, this is why editing the structure away from the bronchial tree does not remove the high density low entropy region from the volume.

From this experiment it shows that the interpretation of the elephant plot is sensitive to accurate contouring. This would be an area to be aware of for future experiments. It may be that some errors in contouring are more important than others. Those that would be more important are those that could appear in the high density low entropy region of the elephant plot.
5.2 Conclusion of preliminary experimental work

Before this part of the project was completed, previous work had used finiteRT to overlap PET-avidity with intra-tumoural CT based texture analysis. The experiments described in this chapter expanded the region of analysis to include whole lung.

In order to achieve this the following variables of texture analysis using finiteRT have been explored: the effect of the tissues included in the region of interest, the filter size, the number of quantisation levels, whether individualised or uniform quantisation is used, the role of contrast, the role of breathing motion and the differences related to the different phases of the 4DCT, alternative analysis tools, including both single point and region of interest analysis, K mean clustering and the effects of these factors in relation to the tumour and the whole lung.

Understanding the effects of these variables aids the interpretation of the texture image and the subsequent data plot. From this work, it is important to standardise as many variables as possible, using a set filter size and number of quantisation levels. Standardising the absolute quantisation levels allows different regions of interest to be compared equally.

Preliminary work has generated the research question: is it possible to identify the difference between tumour and fibrosis in patients who have undergone Stereotactic Ablative Body Radiotherapy (SABR) for NSCLC? This will be explored in the next chapter.

Lung tumours treated with SABR are often straightforward to delineate on a radiotherapy planning scan, however, it can be difficult to identify the tumour bed on post treatment scans as there can be significant inflammation and this inflammation can cause a change in anatomical position of the tumour bed, relative to the lung. Differentiating between tumour and RILI can also be difficult. The aim of the next chapter is to use as objective a process to identify the differences between RILI and tumour, which requires minimal specialist knowledge and avoiding assessment by a clinician at multiple time points.
References

Chapter 6: The TEXAS trial, differentiating between tumour and Radiation Induced Lung Injury (RILI) after Stereotactic Ablative Body Radiotherapy (SABR)

6.1 Background

The previous experimental work described in chapters 4 and 5 outlined the investigative process used to provide an analysis of the texture of a whole lung, meaning each voxel within an image had both a density score and an entropy score. The aim of this chapter is to describe a 2 step process to differentiate between tumour and Radiation Induced Lung Injury (RILI) after SABR.

In the previous chapter, the standard data plot was a 2 axis plot termed the elephant plot, the x axis representing a density score and the y axis representing an entropy score, based on how similar or dissimilar a voxel was to the 26 voxels around it. The data points relating to the tumour were found in a region relating to high density and low entropy, the tip of the ‘trunk’ in the elephant plot. The initial analysis defined this region as including any data points with a density score of 900-1200 and an entropy score of 2 or less. This region co-incided with the tumour in 13 of 15 patients. When the data points were plotted in the texture map, using the original scan co-ordinates, this region of interest did not exclusively include tumour, other structures particularly blood vessels containing intra-venous contrast and the edge of the liver were included in the ROI.

The first part of the work described in this chapter, was to understand what confounding structures appeared in the tip of trunk, as well as tumour. The second part of this chapter was to review the appearance of RILI within the data plot and finally, the third part was to understand whether it is possible to differentiate between tumour and RILI after SABR using TA. The first experiment in this chapter (experiment 24) aimed to confirm that the tumour appeared in the ‘trunk’ of the elephant plot.
6.2 Experiment 24: Is it possible to define a sub region of the data plot that relates to tumour?

**Aim:** The aim of this experiment was to see if it was possible to ensure that the tumour appeared in the ROI defined in the methods.

**Methods:** 8 patients were selected for this experiment. These were patients who did not recur within the first year after having a primary lung tumour treated with SABR. These patients all had a post treatment CT scan with IV contrast at 6 or 7 months.

**Inclusion criteria:**

1. Patients previously treated with Stereotactic Ablative Lung Radiotherapy (SABR) for Non-Small Cell Lung Cancer (NSCLC).
2. Patients either had biopsy confirmed NSCLC or a clinical decision has been made that there is a high probability of NSCLC suitable for SABR.
3. Patients had a pre-treatment pet available, with a minimum of 12 months follow up with a minimum of 2 CT scans.
4. Patient had not recurred after SABR
5. Patient had CT planning scan available

**Exclusion criteria**

1. Patients not had SABR for primary lung cancer or did not receive the full dose/course of radiotherapy
2. Were treated for a lung metastasis from a different primary cancer.
3. Patients had less than 1 years follow up, less than 2 scans available or no pre-treatment PET-CT scan
4. Patients had recurred after SABR

The first step was to plot the high density low entropy sub-region (trunk) of the elephant plot, defined as a density score of 900-1200 and an entropy score of 2 or less. It was suspected that some of these sub regions would contain more than 1 data cluster. These were then plotted individually.

**Results:** Table 1 shows all of the data plots from the whole lung analysis of 8 patients. It also shows the feature plot for the tumour and a sub-region relating to the tip of the trunk, from
the whole lung elephant plot discussed in the methods (density 900-1200 and entropy 2 or less). The right hand column of table 1 shows the sub-region (tip of the elephant’s trunk) that contains tumour. When analysing this region of interest, data points correlating to tumour appeared in 7 of the 8 sub-region analyses. Figures 1-4 show the different data clusters within the high density, low entropy region of the elephant plotted back into the image.

**Discussion:** This experiment aimed to understand what structures appear in the ROI where tumour appears, within the elephant plot. 7 of the 8 patients analysed had data points relating to the tumour, within the defined ROI. Only pt 16 did not appear to have the typical appearance of other tumours, seen in table 1, as there is no data cluster in the tip of the trunk, which represents the high density, low entropy region consistent with tumour. The data plot for the tumour of patient 16 does not contain these data points. It does appear to have data points with an entropy score of 3 or less (seen in table 1). It may be that future analyses may need to include voxels with an entropy score of 3 or less, rather than 2 or less.

**Figure 1:** sub region analysis, replotting data points within the high density low entropy region (tip of the trunk of the elephant plot) using CT spatial co-ordinates. All of the tip of the trunk of the elephant plot is plotted within the tumour.
<table>
<thead>
<tr>
<th>Pt no.</th>
<th>Tumour volume</th>
<th>Lung volume</th>
<th>Data plot of whole lung</th>
<th>Tumour data plot</th>
<th>Sub-region plot</th>
</tr>
</thead>
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<tr>
<td>Pt 6</td>
<td>3.1</td>
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<td><img src="image6.png" alt="Image" /></td>
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<td>3029</td>
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<td><img src="image8.png" alt="Image" /></td>
<td><img src="image9.png" alt="Image" /></td>
</tr>
<tr>
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<td>1774</td>
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<td><img src="image11.png" alt="Image" /></td>
<td><img src="image12.png" alt="Image" /></td>
</tr>
<tr>
<td>Pt 18</td>
<td>14.6</td>
<td>1915</td>
<td><img src="image13.png" alt="Image" /></td>
<td><img src="image14.png" alt="Image" /></td>
<td><img src="image15.png" alt="Image" /></td>
</tr>
<tr>
<td>Pt 5</td>
<td>26.4</td>
<td>1725</td>
<td><img src="image16.png" alt="Image" /></td>
<td><img src="image17.png" alt="Image" /></td>
<td><img src="image18.png" alt="Image" /></td>
</tr>
<tr>
<td>Pt 8</td>
<td>26.8</td>
<td>1846</td>
<td><img src="image19.png" alt="Image" /></td>
<td><img src="image20.png" alt="Image" /></td>
<td><img src="image21.png" alt="Image" /></td>
</tr>
<tr>
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<td>1438</td>
<td><img src="image22.png" alt="Image" /></td>
<td><img src="image23.png" alt="Image" /></td>
<td><img src="image24.png" alt="Image" /></td>
</tr>
</tbody>
</table>

*Table 1: data plots for 8 patients, for whole lung containing tumour, tumour and a sub region analysis of tip of elephant trunk (region of interest including data points with a density of 900-1200 and entropy of 2 or less). X axis= density score. Y axis= entropy score.*
Figure 2: Sub region analysis for patients 7 + 8. For patient 7 left sided data cluster is consistent with contrast and the larger right sided cluster is consistent with the tumour. For patient 8, the larger left sided data cluster includes both tumour and contrast, the smaller right sided cluster includes contrast.

Figure 3: sub-region analysis for patients 16, 18 and 22. The region analysed containing data points relating to tumour in 2 of the 3 patients analysed in this figure and 7 out of 8 overall.
Figure 4: sub region analysis for patient 6. The sub region shows the 3 peaks relate to regions of interest in the texture map. Left peak = liver edge, middle peak = tumour and right peak = IV contrast in a blood vessel.

Of the 8 patients 7 contained more than one data cluster within the ROI. Patient 5 had a single obvious data cluster in the ROI. Figure 1 shows the data points within the ROI for patient 5. When these data points are replotted back into the scan, it shows that all of the data points are within the tumour. Patients 7, 8, 16, 18 and 22 had 2 data clusters. Patients 6 and 17 had 3 data clusters.

Figures 2 and 3 show 5 different patients, who each have 2 data clusters in the ROI representing the tip of the trunk. It shows the 2 separate data clusters replotted back into the original image. Of the 5 different patients illustrated in these analyses, different regions consistently relate to tumour and contrast. The dominant data cluster that represents tumour
appears to consistently have a density score (on the x axis) of between 1000-1150. The density score = Hounsfield Units plus 1000.

Other sub regions show multiple clusters of data. Figure 4 shows that the sub region for patient 6 has 3 obvious clusters of data. These correspond to tumour, a vessel containing IV contrast and the edge of the liver. This suggests that the density range used in the sub-region could potentially be further narrowed.

In summary for the majority of tumours analysed in this small data set, the tumour lies within the set boundaries of the ROI. This would need to be confirmed in larger data sets. In Figures 2-4 it can be seen that the initial contouring is can affect the analysis of the sub region of interest. It shows that confounders such as blurred diaphragm/liver edge or IV contrast can potentially impact on elephant plot analysis.
6.3 Experiment 25: Does the tumour volume correlate with the volume of Radiation Induced Lung Injury (RILI)?

**Aims:** To differentiate between tumour and RILI, more needed to be understand about the natural history of RILI. The hypothesis for this experiment was to see if the volume of post treatment lung injury at a single time point (6 months) increased as treatment volume increased. The aim being to see if there were guiding principles in how RILI develops after SABR.

**Methods:** Patterns of Radiation induced Lung Injury (RILI) are discussed in chapter 3 (section 3.5.1). 5 patterns of lung injury are known to occur, however, there are a combination of either no visible change in the lung parenchyma, the appearance of Ground Glass Opacities (GGO) or the appearance of areas of solid opacification. Areas of GGO are characterised by an increase in the background density of the lung parenchyma, however, airways and blood vessels are still visible. In areas of solid opacification these obscure the appearance of small airways and blood vessels.

The 8 patients whose pre-treatment scans were analysed in experiment 1 were used for experiment 2. These were patients who had at least 2 CT scans in the first year after treatment with SABR for primary lung cancer. These patients did not have recurrence at 12 months. The diagnostic scan 6-8 months after treatment was obtained for each of these patients. Each patient had the following volumes localised: the whole lung ipsilateral to tumour, GGO, solid RILI, total fibrosis and lung minus fibrosis. This was based on the 5 patterns of lung injury identified by Bibault et al (Bibault et al., 2013). The contours of the first 4 patients were edited by and agreed with a Consultant Radiologist.
## Results:

<table>
<thead>
<tr>
<th>Patient number</th>
<th>iGTV volume (cm³)</th>
<th>PTV volume (cm³)</th>
<th>Dose/fraction (Gy)</th>
<th>Max dose (%)</th>
<th>Mean dose to PTV (%)</th>
<th>Min dose to PTV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pt 6</td>
<td>3.1</td>
<td>12.6</td>
<td>54 in 3</td>
<td>125.5</td>
<td>109.3</td>
<td>93.7</td>
</tr>
<tr>
<td>Pt 22</td>
<td>6.2</td>
<td>20.3</td>
<td>55 in 5</td>
<td>133</td>
<td>110</td>
<td>93</td>
</tr>
<tr>
<td>Pt 16</td>
<td>11.2</td>
<td>31.2</td>
<td>54 in 3</td>
<td>130</td>
<td>112</td>
<td>93</td>
</tr>
<tr>
<td>Pt 17</td>
<td>12.1</td>
<td>31.6</td>
<td>55 in 5</td>
<td>128</td>
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<td>93</td>
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<td>55 in 5</td>
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<tr>
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<td>59.2</td>
<td>55 in 5</td>
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<td>110</td>
<td>85</td>
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<tr>
<td>Pt 8</td>
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<td>59.2</td>
<td>55 in 5</td>
<td>130</td>
<td>114</td>
<td>92</td>
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<td>77.3</td>
<td>55 in 5</td>
<td>127</td>
<td>82</td>
<td>112</td>
</tr>
</tbody>
</table>

**Table 2:** Doses/fraction schedules and % doses to GTV+ PTV for patients included in this analysis. Doses are consistent irrespective of GTV and PTV size, suggesting treatment plans and delivered doses are similar across the cohort.
Table 3, analysis of post treatment volumes of total Radiation Induced Lung Injury (RILI), SABR induced ground glass opacities (GGOs) and solid RILI.

Two sets of correlation coefficients were calculated. The first was a correlation coefficient generated for the absolute volume of total RILI, GGO RILI and solid RILI. These results are seen in table 4. It was noted that the volume of the post treatment whole lung ipsilateral to tumour, varied very significantly between patients (range 1563.7 cm$^3$ to 3844.1 cm$^3$). The coefficients were re-analysed, by comparing the GTV to total RILI, GGO RILI and solid RILI as a percentage of the lung volumes. Neither of these approaches showed a likely correlation between the size of the GTV and volume of RILI after SABR. The correlation co-efficients are seen in table 4.
Comparison | Correlation coefficient
---|---
GTV vs total RILI | -0.019
GTV vs GGO RILI | -0.04
GTV vs solid RILI | 0.293
GTV vs % total RILI | 0.072
GTV vs %GGO RILI | 0.049
GTV vs % solid RILI | 0.357

Table 4: correlating GTV with RILI following SABR. Analysis was performed in 2 ways, correlating GTV with absolute volume of total RILI, GGO RILI and solid RILI. The second method was to correlate the volume of fibrosis for total RILI, GGO RILI and solid RILI as a % of the total lung volume from the post-treatment volume.

**Discussion:** Table 2 shows that the SABR dose statistics were similar for the treated tumours, however there was a large variation between the smallest and largest PTV volumes (12.6 cm³ to 77.3 cm³). The iGTV was generated as a volume, which included the gross tumour volume in all positions of the breathing cycle using a 4DCT.

This experiment suggests that tumour size did not obviously correlate with the scale of post treatment lung injury after SABR. It supports the clinical observation that it is difficult to predict the post treatment reaction as other factors may be important, however this cannot be definitively deduced from this analysis, as there are many variables that need to be considered, as well as the very small size of the cohort. As the total lung volumes vary greatly, standardising the volume of RILI to the total volume of the irradiated lung does not improve the correlation. It may be that the volume of lung injury correlates to another technical radiotherapy or dose distribution factor such as: volume of lung receiving a low dose of radiotherapy, length of treatment volume in superior-inferior direction, tumour motion, or whether treatment was delivered in half or full arcs. To conclude definitively that the size of the treatment volume does not correlate with post treatment lung injury would require a much larger cohort to be analysed, this data set was also limited by the fact that there was some variability in the time points of the scans being analysed.
Previously published work has suggested that increased CT density after radiotherapy is associated with a higher dose, increased planning target volume size and increasing time after SABR (Palma et al., 2011). Density increases were more significant in areas of tissue receiving more than 6Gy and plateaued at 40Gy. Understanding the dose of radiotherapy received by different parts of the lung is more difficult to calculate as RILI also causes traction on the lung meaning the tumour bed can be in a different geometric position, in relation to its position in the lung. It is interesting to note that in the results of experiment 25 the only positive weak correlation was between the volume of GTV and volume of solid RILI, when compared to both absolute volume of solid RILI (correlation coefficient 0.29) and when solid RILI is expressed as a percentage of total lung volume (correlation coefficient 0.357).

As SABR is used in patients who are likely to have co-morbidities specifically COPD, defining normal lung tissue compared to acute lung injury may be more complex. This may further complicate understanding RILI after SABR. In this study, 4 initial volumes were reviewed and agreed by a Consultant Radiologist and the volumes were completed by an Oncology Registrar who was experienced outlining lung tumours and had completed Fellowship exams for the Royal College of Radiology. It may be that tighter definitions of RILI are required to ensure only localised inflammation, rather than pre-existing GGO or solid consolidation changes are included.
6.4 Experiment 26: can tumour and RILI be differentiated in patients who have received SABR 6 months previously.

**Aim:** Using the elephant plot, was it possible to differentiate between tumour and RILI after SABR. The hypothesis was that the distribution of data points in the low entropy high density region around the tip of the trunk in the elephant plot, would be different for tumour compared to RILI.

**Methods:** 8 patients who were selected and whose scans were analysed in experiment 24 and 25 were compared to 3 patients who had a local recurrence 6 months after lung SABR. Recurrence was confirmed on PET-CT. These were patients who did not recur within the first year after having a primary lung tumour treated with SABR. These patients all had a post treatment CT scan with IV contrast at 6 or 7 months. The first step was to plot the high density low entropy sub-region, defined as a density score of 900-1200 and an entropy score of 2 or less. The data points included in the sub region of the plot were then analysed and returned to the scan image.

**Results:** Figure 5 shows the ROI post treatment, for the 8 patients who underwent pre-treatment analysis in table 1 and figures 1-4. Figure 6 shows the same region of interest for 3 patients who had tumour recurrence 6 months after SABR for primary lung cancer.
Figure 5a: Comparing the trunk region of the elephant plot before and after treatment. Region of interest defined as region containing data points with a density score of 900-1200 and an entropy score of 2 or less, from 8 patients who received SABR for primary lung cancer and had not recurred at 6 months post treatment. The scale of these plots are the same as in experiments 24 and 25. X axis = density, Y axis = entropy score.
Figure 5b: Comparing the trunk region of the elephant plot before and after treatment. Region of interest defined as region containing data points with a density score of 900-1200 and an entropy score of 2 or less, from 8 patients who received SABR for primary lung cancer and had not recurred at 6 months post treatment. The scale of these plots are the same as in experiments 24 and 25. X axis = density, Y axis = entropy score.
Figure 6: illustrating the sub-region of interest (density 900-1200 and entropy 2 or less) of 3 patients who had FDG-PET CT proven recurrence 6 months after SABR for a primary lung tumour. Patient 11 and 20 show a high density of data points within the region consistent with the tip of the trunk in the elephant plot. The analysed CT scans were taken 6 months after treatment.

Discussion:

The post treatment sub-regions of interest illustrated in the right hand column of figure 5, when compared to those in table 1 (section 6.2) and figure 1-4, shows the spread of data appears different. The sub-regions do not have a pre-dominant trunk in the same position as pre-treatment imaging. None of the post treatment data plots have a high density zero entropy region in the trunk of the elephant plot, whereas 6 of the 8 tumours analysed have a zero entropy region relating to tumour in the pre-treatment imaging.

By comparison 2 of the 3 recurrences (patients 11 and 20) show different patterns to the non-recurrent sub region analyses seen in table 5. Interestingly patient 11 did not have IV contrast due to poor renal function, so the differences in appearance of the 3 patients in figure 6 are not due to contrast, as patients 11 and 20 appear similar.

Comparing the post treatment sub region analyses of recurrers and non-recurrers allows for the generation of hypotheses, but is difficult to produce conclusive results in such a small data set, but it does suggest that the morphology of the data plots may be different.

These data plots do not take into account the spatial relationship between the data points that are similar to each other in terms of entropy and density scores, but not necessarily geometrically close. The sub region analysis of patient 5 who never recurred vs patient 11 who recurred at 6 months are similar. The post treatment reaction in patient 5 appears to be denser than other patients who have not recurred. This would explain the similarity of the
appearance of the tip of the elephant trunk, for patient 11 who recurred and patient 5 who didn’t.

The post treatment analyses of patients 11 and 20 are similar to the appearance of pre-treatment tumour, this technique may be suitable to help differentiate between tumour and RILI after SABR for primary lung cancer, however definitive conclusions cannot be drawn from such a small data set.

**Conclusion Future work**

SABR is an effective treatment for primary lung cancer, with local control rates above 90% (Murray et al., 2016). One of the major clinical difficulties is differentiating tumour recurrence from the significant lung inflammation that can occur as a result of SABR (Huang et al., 2012). From the experimental work in theme 1 of this thesis it is possible to identify a sub-region of interest (the tip of the trunk in the elephant plot) in which the tumour lies before treatment. In a small data set it is possible to generate some hypotheses regarding the differences between tumour recurrence and RILI after SABR. Overall there appear to be fewer data points in the tip of the trunk, when compared to the recurrences. The other major difference between tumour and RILI for data plots 6 months after SABR is that when the data points are replotted in the original image, the data points relating to RILI are much more likely to be spread out across a wider region, whereas those representing tumour are more likely to be clustered together. These observations need to be proven in a larger dataset. Identifying patients who have not recurred is technically challenging when looking at the CT image. TA may make this process more straight forward. Identifying a larger cohort of patients who have local or ipsilateral lung recurrence is more difficult as SABR treatment is effective. In this cohort that the data was extracted from, the 1 year control rate is 97% (Phillips et al., 2017).
Figure 7: comparing different regions of interest within the elephant plot for patient 16 before receiving treatment. The voxels from the data plot are highlighted in red on the texture map. Figure a) shows no tumour, but the presence of contrast when density range is 900-1200 and entropy range is 2 or less. Figure b) shows tumour and contrast when density range is 900-1200 and entropy 3 or less. Figure c) shows less tumour and contrast when density is 1000-1150 and entropy is 3 or less.
The region of the elephant plot, which could be included as the sub-region could be adjusted. For example in the pre-treatment data plot for patient 16 the standard values for the ROI means tumour is not included (figure 8a). By increasing the range of entropy scores from 0 - 2 to 0 - 3, adjusting the entropy score means tumour is included in the sub region (figure 8b). Narrowing the density range from 900-1200 to 1000-1150 reduces the number of voxels in the region representing contrast, but also reduces the region representing tumour. This form of analysis needs to be repeated in a larger data set for both pre-treatment and post-treatment imaging.

Further work is required to analyse these ROIs using an assessment of how the data points relate to each other in space.

Other types of advanced analysis could also add to this. The elephant plot was deliberately kept as a 2D analysis, but a 3rd dimension could be added, other factors could be the spatial relationship as detailed above, or an analysis of the density of data points on the 2D plots. Kernel density estimation would help achieve this.

As a minimum this analysis helps localise ROIs within the lung, which could be areas of interest, and have similar appearance to tumour in terms of density and entropy. Taking patient 20 as an example of a recurrence, It is possible to identify the tumour (15.3cm$^3$) in a whole lung (2777.9cm$^3$), which contains areas of RILI (155.6cm$^3$) ten times the volume of the tumour. Larger data sets need to be analysed to better narrow down the way that RILI and tumour are arranged in space and to identify differences between the two, but this is a very promising early result.
References


Theme 2: CT based sarcopenia assessment and NSCLC

Chapter 7: Assessing weight loss in Non-Small Cell Lung Cancer

7.1. Background to theme 2

As discussed previously lung cancer occurs in a vulnerable and frail population. The previous texture analysis (TA) work in this thesis was applied to an entire lung, aiming to identify tumour and differentiate it from other tissue in the lung. Theme 2 and theme 3 in this thesis involve using TA for a different process. The work completed in theme 1 of this thesis was aiming in particular to differentiate between tumour and lung injury. Themes 2 and 3 are aiming to examine a normal tissue and see if a functional assessment can be extracted from a standard CT scan, by analysing normal tissue. CT scans are commonly used to measure anatomical features such as the dimensions of a tumour, or the site of a tumour or metastases. Simple conclusions can be drawn from imaging, to categorise organ function, for example the presence of bullae in the lung, which are essentially holes in the lung caused by the destruction of elastic tissue in the lung. This means that qualitative statements can be made about organ function, but it is difficult to make quantitative statements, that are quick in implementation and could be incorporated in the standard workflow of a radiology department.

The aims of themes 2 and 3 are to show how texture analysis (TA) can be used to provide a quantitative analysis of organ function from a CT scan. Theme 2 focuses on the investigation of weight loss in metastatic Non-Small Cell Lung Cancer (NSCLC). Theme 3 focuses on identifying lung function and differentiating between fit and unfit patients undergoing radical radiotherapy.

This section focuses on weight loss in lung cancer. Assessing weight loss in NSCLC could have several potential benefits. Firstly to see if assessing muscle loss (sarcopenia) could predict outcome, either using radiological measurements of muscle or TA. Secondly to assess the symptom burden of patients with newly diagnosed NSCLC and finally to see if there was a need for dietetic intervention for malnutrition in patients with NSCLC. No obvious previous literature was found, which incorporated an assessment of malnutrition, cachexia and sarcopenia in advanced NSCLC.
This work was completed in collaboration with the specialist Macmillan Oncology Dietetic service at St Luke’s Cancer Centre, Royal Surrey County Hospital. It includes retrospective analysis of weight loss of patients assessed by the dietetic service for advanced NSCLC, a retrospective analysis of sarcopenia in a cohort of patients with NSCLC and an analysis of the initial cohort of a prospective trial investigating rates of malnutrition, cachexia and sarcopenia in patients with advanced NSCLC. During the experimental work for this trial (DAIL trial, Dietetic Assessment and Intervention in Lung cancer) was set up. I wrote the first draft of the protocol, obtained trust sponsorship, completed the IRAS form, gained funding and achieved ethical approval for the trial. The trial opened at the Royal Surrey County Hospital. The trial is on the NIHR portfolio and reports regularly to the National Cancer Research Institute (NCRI) Lung Cancer Clinical Studies Group.

In summary this chapter illustrates that cachexia (5% or greater weight loss) at the time of dietitian review leads to a significantly poorer overall survival (7.4.1, experiment 1), it shows that the presence of sarcopenia at diagnosis leads to a poorer outcome in lung cancer (7.4.2, experiment 2) and that sarcopenia is assessable in a prospective trial and that a TA measure is statistically significantly associated with sarcopenia in advanced lung cancer (7.5.2).

**7.2 Understanding weight loss: Malnutrition, Sarcopenia and Cachexia**

This section focuses on weight loss in advanced, i.e. incurable, NSCLC. Lung cancer is the second commonest cancer diagnosed in the UK in both men and women. Lung cancer is caused by smoking and occurs in a vulnerable population. Smoking and lung cancer are a disease of poverty (Li et al., 2015, Cooley and Jennings-Dozier, 1998, Gadgeel and Kalemkerian, 2003, Gadgeel et al., 2001) and the risk of lung cancer is inversely proportional to socio-economic status. As well as greater active smoking behaviour, this population is more likely to be exposed to other risk factors such as higher passive smoking rates, occupational exposure, less healthy diets and occupational/environmental carcinogens (Cooley and Jennings-Dozier, 1998). An example of this can be seen in the UK, where it is estimated there would be 9,900 fewer cases of lung cancer if those worst off had the same incidence of lung cancer as the least deprived section of society (taskforce, 2015). As the majority of patients with NSCLC were smokers, many will also have multiple co-morbidities also caused by smoking. These conditions include Ischaemic Heart Disease, Chronic Obstructive Pulmonary
Disease (COPD) and other primary cancers such as bladder cancer. Recent data suggests that nearly a fifth (18%) of patients had 4 or more co-morbidities (Gould et al., 2017). Lung cancer is more common in older patients and the numbers of cases are rising in this population. More than 80% of new cases of lung cancer are diagnosed in the over 60s and more than 40% are diagnosed in men and women over 75 years. The number of cases of lung cancer in over 60’s is rising (Foundation, 2017), particularly in those aged 81 or older, where cases have risen by nearly 1.5 times from 446 per 100,000 in 2004 to 666 per 100,000 in 2012 (Foundation, 2017).

All of the risk factors identified in the paragraph above show that patients with incurable NSCLC have a lot of risk factors for being less fit and frailer. Patient fitness for systemic anti-cancer treatment is made up of many factors, many of these e.g. stage of cancer, the patient is not able to directly influence. Ensuring adequate nutrition is one element that patients can directly influence in the management of their cancer. Others potentially include exercise, physical fitness and psychological factors.

The work in this chapter relates to investigating weight loss in NSCLC and its effects. Weight loss is a broad term that encompasses three different entities. In clinical practice these terms may be used interchangeably, however, in this context it is important to understand where these syndromes overlap and where they are distinct. Malnutrition is weight loss due to inadequate calorific intake, cachexia is an inflammatory metabolic syndrome leading to loss of muscle and possibly fat despite adequate nutrition and sarcopenia is specifically the loss of muscle bulk, muscle function and overall function. These syndromes can occur in other non-malignant medical conditions and sarcopenia can occur as a physiological process as part of aging.

Malnutrition can be defined as a state of nutritional imbalance leading to negative effects on weight and function (Fearon et al., 2011). Cancer cachexia differs from malnutrition as it occurs despite adequate nutrition. Cachexia is defined as 5% or greater weight loss from usual body weight (in absence of starvation) within 6 months, or 2% weight loss with either sarcopenia or a body mass index (BMI) of less than 20 (Fearon et al., 2011, Blum et al., 2014). Refractory (irreversible) cachexia is a marker of poor prognosis and is defined as a survival of less than 90 days. Cachexia is a progressive disorder, leading to decreased physical activity,
adverse psychological side effects, poor performance status and higher mortality rates. The stages of cachexia are illustrated in figure 1. Pre-cachexia is defined as weight loss of 5% or less with accompanying anorexia and metabolic change. Patients with sarcopenia can also have cachexia, depending on the degree of muscle loss. Sarcopenia is defined as a loss of muscle mass and function, leading to the risk of adverse outcomes (Cruz-Jentoft et al., 2010, Muscaritoli et al., 2010, Fielding et al., 2011).

Figure 1. Diagram showing the 3 stages of cachexia, from Fearon et al (Fearon et al., 2011)

### 7.3 Current understanding of weight loss in NSCLC

Patients with NSCLC have co-morbidities, which before a diagnosis of NSCLC can influence their nutritional state. These conditions can cause nutritional deficits independent of a diagnosis of cancer. Malnutrition is common in COPD (Collins et al., 2016, Vermeeren et al., 2006) and is associated with decreased physical work load (Budweiser et al., 2008). A recent study suggests 22% are malnourished. Symptoms associated with COPD include a dry mouth, pain and constipation and all can impact on nutritional status. Patients with more significant fat free mass depletion are more likely to have these symptoms (Norden et al., 2015) and lower muscle mass has been correlated with poor respiratory function (Jeon et al., 2015). Malnutrition has also been associated with poorer outcome in patients with Coronary Artery Disease (Kunimura et al., 2017).

Patients may have a nutritional deficit before being diagnosed with cancer, however, in addition weight loss is common in patients with cancer. In a study of 1,000 patients with locally advanced or metastatic cancer, more than a third had significant weight loss (defined
as greater than 10% weight loss) (Bozzetti and Group, 2009). Twelve percent of patients in this study had lung cancer with a median rate of significant weight loss of 6.6%. As stage of cancer and performance status worsened, so did percentage weight loss.

There are relatively few studies assessing malnutrition in lung cancer [62]. Pre-treatment nutritional assessment has shown that malnutrition is common in lung cancer patients, with an incidence of between 35% and 65% (Kiss et al., 2014a, Percival et al., 2013, Li et al., 2011). There are a number of assessment tools that have been used to identify malnutrition. One is the Mini-Nutritional Assessment (MNA), which has identified that two thirds of patients with metastatic lung cancer are either at risk of malnutrition or are malnourished (Gioulbasanis et al., 2011). The MNA outcome correlated with overall survival. The Subjective Global Assessment is another recognised tool for assessing nutritional status (Detsky et al., 1987), which has been adapted to form the Patient Generated Subjective Global Assessment (PG-SGA) for use in patients with cancer (Jager-Wittenaar and Ottery, 2017). The PG-SGA is useful as it is a multi faceted tool, it aids determination of weight loss, changes in food intake, symptoms of nutrition alterations, limitations of function, presence of metabolic stress and a physical examination. In a study using the PG-SGA 40% of patients with metastatic lung cancer were malnourished and a further 40% were at risk of malnutrition (Li et al., 2011). Patients who were defined as malnourished had an overall survival of 9 months vs 17 months in well-nourished patients in advanced NSCLC. A range of studies have shown that malnutrition is associated with negative clinical outcomes in patients with cancer in general, including poorer quality of life, decreased functional status, increased utilisation of health care services and poorer survival (Kiss et al., 2014a).

A series of studies have assessed nutritional status in surgical patients with NSCLC suitable for radical treatment. Malnutrition was found to be a significant risk factor for early death, in patients’ aged 70 years or older undergoing resection of a primary lung tumour. The cohort was divided into two groups, those that were underweight (BMI <18.5kg/m², Group A, 21 patients) and those that were not underweight (BMI 18.5kg/m² or greater, Group B, 96 patients). BMI and weight loss of 5% or greater before surgery were independent risk factors for 1 year mortality (Fiorelli et al., 2014). In patients undergoing pneumonectomy for lung cancer, 33 of 86 patients were found to have malnutrition. This was assessed using biological
markers of nutrition including albumin and transthyretin (Bagan et al., 2013). In contrast, a study enrolling 146 patients irrespective of age suggested that BMI and surgical outcome did not obviously correlate, however only 109 of 146 patients underwent surgery, patients not undergoing surgery were not included in the analysis (Win et al., 2007). Poor nutritional status and increased mortality has been associated with non-oncological thoracic surgery, such as lung transplantation (Shah and Orens, 2013). As well as assessment tools, functional and imaging measures can assess nutritional status. The correlation between decreased handgrip status and malnutrition has been established in patients with potentially operable NSCLC [67]. In terms of sarcopenia, patients with sufficient muscle loss to be sarcopenic, had a poorer survival when undergoing surgery for stage 1 NSCLC (Tsukioka et al., 2017). In this study, sarcopenia was assessed by measuring the anterior-posterior and medial-lateral diameters of the psoas muscle. These were then multiplied by each other to calculate the surface area and standardised for height. This technique has approved thresholds. If the muscle surface area standardised for height is below the threshold the patient would be regarded as sarcopenic (<55cm² for males and 39cm² for females).

In patients receiving radiotherapy for lung cancer, a retrospective review of 96 patients has shown that 31% lost 5% or more of their usual total body weight (Kiss et al., 2014a). This was more likely if the patients had more advanced disease, or radiotherapy was given with chemotherapy. The dose of radiotherapy to the oesophagus during high dose palliative or radical lung radiotherapy predicted for weight loss. The maximum dose to the oesophagus predicted for weight loss of 5% of greater. A recent study has found that in patients undergoing chemo-radiotherapy for NSCLC, poor performance, low BMI and low muscle attenuation predicted for adverse outcomes (Bowden et al., 2017). BMI is a relatively insensitive marker of weight loss, as a result for many patients it would require a substantial loss of weight to alter their BMI. Of note, this study had a 90 day mortality rate of 11%, which could be regarded as high and could influence their results.

The study by Bowden et al specifically looked at muscle appearance on CT scan. It was found that low muscle attenuation was an independent prognosticator for overall survival. Low muscle attenuation was thought to be myosteatosis, which was the infiltration of muscle tissue by fat (Bowden et al., 2017). This is associated with skeletal muscle wasting, but as with
sarcopenia can be associated with older age, obesity and non-malignant disease. Sarcopenia has been associated with poorer outcome in metastatic renal cell cancer and patients undergoing radical surgery for oesophageal cancer (Nakashima et al., 2017).

In terms of intervening to improve outcomes in lung cancer, randomising patients to dietary advice +/- nutritional supplements did not show a significant benefit, however compliance with the nutritional supplements and completing food diaries was low (Baldwin et al., 2011). A systematic review of dietetic intervention in advanced cancer suggests that intervening can have a positive effect on weight and calorific intake, but study heterogeneity makes it difficult to prove this conclusively (Balstad et al., 2014). Chemotherapy may improve muscle mass in advanced lung cancer (Stene et al., 2015). The lack of definitive benefit in some studies may be in part due to short follow up, analysis of patients with lung cancer along with other tumour types and difficulties in patients reaching adequate calorific intake (Kiss et al., 2014b). A systematic review of exercise and nutrition strategies published in 2013, suggests that they are not harmful and may have beneficial effects on unintentional weight loss for patients with advanced lung cancer. Only 203 patients from 5 studies were included in this analysis, of which only 3 were assessing nutrition. All 3 studies investigated use of a specific supplement rather than the impact of a nutritional assessment (Payne et al., 2013).

Early intervention in metastatic lung cancer shows improved outcomes, a pre-treatment palliative care assessment has been shown to improve overall survival (11.6 months vs 8.9 months) in advanced lung cancer when compared to standard intervention (Temel et al., 2010). This includes identifying malnutrition and addressing nutritional deficits, which can affect a patient’s fitness for treatment. It is interesting to note that the use of dietary supplements did not improve outcome. For example in the trial by Baldwin et al compliance with supplements was 31% in the first week and had declined to 19% in week 6 (Baldwin et al., 2011). This suggests that simply prescribing supplements is ineffective as a simple intervention. As previously discussed patients with advanced NSCLC are likely to have complex symptomatology, this may be why an early palliative care review improves survival. For example a palliative care review for a patient in pain rather than simply providing analgesia allows a nuanced approach that can be individually tailored to the patient, where as providing a strong analgesic lacks any of that subtlety. The limitations of prescribing a drug
without reviewing the patient may include not being educated adequately on how to take it appropriately, may not tolerate it or find its application difficult. The same can be argued for patients who have lost weight. Food intake is one of the few interventions under the control of the patient, they may be intolerant of the supplement, may struggle to eat/swallow it, may have dietary restrictions contra-indicating its use or simply not like the taste. Health beliefs around food may also be complex. A dietetic review can provide the same subtlety for a patient’s calorific intake, as a palliative care review can for pain. Many of the studies have used a supplement, rather than a more complex approach.

Although malnutrition, cachexia and sarcopenia inter-relate these are distinct entities. The aim of this experimental work was to identify how commonly these occur in patients with advanced NSCLC and explain the relationship between them. Whilst screening assessment and prophylactic nutritional support is standard practice for patients with primary cancers of the head and neck and upper GI tract region, this is not the case for those with lung cancer, despite often being a vulnerable, frail patient group with multiple co-morbidities, as well as the fact that exposure to alcohol and tobacco may be similar to those with primary head and neck cancers. Recent ESPEN guidelines have suggested that nutritional screening should be performed at the time of a cancer diagnosis, however, there is a low level of evidence to support this recommendation (Arends et al., 2016). My work aims to add to this knowledge base. I also wanted to understand certain factors including the proportion of patients presenting malnourished, cachectic and sarcopenic with advanced NSCLC. I wanted to identify the proportion of patients who need to see a dietitian pre-treatment, to consider whether this should be standard practice. Overall the key aim of this project was to understand whether sarcopenia identifies those at risk of cachexia and refractory cachexia much earlier, meaning intervention can happen earlier.
7.4 Preliminary experimental work in patients with NSCLC

7.4.1 Experiment 1: Does more than 5% weight loss from usual body weight lead to a poorer outcome? A retrospective review of patients seen by specialist Oncology dietetics service at Royal Surrey County

**Aim:** To identify whether weight loss at time of dietetic review was associated with poorer survival in patients with metastatic NSCLC? Standard practice at St Luke’s Cancer Centre is for health care professional-guided referrals to a Macmillan Oncology Dietitian, this can occur at any time during a patient’s cancer pathway, potentially before, during or after radical or palliative treatment.

**Methods:** As part of the dietetic service, a large database of weight change in patients reviewed by the dietetic team is collected prospectively. In collaboration with the dietitians, the oncology outcome database was interrogated, only patients with metastatic NSCLC were included, any patients with other types of cancer and those with early stage or locally advanced NSCLC were excluded. Percentage weight change was calculated. This data only included patients who had been assessed in person by a Macmillan Oncology Dietitian and so needed to be well enough to attend the hospital for that assessment. Patients were defined as (per the international definition) cachectic if they had lost more than 5% from their usual body weight in the last six months, as recorded on the database (Fearon et al., 2011). The NHS spine was used to identify those patients who had died. Overall survival for cachectic and non-cachectic patients was identified.

**Results and Discussion:** This cohort study showed that cachexia is a significant problem in advanced lung cancer and has an impact on overall survival. It is important to recognize that there maybe a selection bias as only patients seen by the dietetic service were included in this analysis. The vast majority of patients (76%) lost more than 5% of their usual total body weight at the time they were first seen by a Dietitian. Overall survival from time of dietitian review was significantly worse in patients with cachexia vs patients without cachexia (188 days vs 299 days, p=0.0078) (Hug, 2017). In a cohort whose median survival is 6-12 months, the
difference of more than 3 months is significant, however, there may be other factors such as
time to dietitian review, performance status, previous anti-cancer treatment and stage of
disease. Figure 2 shows % weight change in this cohort, patient by patient, it shows that some
patients lost very noteworthy amounts of weight. In this cohort, the median weight change
was -9.4% (range 7.3% to -35.8%).

This study also showed that percentage loss of total body weight is more sensitive than BMI.
In our study, we saw mean BMI decrease from 26.9kg/m² to 23.2 kg/m² (BMI range at time of
review 13.3-62 kg/m²) which is still within the healthy range of 20.0kg/m² – 25.0kg/m².
Therefore using BMI to determine malnutrition and cachexia in lung cancer patients would
not be a true reflection of this population. Other studies have shown that high BMI correlates
with survival, but this means a patient would need to lose a large amount of weight to lower
their BMI, data for the thesis supports the fact that change in BMI is relatively insensitive to
weight loss (Bowden et al., 2017).

![Graph showing a waterfall plot of % weight change by patient. Patients to the left of
the red line have lost more than 5% of usual body weight and were defined as cachectic. 76%
of patients were cachectic in this cohort.](image)
All patients were well enough to attend the cancer centre. 85% (264) of patients were receiving chemotherapy when referred to the dietitian. This data suggests that cachexia is a significant issue in patients receiving active palliative anti-cancer treatment.

Although Performance Status (PS) was not routinely recorded, the fact that patients were receiving chemotherapy with palliative intent suggests their PS was 2 or fitter when treatment was initiated.

This study shows that many patients with metastatic NSCLC lose a lot of weight and the majority are cachectic at the time they are reviewed by an oncology dietitian, it suggests how major weight loss in terms of refractory cachexia impacts on survival. This study was a very helpful starting point in identifying there was a need to further investigate weight loss in this population. The retrospective nature of this project illustrated its major limitation, which was that the time point of dietetic assessment was not consistent in the patient’s journey through diagnosis and treatment. The patients were reviewed when a health professional felt the patient needed to be seen by a dietitian. This lack of consistency would need to be remedied in future work. From this data, it was also not clear whether patients would have been cachectic at diagnosis, or whether this was a phenomenon that developed during treatment, or whether both scenarios could have occurred.
Figure 3: Kaplan-Meier curve showing overall survival for patients with NSCLC classed as those with cachexia or without cachexia. Median survival for cachectic patients was 188 days and 299 days for non-cachectic patients. X= axis time in days.

This cohort data is limited by the fact that TNM staging and tissue type were not routinely recorded, and that usual body weight was self-reported by patients. It did not record the date of diagnosis and so there is likely to be variability in time between date of diagnosis and date of referral to the dietitian. This has the potential to introduce a source of lead time bias, if more weight is lost as more time passes since diagnosis, it could suggest an artificial relationship between weight loss and survival in advanced NSCLC. Although the time point may have been inconsistent, cachexia could have been under-estimated in this cohort as it did not include patients who had lost 2-5% of usual body weight and had co-existing sarcopenia or a BMI below 20. It may underestimate the rate of cachexia in this population, as sarcopenia is common in lung cancer (Stene et al., 2015).

In summary, it was felt that this work highlighted an important area of further investigation. Future work would assess patients at the same time point, the most consistent time point was felt to be diagnosis.
7.4.2 Experiment 2: Is sarcopenia associated in a poorer outcome in NSCLC?

**Aim:** Sarcopenia is a loss of muscle mass and function, in combination with an overall decrease in function. There are multiple ways to assess sarcopenia, this can be radiological or functional in nature. Previous published data has shown that sarcopenia occurred in 14% of patients with stage 1 NSCLC (Tsukioka et al., 2017), when it was assessed by calculating the surface area of the psoas muscle (standardised for height), although in this study sarcopenia did not predict for post-operative complications, it did predict for grade 3 or greater toxicities in patient undergoing surgery for bowel cancer (Jones et al., 2015)

**Methods:** All patients from a lung MDT from July 2012-December 2013 with biopsy proven NSCLC were included. Patients were categorised by age and treatment, the overall data was presented separately (Ezhil, 2016). From this cohort all patients were included who met 2 criteria, firstly patients who had available imaging on the electronic PACS system, which included the transverse processes of the third lumbar vertebra and secondly a formally documented height measurement, available either from chemotherapy records or formal lung function testing.

![Image](image.png)

*Figure 4, example anterior-posterior and medial-lateral measurement of the left and right psoas muscle. The left psoas muscle is outlined in green and the right psoas muscle is outlined in magenta.*
This methodology had been previously tested in peer reviewed literature in early stage lung cancer and colo-rectal cancer (Tsukioka et al., 2017, Jones et al., 2015). The psoas muscle was measured in cm at the widest point anterior-posteriorly (AP) and medial-laterally (ML), at the level of L3 transverse process. The measurements were taken with the measuring line vertical for AP measurements and horizontal for the ML measurements. These measurements were multiplied by each other and divided by the patient’s height (metres). An average was then generated from the left and right psoas muscle. A man with a standardised measurement of less than 55cm²/m² and a women with a measurement of less than 39cm²/m² were considered sarcopenic. An example measurement is seen in figure 4.

**Experiment 2 Results and Discussion:**

Figure 5: Survival curve of sarcopenic vs non sarcopenic patients with Non Small Cell Lung Cancer. P=0.22, there was not a statistically significant difference between the 2 groups. X axis = time in months.
90 patients were identified who met the criteria for this study. 56% were male and 44% female. The mean age was 73 (range 41-88). The median survival of the non-sarcopenic cohort was 15 months vs 12 months (p=0.22) for the sarcopenic cohort, the survival curve is shown in figure 5. Nearly half (47%) of patients were sarcopenic at the time of their diagnostic scan (Phillips et al., 2016).

Although it did not meet statistical significance, sarcopenia is common in NSCLC and appears to be a biomarker of poorer survival. This cohort did include patients with a range of stages of NSCLC. This study did not standardize for stage of disease, age or treatment received, but was aimed to be hypothesis generating in terms of whether assessing patients with lung cancer was possible and practical. The cohort was standardised by time of assessment of sarcopenia, all patients had the assessment on pre-treatment CT imaging either from a diagnostic CT scan or the CT component of the PET-CT scan. The only major difference between the 2 scans was the use of either IV contrast or IV FDG radioactive tracer. This was not felt to have an effect on the sarcopenia assessment as it was measuring muscle dimension.

This study suggests that sarcopenia could be a biomarker for poor outcome in NSCLC cancer and requires further investigation. As an assessment, measuring the psoas muscle is simple, quick, but requires time for trained staff to measure the psoas muscle accurately in a reproducible way. This study shows that it is possible for sarcopenia to be performed on multiple patients (Phillips et al., 2016).
7.5 Conclusions from retrospective work on weight loss in NSCLC

The two experiments on cachexia (defined by weight loss) and sarcopenia both show that weight loss in lung cancer influences outcome. It appears that sarcopenia is a potential biomarker for decreased overall survival. This work also shows that many patients experience weight loss by the time they are reviewed by a dietitian after a diagnosis of NSCLC.

Treating cachexia is difficult, although appetite stimulation or nutritional support can help slow the loss of muscle mass, improve quality of life and reduce malnutrition. Treating symptoms such as nausea and pain can also help improve nutritional status as can graded physical activity. New agents such as ghrelin analogues offer a glimpse of more innovative treatments of cachexia (Temel et al., 2016).

There is some evidence that dietary counseling and nutritional supplements may ameliorate the effects of radiotherapy and chemotherapy, although the exact benefit is not clear. The lack of definitive benefit in these studies may be in part due to short follow up, analysis of patients with lung cancer with other tumour types and difficulties in patients reaching adequate calorific intake (Kiss et al., 2014b). Other studies including patients with advanced lung cancer have not found a benefit in early nutritional advice or use of supplements (Baldwin et al., 2011).

Whilst screening, assessment and prophylactic nutrition support is standard practice for patients with primary cancers of the head and neck region, this is not the case for those with lung cancer. More research is needed to identify the rate of pre-treatment cachexia in NSCLC and then how to implement tools that may improve outcome.

This study shows that cachexia in patients with advanced lung cancer is very common. Many patients with lung cancer are older and can have multiple co-morbidities. As a result, they are a more vulnerable and less fit population and require significant multi-disciplinary support.

This retrospective work aimed to identify potential problems and pitfalls, before considering a prospective cohort study. The high cachexia rate is a compelling argument for further
investigation of nutritional support in lung cancer. As it was difficult to know when weight loss occurred, it was felt that a prospective study including patients at diagnosis would be helpful, to answer the question of whether malnutrition, cachexia or sarcopenia were present at diagnosis or develop later in the disease pathway. In terms of the effect of possible interventions, it was felt it was difficult to predict the proportion of patients who may present with weight loss. This meant it was difficult to complete any sample size calculations. It was also not clear how easy it would be to complete a range of assessments within normal clinical practice. For these reasons it was felt that a pilot study would answer many of these questions and help frame a more accurate clinical question for a randomised control trial.
7.6 DAIL trial (Dietetic Assessment and Intervention in Lung cancer)

7.6.1 Development of the DAIL trial

The trial idea was developed in collaboration with specialist oncology dietitians at the Royal Surrey County Hospital. I presented the trial concept at 2 national oncology clinical trials meetings. Firstly at the National Cancer Research Institute (NCRI) and British Thoracic Oncology Group (BTOG) meeting Clinical trials day in 2016, then to gain patient input it was presented at the NCRI conference ‘Dragons Den’. The idea received support at these meetings. A small amount of funding was obtained in open competition from Chugai. The trial had a successful application to be entered to the National Institute for Health Research (NIHR) clinical trials portfolio.

The final design was a cohort study of patients with incurable NSCLC (defined as stage IIIB or IV). Patients would have a single visit where they undergo a range of assessments. More detail can be found in appendix 3 which includes both the trial protocol and the Patient Information Sheet (PIS).

7.6.2 DAIL trial methodology

The aim of the DAIL (Dietetic Assessment and Intervention in Lung cancer) is to recruit 100 patients according to the inclusion and exclusion criteria below, to complete a range of assessments of weight loss, malnutrition, cachexia and sarcopenia detailed in table 1.

DAIL trial objectives and inclusion/exclusion criteria

Primary Objectives

- To identify the proportion of patients diagnosed with advanced Non-Small Cell Lung Cancer who are malnourished, cachectic and have sarcopenia before anti-cancer treatment.
- To identify the proportion of lung cancer patients who would require dietetic review before anti-cancer treatment.
Secondary Objectives

- To identify whether malnutrition, cachexia and sarcopenia affect overall survival in advanced NSCLC.
- To identify whether sarcopenia predicts for a poor outcome in NSCLC

Inclusion Criteria

- Patients >18 years old who are able to consent to entry into a clinical trial
- Biopsy confirmed Advanced Non Small Cell Lung Cancer (stage IIIb and IV).
- Patient receiving first line anti-cancer treatment

Exclusion Criteria

- Patient declines anti-cancer treatment
- Inability to consent to treatment

The following assessments would be completed by each participant in the trial:

- PG-SGA (malnutrition assessment)
- Charlson Co-morbidity Index (assessment of other medical conditions that the patient has)
- EORTC QLQ C30 core module and LC13 lung cancer module (comprehensive quality of life assessment)
- ECOG performance Status (simple assessment of a patient’s activity level)
- SPARC assessment (2nd comprehensive quality of life assessment)
- Spirometry (respiratory function assessment)
- Hand grip strength (physical function assessment)
- Weight and BMI (based on standard weight and height measurements)
- Routine blood tests (FBC, U+E, LFT)
- Advanced analysis of patients standard diagnostic CT imaging.

7.6.3 Initial analysis of the first 11 patients from the DAIL trial
This analysis is an initial analysis of the DAIL trial. It had 2 aims. Firstly to ensure that completing the assessments outlined in section 7.6.2 was practicable and did not raise any obvious concerns. It includes the first 11 patients included in the DAIL trial. As a result a lot of the statistics are descriptive in nature as it is difficult to draw conclusions on a small proportion of the total trial.

All patients had all of the standard assessments, with the exception of 1 patient not completing hand grip strength. Patients did not obviously object to any of the paper based questionnaires or physical assessments. The co-investigators carrying out data collection felt that the assessments were completed in approximately 30 minutes and this was manageable. If the PG-SGA assessment indicated that the patient required dietetic review, this was completed after the trial assessments were complete. This increased the contact time with each patient to 45 minutes.

1 of 11 patients required review by the dietitian. Imaging was available for all 11 patients. Mean age was 66.3 years (range 53-75 years). 5 patients (45%) were male and 6 (55%) were female. 8 of 11 (73%) were sarcopenic on their diagnostic imaging. 2 patients had a low BMI (defined as under 20.0) and both of those patients were sarcopenic. None of the patients felt they had lost a noteworthy amount of weight in the previous 6 months.

7.6.3.1 Functional assessments
It is difficult to generate conclusions from such a small cohort, however, some initial comparisons were made. Standardised psoas muscle surface area was compared to both hand grip strength (Pearsons correlation co-efficient = 0.27, t-test sarcopenic vs non-sarcopenic p=0.47) and FEV1 (correlation co-efficient =-0.55, t-test sarcopenic vs non-sarcopenic p=0.41).

7.6.3.2 Co-morbidities
8 of 11 patients scored 0 in the Charlson Co-morbidity index, meaning that other than the NSCLC, patients do not have any co-morbidities. The index I used was used in a previous study I contributed to(Okonji et al., 2017). Of the 3 patients that identified co-morbidities, 2 had both COPD and a non-lung malignant tumour, the other patient had diabetes. Of note 8
of 11 met the gold criteria for at least mild COPD (FEV1 <80% predicted), despite the fact that only 2 of the 11 reported they had COPD (Luize et al., 2014). Under-diagnosis of COPD fits with previously published data (Hill et al., 2010). In this study 1003 patients over 40 with more than a 20 pack year smoking history were screened for COPD with spirometry, defined as a FEV1/FVC ratio of <0.7 and an FEV1 of less than 80% predicted. 205 participants had COPD and only 67 (32%) of those with COPD were aware of their diagnosis.

7.6.3.3 Assessing sarcopenia by measuring psoas muscle surface area standardized to height

**Aim:** To see whether patients with advanced NSCLC were sarcopenic at diagnosis by assessing the surface area of the psoas muscle.

**Methods:** This method had been previously used in assessing sarcopenia as described in section 7.4.2 (Jones et al., 2015, Tsukioka et al., 2017, Phillips et al., 2016). The anterior-posterior and medial-lateral measurements were multiplied by each other and divided by the patients height. The result was then compared to the international definition established by Fearon et al, sarcopenia value for males was 55cm$^2$ and for females 39cm$^2$.

**Results:** All 11 patients had suitable, available imaging in order to measure the dimensions of the psoas muscle. Psoas surface measurements ranged from 23.0cm$^2$ to 72.3cm$^2$. 8 patients were sarcopenic, 3 were not.

**Discussion:** This experiment showed that sarcopenia is prevalent in patients with advanced NSCLC before treatment starts. Further follow up within the DAIL trial will indicate whether it has the potential to be a useful biomarker.

7.6.3.4 Texture analysis of the psoas muscle

**Aim:** The aim of this preliminary analysis was to see if it was possible to differentiate between sarcopenic patients and non-sarcopenic patients using texture analysis rather than by measuring the standardized surface area of the muscle.
**Methods:** The psoas muscle was identified and a volume generated to include all of the psoas muscle from the superior to the inferior borders of the third lumbar vertebrae in Eclipse radiotherapy planning software. This scan was exported from eclipse into CERR (Computational Environment for Radiotherapy Research). Left and right psoas muscle regions of interest were segmented from the image in Matlab. The segmented region of interest underwent analysis using finiteRT, using the method identified in experiment 1 chapter 4. The TA is a voxel by voxel comparison of the Region of Interest (ROI) by assessing the Grey Level Co-Occurrence Matrices (GLCM) of the 26 voxels around the voxel of interest. For each patient the left and right psoas were analysed as separate structures.

From previous work highlighted in theme 1 and subsequently in theme 3, three types of analysis were to be carried out. Firstly to compare the mean, median and mode of density and entropy for each patient. Secondly to compare the appearance of the data plots for sarcopenic and non-sarcopenic patients. Thirdly to further interpret the data plots using a measure of density of the data points, in this case using kernel density estimation.

**Results:** 9 patients had available imaging for assessment. 7 patients had the L3 vertebra imaged on a diagnostic CT scan and 2 had the imaging on the CT of an FDG PET-CT. Where possible the diagnostic CT was chosen in preference to the CT from the PET-CT as it would not be routine for patients with advanced NSCLC to have a FDG PET-CT scan.
Table 1: Textural analysis of a segment of left and right psoas muscle in sarcopenic and non-sarcopenic patients. Patients 1-6 are sarcopenic, patients 7-9 are not sarcopenic. Entropy mode is statistically significant different between sarcopenic and non-sarcopenic patients with advanced NSCLC.

Of these 9 patients, 3 were sarcopenic based on the surface area of the psoas muscle at the level of L3. The results are presented in table 1.

**Discussion:** Texture analysis on psoas muscle is possible. This analysis used individualised quantisation. In the analysis of each structure the LMQ was used to aid quantisation, meaning the absolute values of the quantisation levels are different. For uniform quantisation it is not clear whether it should be based on an analysis of non-sarcopenic patients with or without cancer, or from a PET-CT or diagnostic CT.

It is interesting that the T-test comparing texture markers of sarcopenic and non-sarcopenic muscle reaches statistical significance, seen in table 1, however these results are purely for generating a hypothesis. It is essential that statistical tests are completed on the whole DAIL cohort. Table 1 shows that the values obtained from the left and right psoas muscle act as an internal control for the process and are broadly similar. This experiment aimed to see if
TA was feasible, rather than to identify specific outcomes with such a small cohort of patients. It will potentially be further tested when the DAIL trial has completed recruitment.

### 7.7 Summary

This work has shown that cachexia is common in patients with NSCLC and that sarcopenia is common at diagnosis in NSCLC. Sarcopenia was present on diagnostic imaging in 47% (irrespective of stage) in experiment 2 and in 73% of those with advanced (stage IIIb and IV) NSCLC in the early analysis of the DAIL trial (Phillips et al., 2016). The fact that all patients in the DAIL trial had incurable NSCLC is likely to account for the higher rate of sarcopenia. It will be important to see if sarcopenia is a marker of poor outcome in advanced NSCLC.

The DAIL trial will continue to recruit and the aim is to produce a final analysis to assess the primary and secondary outcomes as detailed above.

Weight loss is becoming more important in cancers. Dietetic intervention is established in cancers of the upper GI tract and primary head and neck cancers. Tools to assess whether a patient has malnutrition exist, such as the PG-SGA. This study will help to identify whether a PG-SGA should become part of the standard pre-treatment assessment of patients with advanced NSCLC.

The presence of cachexia and sarcopenia is likely to become substantially more relevant with the development of novel therapeutic options. In the same way that growth factor stimulating medications and bisphosphonates have changed the way neutropenia and bone metastases are managed, the development of systemic therapies for cachexia is likely to change the landscape in terms of how we approach weight loss. Reversing cachexia and sarcopenia cannot be done by nutritional intervention alone.

The trial published by Temel et al. has shown that in patients with cachexia defined as more than 5% weight loss or BMI<20kg/m2 in patients with NSCLC, anamorelin can increase lean muscle mass in the short term, however it does not appear to improve handgrip strength (Temel et al., 2016). Anamorelin is a ghrelin analogue of the ghrelin ligand. It stimulates the ghrelin receptor, which stimulates appetite and has anabolic effects. It achieved this with minimal toxicity, in comparison with previously tested therapies including progestins such as
megestrol acetate. Megestrol improved appetite, but not weight and had a risk of significant side effects including oedema, thrombo-embolic events and an increased risk of death (Ruiz Garcia et al., 2013).

The most striking feature of the sub-group analysis in the anamorelin trial is that the treatment caused statistically significant weight change in patients with a BMI above 18.5 rather below 18.5, PS 0-1 rather than PS 2, in younger patients and in those who did not receive anti-cancer treatment in the form of chemotherapy or radiotherapy. This may suggest that intervening with anamorelin to treat cachexia may be most effective earlier in younger, fitter patients. Other new agents are also potentially available to treat cachexia, enobosarm is a non-steroidal selective androgen receptor modulator (SARM), which in phase 2 trials has shown increase in lean body mass and physical function, this is being tested in phase 3 clinical trials (Dobs et al., 2013, Crawford et al., 2016).
Future work

As data for systemic therapies matures it is likely that biomarkers such as muscle surface area assessment or texture analysis of the muscle be used maybe able to triage patients with weight loss. Defining cachexia using weight loss from usual body weight is subjective and may be inaccurate. Defining weight loss by BMI is an insensitive assessment of weight loss as shown previously in this chapter. Both muscle surface area assessment and texture analysis require further testing, to see if these assessments may help identify suitable patients for systemic therapy for cachexia. It is not clear how closely sarcopenia and weight loss are and whether dietetic intervention may aid both conditions. The DAIL trial will attempt to establish to what degree those with sarcopenia overlap with those who have lost weight with NSCLC. It is also not clear how these conditions change during treatment.

It is likely that new systemic therapies to treat cachexia, if efficacious, will mean that cachexia becomes more relevant, in terms of routinely assessing a wider range of patients for cancer related weight loss. It is likely to change how oncologists perceive cachexia, as it becomes more treatable, in the same way that 5HT3 antagonists have affected chemotherapy induced nausea, or bisphosphonates have affected malignant bone disease.
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Theme 3: Lung function and predicting fitness for radiotherapy from a CT scan

Chapter 8: TEAL (TExtural Analysis and Lung function) study: Predicting lung fitness for radiotherapy from a CT scan.

8.1 Background

The third theme of this thesis is to explore a method used to differentiate between ‘fit’ and ‘unfit’ patients receiving radical radiotherapy for a lung tumour, using data from a standard radiotherapy 4DCT scan of the lungs. This is a novel approach, which does not require extra data and uses standard images generated for radiotherapy planning.

This chapter outlines the background, methodology and results of analysing a small cylinder of lung tissue and correlating it with lung fitness for radiotherapy. It shows that when comparing density and entropy scores for a cohort of fit and unfit patients, there are statistically significant differences. This means that TA could be used as a screening test for fitness for radiotherapy, it may help identify lung fitness in a resource limited setting or a setting where accessing more complex lung function tests, such as gas transfer may be difficult. It could become part of a minimum data set of assessments of fitness, for example assessing lung function using the method below and assessing for sarcopenia through psoas muscle surface area assessment.

CT scans are ubiquitous in managing patients with lung cancer. They are important in staging, radiotherapy planning and assessing treatment response. The major advantages of CT imaging are that it is accessible, relatively inexpensive, quick and there is a great deal of expertise in CT interpretation. CT imaging is quicker and often more tolerable than MRI and PET-CT. It delivers a smaller dose of radiation to the patient, when compared to a PET-CT scan and does not require normoglycaemia. A single CT scan may be the only imaging a patient with metastatic lung cancer would receive before starting treatment.

Within the management of lung cancer, CT scans are commonly used in a relatively simple assessment of measuring tumour size or site, for staging or to determine a treatment response. A patient with lung cancer may have a large number of CT scans during the management of their disease. This imaging represents a pool of potential information that
could be extracted and interpreted, extracting extra data from imaging is termed radiomics. Textural Analysis (TA) is a subtype of radiomics, based on mathematical derivations rather than prior clinical concepts (Materka, 1998). TA uses a range of mathematically calculated features to describe an image or region of an image (often a tumour (Phillips et al., 2017)).

The vast majority of TA used to assess images from patients with lung cancer has been used to assess malignant tissue, however CT data can used to assess normal tissue. For example cardiac CT is able to detect global left ventricular function and was able to assess cardiac wall motion abnormalities with a sensitivity of 90% and specificity of 97% (Kaniewska et al., 2017).

The aim of this project was to see if more advanced analysis of the CT could separate those with adequate from those with inadequate lung function to receive radical radiotherapy. A previous study in correlating lung function with CT appearance, has shown that Forced Expiratory Volume in one second (FEV1) correlated with mean lung density (Moloney et al., 2012). To achieve this, the study required analysis of the whole lung. Other studies have been able to show that TLCO (transfer factor for the lung for carbon monoxide) and FEV1 were able to correlate with volume of emphysema (Sashidhar et al., 2002, Desai et al., 2007, Cerveri et al., 2004, Sanders et al., 1988, Gu et al., 2014). However, none have been used to assess fitness for radiotherapy.

8.2 Assessing lung function

Chronic Obstructive Pulmonary Disease (COPD) is common in patients with lung cancer, as both conditions are most commonly associated with smoking exposure (Gould et al., 2017). COPD is defined as airflow obstruction that is usually progressive, not fully reversible and does not improve significantly over several months. Patients with COPD are a vulnerable population, often with poorer social backgrounds and multiple co-morbidities (Li et al., 2015, Gadgeel and Kalemkerian, 2003, Gadgeel et al., 2001, Gould et al., 2017).

Lung function tests measure many different respiratory parameters. Simple tests such as spirometry measure the volume of air that a patient is able to expel from their lungs after maximal inspiration. One of the markers used is the FEV1, which measures the volume of air expelled in the first second of forceful expiration. FEV1 cannot alone can be used to diagnose COPD using the GOLD criteria, it requires an FEV1/FVC or less than 70% and a clinical history to suggest COPD (Global and Disease, 2017). A predicted value is calculated standardised by
the patient’s height, age and gender. The value obtained by an individual is expressed as a percentage of the predicted value. The lower the % predicted value, the more severe the COPD (Luize et al., 2014).

Spirometry is a simple bedside investigation, however more extensive lung function tests such as measuring gas transfer can give greater information. TLCO measures the diffusion of Carbon Monoxide between alveoli in the lung and blood. It is a marker of the ability of the lung to perform efficient gas exchange and provides a marker of lung fitness.

The majority of available data correlating lung function with radical treatment outcome has been identified in surgical patients, rather than patients receiving radical radiotherapy. Previous studies have suggested that low FEV1 correlates with higher post-operative mortality, for example an FEV1 of below 40% predicts a higher mortality rate (16-50%). The mortality rate rises to 60% or greater if patients have a % predicted FEV1 of less than 30% (Brunelli et al., 2009).

As well as a higher post-operative mortality rate, low TLCO has been associated with an increased risk of readmission to hospital and poorer quality of life (Brunelli et al., 2009). TLCO is an independent prognostic factor for long term survival after curative lung surgery (Liptay et al., 2009). As a result of this data, European guidelines suggest that TLCO should be routinely used to assess for pre-operative assessment of lung function.

In contrast to surgical data, there is little evidence in relation to what level to set a threshold using lung function tests, to decide who is fit for radical radiotherapy. Most data relates to the design of the radiotherapy treatment, instead of whether or not to treat. Low oxygen tension, TLCO and FEV1 have been associated with increased toxicity and morbidity, in some, but not all studies (Brunelli et al., 2009). Factors that need to be taken into account are pre-treatment lung function, size of the irradiated volume, radiotherapy technique, prescribed dose to the tumour, whether concurrent chemotherapy is given and the choice of appropriate markers of lung toxicity such as V20 (volume of normal lung receiving 20 Gray or more). All these factors could affect risk of short and long term toxicity and potentially mortality. The major established predictors of toxicity are treatment related rather than patient related. Using treatment markers such as V20 and mean dose received by the lung predict lung toxicity
in relation to population studies, but don’t take into account how individual patients might respond to the dose of radiotherapy (Marks et al., 2010).

In this study we test the hypothesis that TA of the lung parenchyma in a standard radiotherapy planning CT scan correlates with lung fitness for radiotherapy, using a novel assessment of an apical segment of lung, by calculating a density and entropy score for each volume.

**8.3 Methods**

**8.3.1 Patient selection**

Local ethics approval was gained for this study. Sequential patients who had a 4DCT radiotherapy planning scan with IV contrast and available lung function tests at a single institution were screened for the study. This included patients who were to receive either fractionated radical radiotherapy or Stereotactic Ablative Body Radiotherapy (SABR). By including these patients it was thought it would include patients with a range of lung function, as many patients receive SABR because they are not medically fit for surgical resection of an early stage lung cancer.

Patients were divided into those who were defined as ‘fit’ and those who were ‘not fit’ based on their lung function. For these patients, rather than actual values for FEV1 and TLCO, the % of predicted TLCO and FEV1 were standardised individually for gender, height and age. This means for each patient in the study a % predicted value was generated. As a result it was felt it was not necessary to collect individual data on height, age and gender as the predicted value took account of these variables.

A fit patient was defined as a patient who had both a TLCO and FEV1 of 50% predicted or greater. Unfit patients had either TLCO or FEV1 below 50% predicted. Although there may be patients who would receive treatment below these thresholds, the reasons we chose these values was that it was felt all patients above these thresholds would receive radical treatment assuming they were otherwise fit with an appropriate performance status. To some degree these values were arbitrary, but it was important to identify an appropriate threshold. Patients were excluded if they had previous lung surgery or previous radiotherapy, or did not have both a TLCO and FEV1 % predicted available.
8.3.2 Data Extraction

All patients had undergone the same scanning protocol for a standard 4DCT performed on a GE CT scanner (General Electric, California) scanner. The entire thorax was imaged and the scan was divided into 10 breathing phases. From this scan an Average Intensity Projection (AVIP) scan was generated. The AVIP image set was standardly used for planning. As a result it contained all of the planning data and radiotherapy structures and was used for this analysis. Identical regions of interest were generated on each CT scan using the Eclipse treatment planning system (Varian Medical Systems, Palo Alto, Ca.). A volume of interest (VOI) measuring 4cm by 2.5cm was generated in the apex of the lung contralateral to the tumour. The VOI did not overlap with the PTV in any patient. A 4cm circle was used to draw the structure on 10 consecutive 2.5mm slices, ensuring that chest wall and rib was excluded superiorly and circumferentially, as well as the aortic arch being excluded inferiorly. Figure 1 illustrates the lung volume generated.

![Figure 1](image)

*Figure 1. An illustration of the lung volume identified for a patient within the TEAL study. Volume of interest was 4cm in diameter and 2.5cm long in as apical position as possible when not including chest wall or rib superiorly or aortic arch inferiorly.*
The CT scan was then exported and anonymised within CERR (Computational Environment for Radiotherapy Research). The cylindrical structure was then extracted and analysed using finiteRT software developed in house, as a collaboration between the Royal Surrey County Hospital and the University of Surrey.

The Hounsfield units were quantised into 16 levels and then each voxel in turn was compared to the 26 voxels around it using a Grey Level Co-occurrence Matrix. Each voxel was then assigned an entropy score based on how similar it was to the voxels around it. As previously discussed in chapter 4, standardising the quantisation levels allows structures from different patients to be compared, as it removes the error related to differences in quantisation. This analysis used uniform quantisation, standardised to a patient defined as fit, and had to meet 3 criteria as the ‘gold standard patient’. These were to be a non-smoker, someone who could be defined as fit (FEV1 50% or above predicted value and TLCO 50% or above predicted value) and finally had a standard 4DCT that imaged the whole of their lungs. Only one patient obviously met these criteria and they were used as the gold standard comparison for all the analyses.

**8.3.3 Data analysis**

The initial analysis involved looking at the data plots used previously in analysing the whole lung. A density score based on the original CT scan was generated and plotted on the X axis, entropy score was plotted on the Y axis. Initial analysis of a small number of patients suggested that patients with poor lung function had a greater proportion of data points in the low density and low entropy region of the plot, when compared to analysis of a volume from a patient with better lung function. Figure 2 shows a typical ‘boomerang’ plot from a ‘fit’ patient with good lung function and an ‘unfit’ patient with poor lung function showing a ‘bonfire in the wind’ plot.
Figure 2 shows a ‘boomerang shaped plot’ (plot a) of a fit patient and a ‘bonfire in the wind’ (plot b) of an unfit patient plot. Density is on x axis, entropy is on y axis.

As one of the observed differences between fit and unfit patients was the distribution of data points in the low entropy, low density region of the plot, the first analysis only included points with a density of 200 or less. A second analysis included all data points with a density score of 400 or less and a third and final analysis was performed on the whole volume. Mean, median and mode of both the density and entropy scores were generated for the 2 sub regions and the whole volume analysis. The patients were divided into fit and unfit and compared mean, median and mode density and entropy using a 2 sided unpaired t-test with a significance value of 0.05.

8.4 Results

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<th>Entropy</th>
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<td>Median</td>
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<td>Unfit</td>
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<td>P value</td>
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<tr>
<td></td>
<td>Unfit</td>
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</tr>
<tr>
<td>P value</td>
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<td>0.001888</td>
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Table 2. P values of unpaired 2 tail T-test when comparing fit versus unfit patients.

33 fit and 33 unfit patients were included in this analysis. In the lowest density assessment (0-200) 2 patients did not have any data points below 200, so were excluded from that part.
of the analysis. The three analyses shown in table 2 show that mean, mode and median density, as well as mean and median entropy all have highly statistically significant p values. This suggests that these results are unlikely to be due to chance. The 2 patients not included in the analyses did not affect the overall results.

<table>
<thead>
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*Figure 3. Kernel density estimation plots of 3 patients with adequate lung function versus 3 patients whose lung function would be inadequate for radical radiotherapy. It shows that the area of high probability (in yellow) is in a different part of the data plot in fit and unfit patients.*

Figure 3 shows kernel density estimation, which is another way of presenting the distributions of the data. It is discussed further in the future work section of this chapter.

### 8.5 Discussion
This study has shown that it is possible to differentiate between patients who are fit for radical radiotherapy with good lung function from patients with poorer lung function from data from a CT scan. Comparing fit versus unfit patients using mean, median, mode density score and mean and median entropy score met statistical significance.

The relationship between lung function and fitness for radiotherapy with density and entropy scores is potentially more complex than a correlation with one marker of lung function. It appears that TA helps explain this relationship, as correlations with FEV1 or TLCO individually were low, however separating patients into fit and unfit lead to highly significant p values. Using FEV1 or TLCO alone does not take account of this complexity and it is important to note individual lung function tests are not recommended to be used as a single value to assess patient fitness for radical anti-cancer treatment (Brunelli et al., 2009).

The explanation for this finding in relation to density is likely to be related to the bullae seen in COPD. For patients with worse COPD, they will likely have poorer lung function and be more likely to be categorised into the unfit group. More severe COPD would manifest itself as greater destruction of the elastic lung tissue of the lung, which leads to the formation of ‘holes’ in the lung known as bullae. These bullae would have a lower density than lung tissue, this data suggests that unfit patients are potentially more likely to have more bullae than fit patients, meaning a lower density score.

In relation to entropy, it is not surprising that a higher entropy score is related to lung fitness. Entropy is a measure of disorder. The higher the entropy, the greater the disorder and inversely the lower the uniformity. A section of healthy peripheral lung tissue would contain a variety of tissues, including small airways, blood vessels and alveoli. It would be expected that a range of different densities would be seen in the section of healthy lung parenchyma, which had undergone analysis. The interaction of these different tissues means it is likely that a voxel has a different density to other voxels around it as they contain different tissue. This is likely to explain the reason that the mean entropy is consistently higher in patients with better lung function. Patients with a greater degree of COPD would be more likely to have more lung damage and potentially more bullae, which would appear as low density homogeneous areas in the texture map, meaning the voxels are more uniform i.e. would have lower entropy.
This study used one non-smoker as the ‘gold standard’ patient. This then set the uniform quantisation levels. It is likely it is more important to have uniform quantisation, than the exact levels at which they are set, to allow inter-patient comparisons. As this data was generated from the AVIP of a 4DCT, only patients having radiotherapy were eligible for the study. If this work was repeated on diagnostic CTs, then a cohort of non-smokers could be used to define more generalizable quantisation levels.

Part of the difficulty in integrating advanced analysis of CT images using textural analysis or other radiomic approaches is the interruption of a radiology department’s work flow (Phillips et al., 2017). This limits a lot of analyses as they are either time consuming or require review by a clinician with specialist knowledge before the completion of the analysis. A technique that analyses part of the lung rather than the whole lung is attractive in the interests of time. Using this technique, analysis of the whole lung would take several hours compared to less than 10 minutes for the analysis of a cylinder of lung. The analysis would be automated and it may be possible to automate the generation of the ROI, meaning the analysis does not require a radiographer or radiologist to generate the analysis. Although less detailed than formal pulmonary function tests, this CT analysis is quick and its second major benefit is that it does not require any specialist expertise to identify/contour the region of interest. In this study the regions of interest were drawn by hand, but this process could easily be automated in the future. The speed of analysis and the lack of specialist knowledge needed to complete the analysis means it could easily be incorporated into the standard radiology work flow, before the scan is reviewed by a radiologist for formal reporting.

CT scans are ubiquitous in the management of many common cancers. Toxicities can be difficult to predict. At present there is no straightforward tool to model or predict the effects of SABR on lung function.

If this technique could be used to differentiate fit and unfit patients for radical radiotherapy, it could also be used to screen patients to assess their lung function. From a single CT scan it may be possible to obtain a marker of cardio-pulmonary function. Gaining greater information regarding lung function may also help to develop understand lung injury after radiotherapy. There is not a current effective tool to predict the effects of radiotherapy on lung parenchyma. This work in chapter 8 is hypothesis generating. To achieve these aims outlined above, it would need to be re-confirmed on a larger cohort of patients. The potential
to generate a cardiac assessment from CT data would need to be repeated and assessment of cardio-respiratory function has not yet been attempted on the same cohort of patients.

This work on lung function has helped to inform the experimental work described in theme 1. In theme 1 the whole lung was analysed and volumed. By understanding the appearance of the data plot in patients with good or poor lung function this has the potential to help understand the likely lung function of patients whose whole lung has been analysed using finiteRT.

### 8.6 Future work

The next step would be to perform a prospective study and to further understand the relationship between image texture and lung function. The likelihood that in this experiment differentiating between fit and unfit patients is due to chance is low, which is illustrated by the low p values identified in section 8.4. However, the correlation coefficients between individual parameters such as FEV1 or TLCO with the results of TA (either density or entropy) are low. This means the relationship is more complex. The data in this work shows that the region of interest has lower density and entropy in those who are unfit, when compared to the values from fit patients. More advanced techniques need to be investigated to help differentiate between the two cohorts. Two options to help further classify this data are the use of kernel density estimation to assess the density of data points and a moment analysis to use a series of statistical assessments to help differentiate between the 2 groups.

Figure 2 shows a 2D plot of density vs entropy, but does not take account of the density of the data points. Figure 3 shows 6 data plots, which plot density on the x axis and entropy on the y axis. A third metric is used called the kernel density estimation. This shows where there is an increased density of data points. In kernel density estimation the density of data points calculates the probability of a data point being in a certain region. The probability is higher in a region where there is a greater density of data points, compared to a region with a lower density of data points.

This approach is not limited to lung function and is being expanded in a prospective trial to look at muscle function and muscle bulk in patients with metastatic lung cancer (as described in theme 2). There is established data in predicting cardiac function from CT (Rahaghi et al., 2017). Potentially these techniques could be combined to achieve two aims. Firstly to more
accurately define treatment risk and fitness for treatment. Secondly they could form part of a screening assessment of patient fitness. It is possible that a simple staging investigation could predict or screen for cardiac function, lung function and muscle bulk assessment. This could then predict clinical outcome and treatment toxicity.

References


Chapter 9: Conclusion

9.1 Summary

As part of the work presented in this thesis I set up 2 clinical trials. The first was the DAIL (Dietetic Assessment and Intervention in Lung cancer) trial, a prospective cohort study investigating cancer related weight loss in advanced lung cancer. The second was the TEXAS (TEXtural Analysis after Stereotactic radiotherapy) trial investigating whether it was possible to differentiate between early tumour recurrence and radiation induced lung injury after Stereotactic radiotherapy to a primary lung tumour. These trials helped to answer 4 novel research questions set out in the introduction in chapter 1. In summary these were answered as followed:

1. A robust methodology was generated, which meant an entire lung could be segmented from a CT scan and analysed. This analysis produced the ‘elephant plot’. The elephant plot was an effective tool to detect the presence of tumour in a lung.

2. Initial work from the TEXAS trial has shown that by analysing a sub-region of the elephant plot, it is possible to distinguish between early tumour recurrence and radiation induced lung injury after SABR to a primary lung tumour.

3. The TEAL sub-study showed that using texture analysis meant CT data could be used to distinguish between patients who are fit or unfit for radical radiotherapy.

4. Early results from the DAIL trial have shown that it has been possible to recruit patients and complete the appropriate assessments for malnutrition, sarcopenia and cachexia. Texture analysis has the potential to differentiate between sarcopenic and non-sarcopenic muscle.

Advanced image analysis can generate more information from a standard CT scan, than simple oncological staging. In the work presented in this thesis it has been shown that image analysis in the form of Textural Analysis (TA) can differentiate between tumour and radiation induced lung injury (RILI) after SABR (Stereotactic Ablative Body Radiotherapy), as well as having a role in the analysis of non-malignant tissue. It has established statistically significant differences between sarcopenic and non-sarcopenic patients and patients who are fit for radiotherapy and those who are not, based on two markers of lung function. These approaches are exciting and novel approaches to the use of CT data in patients with cancer.
For TA to become useful in a real time clinical environment the process of ROI identification and analysis needs to be as uncomplicated as possible. One way of simplifying this is to use an ROI that is straightforward to draw, does not require specialist knowledge, is reproducible and could potentially be automated. As this project developed it became clear that TA would be most useful if the ROI could be easily reproducible, as whilst still able to establish differences between 2 groups of patients, e.g. for lung function, those fit and not fit for radiotherapy. By maintaining its simplicity, this means that a ROI has the potential to be either generated by a radiographer at the time of image acquisition, or automatically generated and confirmed by a radiographer on completion of the scan. The aim being that a radiologist could interpret the TA at the same time that they formally report the CT scan. This means that a radiologist would not need to interact with the analysis before it has been completed. By comparison other previously published analyses have required specialist knowledge to identify the specific ROI (Mattonen et al., 2013, Mattonen et al., 2014). Requiring specialist knowledge at multiple time points makes integrating TA techniques into a radiology department and standard workflow more complex. Ideally if TA can present complete data at the first time a radiologist reviews the images, this causes minimal interruption to the workflow.

Generating the analysis for lung function and muscle takes a few minutes. Generating the TA for the whole lung can take several hours, but this could be done overnight, before the scan is formally reported and would not disrupt standard reporting of images. As the TA would be performed on standard staging scans, rather than emergency imaging such as a CTPA (Computer Tomography Pulmonary Angiogram) the time taken for analysis could still be incorporated without disruption.

9.2 Developing the current models

9.2.1 Theme 1: Identifying recurrence after Stereotactic Ablative Body Radiotherapy

The methodology generated for the experimental work discussed in chapters 4-6 shows that TA has the potential to differentiate between tumour and post treatment radiation induced lung injury (RILI) after SABR. This methodology needs expanding to a larger data set. Figure 1
shows plots of the tips of the elephant trunk for patient 8 and patient 20 (figure 1a and b). Figure 1c) shows the same patient who recurred 6 months later, compared to 1d) when the patient did not recur. The 2 plots are very different, figure 1d) shows very few data points, whereas there are a lot of data points in the plot illustrated in figure 1c). It is likely that further assessment of the tip of the elephant trunk could differentiate between tumour and RILI. Possible further analysis could include kernel density estimation or an analysis of the spatial relationship of the data points within the tip of the elephant trunk.

Figure 1: Analysis of the tip of the elephant trunk for 2 patients before and after treatment, patient 8 who did not recur compared to patient 20 who recurred after SABR.

Kernel density estimation is a measure of probability of where a data point will appear, the probability rises in areas where there are more data points. It is possible there could be a
difference in the density of distribution of data points between RILI and recurrence. The data points in the tip of the trunk of the elephant plot are likely to be spread more diffusely when they represent RILI, whereas data points related to tumour are likely to be clustered together in space. Both these techniques potentially give a third dimension to the elephant plot.

Analysing the whole lung means that different regions of the lung could be compared to each other, it has the potential to quantify RILI after SABR and could provide a model for helping to predict or track the degree of RILI after SABR.

9.2.2 Theme 2: Assessing weight loss in lung cancer

Sarcopenia and muscle TA are being assessed prospectively in the DAIL trial. This will tell us whether both methods have the potential to act as a biomarker for outcome. New therapies are emerging for the treatment of cachexia, specifically anamorelin (Temel et al., 2016). The major clinical trials that assessed anamorelin did not take sarcopenia into account as part of the definition of cachexia. It defined cachexia as low BMI or greater than 5% weight loss. None of the 11 patients analysed in the DAIL trial, as the initial cohort, had lost this amount of weight, but 8 of 11 were sarcopenic, suggesting sarcopenia is an early phenomenon and develops before the patient has lost weight, or notices they have lost weight. Weight loss in the DAIL study has been self-reported. From previous observational data, 75% of patients had significant weight loss (defined as >5%) at the time the patient first saw the dietitian (Hug, 2017). In combination this data suggests that weight loss in a population who are fit for treatment, is a late, rather than early phenomenon. In contrast sarcopenia is an early phenomenon and has been associated with poorer outcome in Non-Small Cell Lung Cancer (Phillips et al., 2016).

In the DAIL trial protocol overall survival will be assessed at 6 and 12 months. The patients who are non-sarcopenic and sarcopenic, as well as cachectic or not can be compared to see if sarcopenia or cachexia is a biomarker for overall survival.

9.2.3 Theme 3: Assessing lung function from a CT scan
Data generated for this study from the radiotherapy planning scan needs repeating on diagnostic CT scans, ideally in a prospective study. It also needs further analysis in terms of defining entropy and density values which are likely to indicate poor lung function. A larger data set is likely to give more accuracy in terms of calculating the sensitivity and specificity of this test. Further analysis such as with Kernel Density Estimation as described may also help to improve the sensitivity and specificity.

Establishing lung function from CT imaging is a novel intervention. Although it would be unlikely to replace formal lung function testing, it would provide a useful screening test at an earlier time point. As discussed in more detail below, it could form part of a fitness assessment based on a CT scan.

9.3 Incorporating TA into clinical practice

9.3.1 Understanding treatment delays in lung cancer

It is possible to get more data from a CT scan, with existing standard imaging. This could potentially mean that treatment decisions could be made more quickly, shortening the time from presentation with NSCLC to starting treatment.

Assessing ability to shorten time from presentation to starting treatment and the effects on outcome in NSCLC is a complex relationship between a range of variables. NSCLC often presents late as it may have minimal symptoms in the early stages of the disease. In terms of delays associated with time to treatment in NSCLC, the majority of studies have found that quicker treatment is associated with poorer survival. Three studies have shown that those with a shorter treatment delay were associated with a poorer survival, factors associated with quicker treatment included more advanced stage of cancer, in older patients with poorer general health, suggesting those who are more unwell receive more prompt treatment (Gonzalez-Barcala et al., 2014, Myrdal et al., 2004, Diaconescu et al., 2011). Another study found that patients who were treated with palliative intent had shorter times from first symptom to first abnormal test and from first symptom to pathological diagnosis of NSCLC (Wai et al., 2012). The use of PET-CT has been shown to increase the proportion of patients who received delays in diagnosis to treatment in NSCLC, as an additional test is required
It is perhaps unsurprising that patients being considered for radical treatment take longer to start treatment. This may be in part because they have to undergo extra investigations compared to those being considered for palliative treatment. Patients with metastatic NSCLC would undergo a biopsy and a staging CT scan. Those being considered for radical treatment may require a more invasive biopsy, as well as formal lung function testing, PET-CT imaging and pre surgical anaesthetic risk assessment. Inevitably the need for more investigations can delay treatment. Interestingly surgical data suggests that patients with stage I and II NSCLC had a significantly shorter time from first symptom to surgery \( (p=0.037) \) and first contact with healthcare to surgery \( (p=0.017) \), when compared to patients with stage III and IV NSCLC \( (Christensen et al., 1997) \). Potential delays have been found to affect treatment effectiveness in other types of cancer, specifically in treating breast cancer \( (Gagliato et al., 2014, Bleicher et al., 2016, Chavez-MacGregor et al., 2016) \). Fewer delays and attending for fewer tests, as well as more efficient treatment delivery is likely to benefit patients in terms of less anxiety and attending the hospital on fewer occasions.

9.3.2 A minimum data set, incorporating organ function assessment into TA analysis of a single CT scan

Gaining more information from existing imaging has 3 potential advantages: firstly it may be cost effective in screening for poor organ function and could prevent the use of more detailed tests; secondly it may provide more comprehensive information about an individual that could contribute to a patient fitness assessment in terms of suitability for anti-cancer treatment; third and finally it means clinical decisions could potentially be made more quickly as a CT scan is usually one of the first investigations a patient with suspected lung cancer undergoes.

In this thesis it has been shown that assessing a small region of interest within the lung generates the hypothesis, it may be possible to differentiate between good and poor respiratory function on a CT scan. Recent published data suggests it is possible to extrapolate cardiac function from non-contrast CT data \( (Rahaghi et al., 2017) \). In current UK practice, all NSCLC patients being considered for radical treatment undergo a PET-CT scan. This means non-contrast CT imaging would be available for this cohort. From pre-treatment imaging it
would be possible to identify cardiac function, lung function and a sarcopenia assessment. At present this information requires multiple investigations for cardiac and respiratory assessment, a sarcopenia assessment is not standardly used in clinical practice. It may be possible to assess other organ function from standard imaging with further work. There is published data on MRI TA predicting renal function (Kline et al., 2017) and on investigating kidney function using CT TA in a murine model (Gleason et al., 2002). TA has been used to assess liver haemodynamics, in a small cohort of patients. Differences could be identified on apparently normal imaging, which predicted survival (Ganeshan et al., 2007). It is likely that this forms a screening assessment, rather than a definitive assessment of organ function, however it could also be used to generate a risk score for radical and palliative treatment.

9.3.3 Using existing imaging data to deliver more efficient decision making in Multi-Disciplinary Team Meetings

In England all patients with a diagnosis of cancer must be discussed at a site-specific multi-disciplinary team (MDT) meeting (tumour board). Each MDT will have core members essential for the treatment of that cancer. Core members of a lung MDT are likely to include respiratory physicians, thoracic surgeons, radiologists, pathologist, oncologists and clinical nurse specialists. In these meetings vital investigation results are reviewed and treatment decisions are made. These meetings often happen weekly, so if an investigation is not ready for one meeting, waiting for the next meeting immediately adds a delay to deciding on the management plan for a patient.

In some cancers such as breast cancer, it is standard practice that pathology reports are reported using a proforma, which forms a minimum number of pieces of information, for example the size of a tumour, its oestrogen receptor status or HER2 receptor status. It has been shown that a standard proforma to collect data on histology of tumours causing early breast cancer significantly improved the completeness of histopathology reports (Mathers et al., 2001, Srigley et al., 2009). This meant that the data needed to make clinical decisions was more complete clinicians can make appropriate treatment decisions more quickly. This improves a patient’s care as definitive management decisions can be made more quickly and this may potentially improve outcome. From the work described in this thesis, this principle could be extended to markers of function on fitness in a standard CT imaging. Much of the
published data on TA has been predicting outcome based on tumour assessment (Phillips et al., 2017). This could also be added to a minimum dataset, giving a more complete picture of tumour assessment and patient fitness.

A minimum data set for CT image reporting does not currently exist. Some guidelines exist for CT screening. These guidelines define follow up or investigation of lung lesions identified during screening for lung cancer, based on the risk of malignancy of the lesion. There are 6 levels, level 1 means no lesions are seen, whereas level 5 are frankly malignant lesions and level 6 lesions are biopsy proven cancer. By defining the level the lesion falls into this provides an appropriate follow up schedule (Manos et al., 2014). Something similar could be done using TA to assess patient fitness from a CT scan. As previously described it is possible to extract lung function, muscle bulk and cardiac function from CT imaging. The DAIL trial will help to establish whether sarcopenia correlates with poorer outcome, as well as whether there is an association between muscle bulk, nutritional status, lung function and hand grip strength in advanced NSCLC.

9.4 Future work: Identifying SABR recurrence

The data presented in chapter 2 shows that at present approximately 10% of patients with stage 1 NSCLC receive SABR. However, a third of patients did not receive a documented timely treatment. Previous Dutch data has shown that as the proportion of non-surgical patients receiving SABR increases, the overall survival as a whole increases (Palma et al., 2010).

As the rate of lung cancer in older patients increases, the use of SABR is likely to increase. Its use is also likely to increase in the treatment of oligometastatic cancer. It has shown benefit in oligometastatic lung cancer and randomised trials are under way in other tumour sites such as breast cancer and prostate cancer (Gomez et al., 2016).

Patients undergoing SABR for metastatic disease are likely to be younger and fitter than those receiving SABR for primary lung cancer. This makes overcoming the difficulties in interpreting post treatment imaging more important, particularly in determining recurrence.

The TA identified in theme 1 of this thesis requires a bigger data set to help understand the post treatment effects of SABR on the lung and to identify recurrence. But it does show that TA has the potential to generate significantly more data from standard imaging than is
currently extracted. It also suggests that functional data can be generated from a standard CT scan. This could potentially have a significant impact on stratifying risk and identifying recurrence in patients with lung cancer.

9.5 A grand vision of the future of texture analysis in improving care for patients with lung cancer

This thesis has illustrated that TA can be applied to imaging at 3 major time points in the management of patients with lung cancer. These are diagnosis, treatment and response assessment. These principles are illustrated in figure 2. Previous published studies have suggested TA can be applied to a diagnostic scan to provide a greater certainty of a diagnosis of lung cancer and give information on possible tissue type of the tumour. This thesis has established that a screening patient fitness assessment is possible. It is known that patients with lung cancer have multiple co-morbidities. Functional data generated from these scans could then stimulate earlier referrals to respiratory physicians, cardiologists and allied health care professionals such as dietitians and physiotherapists. This may then allow for prehabilitation while a patient is undergoing diagnostic tests, which can improve functional outcome, cardio-pulmonary fitness and health related quality of life in patients undergoing oncological surgery (Hijazi et al., 2017).

Figure 2: Potential role of TA in managing patients with lung cancer.
TA could provide radiological biomarkers to predict response to radiotherapy or systemic treatment. It could also help prognosticate outcome. As shown in this thesis, TA could improve the assessment of treatment response. By understanding radiotherapy reactions after SABR, it could be the first step in building a model to understand and predict respiratory outcome after radical radiotherapy. As imaging becomes more integral to delivering anti-cancer therapy, particularly in planning and delivering radiotherapy, the quantity of imaging data and potential to extract increasing amounts of additional data is likely to increase significantly in the next few years.
References


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Appendix 1

Publications:


Abstracts:


6. Alobaidli, South, McQuaid, Scuffham, Phillips et al. A dose painting study based on CT intra-tumoral heterogeneity vs FDG PET uptake in NSCLC. Radiotherapy & Oncology. 2017. S1 S841


Posters:

1. Alobaidli, South, McQuaid, Scuffham, Phillips et al. A Dose Painting Study Based on CT Intratumoural Heterogeneity vs. FDG PET Uptake in NSCLC. European Society for Radiotherapy and Oncology Conference, 2016.


9. Stereotactic Ablative Body Radiotherapy (SABR) for oligometastatic cancer. Royal Surrey County Hospital audit day, 2017

Clinical applications of textural analysis in non-small cell lung cancer

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ABSTRACT
Lung cancer is the leading cause of cancer mortality worldwide. Treatment pathways include regular cross-sectional imaging, generating large data sets which present intriguing possibilities for exploitation beyond standard visual interpretation. This additional data mining has been termed “radiomics” and includes semantic and agnostic approaches. Textural analysis (TA) is an example of the latter, and uses a range of mathematically derived features to describe an image or region of an image. Often TA is used to describe a suspected or known tumour. TA is an attractive tool as large existing image sets can be submitted to diverse techniques for data processing, presentation, interpretation and hypothesis testing with annotated clinical outcomes. There is a growing anthology of published data using different TA techniques to differentiate between benign and malignant lung nodules, differentiate tissue subtypes of lung cancer, prognosticate and predict outcome and treatment response, as well as predict treatment side effects and potentially aid radiotherapy planning. The aim of this systematic review is to summarize the current published data and understand the potential future role of TA in managing lung cancer.

INTRODUCTION
Lung cancer is the second commonest cancer diagnosed in the UK after prostate cancer in males and breast cancer in females. It has a very poor prognosis. Patients undergo regular cross-section imaging to diagnose, stage, assess response and undertake surveillance after treatment for lung cancer, which leads to a pool of imaging data that potentially has significant value beyond accurate staging of the patient. CT is a central tool in managing lung cancer. It is relatively inexpensive, quick and widely available. [18F]–2-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (FDG PET-CT) superposes a functional assessment of tumour metabolism. It can greatly aid in, e.g. the identification of malignant lung nodules with a sensitivity of 95% and specificity of 82%, but is less widely available and considerably more expensive. Value-based care provides incentives to maximize information from standard investigations. Radiomics aims to extract and analyse large amounts of advanced quantitative data from medical imaging. Textural analysis (TA) is a subtype of radiomics, an example of an agnostic, rather than semantic, approach within this field, based on mathematical derivations rather than prior clinical concepts.

TA can be used on existing data sets with no further dedicated or specialist imaging required. A considerable body of literature has accumulated in this field. TA has the potential to differentiate between benign and malignant lung nodules,4–15 prognosticate and predict outcome and treatment response, as well as predict treatment side effects and potentially aid radiotherapy planning. The aim of this systematic review is to explain how different TA methods have been investigated in non-small cell lung cancer (NSCLC), and to describe their current applicability and future potential.

METHODS AND MATERIALS
PubMed, Medline and Web of Science were searched using the search terms “textural analysis”, “texture analysis” and “radiomics” with MeSH terms “lung neoplasms”, “non-small cell lung cancer” and “small cell lung cancer”. The search period was January 2010 to December 2016.
341 papers were identified, which were filtered using the terms oncology and English. Papers discussing other primary cancers and duplicates were excluded. This left 104 papers.

What is textural analysis (TA)?
TA uses a range of mathematically calculated features to describe an image or region of an image. Often TA is used to describe a suspected or known tumour. The complexity of the analysis depends on the feature being described. Although different textural features have been generated from a wide range of sources, they can be broadly divided into three categories: first-order (least complex), second-order and higher-order (most complex). Different subcategories of TA are summarized in Table 1. First-order features are often calculated as a single figure describing the texture of the whole volume being analysed. Second-order features describe the relationship between two points, such as two pixels or voxels within the same image. Higher-order features describe the relationship between a pixel and more than one other pixel, i.e. a minimum of three points in space.

First-order textural features use a range of basic statistical methods to express a single measure, including: energy, kurtosis, maximum and minimum intensity, average intensity (median and mean), range of intensities, skewness, SD, uniformity, entropy (irregularity of intensity value distribution) and variance. SD, variance and mean absolute deviation express how the range of intensities are distributed. Skewness measures how much histogram asymmetry there is around the mean. Kurtosis measures the sharpness of the histogram. Randomness can be computed using uniformity and entropy. Entropy is a measure of disorder. The higher the entropy the greater the disorder or heterogeneity. The lower the entropy, the higher the homogeneity. First-order features do not take account of any spatial relationship between different points in an image. Much of the published TA work, particularly related to lung nodules focuses on first-order features of TA.

Second-order textural features describe a relationship between two points within the same region of interest. It can describe the three-dimensional size and shape and a range of values within a tumour. By deriving a region of interest, measurements can be taken of variations across the tumour volume, including entropy, compactness, sphericity, surface area and surface to volume ratio. Describing higher-order textural features is more complex than first- or second-order features, as it involves identifying the relationship between 3 or more points.

TA often requires complex interpretation. It is common to compare clinical interpretation with clinical interpretation

<table>
<thead>
<tr>
<th>Feature</th>
<th>Name of feature</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-order</td>
<td>Mean</td>
<td>Average intensity of values of an image</td>
</tr>
<tr>
<td></td>
<td>Variance</td>
<td>Spread or variation around the mean</td>
</tr>
<tr>
<td></td>
<td>Skewness</td>
<td>Symmetry of intensity values in an image. Skewness = 0 if histogram is symmetrical</td>
</tr>
<tr>
<td></td>
<td>Kurtosis</td>
<td>Indication of histogram flatness, Leptokurtic curves are steeper and platykurtic curves are flatter/less peaked</td>
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<td></td>
<td>Energy</td>
<td>Uniformity of intensity values</td>
</tr>
<tr>
<td>Second-order local</td>
<td>Contrast</td>
<td>Measures amount of local variation in intensity values</td>
</tr>
<tr>
<td></td>
<td>Angular second moment (energy or uniformity)</td>
<td>Measures homogeneity of intensity value distribution in an image</td>
</tr>
<tr>
<td></td>
<td>Homogeneity (inverse difference moment)</td>
<td>Measures the homogeneity of the intensity values of the pixel pair</td>
</tr>
<tr>
<td></td>
<td>Correlation</td>
<td>Measures the linear dependencies of intensity values in an image</td>
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<tr>
<td></td>
<td>Entropy</td>
<td>Measure of randomness of intensity values in an image</td>
</tr>
<tr>
<td></td>
<td>Sum of first-order features (squares, average, entropy, variance)</td>
<td>Measures amount of information in texture</td>
</tr>
<tr>
<td>Higher-order (local)</td>
<td>Complexity</td>
<td>Measures the rate of change in intensity values</td>
</tr>
<tr>
<td></td>
<td>Contrast</td>
<td>Measures the variation of intensity values in an image</td>
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<td></td>
<td>Coarseness</td>
<td>Measures the density of edges in an image</td>
</tr>
<tr>
<td></td>
<td>Texture Strength</td>
<td>Measures how definable (distinguishable) primitive texture is</td>
</tr>
<tr>
<td>High-order (regional)</td>
<td>Grey-level non-uniformity:</td>
<td>Represents the similarity of intensity values in an image</td>
</tr>
<tr>
<td></td>
<td>Run length non-uniformity:</td>
<td>Measures the run length similarity</td>
</tr>
<tr>
<td></td>
<td>Run percentage</td>
<td>Ratio of total number of runs to the total number of possible runs, measuring the homogeneity of runs. For images with most linear structure, the value of run percentage is lowest.</td>
</tr>
</tbody>
</table>
combined with TA. The impact of TA can be assessed by various tools including receiver operating characteristic area under the curve (ROC-AUC) and concordance index (CI). ROC-AUC is an explanation of the “usefulness” of a test assessing sensitivity and specificity, assuming a test can be defined in a binary way, i.e. “positive” or “negative”. ROC-AUC gives a test four outcomes: true negative, true positive, false negative and false positive. The ROC-AUC analyses the true positive rate against the false positive rate, deriving values between 0.5 and 1.0. 0.5 shows a poor test as true positives = false positives, 1 is a perfect test with no false positives. Generally 0.6–0.7 = poor test, 0.7–0.8 = a fair test, 0.8–0.9 = a good test, >0.9 = an excellent test. A second measure is CI, which measures how well a prognostic test distinguishes individuals from a population with or without a particular outcome. Values range from 0.5 (no discrimination) to 1.0 (perfect discrimination). To be significant, a CI measurement should exclude 0.5 from its confidence interval.

Pre-treatment textural analysis (TA)

A wide range of studies have used TA to attempt to define different aspects of lung lesions seen on pre-treatment imaging. TA has been used to differentiate benign or minimally invasive lesions from malignant tissue (particularly lung nodules) using CT,60-10.12-15,50,51 FDG PET-CT52 ultrasound53 and different types of tumour histology,54-56 to aid assessment of the tumour and aid treatment decisions. These features can be combined to predict the likelihood of a nodule being malignant.

TA has also been employed to help classify histological images. An automatic classifier of squamous cell and adenocarcinoma helped aid tissue classification57 and TA of nucleus features has helped aid tissue classification58 and TA of nucleus features has been shown to predict early recurrence of NSCLC.59

Lung nodules

TA has been used to differentiate between different tissues and determine the risk of malignancy of small pulmonary nodules. Pulmonary nodules are focal opacities appearing on imaging that are defined as less than 3 cm in axial diameter; they can be solid, semi-solid or non-solid in appearance.60 CT density [measured in Hounsfield units (HU)] and morphology can be used to assess pulmonary nodules. Solid cancer, non-solid lepidic adenocarcinoma, blood and inactive fibrous tissue all have different HU measurements.61 However, it is still difficult to predict with certainty the pathology of small lung lesions, because up to 39% of lung nodules with a benign CT morphological appearance can be malignant.62

As the use of medical imaging increases, more lung nodules are likely to be identified. Lung cancer screening using low-dose CT has a relative risk reduction of 20% for lung cancer specific survival, when compared with chest radiography in a high risk population. In each of the 3 years of screening, identification of a nodule occurred in 27.3%, 27.9% and 16.8% of the trial population in years 1–3, respectively. Individuals in whom a nodule was identified in years 1 and 2 were not automatically excluded from continuing with screening, but more than 95% of these nodules would be benign.63 TA may aid risk stratification of these lung nodules. This has significant potential to improve the predictivity of screening and reduce the morbidities rendered by biopsy and surgical resection.

As stated, lung nodules can be broadly divided into solid, semi-solid and non-solid. Several studies have aimed to help classify lung nodules into broad categories before further analysis.64,65 Ground glass nodules (GGNs) are non-solid and can be difficult to extract from an image accurately.66 Three studies suggest TA can convincingly determine malignant from non-malignant nodules. The first study capitalized on potential differences in heterogeneity between the nodule edge and centre. The difference was much greater in malignant nodules when compared with inflammatory nodules with ROC-AUC of 0.836.67 In a second study, computer-aided diagnosis of whether a lesion was benign or malignant achieved 94% accuracy in correctly identifying all non-cancerous lesions as benign using a single image slice.68 These results were achieved using all slices of the abnormal lesion.69

In a cohort of 55 patients, CT TA improved specificity from 38.5 to 100% when compared with a FDG PET-CT-CT in differentiating primary lung tumours from granulomatous lung lesions.66 Sensitivity was similar in both groups (75% using five TA features vs 79 with FDG PET-CT %). High entropy (high level of disorder) was more common in primary NSCLCs. Interestingly in this study, using a combination of three textural features generated from a contrast-enhanced CT scan rather than a non-contrast CT scan reduced the sensitivity from 88 to 38%. The reason for this is not clear, but the presence of contrast may obscure the texture of the region of interest. Contrast could potentially act as a marker of vascularity, but as this study suggests, it could obscure textural information. The effect of contrast is not necessarily binary, as the results using contrast could depend on contrast-related factors such as speed of infusion, contrast agent used, amount of infusion given; image-related factors such as delay between contrast and image acquisition and patient-related factors such as cardiac output and body habitus. These factors may require standardization so that they do not unduly influence the TA.

GGNs have a higher malignant probability than solid nodules, while a combination of GGN and solid nodule have an even higher malignant potential (62.5–89.6%).67 although at least half (49–70%) of these partial solid ground glass nodules disappear within 3 months. Analysis was performed aiming to identify textural features that may predict persistent vs transient partial solid ground glass nodules. When textural features were combined with clinical and CT features, differentiating performance significantly increased from 79 to 92.9% (p < 0.05). As with the previous study, Wang et al68 showed that TA can improve diagnostic certainty. In contrast to the previous study, this study analysed the whole tumour, instead of a single image slice. This technique improved sensitivity and specificity from 0.82 and 0.47 to 0.95 and 0.71, respectively.68 3D TA has also been used to differentiate between pre-malignant adenocarcinomas and early invasive adenocarcinomas.56 It is not currently clear how large a region of interest needs to be analysed. There are three possible approaches, 2D analysis of a single slice, 2D analysis of multiple slices or 3D analysis of the whole region of interest. If a single slice is being used, then often this is the largest slice, but cross-sectional area does not definitely correlate with the greatest amount of extractable information. Han et al showed
that generating 2D textural features on multiple slices from 3D data was better than generating them from a single 2D slice. Although 3D data did not improve on multiple 2D slices, it can potentially analyse extra features not available in a 2D analysis. 2D analysis on a single plan on a single slice would not detect differences in other planes, e.g. if the axial plane was used, data regarding the coronal or sagittal plane of the tumour could not be generated. Analysing multiple 2D slices may help identify the most representative 2D slice, but does not overcome the limitations regarding information in 3D.

FDG PET-CT is another type of imaging used to assess lung nodules. In many institutions worldwide FDG PET-CT is less available than CT, but is a very useful tool in identifying malignant lung nodules, with a sensitivity of 95% and specificity of 82%. Tracer uptake can be heterogeneous within a tumour because of areas of necrosis, differences in blood flow, cellular activity, microvessel density or hypoxia. Whilst this review focuses on the exploitable TA features of standard CT scans, where PET-CT data sets are available, additional value can be extracted from these scans. Fractal analysis is a TA methodology that has been studied in this setting. Morphological fractal dimension and density fractal dimension can be generated from CT and PET images of pulmonary images. Combining morphological fractal dimensions and FDG PET-CT or density fractal dimensions improves diagnostic accuracy to above 90% when comparing benign nodules with a primary NSCLC using FDG-PET alone.

MRI is not routinely used to assess lung tumours before treatment. However, a small single institution series suggests that entropy derived from dynamic contrast enhanced MRI may predict progression free survival (PFS). Pre-treatment textural analysis (TA) of primary lung tumours using CT

TA has been shown to have potential as an imaging biomarker to identify the histological subtype of NSCLC. Although many of these studies are relatively small, CT TA radio-genomics is a rapidly expanding field. CT TA has helped to differentiate KRAS oncogene-mutated tumours from pan-wild type tumours, epidermal growth factor receptor (EGFR) mutant tumours from wild type tumours, EGFR-mutated tumours from anaplastic lymphoma kinase (ALK) rearranged tumours, lepidic adenocarcinomas from non-lepidic adenocarcinomas and ALK rearranged tumours from unarranged tumours. Work in progress has identified a correlation between kurtosis (a first-order textural feature) in NSCLC and the expression of a gene coding for a protein that regulates mucin production, Mucin5AC. The expression of this gene is considered a marker of the activation of the MAP kinase signalling pathway. Increased presence of mucin produces lower attenuation with X-rays than soft tissue. This begins to demonstrate the potential for radio-pathological correlation through advanced imaging analysis.

Conventional predictors of outcome in NSCLC include TNM staging, AJCC stage, age, sex, histology, comorbidities and performance status. The use of a biomarker from CT imaging to prognosticate patients’ outcomes, risk of distant metastases and overall survival (OS) is attractive. CT texture features have been correlated with PET-CT SUVmax, tumour staging and degree of tumour hypoxia. A combination of TA features have been identified that predict recurrence in surgical patients and overall survival in patients with adenocarcinoma.

TA can assess many different features and this presents a challenging large experimental space. In 98 patients with stage I-III NSCLC receiving radical radiotherapy, the 15 most predictive textural features were chosen from over 600 features, from pre-treatment CT scans. Risk of distant metastases were divided into high risk and low risk with a CI of 0.62. Use of simple radiomic features were able to predict risk of distant metastases in a discovery and validation set of patients. In a similar study in Stage 3 patients, receiving chemo-radiotherapy, textural features extracted from the gross tumour volume, patients could be divided into high and low risk based on traditional prognostic factors such as staging and features from TA, with a CI of 0.89 and 0.91 for overall survival and locoregional control, respectively. Grove et al showed that morphologically similar tumours could be divided into better and worse prognosis groups and validated this at a separate institution, using convexity and central tumour entropy. More irregular tumours conferred a worse prognosis.

TA in combination with machine learning has been shown to predict recurrence with a high degree of accuracy (CI 0.81) and OS, using the pre-treatment image of a single CT slice of 101 patients who underwent resection of Stage I primary lung adenocarcinoma. The TA used a second-order feature called Riesz wavelets, which were chosen to differentiate between solid component and ground glass opacities. Support vector machine (SVM, a form of machine learning) has been used to classify high risk and low risk lesions, as well as risk of recurrence. The benefit is that SVM can separate non-linear data; it can separate data into two groups that are not obviously distinct when plotted, when methods such as logistic regression are less useful. The more round the tumour (spherical disproportionality) and the greater the tumour heterogeneity, the less likely the response, in patients undergoing neo-adjuvant chemo-radiotherapy for NSCLC. The strength of this study was that treatment effect was assessed by pathological assessment of the surgically resected specimen. In a separate study, CT TA measures were able to predict tumour shrinkage after radical radiotherapy.

A range of TA studies have been performed with broadly similar methodology. A patient cohort with a known outcome measure is identified. A single slice or whole tumour is segmented out from the rest of the scan. A range of first-, second- and higher-order textural features can then be extracted. In many cases, a large number of TA features can be calculated. Features are chosen that correlate with outcome. The difficulty is that different TA features are significant in different studies, using different methods of analyses. An association between TA features and outcome could be statistically significant by chance, if very large numbers of parameters are analysed. Some TA features are dependent on preprocessing of the image before TA is performed, whereas others are independent, which means the independent features were more likely to be robust, as they are not prone to
variations in preprocessing. These concerns limit the reproducibility of many studies and their applicability as a practical clinical tool. Large robust data sets may help to overcome some of these limitations. For example, Palmar et al were able to analyse lung tumours and head and neck tumours in 878 patients with training and validation sets for both tumour types. In this study, radiomic parameters were correlated with stage and prognosis. Reproducibility is a key element in using such a biomarker more widely.

TA can potentially increase the accuracy of nodal staging as lymph nodes can be auto-mapped and identified. TA has been shown to predict whether a lymph node is malignant or not in biopsy proven nodes, with a sensitivity of 81% and specificity of 80% (AUC = 0.87, p < 0.0001). This was achieved using a combination of three textural features: entropy, grey level non-uniformity and run length non-uniformity with three features of shape, which assessed the degree to which a lymph node was circular. Using this combination, 84% of malignant nodes and 71% of benign nodes were correctly classified on a non-contrast CT. However, only half the patients (22 of 43 patients) received a staging PET-CT scan. PET imaging shows a small improvement in diagnostic efficacy when compared with measuring nodal dimensions alone. A published study using commercially available software called TexRAD has shown that it is possible to differentiate malignant nodes from benign nodes with a low sensitivity of 53%, but much improved specificity of 97%, with an ROC-AUC of 83%. TA based on endobronchial ultrasound has been shown to differentiate between benign and malignant nodes using fractal dimension.

**Pre-treatment textural analysis (TA) of primary lung tumours using PET-CT**

FDG PET-CT is used as standard to stage patients potentially suitable for radical treatment for NSCLC. It is becoming increasingly used in managing treatment in NSCLC. Using simple PET metrics such as mean and maximum SUV would not be defined as TA, but analysing tracer uptake can identify heterogeneity across the tumour.

Extracting texture features is dependent on the size and FDG uptake seen on FDG PET-CT imaging. FDG-PET texture features have been found to be prognostic and provides more accurate prognostication than CT TA alone. Simple measures such as SUVmax and metabolically active tumour volume have been associated with OS after radiotherapy and response rates after palliative chemotherapy in metastatic lung cancer. In one study, these metabolic measures have also been found to correlate with first-order textural features, however additional work has suggested that only second-order features correlate with OS. FDG PET-CT-CT has high test-retest and high interobserver stability. In contrast, Cook et al showed that FDG PET parameters (such as SUVmax) did not predict the outcome. FDG PET-CT studies have also been shown to aid the diagnosis of mediastinal lymph nodes. Although FDG is the commonest tracer used in clinical practice, other tracers such as F-fluoromisonidazole, a marker of tumour hypoxia, are available. F-fluoromisonidazole uptake can vary across tumours and therefore, it is possible to assess tracer uptake heterogeneity and to use TA to generate textural features. FDG images take 15–20 min to acquire. As a result, tumour movement caused by respiration during image acquisition appears to affect some, but not all textural measures, e.g. busyness (a measure of intensity change between a voxel and those around it) was 20% higher in the 4D scan, suggesting that as possibly expected blurring means these measures are sensitive to motion. Fried et al identified that a combination of histogram features, co-occurrence matrices (using 2D relationships), shape and volume correlated with OS and locoregional control, but was not externally validated. Further studies have shown that SUVmax and mean, total lesional glycolysis (TLG) and metabolic tumour volume correlated positively with entropy. Energy and contrast had an inverse relationship and that the FDG PET and CT heterogeneity assessments can separately predict OS.

In a pilot study, Wu et al segmented subregions of tumour based on similarity of appearance, using CT and FDG PET-CT. Each tumour was over-segmented into multiple super pixels using K clustering of the FDG PET and CT images. The volume of the metabolically active subregion predicted OS in this patient cohort, with a CI 0.67 and hazard ratio of 2.79 (log rank p = 0.004). These regions appear to be robust against a degree of misregistration, but the PET data does not appear to account for tumour movement. In supporting the use of TA in radiotherapy planning, some CT texture features are robust enough to be identified on linear accelerator based cone beam CT scans from on treatment imaging during radiotherapy. Image quality and the ability to quantify an image is likely to improve as cone beam CT technology quality improves.

The majority of these studies are retrospective. Many studies also use a lot of clinical data alongside to stratify outcome, adding in TA then slightly improves prediction of outcome compared with clinical data alone, rather than the tumour textural features alone predicting outcome. These studies are heterogeneous. They utilize different standards, measurements, equipment and techniques. For this reason, it is difficult to achieve accurate reproducibility. Some studies have heterogeneous cohorts receiving different treatment, either combining tumours that received radiotherapy alone with chemo-radiotherapy or different radiotherapy schedules. Accurate localization and segmentation of tumours on CT imaging is easier to overcome using appropriate windowing, than differences on FDG PET-CT, particularly if 3D PET is used. Some studies have specifically looked at reproducibility and this is an important area of further research. At present, it is unlikely that TA assessment is sufficiently robust to act as a biomarker.

**Assessing treatment response**

Follow-up CT and PET-CT scans both provide additional opportunities for assessment of treatment response beyond simple visual interpretation. SUV intensity on FDG PET-CT imaging may give a faster response than decrease in tumour volume. Early prediction of response to chemo-radiotherapy has been made using PET heterogeneity. In a study by Dong et al, patients undergoing an on treatment FDG PET-CT scan (after receiving approximately two-thirds of total radiation dose), certain textural features...
indicated response to treatment with a higher sensitivity (92 vs 73%) and specificity (84 vs 80%) than baseline PET features.\textsuperscript{112}

Identifying early recurrence after radical radiotherapy can be complex, particularly after stereotactic ablative body radiotherapy (SABR).\textsuperscript{113} SABR describes a battery of methods that facilitate the highly targeted delivery of a high dose of radiotherapy in fewer larger doses to an early stage lung tumour. The centre of the tumour often receives two or three times the biological equivalent dose compared with standard radiotherapy. Pre-treatment textural features can improve prediction of outcome, compared with SUVmax alone.\textsuperscript{29} Compared with other treatment response assessments, the evidence base for using radiomics and textural features in SABR response assessment is relatively advanced. Treatment-related toxicity is also amenable to assessment by TA. Radiation induced lung injury (RILI) consolidation commonly occur after SABR.\textsuperscript{114} Differentiating RILI and tumour recurrence is difficult. When comparing areas of ground glass opacity and consolidation, recurrences were denser and had different textural features than areas of RILI and early response could be predicted.\textsuperscript{31–33} FDG PET SUV >5 or SUV higher than the diagnostic FDG PET-CT suggest recurrence.\textsuperscript{115} Radiomic features have been extracted, which predict early recurrence and are able to improve sensitivity when compared with physician assessment (AUC 0.85, false negative rate 23% vs 99%).\textsuperscript{33} Another study has suggested that perfusion characteristics of RILI and recurrence are different, with the areas of recurrence exhibiting changes in perfusion termed as wash-in and wash out phenomenon, not seen in areas of RILI.\textsuperscript{34} Lung CT TA changes can be identified in patients receiving radical radiotherapy to the oesophagus, this technique not only identified patients who did, and did not, develop radiation pneumonitis, it also quantified it.\textsuperscript{115} It achieved this by comparing randomly generated regions of interest in both pre and post treatment imaging.

In advanced NSCLC tumours, neither volumetric measurements on CT nor RECIST criteria predicted OS.\textsuperscript{35} PET SUVmax has been associated with response to chemotherapy and TKIs,\textsuperscript{36,37} but not with OS.\textsuperscript{38,39} TA could identify response of adenocarcinomas in the metastatic setting but could not identify response in non-adenocarcinomas.\textsuperscript{38} Different textural features have been identified in assessing response to chemo-radiotherapy (found tumour volume, mass, kurtosis and skewness) or an EGFR tyrosine kinase inhibitor (heterogeneities).\textsuperscript{39} 11 C erlotinib PET requires further investigation but has been shown to potentially identify TKI responders and non-responders in a murine model.\textsuperscript{40} Kurtosis after neoadjuvant chemotherapy and intensity variability after tyrosine kinase Inhibitor therapy have been shown to independently predict pathological response.\textsuperscript{39} Having a predictor of response is useful as non-responders could potentially avoid a toxic treatment, which would not benefit them and reduce costs of futile therapy.

Future perspective
The use of TA and radiomics is rapidly evolving. It is attractive as it uses existing imaging data to gain greater information about a tumour or disease state. There has been sufficient work to establish that certain textural features can act as biomarkers. Indeed tumour kurtosis and entropy are entering real-world clinical evaluation as markers of poor prognosis.\textsuperscript{78} However, to become more widespread a range of obstacles require attention. It is important to consider standardization of each step in the process including: acquisition, segmentation (ideally auto-segmentation), analysis and interpretation of the data. TA techniques often require an expert to accurately delineate the tumour. TA requires a significant degree of computing power to generate the analysis, it is not currently integrated into current assessment of imaging in diagnosis and response assessment and TA potentially makes workflow with a radiology department more complex.

Some of these challenges can be overcome. For example, extracting textural features automatically reduces or eliminates interobserver errors,\textsuperscript{116} using an automated technique to delineate tumour volume is more robust than manual delineation\textsuperscript{117} and commercialization and user interface optimization may facilitate the incorporation of TA into radiology department workflows. Many studies have analysed the primary tumour and so at present are more likely to be useful for pre-treatment prognostication, rather than post-treatment assessment.

To gain the full benefit of textural features, identification and classification of features need to be sufficiently robust to overcome various such as patient factors (including positioning, respiration phase and motion management and effects or lack of IV contrast), acquisition and processing variables such as image acquisition power, image slice thickness, image reconstruction algorithms, use of segmentation software and operator variability in tumour delineation. Some texture features are reproducible, while others are highly variable and do not generate the same results with repeat testing.\textsuperscript{118,119} To minimize these variables and identify the changes related to tumours alone many studies standardize their image acquisition process.\textsuperscript{110} Useful biomarkers need to overcome these features or have to be standardized to ensure accurate interpretation of this information.

TA of routine imaging is likely to have a range of uses in the future both within and outside of oncology. With more robust measures of texture it may be helpful in differentiating between benign and malignant lesions, identifying subtypes of malignancy. It will aid surgical and radiotherapy planning and hopefully provide more accurate response assessment. Response assessment is becoming more important as treatment becomes increasingly complex. Standard RECIST size criteria are not adequate for assessing response in immunotherapy as standard RECIST criteria underestimate benefit.\textsuperscript{120} Texture could potentially have a role in assessing how a lesion changes rather than just using size assessment. Assessing response after stereotactic radiotherapy is difficult because of the localized radiotherapy change induced by the treatment. Differentiating between inflammation and tumour is difficult, particularly if a biopsy is inconclusive.

Outside of oncology, TA has already been used to assess hepatic and pulmonary fibrosis\textsuperscript{121} and to see if different lung pathologies can be diagnosed on imaging alone. It can potentially have a role in differentiating tissue anywhere in the body, potentially preventing the need for more invasive tests.
For these reasons, being able to extract more information for standard imaging is an attractive way of getting more “value” from investigations and is likely to be more routinely introduced into clinical practice in the coming years.

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Letter

Benefits of Stereotactic Radiotherapy Fellowships to Clinical Oncology Trainees

Madam — As Clinical Research Fellows in stereotactic radiotherapy, we recognise the growing benefit of acquiring greater technical skills in advanced radiotherapy during our clinical oncology training.

Our involvement in the development of new stereotactic radiotherapy services has helped us to understand the background process in delivering a new treatment technique. This includes the commissioning process, designing treatment protocols and departmental pathways for implementing a new radiotherapy technique and the importance of multidisciplinary working.

In the radiotherapy planning pathway we have had more exposure to imaging in both the selection of suitable patients and tumour localisation. We have also had more time to devote to radiotherapy planning [1]. Benefits include gaining familiarity with new positron emission tomography tracers, potential extension of magnetic resonance imaging and the role of rigid and deformable registration in radiotherapy planning.

We now have a greater understanding of volumetric and fiducial-based image guidance, motion management strategies and online/real-time verification. These specific skills are generally not well developed in our training [2]. We need to be able to act on changes seen at planning and treatment delivery to know when it is appropriate to treat and when there may be a need for an urgent re-plan. Our fellowships have helped to develop our clinical judgement, giving us more confidence to act independently as consultants.

Frequent discussions and presentations on stereotactic radiotherapy to specialist and non-specialist audiences, including current literature reviews, have helped us to understand the techniques better and also improved our communication skills.

Use of advanced radiotherapy techniques, such as stereotactic radiotherapy, image-guided radiotherapy and volumetric-modulated arc therapy, is increasing. We are now more familiar with these techniques, which are essential for clinical oncologists. We think it is important that a developing clinical oncology curriculum should include more exposure to stereotactic radiotherapy.

We would like to acknowledge our supervisors Dr V. Ezhil, Dr K. Franks, Dr R. Shaffer and Dr M. Ajaz for their support during our fellowships.

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References

8. Rate of cachexia in lung cancer
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**Background:** Lung cancer is the second most common cancer diagnosed in men and women in the UK with a very poor 5 year survival (10%). There is a lack of robust data on the stage of cachexia in which patients with lung cancer present. The severity of cachexia can influence overall outcome. Refractory (irreversible) cachexia indicates a poor prognosis of usually less than 3 months.

**Method:** We reviewed all patients diagnosed with primary lung cancer that were reviewed by the Macmillan Oncology Dietitians over a 4 year period at the Royal Surrey County Hospital. Reasons for referral commonly included: weight loss, glycaemic control in diabetes, decreased oral intake and food texture modification. Patients were defined as cachectic if weight loss was >5%.

**Results:** 458 patients were reviewed by the dietitian. 43% were female, 57% were male. Mean and median weight loss of total body weight at referrals was 9.5% and 13% respectively. Mean pre-cancer body mass index (BMI) was 26.9 (kg/m²), mean BMI at referral was 23.0 (kg/m²). 359 patients (78%) were treated with palliative intent. 99 were treated with radical/adjuvant intent. 341 (76%) of this cohort had weight loss from their usual body weight prior to diagnosis.

**Conclusion:** This data suggests cachexia is very common in lung cancer. It is known that early symptom control improves survival in lung cancer. It is not known whether early dietary intervention may improve lung cancer outcomes. Further research is needed. These patients have a BMI within the healthy range of 20–25 kg/m² before and after their cancer diagnosis in spite of significant weight loss. We are seeking ethical approval to prospectively assess the rate of cachexia in lung cancer and its correlation with other simple nutrition assessment tools. We aim to assess clinical outcomes categorised by % weight loss in advanced lung cancer.

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82. Interest of radiochemotherapy in the rectal cancer
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**Background:** We propose the study of treating patients with locally advanced rectal cancer by radiochemotherapy followed by surgery with TME. The objective is to make inoperable patients, operable after the radiochemotherapy and get a pathologic complete response at the maximum of the patients and decrease the rate of local recurrence and distant.

**Method:** During 2008–2011, we have recruited 80 patients in our radiotherapy oncology department of Blida; age is between 18 and 70 years. Radiotherapy (RT) is made at a dose of 45 Gy in the pelvis; the patient received three courses of CT (FOLFOX) for all the radiation therapy. All patients were assigned to surgeons for surgery (TME).

**Results:** Rectal bleeding was found in 89% of patients. 70% of our patients had a low rectal cancer 98% of our patients are classes T3, T4, 78 % N+, and only 21% N−. The RTCT was well tolerated by patients, no side effects Grade 4.77 had surgery 55% of our patients had a conservative surgery. 41% had an abdomino perineal resection. The downstaging affects more 45% of tumors after the RTCT and we have 12% complete pathological response, 61% of objective response. The local recurrence rate is (4%) relapse distance is 22.9%. The average time of relapse was 14 months away. The survival rate at 5 years was 64%. Relapse distance during follow-up of patients operated is 22.9%.

**Conclusion:** Our result of 12% complete response is less than the results of others studies (16% to 21%). Our result of local relapse is similar to international studies. Every patient should have a personalized treatment for all steps (radiochemotherapy, surgery, adjuvant chemotherapy).

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85. Building a weight of evidence to prevent cancer in later life
Gillian Rosenberg, Lucie Hooper, Jyotsna Vorhra
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**Background:** Obesity is the largest preventable risk factor for cancer after smoking. Being overweight as an adult is linked to 10 cancer types, and overweight children are more likely to become overweight adults. Recent data shows that around one in three children leave primary school overweight or obese, with the most deprived children twice as likely to be so. A comprehensive evidence-based childhood obesity strategy is vital in order to prevent obesity related cancers later in life.

**Method:** A multidisciplinary research strategy was developed at Cancer Research UK to build a body of evidence that can directly influence government policy making in obesity. This included a quantitative study to investigate obesity and cancer awareness in the general population; a modelling study to predict future obesity related cancer cases; and qualitative studies to explore obesity-linked behaviours in children.

**Results:** Cancer was not at the forefront of people’s minds when thinking about obesity, with only 26% showing an unprompted awareness of the link. However the projected impact of obesity on cancer is high: if current trends continue it will lead to a further 670,000 cases over the next 20 years. When looking specifically at childhood obesity, it was found that junk food marketing was associated with parental pester power and can override nutritional knowledge.

**Conclusion:** These research studies formed an integral part of the current Cancer Research UK campaign on obesity. The first stage addressed the poor knowledge of obesity and cancer in the general population. The modelling results were a key part of this, alongside existing data on the mechanisms behind the causal relationship of obesity and cancer. Following this, during the development of the government’s childhood obesity strategy, the childhood obesity studies demonstrated to policy makers the importance of taking action to limit advertising exposure in children.

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93. Breast cancer in woman younger than 35 years
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**Background:** Our aim was to report the epidemiological and clinical characteristics of breast cancer in young women and to evaluate the therapeutic Results in Radiotherapy Oncology department of Blida.

**Method:** We report the Results of a retrospective study including 64 patients less than 35 years old treated for breast cancer between January 2010 and December 2014 in our department.
229. Sarcopenia in lung cancer
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Background: Cancer cachexia (loss of muscle mass) is an adverse effect of many common cancers. The presence of refractory (irreversible) cachexia is associated with a very poor overall survival. Sarcopenia (muscle loss) is a feature of cachexia and can be assessed on CT imaging. Cross sectional measurement of the psoas muscle is an accurate, quick and inexpensive assessment of sarcopenia. Sarcopenia is associated with a poor prognosis in Small Cell Lung Cancer. This has not been previously shown in Non Small Cell Lung Cancer (NSCLC). We show the relationship between sarcopenia and overall survival in NSCLC.

Method: Data was collected from an MDT between July 2012 and December 2013. Anterior-posterior and lateral measurements of greatest diameter of psoas muscle were made at level of L3 through the transverse processes from the diagnostic CT. Left and right psoas muscle measurements were taken and standardised for height. Psoas area (in mm)/height (m). Sarcopenia defined as <385mm/m² in females and <585mm/m² in males.

Results: 90 patients were identified retrospectively with appropriate imaging. Cohort was 54% male and 46% female. Mean age 67 years (range 46–85). Of 56 patients with radically treatable cancer (stage I–IIa + T4N2M0), 24 patients (43%) had sarcopenia at diagnosis. Of 31 patients with incurable lung cancer (stage IIIb + IV excluding T4N2M0), 15 had sarcopenia at diagnosis.

Median survival of non-sarcopenic patients was 14 months. Median survival of sarcoptic patients was 12 months (p = 0.2218).

Conclusion: Sarcopenia is common in patients with NSCLC. Sarcopenia assessment using cross sectional measurements of psoas muscle is quick and easy. The presence of radiological sarcopenia may correlate with a poorer overall survival in NSCLC, but did not reach statistical significance. Sarcopenia requires further investigation and will be investigated in a prospective clinical trial, the NAIL trial (Nutrition Assessment and Intervention in Lung Cancer).

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255. Cancer stigma among ethnic minority women
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Background: Qualitative research with ethnic minority groups often finds that participants feel cancer is stigmatised or ‘taboo’. Cancer stigma has also been shown to influence engagement with cancer prevention/early detection behaviours particularly in some ethnic minority groups. To date there have been few studies attempting to quantify perceptions of stigma in ethnic minority populations. We aimed to explore differences in cancer stigma in a sample of ethnic minority women and the association between cancer stigma and attendance at cervical screening.

Method: Women aged 30–60 years were recruited from Indian, Pakistani, Bangladeshi, Caribbean, African and white British backgrounds (n = 720, response rate = 65%). Participants completed face-to-face interviews with a multi-lingual interviewer. We assessed socio-demographics, self-reported cervical screening attendance, and four dimensions of cancer stigma: personal responsibility, awkwardness, avoidance and community level stigma.

Results: There were significant differences by ethnic group for each of the four stigma dimensions (p < .001 for each), with White British women scoring lowest on each. Differences on individual items were striking, for example <5% of Bangladeshi and Pakistani women believed cancer was talked about openly in their community compared to 97% of White British women. Across all ethnic groups, personal responsibility, awkwardness and avoidance scores were significantly lower among those born in the UK, but there were no differences in community stigma. Cancer stigma was significantly associated with increased odds of non-attendance for cervical screening. This was the case for community stigma (OR = 1.09), personal responsibility (OR = 1.12), awkwardness (OR = 1.12) and avoidance (OR = 1.15). Odds ratios were small but highly significant (p < .001).

Conclusion: While low in the general population, cancer stigma is prevalent in ethnic minority groups, even among the younger generation, and is associated with cervical screening status. Interventions to tackle stigma in ethnic minority populations could be a first step to addressing ethnic inequalities in cancer awareness and preventive behaviours.

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264. The meaning of the term ‘breast cancer survivor’ for young women living with a history of breast cancer in the UK
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Background: Despite its usage, ‘cancer survivor’ remains a contested term as not only is there is a lack of consensus over the exact definition and meaning, but there have been strong critiques of ‘survivorship’ by scholars and activists. A recent turn to researching how individuals who have or have had cancer perceive the term ‘cancer survivor’ has had mixed findings. Some people embrace the term, but there are many who do not feel it fits with their own experience, and who resist it. Most existing research has been conducted outside of the UK.

Method: Twenty women diagnosed with breast cancer under the age of 45 took part in semi-structured interviews, and, among other topics, their perceptions of the term ‘breast cancer survivor’ were explored. Social constructionist grounded theory methods were used in order to develop an understanding grounded in the worldviews of the participants.

Results: Only 3 of the twenty women interviewed said they would use ‘survivor’ to describe themselves and many held negative views about the identity in relation to themselves. Reasons for rejecting it included not feeling close enough to death, the fear of recurrence, and the obfuscating of cancer’s ongoing presence in their lives. At the end of curative breast cancer treatment, most young women found themselves in a ‘liminal’ state – neither patients nor survivors – and, therefore, found that the term did not resonate with their experiences.

Conclusion: The term ‘cancer survivor’ may not be appropriate for many young women living with a history of breast cancer for a number of reasons, including that it obscures the long-term and uncertain impact on their lives. Being labelled a ‘survivor’ can be a disempowering experience. Further research is needed but this small study troubles the use of the term in everyday usage to refer to this population.

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 Audit of radiotherapy plan quality for stereotactic ablative radiotherapy (SABR) for stage 1 non-small cell lung cancer

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Background to the audit: 101 patients with non-small cell lung cancer (NSCLC) have been treated with SABR since December 2012. The aim of this audit was to assess SABR plan quality and correlate with clinical outcomes.

Standard, indicator and target: UK SABR consortium guidelines for treatment planning in lung SABR.

Methodology: Radiotherapy planning parameters are prospectively collected for each SABR patient, these were collated with clinical data and the information analysed.

Results of 1st audit round: 98% of SABR plans achieved coverage of 99% of the planned target volume (PTV) with 90% of the prescription dose. 68% achieved 95% coverage of PTV with 100% dose; however, 84% of plans achieved >99% to 95% of PTV, likely within error of dose calculation. Only 2% had a major deviation for target conformity and 1% for intermediate dose conformity. No plans had major deviations for Dmax, organs at risk (OAR) or dose at 2 cm.

Biologically equivalent dose (BED) the dose received by 95% of the PTV was calculated, as it is established that BED >100 Gy (assuming α/β of 10 for tumour) is associated with better local control. Two patients did not receive a BED of >100 Gy; eight due to conservative fractionation and one due to poor coverage. With median follow up of 12 months there have been four local relapses, one of these received BED < 100 Gy due to conservative fractionation.

1st action plan: Conclusions: For the majority of patients we meet planning guidelines for lung SABR. The 95% PTV coverage can be challenging; however, this rarely compromises PTV receiving BED of 100 Gy.

Action plan: Share audit results with multi-professional SABR team. Review plans not meeting guidelines or requiring conservative fractionation in weekly SABR meeting; treatment may go ahead if no other treatment options. Re-audit following introduction of flattening-filter free mode to check impact on plan quality.

References:

Orchestrating timely check cystoscopy after radical radiotherapy to the bladder

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Background to the audit: Patients treated radically for muscle invasive bladder cancer have a high risk of recurrence. For those who have undergone radical radiotherapy (RT), post-RT cystoscopy facilitates prompt surgical salvage if appropriate. Appropriate timing of post-RT cystoscopy requires careful and timely communication between centre providing RT and peripheral urology services.

Standard, indicator and target: National Institute of Health and Care Excellence (NICE) guidelines advocate rigid cystoscopy within three months of completion of RT.

All our patients should:

- Undergo cystoscopy within three months of end of RT, unless evident why not indicated or unable to be performed within this time
- Have end-of-treatment letters sent to peripheral urology services, generated within 14 days of completion of RT.

Methodology: Patients who underwent radical RT to bladder from 2011–2013 identified. Radiotherapy and end-of-treatment letter dates obtained from local records. Peripheral urology clinics contacted for date of first cystoscopy post-RT or reason for not having cystoscopy if appropriate.

Results of 1st audit round: 100 patients who completed RT were identified. 96 patients (96%) either underwent cystoscopy or had a valid reason for not undergoing cystoscopy documented (87% and 9% patients, respectively). Among patients who underwent cystoscopy, seven (8%) and 37 (43%) had procedure within three and four months, respectively. Ninety-eight (98%) had end-of-treatment letters. 48 (48%) had letter typed within 14 days.

1st action plan: Automatic letter to referring urologist indicating likely time of cystoscopy generated at time of RT booking; check this letter has been done at time of RT planning.

Standard agreed end-of-treatment letter to be sent at completion of RT.

Further discussion planned by peripheral urology services regarding dedicated uro-oncology cystoscopy lists. Re-audit 18 months.

References:
1. www.nice.org.uk/guidance/ng2 (accessed 30/03/2016)

Auditor of treatment of older patients with lung cancer

V. Ezhil, L.D. Phillips, L. Gunn, K. Nimako
Clinical Oncology, Royal Surrey County Hospital, Guildford, Surrey, United Kingdom
1. East Surrey Hospital, Redhill, United Kingdom

Background to the audit: Older cancer patients receive less treatment than younger patients.6–7 Detrimental physiological changes occur from age 70.2
Patients were audited as over 70 and under 70 to see if older patients received less treatment.

**Standard, indicator and target:** No standard exists for the proportion of older patients with lung cancer receiving active anti-cancer treatment. We generated our standard from the proportion of under 70s receiving active treatment. Our target was 80% of the proportion of under 70’s receiving treatment.

**Methodology:** Data for patients with biopsy proven lung cancer discussed at the multidisciplinary team (MDT) between 01/07/12 and 31/12/13 was collected and patients were divided into four groups. Under 70 years old radical (stage I-IIa and T4N2), under 70 palliative (other IIb and stage IV), 70+ radical and 70+ palliative.

**Results of 1st audit round:** Data was available for 197 new patients. 13% stage I, 7% stage II, 29% stage III (18% IIa, 11% IIb) and 51% stage IV. Median age was 70 (range 41–95 years). Overall survival was 22 vs 11 months for radical patients under 70 and over 70. Overall survival for palliative patients was four months irrespective of treatment. Radical treatment in over 70s and under 70s was similar (57% vs 52%). Best supportive care as first treatment was 3% and 7% in radical patients under and over 70. It was 5% in palliative patients under 70 and 50% in over 70s. Chemotherapy rates for under 70 vs over 70 was 75% vs 34%. One-third of palliative patients over 70 were too unwell to attend an oncology clinic. 50% of palliative patients over 70 who attended clinic received palliative chemotherapy. The target of 80% of 75% of younger patients (60%) was not reached.

**1st action plan:** Implement a geriatric screening tool (G8) before attending clinic to identify those fit for chemotherapy, aiming to prevent unnecessary clinic attendance.

**References:**

**Stereotactic body radiotherapy (SBRT) for metastatic breast cancer: an audit of the Royal Marsden experience**

D.R. Henderson, A. Kirby, I. Locke, G. Ross, D. Tait, V. Khoo, N. van As

**Radiotherapy, Royal Marsden Hospital, London, United Kingdom**

**Background to the audit:** There is little data specific to breast cancer for SBRT. Case series indicate that SBRT to metastatic disease can be delivered safely with high local control.1

**Standard, indicator and target:** Common terminology criteria for adverse events (CTCAE) Grade 3 toxicity ≤ 5% Local control (LC) at one year ≥ 80%.

**Methodology:** A review of all patients having SBRT for metastatic breast cancer from 2011 to present. A three fraction schedule was given on alternate days, typically prescribed to the 80% isodose. LC and progression-free survival (PFS) were assessed with cross sectional imaging. All patients but one had imaging within six months of most recent follow-up.

**Results of 1st audit round:** Nineteen sites were treated in 17 patients. Median dose was 27 Gray (Gy) (biologically equivalent dose (BED) 3.5–96 Gy). Sites treated: spine (12), other bone (4), sternum (2) and liver (1). Median follow-up was 22 months (inter-quartile range [IQR] 6.9–32.6).

**Treatment settings were:** metachronous (13) and synchronous (2) oligometastatic disease, and widespread metastatic disease for local control (4).

Two patients experienced grade 2 toxicity (nausea; dysphasia). One patient (5.3%) developed grade 3 toxicity due to worsening of a pre-existing vertebral fracture following disease shrinkage, which was treated successfully with surgical stabilisation.

Three patients experienced local failure on imaging (3.2–13.2 months). Estimated LC at one and two years was 82% and 76%, respectively. Estimated PFS in patients with 1–3 sites of disease at one and two years was 79% and 39%, respectively (n=14).

**1st action plan:** Early results from this ongoing audit are reassuring with respect to LC and toxicity. This audit will continue to monitor toxicity associated with this novel treatment. The phase III Conventional care Or Radio-ablation in the treatment of Extracranial metastases (CORE) trial will open shortly, and will determine the benefit of adding SBRT to standard care in the oligometastatic setting.2

**References:**
2. www.ucl.ac.uk/core-study (last accessed 30/03/2016)

**Salvage radiotherapy for relapsed non-small cell lung cancer (NSCLC). Is it worth it?**

F. Colicchio 1, R. Johnston 1, J. McAleese 1, R. Eakin 1, G. Hanna 1

1Belfast City Hospital, Belfast, United Kingdom

1Centre for Cancer Research and Cell Biology, Queens University, Belfast, United Kingdom

**Background to the audit:** Effective surgical salvage for recurrent and second primary NSCLC is possible, with reported five-year survival rates between 8% and 40% and 25% to 53%, respectively.1,2 Although large surgical series have consistently shown that treating recurrences improves survival, this is only feasible in 1 to 4% of patients with isolated local recurrence.3,4 This is not the case with computed tomography (CT) detected second primary NSCLC, which are typically small and detected asymptptomatically more than 90% of the time.

Consequently, such tumors can be resected more than 50% of the time.4 For patients who are unfit for surgery, stereotactic ablative radiotherapy (SABR) enables a curative treatment option, achieving five-year local control rates of approximately 90%, without decreasing patient-reported quality of life.5

Standard, indicator and target:
To assess the effectiveness of salvage irradiation.

**Results of 1st audit round:** 47 patients were treated with salvage radiotherapy between 2006 and 2015. The median age was 71 years (54 to 86). 56% were male. 23% had clinical lung cancer; 43% squamous and 34% adenocarcinoma. 59% performance status (PS) 0–1, 57% were stage I–II. 83% had relapsed after prior surgery, 15% post radiotherapy and one patient post radiofrequency ablation (RFA). The median time from first treatment was 24 months. 10% died within 90 days of therapy and 16% within six months. The median survival was 22 months, two-year overall survival (OS) 47%. At two years 74% had local control and 48% distant control.

The median age was 71 years (54 to 86). 56% were male. 23% had clinical lung cancer; 43% squamous and 34% adenocarcinoma. 59% performance status (PS) 0–1, 57% were stage I–II. 83% had relapsed after prior surgery, 15% post radiotherapy and one patient post radiofrequency ablation (RFA). The median time from first treatment was 24 months. 10% died within 90 days of therapy and 16% within six months. The median survival was 22 months, two-year overall survival (OS) 47%. At two years 74% had local control and 48% distant control.

**1st action plan:** Salvage radiotherapy is an effective and safe treatment in a selected population.

Follow-up protocols should be designed to detect those suitable for salvage therapy.

**References:**
Determining Optimal Array Layouts for Delivering TTFields to the Lungs Using Computer Simulations

**Topic:** Advanced General

**Noa Urman,1 Zeev Bomzon,1 Uri Weinberg,2 Hadas Hershkovich,3 Eilon Kirson,1 Yoram Palti1**

1Novocure Ltd., Haifa/Israel, 2Novocure GmbH, Root D/Switzerland

**Background:** Tumor Treating Fields (TTFields) are low intensity, alternating electric fields in the intermediate frequency range. TTFields disrupt mitosis by interfering with formation of the mitotic spindle. The therapy is FDA approved for the treatment of glioblastoma (GB). A study to assess the efficacy of TTFields in combination with chemotherapy for the treatment of mesothelioma is underway, and a pivotal study testing the efficacy of TTFields in NSCLC is planned. TTFields are delivered through two pairs of transducer arrays applied to the patient’s skin. In-vivo and In-vitro studies suggest that treatment efficacy increases with field intensity. Therefore personalizing the array placement to deliver optimal field distributions is important and is a prerequisite when treating GB patients. However, optimal array layouts for lung cancer patients have not yet been determined. Here we present a finite element simulations-based study investigating optimal array layouts in male and female anatomic models.

**Methods:** The study was performed using the Sim4Life software package and the DUKE and ELLA computational models (ZMT, Zurich, Switzerland). To represent individuals with a variety of body dimensions, the models were linearly scaled. The distribution of TTFields within the thorax of these models was calculated for a set of array layouts. The layouts were ranked with highest scores for those that conformed well to body contours and delivered uniform high intensity fields to the lungs.

**Results:** Uniform field distributions within the lungs are obtained when the arrays are axially-aligned with the parenchyma as much as anatomically possible. Generally, the layouts that received the highest scores were those in which one pair of arrays delivered an electric field from the anterolateral to the posterior-contralateral aspect of the patient, with the second pair inducing the field from the antero-contralateral to the posterolateral aspect of the patient. However, due to body contours, this type of layout does not adhere well to smaller females, potentially hampering the efficient delivery of TTFields. Therefore, for smaller females, a layout in which one pair of arrays is placed on the lateral and contralateral aspects of the patients, and a second set of arrays is placed on the anterior and posterior aspects of the patient is preferred.

**Conclusion:** This study provides important insights into how TTFields distribution in the lungs is influenced by the array layout. These results should be accounted for when developing guidelines for transducer array placement on the thorax.

**Keywords:** Novel Therapies, Tumor Treating Fields, NSCLC, TTFields

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Analysis of the Incidence of Cancer Cachexia in Patients with Advanced Lung Cancer at Referral to a Dietitian

**Topic:** Advanced General

**Adele Hug,1 Iain Phillips,1 Lindsey Allan,1 Jeewaka Mendis,2 Veni Ezhil1**

1St Lukes Cancer Centre, Royal Surrey County Hospital, Guildford/United Kingdom, 2University of Surrey, Surrey Clinical Research Centre, Guildford/United Kingdom

**Background:** Lung cancer is the second most common cancer diagnosed in men and women in the UK with a very poor 5 year survival (10%). There is a lack of robust data on the stage of cachexia in which patients with lung cancer present. The severity of cachexia can influence overall outcomes and a patient’s quality of life. Refractory (irreversible) cachexia indicates a poor prognosis.

**Methods:** We reviewed all patients diagnosed with metastatic primary lung cancer that were referred to the Macmillan Oncology Dietitians over a 4 year period at the Royal Surrey County Hospital. Reasons for referral commonly included: weight loss, glycemic control in diabetes, decreased oral intake and food texture modification. We compared self-reported usual body weight (UBW) to weight at referral. Patients were defined as cachectic if weight loss was >5% and refractory cachexia if survival was <90 days from dietitian review.

**Conclusion:** This study provides important insights into how TTFields distribution in the lungs is influenced by the array layout. These results should be accounted for when developing guidelines for transducer array placement on the thorax.

**Keywords:** Novel Therapies, Tumor Treating Fields, NSCLC, TTFields
Results: 310 patients with incurable lung cancer were reviewed by the dietitian. Mean age was 68.8 (range 36-89). 42% were female, 58% were male. Mean weight loss was 10%. 76% of patients had lost >5% of usual body weight. Mean pre-cancer body mass index (BMI) was 26.9 (kg/m2), mean BMI at referral was 23.0 (kg/m2). Median survival of non-cachectic and cachectic cohorts were different (299 vs 188 days respectively, p=0.0078). 24% (73 patients) had refractory cachexia.

Conclusion: Our study shows cachexia is very common (76%) in lung cancer and affects survival. A quarter of patients had refractory cachexia. BMI is an insensitive measure of weight loss. Early symptom control improves survival in lung cancer and this data suggests patients are routinely being referred too late to a dietitian. Cachexia in lung cancer is a significant clinical problem. Could upfront assessment of cachexia improve outcome in patients with advanced lung cancer? We propose to investigate this further.

Keywords: cachexia, metastatic, dietitian, nutrition

P1.06-011
Altered Body Composition and Fat Loss in Advanced Non-Small Cell Lung Cancer

Topic: Advanced General

Anant Mohan, Rosemary Poulouse, Ashraf Ansari, Randeep Guleria, Karan Madan, Vijay Hadda, G. Khilnani Dept of Pulmonary Medicine and Sleep Disorders, All India Institute of Medical Sciences, New Delhi/India

Background: Assessment of body composition, including fat mass and fat%, is a useful measure of nutritional status in cancer and may help guide nutritional interventions. However, these abnormalities have not been well documented in lung cancer. We aimed to study alterations in parameters of body composition in non-small cell lung cancer (NSCLC).

Methods: A retrospective chart review was conducted of all newly diagnosed patients with NSCLC. Age and sex matched healthy controls were recruited prospectively. Disease staging was done according to the American Joint Committee on Cancer (7th edition). Performance status was assessed using the Karnofsky performance Scale(KPS), and the Eastern Cooperative Oncology Group (ECOG). Details of body composition including basal Metabolic Rate (BMR), total body water (TBW), fat mass, and Fat-free mass (FFM) were calculated by bioelectric impedance method using TANITA TBF 300 body composition analyzer.

Results: A total of 256 patients (83.6% males) and 211 controls (81.5% males) were studied. The mean (SD) age of patients was 54.5(9.0) years, median smoking index was 598 (range, 0-2500) and mean duration of symptoms was 158.3(91.7) days. Median KPS was 80 (range, 40-100). Majority had Stage IV disease (54.7%), followed by Stage III (41.4%) and Stage II (3.9%). All measured components of body composition were significantly lower in NSCLC compared to controls (Table). Among patients with normal body weight (BMI 18.5 – 25 kg/m²), the TBW and FFM were significantly lower compared to their healthy counterparts.

Table: Comparison of body composition between patients and controls

<table>
<thead>
<tr>
<th></th>
<th>Patients (n=214)</th>
<th>Controls(n=172)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age(years)</td>
<td>54.5(8.9)</td>
<td>53.9(9.2)</td>
<td>0.11</td>
</tr>
<tr>
<td>BMI(kg/m²)</td>
<td>20.0(3.5)</td>
<td>24.5(3.8)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Body fat %</td>
<td>16.4(8.3)</td>
<td>21.6(6.6)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Fat</td>
<td>8.8(5.4)</td>
<td>15.9(9.9)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mass(kg)</td>
<td>23.6(10.9)</td>
<td>33.9(6.9)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>FFM(kg)</td>
<td>44.3(7.7)</td>
<td>53.1(6.2)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>TBW(kg)</td>
<td>32.4(5.4)</td>
<td>38.7(4.9)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Females Patients(n=42)</td>
<td>Controls(n=39)</td>
<td>p value</td>
<td></td>
</tr>
<tr>
<td>Age(years)</td>
<td>52.8(8.9)</td>
<td>51.6(8.4)</td>
<td>0.5</td>
</tr>
<tr>
<td>BMI(kg/m²)</td>
<td>20.9(3.9)</td>
<td>28.4(3.5)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Body fat %</td>
<td>23.6(10.9)</td>
<td>33.9(6.9)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Fat</td>
<td>12.4(7.8)</td>
<td>22.2(7.4)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Mass(kg)</td>
<td>35.7(4.7)</td>
<td>41.7(4.9)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>FFM(kg)</td>
<td>26.3(3.3)</td>
<td>30.6(3.6)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Conclusion: NSCLC is associated with significant malnutrition and altered body composition, especially reduction in the percentage of body fat. Nutritional interventions must, therefore, be tailored accordingly for these patients.

Keywords: bioimpedence, lung cancer, body composition

P1.06-012
Central and Peripheral Lung Adenocarcinomas Exhibit Different Timing and Predilection for Distant Metastasis

Topic: Advanced General

Thomas Klikovits,1 Zoltan Lohinai,1 Katalin Fabian,2 Márton Gyulai,3 Andrea Fodor,4 Judit Varga,5

Conclusion: NSCLC is associated with significant malnutrition and altered body composition, especially reduction in the percentage of body fat. Nutritional interventions must, therefore, be tailored accordingly for these patients.

Keywords: bioimpedence, lung cancer, body composition
2% had documented driving advice.

First action plan: 15% nominally suitable to aggressive local therapy did not proceed but reason clearly documented. Most not suitable; uncontrolled disease.

Driving advice poorly documented.

Prospective audit of stereotactic radiotherapy cases proposed in N.I. 12 Cy/2# rarely used.

References

Docetaxol in metastatic prostate cancer
K. Sritharan, S. Karp
North Middlesex Hospital, London, United Kingdom

Category: Prostate

Background to the audit: Docetaxol is used in the management of metastatic prostate cancer. Six cycles are given upfront in hormone sensitive prostate cancer and ten cycles are recommended in castrate resistant disease. ASCO recommends using colony stimulating factors prophylactically when the febrile neutropenia risk is greater than 20%. The dose is 75 mg/m² given every three weeks. Many older men at NMUH were given a dose of 65 mg/m² to ensure tolerability.

Standard: As per the TAX 327 trial[2], rates of febrile neutropenia rates were 3% and in Stampede[3], the rates were 12%.

Indicator:
1. Primary aim of audit is to establish rates of febrile neutropenia and neutropenia in patients receiving Docetaxol.
2. We also explored the rates of response and toxicities between men receiving 65mg/m² versus 75mg/m² of Docetaxol.

Target: Less than 12% of patients receiving Docetaxol develop febrile neutropenia.

Methodology: Audit was performed retrospectively. Patients with metastatic prostate cancer who were prescribed Docetaxol between January 2014 and 2016 were identified using the chemotherapy prescribing system, Chemocare. Further information about admissions was obtained from the hospital computer database and notes.

Results of first audit round:
- 21 patients identified, aged between 54 and 86 years old.
- 8 patients received a dose of 60mg/m² and 13 received a dose of 75mg/m²[2]
- 15 patients had castrate resistant disease and six patients had hormone sensitive disease.
- Rate of neutropenia sepsis was 25% and rate of grade 3–4 neutropenia was 15%. Rate of febrile neutropenia was higher than expected and rate of grade 3–4 neutropenia was in keeping with the trials.
- Rates of response were similar in the 60mg/m²[2] and the 75mg/m²[2] group. The toxicities seemed largely similar in both groups, and the number of hospital admissions was overall less in the 60mg/m²[2] group.

First action plan:
1. Add in a five-day course of prophylactic granulocyte-colony stimulating factor (G-CSF) for patients receiving Docetaxol chemotherapy in metastatic prostate cancer as per ASCO guidelines.
2. The number of patients included in the 2nd part of the audit is small therefore further data is required.

References

Survival outcomes after whole-brain radiotherapy for metastatic melanoma
D. Yang, K. Yip, J. Adlam, H. Laidley, M. Mashar, W. Ye
Department of Clinical Oncology, Ipswich Hospital NHS Trust, Suffolk, United Kingdom

Category: Radiotherapy

Background to the audit: 60% of melanoma patients develop brain metastases (BM)[1]. Whole brain radiotherapy (WBRT) is a commonly used treatment option at our local centre, although it is unclear if patients gain significant improvements in quantity or quality of life. An analysis of overall survival (OS) following WBRT may help determine whether it is being used appropriately. Analysis of 30-day and 90-day mortality after radiotherapy is recommended in the Cancer Reform Strategy.[2]

Standard: Survival outcomes were benchmarked against the expected value for each melanoma disease-specific Graded Prognostic Assessment (DS-GPA) score as published by Sperduto et al.[3]

Indicator: Percentage of DS-GPA subgroups within our cohort meeting or exceeding the standard.

Target: 100%.

Methodology: Data on diagnosis, treatment, and death were collected from the electronic records of all patients with metastatic melanoma who received WBRT at Ipswich Hospital between January 2011 and December 2016. DS-GPA scores were calculated from Karnofsky performance status (KPS) and number of BMs. OS of the cohort was estimated using the Kaplan-Meier method.

Results of first audit round: 23 patients with a mean age of 65 years were audited. 30-day mortality was 9%, 90-day mortality was 43%. The median survival for the whole cohort was 3.29 months, significantly less than the 6.74 months suggested by Sperduto et al. Further analysis of the survival of subgroups on the basis of DS-GPA score was not possible because performance status (PS) was documented in only 52% of patients. Of those with a documented PS, 50% had a KPS of <70, and 21% had a KPS of >90. Earlier death was noted in those with more than one brain metastasis: a single brain metastasis was associated with a mean survival of 62 weeks, 2–3 brain metastases with 14 weeks, and four brain metastases with ten weeks.

First action plan: Improve assessment and documentation of PS to allow calculation of DS-GPA, and facilitate targeting of more aggressive management of intracranial metastases to patients with fewer BMs and better PS, as they may derive greater benefit from alternative treatments such as stereotactic radiosurgery or neurosurgery.

References

Stereotactic radiotherapy for primary lung cancer
I Phillips, R. Flint, B. Hin, V. Ezbil
Royal Surrey County Hospital, Guildford, United Kingdom

Category: Radiotherapy

Background to the audit: Stereotactic ablative body radiotherapy (SABR) is now a standard treatment for non small cell lung cancer. It has an established role in patients who are medically inoperable and randomised trial data
suggests there is significantly less short-term mortality than surgical intervention.\textsuperscript{[1]}

As an established centre for SABR for primary lung cancer and oligometastatic disease we wanted to audit the outcomes of our initial cohort of patients.

**Standard:** For our standard we compared our results to two recent publications. Firstly a meta analysis of early stage primary lung cancer that has compiled clinical outcomes for published randomised control trials and secondly to the first UK case series, both published by St James Institute of Oncology, Leeds.\textsuperscript{[2][3]}

**Indicator:** One-year local control rate.

**Target:** Local control rate of over 90\% at one year.

**Methodology:** We reviewed all patients with available imaging treated between January 2012 and November 2016. More than 50\% of patients have been treated since June 2015. All patients with at least one post-treatment scan, or those who had died before a first scan were included.

**Results of first audit round:** 116 patients had been treated with SABR. They were followed up at seven different district general hospitals. Mean age was 66.5 years (range 56–90). 55\% of patients had a biopsy proven lung cancer, 45\% were radiologically diagnosed with a formal MDT decision of likely primary lung cancer.

Local control rate at one year was 97\%. Median survival is 713 days (95\% CI 579–848 days).

**First plan:** To establish accurate three-year survival data.

To maintain database of SABR patients.

Continue to follow-up SABR patients to see if median survival increases as cohort matures.

**References**


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**Regional audit of timing of surgery in patients receiving short course pre-operative radiotherapy (SCPRT) for rectal cancer**


* Christie NHS Foundation Trust, Manchester, United Kingdom

† University Hospital of South Manchester NHS Foundation Trust, Manchester, United Kingdom

**Category:** Rectal and colon

**Background to the audit:** SCPRT should be considered to reduce local recurrence risk for some rectal cancers where the circumferential resection margin is clear.\textsuperscript{[1][2][3]} SCPRT acute toxicity occurs two weeks from the start of treatment. This may impact on surgical outcomes.\textsuperscript{[4]} However, there is no clear consensus regarding the timing of surgery following SCPRT.\textsuperscript{[2][3]}

**Standard:** 95\% of patients operated within ten days from start of SCPRT. Primary aim: to assess timing of surgery in relation to SCPRT for patients in Greater Manchester and Cheshire.

Secondary aim: to improve the regional pathway.

**Indicator:** The number of days from commencement of SCPRT to surgery, for patients in Greater Manchester and Cheshire.

**Target:** 95\% of patients operated within ten days from start of SCPRT.

**Methodology:** Retrospective audit of patients treated with SCPRT 1/1/14 - 31/3/14 (1st audit) and 1/1/16 – 31/3/16 (re-audit).

Data collected: SCPRT start date and surgical date.

**Results of first audit round:** 43 patients (30 males: 13 females) received SCPRT. The range of days was 5–25 days.

13 out of the 43 (30.2\%) patients underwent surgery within ten days from start of SCPRT.

**First action plan:**

The above results were discussed at the Manchester Cancer Colorectal Pathway Board (MCCPB). Due to inconsistency, it was recommended that patients should receive surgery within 12 total days from the start of SCPRT.

Essentially patients would have SCPRT one week and surgery the following week. To improve the clinical pathway, referrals would include a surgical date to aid SCPRT.

To re-audit patients treated with SCPRT between 1/1/16 and 31/3/16 to assess the implementation of the recommendations.

**Results of second audit round:** 20 patients (12 males: 8 females) received SCPRT.

The range of days was 7–18 days.

19 out of the 20 (95\%) patients underwent surgery within 12 days from start of SCPRT.

**Second action plan:** 95\% of patients operated within 12 days from start of SCPRT was achieved. These results were re-discussed at the MCCPB. The one outlier was discussed to improve the patient pathway.

To re-audit in five years or as deemed clinically appropriate.

**Conclusion:** This simple pathway change has led to a dramatic improvement in time to surgery, in turn improving patient outcomes.

**References**

Intratumoral heterogeneity was reported in the literature to correlate to treatment outcome and overall survival. In this study, a volumetric voxel based map of intratumoral heterogeneity measured from CT images was used to guide dose painting. This approach was compared against dose painting based on FDG PET uptake distributions in regards to the overlap between the boost volumes and the delivered dose to target volumes and organs at risk (OAR).

**Material and Methods**

PET/CT and planning CT images for ten patients diagnosed with advanced inoperable non-small cell lung cancer (NSCLC) were retrieved retrospectively. The gross tumour volume (GTV) contour was used to segment the primary tumour from the CT and PET images. A volumetric voxel based map of intratumoral heterogeneity was generated from tumour CT image using a second-order statistical texture analysis method of grey level co-occurrence matrices. The FDG PET image was converted to SUV map. The low CT intratumoral heterogeneity regions within the generated texture map overlapped with high FDG uptake regions within the PET image (overlap of 65±11%). Hence, two boost volumes were identified, the low CT intratumoral heterogeneity region (Boost_{intratumorale}) and the high FDG uptake region of >50% SUVmax (Boost_{FDG}). A 3mm margin was added to the boost volumes to account for physical uncertainties and these volumes were labelled PTV_{intratumorale} and PTV_{FDG}. Two volumetric arc therapy plans (VMAT) were created for each patient, with a prescribed dose of 84Gy in 32 fractions to PTV_{intratumorale} and PTV_{FDG} and 64Gy in 32 fractions to the remainder of the clinical PTV. The dose to the boost volumes and OARs (spinal cord, oesophagus, normal lung and heart) was measured and compared between the two plans.

**Results**

The dose escalation to the boost volumes in the created plans were shown to be clinically feasible with the dose to OARs within tolerance limits and 95% of the target volume receiving ≥95% of the prescribed dose. When boosting based on PTV_{intratumorale}, the dose to 95% of PTV_{intratumorale} received ≥95% of the prescribed dose for 3 patients while the other seven patients received 80-92% of the prescribed dose. However, 95% of the Boost_{FDG} volume received ≥95% of the prescribed dose for 9 of the 10 patients.

**Conclusion**

The results show the feasibility of dose escalation in advanced NSCLC while keeping to normal tissue constraints. Moreover, the preliminary results suggest that boosting based on intratumoral heterogeneity measured from CT images, results in the high 18F-FDG regions receiving a high dose, indicating the potential of using CT intratumoral heterogeneity generated from standard CT images as a surrogate for functional imaging in dose painting.
Abstract in press European Journal of Surgical Oncology

G8 assessment for patients with lung cancer

I Phillips, K Webb, S Cabral, S Quirin, K Nimako and V Ezhil

Introduction

The aim of this project was to see whether a G8 assessment correlates with an intention to give anti-cancer treatment.

Method

We prospectively assessed all patients attending a respiratory clinic with a new diagnosis of lung cancer using a G8 questionnaire. This information was collected as part of completing an audit cycle approved by East Surrey Hospital audit committee. ‘Fit’ was defined as a G8 score of 15 or higher, ‘unfit’ as lower than 15. Statistical analyses performed were chi-squared and Mann-Whitney tests; p-values were two-tailed with a significant level set at <0.05.

Results

55 assessments were completed between October 2016 and May 2017. Mean age was 61 (range 55-87). 13 patients (24%) presented with stage 1 disease, 6 (11%) with stage 2, 10 (18%) with stage 3 and 26 (42%) with stage 4 disease. 28 had stage 1-3a, 27 patients had stage 3B or 4. 12 patients were fit, and 43 were unfit. Overall 12 out of 12 (100%) of fit patients were intended for at least one kind of treatment, and 37 of 43 (86%) unfit patients were intended for treatment (p=0.3206). 20 patients were considered for radical treatment, and 35 patients were considered for palliative treatment. The mean G8 score for radical patients was 13.4, and the mean score for palliative patients was 10.7 (p=0.00158). Overall, those intended for treatment had a mean score of 12.1, and those who were not intended for treatment had a mean score of 7.9 (p=0.0028). Of the 35 palliative patients, 26 were deemed fit for chemotherapy (mean score 11.5), and nine patients as not fit for chemotherapy (mean score 8.2, p=0.0053).

Discussion

Our results show that the G8 assessment may be a useful tool for assessing fitness to treat in lung cancer and is worth further evaluation in larger studies.
A Dose Painting Study Based on CT Intratumoural Heterogeneity vs. FDG PET Uptake in NSCLC

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\textbf{OBJECTIVES}

Radical radiotherapy ± chemotherapy is the standard of care for treatment of locally advanced Non-Small Cell Lung Cancer (NSCLC). Standard dose escalation of external beam radiotherapy has not led to better treatment outcomes\textsuperscript{1}. CT intratumoural heterogeneity has been shown to correlate with patient survival in NSCLC\textsuperscript{2,3}. We pursued a novel approach to guide dose painting, using volumetric voxel based mapping of intratumoural heterogeneity captured from CT images. This approach was compared against dose painting based on FDG-PET uptake distributions; in regards to the overlap between the boost volumes and the delivered dose to target volumes and organs at risk (OAR).

\textbf{MATERIALS and METHODS}

- PET/CT and planning CT images for ten patients diagnosed with advanced inoperable NSCLC were collected, the gross tumour volume (GTV) contour was used to segment the primary tumour from the CT and PET images.
- A volumetric voxel based map of intratumoural heterogeneity was generated from tumour CT image using a second-order statistical texture analysis method of grey level co-occurrence matrices.
- The FDG PET image was converted to an SUV map.
- The low CT-derived intratumoural heterogeneity regions within the generated texture map overlapped with high FDG uptake regions within the PET image (overlap of 65±11\% SD). Hence, two boost volumes were identified, the low CT-derived intratumoural heterogeneity region (Boost\textsubscript{Heterogeneity}) and the high FDG uptake region of >50\% SUV\textsubscript{max} (Boost\textsubscript{FDG}).
- A 3mm margin was added to the boost volumes to account for physical uncertainties and these volumes were labelled PTV\textsubscript{Heterogeneity} and PTV\textsubscript{FDG}.
- Two volumetric arc therapy plans (VMAT) were created for each patient, with a prescribed dose of 84\textsubscript{Gy} in 32 fractions to PTV\textsubscript{Heterogeneity} or PTV\textsubscript{FDG} and 64\textsubscript{Gy} in 32 fractions to the remainder of the clinical PTV.
- The dose to the boost volumes and OARs (spinal cord, oesophagus, normal lung and heart) was measured and compared between the two plans.

\textbf{RESULTS}

- The dose escalation to the boost volumes in the created plans were shown to be clinically feasible with the dose to OARs within tolerance limits and 95\% of the target volume receiving ≥95\% of the prescribed dose.
- When boosting based on PTV\textsubscript{Heterogeneity}, the dose to 95\% of PTV\textsubscript{FDG} received ≥95\% of the prescribed dose for 3 patients while the other seven patients received 80-92\% of the prescribed dose. However, 95\% of the Boost\textsubscript{FDG} volume received ≥95\% of the prescribed dose for 9 of the 10 patients.

\textbf{CONCLUSIONS}

- The results show the feasibility of dose escalation in locally advanced NSCLC while keeping to normal tissue constraints.
- The preliminary results suggest that boosting based on intratumoural heterogeneity measured from CT images, results in the high 18\textsubscript{F}-FDG regions receiving a high dose, indicating the potential of using CT intratumoural heterogeneity generated from standard CT images as a surrogate for functional imaging in dose painting.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure1.png}
\caption{An example of the GTV, Boost\textsubscript{Heterogeneity}, and Boost\textsubscript{FDG} for a patient from our investigated cohort.}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.png}
\caption{The dose received by 95\% of the Boost\textsubscript{FDG} volume in the boost plans based on PTV\textsubscript{Heterogeneity} labelled VMAT\textsubscript{Heterogeneity} and PTV\textsubscript{FDG} labelled VMAT\textsubscript{FDG}. The dashed line is 95\% of the prescribed dose and the solid line is 100\% of the prescribed dose.}
\end{figure}

\textbf{REFERENCES}

Background
Lung cancer is the second most common cancer diagnosed in men and women in the UK with a very poor 5 year survival (10%)\(^1\).
Cancer cachexia is a progressive disorder, leading to decreased physical activity, adverse psychological side effects, poor performance status and higher mortality rates.
The severity of cancer cachexia can influence overall outcome; refractory (irreversible) cachexia indicates a poor prognosis of usually less than 3 months\(^2\). Cancer cachexia has previously been defined by percentage weight loss from usual body weight, ‘weight loss greater than 5%, or weight loss greater than 2% in individuals already showing depletion according to current bodyweight and height (BMI <20 kg/m\(^2\)) or skeletal muscle mass loss (sarcopenia)’\(^2\).
There is a lack of robust data in advanced lung cancer on the stage of cancer cachexia and whilst screening, assessment and prophylactic nutrition support is standard practice for patients with primary cancers of the head and neck region, this is not the case for those with lung cancer.

Methods
- All patients with advanced lung cancer referred to the oncology dietitian from July 2011 to April 2014 were included
- Height, weight at referral, patient reported usual body weight was collected, and Body mass index (BMI) was calculated.

Results
- 314 patients were included
- Mean age = 68.8 years (36 to 89 years)
- 42% were female, 58% were male
- Mean weight change at referral: -10% (-35.8% to +7.3%)
- 76% of patients had lost >5% of pre diagnosis weight.
- Mean pre-diagnosis BMI: 26.9 kg/m\(^2\)
- Mean BMI at referral: 23.0 kg/m\(^2\).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cachectic (&gt;5% weight loss)</th>
<th>Non cachectic (&lt;5% weight loss)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% weight loss at referral</td>
<td>-12.9</td>
<td>-2.1</td>
</tr>
<tr>
<td>Mean pre-treatment BMI (kg/m(^2))</td>
<td>25.7</td>
<td>25.1</td>
</tr>
<tr>
<td>Mean post treatment BMI (kg/m(^2))</td>
<td>22.4</td>
<td>24.5</td>
</tr>
</tbody>
</table>

Conclusion
- It is known that early symptom control improves survival in lung cancer\(^3\).
- Cancer cachexia is very common (75%) in patients with advanced lung cancer at time of dietitian review.
- BMI is a poor marker of weight loss. These patients have a BMI within the healthy range of 20-25 kg/m\(^2\) before and after their cancer diagnosis in spite of significant weight loss.
- It is not clear how common malnutrition, cachexia or sarcopenia is at presentation in lung cancer.
- Could up front dietetic assessment and counselling improve patient experience and outcome in patients with advanced lung cancer?
- Ethical approval is being sought to prospectively assess the rate of cancer cachexia in lung cancer and its correlation with other simple nutrition assessment tools in the NAIL trial (Nutrition Assessment and Intervention in Lung Cancer).

References

We would like to thank Macmillan for an educational grant to attend the 2016 NCRI conference.

Correspondence to: a.hugg@nhs.net
Introduction
Cancer cachexia is a multifactorial syndrome characterised by a loss of muscle mass and function and is an adverse effect of many common cancers. The presence of refractory (irreversible) cachexia is associated with a very poor overall survival. Radiological sarcopenia is a feature of cancer cachexia and can be assessed on CT imaging. Sarcopenia refers to the loss of muscle mass, power and function (1). Cross sectional measurement of the psoas muscle is one method of assessing radiological sarcopenia. It is an accurate, quick and inexpensive assessment of sarcopenia as the imaging forms part of a patient’s standard staging investigations.

Methods
This was a feasibility study to assess how manageable it was to measure sarcopenia. Data was collected from an MDT between July 2012 and December 2013. All patients with biopsy proven lung cancer from this period were eligible. Patients were included if they had a formal recorded height measurement as part of lung function testing or the electronic chemotherapy record. Anterior-posterior and lateral measurements of greatest diameter of psoas muscle was made at level of L3 through the transverse processes from the diagnostic CT. Left and right psoas muscle measurements were taken and standardised for height. As per figure 1. This measure had previously been found to be equivalent to more complex methods (2). The cut off value for men was 390mm/m² and 550mm/m² for women. These are from internationally agreed consensus guidelines (3).

Results
• 90 patients were identified retrospectively with appropriate imaging and recorded height data
• 56% were male, 44% female
• Mean age was 73 (range 41-88)
• 47% of patients with lung cancer were sarcopenic
• Median survival of non-sarcopenic patients was 15 months. Median survival of sarcopenic patients was 12 months (p= 0.22).

Discussion and future recommendations
• Sarcopenia is common in patients with lung cancer.
• Sarcopenia assessment using cross sectional measurements of psoas muscle is quick, easy, inexpensive and reproducible.
• Combining this assessment with weight loss could measure cancer cachexia.
• There is an association between sarcopenia and survival.

References
1. Cruz-Jentoft et al. 2010, Age and Aging, 39(4)412-23
2. Jones et al. 2015, Colorectal disease, 17(1)20-26
3. Fearon et al. 2011, Lancet Oncology 12(5) 489-495

Correspondence to Iain Phillips – iain.phillips1@nhs.net
Audit of treatment received by older patients with lung cancer between July 2012 – December 2013

Philips I, Gunn L, Nimako K, Ezhil V
St Lukes Cancer Centre – Royal Surrey County Hospital

Background
40% of lung cancer cases occur in over 70’s. It is perceived that older patients with other common cancers are under treated and less likely to enter clinical trials [1-6]. We completed an audit to review our management of patients over 70 versus under 70 in both the radical and palliative setting.

Standards, Indicators and Targets
No standard exists for the management of older patients with lung cancer. We generated our standard from the number of patients treated in the under 70 group. Our target was that 80% of the proportion of under 70’s, receiving treatment in the over 70’s.

Methodology
Data was collected for patients with biopsy proven lung cancer discussed at the MDT between 01/07/12 and 31/12/13. Patients were divided into 4 groups based on their suitability for treatment as per the MDT.
• Under 70 years old radical (stage I-IIa and T4N2)
• Under 70 palliative (other IIb and stage IV)
• Over 70 years radical
• Over 70 years palliative

Results
Data was available for 197 new patients. 13% stage I, 7% stage II, 29% stage III (18% IIia, 11% IIib) and 51% stage IV. Median age was 70 (range 41-95 years).

Overall survival for radical patients under 70 was 22 months versus 11 months in the over 70’s group. Irrespective of age, overall survival for all palliative patients, including those who had best supportive care alone, was 4 months.

Radical treatment rates in over 70’s and under 70’s were similar (57% vs 52%). For those with disease amenable to radical treatment, similar rates were referred for best supportive care irrespective of age (3% and 7%). For those with metastatic lung cancer 5% of under 70’s were referred for best supportive care compared with 50% in over 70’s.

For those with metastatic disease, 75% of under 70’s received palliative chemotherapy. 1/3 of patients over 70 were too unwell to attend clinic, a further 1/3 attended but were unfit for treatment following clinic assessment. Therefore 34% over 70’s received palliative chemotherapy.

Conclusion
• Radical treatment rates for the patients >70y are equivalent to younger patients.
• Patients >70y with metastatic lung cancer are less likely to receive palliative chemotherapy.
• Patients >70y with metastatic disease are 10 times more likely to be referred for best supportive care.

Actions
To implement a geriatric screening tool (G8) before attending clinic and correlate with those identified as fit for chemotherapy.

References
Choosing the appropriate Cone Beam CT mode for treating abdominal metastases with SABR on a Linear Accelerator

Royal Surrey County Hospital, Guildford.

Introduction
As a Commissioning Through Evaluation (CTE) centre we wanted to formalise our Cone Beam CT (CBCT) protocol for treating patients with abdominal level oligometastases. We wanted to compare different imaging modes when treating patients eligible for Stereotactic Ablative Body Radiotherapy (SABR) through CTE using VMAT. Patients receive 3 CBCTs during each treatment. Abdominal CBCTs are often limited by bowel gas obstructing soft tissue visualisation, leading to difficulties in target matching.

Methods
Patients undergo a ‘day 0’ dry run of their radiotherapy. The treatment is delivered in 2 arcs as VMAT. For each fraction of treatment a patient received a pre-, mid and post-treatment CBCT. They had at least 1 pelvic mode and 1 spotlight mode CBCT with the same slice thickness (usually 2mm) during each fraction of treatment.

We used the standard deviation as a metric to determine whether Pelvis or Spotlight mode was better at abdominal soft tissue visualisation. An area of bowel gas artefact, fat and other tissue were chosen on each Spotlight and pelvis modes.

Power standard deviations would reflect better image reconstruction of homogenous regions, leading to greater confidence in soft tissue matching.

<table>
<thead>
<tr>
<th>ROI</th>
<th>Standard Deviation in ROI</th>
<th>T-test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spotlight</td>
<td>Pelvis</td>
<td></td>
</tr>
<tr>
<td>Tissue</td>
<td>43</td>
<td>39</td>
</tr>
<tr>
<td>Fat</td>
<td>41</td>
<td>38</td>
</tr>
<tr>
<td>Artefact</td>
<td>73</td>
<td>69</td>
</tr>
</tbody>
</table>

Discussion and future recommendation
• there was no statistical significance between the Spotlight and Pelvis mode
• the average standard deviation was marginally lower for the Pelvis mode in all three regions.
• Due to the faster acquisition time and overall lower dose the spotlight mode has been favoured for soft tissue matching.
• Radiographers have also commented their preference for the mode.

References

CBCTs were matched to the planning CT via bony registration for 18 separate fractions over 9 patients. Pelvis and Spotlight CBCTs were taken within 20 minutes of each other giving a near simultaneous comparison of on-treatment image acquisition. Once registered, a 2x2cm ROI was positioned within areas of related tissue in the same space on both CBCTs and CT to measure the mean and standard deviation in the HU numbers.
Introduction
As a designated Commissioning Through Evaluation (CTE) Stereotactic Ablative Body Radiotherapy (SABR) centre, we evaluated the service given to patients who have received SABR for primary lung cancer or to oligometastases within CTE.

Methods
We surveyed a random sample of patients who received their treatment under the care of 1 consultant. Patients were eligible if they were 4 weeks from completion of treatment. Patients were given the feedback form after their clinic appointment.

Patients were asked the following:
1. Did they receive enough information about the treatment?
2. Did they receive enough information about medication needed for the treatment?
3. Was the treatment delivered in a timely manner?
4. Would they have the treatment again?

All answers were graded 1 to 5. 1=strongly disagree, 3=neither agree or disagree, 5=strongly agree. We also asked patients for specific comments to improve the service.

Results
We surveyed 33 patients. 28 patients had treatment to a primary lung tumour. 5 patients were treated within CTE. Average age was 77.9 (range 55-91).

100% of patients agreed/strongly agreed that they received sufficient information about the treatment, felt it was delivered in a timely manner and would have it again. 97% of patients agreed/strongly agreed that they had been well informed regarding the treatment. 88% of patients felt they had been well informed about medications required.

Mean travelling distance between home and hospital was 17 miles (range 2.8-44.7) and mean travelling time was 28 minutes (range 7-53).

Discussion
• Our patients had a positive experience receiving SABR treatment under our care.
• We have developed specific patient information for patients attending the clinic for Lung SABR.
• The comments directly informed our patient information sheet now given to patients to further improve their experience.
• To minimise delays and as some patients travel a significant distance for SABR we aim to perform a radiotherapy planning CT scan on the day of the new patient appointment.

Patient Comments
“Excellent Treatment all round.”
“I had perfect treatment”
“The whole treatment was easy and staff were brilliant”
“Everything was done to make the process as good as it could be”
“Warn about MRI, uncomfortable and noisy”
“More information on medication, particularly steroids”
“Bit uncomfortable lying flat for an hour”
“Rather a long delay between diagnostic scan and start of treatment”
Analysis of the Incidence of Cancer Cachexia in Patients with Advanced Lung Cancer at Referral to a Dietitian


St Luke’s Cancer Centre – Royal Surrey County Hospital, Guildford, Surrey, United Kingdom

Background

Lung cancer is the second most common cancer diagnosed in men and women in the UK with a very poor 5 year survival (10%) 1. Cancer cachexia is a progressive, multifactorial syndrome, leading to decreased physical activity, adverse psychological side effects, poor performance status and higher mortality rates. The severity of cancer cachexia can influence overall outcome; refractory (irreversible) cachexia indicates a poor prognosis of usually less than 3 months 2. Cancer cachexia has previously been defined by percentage weight loss from usual body weight, weight loss greater than 5%, or weight loss greater than 2% in individuals already showing depletion according to current bodyweight and height (BMI <20 kg/m2) or skeletal muscle mass loss (sarcopenia)3. There is a lack of robust data in advanced lung cancer on the stage of cancer cachexia and whilst screening assessment and prophylactic nutrition support is standard practice for patients with primary cancers of the head and neck region, this is not the case for those with lung cancer.

Methods

• Data was collected prospectively from June 2011 until July 2015.
• On referral to the dietitian date of birth, sex, treatment, actual weight, height, self reported usual body weight (UBW) were recorded.
• Age at referral was calculated and date of death was obtained from the NHS Spine and used to calculate overall survival from referral to the dietitian.
• Weight loss was calculated from UBW and body mass index (BMI) calculated.

Results

• 314 patients with advanced lung cancer were reviewed by the dietitian; average 94 each year.
• Mean age was 68.8 (range 36 to 89). 42% were female. 58% were male.
• Mean weight loss was -10% (range -35.8% to +7.3%). 76% of patients had lost >5% of pre diagnosis weight.
• Mean pre-diagnosis BMI was 26.9kg/m2, mean BMI at referral was 23.0kg/m2.
• Reasons for referral commonly included: weight loss, glycaemic control in diabetes, decreased oral intake and food texture modification.
• Median survival of non-cachectic and cachectic cohorts were different (299 vs 188 days respectively, p=0.0078)

Conclusion

• It is known that early symptom control improves survival in lung cancer 3.
• Cancer cachexia is very common (75%) in patients with advanced lung cancer at time of dietitian referral .
• BMI is poor indicator of weight loss. These patients have a BMI within the healthy range of 20-25 kg/m2 before and after their cancer diagnosis in spite of significant weight loss.
• It is not clear how common malnutrition, cachexia or sarcopenia is at presentation in lung cancer.
• Could up front dietetic assessment and counselling improve patient experience and outcome in patients with advanced lung cancer?
• We are seeking ethical approval to prospectively assess the rate of cancer cachexia in lung cancer and its correlation with other simple nutrition assessment tools in the DAIL trial (Dietetic Assessment and Intervention in Lung Cancer).

References


From Fearon et al. 2011, Lancet Oncology 12(5):489-495

Kaplan-Meier curve p=0.0078

% weight loss at referral to the Registered Dietitian

n= 235
>5% wt loss

n= 75
<5% wt loss
No or precachexia

n= 235
>5% wt loss

n= 75
<5% wt loss
No or precachexia

All correspondence to a.hugg@nhs.net or iain.phillips1@nhs.net

We would like to thank Chugai for an educational grant to attend the 2016 World Conference on Lung Cancer 2016
Predicting lung function and fitness for radiotherapy from a CT scan

St Lukes Cancer Centre – Royal Surrey County Hospital
Centre for Vision, Speech and Signal Processing, Univ of Surrey

Introduction
Lung cancer is the commonest cause of cancer death worldwide. It is the second commonest cancer diagnosed in both men and women in the UK. CT scans are ubiquitous in assessing and managing lung cancer in the developed world. CT scans show anatomical information using density measured in Hounsfield Units (HU). Texture analysis (TA) can provide greater information about an image. The aim of this project was to see if TA outcome measures correlated with lung function using a region of interest from a patient’s CT scan.

How do you analyse texture?
Texture analysis (TA) is a way of getting data from an image or region of interest within an image. There are a range of ways of achieving this, in this study a voxel in an image was compared to the 26 other voxels around it, to see if they were similar or different. This built a map of similarity and difference rather than of density, as seen in a normal CT scan.

Methods
Patients were included if they had a diagnosis of lung cancer, and had both pre-treatment formal lung function tests and the radiotherapy planning CT scan available. A 4 x 2.5cm segment of lung from planning CT scan was extract and analysed as seen in figure 1. The entropy score was derived software using a GLCM (Grey Level Co-Occurrence Matrix) developed in house. Average (mean, median and mode) entropy score and density score (in HU) were derived for each volume. These scores were compared to % predicted FEV1 (volume of air expelled in 1 second) and TLCO (lung gas transfer function). Pearson correlation coefficient was used to analyse associations between different measures of texture and lung function (both FEV1 and TLCO).

Results
20 patients were included. When lung function is tested is it is calculated by comparing to a % predicted value standardized using height, gender and age. Range of % predicted value FEV1 ranged from 25-100%, TLCO from 43-112%. Highest correlation was between mode density and TLCO (0.81).

<table>
<thead>
<tr>
<th></th>
<th>Mean HU</th>
<th>Median HU</th>
<th>Mode HU</th>
<th>Mean entropy</th>
<th>Median entropy</th>
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</tr>
</thead>
<tbody>
<tr>
<td>FEV1</td>
<td>0.49</td>
<td>0.50</td>
<td>0.55</td>
<td>0.62</td>
<td>0.65</td>
<td>0.68</td>
</tr>
<tr>
<td>TLCO</td>
<td>0.7</td>
<td>0.72</td>
<td>0.81</td>
<td>0.60</td>
<td>0.64</td>
<td>0.59</td>
</tr>
</tbody>
</table>

Table 1 shows Pearson correlation co-efficients between measure of lung function (either TLCO or FEV1) and a measure of density of entropy.

Discussion
1. Lung function appears to correlate with scan appearance.
2. Extracting extra data from routine medical imaging is possible.
3. It may be possible how is fit for radiotherapy based on scan appearance.
Introduction
Royal Surrey County Hospital (RSCH) has been designated as a national centre able to treat oligometastases using Stereotactic Ablative Body Radiotherapy (SABR). SABR is a form of highly targeted radiotherapy, giving a radical treatment in fewer, larger doses, when compared to normal radical radiotherapy. Oligometastases are 1-3 areas of cancer that have metastasized from the original tumour. The hypothesis for treating oligometastases is that by controlling clinically apparent disease, this can prevent the need for systemic treatment and possibly improve overall survival. Recent data suggests that SABR treatment after chemotherapy in Non-Small Cell Lung Cancer significantly improves progression free survival (12 months vs 4 months) when compared to maintenance chemotherapy.

Examples of a treated spinal metastasis

Treating entire vertebral body, whilst keeping spinal cord dose within its tolerance

Methodology
Descriptive statistics have been used to present the nominal data collected. The sample group included all patients who have received SABR for oligometastases treated by the SABR team at RSCH, through the CTE (Commissioning Through Evaluation) programme. Clinical outcomes measured were; Local control rate, distant control rate and the relapse free rate.

Results
We have treated 51 lesions in 41 patients. Mean age at treatment 72 years old (range 36-90). 27% female and 73% male. Of the lesions treated 37% were lymph node metastases, 35% lung metastases, 25% bone metastases, and 2% adrenal metastases. The commonest primary tumour was prostate cancer (24%), melanoma (15%), colorectal (15%), lung (12%), breast (12%) and renal cell (10%). Mean follow up to date is 169 days, with local and distant control rates of 90% and 85% respectively. Relapse free rate at 6 months of follow up was 75%.

Conclusions
Although the follow up for this cohort is immature, our data suggests the majority of patients (75%) with incurable cancer, do not need further anti-cancer therapy within 6 months of treatment.

References

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Stereotactic Ablative Body Radiotherapy (SABR) for oligometastatic cancer
Phillips, I. Kelly, M. Jones, R. Lamont, K. and Ezhil, V.
Radiotherapy, Royal Surrey County Hospital NHSFT

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Stereotactic Ablative Body Radiotherapy (SABR) for oligometastatic cancer
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Radiotherapy, Royal Surrey County Hospital NHSFT

---

Stereotactic Ablative Body Radiotherapy (SABR) for oligometastatic cancer
Phillips, I. Kelly, M. Jones, R. Lamont, K. and Ezhil, V.
Radiotherapy, Royal Surrey County Hospital NHSFT
Introduction

Stereotactic Ablative Body Radiotherapy is now a standard treatment for Non Small Cell Lung Cancer. It has an established role in patients who are medically inoperable due to co-morbidities or poor lung function, or patient choice.

A pooled analysis of 2 randomised trials that recruited fewer patients than anticipated by Chang et al. suggests there is significantly less short term mortality than surgical intervention.

Improved 3 year overall survival SABR vs surgery of 95% (95% C.I 85–100) vs 79% (64–97) (1). Grade 3 toxicities 10% in the SABR vs Grade 3-4 toxicities 44% in the surgery group.

The Royal Surrey County Hospital is a commissioned centre for SABR for primary lung cancer and oligometastatic disease within the Commissioning Through Evaluation (CTE) programme.

As part of our commitment to improve patient care and quality improvement, we carried out an audit to review the outcomes of our initial cohort of patients treated with lung SBRT.

Standard

For our standard we compared our results to two recent publications.

Firstly a meta analysis of early stage primary lung cancer that has compiled clinical outcomes for published randomised control trials secondly to the first UK case series, both published by St James Institute of Oncology, Leeds (2,3). 1 year local control from meta-analysis was and 98% in the published case series. From 15 published studies the mean 1 year local control rate was 87% (range 78-100%).

Indicator: 1 year local control rate.

Target: Local control rate of over 90% at 1 year

Methodology

All patients treated with SABR between January 2012 and November 2016, with available imaging, and a diagnosis of primary lung cancer (biopsy or radiologically confirmed) were reviewed.

All patients with at least 1 post treatment scan, or those who had died before a first scan were included.

Imaging reports were obtained from 7 referral hospitals.

References


Results

Local control rate at 1 year was 97%.

116 patients were treated with SABR.

Follow-up occurred at 7 different district general hospitals.

More than 50% of patients have been treated since June 2015.

Mean age was 66.5 years (range 56-90).

55% of patients had a biopsy proven lung cancer, 45% were radiologically diagnosed with a formal MDT decision of likely primary lung cancer.

Median survival is 713 days (95% CI 578-848 days).

All patients were staged with a PET-CT

Conclusions

Our data shows that we achieved the 1 year local control rate for SABR or NSCLC which was above the target of 90% at 97%.

Action Plan

To establish accurate 3 year survival data.

To maintain database of SABR patients.

Continue to follow up SABR patients to see if median survival increases as cohort matures.
Appendix 2

TEXAS trial: TEXtural Analysis after Stereotactic radiotherapy

Understanding the Relationship between PET-CT and CT textural analysis before and after radical radiotherapy in Non-Small Cell Lung Cancer.

Sponsor: Royal Surrey County Hospital
Funder: Royal Surrey County Hospital
Protocol Version and Date Version 1.2 May 2017
Trial Management Group
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Glossary

AE  Adverse Event
BMI  Body Mass Index
CBCT  Cone Beam Computer Tomography Scan
CT  Computer Tomography
CTE  Commissioning through evaluation
CVSSP  Centre for Vision, Speech and Signal Processing, Univ of Surrey
EBRT  External Beam Radiotherapy
Gy  Gray (unit of radiotherapy dose)
GTV  Gross Tumour Volume
HR  Hazard Ratio
IMRT  Intensity Modulated Radiotherapy
ITV  Internal Target Volume
NSCLC  Non-Small Cell Lung Cancer
PET-CT scan  Positron Emission Tomography-Computer Tomography Scan
PTV  Planning Target Volume
RSCH  Royal Surrey County Hospital
SABR  Stereotactic Ablative Radiotherapy
VMAT  Volumetric Modulated Arc Therapy
1. Protocol Summary

<table>
<thead>
<tr>
<th>TITLE:</th>
<th>TEXAS trial: TEXtural Analysis after Stereotactic radiotherapy</th>
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<tr>
<td>SHORT TITLE</td>
<td>TEXAS trial</td>
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<tr>
<td>SPONSOR</td>
<td>Royal Surrey County Hospital</td>
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<td>FUNDER REFERENCE</td>
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<td>DESIGN:</td>
<td>Pilot study, retrospective cohort study</td>
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<td>OVERALL AIM:</td>
<td>To understand textural changes of the tumour and surrounding lung tissue, when primary lung tumours receive Stereotactic Ablative Body Radiotherapy (SABR).</td>
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<td>PRIMARY OBJECTIVES:</td>
<td>• To identify whether it is possible to predict recurrence of primary lung tumours using textural analysis of post treatment CT scans of patients previously treated with Stereotactic Ablative Body Radiotherapy (SABR).</td>
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<td>SECONDARY OBJECTIVES:</td>
<td>• To identify whether it is possible to predict a pattern of radiation induced lung injury after SABR</td>
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<td>• To see if textural analysis can predict lung function in patients having radical radiotherapy using the 4DCT scan (TEAL sub-study)</td>
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<td>Target Accrual</td>
<td>30 patients for TEXAS study</td>
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<td>60 patients for TEAL (Textural Analysis and Lung Function) sub study.</td>
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<td>Inclusion criteria</td>
<td>• <strong>TEXAS study</strong></td>
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<td></td>
<td>• Patients previously treated with Stereotactic Ablative Lung Radiotherapy (SABR) for Non-Small Cell Lung Cancer (NSCLC).</td>
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<td>• Patients have pre-treatment pet available, with a minimum of 12 months follow up with a minimum of 2 CT scans, unless they have recurred within 12 months.</td>
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<td></td>
<td>• Patient needs pre-treatment and recurrence PET-CT available.</td>
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<td></td>
<td>• <strong>TEAL sub-study</strong></td>
</tr>
<tr>
<td></td>
<td>• Patients had a 4DCT planning scan at Royal Surrey County Hospital</td>
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</table>
• Patient have lung function test results available including FEV1 and TLCO.

### Exclusion criteria

- **TEXAS study**
  - Patients not had SABR for primary lung cancer or did not receive the full dose/course of radiotherapy
  - Were treated for a lung metastasis from a different primary cancer.
  - No recurrence cohort, have less than 1 years follow up, less than 2 scans available or no pre-treatment PET-CT scan
  - Recurrence cohort, no PET-CT pre-treatment or on recurrence
  - Did not receive the full dose of radiotherapy
- **TEAL sub study**
- Lung function tests not available

### Number of sites
2

### Duration of recruitment
This is a retrospective study so patients will be identified from an existing SABR database.

### Duration of patient follow-up
N/A

### Definition of end of trial
N/A

### Background
Lung cancer is the second commonest cancer diagnosed in the UK in both men and women. Overall survival for all comers for Non-Small Cell Lung Cancer (NSCLC) is 10% at 5 years.

Lung cancer is caused by smoking and is more common in older patients. Forty percent of cases are diagnosed in patients aged 75 or over. These patients are more likely to have multiple co-morbidities also caused by smoking. Because of these many patients with early stage lung cancer are likely to be less fit and so not suitable for surgical treatment. In this population radical (curative) external beam radiotherapy (EBRT) is an important treatment in managing lung cancer.

Stereotactic Ablative Body Radiotherapy (SABR) is a method of delivering radical radiotherapy to patients not fit for/or who decline surgical resection or standard radical radiotherapy of early stage (T1-T2a N0 M0) lung tumours [1]. Radiotherapy for NSCLC (Non-Small Cell Lung Cancer) is usually given in small daily fractions (2 Gray per treatment) over 4 or 6 weeks. SABR is given in 3-8 fractions over 1-3 weeks [1]. Each fraction is 7.5Gy-18Gy. The larger fraction size means a higher biologically effective dose is given to the tumour, in a fewer number of fractions over a much shorter period of time. The dose distribution across the tumour is different in SABR compared to standardly fractionated radiotherapy. Standard radical radiotherapy aims to cover the tumour with a
homogenous dose, which is mandated to be 95-107% of the prescribed dose [2]. In SABR the dose varies across the tumour with a high peak in the middle. This means the dose outside the tumour has a very steep fall off, so less lung is irradiated. As a result patients whose lungs could not tolerate surgery or standardly fractionated radical radiotherapy are suitable for SABR. In retrospective series SABR appears to have outcomes similar to surgery [3, 4], although clinical trials have struggled to recruit patients for a direct head to head comparison [5]. The dose of radiotherapy is targeted using Intensity Modulated Radiotherapy (IMRT) or Volumetric Modulated Arc Therapy (VMAT), this means the dose of radiotherapy can be varied across the radiotherapy field through movement of multi-leaf collimators (MLCs). This shapes the radiotherapy beam during treatment. IMRT radiotherapy plans often have 7 or 9 fields delivered from different directions. VMAT is delivered with the linear accelerator moving in an arc as the treatment is delivered. This spreads the low dose level of radiotherapy across the patient in an arc.

Radiotherapy is planned on a CT (Computer Tomography) scan. For SABR planning a patient undergoes a 4D-CT scan. This divides the CT scan into 10 respiratory phases and accounts for tumour movement during the breathing cycle. Two composite volumes are created using the 4DCT. These are the CT average, which is an average across the breathing cycle and the CT-Maximum Intensity Projection (MIP). Organs at risk are volumed on the average scan and the tumour is volumed using the MIP, to account for all positions of the tumour during the breathing cycle. As this Gross Tumour Volume (GTV) is a composite of all breathing phases it can also be described as an Internal Target Volume (ITV) as it accounts for tumour movement. A margin is added to the ITV to account for set up error and is termed the Planning Target Volume (PTV).

Textural analysis has the potential to gain more prognostic information about a tumour or its response to treatment, such as after radiotherapy. It is a technique of advanced imaging analysis to gain extra information from a standard diagnostic image, such as a CT or PET-CT scan. The aim of this study is to understand whether textural analysis can elicit more information for CT scans as a prognostic marker before treatment and a more complex analysis after a patient has received SABR, particularly whether textural analysis can predict recurrence of primary NSCLC tumours.

**Literature review**

**Efficacy of SABR**

A comparison from the SEER database in America suggests that SABR has a definite role in treatment of early stage NSCLC. In a review of over 10,000 patients, 5 treatment modalities were explored [6]. These were surgery (lobar resection and sub-lobar resection), conventionally fractionated radiotherapy and stereotactic radiotherapy. The commonest treatment was lobar resection (59%), followed by conventional radiotherapy (14.85%), then sub lobar resection (11.7%), then observation (12.6%) and finally SABR (1.1%). In this analysis the median age was 75 years and old nearly a third of patients (29%) had severe co-morbidities. Using Cox regression SABR was associated with the lowest risk of death within 6 months (HR 0.48 95% C.I 0.38-0.63) when compared to lobectomy.
After 6 months lobectomy had the best disease specific survival. With a median follow up of 3 years lobectomy had a similar outcome when compared to SABR (HR 0.71, 0.45-1.12). Conventional radiotherapy (HR 1.97, 1.31-2.96, p=0.001) and observation (HR 2.10, 1.37-3.08, p=<0.001) were both significantly poorer when compared to SABR. This analysis is limited by the small numbers of patients who received SABR, particularly compared to surgery. A subsequent analysis has suggested that lobectomy is better than sub lobar resection or SABR, but SABR remains a beneficial treatment for those not suitable for surgical resection [7]. It also establishes that SABR is a better treatment when compared to conventionally fractionated radiotherapy for smaller lung tumours [8]. In older patients retrospective data suggests SABR improves overall survival compared to observation in patients who would not be fit for surgical treatment [9].

There is little published work regarding SABR and textural analysis. Textural analysis uses a range of mathematical features to describe a region of an image. In this context it is used to describe a tumour. Standard imaging such as a CT scan shows differences in density. Other measures such as heterogeneity can be calculated. Heterogeneity measures the level of disorder or dis-similarity, which can occur at a genetic and a supra-cellular level, as well as on an image. Tumours can vary in their blood supply and vascularity, cell density, level of oxygen delivery, hypoxia or in the rate of proliferation. These radiobiological changes confer greater sensitivity or resistance to radiotherapy. The difference in biology across the same tumour and between different tumours means there is a range of radio-sensitivity and therefore a range of responses to treatment.

Two standard imaging modalities that are used to assess lung tumours are CT and PET-CT (Positron Emission Tomography-Computer Tomography). The benefit of performing a PET-CT scan is that it gives functional information. The commonest tracer used in PET-CT scans in clinical practice is FDG (Fludeoxyglucose). For this trial CT scans will be used for the analysis in the form of stand-alone CT imaging and the CT of PET-CT scans.

The complexity of a textural analysis technique depends on the feature being described. Although different textural features have been generated from a wide range of sources, they can be broadly divided into three categories: first-order (least complex), second-order and higher-order (most complex). First-order features are simplest and can often be described as a single figure and describe the whole volume being analysed. Second order features describe the relationship between 2 points, such as 2 pixels or voxels. Higher order features describe the relationship between a pixel and more than one other pixel, i.e. a minimum of three points in space.

First-order textural features use a range of basic statistical methods to express different measures. Commonly used textural features include energy, entropy, kurtosis, maximum and minimum intensity, average intensity (median and mean) and range of intensities, skewness, standard deviation, uniformity, entropy (irregularity of intensity value distribution) and variance. Standard deviation, variance and mean absolute deviation measure how the range of intensities in a histogram are dispersed. Skewness measures how much histogram asymmetry
there is around the mean. Kurtosis measures the sharpness of the histogram. Randomness can be computed using uniformity and entropy. Entropy is a measure of disorder. The higher the entropy the greater the disorder or heterogeneity. The lower the entropy, the higher the homogeneity. The majority of published textural analysis work focuses on first order features of textural analysis.

Second-order textural features describe a relationship between two points. By taking each point in turn and comparing it to all points around it, a three dimensional comparison can be built up. It can then describe the three-dimensional size and shape and a range of values within a tumour. By deriving a tumour volume, measurements can be taken of variations across this volume, these include entropy (measure of randomness of values within an image), compactness, sphericity, surface area, and surface to volume ratio.

A wide range of studies have used textural analysis to attempt to define different aspects of lung lesions seen on pre-treatment imaging. Textural analysis has been used to differentiate benign from malignant tissue (particularly lung nodules), different types of tumour histology [13, 14], to aid assessment of the tumour and aid treatment decisions. Textural differences have been identified in images from PET-CT scans. They suggest that non-malignant tissue is more homogeneous than malignant tissue and adenocarcinoma is more homogeneous than squamous cell carcinoma [15].

Conventional predictors of outcome in NSCLC include TNM staging, AJCC stage, age, sex, histology, co-morbidities and performance status. The use of a biomarker from CT imaging to prognosticate patients’ outcomes, risk of distant metastases and overall survival is attractive because CT imaging is ubiquitous within the management of NSCLC.

A common way of analysing tumours for textural analysis is to delineate the tumour and segment it out of the scan. The segmented structure (which is analogous with the primary tumour) can then be analysed. Statistical features of the tumour can be identified and plotted against an outcome measure such as disease free survival or overall survival. Features that give a strong correlation could potentially act as biomarkers for those with poorer survival[16]. CT texture features have been correlated with PET-CT SUVmax, tumour staging and degree of tumour hypoxia [17, 18].

A range of studies have been performed with a broadly similar method. A patient cohort is identified with a known outcome such as overall survival or progression free survival. Either a single slice or the whole tumour is identified and segmented out from the rest of the scan. A range of different commercially available software such as TexRAD and MaZda is available. Other studies have used in house software. A range of first, second and higher order textural features can then be extracted. In many cases a large number of textural/mathematical features can be calculated. Features are chosen that correlate with outcome. The difficulty is that different textural features are significant in different studies, using different methods of analyses. In some studies hundreds of features are analysed and compared. This means that statistically significant textural features could be
identified by chance, despite there not being any actual correlation. The consequence is that this limits the reproducibility of many studies.

Many studies use clinical data alongside textural analysis to stratify outcome. Many are retrospective. In many cases textural analysis improves prediction of outcome compared to clinical data alone, rather than the tumour textural features alone predicting outcome. These studies often utilise different standards, measurements, imaging equipment and techniques. As a result it is difficult to achieve accurate reproducibility. It is also difficult to identify sufficiently large cohorts, some studies have heterogeneous cohorts receiving different treatment, either combining tumours that received radiotherapy alone with chemoradiotherapy or different radiotherapy schedules.

At present it is unlikely that a prognostic measure would affect a treatment decision. A ‘good’ or ‘bad’ prediction of response to radical treatment would change not currently alter a management plan, but it is important to have as many robust biomarkers as possible as clinical trials and treatment strategies could be stratified according to these biomarkers.

In the UK CT imaging is the standard follow up tool for lung cancer. PET-CT maybe used following radical treatment to identify recurrence. SUV intensity on PET-CT imaging may give a faster response than decrease in tumour volume [19]. Identifying early recurrence after radical radiotherapy can be complex, particularly after stereotactic radiotherapy [20].

In order to be of benefit textural features, identification and classification of features needs to be sufficiently robust to overcome features including patient variables (including positioning, respiration phase and motion management and effects of contrast or lack of contrast), acquisition and processing variables such as image acquisition power, image slice thickness, image reconstruction algorithms, use of segmentation software and operator variability in tumour delineation. To minimise these variables and identify the changes related to tumours alone many studies standardise their image acquisition process [21]. Useful biomarkers need to overcome these features or have to be standardised to ensure accurate interpretation of this information.

Robust textural features have the potential to give the clinician significantly more information in the clinic. As so many features can be extracted, the challenge is to extract useful information, which is, reproducible, prognostic and predictive. This is likely to require prospective data collection. At present large numbers of textural features are often analysed. This has two consequences, firstly a large number of variables means that it is possible that some features may correlate with outcome by chance. Secondly it is easy to become overwhelmed by the level of information and number of textural features that can be derived. Establishing robust biomarkers, means they can then be incorporated into appropriate clinical trials.
For these reasons, being able to extract more information for standard imaging is an attractive way of getting more ‘value’ from investigations and is likely to be more routinely introduced into clinical practice in the coming years.

**SABR and Textural Analysis**

Pre-treatment textural features can improve prediction of outcome, compared to SUVmax alone [22]. Compared to other treatment response assessments, there is an evidence base for using radiomics and textural features in SABR response assessment. This is perhaps unsurprising given the technological and imaging requirements needed to deliver SABR. The lung reacts to SABR differently to standardly fractionated radiotherapy.

After SABR significant local inflammation can occur. An example is Radiation Induced Lung Injury (RILI). This is difficult to differentiate from tumour recurrence by appearance alone (illustrated in figure 1). Manual and automatic delineation of the areas of ground glass opacity and consolidation showed that early recurrences were denser and had different textural features than areas of RILI and can predict early response [23-25]. PET SUV >5 or SUV higher than the diagnostic PET-CT suggests recurrence [20]. Radiomic features have been extracted, which predict early recurrence and are able to improve sensitivity when compared to physician assessment (AUC 0.85, False negative rate 23% vs 99%) [25].

A textural analysis tool has been developed in collaboration with the Centre for Vision, Speech and Signal Processing at the University of Surrey. It has been shown that FDG-PET uptake correlates with areas of homogeneity in the tumour. Each voxel is compared to the voxel next to it in all directions, this allows a map of entropy (disorder) to be built up. The analysis can potentially be used across whatever structure is segmented (extracted) from a CT scan.

![Figure 1](image)

Figure 1. adapted from Mattonen et al. [26] Solid black line represents tumour in 1st image of both recurrence and benign lung injury. Dotted line represents area of interest and ground glass opacification.
This baseline use of tumour specific textural analysis formed the basis of this study. The aim of the experiments so far and future work is to identify whether textural analysis using this method can distinguish patients with good and poor lung function and between tumour and fibrosis in CT scans of patients who have received SABR.

**Rationale for study**

The aim of this study is part of an overarching project to extract more information from CT scans, which are part of standard imaging for patients with lung cancer. The TEAL sub study aims to identify more information from a patient’s pre-treatment imaging.

The TEXAS study is using this concept to extract more post treatment information from routine CT scans. In patients who have received SABR for early stage NSCLC, it is difficult to identify areas of recurrence and differentiate this from an acute lung injury or inflammation after SABR. This is more common where radiologists are not commonly reviewing post SABR imaging. CT textural analysis provides a potentially useful tool in identifying early recurrence. Traditionally patients who would undergo SABR would not be suitable for salvage treatment, however SABR is now being used for the treatment of oligometastatic disease in a wider group of patients who are often fitter than those with primary NSCLC. It is becoming more important to be able to identify when local recurrence/progression occurs.

Standard follow up of patients who have undergone radical treatment for NSCLC involves routine CT scans. Textural analysis of CT scans is an attractive tool because of the widespread availability of CT imaging compared to PET-CT imaging. If prognostic factors for CT texture can be established, this may give greater information to clinical oncologists managing NSCLC.

Textural analysis is a broad field using a range of imaging analysis techniques. This is a pilot study to explore the applications of texture analysis before and after SABR to the lung. This study will use 2 methods to assess the benefits of using CT textural analysis in pre-treatment imaging to assess lung function and post treatment imaging to assess response to SABR.

The software is able to compare like for like image voxels in all directions. Each voxel in an image has a relationship with 26 voxels around it (as illustrated in figure 2). This builds up a second order map of entropy. This means that it is possible to build a map of the relative intensities of the tumour and the surrounding lung. The advantage of using this is that a map can be derived for the whole lung. In SABR the position of the ablated area of the lung, which previously contained tumour often alters its anatomical position within the lung, due to the inflammatory and fibrotic reaction of the lung.

The aim of using the post treatment tool is to improve diagnostic certainty in identifying recurrence on a standard staging CT scan. Being able to identify recurrence in previously treated primary lung tumours after stereotactic radiotherapy has several advantages. It could mean that fewer PET-CTs are
required to confirm recurrence; it may provide more information where PET-CT access is limited or not available; it may potentially reduce the need for unnecessary biopsy; particularly in a population that are much more likely to experience complications of a biopsy such as pneumothorax.

Figure 2. Central white sphere has a relationship with 26 voxels around it.
3. Trial Objectives

Primary
To identify whether it is possible to predict recurrence of primary lung tumours using textural analysis of post treatment CT scans of patients previously treated with Stereotactic Ablative Body Radiotherapy (SABR).

Secondary
- To identify whether it is possible to predict a pattern of radiation induce lung injury after SABR
- To see if textural analysis can predict lung function in patients having radical radiotherapy using the 4DCT scan (TEAL sub-study)

4. Trial design
The trial will be a retrospective analysis of patients who have completed Stereotactic Ablative Body Radiotherapy (SABR) for primary NSCLC or presumed NSCLC.

Three cohorts of patients will be identified.

TEXAS Cohort 1: Patients treated with SABR for NSCLC who have a minimum of 1 years follow up and have at least 2 diagnostic post treatment CT scans, where there is no evidence of local tumour recurrence.

TEXAS Cohort 2: Patients treated with SABR for NSCLC who have a PET proven local recurrence.

TEAL sub-study cohort (including patients from TEXAS cohort 1 and 2). Patients who have undergone a planning 4DCT at Royal Surrey County Hospital of their whole lungs and have pre-radiotherapy formal lung function available.

5. Patient Population
All patients who have been treated for localized primary NSCLC at the Royal Surrey County Hospital will be eligible for entry into this study.

Inclusion
- **TEXAS study**
- Patients previously treated with Stereotactic Ablative Lung Radiotherapy (SABR) for Non Small Cell Lung Cancer (NSCLC).
- Patients either had biopsy confirmed NSCLC or a clinical decision has been made that there is a high probability of NSCLC suitable for SABR.
- Cohort 1: No recurrence of cancer after SABR,
  - Patients have pre-treatment pet available, with a minimum of 12 months follow up with a minimum of 2 CT scans, unless they have recurred within 12 months.
- Cohort 2: Recurrent lung cancer after SABR (either ipsilateral recurrence or local recurrence)
- Patient needs pre-treatment and recurrence PET-CT available.
- **TEAL sub-study**
- Patients had a 4DCT planning scan at Royal Surrey County Hospital
- Patient have lung function test results available including FEV1 and TLCO.

**Exclusion**
- **TEXAS study**
  - Patients not had SABR for primary lung cancer or did not receive the full dose/course of radiotherapy
  - Were treated for a lung metastasis from a different primary cancer.
  - No recurrence cohort, have less than 1 years follow up, less than 2 scans available or no pre-treatment pet-ct scan
  - Recurrence cohort, no pet-ct pre-treatment or on recurrence
  - Did not receive the full dose of radiotherapy
- **TEAL sub study**
  - Lung function tests not available

### 6. Patient Recruitment

**Consent**

Consent will not be sought from patients to participate in the study.

The study involves retrospective analysis from patients who have received SABR treatment for Lung cancer. As a result of their disease many of the patients who are eligible for this study would no longer be alive to provide consent. For those who are still alive many would suffer from a number of comorbidities and it is not felt appropriate to invite them back to the hospital to consent to a study that is not going to change their future treatment.

To maintain patient anonymity data will be collected from eligible patients by the clinical team and provided to the research team in an anonymised form for analysis. No patient identifiable data will be available to the research team.

The initial stage of the TEXAS trial will be to identify 10 patients for the non-recurrence cohort. The first step will be to identify a ‘normal’ pattern of fibrosis.

The second stage will be to increase the non-recurrence control cohort to 20-30 patients. They will then be compared to 5-10 local or ipsilateral lung recurrences. Local recurrences are rare following SABR.

60 patients who are eligible for the TEAL sub-study will be identified from an internal RSCH database of patients who have received radical
radiotherapy (including both SABR and standardly fractionated radiotherapy) at RSCH.

7. Trial Treatment

The treatment that patients received was standard SABR for primary lung tumours as documented in Royal Surrey County Hospital Clinical Protocol for Stereotactic Ablative Body Radiotherapy (SABR). The document number is RT-PT56v1. It is available on QPulse at RSCH and is in appendix 1.

Patients were given a prescription for 4mg of dexamethasone to be taken before radiotherapy on each day of treatment. This is standard management at RSCH. If there is concern regarding lung inflammation a steroid inhaler was given to the patient to take during their treatment.

Standard post treatment staging CT scans will be used for this analysis. The trial does not ask for any additional or different imaging. All patients underwent standard treatment and standard clinical and imaging follow up. Neither the TEXAS study nor the TEAL sub-study ask for any additional investigations or changes in treatment or follow up.

8. Assessments

For the TEXAS study each patient will have a duplicate pseudo anonymised copy of their radiotherapy plan created within Eclipse (radiotherapy planning computer system) at RSCH. All appropriate scans will be requested through the Information Exchange Portal (IEP). Post treatment diagnostic scans will be imported electronically from the PACS system at RSCH into Eclipse. Importing scans from PACS into the anonymised radiotherapy plan, automatically anonymises the imported scan. The whole lung will then be volume (see guidelines below). Importing these scans into an anonymised patient record anonymises the patient name. The scans will exported from the radiotherapy system and anonymised to ensure that all identifiable information has been removed. The anonymised scan will then be exported from Eclipse into Matlab on a password protected and encrypted University of Surrey computer. The lung volume will be extracted from the CT scan using CERR (Computational Environment for Radiotherapy Research) software (ref). A textural map will be processed to create a map of relative entropy using software developed in collaboration with the Centre for Vision, Speech and Signal Processing, University of Surrey.

For the TEAL sub-study, a region of interest will be drawn on a duplicate structure set within the radiotherapy planning system. This structure will then be anonymised and exported. It will be analysed in the same manner as patients in the TEXAS trial. This anonymised texture map will then be analysed.

Lung localisation guidelines

The aim is to keep the localisation of the whole lung consistent between patients and between scans of the same patient. Broadly the lung volume aims to exclude
the left and right main bronchus, lobar bronchi, hilum and any large blood vessels over >1cm. Superiorly and laterally the lung volume is bordered by ribs. The lung volume should not include any rib. Medially the lung is bordered by mediastinum, hilum and heart. Inferiorly the lung is bordered by diaphragm and liver or spleen. The proximal bronchial tree should be excluded from the lung volume. UK SABR consortium guidelines define the bronchial tree as: “The most inferior distal 2cm trachea, carina, right and left mainstem bronchi, right and left upper lobe bronchi, the bronchus intermedius, right middle lobe bronchus, 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.” The hilum that would be defined as hilar lymph node (station 11) will be excluded.
Figure 3. Adapted from Chapet et al, definition of station 11 lymph node [28].

**TEAL sub-study voluming guidelines**

A 4 cm circle is selected from eclipse drawing functions. The aim is to volume a cylinder of lung tissue 4cm in diameter including continuous 10 slices of the CT-AVERAGE phase of the 4DCT. The structure should be drawn superior to inferior. The first slice should be as apical as possible, but the volume should not include any tissue other than lung tissue. See figure 4. for an example structure. For left sided tumours, if the inferior part of the left sided structures includes the aortic arch, the structure should start 1-2 slices lower with the volume started as laterally as possible to avoid the aortic arch.

![Figure 4](image_url)

Figure 4. Cylinder of lung tissue which will be analysed in the TEAL study.

**9. Data Management**

Patients will have a range of characteristics of the patient and tumour staging collected, as well as date of relapse and date of death. This information will be collated and kept confidentially at St Lukes Cancer Centre, Royal Surrey County Hospital.

Cases will be identified on the SABR database, created by the scientific computing department at Royal Surrey County Hospital. The database is made up of a relational database which resides on a dedicated database server and a web portal (which accesses the database server) which resides on a dedicated web server.
Both servers are only accessible within the hospital network. No external access is possible. The database server is secured behind a dedicated firewall which only allows communication specific IP addresses on specific ports within the hospital network. Both servers are fully patched CentOS servers with all standard security. Access to root accounts is available to a small number of Scientific Computing staff. Both servers reside on a virtualisation platform which is cloned to ensure uptime. Access to the web portal is restricted by username/passwords over an SSL connection. Timeouts for connectivity are currently set at 15 minutes. All activity on the web portal is logged for auditing purposes. The database server storage is an NFS mounted NAS server which is setup in a high availability structure. The database server is backed up twice a day to an encrypted gzip file which is stored on a separate NAS high availability cluster in a separate location within the hospital site. Delete procedures exist which are capable of removing a patients data from the database, backups and logs.

Patients for recurrence and non-recurrence cohort will be identified by a Clinical Oncologist who treats NSCLC with SABR.

Unanonymised scans will be stored on RSCH PACS or Eclipse computer systems. Both the computers on which the systems are accessible are password protected. The anonymised scans and texture maps will be stored on a password protected University of Surrey computer.

Patients will be selected and pseudo-anonymised within eclipse (radiotherapy planning system) by creating a ‘phantom’ anonymised copy of the patients planning CT scan and a copy of the structures drawn on the original planning CT. Post treatment CT scans will then be imported from Royal Surrey County Hospital electronic imaging (PACS) system. Where multiple series of images exist, the key images to import are axial 5mm slices. Importing the scans into the phantom radiotherapy scan anonymises any patient identifiable information. The scans will then be exported as DICOM data with an associated radiotherapy structure set. These anonymous files can then be imported into either matlab for 3D textural analysis or TexRAD.

Data Analysis
This study will comprise 2 cohorts of patients for the TEXAS study, those whose tumour locally recurs and those where there is no evidence of recurrence.

The data points created by the texture map give an entropy score. Entropy is a measure of disorder. High entropy is equivalent to more disorder, which can also be described as more heterogeneity. This means that low entropy is equivalent to high homogeneity or uniformity.

The entropy score for each voxel will be plotted against the Hounsfield Unit (HU) for that voxel. This will give a plot of data points. The aim is to use these plots to see if it is possible to identify features of recurrence by plotting all the data, when compared to a control group where the tumour hasn’t recurred. This analysis will
aim to match a number of patients who haven't recurred (to act as a control) with a patient who has recurred

10. Adverse Events

- This study is a retrospective analysis of post treatment CT scans, adverse events will not be collected.

Reporting procedures

11. Trial monitoring

The CI will facilitate any local monitoring by the R&D quality manager, REC review and provide access to source data as required.

Following any monitoring a report will be provided which will summarise the visit and documents, along with any findings. The CI will be responsible for ensuring that all findings are addressed appropriately.

Additional monitoring will be scheduled where there is evidence of suspicion of non-compliance with the Trial protocol.

12. Trial closure

End of Trial

Upon the end of trial a “declaration of end of trial” form will be submitted to REC, as required.

Archiving trial documents

Following the end of trial arrangements for non-essential confidential documents will be destroyed. Essential documents will be securely archived for 5 years.

Early closure of the trial

The trial may be stopped early upon recommendation.

13. Sponsorship

The trial will be sponsored by Royal Surrey County Hospital

14. Indemnity

Royal Surrey County Hospital Foundation Trust holds professional liability insurance to meet the potential legal liability of the sponsor and employees for harm to participants arising from the design and management of the research.
Indemnity to meet the potential legal liability of the investigators/collaborators for the harm of participants arising from the conduct of the research is provided by the NHS Indemnity scheme or through professional indemnity.

15. Publication
The results of this study will be published by peer-reviewed journals and presented at national and international oncology and radiology conferences.

References
14. Wu, W., **Exploratory Study to Identify Radiomics Classifiers for Lung Cancer Histology.** Frontiers In Oncology, 2016. 6: p. 71.


Appendix 3

**Dietetic Assessment and Intervention in Lung cancer (DAIL) study**

**Sponsor:** Royal Surrey County Hospital

**Funder:** Chugai

**Protocol Version and Date**

**Version 1.5**

18th November 2016

**Trial Management Group**

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<table>
<thead>
<tr>
<th>Abbreviation</th>
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<td>AE</td>
<td>Adverse Event</td>
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<tr>
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<td>BMI</td>
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<td>BTS</td>
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<td>Chief Investigator</td>
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<td>Mini-Nutritional Assessment</td>
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<td>NSCLC</td>
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<tr>
<td>PG-SGA</td>
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<td>Subjective Global Assessment</td>
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<td>Urea and Electrolytes</td>
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1. Protocol Summary

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<th>TITLE:</th>
<th>Dietetic Assessment and Intervention in Lung cancer (DAIL) study</th>
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<td>DESIGN:</td>
<td>Prospective cohort study</td>
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<td>To quantify the number of patients with Non-Small Cell Lung Cancer (NSCLC) who present with malnutrition, cachexia and/or sarcopenia before starting anti-cancer treatment.</td>
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<td>PRIMARY OBJECTIVES:</td>
<td>• To identify the proportion of patients diagnosed with NSCLC who are malnourished, cachectic and have sarcopenia before anti-cancer treatment.</td>
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<td>• To identify the proportion of lung cancer patients who would require dietetic review before anti-cancer treatment.</td>
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<td>SECONDARY OBJECTIVES:</td>
<td>• To identify whether malnutrition, cachexia or sarcopenia affects overall survival in metastatic NSCLC.</td>
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<td>• To identify whether sarcopenia predicts for a poor outcome in NSCLC</td>
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<td>Target Accrual</td>
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<td>• All patients should have biopsy confirmed Advanced NSCLC (stage IIIb and IV).</td>
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<td>• Patient receiving first line systemic palliative anti-cancer treatment.</td>
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<td>Exclusion criteria</td>
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<td>• Patient declines anti-cancer treatment</td>
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<td>----------------------------------------------------------------------------------------------------------</td>
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<td><strong>Definition of end of trial</strong></td>
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2. Background
Lung cancer is the second commonest cancer diagnosed in the UK in both men and women. Over 43,000 cases are diagnosed a year, over 35,000 deaths occur a year and there is a 5 year survival of 10% and 10 year survival of only 5% [1]. It is the commonest cancer worldwide in terms of both incidence and mortality.

Lung cancer is caused by smoking and is more common in older patients. It is a disease of poverty [2]. It has been associated with a higher incidence in areas with higher unemployment, lower socioeconomic position and a less educated population.

As the majority of lung cancer is associated with tobacco exposure, these patients are more likely to have multiple co-morbidities also caused by smoking. Exposure to tobacco is associated with numerous co-morbidities including Ischemic Heart Disease (IHD), Chronic Obstructive Pulmonary Disease (COPD) and other cancers including bladder cancer. Evidence shows that being a smoker at 25 years old means a patient is 50% less likely to live to 79 years old excluding all factors. Smokers on average live 10 years less than non-smokers, with a mortality rate three times higher than non-smokers [3].

More than 80% of new cases of lung cancer are diagnosed in the over 60’s and more than 40% are diagnosed in men and women over 75 years.

In the current healthcare environment it is important to use all available resources to maximize outcomes in lung cancer. This includes addressing malnutrition, cachexia and nutritional deficit, as this can affect fitness for treatment.

2.1 Literature review

2.1.1 Nutrition and COPD
Malnutrition can be defined as a state of nutritional imbalance leading to negative effects on weight and function and is common in COPD [4]. Poor respiratory function has been correlated with poor muscle mass [5]. Symptoms associated with COPD include a dry mouth, pain and constipation and all can impact on nutritional status. Patients with more significant fat free mass depletion are more likely to have these symptoms [6]. Malnutrition is also associated with decreased physical workload in this patient group [7]. Oral nutrition supplements have been shown to improve body weight and handgrip strength, as well as decrease airflow limitation in patients with COPD [8]. The most recent Cochrane Review on stable COPD and nutrition suggests that malnourished patients with COPD can improve respiratory muscle strength and overall health related quality of life with nutritional support [9]. British Thoracic Society (BTS) guidelines suggest that patients with a low Body Mass Index (BMI) (<20 kg/m²) should be offered nutritional support. Many patients with lung cancer will have underlying COPD and will need to cope with the additional burden of managing their COPD as well as lung cancer.
2.1.2 Nutritional status in cancer

Cachexia is a progressive disorder, leading to decreased physical activity, adverse psychological side effects, poor performance status and higher mortality rates. The model of cachexia can be divided into three phases, pre-cachexia, cachexia and refractory (likely irreversible) cachexia [10, 11]. Refractory cachexia is characterized by poor overall survival (less than 3 months). Cachexia has previously been defined by percentage weight loss from usual body weight, ‘weight loss greater than 5%, or weight loss greater than 2% in individuals already showing depletion according to current bodyweight and height (BMI <20 kg/m²) or skeletal muscle mass loss (sarcopenia)’ [10].

Pre-treatment nutritional assessment has shown that malnutrition is common in lung cancer patients, with an incidence of between 35% and 65% [12, 13]. A range of studies have shown that malnutrition is associated with negative clinical outcomes in patients with cancer in general, including poorer quality of life, decreased functional status, increased utilisation of health care services and poorer survival [12].

In a study of 1,000 patients with locally advanced or metastatic cancer, more than a third had significant weight loss (defined as greater than 10% weight loss) [14]. Twelve percent of patients in this study had lung cancer. Median rate of significant weight loss was 6.6%. Overall weight loss percentage increased as performance status worsened. Weight loss was more significant with more advanced cancers compared to stage 1 cancers.

In view of the fact that many patients with lung cancer are likely to be older, have co-morbidities and come from a lower socio-economic background, we investigated the proportion of patients who presented with cachexia and refractory cachexia in advanced lung cancer at the time of referral to the dietitian, 73% of patients were cachectic and 25% had refractory cachexia.

In a prospective series of patients aged 70 years or older undergoing resection of a primary lung tumour, malnutrition was found to be a significant risk factor for early death. The cohort was divided into two groups, those that were underweight (BMI <18.5kg/m², Group A, 21 patients) and those that were not underweight (BMI 18.5kg/m² or greater, Group B, 96 patients). BMI and weight loss of 5% or greater before surgery were independent risk factors for 1 year mortality [15].

In patients undergoing pneumonectomy for lung cancer 33 of 86 patients were found to have malnutrition. This was assessed using biological markers of nutrition including albumin and transthyretin [16]. Malnutrition did predict for increased morbidity and mortality in patients undergoing pneumonectomy. A study enrolling 146 patients irrespective of age by Win et al suggested that BMI and surgical outcome did not obviously correlate, however only 109 of 146 patients underwent surgery, patients not undergoing surgery were not included in the analysis [17]. Poor nutritional status and increased mortality has been associated with non-oncological thoracic surgery, such as lung transplantation [18].
There is some evidence that dietary counseling and nutritional supplements may ameliorate the effects of radiotherapy and chemotherapy, although the exact benefit is not clear. The lack of definitive benefit in these studies may be in part due to short follow up, analysis of patients with lung cancer with other tumour types and difficulties in patients reaching adequate calorific intake [19].

Whilst screening assessment and prophylactic nutrition support is standard practice for patients with primary cancers of the head and neck region, this is not the case for those with lung cancer. Radical lung radiotherapy (with or without chemotherapy) for lung cancer is associated with acute toxicities that can adversely affect nutritional intake. A retrospective review of 96 patients has shown that 31% lost 5% or more of their usual total body weight [12]. This was more likely if the patients had more advanced disease, or radiotherapy was given with chemotherapy. The dose of radiotherapy to the oesophagus during high dose palliative or radical lung radiotherapy predicts for weight loss. The maximum dose to the oesophagus as well as absolute length of oesophagus receiving 40Gy or higher did predict for weight loss of 5% of greater.

A systematic review of exercise and nutrition strategies published in 2013, suggests that they are not harmful and may have beneficial effects on unintentional weight loss for patients with advanced lung cancer. Only 203 patients from 5 studies were included in this analysis, of which only 3 were assessing nutrition. All 3 studies investigated use of a specific supplement rather than the impact of a nutritional assessment [20].

2.1.3 Evidence in other cancers
Nutrition support is more established in other tumour sites such as upper gastrointestinal and head and neck cancers. For this reason all patients undergoing radical treatment for a primary head and neck or oesophageal cancers are routinely screened for nutritional deficit.

Oesophageal cancer is less common than lung cancer. It is the 13th commonest cancer in the UK with a 5 year survival rate of 15% with 80% of cases occurring in people aged 60 years or older [21].

As with lung cancer, multi-modality treatment is better than surgery or radiotherapy alone. These patients are likely to experience significant barriers to maintaining their nutritional status such as dysphagia and cachexia induced by the cancer. Weight loss is associated with a poorer outcome in oesophageal cancer [22]. Up to 79% of patients experience weight loss.

Obesity is a risk factor for developing adenocarcinoma of the oesophagus; many patients present as obese, but have ongoing weight loss. These patients have mechanical factors preventing adequate nutrition, which could include pain, reflux, dysphagia and fatigue. Patients may have altered their diet with the onset of symptoms, which may be several months before diagnosis. These symptoms may worsen with anti-cancer therapy. Pre diagnosis weight loss has also been identified with poorer survival [23]. Treatment with neo-adjuvant chemotherapy potentially improves survival. It can have a positive effect on symptoms by
shrinking the tumour, but the side effects of the tumour and toxicities of the treatment have the potential to negatively affect nutritional status.

2.1.4 Nutrition screening tools
Ranges of physical assessments have been used to attempt to gain insight into clinical outcomes in lung cancer [24].

The Mini-Nutritional Assessment (MNA) was initially used to screen for malnutrition in older patients. In lung cancer it has been shown that two thirds of patients are either at risk of malnutrition or are malnourished [25]. The MNA outcome correlated with overall survival. It also correlated with depression and low mood, but not with anxiety.

Subjective Global Assessment (SGA) has been used in patients with lung cancer. Patients who were defined as malnourished had an overall survival of 9 months vs 17 months in well-nourished patients in advanced NSCLC [26].

The SGA was adapted to form the Patient Generated Subjective Global Assessment (PG-SGA) which is validated for use with oncology patients [27]. It includes a range of factors including determining weight loss, changes in food intake, symptoms of nutrition alterations, limitations of function, presence of metabolic stress and a physical examination. Li et al. established that 40% of patients with advanced lung cancer were malnourished and another 40% were at risk of malnutrition [28].

Functional measures can assess nutritional status. Decreased handgrip status and malnutrition has been established in patients with potentially operable lung cancer [29]. Other methods such as Bioelectrical Impedance Analysis can be used to estimate body composition.

2.1.5 Sarcopenia
Sarcopenia is defined as a loss of muscle mass [10]. It has been associated with poorer outcome in metastatic renal cell cancer. It can be measured quickly and simply by calculating the area of the psoas muscle [30]. A small study has suggested that maintaining or improving weight with chemotherapy is a positive predictor in lung cancer. It did not show that sarcopenia predicted outcome.

2.1.6 Machine Learning in lung cancer
Machine learning is a way of using a computer programme to identify important features within a dataset, which can then be used to predict outcome in a new dataset. There are different methods of classifying data. An example is the use of SVM (Support Vector Machines). They can used to classify different data, for example lung cancer patients at high risk and low risk of cachexia. The benefit being that SVM can separate non-linear data, meaning it can separate data into 2 groups that are not obviously distinct when plotted on a scatter chart. In this situation methods such as logistic regression could not be used. Machine learning
has not previously been applied to identifying prognostic markers in nutritional status for lung cancer.

### 2.2 Rationale for study

In view of the multiple co-morbidities, high symptom burden and the fact that many patients are older and less fit, lung cancer is a difficult illness to treat. It also commonly occurs in patients that are older, less well-off and less educated, resulting in higher rates of admission to hospital than other common cancers [31]. They are a more vulnerable population and weight loss is known to predict for outcome [32].

Standard practice at St Luke's Cancer Centre (SLCC) is for health care professional-guided referrals to a Macmillan Oncology Dietitian. As described previously, 40% of patients with advanced lung cancer are malnourished, with a further 40% at risk. Our own audit data suggests that 75% of patients with advanced lung cancer are cachectic when first reviewed by the dietitian. (Cachexia in this context is defined as >5% weight loss from usual body weight). A quarter of patients had refractory cachexia (survival <90 days) when referred to the dietitian. This suggests that a strategy to screen patients for malnutrition/cachexia on diagnosis is advisable. It also allows for the earliest possible nutritional intervention.

Early symptom intervention with specialist palliative care in patients with metastatic lung cancer has been shown to provide a significant improvement in overall survival of 11.6 months vs 8.9 months (p=0.02)when their anti-cancer treatment was the same[33]. Nutritional support is a simple and inexpensive intervention that may improve symptoms and outcomes in lung cancer. There is a paucity of data in prospectively assessing nutritional outcomes in lung cancer [34].

A previous study randomizing patients to dietary advice +/- nutritional supplements did not show a significant difference, but compliance with taking the nutritional supplements and completing food diaries was low [35]. Standard dietetic practice usually involves first line food fortification advice, followed by nutritional supplements if patients are not able to maintain adequate oral intake. A systematic review of dietetic intervention in advanced cancer suggests that intervening can have a positive effect on weight and calorific intake, but study heterogeneity makes it difficult to prove this conclusively [36]. Chemotherapy may improve muscle mass in advanced lung cancer [37].

In this study we want to better understand the proportion of patients with advanced lung cancer who present with cachexia, malnutrition and/or sarcopenia, before their treatment is initiated. This will subsequently establish the extent of the need for dietetic intervention in this patient group. We anticipate that the results of this initial study will then inform a further randomized study looking at the effects of dietetic intervention in lung cancer patients.

### 3. Trial Objectives
3.1 Primary Objectives

- To identify the proportion of patients diagnosed with advanced Non Small Cell Lung Cancer who are malnourished, cachectic and have sarcopenia before anti-cancer treatment.
- To identify the proportion of lung cancer patients who would require dietetic review before anti-cancer treatment.

3.2 Secondary Objectives

- To identify whether malnutrition, cachexia and sarcopenia affect overall survival in advanced NSCLC.
- To identify whether sarcopenia predicts for a poor outcome in NSCLC

4. Trial design

The trial will be a prospective cohort study, open to all patients at SLCC in the Royal Surrey County Hospital (RSCH) and Ashford and St Peters Hospital (ASPH) receiving treatment for advanced primary NSCLC.

5. Patient Population

*The study will recruit 100 patients. Patients are eligible for the study if all the inclusion criteria are met and none of the exclusion criteria apply.*

5.1 Inclusion criteria

- Patients >18 years old who are able to consent to entry into a clinical trial
- Biopsy confirmed Advanced Non Small Cell Lung Cancer (stage IIIb and IV).
- Patient receiving first line anti-cancer treatment

5.2 Exclusion criteria

- Inability to consent to treatment
- Patient declines anti-cancer treatment

5.3 Sample Size calculation

This is a pilot study to identify the incidence of malnutrition, cachexia and sarcopenia in patients with advanced NSCLC. The size of the difference in outcome between those is not known. The aim of this study is to quantify these differences to aid sample size calculations for a larger study.

6. Patient Recruitment

Patients will be identified by the clinical team and invited to participate by the research team when attending the new patient clinic.

If the patient is interested, the research team will explain the study and give them a copy of the patient information sheet to review. The patient will be given the opportunity to ask any questions they may have about the study and will be given a minimum of 24 hours to decide if they would like to participate.
Eligible patients will be invited to consent when they attend their next appointment. Consent will be obtained by a suitably qualified person in accordance with international GCP guidelines. It is anticipated that many patients will be entered into the trial when they attend their nurse led clinic appointment.

The research team will emphasize that non-participation will not adversely affect any aspects of their care.

7. Trial Treatment
Each patient consented to the study will receive 1 mandatory assessment. If this assessment suggests that a patient needs to be reviewed by a dietitian, they will be referred to their local dietetic service.

8. Schedule of Assessment
Assessment Visit 1
Visit 1 is to be completed before or on the day that the patient has completed their first dose of systemic chemotherapy.

The following assessments will be completed and recorded by the research team during the visit:
- PG-SGA
- Charlson Co-morbidity Index
- EORTC QLQ C30 core module and LC13 lung cancer module
- ECOG performance Status
- SPARC assessment
- Spirometry
- Hand grip strength
- Weight and BMI
- Routine blood tests (FBC, U+E, LFT)

In addition to the above, by consenting to the study the patients are allowing the research access to their diagnostic CT scan. The scan will undergo texture analysis to assess body composition pre-treatment and access for sarcopenia. Scans will imported into the eclipse radiotherapy planning system. The relevant section of the appropriate muscle will be outlined. The CT scan will be exported and anonymised. It will be transferred to a password protected University of Surrey PC as DICOM data. The texture analysis will take place on a University of Surrey computer and does not require any patient identifiable information.

If the results suggest that a patient needs to be reviewed by a dietician, they will be referred to their local dietetic service as per standard practice.

Follow up
Patients will be seen by a dietitian following their assessment as clinically indicated. These visits will not form part of the study. Once the patient has completed their baseline assessment they have completed their participation in the trial.
Patients will not be required to attend any follow up visits however survival status will be monitored at the following time points.
9. Data Management
Data will be collected using paper data sheets that will be kept in the patients notes and transcribed onto an electronic CRF. Electronic data will be stored on a password protected computer and encrypted USB storage device. Both paper and electronic files will be stored securely in a locked office.

Data will be stored in accordance with the data protection act 1998. Access to data will be restricted to members of the research team. Patient data will be anonymised by assigning a unique study number and all identifiable patient information will be removed.

9.1 Data Analysis
Data will be analysed by the research team with help from statisticians from the Surrey Clinical Research Centre. An initial analysis will occur at the completion of the study to describe the treatment received by patients who are malnourished/cachectic/sarcopenic, and those who are not malnourished. 2 planned survival analyses will occur at 6 months and 1 year.

For a cohort of 100 patients, survival to, or death before 1 year will be observed, death beyond 1 year being regarded as censored data. Time to death will be analysed in a Cox proportional hazards model, with explanatory variables being the following baseline patient characteristics: a) patient malnourished/cachectic/sarcopenic (yes/no), b) patient no older than 70 years (yes/no) and c) patient exposed heavily to smoking (yes/no). Separately for each of these dichotomous explanatory variables, a pair of Kaplan-Meier curves of survival will be plotted. This analysis will be repeated at 1 year.

In addition machine learning approaches will be used, such as support vector machine models. Multivariate analysis (MVA) is a long established technique to analysis complex data for correlations between sets of variables and outcome measures.

Machine learning is a set of approaches that are starting to be used in the analysis of complex medical data and constitute a fundamentally different approach to MVA. As part of the advanced analysis the psoas muscle of the patient will be measured to assess its surface area. The muscle will also undergo a form of CT analysis called texture analysis, which will be performed on the diagnostic CT scan.

Diagnostic CT scans will be requested from the trust where the scan was performed through the Image Exchange Portal (IEP) and transferred to the Royal Surrey County Hospital for analysis. IEP is a secure and confidential method of transferring scans within the NHS.

The diagnostic CT scan data will be imported into eclipse (radiotherapy planning software). The relevant structure will be volume. The scan will be exported as anonymized DICOM data into a research radiotherapy programme.
The selected structure will be extracted and analysed using matlab and software developed within the Centre for Vision, Speech and Signal Processing at the University of Surrey.

The goal of using the standard statistical analysis and machine learning, is to determine if they show different aspects of the data and hence if we can extract more useful information from the combination of approaches. The goal of Sarcopenia and textural analysis is to see whether advanced CT analysis can be a useful imaging biomarker for outcome or nutritional status in NSCLC.

10. Adverse Events
The intervention in this study is a dietetic assessment. This is not expected to lead to adverse events. It is common for patients to be admitted to hospital with metastatic lung cancer. The collection and reporting of adverse events will not alter the outcome of our clinical trial.

11. Trial monitoring
The CI will facilitate any local monitoring by the R&D quality manager, REC review and provide access to source data as required.

Following any monitoring a report will be provided which will summarise the visit and documents, along with any findings. The CI will be responsible for ensuring that all findings are addressed appropriately.

Additional monitoring will be scheduled where there is evidence of suspicion of non-compliance with the Trial protocol.

12. Withdrawal of a patient
Patients can withdraw their consent from the trial at any stage. If a patient explicitly states that they no longer wish to take part or contribute to the trial, their decision must be respected. The patient’s withdrawal from the trial will be recorded in the patient’s notes. All data collected up to the point of withdrawal will be included in the trial analysis. However if the patient withdraws consent for their data to be used the data will be destroyed immediately.

If a patient is considered no longer to be eligible or the responsible clinician feels it is no longer appropriate for the patient to take part then this must be documented, indicating the reason for withdrawal, in the patient notes.

13. Trial closure
13.1 End of Trial
Upon the end of trial a “declaration of end of trial” form will be submitted to REC, as required.
13.2 Archiving trial documents
Following the end of trial arrangements for non-essential confidential documents will be destroyed. Essential documents will be securely archived for 5 years.

13.3 Early closure of the trial
The trial may be stopped early upon recommendation.

14. Sponsorship
The trial will be sponsored by Royal Surrey County Hospital Foundation Trust.

15. Indemnity
Royal Surrey County Hospital Foundation Trust holds professional liability insurance to meet the potential legal liability of the sponsor and employees for harm to participants arising from the design and management of the research.

Indemnity to meet the potential legal liability of the investigators/collaborators for the harm of participants arising from the conduct of the research is provided by the NHS Indemnity scheme or through professional indemnity.

16. Publication
The results of this study will be published by peer-reviewed journals and presented at local and international conferences.

17. References


Appendix 4

Developing a method for operator independent tumour recognition using 2nd order textural analysis of a whole lung, generated from Computer Tomography data

4.1 Background

Differentiating between tumour and Radiation Induced Lung Injury (RILI) is difficult, even to the expert eye, as radiological features of recurrence can often be seen benign RILI (Huang et al., 2012, Nguyen et al., 2017, Ronden et al., 2018). The aim of this work was to attempt to solve this difficult clinical problem; to understand whether TA could be used to differentiate between a tumour and RILI after SABR for primary lung cancer. This would be achieved by identifying a methodology that required limited assumptions regarding the spatial characteristics of the tissue, as well as being able to potentially analyse the whole lung and differentiate between tissues. By analysing a greater volume of lung using an analysis that could take account of spatial variations, more complex interactions could be investigated, identified and understood. As well as understanding the spatial variations, analysing large volumes of lung tissue overcomes the difficulty in identifying the tumour bed after treatment. This is because after SABR, RILI can occur in large parts of the lung. RILI can also cause traction within the lung meaning the geographical position of the tumour bed changes.

4.1.1 Choice of software

TA can be undertaken using commercial software, such as TexRAD (TexRAD Ltd, Cambridge, UK). When using TexRAD the user identifies a region of interest on a single slice of a CT scan. This undergoes first order TA and the region of interest generates a single number to represent a texture measure, for example skewness or kurtosis. This analysis can then be applied to clinical outcome, for example comparing patients with tumours that have relapsed early vs never relapsed to see if the texture measures are statistically different.

TexRAD was considered unsuitable for this project for a number of reasons. Firstly with a first order, single slice analysis, it would not be possible to take account of spatial variations or patterns, both within a tumour or an area of RILI and between tumour and RILI. Analysis needed to take account of sub regions within the lung as both a tumour and RILI could exist concurrently. Secondly, by not capturing all of the data regarding either tumour or RILI, it is
more difficult to identify any patterns within tumour and RILI, which would allow the different areas of the lung to be easily differentiated. This would not be possible with TexRAD. TexRAD is very user dependent and would require the user to have sufficient knowledge to identify the abnormality or region of interest.

TexRAD was unable to compare sub-regions within a region of interest without repeatedly re-drawing contours. These limitations meant TexRAD was not suitable to pursue this project.

As TexRAD was not thought to be suitable, alternative software that could use second order TA was investigated. FiniteRT is software used for TA, it was developed in a collaboration between the University of Surrey and the Royal Surrey County Hospital. Before the work described in this thesis, finiteRT had been limited to analysing tumours. It was used to investigate and correlate intra-tumoural heterogeneity on CT imaging with FDG-PET avidity, within the Gross Tumour Volume (GTV) of primary lung cancers, which were to be treated with radical radiotherapy (Alobaidli et al., 2017). This means that the previous study by Alobaidli et al focused on the analysis of the GTV as the region of interest. The region of interest was extracted from single phase non-contrast images from the CT component of the PET-CT scan. As a result it did not have to contend with variables that would need to have been taken account of, if larger regions of interest were to be analysed.

In order to develop as user-independent process as possible, the work outlined in this thesis had to take account of many more variables, when compared to the previous project. New variables e.g. presence of IV contrast or analysis of larger ROIs needed to be accounted for to understand their downstream effect on the TA results. This chapter covers the initial work on expanding the region of interest from the tumour to the whole lung. To develop the methodology required active participation in developing the software as well as investigating the effects of different variables.

By participating in the software development, it became obvious that this tool could have wider applications in analysing CT data, other than in analysing post treatment reponse. Two examples of this are explored in themes 2 and 3 of this thesis.

FiniteRT was chosen as software to persue differentiating between tumour and RILI after SABR, principally because it can take account of spatial relationships between sub-regions of a texture plot. It achieves this by using a second order feature of TA called grey level co-
occurrence matrices (GLCM), to create a map of heterogeneity. The GLCM identified runs of grey levels in the 13 directions of the 26 surrounding voxels. The heterogeneity is expressed as an entropy score. Entropy is a measure of disorder. The calculation used for entropy in finiteRT is:

\[
Entropy = -\sum_{i=1}^{N} \sum_{j=1}^{N} P(i,j) \log P(i,j)
\]

(Alobaidli, 2017)

Essentially, the software divides the region of interest into voxels, before making a voxel by voxel comparison, assessing its similarity or dissimilarity to the 26 voxels immediately surrounding it. The larger the structure the longer it takes the software to process the information. For comparison analysing a tumour volume would take several minutes and analysing an entire lung would take several hours. Each time a variable within the software is changed, the analysis needs to be re-run.

The software characterises the image using the GLCM to identify how often pairs of pixels with a specific value appear relative to the position of the voxel in space. FiniteRT assigns the voxel an entropy score. The higher the entropy score, the more dissimilar a voxel is to voxels around it. Inversely, a low entropy score means a voxel is similar (more uniform) to the voxels around it. Entropy is inversely proportional to uniformity.

The aim of the project was to differentiate between tumour and RILI. The software has different variables that can be altered. It was important to understand how altering these variables might maximise the differences between tumour and RILI. Firstly the size of the filter can be set. The filter size is the size of the window the software uses to analyse each voxel. The software also sets the number of levels the data is divided or digitised into, which are the quantisation levels. Quantisation is when a continuous variable is divided into a pre-set number of discrete levels. The software makes a comparison between voxels by comparing data already divided into quantisation levels, rather than by comparing the absolute value of the voxel. The software calculates the quantisation levels for each analysis using a Lloyd Max quantiser (LMQ). Quantisation is described as the process of dividing up a continuous range of values into non-overlapping sub-ranges. This means that similar absolute values are grouped together. A value can then be given to each sub-region. The LMQ then divides
absolute values into the set number of levels (bins) exactly half way between each level. The LMQ chooses quantisation levels in such a way that the difference between the quantised image and the original image are minimised. The equation used in LMQ was:

\[ E = \sum_{i=1}^{L} \int_{t_i}^{t_{i+1}} (x - r_i)^2 p_x(x) dx \]

(Alobaidli, 2017)

This method of quantisation assigns thresholds based on the range of values within a region of interest. If the contents of the ROI are different, the spread and quantity of specific density values are different, the absolute density values at which the software defines the quantisation levels will be different. For example if there are 2 ROI’s, one contains just lung tissue and one contains lung and bone, the actual values at which the quantisation levels are set are likely to be different. This type of quantisation has been termed individualised quantisation.

It is also possible to standardise the quantisation levels, so that 2 or more structures are analysed using identical absolute values for quantising the data. The comparison of two or more regions of interest using identical quantisation levels has been termed uniform quantisation. The initial version of finiteRT used individualised quantisation. As more work was completed it became apparent that uniform quantisation would be useful. Previous data has suggested that there are 2 methods to define quantiation levels, one by dividing the range of values into equally spaced levels (bins) where the bin size varies for each image and the second standardises the quantisation by maintaining a constant intensity resolution. The second method, which is comparable to uniform quantisation is more robust to intra- and inter-image assessment (Leijenaar et al., 2015). As part of this project finiteRT was developed so that it could use either uniform or individualised quantisation.

The aim of this work was to provide an analysis for large ROIs. As a result there were a wider range of variables that needed to be taken account of. Understanding how the texture maps and entropy scoring changes when the variables are altered has two benefits. Firstly in understanding which variables alter the outcome of the TA and secondly, which variables may help maximise the ability to identify the tumour.
These variables were divided into 2 groups, relating to understanding the effects of changing the software variables in finiteRT altering the results of the TA e.g. number of quantisation levels, then in understanding the imaging variables that might affect the pre-TA captured image e.g. presence or absence of IV contrast. An overview is given in figure 1.

The ROI analysed, filter size and number of quantisation levels analysed were TA variables, the first group as identified above. Exploring the effect of altering these variables formed the first part of the experimental work in this chapter (section 4.2).

The second category of variables that may influence the analysis were the imaging variables. These were thought to include use of multi-phase radiotherapy planning scans, regions of interest containing tissues other than tumour or larger than the tumour, effects of intravenous contrast, breathing phase of the scan or the ability to interpret post treatment imaging. This work describes the process of developing a model to understand the variables necessary to process and interpret a texture map of a whole lung, both before and after Stereotactic Ablative Body Radiotherapy (SABR).
Before any work was done, it was not clear whether finiteRT could generate texture maps for structures larger than a tumour. As a result the initial step was to establish whether it was possible to generate texture maps beyond a tumour (including surrounding lung) in pre-treatment and post-treatment CT scans.
4.2 Defining the experimental space 1: Preliminary work on software related variables

4.2.1 Experiment 1: Does the analysis of structures larger than the GTV alter the appearance of the texture map?

**Aim:** To identify how the appearance of a texture map changes when the contents of the ROI are altered, specifically, when the ROI including Gross Tumour Volume (GTV) is expanded to include GTV plus additional lung tissue. The hypothesis is that the appearance does not change as the proportion of lung vs tumour within the ROI increases.

**Methods:** A generic method for generating a texture map:

1. Import scan into radiotherapy planning system (Eclipse); each patient has an anonymised phantom radiotherapy plan for this purpose as part of the TEXAS trial (see appendix 2).
2. Ensure GTV is outlined on CT planning scan. The GTV is localised on the Maximum Intensity Projection (MIP) as an iGTV, using a structure set saved on the CT average. If the scan is a post treatment scan, contour abnormal area, portion of lung or whole lung as appropriate, check that tumour volume is included within lung volume. This is especially important if the tumour is adjacent/abutting the chest wall. For pre-treatment scans the GTV was outlined by the Clinical lead for SABR and a Consultant Clinical Oncologist with 10 years’ experience in treating patients with SABR.
3. Export DICOM data from eclipse including the radiotherapy structure set.
4. Load matlab software and CERR software (Computational Environment for Radiotherapy Research) (Deasy, 2016). Import DICOM data into CERR and save as a matlab file.
5. Segment (extract) structure from CT scan, using structure number in CERR.
6. Run TA. Each analysis has 3 variables: these are number of quantisation levels, filter size (in mm) and the structure being analysed. The code also stores a patient number.
7. This gives a map that can be viewed in matlab. These texture maps are displayed in grey scale, with a range of entropy values starting at 0 (most homogeneous). The higher the score the higher the entropy (heterogeneity). 0 entropy areas are black, heterogeneous areas appear as white. The majority of entropy values are below 5.0.
For this first experiment, the relevant planning scan was imported into eclipse, pre-existing structures were used for these expansions. As a result a patient was identified, who underwent radical fractionated lung radiotherapy rather than sabr, as the patient had a GTV, CTV and PTV. This patient had a tumour within the lung that was not in contact with central structures or the chest wall. The GTV was identified. For the first map generated from the pre-treatment scan, the CTV and PTV were used as surrogates for an expanded margin from the GTV. This experiment used the 8 quantisation levels and a 5x5mm filter. The filter gives the size of subunits that the ROI is broken down into.

**Experiment 1 Results:** Figure 2 shows 3 texture maps generated from the GTV, CTV (GTV+6mm) and PTV (GTV+11mm) of the same lung tumour. The standard appearance of a tumour after TA in previous projects is a black homogeneous centre with a rim of heterogeneity (appearing in white) (Alobaidli et al., 2017). All tumours that had been used were Non-Small Cell Lung Cancers. Figure 1 illustrates that the appearance of these images are similar when more lung is included in the texture map. When a larger area of lung is analysed, the central area of homogeneity and the visual structure of the map is maintained as the size of the ROI increases.

*Figure 2: Texture map analysing a region of interest equivalent to tumour plus a radiotherapy planning margin. a) tumour texture map for patient 4, b) tumour texture map + 6mm (CTV) and c) tumour texture map +11mm (PTV). Texture map has a stable appearance when increasing amounts of lung are included in the ROI. Black central area = homogeneous region= tumour, white= greater heterogeneity.*
Figure 3. CT image defining a region of interest equivalent to tumour plus increasing concentric margins. Structures related to patient 3 GTV, GTV +5mm, +10mm, +15mm and +20mm. Pink contour represents GTV.

The second part of this experiment was to perform uniform isotropic expansions of the GTV by 5, 10, 15 and 20mm for 3 patients. I wanted to understand how enlarging the ROI, which underwent TA affected the resultant texture map. Figure 3 shows how the volumes relate to the GTV on the original CT image for patient 3. Figure 4 compares texture maps from 3 different patients using the same margin expansions. It is interesting to note that the volume of the tumour from patient 9, is much smaller and does not appear to have a central homogeneous region. A hypothesis to be tested in further experiments could be that tumours need to be above a certain size to have a central homogeneous region within the tumour.
In figure 4, the images from left to right show increasing size of the ROI. Although the images appear broadly similar, it was also important to understand the effect of increasing the size of the ROI on the individualised quantisation levels selected by the software. Table 1 shows the quantisation levels selected by the software for these 3 patients, when the ROI is increased. As the quantisation levels are chosen automatically by the software for each analysis using LMQ, I wanted to understand the effect of increasing the ROI size on the specific values chosen for quantisation. Table 1 shows that the quantisation levels for patient 3 change subtly as more lung is included in the ROI. Figure 3 shows that as the volume enlarges, an increasing amount of lung is included. As more lung is included the proportion of lung parenchyma vs tumour included in the analysed volumes increases. Lung tissue has a lower density than tumour when measured in Hounsfield Units. FiniteRT manages this change by lowering the value of the first (lowest) quantisation level, but changes the mean distance between the levels by less than 10%. Visually the texture maps do not appear significantly different; however, there are subtle changes in the automatic individualised quantisation levels, selected by finiteRT. This experiment shows that increasing the proportion of lung tissue within the ROI does not change the gross appearance of the texture map, but it does affect the precise values at which the data is quantised. When comparing GTV against GTV
with more lung tissue in the analysed volume, the range of values increased and the maximum and minimum values were further apart in intensity; hence the mean intensity distance between each level increased.

In patients 4 + 9 there are significant differences between the quantisation levels for the GTV and the other analysed structures (illustrated in table 1). The volumes are illustrated in figure 5. It shows that the GTV structure includes lung and tumour, but all other structures for patients 4 and 9 have a portion of chest wall included.

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Table 1. Comparing the optimised quantisation levels selected using the Lloyd Max Quantiser in a sequential analysis of 3 patients. GTV quantisation levels are similar in 3 tumours from different patients GTV= Gross tumour volume, 1-8 indicate levels of quantisation selected by finiteRT software. Q-levels=quantisation levels. Mean diff between Q levels=mean difference between quantisation levels 1-8 for each structure. Pts 4 + 9 includes tumour, lung and a large amount of chest wall, as chest wall is dense the higher quantisation levels are very different in pt4 + pt 9 GTV+20 compared to pt 3 GTV+20. The differences in the structures is illustrated in figure 3. Distortions as isotropically grow GTV argue for per patient calibration.
Figure 5. Illustrating how growing isotropic margins around primary lung tumours commonly includes other tissues and structures. Comparing 3 GTVs (most central structure) as well as GTV+5mm, 10mm, 15mm and 20mm. a) = patient 3, b) = patient 4, c) = pt 9. Red= structures involving lung, tumour and chest wall, Green=structures involving lung and tumour. This means that generating the ROI is not completely user independent, but quantising a ROI including chest wall affects the quantisation and may affect the subsequent analysis.

Experiment 1 Discussion: This experiment shows it is possible to generate texture maps that are recognisable from ROIs when they include regions beyond the limit of the tumour, when compared to texture maps of the tumour alone. The contents of the ROI changes the absolute quantisation levels, although the appearance of the TA map images in this preliminary analysis remain the same. This would need to be confirmed by increasing the number of ROIs analysed in this dataset.
4.2.2 Experiment 2: Does the appearance of a texture map alter when varying filter sizes are used in the analysis?

**Aim:** As part of the preliminary work it is important to understand the effects of the different parameters that affect the analysis of a ROI texture map. In this experiment changes in filter size were investigated. The filter size is the size of subunit analysed as part of the texture map. Understanding the effects of altering the filter size could affect future analyses.

**Methods:** Using the same method as previously a texture map was generated for the GTV, Further ROIs were generated from the GTV plus an isotropic margin of 5, 10, 15 and 20mm. This meant each GTV generated five different ROIs, which were each analysed as a separate structure. These structures were initially analysed using 8 quantisation levels and a 5x5mm filter. Previous work was completed with a 5x5 filter and it was felt reasonable to test a larger and smaller filter than previously investigated. The ROIs analysed with a 5x5mm filter were compared with the same ROIs analysed with a 3x3mm and 7x7mm filter.

**Results:** Figure 6 shows the same slice of the texture map, with increasing margins (in mm), these ROIs were analysed with filters set at 3x3mm, 5x5mm and 7x7mm. Original work using finiteRT was carried out using a 5x5mm filter. The result of this experiment was that using a different filter size does not broadly change the appearance of the texture maps. This means the appearance of the texture maps are robust to changes in filter size, however, it does appear to alter the level of detail. When reviewing all the slices of each texture map the size of the homogeneous central region did not appear significantly different and the nomenclature of the texture map remains the same. Reducing the filter size from 5 x 5mm to 3 x 3mm or increasing it to 7x7mm did not seem to give any extra information, so a pragmatic decision was made to continue with a 5x5mm filter, as previous work had used this filter size.
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Table 2: Texture analysis of same ROI using 3 different filter (subregion) sizes. The results suggest that when comparing a 3x3mm, 5x5mm and 7x7mm filter within FiniteRT, the values at which the LMQ sets the quantisation levels is independent of filter size, e.g. GTV with 3x3, 5x5 and 7x7 filters highlighted in green all have the same values.

The quantisation levels used in the analysis displayed in table 2, were set using individualised quantisation. Table 2 shows that the quantisation levels using the LMQ is independent of filter size in this analysis.
Figure 6: Comparing texture maps of the same Regions of Interest with different filter sizes. 3x3mm filter compared to 5x5mm and 7x7mm filter with different expanded volumes around GTV (in mm). The images are organised in the same way with a central homogeneous region seen in black with a rim of high heterogeneity seen in white. This is surrounded by a region of lower heterogeneity representing lung tissue. The resolution of the lung tissue is more clearly seen in the image using a 3x3mm filter compared to 5x5 and 7x7mm filters.

**Experiment 2 Discussion:** The result of this experiment suggests that using different filter sizes do not broadly change the appearance of the texture maps illustrated in figure 6. The central homogeneous region of the tumour is present in all of the texture maps in figure 6. Altering filter size does appear to change the resolution of the sub-region of the ROI that represents lung tissue, a smaller filter size gives more detail, which is perhaps a predictable result. Altering the filter size does not appear to change the absolute values assigned to the different quantisation levels illustrated in table 2. The observations from this preliminary analysis would ideally need to be tested in a larger cohort of patients. There is sufficient
variation between filter sizes, that it generates the hypothesis that when comparing different ROIs the same size filter should be chosen and used in all comparisons.

4.2.3 Experiment 3: Does the appearance of a texture map alter when a different number of quantisation levels are used in the analysis?

Aim: Is the appearance of the texture map sensitive to the number of levels that the data is quantised into?

Experiment 3 Methods: The same structures were analysed as in experiment 2; however in this experiment the filter size was kept constant at 5x5mm and the analysis was re-run with 8, 16 and 32 quantisation levels. Results are shown in figure 7.

Experiment 3 Results:

Figure 7: texture maps of a ROI including tumour plus a margin using different numbers of quantisation levels. (e.g, GTV+5 = GTV + 5mm margin) analysed with a 5x5 filter using 8, 16 and 32 quantisation levels. The central area of homogeneity became less distinct as the number of quantisation levels increased. The central homogeneous region representing the centre of the tumour became less black and increasingly grey. This illustrates that the previously homogeneous central region of the tumour becomes less uniform as the number of quantisation levels increases.
**Experiment 3 Discussion:** From experiment 1 and 2 it seemed that increasing the size of the texture map to include more lung tissue did not affect its ability to identify areas of homogeneity. Therefore it was decided at this point to standardise the number of quantisation levels to 8 for two reasons, firstly previous work identified the homogeneous region of the tumour and its relationship to PET avidity used 8 quantisation levels (Alobaidli et al., 2017). Secondly and most importantly, using 8 levels appeared to maintain the central homogeneous region of the tumour more robustly than 16 or 32 levels. Maintaining the central homogeneous region of the tumour meant the tumour should be easy to identify in the texture map image. Although this decision was revisited at a later date when much larger ROIs were analysed, the principle of maintaining intra-tumoral homogeneity remained a central feature in the subsequent analysis, so the tumour centre could be easily identified.
4.3 Defining the experimental space 2: Preliminary work on image related variables

4.3.1 Experiment 4: Does the breathing phase from a 4DCT affect the appearance of a texture map, when a GTV is analysed? Effects of tumour movement on the texture map of the GTV

Experiment 4: Understanding the effects of tumour movement on the GTV

**Aim:** From the work in experiments 1-3 it was established that although the texture map subtly alters when the contents of the analysed ROI are altered, altering the number of quantisation levels and the filter size does not lead to obvious or gross changes in the appearance of the texture map. Whichever settings are used the central homogeneous region of the tumour is maintained and therefore it is easier to identify a pre-treated tumour within the texture map. The preliminary texture related experiments were all completed on scans from 1 scanner. Radiotherapy CT scans are not used for diagnosis and aim to provide a model of the patient for planning radiotherapy treatment. When a tumour of the upper abdomen or thorax is treated with radiotherapy, a 4DCT scan can be used to assess and compensate for tumour movement during respiration. The scan divided respiration into 10 phases (CT0, CT10 … CT90). CT0 correlates with maximum inspiration and CT50 with maximum expiration. Two composite volumes are standardly generated from these 10 phases, which are the AVIP (Average Intensity Projection) and the MIP (Maximum Intensity Projection). A single phase gives the best image definition, MIP illustrates the maximum motion related to a structure and the AVIP is equivalent to the average position of a structure i.e. the position of a structure during most of its time during the breathing cycle. As a result standard practice is to contour organs at risk on the AVIP sequence and use the MIP to ensure the tumour’s position has been covered in all of the breathing cycle. Using this technique minimises the risk of a systematic error caused by a geographical miss of the tumour, due to respiratory movement. Data has shown that using the MIP and reviewing the 4DCT ensures best coverage of the tumour (Ezhil et al., 2009).

**Methods:** The GTV was copied from the AVIP to the MIP, CT0 and CT50 phases of the 4DCT of a patient that met the criteria for SABR for a primary lung tumour. These structures were then analysed allowing the software to choose optimised quantisation levels for each structure. All the 4D scans were completed using Advantage 4D software (General Electric),
the binning was completed using amplitude. Quality control is completed 3 monthly for the 4D acquisitions, compared to monthly and daily Quality Control for normal scanning.

**Experiment 4 Results:**

![Figure 8: showing texture map analysing a Region of Interest equivalent to the GTV using 4 different phases of the 4DCT radiotherapy planning scan. These maps analysed the GTV for patient 5 using data extracted from CT0, CT50, CTAVIP and CTMIP.](image)

<table>
<thead>
<tr>
<th></th>
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<th>5</th>
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<td>620</td>
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*Table 3, showing the 8 quantisation levels for the four phases of the GTV illustrated in figure 7.*

CT0 and CT50 are very similar in appearance, with the rim of the tumour in slightly different positions showing the data is taken from different phases of the breathing cycle. The CTAVIP shows a blurred heterogeneous rim, which would be explained by the fact that the AVIP is an average over the whole breathing cycle. The image from the CTMIP shows the largest homogeneous region of tumour and that the heterogeneous rim fits the outer edge of the structure, explained by the MIP accounting for all positions of the tumour. The images do not appear significantly different. The ITV for pre-treatment analyses was taken from the CTAVIP. This was a pragmatic decision as the AVIP contained the radiotherapy structure set and planning data. It was encouraging that all of the maps in figure 6 maintain the central homogeneous region, as post treatment scans would likely take place in an equivalent of CT0 (deep inspiratory breath hold). It also means that if patients are unable to hold their breath...
during a scan, any blurring in post treatment scans would not cause the loss of the central homogeneous region.

**Experiment 4 Discussion:** Analysing ROIs (seen in figure 8) corresponding with the GTV segmented from different phases of the 4DCT does not obviously change the appearance of texture map relating to the tumour. Most importantly it does compromise the presence of the central homogeneous region of the tumour. These images were taken from a ROI that corresponded with an iGTV, which accounted for tumour motion. As a result CT0 and CT50 are single phases of the 4DCT, where as CTAVIP and MIP are composite volumes from all phases of the scan. For this reason it is not surprising that the central homogeneous regions of the ROIs in figure 8 are subtly different shapes.
4.3.2 Experiment 5: Does the presence of intra-venous contrast affect the appearance of a texture map generated from the GTV?

**Aim:** Contrast is known to affect the texture of tumours (Dennie et al., 2016). IV (intra-venous) contrast used in CT scans is radio-opaque and has a high density when measured in Hounsfield Units. As tumours are likely to take up contrast I wanted to compare tumours for the same group of patients from the AVIP of the radiotherapy planning scan with the CT component of their diagnostic PET-CT scan. Use of IV contrast was standard in SABR patients treated at RSCH using a standard protocol, in all patients who had adequate renal function and did not have an obvious contra-indication to IV contrast.

The CT component of the PET-CT is performed in free breathing, so should be similar in nature to the AVIP. The PET-CT scan is often the final imaging diagnostic test before a patient is considered for SABR, so these scans were chosen as changes due to progression of the tumour were kept to a minimum.

**Experiment 5 Methods:** The GTV from the AVIP (GTV-AVIP) was registered and copied to the CT of the PET-CT scan (GTV-PET). GTV-AVIP and GTV-PET were segmented from their respective scans and analysed using finiteRT.

<table>
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*Figure 9, Comparing the effects of contrast on the appearance of texture maps from contrast and non-contrast CT scans. This was achieved by comparing appearance of a texture map from CT from non-contrast PET-CT, with pre-treatment contrast enhanced radiotherapy planning scan for 3 different patients.*
### Table 4:

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Table 4, showing 8 quantisation levels for GTV+20mm from a PET-CT and radiotherapy planning CT for 3 patients.

**Experiment 5 Results:** Figure 9 shows there is no noticeable difference in appearance of the central homogeneous region of the texture map, whether or not the scan contains contrast.

Although the contrast slightly alters the quantisation levels seen in table 4, they are not very different, but it does show that contrast is a variable that needs to be considered.

**Experiment 5 Discussion:** Contrast does not change the way the image is configured in these 3 patients, but does affect quantisation. Ideally in comparing ROIs between patients the scan images would either all be taken with or without contrast. To confirm this finding, ideally a larger cohort of patients would be need to be analysed.
4.3.3 Experiment 6: What is the effect of Stereotactic Ablative Body Radiotherapy on the appearance of a lung tumour in a texture map?

**Aim:** As the aim of this project was to use the texture analysis tool in both pre- and post-treatment scans, it is important to understand the effect of treatment on the texture map. It is also likely that patients will have their follow-up scan in a different hospital, on a different scanner to the radiotherapy planning scan, which needs to be taken into account, as well as the effects of treatment. It is very unlikely that patients will have any follow up scans on the same scanner, on which they had their radiotherapy planning scan. As well as the difference in scanner, the scanning protocol is likely to be different. There are 3 potential different scans that a patient is likely to undergo, initially a diagnostic CT, then a PET-CT for more accurate staging and finally a radiotherapy planning CT. The CT component of the PET-CT is performed in free breathing and the patient receives an intra-venous radioactive tracer rather than IV contrast, secondly the radiotherapy planning CT scanner with IV contrast and the average phase composed of multiple phases of a patient breathing freely, the third type of scan is a diagnostic CT scanner with the patient in inspiration breath hold using IV contrast.

**Methods:** 3 patients had all available CT imaging assessed. The region of interest (GTV) was identified in a pre-treatment CT component of PET-CT, radiotherapy planning CT and post treatment scans. The GTV was isotropically expanded using eclipse radiotherapy planning software, to create GTV + 20mm. In all the analyses 8 quantisation levels and a 5x5mm filter were used.

**Results:**

Figure 10 shows the changes in tumour bed after treatment over time. The first and second columns of figure 10 show that the presence or absence of contrast as also seen in figure 9. This experiment was testing texture appearance on different scanners and response to tumour over time. It is well established that after SABR there can be significant post treatment inflammation in the lung, which can make it difficult to identify the treated tumour as well as the fact that the tumour bed can change position in the lung as a result of the inflammation. Post treatment lung injury can be termed RILI (Radiation Induced Lung Injury). RILI can be difficult to distinguish from tumour (Huang et al., 2015).
Figure 10: comparing texture maps of GTV+20mm between CT of PET-CT, radiotherapy planning scan and diagnostic post treatment CT scans. All analysis used 8 quantisation levels and a 5x5mm filter. These 3 patients were chosen as they had not had a recurrence >2 years post SABR treatment.

In patient 4 the central region is visible on the diagnostic PET-CT and planning scan, it is smaller at 4 months and is not obvious at 20 months, but reappears at 26 months. It may be that as the acute lung reaction has settled and more organised fibrosis is establishing itself, this forms a homogeneous region. In patients 3 and 5, the central homogeneous region of the tumour disappears after treatment and does not reappear.

Experiment 6 Discussion: These results suggest that the textural appearance of lung tumours treated with SABR can significantly change after treatment. In these 3 examples of patients whose tumour has not recurred after SABR, the central homogeneous region gets smaller and disappears after treatment. The distortion of the central homogeneous region of the tumour can be seen in the first post treatment scan in all 3 patients and continues in the second post treatment scan. This experiment raises the question of whether it may be possible to differentiate between tumour and RILI early after SABR. This would need to be tested on a larger cohort of patients, ideally with similarly timed post treatment imaging.
4.3.4 Conclusion of work from section 4.1-4.3

From the work outlined in section 4.2 and 4.3, it can be concluded that all the variables affect the appearance of the texture map, but mostly in subtle ways. In combination these could have a profound effect on the ability to compare similar structures between patients. The aim of this preliminary work was to understand, which variables were important. Perhaps unsurprisingly, all the identified variables are important, however although these factors influence the analysis, they do not appear to affect the architecture of the texture map and its appearance is largely unchanged. In conclusion the appearance of the texture map generated from the analysis is robust to these variables. To maximise the accuracy of future analysis further work aimed at standardising the analysis needed to be completed, to minimise the effect of as many independent variables as possible.

At this point it was felt that any future analysis would need to fix the filter size and number of quantisation levels and consider exploring uniform quantisation. Analysis would also aim to use scans with IV contrast in an identified breathing phase.

It was felt that fixing the quantisation levels using uniform values, rather than allowing the software to choose individualised quantisation levels, would mean that differences in the texture maps were due to the tumour, not the software. It offered two other benefits. Firstly, it would also allow the entropy (disorder) scores generated from the analysed structures to be directly compared. Secondly, fixing quantisation levels means the quantisation levels are not determined by the content of the texture map. For example, by fixing the quantisation levels it does not matter whether a dense structure, such as chest wall, is inadvertently included in a region of interest, which should only include lung and tumour. In a clinical context it reduces the need for specialist knowledge to volume a region of interest and minimises the effects of any errors in generating a region of interest.

Going forward from this point, it was felt that further analyses should aim to include either large sections of lung or if possible the whole lung. Generating a contour of the lung requires less specialist knowledge than identifying the tumour bed (particularly in post treatment imaging) and ensures that all post treatment inflammation would be included. To date all work had been completed on the GTV plus a margin of lung. If further analysis were to include large sections of lung tissue, then this would lead to a more complex analysis of the texture
map, as the appearance of normal tissue as well as abnormal tissue would need to be accounted for. The texture analysis would also take a lot longer to process using finiteRT.
4.4 Calibrating the texture map analysis

4.4.1 Experiment 7: Generating texture maps of large sections of lung containing tumour

**Aim:** As discussed above, analysing larger sections of lung allows for the need for less specialist knowledge in voluming the tumour. It also allows for a more agnostic (user-independent) approach to generating the texture maps. The aim of this experiment was to see whether it was technically possible to segment and process large regions of interest equivalent to large sections of lung. It was also important to understand whether analysing large ROIs affects the texture map appearance. Understanding the effects of analysing larger sections of lung was important as it requires less specialist knowledge to contour a volume of lung when compared to voluming a tumour or area of lung injury.

**Methods:** In this experiment the GTV and 3 expansions on the GTV were analysed. All 3 expansions include all lung tissue circumferentially around the GTV, the volume was then

![Figure 11: A comparison between GTV and 3 expanded volumes, including the whole lung circumferentially with 2, 3 and 5cm superiorly and inferiorly to the GTV. Below the texture maps is the original pre-treatment CT image.](image)

**Methods:** In this experiment the GTV and 3 expansions on the GTV were analysed. All 3 expansions include all lung tissue circumferentially around the GTV, the volume was then
grown 2, 3 and 5 cm superiorly and inferiorly within the lung. The volume was edited back to only include lung tissue and tumour, aiming to exclude chest wall and mediastinal structures.

Figure 12: Comparing texture maps of slices of whole lung from a CT scan between CT of PET-CT, radiotherapy planning scan and diagnostic post treatment CT scans. shows the same analysis as in figure 11, but for the pre-treatment CT scan and 2 post treatment CT scans. The appearance of the texture maps are unchanged in this patients when the amount of lung tissue included in the texture map is increased.

**Results:**

Figure 11 shows the appearance of slices of texture analysis of all of the lung tissue in the axial plane. Figure 12 shows the same analysis in sequential scans both before and after treatment. The maps do not appear any different, so including more lung does not alter the appearance of the texture map.

**Experiment 7 Discussion:** This experiment shows that in multiple axial CT images of this patient including a large proportion of lung tissue in a texture map, does not alter the appearance of the texture map. Figure 11 shows that increasing the volume of lung in a cranial-caudal direction does not affect the appearance of the axial texture map.
4.4.2 Experiment 8: Standardising quantisation of lung sections to GTV

**Aims:** The aim of this experiment was to see if there was a difference in the appearance of the image standardised to GTVs generated from 3 different phases of the 4D radiotherapy planning scan, because it was important to understand the effects of using different phases of the 4DCT as a ROI for TA. Analysing different breathing phases of the 4DCT did not affect whether a central homogeneous region of the tumour was detected within the texture map, as discussed in experiment 4, but it was important to ensure that it did not have an effect on the analysis of large volumes of lung.

**Methods:** A section of lung including all lung circumferentially and 5cm superior and inferior to the GTV was extracted from the CT scan, this included most of the lung ipsilateral to the tumour. A limited region including GTV only was analysed by finiteRT using optimal quantisation separately for CT0, CTAVIP and CTMIP. This was to see what effect of the individualised quantisation using the LMQ was for the different phases of the 4DCT. The CT0, MIP and AVIP were then used to standardise the quantisation of the much larger lung section seen in figure 12.

**Results:**

FiniteRT took account of the large proportion of lung compared to tumour in calculating the optimised quantisation levels using the Lloyd Max quantiser. The effect of the individualised quantisation was that more heterogeneity in the lung parenchyma was identified compared to using individualised quantisation from the analysed structured when compared to using quantisation levels from the analysis of the GTV from either CT0, CTAVIP or CTMIP. In all 4 analyses the central homogeneous region was visible and broadly similar, but the structures analysed using uniform quantisation levels standardised to tumour showed a lot less heterogeneity within the lung parenchyma. Figure 13 shows a post treatment scan taken 6 months after delivery of SABR. All of the lung appears heterogeneous in the optimally quantised structure (column a), whereas the images generated using uniform quantisation (columns b), c and d), differentiate between post treatment RILI on the left of these images (also seen in column e) on the original CT image) and the uninflamed lung on the right of the image.
Figure 13: analysis of whole lung section standardised to different uniform quantisers. Column a) uses optimal quantisation, column b-d) use uniform quantisation to CTO, CTAVIP and CTMIP. Column e) shows the original CT image.

From this analysis, the quantisation levels appropriate to a tumour, aid interpretation of the lung parenchyma texture map. All of the analyses show an area on the left outer rim of the image that is consistent with the previously irradiated tumour bed, although it is not clear whether this is tumour or RILI. By comparing the tumour bed seen in figure 12 and 13, it illustrates how it changes position within the lung after treatment.
Figure 14: Comparison of texture maps of a CT scan 6 months after SABR using different uniform quantisers. Column a) uses individualised quantisation, column b-d) use uniform quantisation to CT0, CTAVIP and CTMIP. Column e) shows the original CT image. In column a) all of the lung is heterogeneous, whereas in column b-d) only the inflamed lung appears heterogeneous.

**Experiment 8 Discussion:** Standardising large volumes of lung tissue from post-treatment imaging to quantisation levels from the GTV of CT0, CTAVIP or CTMIP from the pre-treatment scan, means that it is possible to differentiate between RILI and normal lung, when compared to analysis using individualised quantisation from the lung volume. This can be seen by comparing column a) to columns b)-d) inclusive in figure 14.
4.4.3 Experiment 9: Combining CT images and texture maps

**Aim:** From the texture analyses to this point, it was evident that the tumour could be identified before treatment, but the tumour bed was more difficult to identify after treatment as the central homogeneous region of the tumour became disrupted, particularly in the first few months after treatment. Would the combination of original CT data and the texture map give greater information about the response of the tumour and the lung to radiotherapy?

Tumour is represented as a black homogeneous region in the texture map and as a grey/white (depending on windowing) dense region in the original CT image. As a tumour is dense and has low entropy, if the texture map was inverted, i.e. low entropy/high homogeneity would appear white. This experiment aimed to combine an inverted texture map with the CT data, potentially meaning a white region would represent low entropy and high density, a grey region would represent either a low entropy and low density or high density and high entropy and a black region would represent high entropy and low density.

**Methods:** I collaborated with a PhD student in CVSSP to adapt the finiteRT code to display both the standard texture map of a section of lung and an inverted texture map. The image was converted from a Matlab file into a NifTi file. The same code generated a NifTi file for the edited lung volume using the original CT data. These 3 files were then overlaid in an imaging programme called ITK Snap (Yushkevich et al., 2006).

**Results and Discussion:** Slice 38, 39 and 40 of figure 15 shows that the combination of inverted texture map and CT scan clearly identifies the tumour before treatment. Figure 16 shows the most representative slice of pre-treatment and post treatment images for a single patient showing the tumour identified as a region of low entropy and high density. Row a) shows the pre-treatment image. Row b) shows a slice of CT scan, texture map and combined map 3 months after SABR. In the whole texture map for this patient, the only homogeneous solid (i.e. white region) is seen in this slice. The high density low entropy region seen in white in the centre of the 3 images decreases in size very significantly when comparing the pre-treatment and 3 month post treatment image. This change occurs despite the fact the tumour appears broadly similar on the pre-treatment and 3 month post treatment CT image. It suggests that since the treatment, the gross appearance of the tumour is unchanged on CT, but the grey levels of the tumour have become a lot more heterogeneous after treatment.
This can be seen comparing the combined texture map (central image) in row a) and b) in figure 15. The combination of textural analysis and CT data gives a lot more information about an area, which is essentially unchanged on a CT scan after SABR.

Figure 15: Comparison of texture map, CT data and combined inverted texture map and CT data of a tumour before SABR. The central white area of the combined map illustrates tumour.

A central low homogeneity region is re-established 6 months after treatment, this is seen in figure 15 row c) and maintained 1 year after treatment, seen in row d). However, this region is grey, rather than white suggesting there is a difference between the pre-treatment tumour, which is dense and low entropy and the post-treatment lung reaction, which is dense, but not of low entropy, so appears grey rather than white.
Figure 16, comparison of texture map, CT data and combined texture and CT data pre-treatment and post treatment after SABR for a patient who did not relapse (patient 5).

The area of homogeneity seen in figure 16 row c) is much closer to the chest wall, than the previously treated tumour. Its gross appearance on CT suggests it is the tumour bed, which has moved position in response to RILI, it is not clear whether 6 months after treatment, this represents a degree of residual tumour or an organised area of homogeneous fibrosis. Interestingly 1 year after treatment, the central homogeneous region has disappeared, it has been replaced by a grey region, different in appearance to the white region of the pre-treatment tumour in the ipsilateral upper lobe, which suggests a dense, but non-uniform area of fibrosis. This grey region can be seen in figure 15, row d).
Figure 17, comparison of texture map, CT data and combined texture and CT data pre-treatment and post treatment after SABR for a patient who had a late relapse 3.5 years after radiotherapy (patient 3).

From this experiment it seems that the changes in the tumour and lung can be mapped using this combined analysis. It suggests that adding texture analysis to a standard CT scan does increase the amount of information available; it may also help to understand and map the process of acute lung injury and subsequent fibrosis after SABR. In contrast figure 17 compares a patient who had a late relapse after radiotherapy. The central homogeneous white region that represents tumour, can be seen in row a). This patient had FDG PET-CT proven likely nodal relapse at 3.5 years. Although the patient had no proven relapse earlier.
than 3.5 years, an area of dense homogeneity can be seen 1 and 2 years after treatment. This is much larger at 3.5 years after treatment and correlates with the area of FDG avidity.

This analysis technique may help for further work in the future and formed part of the analysis in the final study. The most significant finding so far is illustrated in figure 16 rows a) and b), which shows just how significantly the texture of the primary tumour changes, pre and post SABR, when the radiological abnormality on CT imaging appears very similar. This suggests that the texture map could differentiate between ‘active’ pre-treatment tumour and ablated post treatment tumour.
4.4.4 Experiment 10: identifying a tumour signature

**Aim:** The texture map generates an image, based on entropy scores. Entropy is a measure of disorder, the higher the entropy, the higher the disorder and the lower the uniformity or similarity. The tumours appeared as lower entropy structures in the texture map. This is different to most published data, where heterogeneity is associated with tumours and high heterogeneity is often associated with a poorer prognosis (Phillips et al., 2017).

Entropy usually produces a score between 0.00 and 4.99 in finiteRT. With most values being below 4.0. The centre homogeneous region of a tumour would have an entropy value of 0. The aim of this project was to see if different tumours had similar entropy scores.

**Methods:** ITK snap is an imaging programme that was used to combine the texture map with the CT data by converting the data into Nifti file format. It was able to provide histograms of the range of intensities seen within an image. The maximum and minimum entropy intensities from the texture map alone were measured and the maximum and minimum intensities of the inverted texture map combined with the CT scan data. This is seen in table 5. The entropy scores were derived directly from the texture map. The combined score from the inverted texture map and the CT scan was generated by inverting the texture map by taking the maximum value of heterogeneity and subtracting the whole texture map, which maintained the 0 entropy central region of the tumour. This gives a range of intensities and a range of texture entropy values, with positive and negative values possible.

**Experiment 10 Results and Discussion:** Table 5 shows the range of intensity values found in this experiment. The values for the tumour entropy score are all similar. From this data, it appears that for tumours to have a homogeneous region, which is seen as a white region on the combined texture/CT data image the tumour needs to be above a certain size. The maximum intensity values for the tumours of patient 6 and 9 were much lower than the other 8 patients, viewing the texture maps for patients 6 and 9 confirmed they do not have a central homogeneous region. This suggests that in this case series the tumours with a volume of greater than 3.1cm$^3$ to have a central homogenous region, whether a minimum resolution exists above a specific value requires many more tumours to be analysed.
Table 5, this table shows the maximum and minimum entropy scores from the texture map of the tumour. It also shows the range of intensity values per tumour when an inverted texture map is combined with the density data from the CT scan. The 2 smallest tumours have a lower maximum combined intensity as they do not have a visible low entropy core of the tumour.

Figure 18, nomenclature of texture map from combined data from inverted texture map and CT data. Central homogeneous region seen on texture map correlates to an intensity value of above 4000. It is surrounded by a very negative intensity region, which then decreases as distance from tumour rim increases.
Figure 18 shows the appearance of an example of a texture map containing a tumour with a central homogeneous region. This existed for all combined data for all patients in table 5 except patients 6 and 9.
4.4.5 Experiment 11: Identifying the signature of organs at risk

Aim: To identify whether certain organs at risk have a specific entropy value/texture signature that can be identified within a texture plot. If organs at risk/normal structures could be identified in the texture maps, these values could be excluded, potentially leaving the remaining data points as the tumour.

**Experiment 11 Methods:** 4 different organs were identified, these were lung tissue, liver, bone and aorta/contrast. A volume defined by a 3cm diameter circle of lung or liver tissue repeated on 8 consecutive slices (slices 2.5mm apart) within a region of lung or liver, for bone and aorta a 2cm diameter circle was used. For the bone volume of interest 5 consecutive slices within a thoracic vertebra were identified. For the aorta 8 consecutive slices of the descending aorta were volumed.

The first time that texture maps for liver, bone and aorta were generated, finiteRT was not able to generate texture maps because the lesions were too homogeneous. The regions of interest for liver, bone and aorta were redrawn to include the organ of interest and an area of lung, ensuring sufficient heterogeneity to generate a texture map. Figure 19 shows the 4 final volumes.
Figure 19, Volumes for liver, bone and aorta had to include a region of lung so that there was sufficient heterogeneity for finiteRT to generate a texture map. a) liver, b) bone, c) lung and d) aorta regions of interest. Texture maps containing only bone, liver and contrast did not have sufficient heterogeneity to allow a texture map to be generated.

**Experiment 11 Results and Discussion:** Table 6 shows data from the texture maps. The maximum and mean entropy for each patient are similar. The mean of the maximum entropy for bone and aorta are higher than liver and lung suggesting that bone and aorta have a greater degree of heterogeneity than liver and bone. It could be expected that liver parenchymal tissue is homogeneous, but for lung this is more surprising as it is a section of lung which is an interaction between airways, blood vessels and alveoli. Density information from the scan was then combined with the inverted texture map. The wider range of scoring was seen in the 2 densest structures, aorta (containing radio-opaque IV contrast) and bone. Whereas the range between maximum in liver was narrower and in lung narrower still. From this experiment in a very small sample of patients, the range of texture values did not obviously differentiate a signature for different organs.

As a result, it was necessary to consider a more complex analysis of the numerical values generated from a texture map.
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<th>Patient no.</th>
<th>Max entropy score</th>
<th>Min entropy score</th>
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<th>TextInv Min</th>
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Table 6, showing max and minimum entropy scores for each patient for different normal structures. TextInv Max and Min show maximum and minimum values from combined data from inverted texture map and CT data. It was not possible to generate a texture map from bone for patient 4.
4.4.5 Conclusion of section 4.4

Experiment 7 showed that it was technically feasible to generate a texture map for large sections of lung from a CT scan. Experiment 8 showed that it was possible to generate texture maps for the same large sections, as well as then standardising the quantisation levels to pre-determined levels. This meant that uniform standardisation could be achieved if different structures were compared using the same quantisation levels. Experiment 9 tried to gain greater information from combining the texture map using entropy scores with the density data from the original CT scan. Using an inverted texture map, so that white was low entropy and increased density was white, meant it was possible to identify dense regions with a low entropy score. For the first experiment (seen in figure 15) the combined texture map showed that the tumour on the pre-treatment and 3 months post treatment CT scan had a similar radiological appearance, but looked very different on the combined map. Unfortunately this result was not repeated in other patients. It was felt that although visually interesting, the combination of entropy score and density did not add more information. Experiment 10 and 11 attempted to identify whether different tumours had similar combined entropy/density scores, as well as seeing if different organs had different combined scores.

In summary these combined texture maps required artificial manipulation of the texture data and this was felt it could introduce a source of error, or allow the results to be manipulated to show differences between patient populations when there wasn’t an actual difference.
4.5 The ‘elephant plot’ An expression of combined CT and texture data as a hypothesis generating tool

From the previous work in this chapter, it appeared that adding more complexity to the analysis did obviously help differentiate between tumour and other structures.

Each data point had 3 pieces of information: a density score, an entropy score and its position in space. These analyses did not use these pieces of data to the greatest advantage.

As a result the data was plotted with a density score on the x axis and the entropy score on the y axis. This was initially plotted for a whole lung containing tumour and as a separate analysis, the whole contra-lateral lung that did not contain tumour. These can be seen in figure 20. The data plot labelled a) shows the lung containing tumour and the data plot labelled b) shows the contra-lateral lung, which does not contain tumour.

In this example the tumour makes up approximately 1% of the lung volume and yet it is easy to see that when compared to the lung that doesn’t contain tumour, the ‘trunk’ of the elephant plot, which is analogous with tumour is easy to identify. At this point it was felt that the elephant plot may be a useful tool in determining the presence of tumour in a lung, following SABR for primary lung cancer. Chapter 5 explores the initial analysis using the elephant plot.
Figure 20, An ‘elephant plot’, a data plot of density (x axis) vs entropy score (y axis) for each data point from a whole lung segmented from a radiotherapy planning CT scan. a) is the lung ipsilateral to the tumour, b) is the contra-lateral lung. The absence of the ‘trunk’ of the elephant in b) suggests that this may be a useful tool to identify the presence of tumour in a lung.
Figure 21 compares a data plot of density and entropy comparing a whole lung vs a whole CT scan of the thorax. For both plots (x axis, density score = Hounsfield Unit + 1000 = electron density) and entropy (y axis), figure a) = whole scan, figure b) = whole lung ipsilateral to the tumour.

The elephant plot illustrated in figure 20 shows how data points were distributed when a whole lung was identified and analysed. From the initial project concept the aim was to keep the ROI as simple as possible to minimise the technical knowledge needed to process it. Despite processing the whole lung, it is still possible to easily identify the tumour within the elephant plot. As a step on from identifying the whole lung, a whole scan was processed using both the LMQ quantisation method and a uniform quantisation, which is discussed in chapter 5. Figure 21 shows the elephant plots for a whole scan. This shows that analysing a whole scan rather than a whole lung leads to a very wide trunk, making it difficult to differentiate between structures. From figure 21 it is possible to see that some localisation of the ROI is required, when compared to the elephant plot for the lung.
References

Alobaidli, S. Functional Imaging and Texture Analysis in Radiotherapy Planning (FiNiTe RT), 2016. Dissertation, University of Surrey.

ALOBAIDLI, S. 2017. *Functional imaging and texture analysis in radiotherapy planning*. PhD, University of Surrey.


