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Radiotherapy for the Treatment of Pain in Malignant Pleural Mesothelioma

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Declaration

I declare that this thesis has been written by me and has not been previously submitted for a higher degree. It was undertaken during my post as a Clinical Research Fellow at the University of Edinburgh. All chapters were written by me. Where others have been involved, this has been acknowledged in the co-author section of publications resulting from this work.

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Abstract

Aims: The primary aim of this thesis was to explore the role of palliative radiotherapy in the treatment of pain in malignant pleural mesothelioma (MPM). The effect of radiotherapy on other symptoms was also examined. Biomarkers which might predict response to radiotherapy (Quantitative Sensory Testing – QST) were explored and objective evidence of response was sought via interpretation of Computed Tomography (CT) scans. The thesis also examined the role of Positron Emission Tomography (PET)-CT in radiotherapy planning and characterising pain in MPM.

Methods: A narrative review of the challenges of pain management in MPM and a systematic review of the evidence supporting the use of palliative radiotherapy for pain control in MPM, were undertaken. In addition, a multi-centre, single arm phase II trial was conducted which examined the role of radiotherapy in pain control in MPM. This trial also assessed the role of PET-CT in radiotherapy planning and allowed for a characterisation of MPM-related pain. These components form the basis of this thesis.

Results: Palliative radiotherapy at a dose of 20 Gy in five daily fractions using 6 Megavoltage (MV) photons improves pain in a significant proportion of patients with MPM. It does not have a beneficial effect on other symptoms or on quality of life. QST does not appear to be a useful clinical biomarker indicating likelihood of response to radiotherapy. Objective evidence of response via CT is low. Incorporation of PET-CT in the radiotherapy planning process alters the anatomical location of the target volume in patients with MPM. There is also an association between the Standard Uptake Value (SUV) uptake and pain, with the areas with highest SUV uptake being associated with the areas of pain. PET-CT

results in upstaging of a significant proportion of patients. Pain is often severe and debilitating for patients with MPM and it has often a combination of neuropathic and nociceptive mechanisms. The presence of a neuropathic component to the pain is not associated with an increased likelihood of response to radiotherapy.

Conclusions: Radiotherapy is effective at relieving pain in a proportion of patients with MPM and should be considered for all patients with MPM-related pain. PET-CT improves multiple parameters in the radiotherapy planning process compared with CT alone. QST parameters have not been shown to predict those patients who are likely to respond to radiotherapy.

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Abbreviations

APS	Average Pain Score
BD	Twice daily
BLF	British Lung Foundation
BOC	Beatson Oncology Centre
BPI	Brief Pain Inventory
BTS	British Thoracic Society
BWoSCC	Beatson West of Scotland Cancer Centre
CGD	Centre of Gravity Distance
CI	Confidence Intervals
COI	Conformity Index
CRP	C-Reactive Protein
CRU	Clinical Research Unit
CRUK	Cancer Research United Kingdom
CT	Computerized Tomography
CTRad	Clinical and Translational Radiotherapy Research Working Group
DRR	Digitally Reconstructed Radiograph
ECOG	Eastern Cooperative Oncology Group
EPaS	Edinburgh Palliative and Supportive Care Group
EORTC QLQ-C30	European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire
E-PET-CT	Enhanced Positron Emission Tomography Computerized Tomography
ERS	European Respiratory Society

ESTS	European Society of Thoracic Surgeons
FDG	Fluoro-deoxy-glucose
FSS	Fatigue Severity Scale
GG&C	Greater Glasgow and Clyde
GTV	Gross Tumour Volume
Gy	Gray
HADS	Hospital Anxiety and Depression Scale
ICRU	International Commission on Radiation Units
IHTAB	In House Studies Advisory Board
IQR	Inter Quartile Range
JHMRF	June Hancock Mesothelioma Research Fund
LANSS	Leeds Assessment of Neuropathic Symptoms and Signs
MARS	Mesothelioma And Radical Surgery
MDC	Mean Distance to Conformity
MDT	Multi Disciplinary Team
MDTH	Mechanical Detection Threshold
MPT	Mechanical Pain Threshold
MV	Megavoltage
MIS	Mean Interference Score
MPM	Malignant Pleural Mesothelioma
MPQ	McGill Pain Questionnaire
n	Number
NHS	National Health Service
NRS	Numerical Rating Scale
OCV	Over Contoured Volume

OD	Once daily
PACS	Picture Archiving and Communication System
PCC	Percutaneous Cervical Cordotomy
PET-CT	Positron Emission Tomography Computerized Tomography
PMRT	Palliative Medicine Research Team
PIS	Patient Information Sheet
PIT	Prophylactic Irradiation of Tracts in patients with malignant pleural mesothelioma
PTV	Planning Target Volume
QDS	Four times daily
QST	Quantitative Sensory Testing
R&D	Research and Development
RECIST	Response Evaluation Criteria In Solid Tumours
RMG	Radiotherapy Management Group
RTMSS	Radiotherapy for the Treatment of Mesothelioma Symptom Study
SD	Standard Deviation
SF-MPQ	Short Form McGill Pain Questionnaire
SMART	Surgical and large bore pleural procedures in malignant pleural Mesothelioma And Radiotherapy Study
SNRI	Selective Noradrenaline Reuptake Inhibitor
SPSS	Statistical Package for the Social Sciences
SUV	Standard Uptake Value
SYSTEMS	SYmptom STudy of radiothErapy in MeSothelioma

TDS	Three times daily
UCV	Under Contoured Volume
WHO	World Health Organisation
WPS	Worst Pain Score

Chapter 1. Introduction

1.1. Overview

The French pathologist, Joseph Lieutaud, is credited with first describing a possible chest wall (pleural) tumour in 1767.[1] For many years however, tumours of the pleura were considered to be secondary tumours, as it was felt that primary tumours could not arise there. By the start of the twentieth century, opinion had changed and it was accepted that primary pleural tumours were an entity. The term mesothelioma was first used in 1909 by J. G. Amani,[1] with the first possible link between asbestos exposure and mesothelioma being made by the pathologist Steven Gloyne in 1935.[2]

A seminal study which supported the link between asbestos exposure and mesothelioma was published in 1960.[3] This study examined 33 South Africans who were either miners or lived near a mine where crocidolite asbestos was harvested. The study had two main findings; firstly, exposure to asbestos was associated with the development of malignant pleural mesothelioma (MPM) and, secondly, the average period between exposure and developing MPM was 40 years. Since then it has been accepted that asbestos exposure and the development of MPM, are linked.

Asbestos refers to a group of naturally occurring fibrous minerals found in rock and soil. It has been used in the construction industry for centuries due to its desirable properties including resistance to fire, chemical or electrical damage, tensile strength and its relatively inexpensive cost. It has been used commonly for electrical and building insulation and also in ship building.

There are two categories of asbestos; serpentine (chrysotile) and amphibole (crocidolite, tremolite, anthophyllite, amosite and actinolite). Chryosite - “white asbestos”, crocidolite - “blue asbestos” and amosite - “brown asbestos” are the three most commonly used forms of asbestos. Due to health concerns, the use of asbestos has been banned in the UK since 2009. If asbestos fibres remain intact, they pose little risk to health. However when the fibres are damaged, released into the air and subsequently inhaled, then they can be detrimental to health.

Exposure to asbestos fibres can have various effects. It may cause pleural plaques, asbestosis, lung cancer or MPM.

Pleural plaques are areas of scar tissue on the pleura (lining of the lung). They may be seen on X-ray or CT imaging and indicate that the individual has been exposed to asbestos. They are not pre-malignant and usually do not cause symptoms.

Asbestosis is an interstitial pneumonitis and fibrosis caused by deposition of asbestos fibres within the lung. The risk of developing asbestosis increases with cumulative exposure and with time since initial exposure. Treatment is symptomatic.[4]

Lung cancer may also be caused by exposure to asbestos. Smoking and asbestos exposure are the two most common risk factors for lung cancer with 9-15% of cases attributed to asbestos.[5] Smoking and asbestos exposure are synergistic in terms of their risk of developing lung cancer.[6] The connection between asbestosis and lung cancer is not currently clear. Asbestosis is associated with significant exposure to asbestos and so may signify an increased risk of cancer.

Alternatively, the inflammation associated with asbestosis may trigger carcinogenesis.

The malignancy most commonly associated with asbestos exposure is MPM, which will be discussed further.

1.2. Epidemiology

The majority of cases of MPM are associated with asbestos exposure. However, in some patients, there may be no obvious exposure to asbestos. Other carcinogens known to cause MPM include radiation, exposure to the simian virus 40 and the mineral fibre erionite.[7] The latency period between exposure and the development of MPM may be in the region of 30-40 years. In 2010, over 2500 people were diagnosed with MPM in the UK with a male:female ratio of approximately 5:1 (total new cancer diagnoses in the UK for 2010 were 324,579). Over 2000 people in the UK died of MPM that same year.[8] The UK standard mortality rate for MPM is shown in Figure 1.

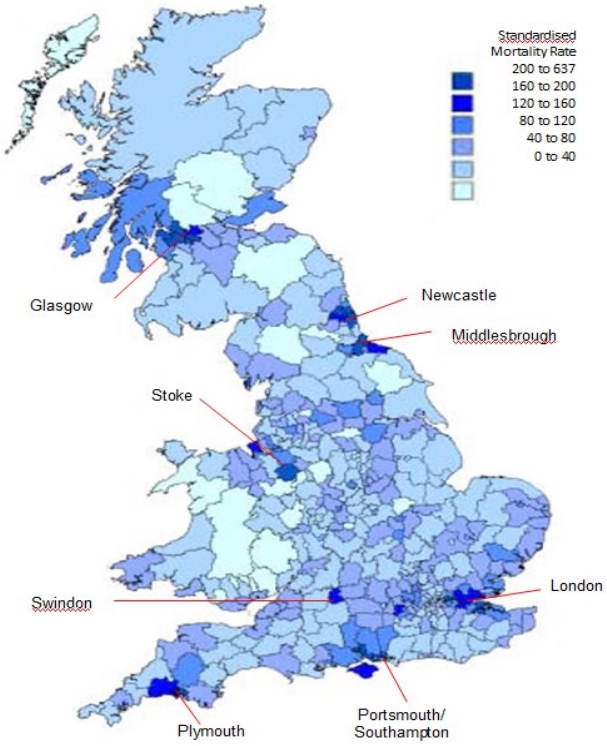

Figure 1 - UK Standard Mortality Rate for MPM[9]

It is thought that the incidence of MPM has already peaked in the USA. However, in other countries such as China, Russia, Brazil and India, asbestos continues to be produced. Due to this, exposure to asbestos is still on the rise in these countries and it is thought that the incidence of MPM is yet to peak in these countries. Predicting the level of increased incidence in these countries is extremely difficult. [1] Several countries do not keep accurate records of MPM incidence however it is known that Australia has the second highest mortality rates in the world, second only to the UK. Asbestos was extensively used in Australia from the 1950's to the 1970's. In 2007, 551 Australians died from MPM. It is thought that the incidence in Australia will peak between 2014 and 2021.[1]

The natural history of MPM incidence is still unknown. It is estimated that exposure to asbestos in the UK peaked in 1963 and therefore, due to the latency period, it is anticipated that mortality will peak in 2016 and decline rapidly after that. Although the worldwide incidence of MPM is not known, it is generally accepted that the rates in Great Britain are among the highest in the world.[8] Given the long latency period, it is not surprising that 80% of patients diagnosed with MPM are over the age of 65.[8] Therefore, MPM primarily affects an elderly population and remains a public health issue today.

1.3. Pathophysiology

MPM is a tumour which originates in pleural lining of the lung. In this lining there is a membrane called the mesothelium which is also present in other body cavities, however the reason for development of mesothelioma in the pleura is likely to be due to direct contact between this lining and asbestos fibres.

Much progress has been made in recent years in our understanding of the pathophysiology of MPM. (See Figure 2.) However, exactly how exposure causes MPM is not fully understood. It has been shown that, following inhalation of asbestos fibres, an acute inflammatory reaction can be seen with inflammatory cytokines, macrophages and neutrophils present in large numbers. These inflammatory changes are followed by mesothelial cell proliferation.[10] The activated inflammasone, a component of macrophages or mesothelial cells that leads to the production of angiogenic, growth-promoting and chemotactic cytokines, is felt to play a role in the ongoing inflammation.[11] Furthermore, a number of defects in the molecular signalling pathways and disruption of cell

cycle control are seen in MPM.[11] In addition, it is known that in 40-50% of mesotheliomas, the tumour suppressor gene, Neurofibromatosis Type 2 (NF2), is inactivated.[12] This tumour suppressor gene negatively regulates the cyclin D1 regulatory axis. It is also known that tumour necrosis factor-alpha and nuclear factor-kB signalling play key roles in the response of human mesothelial cells to asbestos.[13]

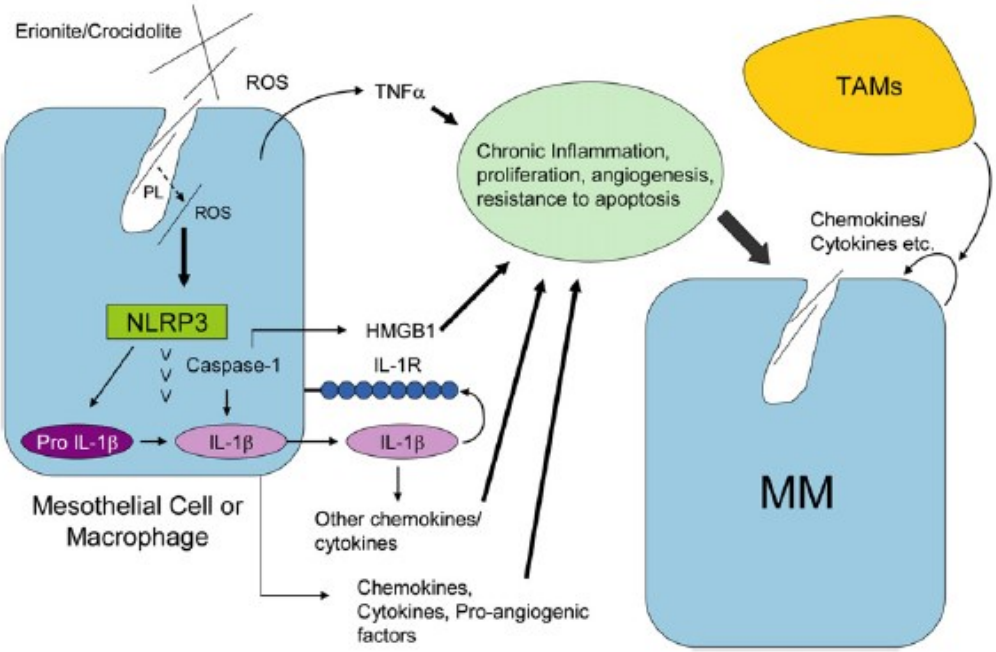

Figure 2 - Pathophysiology of MPM[11]

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1.4. Symptoms of MPM

Most patients are symptomatic at the time of diagnosis of MPM. The most common symptoms are chest pain and breathlessness, occurring in 25-90% and 34-46% of patients respectively.[14-16] Patients also commonly suffer from

lethargy, cough and sweating.[16] Pain, the most common symptom, is discussed extensively in chapter 2.

1.5. Diagnosis of MPM

Typically, the first investigation performed in patients suspected of having MPM, is a chest x-ray. This may show pleural thickening or a pleural effusion, as seen in Figure 3. These findings can be suggestive of MPM but are not diagnostic.

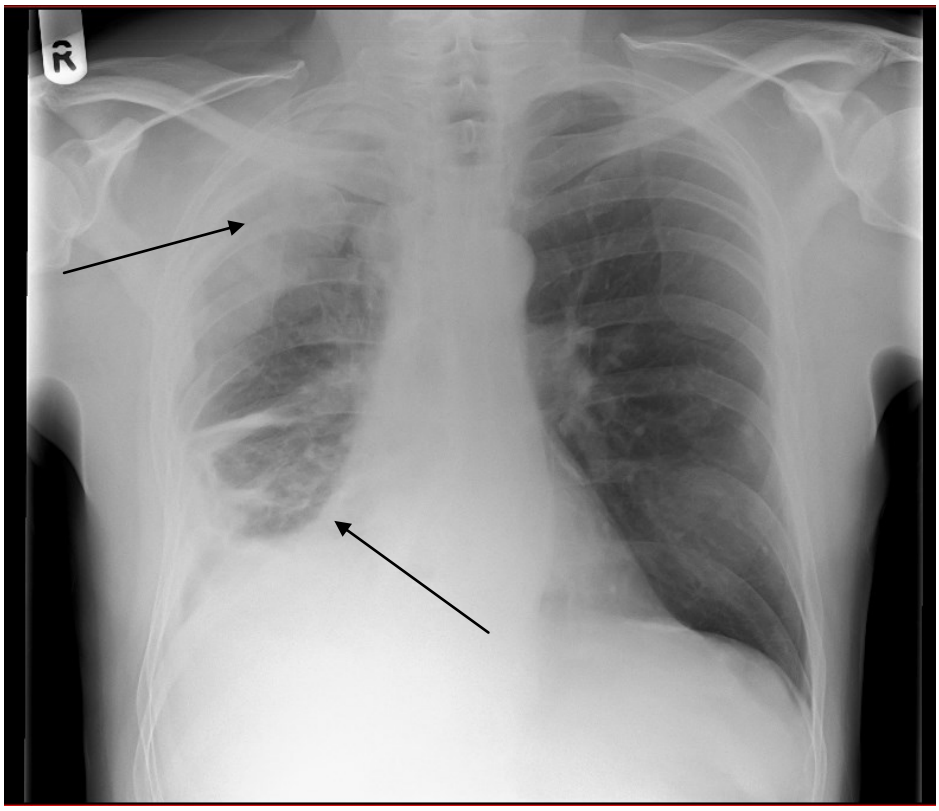

Figure 3 - Chest X-ray showing typical features of MPM with pleural thickening as indicated by the arrows. X-ray taken from national archive from a patient in the SYSTEMS study

The next investigation is usually a CT scan which gives a more detailed image of the chest and abdomen and can provide further weight to support a diagnosis of MPM, as shown in Figure 4.

Figure 4 - Axial CT image showing MPM encasing the right lung and invading through right anterior chest wall as indicated by the arrow. CT taken from national archive from a patient in the SYSTEMS study

However, pathological confirmation through histology remains the cornerstone of diagnosis of MPM, though reliable diagnosis remains difficult in some cases, especially if biopsy samples are small. Biopsies may be obtained via thoracoscopy - Figure 5.

Figure 5 - Thoracoscopy

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Neoplastic invasion is generally regarded as the key factor in diagnosing MPM as opposed to reactive mesothelial hyperplasia.[17, 18] Key histological features can be seen in Figure 6 and Figure 7.

Unfortunately, sometimes the biopsy can be inconclusive or the patient may not be fit enough to consider a biopsy. In these situations, a clinical diagnosis of MPM may be made if there is radiological evidence strongly suggestive of MPM in a patient with a known history of asbestos exposure. In such circumstances, a post mortem must be performed since MPM is an occupational disease and must be discussed with the Procurator Fiscal (coroner) in Scotland. Although histological diagnosis remains the gold standard for diagnosing MPM, there is some evidence suggesting that proteomics may be an alternative option in

diagnosing MPM. A study of 117 patients with a histological diagnosis of MPM and 142 individuals with a history of asbestos exposure but no diagnosis of MPM, analysis of serum was conducted.[19] As a result, a 13-biomarker panel was discovered which detected MPM with an accuracy of 92%. This biomarker panel may be helpful in detecting early stage disease given 88% were detected at stage I and II.

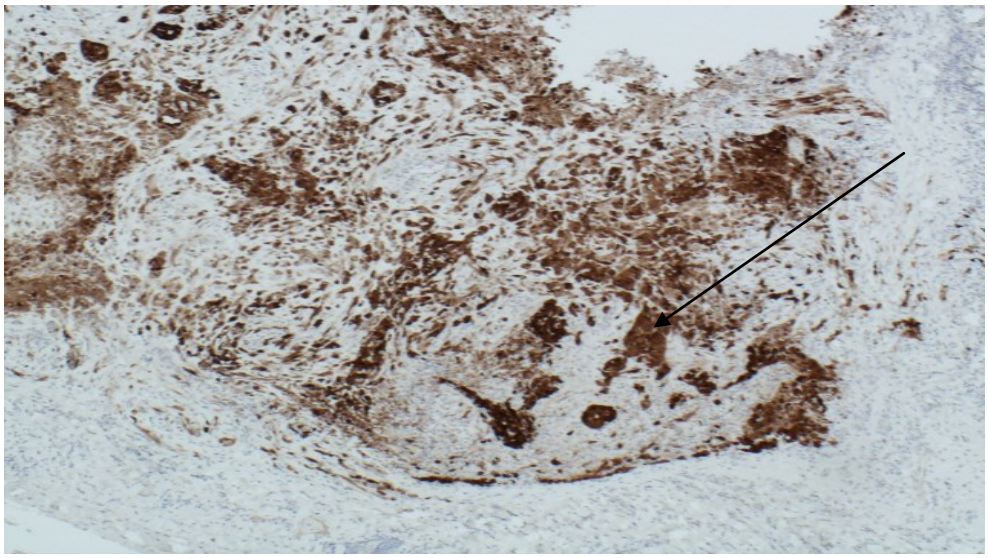

Figure 6 – Histological Features (1)

Positive calretinin staining giving the diagnosis of epithelioid mesothelioma as indicated by the arrow

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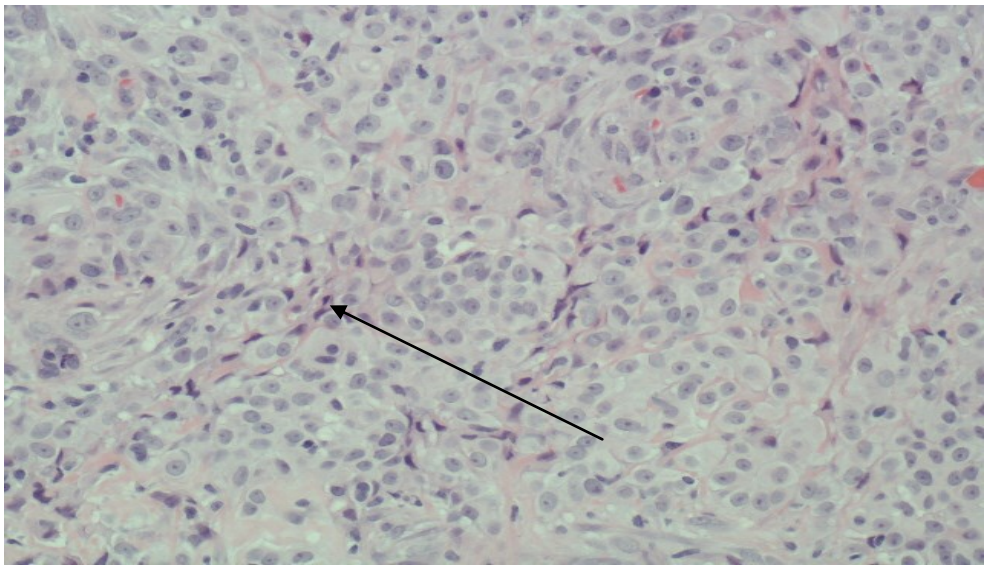

Figure 7 – Histological Features (2)

Hematoxylin and eosin staining showing the mesothelioma cells at high power as indicated by the arrow.

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There are three main histological subtypes of MPM. The most common is epithelioid accounting for approximately 50% of cases; sarcomatoid accounts for 16% and there is a mixed histological pattern in the remainder of cases.[20] It is well recognised that epithelioid histology is associated with the best prognosis.[21, 22]

1.6. Treatment of MPM

There is still much debate as to the optimal management of MPM. In broad terms, the treatment options include surgery, chemotherapy, radiotherapy and best supportive care. As with all cancers, the performance status of the patient is key in deciding the optimal treatment to offer the patient. The Eastern

Cooperative Oncology Group (ECOG) scale is the most commonly used measure to assess performance status, in clinical practice.[23]

1.6.1. Surgery

For patients with good performance status who have disease limited to the chest, the main debate is whether they should be considered for radical surgery, traditionally extra pleural pneumonectomy (EPP), followed by chemotherapy and radiotherapy in a tri-modality approach. The Mesothelioma And Radical Surgery (MARS) study showed that EPP patients had a poorer survival than those who did not undergo EPP.[24] Due to this study, this option has fallen out of favour in the UK.[24] However, some in the international community refute the conclusions of the MARS study and so EPP is still offered in certain parts of the world.[25] Therefore, there is a divide between the UK and the rest of the world in terms of the surgical management of MPM patients. Given the significant morbidity and mortality associated with EPP surgery, there has been a trend towards performing pleurectomy/decortication for certain patients with MPM.[26]

1.6.2. Chemotherapy

Two phase III studies have shown a survival advantage for platinum/antifolate combination chemotherapy. The first of these studies randomised patients between single agent cisplatin and cisplatin in combination with pemetrexed. Median survival was 9.3 months for cisplatin and 12.1 months for the combination arm.[27] The second study compared cisplatin with cisplatin and raltitrexed and achieved a survival advantage of 2.6 months for the

cisplatin/raltitrexed arm.[28] In view of these results, the British Thoracic Society (BTS) recommends that all patients with MPM who have a performance status of 0-2 should be given the opportunity to discuss the merits of chemotherapy. It is worth noting, however, that in another study of 146 patients diagnosed with MPM, only 54 were considered fit for consideration of chemotherapy. Of these, only 26 underwent chemotherapy, so this treatment may not be suitable for the majority of patients diagnosed with MPM.[29]

1.6.3. Radiotherapy

Radiotherapy may be given in three broad areas in MPM:

As part of tri-modality therapy in the radical setting

At drain sites to try to prevent drain site metastases

In the palliative setting to help with symptom control

As already discussed, tri-modality therapy is not currently offered in the UK and there are no randomised data to support its use. The role of prophylactic drain site irradiation is the subject of two current UK-wide studies, SMART and PIT, the results of which are eagerly awaited.[30, 31]

Radiotherapy may be offered to help palliate some of the symptoms of MPM.[32, 33] By far the most common use in this setting is in the palliation of pain. However, there is limited evidence to support the use of radiotherapy in this situation and further work in this area is needed.[34] For example, the optimal dose and fractionation that should be used is not known since there are no randomised trials examining this.

The optimal method with which to assess response to radiotherapy in MPM is not known. While CT scanning is commonly used in many situations in Oncology, such as initial staging and assessing response to chemotherapy, it is not commonly performed to assess response to palliative radiotherapy. However, a recent study which evaluated the role of palliative radiotherapy in MPM performed CT scans two months after radiotherapy and quoted a 43% response rate along with a clinical response rate at two weeks of 57%.[35] This was the first study in MPM to show a radiological response to radiotherapy. However, the authors did not state whether those who responded radiologically, also responded clinically. Therefore, the association between clinical and radiological response is unknown and warrants further investigation.

Defining the target volume in MPM is difficult since the disease spreads diffusely across the pleural surface and delivering palliative radiotherapy to a large area is potentially very toxic. Therefore, when palliative radiotherapy is given, the clinician is left with the challenge of treating effectively whilst balancing the risks of toxicity, in a treatment with palliative intent.

[F-18]-fluoro-deoxy-glucose (FDG) positron emission tomography computerized tomography (PET-CT) has become established as an essential imaging modality in many tumour types such as non-small cell lung cancer, lymphoma and oesophageal cancer.[36-38] It is beginning to be used in several settings in MPM. Studies have demonstrated the usefulness of FDG PET-CT in pre-operative imaging, differentiating benign from malignant disease, evaluation of response to

chemotherapy and in prognostication based on the intensity of FDG uptake in MPM.[39]

There is, however, emerging evidence that PET-CT may be of use in radiotherapy planning in MPM. Pehlivan and co-workers have conducted preliminary work examining the role of PET-CT in radiotherapy planning in MPM.[40] In comparison with CT, they demonstrated that incorporating PET-CT into radiotherapy planning resulted in significant reductions in Gross Tumour Volume (GTV), Clinical Target Volume (CTV) and Planning Target Volume (PTV). With these reductions in target volumes, the authors hypothesized that dose escalation of radiotherapy to previously unachievable levels may now be possible. However, lack of intensity modulated radiotherapy (IMRT) in this work meant that developing sophisticated plans to deliver radical or high palliative doses to these patients, was not possible. Therefore, the role of FDG PET-CT in radiotherapy planning in MPM warrants further investigation.

1.7. Prognosis in MPM

Unfortunately, prognosis in MPM remains poor. Over a 10 year period from 1984 to 1993, 204 patients were entered into five European Organisation for the Research and Treatment of Cancer (EORTC) phase II studies.[41-44] The median survival was 12.6 months from diagnosis and 8.4 months from study entry.[45] Other studies quote median survival figures of a year or less.[16, 46, 47] Single institution studies of tri-modality therapy quote median survival figures of up to five years for node negative tumours.[48] While prognosis is poor in MPM, it has been suggested that certain factors can divide patients into

good and poor prognostic groups.[45] Poor performance status, a high white cell count, male gender, uncertainty regarding histological diagnosis and sarcomatoid subtype were all identified as poor prognostic factors based on the survival of 204 patients entered into the EORTC studies.[41-44] Taking these into account, if patients had more than two of these factors, they were classified as poor prognosis with a 1 year survival of 12%. Those with two or fewer factors had a 1 year survival of 40%.

1.8. Thesis Overview

This thesis examines mesothelioma with a key focus on the role of radiotherapy for pain control in MPM. It is largely informed by the SYSTEMS study which was a multicentre phase II study. The thesis overview is shown in Figure 8.

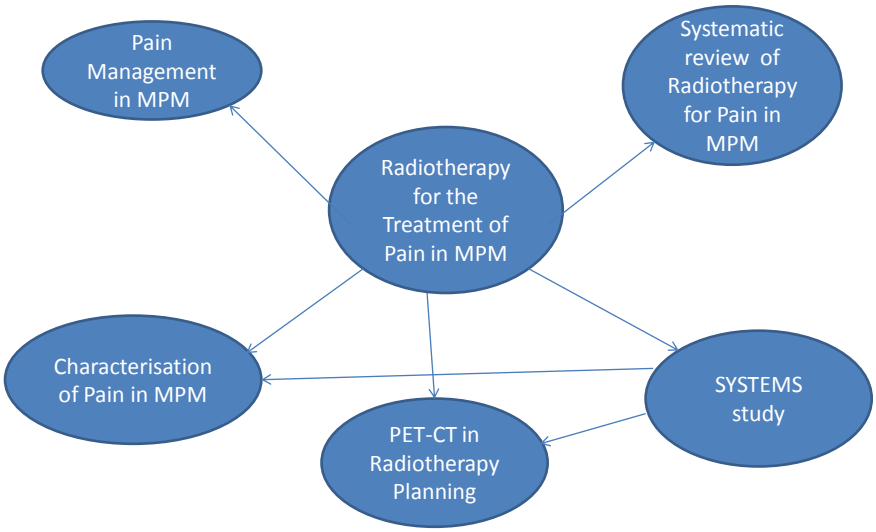

Figure 8 - Thesis overview

1.9. Aims of this Thesis

The overall aim of the thesis is to examine key aspects of radiotherapy in MPM.

These are detailed as follows:-

To undertake a critical review of pain management in MPM.

To undertake a systematic review of the literature examining the current evidence for radiotherapy in the relief of pain in MPM.

To establish whether radiotherapy is beneficial in treating pain in MPM.

To assess whether radiotherapy affects other key symptoms such as breathlessness, fatigue and distress, using validated questionnaires.

To examine the effect of radiotherapy on tumour bulk, using CT scanning.

To assess the toxicity of radiotherapy.

To examine possible biomarkers of radiotherapy response.

To assess the role of PET-CT scanning in radiotherapy planning.

To characterise pain in MPM.

Chapter 2. Pain Management in Mesothelioma

2.1. Introduction

Cancer pain can be divided into acute and chronic pain syndromes.[49] Acute cancer pain is usually caused by a definable acute illness.[49] It has a definite onset and its duration is predictable and limited. Chronic cancer pain is differentiated from acute pain by its longevity and is regarded as pain lasting more than 12 hours a day. Approximately 75% of all cancer patients suffer from chronic pain.[50]

In MPM, pain usually affects the chest, in keeping with the underlying disease. However the cause of chest pain in MPM is multifactorial. Pain may be due to direct tumour infiltration of ribs, nerve roots, intercostal nerves, chest wall or, in some cases, due to the tumour invading the neurovascular bundle. In addition, in patients who undergo surgery, post thoracotomy pain is common.[51] The pain associated with MPM is often more severe and difficult to treat than pain caused by lung cancer.[52]

The pathophysiology of pain in MPM is generally a combination of nociceptive and neuropathic pain, termed mixed pain. Therefore, managing this pain can be extremely difficult and multiple analgesics, which target different pain mechanisms, are often required. Unfortunately, patients may continue to suffer from severe pain despite multiple analgesics and so other options to consider for these patients include palliative radiotherapy, chemotherapy, neuraxial pain techniques, and cordotomy. All these therapeutic options will be discussed.

The difficulties of pain management in MPM are perhaps best illustrated via a case history.

2.2. Case history

A 68-year-old man presented to his local hospital with severe right-sided chest pain and breathlessness. He had worked as an apprentice carpenter in the shipbuilding industry many years ago. A chest X-ray was performed which showed a right-sided pleural effusion and pleural thickening. A CT scan, Figure 9, including a CT guided biopsy, was performed with pathology confirming MPM of sarcomatoid type. Treatment options were discussed with the patient. Chemotherapy was declined by the patient due to low likelihood of benefit. The patient agreed that treatment would be symptomatic only.

The gentleman described his pain as “stabbing and shooting”, suggesting a neuropathic component. He also stated that it was severe in intensity. Prior to admission, he had been taking tramadol (400mg daily) and gabapentin (900mg daily). During his admission, he was commenced on 40mg of morphine sustained release tablets (every 12 hours), 15mg of immediate release morphine tablets when needed for pain, and a lidocaine patch applied over the chest wall. Tramadol was discontinued.

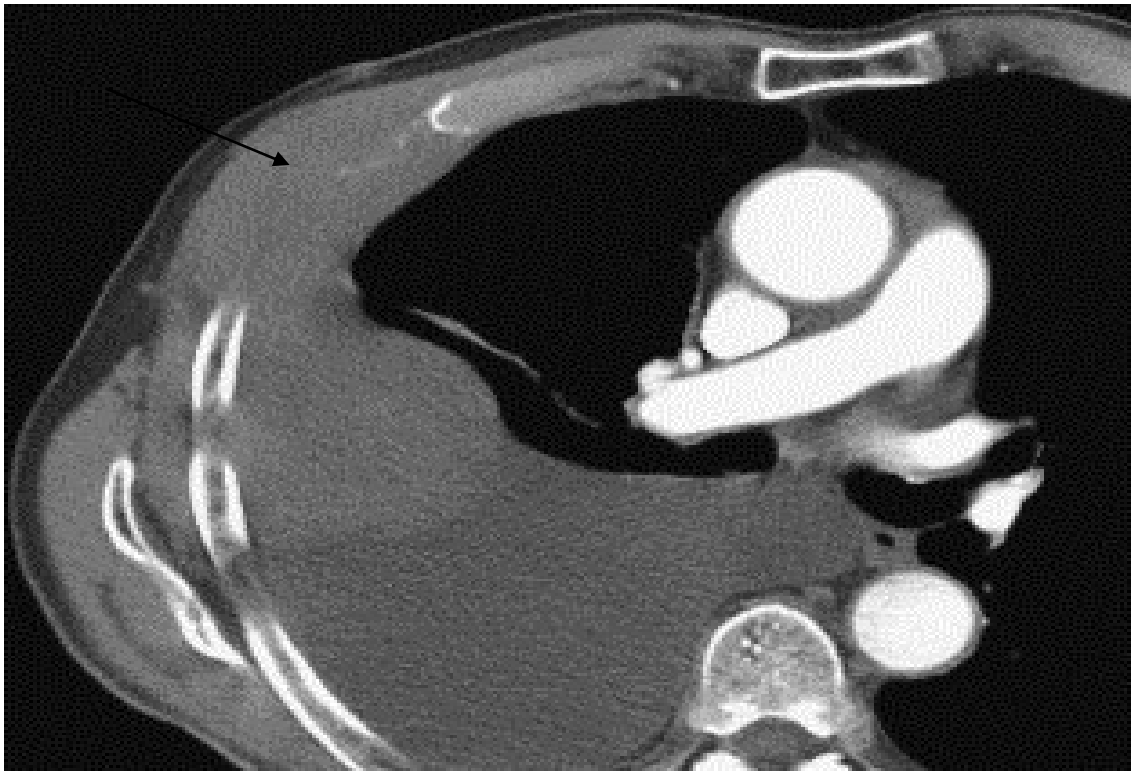

Figure 9 - CT scan - MPM invading chest wall as indicated by arrow. CT is from a patient in the SYSTEMS study and taken from the national archive

Pain continued to be problematic and when his morphine dose was escalated, he developed signs of opioid toxicity (muscle jerks and pseudo-hallucinations). He was therefore switched to oxycodone sustained release tablets (30mg twice daily). With this, his opioid toxicity improved, though was still present. His gabapentin was increased to 1800mg daily and he remained on a lidocaine patch. Despite all this, his pain remained poorly controlled. At this point, he received radiotherapy with the aim of improving his pain. Using 6MV photons, 20 Gy in 5 daily fractions of radiotherapy were administered which brought about a temporary improvement in his pain but six weeks after treatment, his pain was as severe as it had been prior to his radiotherapy. Following this, he was considered for cordotomy but unfortunately died before he was able to receive this.

This case illustrates some of the difficulties patients with MPM face in terms of pain management. Despite multiple analgesics and palliative radiotherapy, his pain remained poorly controlled. The complex pathophysiology of pain in MPM combined with suboptimal analgesics means that achieving pain control can be difficult, though it should be noted that not all cases of MPM are as challenging as this.

2.3. Principles of pain control in MPM

Given that the pain associated with MPM is often multifactorial, patients are often on several drugs, which work via different mechanisms of action. Opioids are commonly used and its effects are mediated by specific opioid receptors both within the central nervous system and peripherally.[53] Adjuvant analgesics are commonly added if opioids are not controlling the pain adequately. Antidepressants are the most commonly used adjuvant analgesics. These drugs are thought to enhance availability of monoamines at synapses within neural pathways that are part of the descending pain modulation system. The most important modes of action include inhibition of norepinephrine reuptake and serotonergic and dopaminergic effects.[53] Anticonvulsants have also been used as adjuvant analgesics. Gabapentin and pregabalin act at the alpha-2-delta voltage gated subunit of the calcium channel in the dorsal horn.[53]

It is always important to weigh up the potential benefits of multiple analgesics against the possibility of cumulative toxicity, drug interactions and patient compliance. The key components of analgesic treatment are detailed below. Commonly used medications and doses are detailed in Table 1.

Table 1- Drugs and dose ranges commonly used for pain management in MPM

Drug Name	Type of Analgesic	Typical Starting Dose	Maximum daily dose
Paracetamol	Non Opioid	1g QDS	4g
Diclofenac	Non Opioid	50mg TDS	150mg
Codeine Phosphate	Weak Opioid	30-60mg QDS	240mg
Morphine	Strong Opioid	10mg every 4-6 hours	No maximum dose
Oxycodone	Strong Opioid	5mg every 4-6 hours	No maximum dose
Hydromorphone	Strong Opioid	1.3mg every 4-6 hours	No maximum dose
Gabapentin	Adjuvant	300mg OD	3.6g
Pregabalin	Adjuvant	75mg BD	300mg
Amitriptyline	Adjuvant	10mg OD	150mg
Lidocaine	Adjuvant	5% patch 12 hours on, 12 hours off	5% patch 12 hours on, 12 hours off
Fentanyl	Strong Opioid	12mcg per hour. Change every 72 hours	No maximum dose
Ketamine	Adjuvant	5mg BD	No maximum

			dose

Abbreviations: OD, once daily; BD, twice daily; TDS, three times daily; QDS, four times daily

The World Health Organisation's (WHO) Analgesic Ladder for Cancer Pain Relief is recognised as the gold standard for treatment of cancer pain,[54] Figure 10, and its principles have been continued in new guidelines.[55, 56] It is easy to follow and can be applied to all types of pain, irrespective of aetiology. The first step on the ladder recommends using paracetamol or non-steroidal anti-inflammatories. If pain remains poorly controlled then patients should move on to step two, which involves the use of weak opioids such as codeine. However, most patients with pain from MPM will move quickly to step three of the ladder which recommends strong opioids plus or minus non-opioids or adjuvant analgesics. Therefore, step two may be skipped and a step three opioid used as the first line opioid.[55] Morphine remains the most commonly used strong opioid, although there are now a multitude of others available and often patients may have to try several different strong opioids, in an attempt either to improve analgesic benefit/reduce side effects or both.[55]

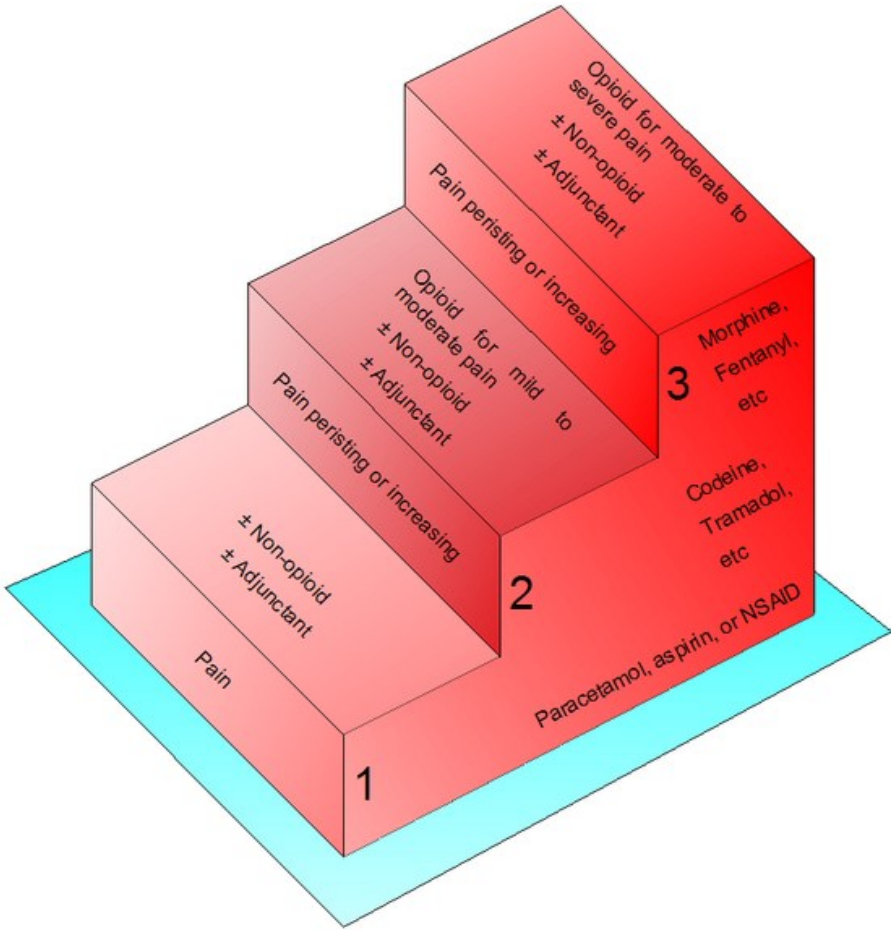

Figure 10- WHO Analgesic Ladder taken from www.who.int[54]

2.3.1. Opioids

Given the severity of pain associated with MPM, the majority of patients will require opioid analgesia, with morphine being the most commonly used. It comes in both immediate and sustained release preparations, which are equivalent in terms of analgesic benefit.[57, 58] Immediate release preparations are favoured by many for initial dose titration and subsequent breakthrough analgesia, while sustained release preparations are more typically saved for long term use.[59] However, a direct titration using sustained released opioids is equally feasible.[57] Patients may require large quantities of opioids to help control their pain. It is not uncommon, on these large doses, for patients to develop toxicity,

with symptoms such as somnolence, myoclonic jerks, cognitive impairment and hallucinations being prevalent. In these circumstances, most clinicians would favour a switch to another opioid such as oxycodone.

2.3.2. Adjuvant Analgesics

Adjuvant analgesics are drugs whose main indication is not analgesia but they have analgesic properties. Adjuvants are used in many types of pain including neuropathic pain. They can be used in combination with opioid analgesics or in isolation. In MPM, adjuvant analgesics are often used in combination with opioids.[60] Given that there appears to be a significant neuropathic component to the pain in MPM, it is not surprising that these drugs are commonly used in these patients. There are several different types of adjuvant analgesics which can be helpful.

2.3.3. Antidepressants

A Cochrane review summarised the evidence for the use of antidepressants in non-malignant neuropathic pain.[61] Tricyclic antidepressants are the most commonly used in neuropathic pain. Amitriptyline has a marginally greater analgesic effect compared to other tricyclic antidepressants such as nortriptyline. Selective Noradrenaline reuptake inhibitors (SNRI) such as duloxetine and venlafaxine may be of benefit in neuropathic pain, with duloxetine being favoured due to a better side effect profile.[62, 63]

2.3.4. Anticonvulsants

There is good evidence that anticonvulsants are effective in neuropathic pain.[64] Gabapentin has been used in the treatment of neuropathic pain for many years and is recommended as a first line treatment.[65] It is generally well tolerated although its dose limiting toxicity is usually somnolence. Pregabalin works in the same way as gabapentin and there is good evidence of its efficacy as an analgesic.[66-68] A recent prospective, placebo controlled, randomised controlled study compared pregabalin with gabapentin and amitriptyline for neuropathic cancer pain. The results suggested that all these drugs were effective in relieving cancer-related neuropathic pain but that pregabalin was associated with the greatest reduction in pain scores.[69]

2.3.5. Ketamine

There is some evidence supporting the benefit of ketamine in cancer pain.[70] If symptoms exist which are suggestive of central wind-up, such as pain on light touch or increased pain to any painful stimulus, then ketamine may be helpful. Furthermore, ketamine may renew opioid response when opioid doses are being increased with reduced response.

2.3.6. Topical analgesics

Topical analgesics can play a role in the treatment of pain in MPM, with topical 5% lidocaine patches being the most commonly used. The main benefit of these patches is the lack of systemic side effects with local skin irritation being the common side effect. Though there have been no prospective studies in cancer patients, a retrospective review from Australia looked at 97 patients treated with

lidocaine 5% patches and the results supported its use in post herpetic, post-surgical and cancer related neuropathic pain.[71] The high potency 8% capsaicin topical patch has proven efficacy in post herpetic neuralgia.[72] A single application of the patch for 30-60 minutes can result in pain relief for up to three months.

2.4. Radiotherapy

Many patients with MPM will continue to suffer from severe pain despite multiple analgesics, therefore, radiotherapy is often considered for these patients. However, there is a dearth of evidence to support its use in any setting in MPM. Despite this, radiotherapy for pain relief is recommended in guidelines from the European Respiratory Society in collaboration with the European Society of Thoracic Surgeons.[73]

Perhaps the most convincing evidence in favour of radiotherapy to help pain comes from a study where 22 patients with MPM and pain were treated with hemi thoracic irradiation at a dose of 30 Gy in 10 daily fractions. Patients were treated with Cobalt-60 machines. Of the 19 patients assessable at three months, 13 had an improvement in their pain scores, with no increase in their analgesic requirements, though the median duration of response was only two months.[33]

A recent study looked at palliative radiotherapy at a dose of 36 Gy in 12 fractions.[35] Radiotherapy was not given to the entire hemi-thorax but instead was directed to the area that was felt to be the source of the pain. The radiotherapy was given in this way because hemi-thoracic irradiation was felt to

be too toxic. The study showed that pain had improved in over 50% of patients two weeks after treatment. However, this was prospectively. Interestingly, CT scans were performed on these patients two months after radiotherapy and a response rate of 43% was reported, suggesting that, at an adequate dose, MPM may in fact be a radiosensitive disease.

MPM has traditionally been regarded as a radioresistant disease and is felt to be intrinsically more radioresistant than the surrounding tissues.[74, 75] The only study to have looked at the radiosensitivity of MPM irradiated mesothelial cell lines with two Gray.[76] The alpha/beta ratio of the most sensitive cell lines were almost an order of magnitude greater than those of the two most resistant cell lines.[76] Given the lack of response to radiotherapy when given in 2 Gy per fraction[77] and the encouraging radiological response rate seen when a hypofractionated regime is given,[35] it could be that, MPM may be more radiosensitive than previously thought if a hypofractionated regime is chosen.

The mechanisms by which radiotherapy reduces pain are not fully understood.[78, 79] An attempt was made to identify the mechanisms by which radiotherapy reduces bone pain in mouse models.[79] It was suggested that, with regard to bone pain, radiotherapy may help pain by reducing the cancer burden and by reducing osteolysis.

2.5. Chemotherapy

Several chemotherapeutic agents have been studied in this disease. Phase II trials have investigated the role of cisplatin, doxorubicin and gemcitabine but the results have been largely disappointing.[80-82] However, cisplatin has been

shown to be the most effective single agent and was used as the control arm in two phase III trials.[83]

Vogelzang et al conducted a phase III study comparing cisplatin and pemetrexed in combination with cisplatin alone.[27] The study demonstrated a survival advantage for the combination regime with a median survival of 12.1 months versus 9.3 months for cisplatin alone. Median time to progression and response rates were also superior in the combination arm. Part way through the trial, folic acid and vitamin B12 were added. This significantly reduced toxicity in the combination arm. Similar survival results were seen in a phase II study where patients received carboplatin and pemetrexed suggesting that this combination could be an alternative treatment.[84] This regime was well tolerated with low rates of grade 3 and 4 neutropenia and anaemia.

A second phase III trial compared cisplatin alone with cisplatin and raltitrexed.[28] The trial recruited 250 patients. Again, a survival advantage was seen for the cisplatin and antifolate arm with a median survival of 11.4 months versus 8.8 months for the cisplatin alone arm. The main toxicities were neutropenia and emesis which were twice as common in the combination arm.

Quality of life data have been published from the raltitrexed/cisplatin phase III study.[85] These data showed that pain scores remained constant throughout treatment. The authors concluded that, in a disease with such a poor prognosis as MPM, stabilization of pain was a positive finding. However, the same data could also be interpreted as showing that chemotherapy does not improve pain control

in MPM. Therefore, chemotherapy should be prescribed in this disease in an attempt to improve survival rather than to improve pain. If symptom improvement is the aim, then other treatment options should be considered.

Although chemotherapy can be offered, a retrospective review of MPM patients showed that, of 156 patients diagnosed, only 54 were deemed of adequate performance status to be offered chemotherapy, and ultimately only 27 patients received chemotherapy. Therefore, this treatment is not widely used in this population. [29]

2.6. Epidural or intrathecal treatment (Neuraxial)

Epidural or intrathecal treatments, usually with a combination of an opioid and a local anaesthetic, are alternative pain treatments for patients where other analgesics and radiotherapy fail to give pain relief. Local anaesthetics lessen the need for opioids and thereby minimize opioid induced adverse effects. However, epidural or intrathecal pain therapies are invasive, are associated with a risk for infections, and require very close follow-up.[86]

Intra pleural analgesia, which involves administering local anaesthetics into the pleural space, has been described and felt to be effective for some malignancies.[87] However, no data exist for this procedure in patients with MPM and, therefore, stating a case recommending such a treatment in this patient group is difficult.

2.7. Cordotomy

Despite all of the above interventions, many patients with MPM continue to suffer from severe pain. In these instances, there may be a role for percutaneous cervical cordotomy (PCC). This procedure interrupts the spinothalamic tracts at the level of C1/2 and causes loss of pain sensation contralaterally. Unfortunately, there are no prospective, randomised data on the role of cordotomy in MPM. The evidence comes from case series such as that by Jackson et al.[51] They performed a retrospective review of 52 patients with MPM who underwent PCC. Their results showed that over 80% of patients were able to reduce their opioid requirements after the intervention and 38% stopped opioids completely. At nine weeks post PCC, 18 patients had a recurrence in their pain requiring an increase in analgesia. Mild weakness was noted in four patients and dysaesthesia was noted in two patients. The authors concluded that PCC had a low complication rate and was successful in treating pain associated with MPM.

A Turkish group reported on 165 patients who underwent PCC, 19 of whom had MPM.[88] Of these 19 MPM patients, 13 were followed up for a median of 5.9 months with six patients being lost to follow up. The only complication reported was one case of post cordotomy dysaesthesia and all patients had an improvement in pain after the procedure. The authors recommend that all patients with local pain due to MPM should be considered for PCC.

2.8. Conclusions

The pain associated with MPM is extremely challenging to manage. Patients will often require a variety of analgesic drugs, since opioids alone are often

insufficient to control the pain. It is not uncommon for patients to be on paracetamol, anti-inflammatories, opioids and adjuvant analgesics in addition to topical treatments. For some, this combination of drugs may provide adequate analgesia. However, many patients continue to suffer from pain despite this cocktail of drugs. In these patients, other options should be considered. Chemotherapy, while offering a potential survival advantage, does not appear to have a significant impact on pain. Radiotherapy may be of benefit to some patients, though prospective randomised data are lacking. Finally, again, despite a lack of prospective randomised data, neuroaxial pain therapy or cordotomy should be considered for patients whose pain is refractory to other treatments.

Chapter 3. Radiotherapy for the Treatment of Pain in Malignant Pleural Mesothelioma: A Systematic Review

3.1. Introduction

As discussed in chapter 2, radiotherapy can be given as a treatment option for pain control in patients with MPM. This chapter presents a systematic review which examines the evidence supporting the use of radiotherapy in treating pain in patients with MPM.

3.2. Methods

Ethical approval was not required for this systematic review. The following databases were searched electronically: Medline (1946-2013), Embase (1974-2013) and CENTRAL (The Cochrane Library Issue 9, 2012). The keywords and search strategy are outlined in Appendix 1. The date of the last literature search was 5th February 2013.

3.2.1. Eligibility Criteria

Studies which met the following criteria were eligible:

MPM diagnosed histologically or radiologically

Radiotherapy given with the intent of improving pain

Documentation of the dose and fractionation of radiotherapy given

Response rates to radiotherapy reported

All types of study design potentially eligible

Studies published in English language

Prospective assessment of pain response desirable but not essential.

3.2.2. Appraisal Process

Titles and abstracts of all the articles were reviewed independently by two authors (NM and BL). If the articles were thought to be potentially relevant, in accordance with the eligibility criteria, they were retrieved in whole. These were also reviewed independently by NM and BL. If both authors agreed that the articles met the eligibility criteria, they were included in this review. Where there was disagreement, the papers were discussed and a consensus reached. If there was doubt as to whether an article should be included or not, the primary authors were contacted to see if further information was available which might help to decide whether the study should be included or not.

The potential for quantitative synthesis and meta-analysis was assessed. However, due to the small number of papers, limited reported information in many studies and varying primary endpoint measures, quantitative synthesis of results was not possible. Therefore, the salient findings of each paper are presented.

3.3. Results

The following number of articles was retrieved: 462 (Medline), 1007 (EMBASE) and 11 (Central). The literature search results are shown in Figure 11. Following the appraisal process described, eight articles were eligible

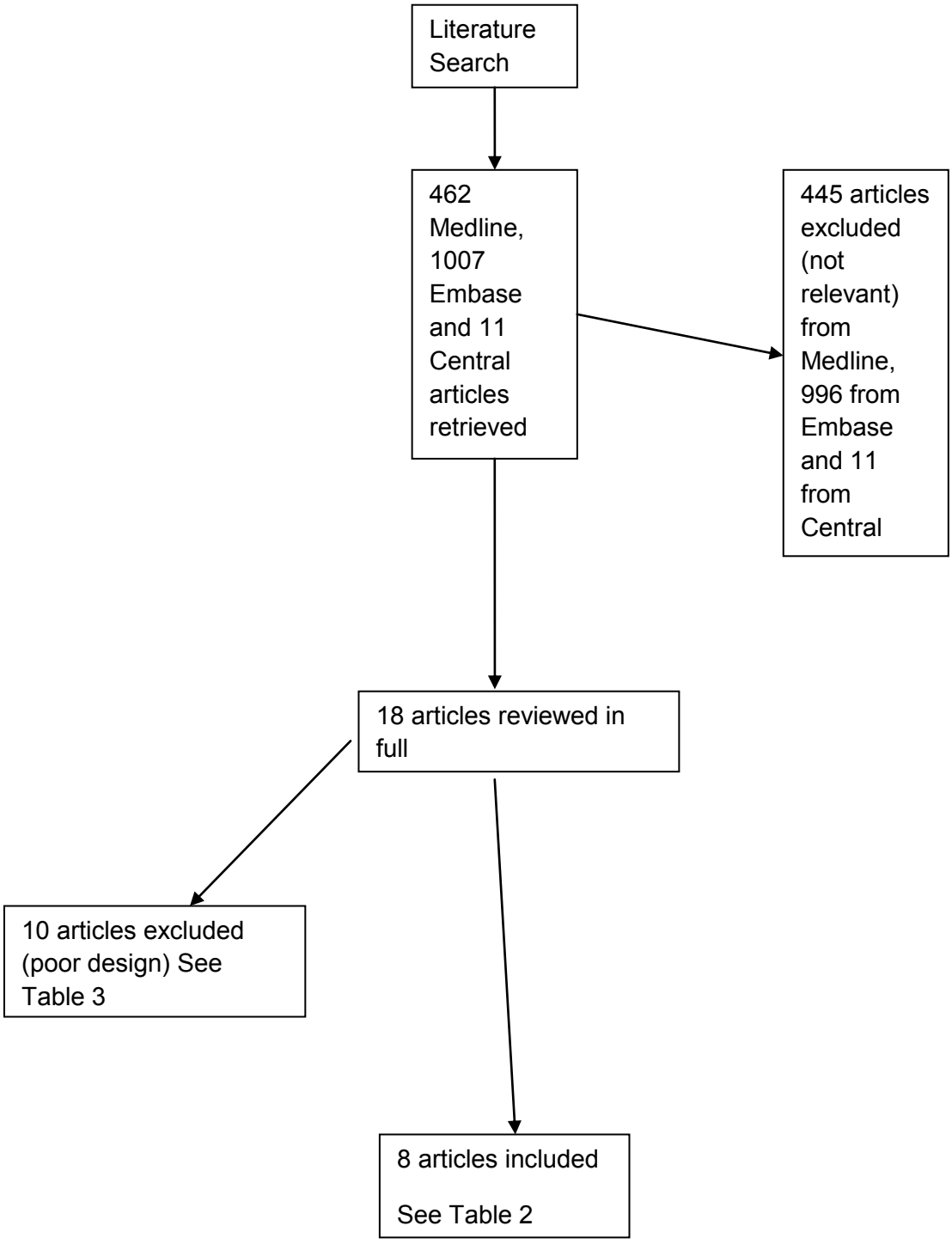

Figure 11 - Literature search results

Articles which met the eligibility criteria are shown in Table 2. Key aspects of each study are detailed. It is noted that no patients in any of the studies received pemetrexed based chemotherapy.

Excluded articles are shown in Table 3. Most were excluded as either they did not examine whether radiotherapy improved pain control in MPM or they did not document response rates.

In the majority of studies, pain response was assessed via retrospective case note review.[14, 32, 35, 89-91] Pain scores were only assessed prospectively in two studies. [33, 77] Patient numbers ranged from 19 to 189. All the studies are from single institutions with no multi centre studies performed. Dose and fractionation ranged from eight Gy in one or two fractions to 60 Gy in 30 fractions. The reported benefit ranged from no benefit seen to 69% response.[32, 77]

Table 2 - Summary of papers included in the review

Study	N*	Design	Dose (Gy)/ Fractionation	Target volume **	Measure of pain response***	Recorded Response	Diagnosis Histology/ Radiology	Comments	Lev evi
Jenkins 2011 [35]	50	Retrospective case series	36/12	Pain directed	Descriptive only	54%	Histology	CT scanning 2 months after RT performed showing a 43% RR. No comment on association between radiological and clinical response	3
El Hossieny 2010 [90]	26	Retrospective case series	Various including 50/25, 40/20, 30/10	Not documented	Not documented.	57%	Histology	Marked heterogeneity in dose and fractionation in this retrospective case series and no mention of how RR was recorded	3
De Graaf-Strukowska 1999 [14]	189	Retrospective case series	Various, mainly 30/15 and 36/9	Hemithorax until 1987 then pain directed from 1987 onwards	Descriptive only	50% for 4Gy per fraction, 39% for <4Gy per fraction	Histology	Change in fraction size not due to randomisation but rather reflective of a change in policy to treat sites of symptomatic disease only rather than covering the entire volume of disease	3
Linden 1996 [77]	47	Single arm phase II	40/20	Hemithorax	Prospective pain score 0-4	Mean pain score of 0.8 at baseline and 1.2 one month post RT	Histology	All patients referred to this institution entered into uncontrolled phase II study. Only 5 patients on opioids at study baseline and 27 had baseline pain score of 0	2 -
Davis 1994 [89]	71	Retrospective case series	Various from 8/1 to 60/30 but mainly 20/5 and 30/10	Not documented	Descriptive only	60%	Histology	Authors acknowledged that follow up information detailing symptomatic response was inadequate. A wide variety of doses and fractionation schedules were prescribed. Confounding factors such as analgesic and steroid use and their influence on treatment were difficult to assess.	3
Bissett 1991 [33]	22	Prospective single arm phase II	30/10	Hemithorax	Prospective using three tools	68%	Histology for 17, radiology for 5	Cobalt-60 machines used.	2 -
Ball 1990 [32]	20	Retrospective case series	Various, mainly 20/5 and 30/10	Pain directed	Not documented	69%	Histology	Not clear from article how or when response was assessed.	3
Gordon 1982 [91]	19	Retrospective case series	Various from 8/2 to 58/29	Not documented	Palliation index 0-4 of response to RT from retrospective casenote review	38%	Histology	Marked heterogeneity in dose and fractionation in this retrospective case series	3

- *Number of patients in study **(hemithorax versus pain directed) *** method of recording Abbreviations: RT – radiotherapy RR – response rate

Table 3 - Excluded Papers

Author and year	Title	Reason for exclusion
Simone 2012 [92]	Palliative care in the management of lung cancer: Analgesic utilization and barriers to optimal pain management	Web based questionnaire on analgesic use in lung cancer and mesothelioma patients
Barbieri 2012[93]	Effects of combined therapies on the survival of pleural mesothelioma patients treated in Brescia, 1982-2006	Retrospective review. No mention of dose, fractionation or measures to assess analgesic benefit
McAleer 2009 [94]	Radiotherapy in malignant pleural mesothelioma	Review article
Stathopolous 2005 [95]	Mesothelioma: Treatment and Survival of a Patient Population and Review of the Literature	No mention of fractionation in this study
Munter 2005 [96]	Stereotactic intensity-modulated radiation therapy (IMRT) and inverse treatment planning for advanced pleural mesothelioma	Feasibility study looking at IMRT, not a study looking at pain relief from radiotherapy
Zierhut 2004 [97]	Radiation therapy of mesothelioma: the Heidelberg experience and future aspects	No pain scores or assessments performed to assess response to radiotherapy in this retrospective review. No response rate documented
Calavrezos 1988 [98]	Malignant mesothelioma of the pleura	No mention of radiotherapy in the paper
Law 1984 [99]	Malignant mesothelioma of the pleura: a study of 52 treated and 64 untreated patients	No mention of how pain or pain relief was measured. Radiotherapy not clearly given with intent of improving pain
Wanebo 1976 [100]	Pleural mesothelioma	No comment on pain response or if any measures of pain were undertaken
Shearin 1976 [101]	Malignant pleural mesothelioma	Retrospective review of all MPM patients rather than specifically patients with pain who have undergone radiotherapy

3.4. Discussion

Based on the studies presented in this review, the evidence for radiotherapy in treating pain in mesothelioma ranges from Level 2- to 3.[102] Therefore, firm recommendations on the role of radiotherapy in the relief of pain in MPM cannot be made. Due to a combination of poor study design and small numbers of patients, none of the studies fully examines the role of radiotherapy in the treatment of pain in MPM. Indeed, in four of the eight studies, assessment of pain response was retrospective and in two of the other studies, it is not clear as to how the reported response rate was derived.[14, 32, 35, 89-91] These papers would have benefited from a prospective evaluation of pain response. The studies included in this review present little data on toxicity which would obviously be an essential requirement for future studies.

In the studies included in this review, reported response rates vary from no benefit seen to 69%.[32, 77] Bissett's study provides the strongest evidence for radiotherapy in this setting.[33] This prospective study used clear measures of pain response and reported a 68% response rate. However, hemi thoracic irradiation is rarely used nowadays due to concerns over toxicity. The only other study which assessed pain response prospectively was limited by the fact that 27 of the 47 patients in the study had no pain at study entry.[77] Therefore, showing any improvement in this group would be difficult and it is not surprising that this study did not show a benefit in pain scores after irradiation.

The most recent study in this review, by Jenkins et al, is to be commended since response was evaluated with a CT scan two months after treatment.[35]

However, the study is limited by the lack of validated pain assessment tools. Two ongoing randomised phase III UK studies assessing the role of prophylactic drain site irradiation are prospectively assessing pain response.[30, 31]

Although there is limited evidence to support radiotherapy for pain in MPM, it is recommended by the British Thoracic Society (BTS) as well as the European Respiratory Society and the European Society of Thoracic Surgeons (ERS/ESTS) [73, 103] However, the lack of strong evidence suggests that further work examining radiotherapy for pain in MPM is needed.

Studying the role of radiotherapy in MPM is challenging. Firstly, it is a cancer that is associated with a poor survival.[14, 89] Even if patients do achieve a benefit in terms of pain response, this may be offset by a significant decline in performance status.[33] In these situations, patients might find it difficult to see a benefit from radiotherapy when their quality of life has deteriorated significantly. Secondly, there are several issues that are unique to MPM in terms of radiotherapy planning which make it a problematic area to study. Historically, attempts were made to encompass the entire volume of disease using hemi thoracic irradiation.[14, 33, 77] However, more recently, clinicians have tended to focus on treating sites of bulk disease, in an attempt to reduce toxicity and give larger doses to smaller areas.[35] In addition, treating the whole tumour to a dose sufficient to produce a response using traditional radiotherapy methods would be very toxic and not warranted in this patient population with limited life expectancy.[104] There have been no studies that have compared the two approaches. Instead, there has simply been a general trend towards treating

smaller field sizes in an attempt to reduce toxicity. Furthermore, radiotherapy prescribing in MPM is crude. For example, with bony metastatic disease, it is usually fairly easy to identify the painful lesion due to such features as bony destruction or erosion into a joint. Radiotherapy can then be targeted to that area with reasonable confidence that the correct area has been treated. However, with MPM, the pain is often widespread and may or may not correspond to disease bulk on CT imaging. The treating radiotherapist may have to compromise by directing treatment to areas of disease, which may or may not wholly correspond to pain. If radiotherapy is then not delivered to the appropriate area, the incorrect conclusion could be drawn that radiotherapy is not effective in pain palliation in this disease. However, if further imaging or other techniques were able to help the clinician target the radiotherapy more precisely to the area responsible for the pain, the potential palliative benefit of radiotherapy could increase significantly.

Platinum/antifolate combination chemotherapy has become established as a treatment option for MPM which can be given with the aim of improving survival.[27, 28] Quality of life data from one of these studies have been published.[85] These data suggest that pain scores remained constant throughout chemotherapy. The authors concluded that stabilization of this and other parameters in a disease with as poor a prognosis as MPM was clinically significant. However, these data can similarly be interpreted as showing that chemotherapy provided no improvement in pain for these patients and so the benefit of chemotherapy in terms of symptom improvement is controversial. Furthermore, many patients diagnosed with MPM are not of adequate performance status to receive chemotherapy and very few actually receive this

treatment.[29] Therefore, chemotherapy does not appear to be an effective alternative treatment option to alleviate pain in MPM.

3.4.1. Future work in this area

There is clearly scope for further work in this area. Any future studies looking into the role of palliative radiotherapy in MPM should ideally involve optimising analgesia (both opioids and adjuvants) prior to radiotherapy delivery. This is imperative since a reduction in pain after radiotherapy is impossible to interpret if opioid requirements have increased significantly in that time. Furthermore, validated pain assessment tools should be used. An improvement in pain at six weeks is a meaningful primary endpoint for response to radiotherapy for bone metastases.[105, 106] The optimal time to assess response to radiotherapy in MPM is not known but four to six weeks would seem to be reasonable. Consideration should be given to studies with two dose levels to look for radiobiological effect. Furthermore, with modern day radiotherapy techniques such as RapidArc, it is possible to deliver higher equivalent doses to tumour while managing to limit dose to organs at risk, potentially allowing the possibility of randomised dose escalation studies.

As outlined above, deciding what areas of disease to treat and what to omit is a real challenge for the clinical oncologist. At present, radiotherapy planning in MPM is driven by CT. PET-CT is now part of standard practice in the radiotherapy planning of non small cell lung cancer.[107] It also has a role in some aspects of MPM such as staging and assessing chemotherapy response.[108, 109] However the benefits of PET-CT over standard CT, in

defining clinical target volume in MPM are unknown and merit investigation. A phase II study which addresses many of these issues is currently underway. (ISRCTN number: 10644347) This study aims to recruit 40 patients who will receive radiotherapy for pain control. The primary aim of the study is to establish the percentage of patients whose pain responds to 20 Gy in 5 daily fractions using 6 MV photons.

In the age of personalised medicine, future research to identify biomarkers which are predictive of radiotherapy response would be of interest. While oestrogen receptor status is a well-established biomarker of response to hormonal therapy in breast cancer, very few such biomarkers exist with regards to radiotherapy response.[110] In nasopharyngeal cancer, it has been proposed that dysregulation of certain proteins may be involved in radioresistance.[111] It has also been proposed that, in bone metastases, certain features from quantitative sensory testing may be of value in predicting response to radiotherapy.[112] Such biomarkers would be helpful in MPM. If it can be predicted that there is a high probability that radiotherapy would be futile, then several visits to a cancer centre that may be a distance from the patient's house could be avoided and management focused on other interventions.

3.5. Conclusion

In conclusion, the role of radiotherapy in the palliation of pain in patients with MPM remains uncertain. Future work in this area should evaluate pain response prospectively using validated pain assessment tools and ideally should be

performed with modern day radiotherapy techniques such as RapidArc aiming for randomised dose escalation studies. Studies which examine optimisation of radiotherapy planning and delivery and potential biomarkers of analgesic response are eagerly awaited.

Chapter 4. Methodology

4.1. Overview

It was clear that to meet the aims of this thesis, a clinical study would need to be developed. To this end, the SYmptom STudy of radiothErapy in MeSothelioma (SYSTEMS) was developed through peer review and subsequent funding. This chapter describes the development and methodology of the SYSTEMS study, which included a characterisation of MPM-related pain and a sub-study examining the role of PET-CT in radiotherapy planning in mesothelioma.

4.1.1. Peer Review

4.1.1.1. National Cancer Research Institute

Once the initial study protocol was developed in 2011 (termed Radiotherapy for the Treatment of Mesothelioma Symptoms Study [RTMSS] initially), it was presented at the Clinical and Translational Radiotherapy Research Working Group (CTRad) of the National Cancer Research Institute (NCRI) on the 9th November 2011. Positive feedback was received which helped to guide the methodology and formal endorsement was secured.

4.1.1.2. Beatson West of Scotland Cancer Centre

The study was submitted to the In-House Trials Advisory Board (IHTAB) at the Beatson West of Scotland Cancer Centre (BWoSCC). IHTAB is an executive committee of the Cancer Research UK, Clinical Trials Unit, based in the Beatson. The group provides peer review for all studies which potentially are to be run through the trials unit and agrees on administrative responsibility, should

the study take place. The board was fully supportive of the study and agreed that, following successful procurement of funding, the study would be taken on as an investigator led trial within the Cancer Research UK, Clinical Trials Unit based in the BWoSCC.

4.1.2. Funding

The two year period of research was funded through grants from the June Hancock Mesothelioma Research Fund (JHMRF) and the Beatson Oncology Centre (BOC) Fund. The JHMRF awarded the Brother Peter Fellowship to support 50% of the costs of this research - Appendix 3. The BOC fund supported the remaining 50% of the costs - Appendix 3. This joint funding supported my salary and other research related costs such as clinical trial unit support. Funding for the PET-CT sub-study was supported by a grant from the British Lung Foundation (BLF) - Appendix 3.

4.1.3. Ethics

The study was approved by the West of Scotland Research Ethics Service - Appendix 6. The study was assigned International Standard Randomised Controlled Trial Number (ISRCTN) 10644347 and was badged by the NCRI. (http://public.ukcrn.org.uk/Search/StudyDetail.aspx?StudyID=14124).

Procedures of the Declaration of Helsinki and Good Clinical Practice were followed. Written informed consent was provided by all patients - Appendix 4.

4.1.4. Research & Development (R&D)

R&D approval was received from respective departments. The study, now called SYSTEMS, opened to recruitment on the 14th June 2012.

4.2. Patients and Methods

4.2.1. SYSTEMS study overview

A multi-centre single arm phase II study of radiotherapy (20Gy in 5 daily fractions using 6 MV photons) for the treatment of pain in patients with MPM. The study design was informed by feedback received following grant and CTRad review.

4.2.2. Considerations in Study Design

There was much debate as to the optimal design for the SYSTEMS study. Consideration was given to a randomised controlled trial comparing radiotherapy with best supportive care since the evidence in support of radiotherapy in this situation is limited. However, palliative radiotherapy is recommended for pain control in both the British Thoracic Society (BTS) and European Respiratory Society/European Society of Thoracic Surgeons (ERS/ESTS guidelines.[73, 103] Therefore, it was not felt appropriate to design a study where one of the arms contradicted these guidelines. Furthermore, there was concern that patients might not consent to a study with a best supportive care arm when the standard treatment outwith the study setting was to receive the intervention.

Once a study design incorporating a best supportive care arm was ruled out, thought was given to proceeding with a randomised study comparing different doses and fractionations in order to establish a gold standard regimen. In order to calculate the sample size required to demonstrate a difference in efficacy between two arms, the anticipated response rate to one of the arms would have to

be known. Again, given the limited data on the subject, no such accurate estimates could be made. If an inaccurate estimation were made, the expected study numbers could be imprecise. This would impact significantly on the likelihood of such a study providing the answer that was sought at the start of the study i.e. what the actual response rate to radiotherapy is in this setting. In view of this, it was decided that the primary objective of SYSTEMS was to establish the percentage of patients who had an improvement in pain following a standard dose of radiotherapy. It was anticipated that the results of the SYSTEMS study could then inform the basis of a subsequent randomised phase II study.

There was much discussion as to whether to include only patients with a histological diagnosis or those patients with a diagnosis made following Multi Disciplinary Team (MDT) consensus. The decision was made to include the latter as this reflects clinical practice. The respiratory physicians in the West of Scotland were particularly influential in recommending including such patients given the difficulty that obtaining a histological diagnosis can present in this patient group. Furthermore, since MPM is an industrial cause of death, all cases require to be discussed with the procurator fiscal in Scotland and the coroner in England. Therefore, patients without a histological diagnosis should undergo a post mortem at which time a histological diagnosis can be made. It is noted that a histological diagnosis remains the cornerstone of cancer diagnosis and the decision to include non histologically diagnosed patients was not taken lightly. Attempts at histological diagnosis were encouraged whenever possible.

4.2.3. Study Design

A multi-centre single arm phase II study of radiotherapy (20Gy in 5 fractions) for the treatment of pain in patients with MPM. A study schema is shown in Figure 12. More frequent pain assessments were considered to help identify the optimal time to assess response. However, given that most patients were likely to be recruited from the West of Scotland and the prognosis was likely to be poor, more frequent hospital visits were felt to be too much of a burden for the patients and the visit schedule that was finalised on was felt to be sufficient.

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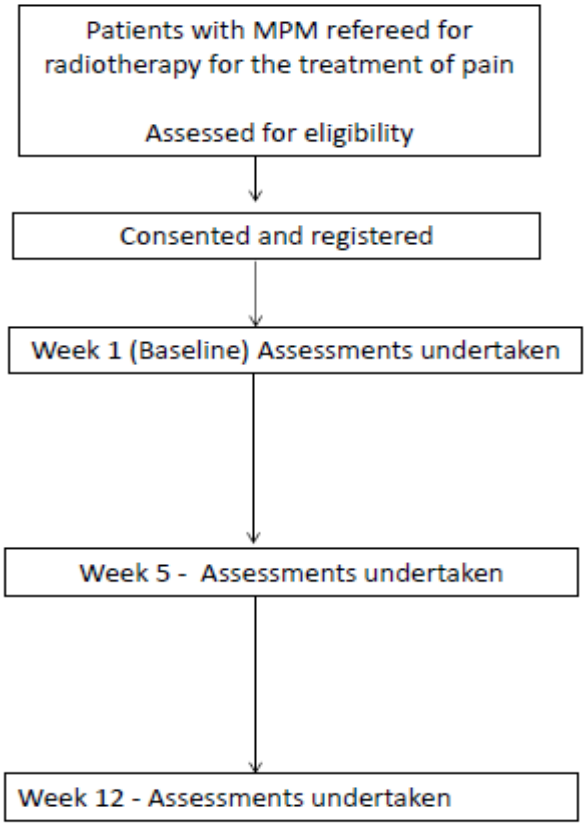


Figure 12 - Study schema

4.2.3.1. Pre Study Assessments

One of the challenges of conducting a study examining a pain intervention in patients with advanced cancer is that changes in analgesia may occur during the study period. In such cases, it becomes very difficult to disentangle any improvements in pain as a result of the study intervention from any changes in concomitant analgesia. One of the ways this can be addressed is by stabilising pain and analgesia prior to study entry. This approach was adopted for potential patients in the SYSTEMS study. Prior to study consent, patients were reviewed by Drs. MacLeod and Laird (Palliative Medicine), often with multiple visits or telephone consultations over several weeks, enabling background analgesia to be optimised and pain stabilised, where possible, before study entry. This also resulted in some patients' analgesia improving to the extent that their pain was no longer severe enough for study entry. Following optimisation of analgesics, if patients were eligible, written informed consent was obtained. Study assessments and timepoints are outlined in Table 4.

4.2.4.

At the baseline visit, an assessment of performance status was made along with a physical examination. All previous treatments for MPM – surgery, chemotherapy or radiotherapy - were documented along with the medication history which listed all medicines taken in the previous 24 hours. Baseline toxicity assessment was performed and all study questionnaires were completed. In order to improve compliance, rather than leaving the patient to complete the questionnaires, a study investigator completed the questionnaires based on the answers received from the patient. Quantitative sensory testing (QST) was performed.

QST is essentially a detailed sensory examination of an area of the body and is described here. The painful area was mapped out. Dynamic mechanical allodynia was assessed using a standardised calibrated brush (Senselab 0.5mN Somedic, Sweden) stroked over a length of skin bilaterally. The contralateral chest wall acted as the control area. The patient was asked to describe how this sensation compared with the control area (hyperaesthesia, hypoesthesia or unchanged) and, if painful, was rated with a VAS of 0-10.

Mechanical Detection Threshold (MDTH) and Mechanical Pain Threshold (MPH) were assessed with Von Frey monofilaments (Somedic, Sweden) using the Method of Levels technique to establish thresholds.[113] These constitute a series of 17 filaments of varying thickness, calibrated according to the force required to bend them. Mechanical pain sensitivity (hyperalgesia) was tested using noxious pin prick stimulus (Neurotips Owen Mumford). Response to warm (40 degrees Celsius) and cool sensation (25 degrees Celsius) was assessed using thermal rollers (Rolltemp, Somedic, Sweden). For all the stimuli, except for MDTH and MPH, actual thresholds were not measured. Responses were recorded as increased, reduced or equivalent sensation as the normal control side.[112]

An American proteomics company, SomaLogic, has produced a 13-biomarker panel which may have a role in the diagnosis of MPM.[19] Before the study opened to recruitment, there was a verbal agreement with the company to take blood samples from patients at baseline and week 12. The aims of these blood

tests were twofold. The first aim was to validate the biomarker panel. The second aim was to explore the possibility that proteins could be identified which might help to predict a response to radiotherapy. On completion of the trial, SomaLogic were contacted regarding the shipping of the samples. At that time, we were informed that SomaLogic no longer had an interest in MPM and that the samples would not be analyzed. Therefore, no data on these samples can be presented in this thesis. However, the samples remain stored and future analyses may be performed on these samples.

4.2.5. Week 1 Visit

Patients were seen eight (+/-three) days after the start of radiotherapy for their week 1 visit. At this consultation, current medication was recorded, including analgesics in the past 24 hours. Any toxicity from radiotherapy was documented and the questionnaires were repeated. Current symptoms were documented. Following the week 1 visit, patients received weekly phone calls in order to monitor symptoms and assess analgesic requirements.

Table 4 - Study Assessments

	Baseline	Week 1	Week 5	Week 12
Day	**1**	**8 +/- 3 days**	**35 +/- 5 days**	**84 +/- 7 days**
Informed consent	**X**			
Inclusion/exclusion	**X**			
Vital signs	**X**	**X**	**X**	**X**
Medical history	**X**	**X**	**X**	**X**
Medication history	**X**	**X**	**X**	**X**
Treatment history	**X**	**X**	**X**	**X**
Physical examination	**X**	**X**	**X**	**X**
ECOG Performance status	**X**	**X**	**X**	**X**
CT SCAN [1]	**X**			**X**
Toxicity Assessment	**X**	**X**	**X**	**X**
QST	**X**		**X**	**X**
STUDY QUESTIONNAIRES:				
Brief Pain Inventory	**X**	**X**	**X**	**X**
LANSS	**X**	**X**	**X**	**X**
MPQ	**X**	**X**	**X**	**X**
HADS	**X**	**X**	**X**	**X**
EORTC QLQ C-30 & LC13	**X**	**X**	**X**	**X**
FSS	**X**	**X**	**X**	**X**
NRS Dyspnoea	**X**	**X**	**X**	**X**
NRS night sweats	**X**	**X**	**X**	**X**

[1] within 8 weeks of first fraction of RT

4.2.6. Week 5 visit

Patients were seen 35 (+/-5) days from the start of radiotherapy. At this visit, all the study visits performed at week 1 were repeated. In addition, QST was repeated. A CT scan was requested to be performed prior to the week 12 visit. Week 5 and 12 visits were scheduled to take place in the hospital. However, if patients were unable to attend, efforts were made to see them at home. After the week 5 visit, the weekly phone calls continued until the week 12 visit.

4.2.7. Week 12 visit

At the week 12 visit, all assessments undertaken at week 5 were repeated. In addition, the CT scan result was discussed with the patient. Following this visit, patients were discharged back to their local oncology teams and study involvement ceased. During the course of the study, if patients' analgesia required to be altered, this was done as per usual clinical practice.

4.2.8. Study Centres

The study was conducted in three regional oncology centres in the UK; the BWoSCC in Glasgow, Edinburgh Cancer Centre and Weston Park Hospital in Sheffield. The study initially opened in Glasgow since the West of Scotland has one of the highest incidences of MPM in the world. Edinburgh was then opened as a study site. Although there is not a high incidence of MPM in the east of Scotland, the Palliative Medicine Research Team (PMRT) in Glasgow is a component of the Edinburgh Palliative and Supportive Care Group (EPaS) at the University of Edinburgh, led by Professor Marie Fallon. Finally, Sheffield was

added as a recruitment centre in May 2013, as there was a drive to boost recruitment and Sheffield had expressed an interest in becoming a recruiting centre.

4.2.9. Patients

In the SYSTEMS study, patients were recruited or excluded according to the following criteria:

4.2.9.1. Inclusion Criteria

1. ≥18 years of age
2. Histological or MDT diagnosis* of mesothelioma
3. Able to complete study assessments
4. Life expectancy of at least 3 months based on clinical judgement
5. Due to receive radiotherapy for pain resulting from mesothelioma (defined as index site)
6. ECOG Performance Status 0-2
7. CT scan within 8 weeks of radiotherapy
8. Worst pain ≥4/10 (0-10 Numeric rating scale) corresponding to the index site.

* MDT diagnosis consisted of a good history of asbestos exposure and CT imaging consistent with MPM

4.2.9.2. Exclusion criteria

1. Received chemotherapy or radiotherapy in the preceding six weeks that is likely to alter pain at the index site during the duration of the study

2. Planned chemotherapy during the period of the study that is likely to alter pain during the course of the study

3. Psychotic disorders or cognitive impairment

4. Co-existing lung tumours at the time of study entry

5. Pregnancy or breastfeeding.

4.3. Radiotherapy

4.3.1. Rationale for Chosen Regimen

The optimal dose and fractionation to be used in the treatment of pain in MPM is not established. Therefore, the choice of regimen in the SYSTEMS study was discussed at CTRad to help inform the choice. There are certain features of MPM that would suggest that a hypofractionated regimen would be preferable to a conventional fractionation schedule. The likelihood of improving outcomes by increasing dose per fraction varies among tumour types and is determined by the alpha/beta ratio of the tumour. Rapidly proliferating squamous cell carcinomas, such as head and neck and cervical cancer, have high alpha/beta ratios and benefit from treatment with small doses per fraction. Many non-squamous tumours with lower proliferation rates have low alpha/beta ratios and hence benefit from higher doses per fraction.[114, 115] While there are few data from which to estimate the alpha/beta ratio for MPM, its non-squamous histology, relatively low proliferation index, mesenchymal origin and apparent radioresistance are all consistent with a low alpha/beta ratio. Furthermore, in the palliative setting it is usual practice to deliver a short, hypofractionated schedule.[116] However, given that MPM is perceived to be a relatively

radioresistant tumour, consideration was given to a "hot" dose such as 36 Gy in six fractions treated over two weeks. Ultimately though, since this study was designed primarily to assess response rates to radiotherapy, it was felt that using a dose and fractionation that thoracic oncologists are familiar with was preferable. Twenty Gy in five fractions is a standard treatment regime used in the palliative setting in lung cancer and is recommended in the Royal College of Radiologists guidelines.[117] Favourable response rates with acceptable toxicity have been reported with this regimen.[118] Given the poor prognosis in MPM, it was felt that delivering a regime with little toxicity was highly desirable.

4.3.2. Radiotherapy planning

4.3.2.1. Patient data acquisition

A planning CT scan was performed on all patients on a General Electric light speed 16 slice scanner using the local thorax imaging protocol. Patients were scanned in the treatment position and asked to breathe normally. If tolerated, patients were treated with arms above their head. This position was selected as it is the conventional position for radical radiotherapy for lung cancer at the BWoSCC. Although when palliative treatment is being administered, patients are often treated with their arms down, the chosen position allowed more complex plans to be used if necessary. Continuous 2.5mm slices were acquired throughout the entire volume of both lungs from the cricoids process down to the iliac crest. Prior to the planning CT scan, patients were examined in a side room and radio-

opaque wire markings were placed on the skin at the outer aspects of the painful areas, in order to help the clinician correlate the area of pain with the CT findings.

4.3.2.2. Treatment Planning

The first 12 patients in the SYSTEMS study and all patients in Edinburgh and Sheffield were planned using virtual CT sim placement using Advantage Windows version 4.3. Treatment was typically given in the form of a parallel pair though, occasionally, direct fields were used. Following Radiotherapy Management Group (RMG) approval, subsequent patients were volumed with an Eclipse plan produced by the physics team in the BWoSCC patients.

The gross tumour volume (GTV) was defined as the volume of tumour that was felt to be responsible for the pain. Before having their planning CT scan, all patients were seen in a side room and wire markings placed on the skin to delineate the painful area. No attempt was made to include the entire volume of disease.[35] The GTV was outlined on each CT slice and grown by 1-2cm to form the planning target volume (PTV). Given that this was a palliative treatment, the GTV was not grown to produce a clinical target volume. Dose volume histograms (DVH's) for organs at risk (OAR's) were calculated in order to obtain full knowledge of the dose distribution. For all tumours, this involved outlining the oesophagus, heart, lungs and spinal cord. For right sided tumours, the liver was outlined whilst the stomach and spleen were outlined for left sided tumours. The ipsilateral brachial plexus or kidney was outlined if the PTV was within 5cm of it.

4.3.2.3. Dose specification and treatment

Patients were treated on a linear accelerator operating at 6 or 10MV. The prescribed dose was 20 Gy in 5 daily fractions of 4 Gy. With Eclipse planning, the aim was to have homogeneity between 95% and 107% of the ICRU reference point across the PTV, according to the International Commission on Radiation Units (ICRU) reports 50 and 62. However, as this was a palliative treatment, the ultimate decision on whether or not to accept the plan was at the discretion of the treating Clinical Oncologist. The rationale for having an Eclipse plan for these patients was primarily to enable dose to OARs to be evaluated and to correlate this dose with acute toxicity. In general, the Eclipse plans were aiming to be straightforward plans, such as a parallel pair, in order to reflect the way in which most patients are treated outwith a study setting.

4.3.2.4. OAR Definition

Lungs: Contoured on every slice from apex to base.

Oesophagus: Outlined on every slice from the cricoids cartilage down to the gastro-oesophageal junction.

Spinal Cord: The spinal cord was outlined 5cm above the superior border of the PTV and 5cm below the inferior border of the PTV.

Heart: Contoured on all slices. The cranial border was taken as the infundibulum of the right ventricle and the apex of both atria. The great vessels were excluded as much as possible. The caudal border was defined as the lowest part of the left ventricle's inferior wall that was distinguishable from the liver.

Liver: The whole liver was outlined for right sided tumours.

Kidneys: If the PTV fell within 5cms of the kidney, the whole of the ipsilateral kidney was outlined and, if there was concern regarding dose to the contralateral kidney, it too was outlined.

Stomach: The whole of the stomach was outlined for left sided tumours.

Spleen: The whole of the spleen was outlined for left sided tumours.

Brachial plexus: The brachial plexus was outlined if it was within 5cm of the upper border of the PTV.

4.3.2.5. OAR Constraints for Radiotherapy Planning

No data exist to guide OAR constraints for hypofractionated radiotherapy. However, given that this was a palliative treatment given with the aim of improving patients' symptoms and wellbeing, there was caution with regard to dose constraints to OAR's. Therefore, the following guidelines were established by the study investigators.

Lung: No fixed upper limit of irradiated lung was set but keeping the volume receiving 20 Gy to <25% was strongly recommended.

Oesophagus: The length of oesophagus in the treatment field was minimised where possible. However, 20 Gy in 5 fractions is a common palliative dose for oesophageal tumours and so no upper limit of oesophageal length within the PTV was set.

Spinal Cord: As with oesophagus, the length of spinal cord within the treatment field was minimised where possible. Again, however, 20 Gy in 5 fractions is a common palliative dose to give to the spinal cord and so no upper limit on spinal cord length was set.

Heart: Dose constraints to the heart were difficult to quantify as there are at least 4 targets; the myocardium, coronary arteries, conduction system and pericardium. Dose to the heart was minimised where possible with shielding considered, especially for left sided tumours.

Liver: Dose to the liver was minimised where possible as the side effects of radiation hepatitis may negate any potential benefit from radiotherapy. There was scope within the protocol to permit more detailed radiotherapy planning in order to minimise the dose to the liver.

Kidneys: Given that the kidneys are relatively radiosensitive, shielding to the ipsilateral kidney was recommended for low lying tumours. If this was not possible, the contralateral kidney was completely spared.

Stomach: Dose to the stomach was minimised where possible to reduce acute toxicity, mainly nausea and vomiting.

Spleen: For low lying left sided tumours, consideration was given to shielding the spleen in order to reduce the dose received.

Brachial Plexus: For apical tumours, it was likely that at least part of the brachial plexus would lie within the PTV. It was felt that 20Gy in 5 fractions was within the tolerance of the brachial plexus and so PTV coverage was not compromised in order to reduce the dose to the brachial plexus.

4.3.3. CT assessment

In order to be eligible for the study, all patients were required to have undergone a staging CT of chest and abdomen within 8 weeks of radiotherapy. For many radical studies, a CT scan is required to be performed within 4 weeks of radiotherapy. However, as this was a palliative radiotherapy study, it was felt appropriate to lengthen this to 8 weeks. The time between the CT and start of radiotherapy was minimised where possible. All patients underwent CT scanning at 12 weeks to assess response. A consultant radiologist who specializes in thoracic malignancies reviewed the baseline and week 12 CTs on a workstation using the Carestream PACS system. He was provided with a digitally reconstructed radiograph (DRR) outlining the treatment field for each patient. The radiologist was blinded as to the clinical response of each patient. Response was assessed using the modified Response Evaluation Criteria In Solid Tumours (RECIST).[119] Within the treatment field, tumour thickness perpendicular to the chest wall or mediastinum was measured in two positions at three separate levels on thoracic CT scans. The sum of the six measurements defined a pleural uni-dimensional measure. If it was not possible to identify three separate levels of tumour in the treatment field or two positions within the same CT slice, as many tumour measurements as possible within the treatment field were made.

A complete response was defined as disappearance of all visible disease with no new disease appearing within the treatment field. A partial response was defined as a $\geq$30% reduction in the total sum of the lesions. Stable disease was defined as a <30% reduction and <20% increase in the size of the sum of the lesions. Progressive disease was defined as a $\geq$20% increase in the sum of the lesions as per RECIST 1.1 guidelines.[120] The association between radiological response,

as outlined above, and clinical response, assessed via a 30% drop in the BPI score at 5 weeks, was compared.

4.4. Assessments

4.4.1. Brief Pain Inventory (BPI)

All questionnaires utilized in this study are attached in Appendix 5.

The BPI is a multi-dimensional pain assessment tool. It was designed to serve two purposes; to measure the intensity of pain and to assess the level of interference of pain on daily function. It was developed for use in cancer patients and has been extensively validated in both cancer and non cancer patients.[121-123]

All questions in the BPI relate to the previous 24 hours. The section on pain intensity asks the worst, least and average pain as well as the pain right now. Subjects are asked to score each answer from 0-10 where 0 is “no pain” and 10 is “pain as bad as you can imagine”. It also asks the participant to rate the percentage of pain relief they experience from whatever pain treatments or medications they are currently on, ranging from 0-100.

The second section of the BPI focuses on the level of interference of pain on the subject’s lifestyle, namely their general activity, mood, walking ability, normal work, relations with other people, sleep and enjoyment of life. Again the scores are from 0-10 with 0 corresponding to “does not interfere” and 10 representing “completely interferes” with each question that has been asked.

Once the questionnaire has been completed, the total BPI score can be calculated and repeated to assess the impact of an intervention on the subject's pain. For the study, the total score at baseline was calculated. A pain response was taken as a 30% drop in BPI score from the baseline assessment.[123]

4.4.2. Short Form McGill Pain Questionnaire (SF-MPQ)

The MPG is a scale for assessing pain using verbal descriptors. It was designed to allow patients to express the intensity and quality of their pain.[124] A short form version was developed in 1987.[125] In 2009, this was further modified in order to develop a single measure for both neuropathic and non-neuropathic pain.[126] Amongst other purposes, it was planned that this questionnaire, SF-MPQ2, could be used in treatment response studies.

4.4.3. Leeds Assessment of Neuropathic Symptoms and Signs (LANSS)

The LANSS was developed in 2001 as a tool to identify patients who are likely to have neuropathic pain.[127] It has been extensively validated.[128, 129] The assessment consists of two sections; a pain questionnaire and sensory testing. In the pain questionnaire, subjects are asked five yes/no questions concerning their pain. With the sensory testing, the subject is examined for allodynia and for altered pin-prick threshold. Combining the scores for the questionnaire and the sensory testing gives a maximum score of 24. A score of $\geq$12 suggests that neuropathic mechanisms are likely to be contributing to the patient's pain, whereas a score of <12 suggests that neuropathic mechanisms are unlikely to be contributing to the patient's pain.

4.4.4. Hospital Anxiety and Depression Scale (HADS)

The HADS is a self-assessment scale used to screen for anxiety and depression. The scale has been validated.[130, 131] There are 14 questions in total, seven looking at depression and seven at anxiety. Each question has four possible answers which are rated from 0-3 with the higher the score, the worse the symptom. The maximum score is 42. A score of $\geq$ 15 is suggestive of a major depressive disorder.[132]

4.4.5. Fatigue Severity Scale (FSS)

The FSS is an instrument designed to determine the level of fatigue from which a subject is suffering. There are nine statements and the subject is asked to rate their level of agreement with the statement from 1 (completely disagree) to 7 (completely agree) giving a maximum score of 63. The final score represents the mean value of the nine scores. It was developed in 1993 and has been validated in different illnesses.[133, 134]

4.4.6. Numerical Rating Scale for Dyspnoea (NRS)

Given that dyspnoea is one of the most common symptoms in MPM, it was felt that having an assessment of dyspnoea at each study visit was important. Therefore, a NRS was used ranging from 0-10 where 0 was “no dyspnoea” and 10 was “dyspnoea as bad as the patient could imagine”.

4.4.7. Numerical Rating Scale for Night Sweats

It has been noted in previous studies that night sweats are a common symptom in MPM.[16] Therefore, it was felt that monitoring the effect of radiotherapy on night sweats would be worthwhile. As there is no standard scale to assess night sweats, a NRS was constructed. Scores ranged from 0-10 with 0 corresponding to "no night sweats" and 10 being "night sweats as bad as the patient can imagine".

4.4.8. European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)

The EORTC QLQ-C30 is a validated questionnaire designed to assess the quality of life of cancer patients.[135] It incorporates nine multi-item scales: five functional scales (physical, role, cognitive, emotional and social); three symptom scales (fatigue, pain, and nausea and vomiting); and a global health and quality-of-life scale.

As can be seen in the paragraphs above, with the exception of the NRS for night sweats, all of the questionnaires used in the SYSTEMS study have been validated. The first step in the validation process involves a questionnaire being proposed as a potential way of measuring a symptom, e.g. pain. The validation comes when the questionnaire is tested on a different set of patients and similar results are obtained.[136]

4.5. PET-CT Sub-study

As part of the SYSTEMS study (ISRCTN 10644347), a subgroup of patients underwent PET-CT scanning. The study was performed in the BWoSCC. The

study was approved by the institutional review board and all subjects provided written informed consent. Eligibility criteria were as per the main SYSTEMS study. Consecutive patients were recruited from May 2012 until December 2013.

All patients underwent CT-based radiotherapy planning prior to PET-CT imaging. All planning CTs were captured on LightSpeed Simulator LS RT 16 GE Medical CT scanner (GE Medical systems, Crawley, UK) using a 120kV automatic mA modulation range of 15-240mAs with 50cm Dual Field of View. Radio-opaque wire markers were positioned on the patient on the outer aspects of the painful areas to help correlate clinical and radiological findings. The Gross Tumour Volume (GTV) was defined as the volume of tumour that was felt by the clinician to be responsible for the pain. The GTV to PTV margin was 1.5cm. All patients were treated with 20 Gy in five fractions using a Varian Linear Accelerator.

Prior to undergoing PET-CT imaging, patients were fasted for at least six hours and then imaged one hour after injection of 400MBq Fluorine-18-Fluorodeoxyglucose (^{18}F-FDG). Imaging was performed using an integrated PET-CT system (Discovery-690, General Electric (GE) System, Milwaukee, WI, USA). To replicate the radiotherapy treatment position, patients were positioned supine on a radiotherapy flat bed insert and immobilised using a CIVCO posirest-2. LAP lasers were then used to position the patient centrally in the scanner. Whole body CT images were acquired using a 120kV automatic mA modulation range of 15-240mAs. The encompassed field of view was from the skull base to the upper thigh, with reconstructions performed at 2.5mm

increments. This was followed by whole body PET acquisition, encompassing the same transverse field of view as the CT. PET attenuation correction was based on the CT data and images were corrected for scatter and iteratively reconstructed using Time of Flight and SharpIR on a 192x192 matrix. All acquired images and SUV data were exported to a dedicated GE workstation (ADW 4.5) for viewing and reporting.

PET-CT images were assessed together, three months after the final patient received radiotherapy, in order to reduce recall bias. PET-CT images were transferred to a radiotherapy treatment planning system (Eclipse 10.0.42) into DICOM RT format. PET-CT images were then fused with CT planning images, termed Enhanced PET-CT (E-PET-CT). The window and level for the PET images were set according to a previously described protocol using a 7g/ml threshold.[137] To enable evaluation of whether SUV correlated with pain, maximum SUV (g/ml based on body weight) were recorded for both irradiated tumour and for tumour outwith the radiation field.

Contouring was performed by three clinicians independently. Each clinician outlined a GTV and PTV based initially on the standard radiotherapy planning CT scan. Once each clinician had contoured all patients, they were then permitted access to the E-PET-CT. At this time, each clinician re-contoured a GTV and PTV using the E-PET-CT images again for all patients.

The PET-CT scan did not influence the thoracic radiotherapy which the patients received. In order to ensure this was the case, patients had their radiotherapy

planned before they had undergone their PET-CT. It was also ensured that the patients had not started radiotherapy before having their PET-CT.

4.6. Study endpoints

4.6.1. Primary

As the primary aim of the SYSTEMS study was to examine if radiotherapy is an effective treatment for MPM, the primary endpoint was to assess if there was a clinically significant improvement in pain 5 weeks following radiotherapy. A clinically significant improvement in pain was defined as a > 30% reduction from baseline in total BPI score.[123]

4.6.2. Secondary

There were a large number of secondary endpoints, all of which were exploratory in nature. The rationale for this was to inform future randomised studies examining radiotherapy in MPM. Endpoints were assessed at weeks 1, 5 and 12 weeks post radiotherapy with the primary analysis at week 5, unless otherwise stated.

Secondary endpoints were as follows:

To examine the effect of radiotherapy on pain at weeks 1 and 12 post radiotherapy, assessed using the BPI. A clinically significant improvement in pain was defined as a > 30% reduction from baseline in total BPI score [121]

To examine the effect of radiotherapy on dyspnoea using a numerical rating scale (NRS) for dyspnoea [138]

To examine the effect of radiotherapy on mood using the HADS [139]

To examine the effect of radiotherapy on quality of life using the EORTC QLQ-C30 questionnaire (version 3.0) including lung cancer module EORTC QLQ-LC13 [135]

To examine the effect of radiotherapy on fatigue using the Fatigue Severity Scale (FSS) [134]

To examine the effect of radiotherapy on night sweats. This was assessed using an NRS for night sweats

To characterise pain in MPM using the LANSS and the MPQ[125, 127]

Quantitative Sensory Testing (QST) was performed in the West of Scotland patients to examine the somatosensory components of the index site and to identify any clinical biomarkers which may predict those more likely to respond to radiotherapy. This was performed at weeks 5 and 12 post radiotherapy and compared with baseline

To assess radiotherapy toxicity at weeks 1, 5 and 12 as per the Common Toxicity Criteria for Adverse Events (CTCAE) 4.0

To examine the effect of radiotherapy on tumour bulk. This was assessed by comparing CT scans at baseline with scans performed 12 weeks after radiotherapy

To evaluate the relationship between the systemic inflammation and symptoms (pain, mood, dyspnoea, fatigue). Inflammation was assessed using CRP

To examine if incorporating PET-CT data alters the Gross Tumour Volume (GTV) by more than 20%? (this cut off level was based on previous work and felt to be clinically significant)[140]

To examine whether SUV uptake on PET-CT imaging is suggestive of increased likelihood of response to radiotherapy

To examine whether PET-CT alters staging.

4.7. Statistical Considerations

4.7.1. Sample size calculation

The sample size was determined by the availability of patients and the fixed duration of the study. On average, in one year, 36 patients were treated with radiotherapy for pain in Glasgow and Edinburgh. Therefore, an estimate of 36 patients per year was felt to be feasible.

The study aimed to recruit 40 patients over an 18 month period. Previous experience in cancer pain trials suggests that patients are keen to participate in clinical trials, with fewer than 10% of eligible patients declining to participate.[141] It was anticipated that this would be the case, especially as this was a non-interventional study. Based on historical data, approximately 54 patients should potentially have been eligible in this period, indicating that the proposed sample size seemed achievable. An analysis of the MPM patients treated with radiotherapy in 2010 in Glasgow shows that 73% lived greater than 3 months following radiotherapy. Therefore the majority of study patients should have been able to complete all assessments.

To answer the primary endpoint, a sample size of 40 patients was calculated and this allowed the proportion of responders to be estimated within +/-15.5%, depending on the true underlying proportion. Table 5 shows the precision and corresponding 95% confidence interval (CI) limits that would be achieved for a range of proportions.

Table 5 - Proportion of responders

		95% CI	
Proportion of patients	Precision	Lower limit	Upper limit
20%	12.4%	7.6%	32.4%
30%	14.2%	15.8%	44.2%
40%	15.2%	24.8%	55.2%
50%	15.5%	34.5%	65.5%
60%	15.2%	44.8%	75.2%
70%	14.2%	55.8%	84.2%
80%	12.4%	67.6%	92.4%

4.7.2. Analysis

The primary analysis determined the proportion of patients for whom radiotherapy is an effective means of treating pain in MPM at 5 weeks post radiotherapy, where a clinically significant improvement in pain is defined as a > 30% reduction from baseline in total BPI score. The proportion of responders is presented along with the corresponding 95% CI.

4.7.2.1. PET-CT analysis

The difference in overall treatment volumes (%) between CT and E-PET-CT was assessed. The concordance in volumes (GTV) outlined between CT and E-PET-CT was calculated using the Conformity Index (CI). A CI of 1 represented

complete concordance between the CT and E-PET-CT while a value of 0 represented no concordance.[142]

CT was defined as the reference parameter and E-PET-CT was the evaluation parameter. The difference in shape of treatment areas between CT and E-PET-CT was assessed using Mean Distance to Conformity (MDC). The Centre of Gravity Distance (CGD) assessed the difference from the central point of the reference volume and the evaluation volume. The under contoured volume (UCV) was the volume that was contoured in the reference volume but not contoured in the evaluation volume and is expressed as a percentage. The over contoured volume (OCV) is the volume that is contoured in the evaluation volume that is not contoured in the reference volume and is expressed as a percentage. These parameters were calculated using ImsimQA version 3.0.77.

Patients whose pain improved following radiotherapy were defined as pain responders. A pain response was defined as a 30% drop in the BPI score 5 weeks after radiotherapy.

To facilitate analysis, parameters were averaged across the three clinicians for each patient. The comparison between E-PET-CT and CT was made using a Wilcoxon signed rank test. All analyses were performed in SPSS v22.0 (Chicago IL.). An exploratory analysis of maximum standard update value (SUV) was performed to see if there were any potential association between these values and pain response or overall survival.

4.7.2.2. Analysis for Pain Characterisation Study

A clinician completed the questionnaires with all patients and the same clinician undertook QST in order to reduce inter-observer variability.

Patient demographics and pain characteristics (MPQ, BPI) were summarised using proportions, and means and standard deviations (SDs) or medians and inter-quartile ranges (IQRs) as appropriate. BPI "average pain" and "worst pain" scores were related to the BPI interference scale using Spearman's correlation. A further analysis of the BPI interference scale was undertaken to compare those patients with, and those without, neuropathic pain, using Mann–Whitney tests.

4.7.3. Statistical Reporting

Throughout, means and SD, or medians and interquartile ranges (IQR) are used. CI are reported as 95%.

Chapter 5. Results – Is radiotherapy useful for treating pain in MPM?

5.1. Participant Disposition

The participant disposition is shown in the CONSORT diagram in Figure 13. From June 2012 until December 2013, 40 patients consented to the trial. Of these, 37 patients started radiotherapy, with 35 completing their prescribed course. All sites of pain were in the chest.

5.2. Demographics

Patient demographics are shown in

Table 6. Thirty-five patients were male and the median age (IQR) was 71.50 (65.00-76.00) years. The most common histological type of mesothelioma was epithelioid which was present in 21 patients (56.8%) and the majority of patients were PS 1 or 2. The median survival from the time of trial registration was 93 days (CI 68-118). However, this differed depending on histological subtypes - epithelioid 124 days (83-165) versus sarcomatoid 65 (37-93), p=0.04. The mean (SD) time from initial diagnosis to study entry was 249.41 days (274.16). The median (IQR) baseline BPI score was 57 (42.0-65.5) and the median (IQR) baseline opioid dose was 55mg (25-210).

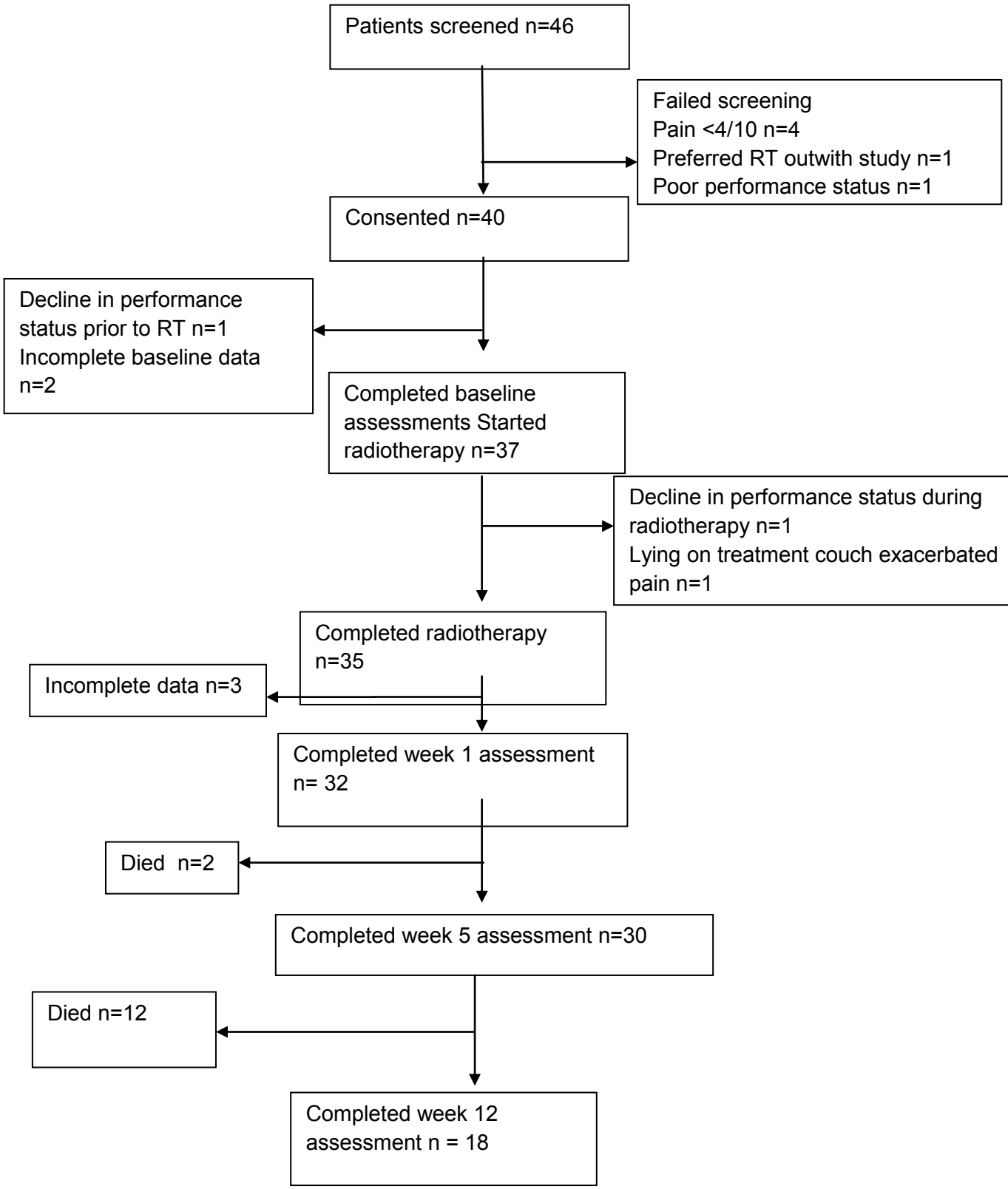


Figure 13 - Participant Disposition

Table 6 - Patient Demographics

Characteristic		n	%	Median	IQR
Male Sex		35	87.5		
ECOG					
	0	3	7.5		
	1	18	45.0		
	2	19	47.5		
Time from diagnosis to study entry (days)				127	57-356
Mesothelioma Histology	Epithelioid	21	56.8		
	Sarcomatoid	10	27		
	Mixed	3	8.1		
	Other	3	8.1		
	Not available	3			
Metastases	Present	11	28.9		
	Absent	28	71.1		
	Unknown	1			
Previous anti-cancer therapy	Chemotherapy	14	36.8		
	Radiotherapy	1***	2.5		

*SD – Standard Deviation **IQR – Interquartile Range *** Patient received port site radiotherapy

5.3. Primary Endpoint

At the time of primary endpoint assessment (week 5), 30 patients were evaluable. Three patients did not start radiotherapy, two patients failed to complete radiotherapy, two patients had died before week 5 and three further patients had deteriorated to the point that they were no longer able to complete the assessment - Figure 13.

The primary endpoint, based on an intention to treat analysis, was met by 14 patients (35%) who had a clinically significant improvement in pain 5 weeks post radiotherapy. Nine patients (22.5%) had an improvement of $\geq$ 60% in BPI score with five patients (12.5%) having a complete response (100% improvement in BPI). Therefore, based on a complete case analysis of 30 evaluable patients at week 5, 47% (CI 28.3-65.7) of patients responded to the radiotherapy. Of the 14 patients who responded to radiotherapy, eight had epithelioid histology, four had sarcomatoid and two had mixed histology. As a percentage of the total number of each of these histological subtypes, 38% of epithelioid patients responded, 40% of sarcomatoid and 66.6% of mixed histology. There was no statistically significant difference between histological subtypes in terms of response, $p>0.05$.

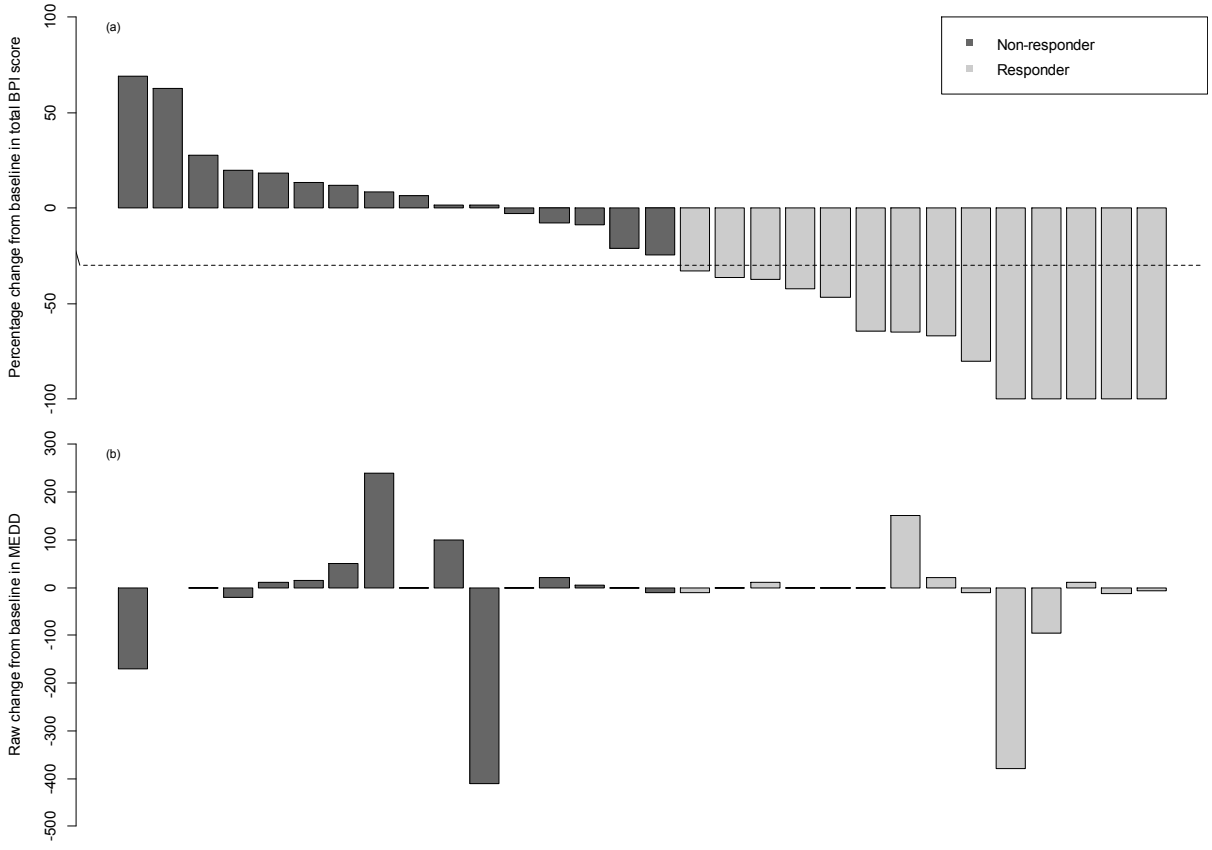
5.4. Secondary Endpoints

5.4.1. Pain Response

At weeks 1 and 12, the pain response rate was 27.5% (CI: 14-6%-43.9%) and 15.0% (CI: 5.7%-29.8%) respectively, on an intention to treat analysis. Based on a complete case analysis, the proportion of pain responders at week 1 was 36.7% (CI: 19.9%-56.1%) and at week 12 was 33.3% (CI: 13.3%-59.0). Although 32 patients completed the week 1 assessment, two of them had incomplete data and so were not evaluable. Eighteen patients were evaluable at week 12.

The changes in opioid dose and pain (BPI) per responder status is shown in figure 14.

Only four responders had an increase in their opioid dose between study baseline and endpoint, and in only one patient was this >20mg (MEDD). There was no difference in mean opioid dose between baseline and endpoint in the responders, p=0.627. There was no difference in the percentage change from baseline MEDD at week 1 (p = 0.577) or week 5 (p = 0.355) between responders and non-responders. Of the 14 responders, nine were on simple and eight on adjuvant analgesics at baseline. A similar proportion (16/24) of the non-responders were on simple analgesics at baseline. Although a slightly higher proportion (17/24) of non-responders were on adjuvant analgesics at baseline compared with responders, this was not statistically significant, p=0.391. Throughout the duration of the study, only one patient was started on an adjuvant analgesic. Therefore, the improvement in pain is likely to be due to radiotherapy rather than analgesia.



Patient number of those evaluable at week 5 (1-30)

Figure 14 – Changes in Pain/Opioid Dose following radiotherapy.

(a) Waterfall plot of percentage change from baseline to week 5 in total BPI score, and (b) corresponding raw change from baseline to week 5 in MEDD. The dotted line indicates a 30% reduction from baseline BPI score, the "response" criterion.

5.4.2. Quality of Life

There was no change in global QoL for patients throughout the study when taken as a whole group. However, there was a trend suggesting an improvement in QoL in responders and a decline in global QoL in non-responders, although this was not statistically significant. The median improvement in QoL in responders was 12.50 (IQR -16.67 – 41.67) compared with a median decline of 12.50 (IQR -25.00 – 0.00) in non-responders. In terms of specific quality of life components, there was a worsening of fatigue, appetite loss and nausea/vomiting scores. Fatigue scores at week 12 ($p = 0.040$) and nausea/vomiting at week 1 ($p = 0.017$) had significantly increased. There

were, however, improvements in pain, dyspnoea, insomnia and constipation. Pain scores at week 1 ($p = 0.005$) and 5 ($p = 0.034$) and dyspnoea at week 1 ($p = 0.037$) were significantly lower. There was no significant difference between responders and non-responders in the change in dyspnoea score at week 5 (responders: median change 0, IQR -33 to 33; non-responders: -16.67, IQR -33 to 0; $p = 0.203$). The greater improvement in non-responders may be due to the baseline dyspnoea score being higher than for responders, although not significantly so ($p = 0.148$). Only one patient had a cough which was recorded as grade 2 at all times including baseline.

5.4.3. Other Symptoms

The effect of radiotherapy on other key symptoms is shown in Table 7. There was no significant change in any other secondary endpoints with the exception of night sweats which improved by week 5 ($p=0.01$).

Table 7 - Symptom assessments between trial baseline and other timepoints

Symptom (score)	Baseline mean (SD)	Week 1		Week 5		Week 12	
		Mean (SD)	p	Mean (SD)	p	Mean (SD)	p
Dyspnoea (0-10)	4.46 (2.47)	4.19 (2.84)	0.44	5.26 (2.35)	0.09	4.95 (3.08)	0.26
Sweats (0-10)	3.44 (3.58)	3.16 (3.29)	0.22	2.00 (3.02)	0.01	1.79 (2.74)	0.43
HADS Anxiety (0-21)	5.86 (4.17)	4.90 (4.15)	0.23	5.66 (4.58)	0.85	6.41 (4.93)	0.52
HADS Depression (0-21)	6.86 (3.41)	6.97 (4.09)	0.83	7.41 (4.15)	0.30	7.65 (3.55)	0.18
Fatigue (0-63)	49.08 (11.88)	45.30 (13.71)	0.13	48.21 (11.29)	>0.99	49.00 (13.76)	0.51

5.4.4. Toxicity

In Table 8, the percentage of patients with the most common symptoms and probable side effects from radiotherapy are reported. Differentiating side effects of radiotherapy from symptoms due to disease progression is extremely difficult. Therefore, symptoms were graded at baseline and at each visit. For instance, the incidence of grade 2 dyspnoea was 45.9% at baseline and 45.5% at week 5. As can be seen from Table 8, there was no worsening in any symptoms at week 5

follow up compared with baseline. As such, it is concluded that the treatment was well tolerated with minimal toxicity. Only one patient had a delay in delivery of their radiotherapy due to radiotherapy induced odynophagia, however this patient had an apical tumour and their larynx was within the radiotherapy field. The patient had been given additional analgesia as prophylactic cover but had not taken it. On commencing the analgesia, the patient's odynophagia improved considerably and he completed the radiotherapy.

Table 8 - CTCAE Grades for selected AEs at each trial timepoint

		Baseline		Week 1		Week 5		Week 12	
		n	%	n	%	n	%	n	%
Anorexia	Grade 0/1	31	83.8%	31	83.8%	30	90.9%	17	85.0%
	Grade 2	4	10.8%	4	10.8%	3	9.1%	3	15.0%
	Grade 3	2	5.4%	2	5.4%	0	.0%	0	.0%
	Not assessed/ deceased	0	.0%	0	.0%	4	.0%	17	.0%
	Total	37	100.0%	37	100.0%	37	100.0%	37	100.0%
Dyspnea	Grade 0/1	17	45.9%	18	48.6%	14	42.4%	10	50.0%
	Grade 2	17	45.9%	17	45.9%	15	45.5%	6	30.0%
	Grade 3	3	8.1%	2	5.4%	4	12.1%	4	20.0%
	Not assessed/ deceased	0	.0%	0	.0%	4	.0%	17	.0%
	Total	37	100.0%	37	100.0%	37	100.0%	37	100.0%
Fatigue	Grade 0/1	13	35.1%	15	40.5%	12	36.4%	9	45.0%
	Grade 2	14	37.8%	14	37.8%	10	30.3%	6	30.0%
	Grade 3	10	27.0%	8	21.6%	11	33.3%	5	25.0%
	Not assessed/ deceased	0	.0%	0	.0%	4	.0%	17	.0%
	Total	37	100.0%	37	100.0%	37	100.0%	37	100.0%
Hyperhidrosis	Grade 0/1	35	94.6%	37	100.0%	31	93.9%	20	100.0%
	Grade 2	2	5.4%	0	.0%	2	6.1%	0	.0%
	Not assessed/ deceased	0	.0%	0	.0%	4	.0%	17	.0%
	Total	37	100.0%	37	100.0%	37	100.0%	37	100.0%
Pain	Grade 0/1	22	59.5%	35	94.6%	32	97.0%	18	90.0%
	Grade 2	4	10.8%	2	5.4%	1	3.0%	1	5.0%
	Grade 3	11	29.7%	0	.0%	0	.0%	1	5.0%
	Not assessed/ deceased	0	.0%	0	.0%	4	.0%	17	.0%
	Total	37	100.0%	37	100.0%	37	100.0%	37	100.0%
Pleuritic pain	Grade 0/1	27	73.0%	22	59.5%	16	48.5%	9	45.0%
	Grade 2	7	18.9%	6	16.2%	10	30.3%	6	30.0%
	Grade 3	3	8.1%	9	24.3%	7	21.2%	5	25.0%
	Not assessed/ deceased	0	.0%	0	.0%	4	.0%	17	.0%
	Total	37	100.0%	37	100.0%	37	100.0%	37	100.0%

5.4.5. CT response

Changes in disease bulk, assessed using CT, are shown in Table 9. Only 18 patients were alive and/or well enough to undergo the week 12 CT. Of these, there was only one partial response, as assessed by the modified RECIST criteria for assessment of response in MPM.[119] None of the five patients who had radiologically progressive disease had a drop in their BPI score.

Table 9 - CT response at 12 weeks evaluated as per modified RECIST 1.1

		n	%
Assessment of overall response in target lesions	CR[1]	0	0%
	PR[2]	1	2.5%
	SD[3]	13	32.5%
	PD[4]	5	12.5%
	Not evaluable	21	52.5%
	Total	40	100.0%

[1]CR – Complete Response [2]PR – Partial Response

[3]SD – Stable Disease [4]PD – Progressive Disease

5.4.6. Planning Volumes

The median Planning Target Volume (PTV) was 1046.70cm^3 (IQR 731.50-1339.90). There was no difference between the median PTV for responders - 1004.00cm^3 (IQR 585.20-1312.00) - and non-responders - 1104.85cm^3 (IQR 795.00-1356.85) suggesting the size of the PTV does not correlate with the magnitude of response. A typical radiotherapy plan is shown in Figure 15.

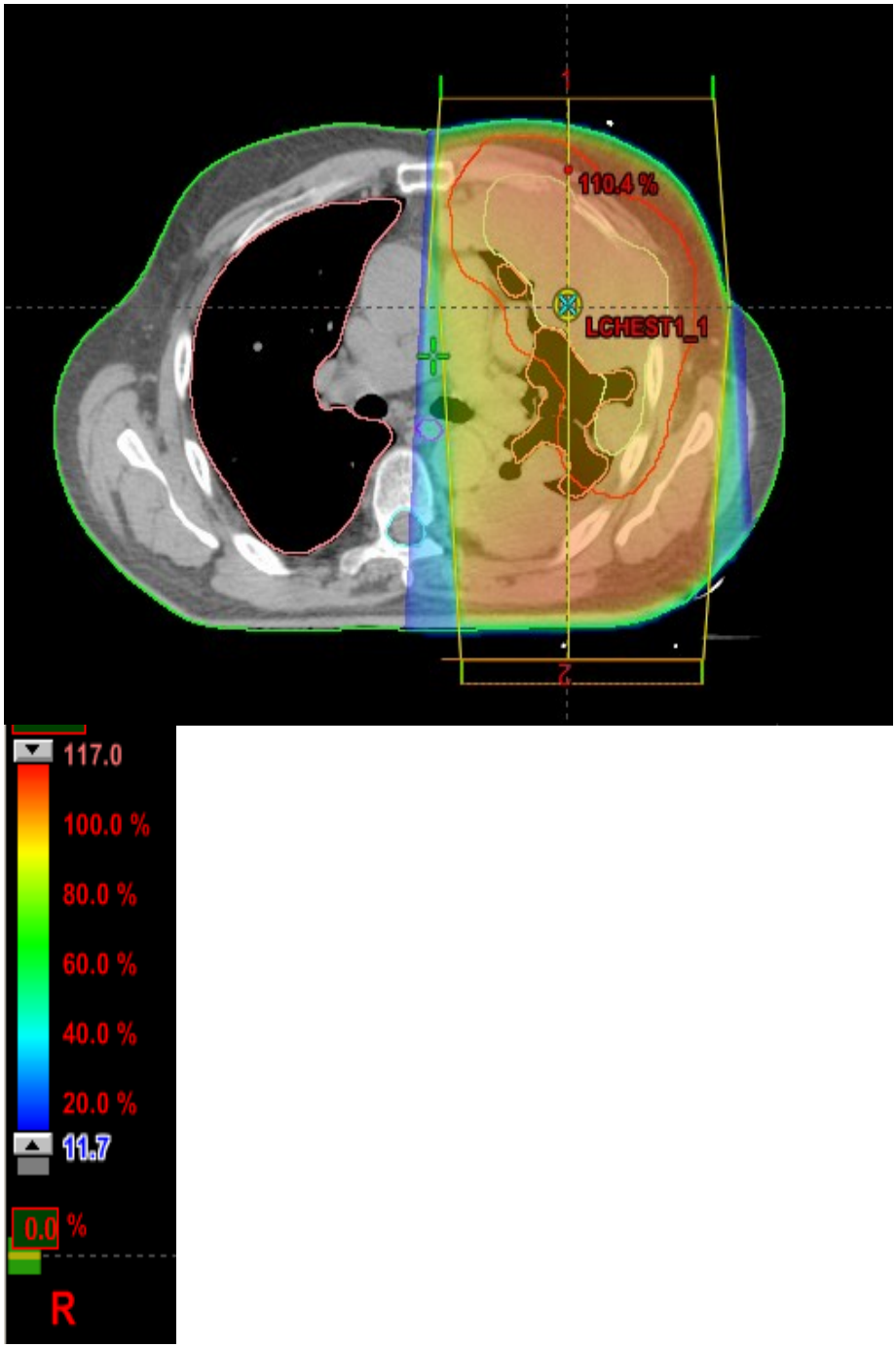


Figure 15 – Radiotherapy Plan of a patient in the SYSTEMS study taken from the radiotherapy planning system at the Beatson WoSCC

Typical radiotherapy plan showing dose distribution with parallel opposed pair beam arrangement

The median survival of responders was 106 days (IQR: 86 to 126 days). Median survival was slightly lower in non-responders at 93 days (IQR: 18 to 168 days) but the difference was not statistically significant ($p = 0.465$).

Chapter 6. Results: F-18 FDG PET-CT influences target delineation when combined with standard CT-based radiotherapy planning in malignant pleural mesothelioma

6.1. Demographics

Sixteen patients were included in this part of the study and patient characteristics are shown in Table 10. All patients had a histological diagnosis of MPM. The majority of patients were male (n=14) and the median age (IQR) was 75 years (65-79). Median survival was 4.1 months (95% CI: 2.6 months to 5.5 months) from time of study registration. One patient was excluded from the study as he had a small, palpable tumour lump that was delineated by palpation rather than by imaging. Therefore, 15 patients were included in the analysis. In all patients, there was abnormal SUV uptake in the thorax.

PET-CT resulted in upstaging of 9 of the 16 patients (56%), compared with conventional CT imaging. One patient was upstaged from T3 to T4 (6%), four patients had upstaging of nodal disease (25%) and five patients were found to have metastatic disease (31%), one of whom also had nodal upstaging. In two of these patients, this led to palliative radiotherapy being delivered, one of whom had impending spinal cord compression at the level of C5 which was above the scanning level of the staging CT, as seen in Figure 16. The bone metastases were not seen on the conventional CT of either patient.

Table 10 - Patient Demographics (N=16)

	n	%
Sex (M/F)	14/2	87.5/12.5
PS (ECOG) 0/1/2	2/9/4	13/60/27
Mesothelioma Histology		
Sarcomatoid	3	18.8
Epithelioid	11	68.8
Mixed	2	12.5
Previous Mesothelioma therapy		
Chemotherapy	5	33
Radiotherapy	0	0

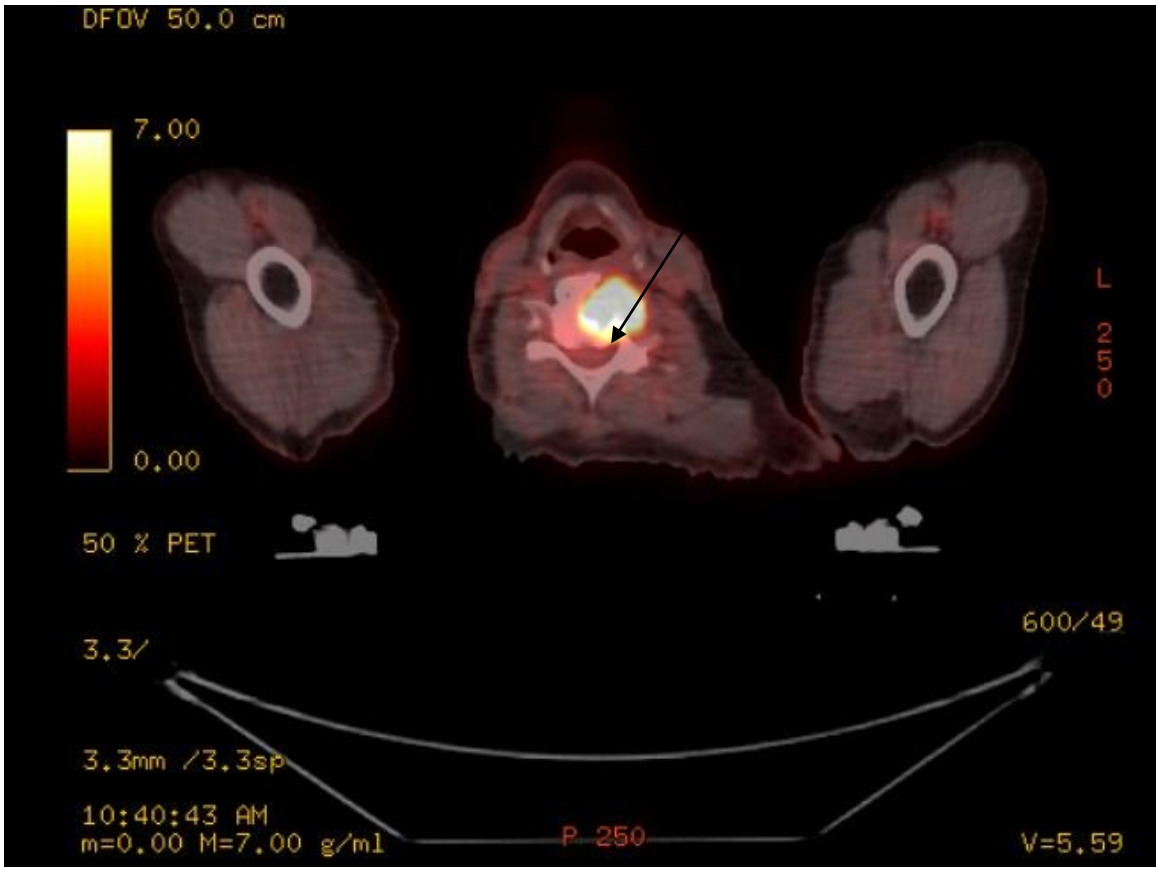


Figure 16 - PET-CT of a patient from the SYSTEMS study. Image taken from the National PACS archive. Area of spinal cord compression shown by arrow

Image showing impending spinal cord compression not seen with conventional CT

6.1.1. Volume size as delineated via CT and E-PET-CT

Differences in PTV volumes delineated using CT and E-PET-CT are shown in

Patient number (1-15)

Figure 17 In nine patients, PTV was larger when delineated using E-PET-CT compared with CT and in six patients it was smaller. Median E-PET-CT defined volume was increased by 4.14% compared with CT (IQR: -32.09% smaller to +22.25%) but this was not statistically significant (p=0.65).

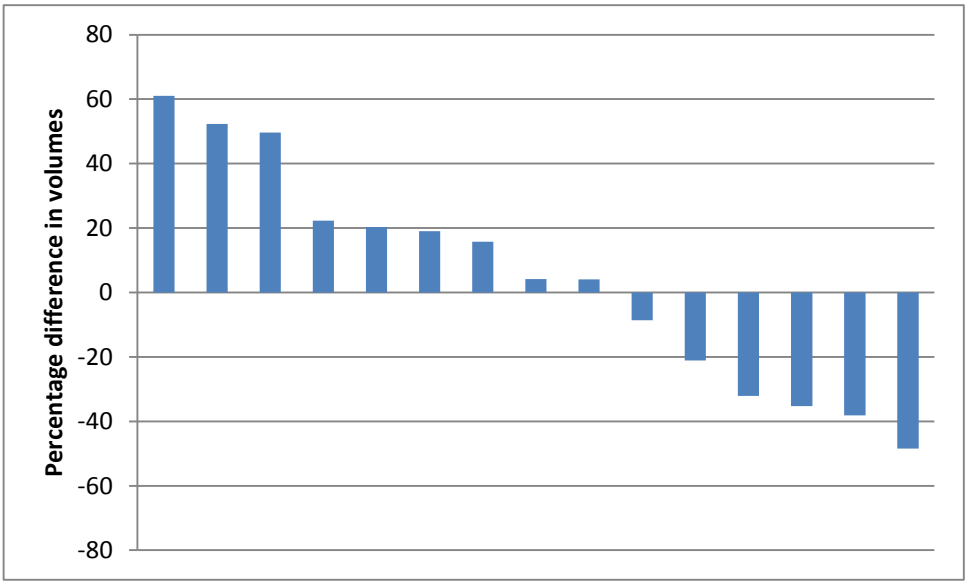


Figure 17 – Changes in Radiotherapy Planning using PET-CT

Waterfall plot of median percentage difference in volumes (%) outlined by E-PET-CT and CT. A positive difference indicates the volume outlined with E-PET-CT is greater than with CT alone (n=15)

6.1.2. Differences In Contouring Among Three Clinicians

Analysis of CI, MDC, CGD, under/over-contouring and volume mismatch is shown in

Table 11. The low value for CI (0.30) and high values for MDC (21.47mm) and CGD (16.40mm) as well as the high percentage of over- and under-contouring (44.00 and 46.67%, respectively), indicate significant discrepancies in the anatomical location of volumes outlined using CT or E-PET-CT.

Table 11 - Summary data of key parameters comparing CT alone with E-PET-CT (n=15)

Parameter* (Unit/range)	Median	IQR
CI (0-1)	0.30	0.24 - 0.38
MDC (mm)	21.47	16.73 - 33.70
Volume Difference (%)	4.14	-32.09 - 22.25
Total Volume Mismatch (%)	92.33	77.33 – 130.33
CGD (mm)	16.40	11.80 – 33.87
UC Vol (%)	44.00	34.33 – 72.50
OC Vol (%)	46.67	34.00 – 55.00

Figure 18 and Figure 19 show representative images illustrating differences in GTV contouring between individual clinicians when CT and E-PET-CT datasets were used to guide volume delineation.

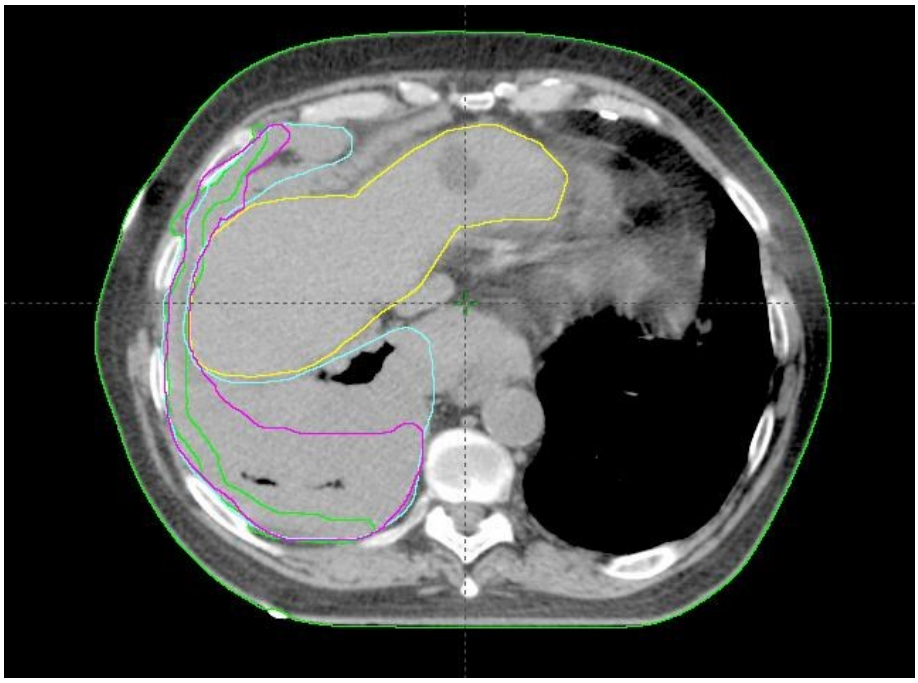


Figure 18 - CT planning in MPM. Image taken from the radiotherapy planning system at the Beatson WoSCC

Image showing the differences in GTV outlining using CT alone by 3 clinicians.

Green outline is clinician 1, pink is clinician 2 and cyan is clinician 3

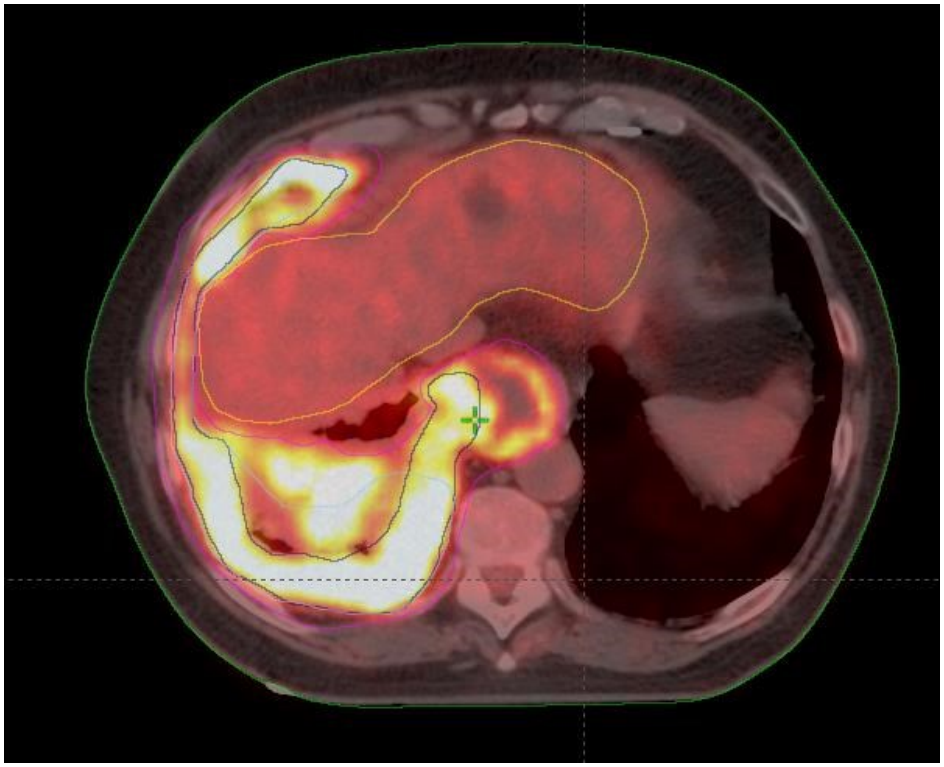


Figure 19 – E-PET-CT planning in MPM. Image taken from the radiotherapy planning system at the Beatson WoSCC

Image showing the differences in voluming using E-PET-CT by 3 clinicians. Green outline is clinician 1, pink is clinician 2 and cyan is clinician 3

6.1.3. PET-CT Analysis

At the time of PET-CT acquisition, median blood glucose concentration was 5.0 mmol/l (range 4.2-6.3). Median SUV max was 17.6 (IQR 12.5-23.0). Median survival in patients with SUV max less than 17.6 was 3.7 months (95% CO 3.3-4.1) compared with 4.1 months (95% CI 0-9.6) for patients with SUV max greater than 17.6, a difference that was not statistically significant.

There was an association between SUV max and pain with SUV max being higher in the irradiated area than the non-irradiated area. The median difference in SUV max between these areas was 4.0 (IQR 0.8-8.6), p=0.035.

Median SUV max for pain responders was 11.7 (IQR 11.7-22.1: n=5) compared with 16.7 (IQR 14.2-23.3: n=11) for non-responders. The variability and difference in group sizes makes it impossible to draw any robust conclusions about differences between responders and non-responders using SUV parameters. However, there would appear to be no obvious diference between the groups with regards to SUVmax (p=0.267).

Chapter 7. Characterisation of Pain in MPM

7.1. Demographics

Forty patients consented to the study, 37 of whom completed the baseline assessments, see

Table 6. The median age was 71.50 years (IQR 65.00-76.00) and median time from diagnosis to study entry was approximately four months (IQR 2-12). All patients were performance status 0-2. Epithelioid MPM was the most common histology, being present in 21 (56.8%) patients. Fourteen patients had completed platinum/pemetrexed based chemotherapy.

7.1.1. Analgesic Use

Analgesic use is shown in Table 12. Strong opioids were used by 32 patients (84.2%) whereas only three patients (7.9%) were on weak opioids. Twenty five patients (65.8%) were on adjuvant analgesics with the same number of patients on simple analgesics.

Table 12 - Number of patients taking each type of analgesia at baseline

Analgesia	**n**	**%**
Simple Analgesia	25	65.8
Adjuvant Analgesia*	25	65.8
Weak Opioid	3	7.9
Strong Opioid	32	84.2
Adjuvant analgesic and strong opioid	24	64.9

*14 patients on pregabalin, 8 on gabapentin, 3 on amitriptyline

7.1.2. Pain characteristics

The sensory component of the SF-MPQ is shown in Figure 20. The words most commonly chosen to describe the pain were "aching", "tender" and "sharp" being reported by 32 (86.5%), 29(78.4%) and 27(73%) of patients respectively.

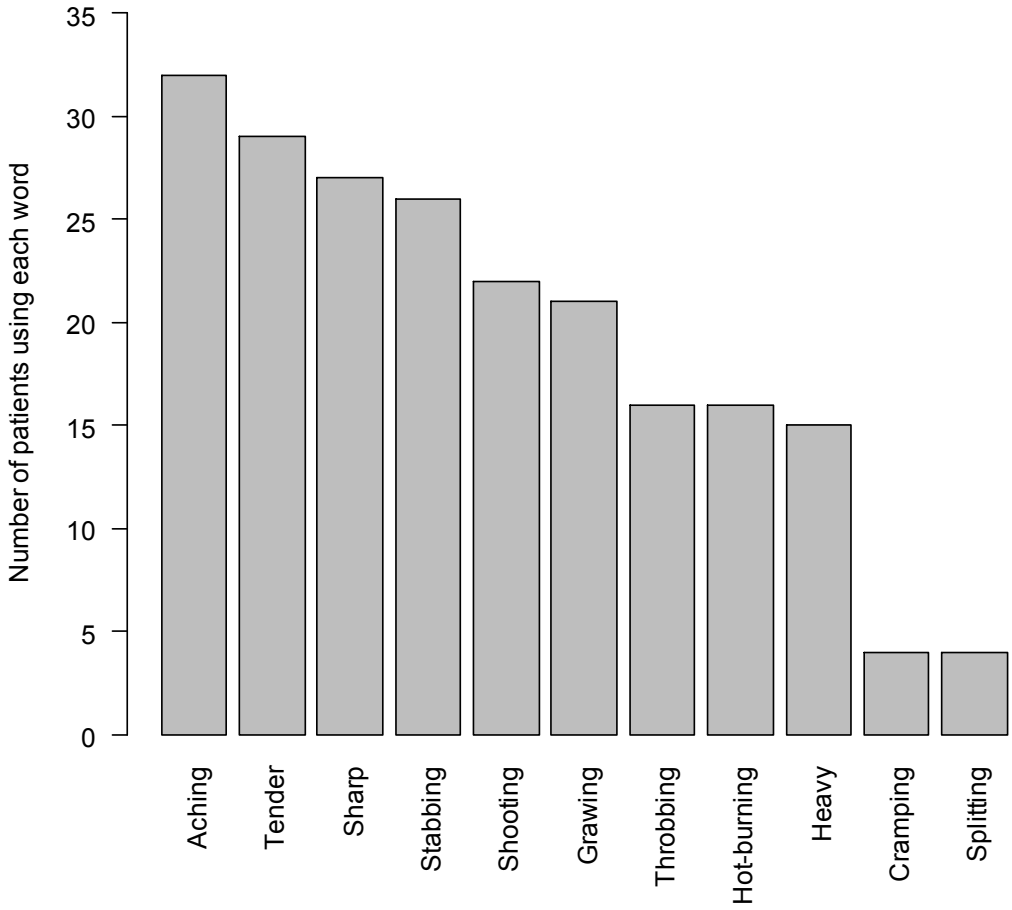


Figure 20 – SF-MPQ

Frequency of words used in the SF-MPQ (Sensory component) to describe the pain, based on 37 completed baseline questionnaires.

Figure 21 shows the individual components of the BPI. The median (IQR) for average pain and worst pain was 4 (4-6) and 8 (6-8) respectively. General activity, normal work and enjoyment of life scored the highest on the interference scores. Relationships appeared to be relatively unaffected by the pain.

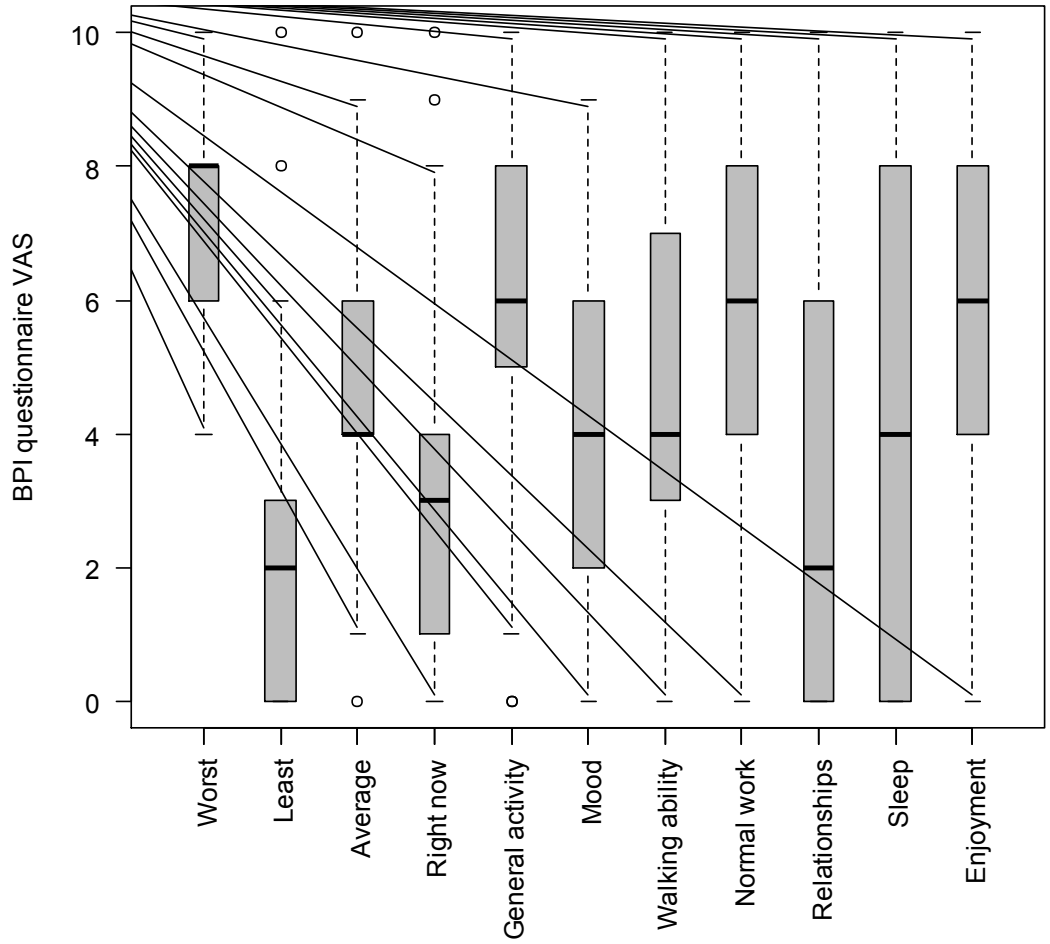


Figure 21 – BPI

Boxplots of visual analogue components from baseline BPI questionaire

Figure 22 shows scatterplots of the mean interference scores (MIS) from the BPI measured against worst pain score (WPS) and average pain score (APS) from the

BPI. The Spearman's Correlation Coefficient for the MIS from the BPI and the WPS was 0.567, p<0.001. The Spearman's Correlation Coefficient for MIS and APS was 0.556, p<0.0005. This shows a moderate positive association in worst and average pain scores with the mean interference score.

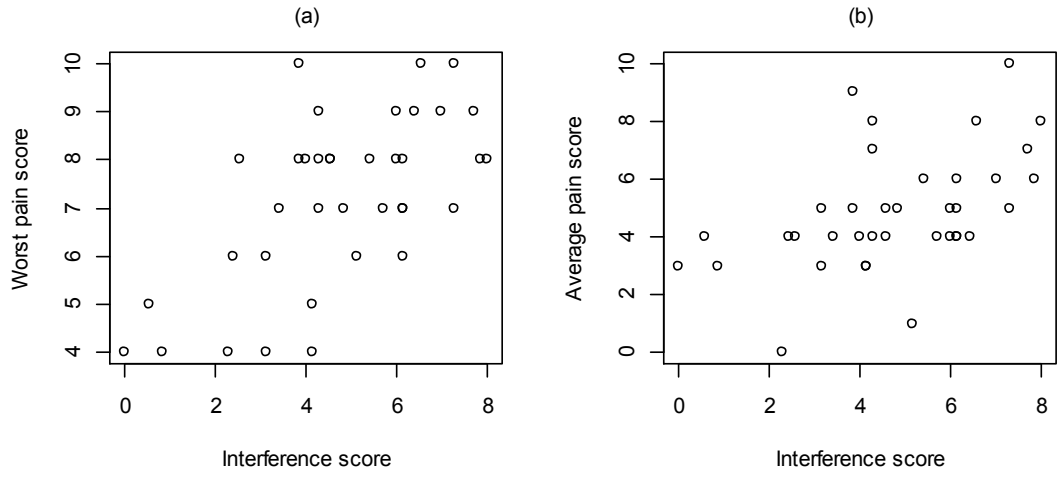


Figure 22 – Pain Score Scatterplots

Scatterplots of (a) worst pain score and (b) average pain score against interference score from baseline BPI questionnaire

7.1.3. LANSS

Eleven patients, 31.4%, had a total LANSS ≥12 while 24 (68.6%) patients, had a LANSS < 12. An analysis was performed to assess whether there was any association between total LANSS, BPI and MPQ.

The median total BPI for patients with a LANSS <12 was 52 (IQR 41.00 - 59.50) versus 69.50 (IQR 61.00 – 84.00) for patients with a LANSS ≥12, p=0.004. Similarly, comparing the LANSS with the SF-MPQ, the median SF-MPQ for those with a LANSS <12 was 10.00 (IQR 8.00 – 13.50) versus 15.00 (IQR 12.00

– 18.00) for patients with a LANSS ≥12, p=0.012. These data show that patients with a high LANSS also have a high BPI and a high SF-MPQ (see Figure 23), Spearman's correlation coefficient 0.56 (p<0.001).

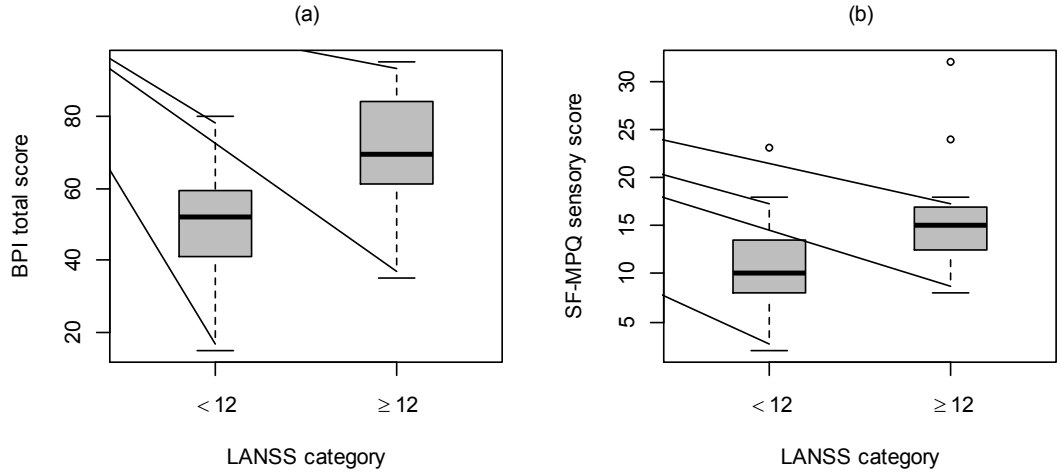


Figure 23 – Pain per LANSS category

Boxplots of (a) total BPI and (b) MPG sensory scores at baseline split by LANSS category

Response to radiotherapy was assessed looking at baseline LANSS and SF-MPQ. There was no evidence that the likelihood of response to radiotherapy is determined by the LANSS or SF-MPQ, p>0.05.

A clinical diagnosis of neuropathic pain was made in 20 patients. Of the 11 patients with a positive LANSS, eight also had a clinical diagnosis of neuropathic pain (73%). However, 11 of 24 patients with a LANSS <12 also had a clinical diagnosis of neuropathic pain (45.8%) suggesting that the LANSS may not be a particularly effective screening tool in this patient group, given the high false negative rate. Furthermore, a clinical diagnosis of neuropathic pain did not predict response to radiotherapy, with six patients with a clinical diagnosis of

neuropathic pain responding and eight patients without such a clinical diagnosis responding.

7.1.4. QST results

All QST parameters assessed in the hemithorax affected by MPM were compared to the contralateral side. These data are presented in Table 13. Sensation was assessed on the non affected side first using a brush and the result of the non affected side was regarded as normal. Sensation was then assessed on the affected side and the patient was asked whether they were more aware or less aware of the brush on this side or whether it was not different from the non affected side. If the patient was more or less aware of the brush on the affected side, this was regarded as abnormal sensation. Abnormal sensation to brush stimuli was seen in 13 patients (50%). Detection threshold was altered in 29 patients (87.9%). In terms of pain threshold, this was abnormal in n=16 (78.8%) of patients. Sensation to cold stimuli was altered in 24 of patients (75%). With regards to the warm stimuli, this was altered in 19 patients (59.4%). Pin prick sensation was abnormal in 19 (63.4%). Finally, in terms of wind up, this was abnormal in 21 (70%).

Table 13 - QST assessments of test versus control area at baseline

	Increased	Reduced	No different to control area	Missing	Total
Brush	5	8	13	14	40

	19.2%	30.8%	50.0%	-	100.0%
Detection Threshold	12 36.4%	17 51.5%	4 12.1%	7 -	40 100.0%
Pain Threshold	11 33.3%	15 45.5%	7 21.2%	7 -	40 100.0%
Cool	13 40.6%	11 34.4%	8 25.0%	8 -	40 100.0%
Warm	13 40.6%	6 18.8%	13 40.6%	8 -	40 100.0%
Pin Prick	8 26.7%	11 36.7%	11 36.7%	10 -	40 100.0%
	Present	**Absent**	**No different to control area**	**Missing**	**Total**
Wind Up	6 20.0%	15 50.0%	9 30.0%	10 -	40 100.0%

Further analyses were performed to ascertain whether there was an association between specific QST characteristics, namely pin prick, hot and cold sensation, and the scores obtained in the BPI, LANSS or MPQ. The median MPQ score in those with abnormal QST cool sensation was 12 (IQR 9.5 – 16.5) compared with a median MPQ score of 6.5 (IQR 5.0 – 11.5) in those with normal cool sensation. This was a significant difference between those two groups of patients ($p = 0.016$). There was no such relationship between MPQ and normal or abnormal hot sensation ($p = 0.697$). There was also no relationship between total BPI and any of the three selected QST assessments. With regards to the QST data and LANSS, all eight patients, in whom pin prick sensation was assessed, who had a LANSS $\geq$ 12, had abnormal pin prick sensation whereas only nine of the 20 patients (45%) with a LANSS < 12 had abnormal pin prick sensation ($p = 0.010$).

Analysis was also performed to investigate whether there were any particular QST characteristics which would suggest a higher likelihood of response to radiotherapy. Unfortunately, no such association was seen though the numbers were small.

Chapter 8. Discussion

8.1. Is Radiotherapy an effective treatment for pain in MPM?

The SYSTEMS study is the largest trial to date which examines the role of radiotherapy in MPM and the first to use validated assessment tools in this setting. The findings support the hypothesis that radiotherapy is an effective treatment for a proportion of patients with MPM related pain, with 35% of assessable patients experiencing a clinically meaningful improvement in their pain. Of these, 12.5% had a complete improvement in their pain. There were no specific features that differentiated the complete responders from the other patients though this may be due to the small number of complete responders. There was no association between pain response and improvement in any other symptoms, therefore, palliative radiotherapy in MPM should only be considered for pain control.

8.1.1. Previous Work In This Area

There is a lack of previous work in this area, with which to compare our findings, as shown in a recent systematic review.[34] The only other prospective study which has examined radiotherapy in MPM reported on 22 patients who were treated with hemi-thoracic irradiation using Cobalt-60 machines at a dose of 30 Gy in 10 fractions. Pain scores improved in 13 patients one month after radiotherapy with no increase in analgesic requirements. Validated pain assessment tools were not used in this study as none was available at the time.[33]

The findings of the present study are therefore of interest and provide evidence to support radiotherapy as a useful modality for treating pain in MPM. Of particular note is that in 12.5% of patients a complete analgesic response was recorded, providing grounds for optimism for future work in this area.

8.1.2. Specific Study Characteristics

There are certain characteristics of the study population which should be highlighted. Only 35% patients had received prior chemotherapy, which is lower than would be anticipated for patients with MPM. Also, the median age of patients in the study was 71 years compared to 60 years in previous studies examining the use of chemotherapy in MPM.[27, 28] Furthermore, an epidemiological study showed that, over a four year period, only 54 of 146 patients were considered fit for chemotherapy and of them, only 28 (18%) received chemotherapy.[29] Therefore the figure reported in the present study appears to be representative of the population from which the study patients were recruited.

The percentage of patients in the study with epithelioid histology was 56.8%. This is perhaps lower than would have been anticipated and is certainly lower than either of two phase III chemotherapy trials which showed a survival advantage for cisplatin in combination with an anti-folate agent.[27, 28] Sarcomatoid histology, seen in 27% of patients in this study compared with between 1% and 8% in the chemotherapy studies, is associated with a significantly worse prognosis than epithelioid histology.[27] This would suggest

that patients receiving radiotherapy for pain control are a very different population from those studied in previous chemotherapy trials.

Despite the improvement in pain control, there was no improvement in QoL or other symptoms, although there was a trend towards improved QoL in those who responded to radiotherapy. There may be many explanations for this: primarily, these patients are near the end of life as shown by the median survival of 3.1 months in this trial. Quality of life naturally deteriorates during this time and multiple symptoms co-exist in MPM such as dyspnoea and fatigue which are unlikely to be influenced by an improvement in pain. Similar results have been found in chemotherapy studies in MPM where no QoL improvements have been observed.[16] This may also reflect a generic problem associated with attempts to study QoL outcomes in patients with advanced cancers, in which patient attrition and general deterioration make it very difficult to detect treatment related changes in QoL.

As can be seen from the short median survival of patients in the SYSTEMS study, this is a frail population with poor life expectancy. Given that there were a number of questionnaires needing completed at each visit, it was felt to be in the patients' best interests for a study investigator to help the patient complete the questionnaires. Although this is not how these questionnaires were validated, it proved to be a most useful decision as many patients found the help provided by the study investigator to be most useful. Also, on several occasions, it became clear to the investigator that some patients were struggling to complete all the questionnaires. In these situations, the study investigator did not ask the patient

to complete all questionnaires and finished the consultation early. Had this approach not been adopted, the patient may have struggled on and put themselves under unnecessary stress in the process.

8.1.3. Study Limitations

The main limitation of the study was the small sample size. However, this was designed as a single arm observational trial and the main aim was to inform future, larger scale studies; this has been achieved. Another limitation was the very high attrition rate within the trial with only 75% of patients being evaluable five weeks after radiotherapy. This highlights the poor survival of these patients and the fact that, by the time most patients with MPM develop significant, uncontrolled chest pain, they are usually at an advanced stage of their illness. A potential limitation was the choice of radiotherapy regimen. There is no consensus on the standard radiotherapy technique for treating patients with MPM with palliative intent, so a rather conservative dose and regimen were selected because of wide use in the study centres. We cannot comment on whether pain improvement persisted beyond the twelve weeks of the study.

8.2. The role of PET-CT in radiotherapy planning in MPM

8.2.1. Main Findings

The findings from the PET-CT sub study show that incorporation of PET-CT imaging in the radiotherapy planning process alters the anatomical location of the target volume in patients with MPM. There was an association between SUV max and location of pain with the painful (irradiated) area having a higher SUV max than the non-painful (non-irradiated) area. This did not translate into

increased response rates to radiotherapy in patients with higher SUV max values. PET-CT also upstaged a large percentage of patients. In two patients this led to palliative radiotherapy being delivered to sites of painful bony disease. One of these patients had imminent spinal cord compression in the cervical spine.

8.2.2. Previous Work

Comparing our findings to previous work is difficult as, to date, only one other study has examined PET-CT in radiotherapy planning in MPM.[40] Pehlivan and co-workers examined 13 patients and outlined GTV and PTV using both CT and fused PET-CT. All target volume delineation was performed by one radiation oncologist and checked by another. The GTV comprised of macroscopic primary tumour along with involved hilar and mediastinal lymph nodes. The authors found that in 12 of the 13 patients, the GTV and PTV were significantly smaller using the fused PET-CT images – mean GTV reduction of 47.1% (+/- 28.4%). The main difference between the previous work and the present study is that we assessed palliative radiotherapy planning as opposed to radical radiotherapy which may well account for differences in the findings.

8.2.3. Implications Of Study Results

The present study increases the knowledge base in two ways. Firstly, the use of PET-CT significantly alters the location of the target volume. It is also of interest that the SUVmax was higher in the irradiated areas, which, by default, were the areas where pain was the most severe. This association had not previously been reported in lung cancer or MPM per se, however it had been demonstrated that increased SUV uptake is associated with increased pain and subsequent response

to radiotherapy in bone metastases.[143] The present study was not powered to examine whether increased SUVmax predicted increased the likelihood of response to radiotherapy, but this would be of interest in future work. Indeed PET-CT based treatment planning could be used to target all metabolically active disease, which, presumably, causes the most pain.

With regards to factors which influence SUV uptake, it has been shown that infection in patients with prosthetic hips can be readily identified via FDG PET-CT.[144] Furthermore, inflammation has been shown to be associated with increased SUV uptake.[145] No studies have looked at SUV uptake from FDG PET-CT in relation to the pathophysiology of pain.

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8.2.4. Current Role of PET-CT in MPM

PET-CT is being used with increasing frequency in MPM. It can play a role in differentiating benign from malignant lesions and help target the most suitable lesion for biopsy.[146] In addition, it has been shown to be effective in pre-operative imaging, particularly with regards to detecting distant metastases.[147, 148] Given the diffuse, infiltrative nature and asymmetric growth pattern of MPM, measuring response to treatment with CT is extremely difficult. One study looked at changes in total glycolytic volume (TGV) in PET-CT and suggested that a decrease in TGV after chemotherapy, related to a survival advantage.[109]

PET-CT can also be helpful for radiotherapy planning when there is significant atelectasis. Although contouring with PET-CT is generally smaller than with CT alone, one study did show that contouring with PET-CT can produce larger

volumes than when contouring with CT, which may be due to resolution effects.[149]

PET-CT may also be useful in estimating prognosis. For instance, the presence of metastatic disease on PET-CT has, not surprisingly, been shown to be associated with poorer survival.[150] Furthermore, one study showed that patients who had an SUV max greater than 10 had decreased survival.[151] These findings were not replicated in the present study though this may be due to the small sample size and number of survival events. It is important to emphasise that there are many factors which can influence the SUV value such as blood glucose and timing from injection of the FDG to acquisition of the images so making cross study comparisons is difficult.[152]

8.2.5. Study Limitations

The current study has limitations. As has already been mentioned, the sample size is small which is a perennial problem in rare cancers. However, this is the largest study to date looking at PET-CT in radiotherapy planning in MPM. On reviewing the size of the GTV outlined by each clinician, it became clear that there was widespread variation in contouring. This degree of subjectivity is difficult to avoid since it is not known whether covering all PET avid disease is necessary for radiotherapy to be effective in terms of reducing pain. It is not known whether treating central disease is necessary or whether radiotherapy should focus on more peripheral disease looking, for instance, for chest wall invasion or nerve root irritation.

8.3. Characterising pain in MPM

8.3.1. Main Findings

Pain is a significant problem in MPM and patients scored highly on all pain questionnaires. Pain also significantly impacted on day to day function and high levels of worst and average pain were associated with functional interference.

Pain in MPM has been reported as having a strong neuropathic component; related to its local effects on the neurovascular bundle.[153] It was of interest that in the present study, only 20 patients (54%) had a clinical diagnosis of neuropathic pain and in such patients it would be reasonable to use appropriate neuropathic agents. Pain response to radiotherapy did not appear to be affected by the presence of a neuropathic element to the pain, with a similar proportion of patients responding to radiotherapy in both groups. Of the 20 patients who had a clinical diagnosis of neuropathic pain, only eight had a positive LANSS. In addition, 11 of the 24 patients with a negative LANSS had a clinical diagnosis of neuropathic pain. Based on these data, it would appear that the LANSS is not a particularly effective screening tool for neuropathic pain in MPM.

8.3.2. Previous Work

This is the first study that characterises pain in MPM, therefore, we are unable to compare our findings with other previous work. However, similar work has been performed on cancer-induced bone pain (CIBP).[154] The work on CIBP showed that WPS was more closely correlated to MIS than APS. It is accepted that background pain in CIBP is easier to control than incident pain, but in MPM related pain, it would appear that both WPS and APS correlate with MIS,

suggesting that both background pain and incident pain are problematic in MPM patients. Therefore, the aim of analgesia should be to target both background and incident pain.

8.3.3. MPQ Descriptors

With regards to the SF-MPQ descriptors, the most commonly used words in this study were “aching”, “tender” and “sharp”. In previous work examining CIBP, the most commonly used descriptors were “dull”, “sore”, “hurting” and “heavy”.[154] This would suggest that the character of pain in MPM is different and that, in part, this may be due to its underlying complex mechanism; nociceptive and neuropathic in combination.

8.3.4. QST

QST has never been studied in MPM patients. However, it has been studied in patients undergoing palliative radiotherapy for CIBP.[112] In CIBP, the main finding was that those patients who had normalisation of abnormal warm sensation, had greater improvements in pain scores.[112] This suggests that patients who have alteration in certain sensory characteristics are more likely to respond to radiotherapy. The present study did not show that any QST parameters predicted response to radiotherapy, despite marked sensory abnormalities in the affected side, with the majority of patients having altered pinprick, warm and cool sensation, as well as altered detection threshold; however the study was not powered to assess this.

It has been demonstrated that pain in MPM improves following radiotherapy in approximately 50% of patients.[155] Whilst these findings are encouraging they do mean that many patients who are treated with radiotherapy do not get an improvement in their pain. If biomarkers were identified which predicted those patients who were more likely to respond to radiotherapy, this may allow treatment to be stratified accordingly. The present study does not identify any factors. However it was not powered for this. Future studies examining radiotherapy for the treatment of pain in MPM should include biomarker collection to allow any predictive factors to be identified.

8.3.5. Study Limitations

The small sample size is a clear limitation and thus limited inference can be made from the findings. The sample size was based on the likely availability of patients and the fixed length of the study. All of the present aims were exploratory and should be examined further in larger cohorts. Another limitation is that the LANSS is a screening tool for neuropathic pain and not diagnostic.

8.4. Future Work

The improvement in pain seen in patients in the SYSTEMS study provides grounds for optimism in this area. Future work should examine dose escalation, both in terms of total dose and dose per fraction, since the likelihood of improving outcomes by increasing dose per fraction varies among tumour types and is determined by the α/β ratio of the tumour. While rapidly proliferating squamous cell carcinomas, such as head & neck or cervical cancer, have high α/β ratios and benefit from treatment with small doses per fraction, many non-

squamous tumours with lower proliferation rates have low α/β ratios and hence benefit from higher doses per fraction.[114, 115] While there are few data from which to estimate the α/β ratio for MPM, its non-squamous histology, relatively low proliferation index, mesenchymal origin and apparent radioresistance are all consistent with a low α/β value. This approach would also have the advantage of reducing hospital visits and delivering palliative treatment in a timely fashion, which are clearly important issues in patients with limited survival.

There is increasing evidence that not all tumour types respond to multiple small radiotherapy doses and growing support for the use of hypofractionated regimes in the palliative and curative treatment of selected tumour types.[156-158] Therefore dose escalation studies, ideally delivered using advanced radiotherapy techniques (e.g. intensity modulated radiotherapy) to help provide adequate coverage of bulky areas of disease, while sparing critical normal tissues including lung and liver, would seem the obvious next step. Indeed, funding has been secured for a follow on study, SYSTEMS 2, comparing 20 Gy in 5 daily fractions with 36 Gy in 6 fractions on alternate days. The hypothesis in this study is that by increasing the dose of radiotherapy, a higher proportion of patients will experience improved pain control.

The role of PET-CT in radiotherapy planning could be researched further by looking at its potential role in radical radiotherapy planning. Radical radiotherapy in MPM is challenging given the very large fields required to cover the entire pleura and the multiple OARs which need to be considered. Given that MPM is so avid on PET-CT, this investigation could prove helpful in target

delineation. With advancing radiotherapy techniques, such as RapidArc, then delivering a radical dose of radiotherapy to the pleura may be possible.

In terms of palliative radiotherapy, it would appear that the next step would be a study looking at pain outcomes in patients who were randomised to have their radiotherapy planned with the addition of PET-CT, compared with those who had radiotherapy planned using standard CT. In the PET-CT sub study described in this thesis, the area of pain corresponded to the highest SUVmax on the PET-CT. This may help with target delineation which could subsequently result in improved palliation and pain control.

Chapter 9. Conclusion

My thesis set out to examine radiotherapy for the treatment of pain in MPM. Pain can be a major problem in this condition and is not managed particularly effectively with standard analgesics. Some patients continue to experience severe pain despite intensive palliative medicine input and are often referred for non pharmacological pain interventions. Radiotherapy is one such intervention for this pain but a strong evidence base for this is lacking. Most studies in this setting are retrospective and no consensus can be reached, based on the currently available data, as to the optimal dose and fractionation that should be delivered. Given the huge variety in reported response, prior to the SYSTEMS study, it was not possible to give an accurate estimate as to the likelihood of symptomatic benefit.

With the high incidence of MPM in the West of Scotland, it seemed appropriate that a study looking at radiotherapy for pain control in this population should be based in this geographical area. However, conducting such a study in MPM patients is challenging for a variety of reasons, not least because of the poor functional status of the patients. Furthermore, radiotherapy for pain control is not standardised with confusion as to whether large treatment fields should be used with the risk of increased toxicity or treating smaller areas with the risk of not treating the area of disease that is causing the pain. In addition, by the time most patients with MPM develop severe pain, they are often approaching the final stages of their lives which again makes conducting a study in this group of patients difficult. Despite these challenges, the SYSTEMS study recruited successfully and is the largest prospective study ever conducted in this

population. The study showed that palliative radiotherapy can be an effective method of treating pain in MPM, and, in a proportion of patients, can be associated with dramatic improvements in pain. The use of wire markings in the radiotherapy planning stage proved highly successful at helping to localise the area of tumour to be targeted, and helped to confirm that large fields are not necessarily required for patients to obtain symptomatic benefit. These findings provide a foundation for current practice and highlight that radiotherapy studies in advanced cancers and complex tumours such as MPM are feasible.

The PET-CT sub study also provided useful data. Disease was PET avid in all patients and PET-CT improves multiple parameters in radiotherapy planning, compared to CT alone, including the conformity index and the centre of gravity distance. PET-CT also resulted in upstaging in a significant percentage of patients and should be considered as a staging investigation prior to any radical treatment.

Funding has been secured from the June Hancock Mesothelioma Research Fund (£249,932) for a dose escalation study. It was hoped that the work within this thesis would inform future work in MPM and this aspect is being realised. Improving the care of patients with mesothelioma remains a priority and it is hoped that the research presented within this thesis has moved the research agenda forward.

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Publications resulting from this work

MacLeod N, Chalmers A, O'Rourke N, Moore K, Sheridan S, McMahon L, Bray C, Stobo J, Price A, Fallon M, Laird B. Is radiotherapy useful for treating pain in mesothelioma? A phase II trial. Journal of Thoracic Oncology 2015

MacLeod N, Price A, O'Rourke N, Fallon M, Laird B. Radiotherapy for the treatment of pain in malignant pleural mesothelioma: A systematic review. Lung Cancer (2013), http://dx.doi.org/10.1016/j.lungcan.2013.11.004

MacLeod N, Stobo J, O'Rourke N, Hicks, Moore K, Sankaralingam M, Oommen K, Bray C, McMahon L, Poon FW, Han S, Findlay C, Chalmers A, Fallon M, Laird B F-18 FDG PET-CT versus standard CT in radiotherapy planning in malignant pleural mesothelioma; an exploratory study. Reports of Radiotherapy and Oncology 2015. DOI:10.17795/rro-3999

MacLeod N, Klepstad P, Fallon M, Laird B. Pain management in mesothelioma. Journal of Palliative care & Medicine 20155(4) http://dx.doi/10.4172/2165-7386.1000223

Awaiting Publication

Pain in malignant pleural mesothelioma: a prospective characterisation study. **MacLeod N**, Bray C, Stobo J, Fallon M, Laird B. Paper submitted to Cancer Pain and Palliative Care. Resubmitted January 2016 following reviewers' comments

Appendix 1 – Literature Search

Database: **Ovid MEDLINE(R) <1946 to February Week 1 2013**>

Search Strategy:

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1 (tumour$ and pleura).tw. (526)

2 (tumour$ and peritoneum).tw. (317)

3 (tumour$ and pericardium).tw. (157)

4 mesothelioma.tw. (9750)

5 (1 or 2 or 3) and 4 (201)

6 (pleura$ and neoplasm$).tw. (1318)

7 4 and 6 (370)

8 exp Pleural Neoplasms/ (10417)

9 4 and 8 (4509)

10 exp Mesothelioma/ (10661)

11 mesothelioma$.tw. (10535)

12 5 or 7 or 9 or 10 or 11 (12725)

13 exp Radiotherapy/ (127441)

14 exp Radiation Oncology/ (2291)

15 (thoracic$ and radiotherap$).tw. (2223)

16 (thoracic$ and radiation$).tw. (2594)

17 (radiation and therap$).tw. (68794)

18 13 or 14 or 15 or 16 or 17 (170438)

19 12 and 18 (491)

20 exp mesothelioma/ (10661)

21 exp Pleural Neoplasms/ (10417)

22 ((pleur$ or mesothelioma$) adj2 (malignan$ or tumor$ or tumour$ or oncolog$ or neoplas$ or cancer$ or carcinom$)).ti,ab. (9214)

23 mesothelioma$.ti,ab. (10535)

24 21 and 23 (4755)

25 20 or 22 or 23 or 24 (15547)

26 exp Radiation Oncology/ or exp Radiotherapy/ (128695)

27 rt.fs. (149152)

28 (radiotherap$ or irradiat$ or radiation$).ti,ab. (392148)

29 26 or 27 or 28 (464267)

30 exp palliative care/ or exp terminal care/ or exp hospice care/ or exp hospices/ (72184)

31 (palliative adj2 care).ti,ab. (11827)

32 (end adj2 life).ti,ab. (9501)

33 (palliat$ or EOLC or dying).ti,ab. (62722)

34 (terminal$ adj2 (ill$ or patient$ or care)).ti,ab. (8723)

35 30 or 31 or 32 or 33 or 34 (112246)

36 25 and 29 and 35 (163)

37 19 or 36 (572)

38 limit 37 to (english language and humans) **(462)**

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Database: **Embase <1974 to 2013 February 05>**

Search Strategy:

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1 (tumour* and pleura).tw. (743)

2 (tumour* and peritoneum).tw. (469)

3 (tumour* and pericardium).tw. (228)

4 mesothelioma.tw. (12671)

5 (1 or 2 or 3) and 4 (291)

6 (pleura* and neoplasm*).tw. (1732)

7 4 and 6 (486)

8 exp pleura tumor/ (9767)

9 4 and 8 (4949)

10 exp mesothelioma/ or exp malignant mesothelioma/ or exp pleura mesothelioma/ (15572)

11 mesothelioma*.tw. (13676)

12 5 or 7 or 9 or 10 or 11 (17636)

13 exp radiotherapy/ (345183)

14 (thoracic* and radiotherap*).tw. (3381)

15 (thoracic* and radiation*).tw. (3993)

16 (radiation and therap*).tw. (96734)

17 13 or 14 or 15 or 16 (382277)

18 12 and 17 (1208)

19 exp mesothelioma/ or exp malignant mesothelioma/ or exp pleura mesothelioma/ (15572)

20 exp pleura tumor/ (9767)

21 ((pleur* or mesothelioma*) adj2 (malignan* or tumor* or tumour* or oncolog* or neoplas* or cancer* or carcinom*)).ti,ab. (12294)

22 mesothelioma*.ti,ab. (13676)

23 20 and 22 (5209)

24 19 or 21 or 22 or 23 (21484)

25 exp cancer radiotherapy/ or exp radiotherapy/ (345183)

26 (radiotherap* or irradiat* or radiation*).ti,ab. (526381)

27 rt.fs. (231732)

28 25 or 26 or 27 (698149)

29 exp palliative therapy/ or exp terminal care/ or exp hospice care/ or exp hospice/ (92654)

30 (palliative adj2 care).ti,ab. (17191)

31 (end adj2 life).ti,ab. (12740)

32 (palliat$ or EOLC or dying).ti,ab. (85063)

33 (terminal$ adj2 (ill$ or patient$ or care)).ti,ab. (10812)

34 29 or 30 or 31 or 32 or 33 (145579)

35 24 and 28 and 34 (323)

36 18 or 35 (1332)

37 limit 36 to (human and english language) **(1007)**

Database: **Central**

#1 MeSH descriptor: [Mesothelioma] explode all trees 82

#2 mesothelioma:ti,ab,kw (Word variations have been searched) 140

#3 #1 or #2 140

#4 MeSH descriptor: [Radiotherapy] explode all trees 4505

#5 radiotherapy:ti,ab,kw (Word variations have been searched) 9707

#6 #4 or #5 10488

#7 #3 and #6 16 (13 of which were in CENTRAL database)

CENTRAL -- 11 , of which we chose **0**

Appendix 2 – CTRad Review

Title of Proposal: Radiotherapy for the Treatment of Mesothelioma Symptoms Study (RTMSS)	
Researchers: Nicolas MacLeod, Barry Laird, Anthony Chalmers, Noelle O'Rourke, Glasgow	
Does the proposal address an important question? Is it timely? Is it a priority?	Yes. Whilst this is an important pragmatic trial design it could be more ambitious. Yes. Significant unmet need. Yes.
Are the aims achievable? Methodologically strong? Practically feasible?	Yes. Perhaps there is scope for more ambitious aims? The use of QST is novel and interesting. Might be worth considering addition of QoL analysis to BPI scoring. BPI scores could be taken more frequently. RT regimen should be standardised (ie 20 Gy/5F or 30 Gy/10F). Not clear why there needs to be a 6 week wash-out period from prior chemotherapy. Not clear that CT-planned palliative RT to 20 Gy in 5F would be generalisable in follow-on studies. Localisation of the component of pleural disease that causes pain may be difficult. Yes. Recruitment at 40 patients over 18 months should be achievable in these centres (Glasgow and Edinburgh).
Are there ways in which this project could be improved? Translational research? Imaging?	See comments above. There are plans for tissue collection, but they appear to have no discernable connection to the main study. For response only.
Is it potentially fundable? If so what is the best target funding committee / funder?	Yes. Mesothelioma-specific charity?
What needs to be done next?	Clarify issues above and re-discuss through CTRad Workstream 3 Grading: Amber

Appendix 3 – Funding

The June Hancock Mesothelioma Research Fund

Dr Barry J A Laird
Clinician Scientist in Palliative Medicine
The University of Edinburgh

18 December 2011

Dear Dr Laird,

The Brother Peter Clinical Fellowship

An evaluation of radiotherapy in the treatment of symptoms in malignant pleural mesothelioma (RTMSS)

The June Hancock Mesothelioma Research Fund (JHMRF) is pleased to award the Brother Peter Clinical Fellowship to Dr Nicholas MacLeod to support an MD study under the supervision of Dr Barry Laird and Professor Anthony Chalmers. On behalf of the Board of Trustees I am therefore delighted to confirm the allocation of £74,800 over two years to employ Dr MacLeod as a Research Fellow from 01 March 2012 (subject to the employment conditions of the University of Edinburgh being met).

The JHMRF gratefully acknowledges the cooperation of the Beatson West of Scotland Cancer Centre in supporting this award.

Building research capacity in supportive and palliative care in mesothelioma is a high priority for the JHMRF. The trustees wish Dr MacLeod every success with his project, and look forward to receiving an update on progress in due course.

With kind regards.

Yours sincerely,

Dr. K. M. Hill

Trustee

The June Hancock Mesothelioma Research Fund is a UK registered charity
Registration number: 1121784

Acute Services Division

Regional Services Directorate

The Beatson Oncology Centre Fund
The Beatson West of Scotland Cancer Centre
1st Floor Tom Wheldon Building
1053 Great Western Road
GLASGOW
G12 0YN

Tel 0141 301 7694
Fax: 0141 301 7692
Email: janet.grove@ggc.scot.nhs.uk

NHS Greater Glasgow and Clyde

THE beatson WEST OF SCOTLAND CANCER CENTRE

Dr Barry Laird
Edinburgh Cancer Research Centre (CRUK)
Western General Hospital
Crewe Road
EDINBURGH
EH4 2XR

Date : 6 January 2012
Your Ref :
Our Ref : AGR/JG

Dear Dr Laird Barry

Your application to the Beatson Oncology Centre Fund for funding to support the RTMSS Study was considered by the Finance Committee. It was agreed that the Fund would allocate the amount of £74,800 to support two years, commencing on 1 March 2012. The funds allocated are to partially support the salary of Dr Nicholas MacLeod.

Yours sincerely

Gerry

A G Robertson
Chairman

Delivering better health

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40368

25 February 2016

Dr Barry Laird

Institute of Genetics and Molecular Medicine

University of Edinburgh

Edinburgh Cancer Research Centre

Western General Hospital, Crewe Road South

Edinburgh EH4 2XR

Dear Dr Laird

I am pleased to confirm the award of a British Lung Foundation research grant as detailed below.

The grant is subject to our Grant Regulations and Conditions, dated June 2011, as enclosed. Any changes to these will be advised and it is your responsibility and that of the Host Institution to take appropriate action to comply with these changes.

Grant Holder(s):

i) Principal Grant Holder: **Dr Barry Laird**

ii) Co-Grant Holder(s): **Dr Nicholas Macleod, Prof Anthony Chalmers, Dr Noelle O'Rourke, Prof Allan Price, Prof Marie Fallon, Dr F W Poon and Dr Kevin Blyth**

Title of Research: **An examination of [F-18]-fluoro-deoxy-glucose Positron Emission Tomography Computed Tomography (PET-CT) in radiotherapy planning and assessing treatment response in malignant pleural mesothelioma**

Type of Award:	Duration:	Amount awarded:
Asbestos Pump-Priming Grant	**16 months**	**£24,631**

Grant take-up

Before the grant may be activated we must have received:

i) The Acceptance Form attached to this letter signed by you as Principal Grant Holder and on behalf of: Dr Nicholas Macleod, Prof Anthony Chalmers, Dr Noelle O'Rourke, Prof Allan Price, Prof Marie Fallon, Dr F W Poon and Dr Kevin Blyth

ii) The Acceptance Form attached to the Award of Grant Letter dated 25 February 2016 which has been sent to your finance officer/bursar, signed on behalf of the Host Institution.

iii) If applicable, a copy of the written approval(s) from the Host Institution's Ethical Committee(s) and details of the relevant Home Office Licences – see paragraph 11 of the Regulations.

You are asked to give the start date of the project on the Acceptance Form and your attention is drawn to paragraph 2 of the Regulations with regard to delays in starting your research.

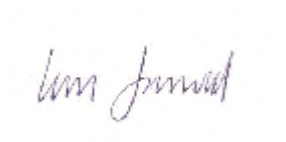
Claims for re-imbursement under the grant should be made by your finance officer/bursar in accordance with paragraph 5 of the Regulations, quoting the

grant reference number **APP12-12.** This reference number should be quoted in all correspondence relating to this grant.

Finally, apart from funding research, the BLF is committed to providing information and support to people with lung disease and it is very important for our supporters to receive feedback about the research we are funding. I would therefore like to draw your attention particularly to paragraphs 13-16 of the Regulations.

I look forward to hearing from you.

Yours sincerely,



Ian Jarrold

Head of Research

Appendix 4 – Ethics Approval and Consent Form

WoSRES
West of Scotland Research Ethics Service

NHS
Greater Glasgow and Clyde

West of Scotland REC 3
Ground Floor – The Tennent Institute
Western Infirmary
38 Church Street
Glasgow G11 6NT
www.nhsggc.org.uk

Dr Barry Laird
Clinician Scientist and Honorary consultant
Edinburgh University
Institute of Genetics and Molecular Medicine
Edinburgh Cancer Research Centre (CRUK)
Western General Hospital
Edinburgh
EH4 2XR

Date 8th June 2012
Your Ref
Our Ref
Direct line 0141 211 2123
Fax 0141 211 1847
E-mail Liz.Jamieson@ggc.scot.nhs.uk

Dear Dr Laird

Study title: **Symptom Study of Radiotherapy in Mesothelioma Study: A single arm phase II**
REC reference: **12/WS/0134**

Thank you for your letter of 06 June 2012, responding to the Committee's request for further information on the above research and submitted revised documentation.

The further information has been considered on behalf of the Committee by the Vice Chair. The Vice Chair agreed that the recruitment process as outlined in your response to the Provisional Opinion letter was a sensible approach for this patient group.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Covering Letter		08 May 2012
GP/Consultant Information Sheets	1	02 May 2012
Investigator CV		06 May 2012
Other: Study Visit Summary	1	02 May 2012
Other: CV Student - Dr NJL Macleod		03 May 2012
Other: CV Student - Dr A Chalmers		03 May 2012
Participant Consent Form: with Tracked Changes	2	05 June 2012
Participant Information Sheet: with Tracked Changes	2	05 June 2012
Participant Information Sheet: Clean on Headed Paper	2	05 June 2012
Protocol	1	03 May 2012
REC application		08 May 2012
Response to Request for Further Information		06 June 2012

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

12/WS/0134 **Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely

Liz Jamieson

Liz Jamieson
Committee Co-ordinator
On behalf of Eoin MacGillivray, Vice Chair

Enclosures: "After ethical review – guidance for researchers"

Copy to: *Dr Nathaniel Brittain, R&D - NHS Greater Glasgow and Clyde*

Acute Services Division

Regional Services Directorate

NHS Greater Glasgow and Clyde

PATIENT CONSENT FORM

Study number:

Patient identification number for this trial:

SYSTEMS: Symptom Study of Radiotherapy in Mesothelioma

Name of researcher: Dr *Nicholas MacLeod*

	Please initia
1. I confirm that I have read and understood the information sheet for the study (Version 4 dated 09 Jan 2013) and have had the opportunity to ask questions.	☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving reason, without my medical care or my legal rights being affected.	☐
3. I agree that relevant sections of any of my medical notes and data collected during the study, may be looked at by responsible individuals from the Cancer Research UK Clinical Trials Unit (Glasgow), the trial sponsors and the regulatory authorities where it is relevant to my taking part in research and for audit and monitoring purposes. I give permission for these individuals to have access to my records.	☐
4. I understand that my GP will be informed of my participation in the study and will be updated of my progress whilst on the study.	☐
5. I agree to 2 additional blood samples being taken and analysed to measure inflammatory response.	☐
6. **(OPTIONAL)** I agree to an additional 2 blood samples being taken, processed and sent to USA to be analysed to measure 'mesothelioma signature' and also screen for novel biomarkers.	☐
7. **(OPTIONAL)** I agree to an additional pre treatment PET-CT scan to assess the role of PET-CT in radiotherapy planning.	☐
8. I agree to undertake Quantitative Sensory Testing to assess the level of my pain.	☐
9. I agree to take part in the study, which is to assess if radiotherapy treatment is beneficial in treating pain and other symptoms in malignant pleural mesothelioma.	☐

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Name of patient	Date	Signature
Name of person taking consent (if different from researcher)	Date	Signature
Researcher	Date	Signature

Copies: 1 for patient; 1 for researcher; 1 to be kept with hospital notes

Appendix 5 - Questionnaires

CANCER RESEARCH UK Clinical Trials Unit, Glasgow	**L141 (SYSTEMS)** **PATIENT QUESTIONNAIRE BOOKLET**
Symptom Study of Radiotherapy in Mesothelioma Study: A single arm phase II	
PATIENT INITIALS: *(forename)* ____ *(surname)* ____	**DATE of BIRTH:** __ / ____ / ____
TRIAL NUMBER:	**CHI/NHS NUMBER:**
WEEK NO ***Please tick as appropriate*****:**	☐**BASELINE, date:** __ / ____ / ____ ☐**WEEK 1, date:** __ / ____ / ____ ☐**WEEK 5, date:** __ / ____ / ____ ☐**WEEK 12, date** __ / ____ / ____

Please tick to when each questionnaire has been completed:	
Brief Pain Inventory	
LANSS	
MPQ	
HADS	
EORTC QLQ C-30 & LC13	
FSS	
NRS Dyspnoea & NRS night sweats	

STUDY ID #: L141 DO NOT WRITE ABOVE THIS LINE HOSPITAL #: _____

Brief Pain Inventory (Short Form)

Date: ____/____/____ Time: _____

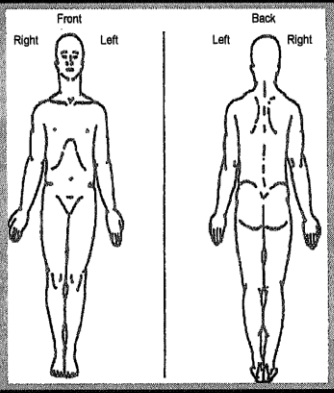
Name: _____ _____ _____

Last First Middle Initial

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

CTU Version 1: 12.07.12
Please return completed form to: CRUK Clinical Trials Unit, Level 0, The Beatson West of Scotland Cancer Centre, 1053 Great Western Road, Glasgow, G12 0YN.

STUDY ID #: L141 DO NOT WRITE ABOVE THIS LINE HOSPITAL #: _____

Date: ___/___/____ Time: _____

Name: _____ _____ _____

Last First Middle Initial

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
No Relief — Complete Relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely Interferes

B. Mood

0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely Interferes

C. Walking Ability

0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely Interferes

D. Normal Work (includes both work outside the home and housework)

0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely Interferes

E. Relations with other people

0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely Interferes

F. Sleep

0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely Interferes

G. Enjoyment of life

0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely Interferes

Page 2 of 2

MCGILL SHORT FORM PAIN QUESTIONNAIRE

Initials (forename, surname): ___ ___ Today's Date:___/___/_____

This abbreviated version of the McGill Pain Questionnaire (SF-MPQ) consists of 15 descriptors (11 sensory; 4 affective) which are rated on an intensity scale as 0 = none, 1 = mild, 2 = moderate or 3 = severe. In this study only the sensory component of the SF-MPQ are used as these are specific for neuropathic pain. This validated tool is useful in this situation where the standard MPQ would take a considerable time to administer yet data is desirable.

I. Pain Rating Index (PRI):

These words below describe pain in the past 24 hours. Please place a check mark (√) in the column that represents the degree to which you feel that type of pain.

	None		Mild		Moderate		Severe
Throbbing							
Shooting							
Stabbing							
Sharp							
Cramping							
Gnawing							
Hot-Burning							
Aching							
Heavy							
Tender							
Splitting							

THE LANSS PAIN SCALE

Leeds Assessment of Neuropathic Symptoms and Signs Pain Scale

Initials (forename, surname): ___ ___ Today's Date:___/___/_____

This pain scale can help to determine whether the nerves that are carrying your pain signals are working normally or not. It is important to find out in case different treatments are needed to control your pain.

A. PAIN QUESTIONNAIRE (to be completed by patient)

- Think about how your pain has felt over the last week.
- Please say whether any of the descriptions match your pain exactly by ticking either the NO or YES box for each question.

1) Does your pain feel like strange, unpleasant sensations in your skin? Words like prickling, tingling, pins and needles might describe these sensations.

a) NO – My pain doesn't really feel like this ☐ (0)

b) YES – I get these sensations quite a lot ☐ (5)

2) Does your pain make the skin in the painful area look different than normal? Words like mottled or looking more red or pink might describe the appearance.

a) NO – My pain doesn't affect the colour of my skin ☐ (0)

b) YES – I've noticed that the pain does make my skin look different from normal .... ☐ (5)

3) Does your pain make the affected skin abnormally sensitive to touch? Getting unpleasant sensations when lightly stroking the skin, or getting pain when wearing tight clothes might describe the abnormal sensitivity.

a) NO – My pain doesn't make my skin abnormally sensitive in that area ☐ (0)

b) YES – My skin seems abnormally sensitive to touch in that area ☐ (3)

4) Does your pain come on suddenly and in bursts for no apparent reason when you're still? Words like electric shocks, jumping and bursting describe these sensations.

a) NO – My pain doesn't really feel like this ☐ (0)

b) YES – I get these sensations quite a lot ☐ (2)

5) Does your pain feel as if the skin temperature in the painful area has changed abnormally? Words like hot and burning describe these sensations.

a) NO – I don't really get these sensations ☐ (0)

b) YES – I get these sensations quite a lot ☐ (1)

B. SENSORY TESTING (to be completed by Clinician)

Skin sensitivity can be examined by comparing the painful area with a contra lateral or adjacent non-painful area for the presence of allodynia and an altered pin-prick threshold (PPT).

1) **ALLODYNIA**

Examine the response to lightly stroking cotton wool across the non-painful area and then the painful area. If normal sensations are experienced in the non-painful site, but pain or unpleasant sensations (tingling, nausea) are experienced in the painful area when stroking, allodynia is present.

a) NO – normal sensation in both areas..... ☐ (0)

b) YES – allodynia in painful area only..... ☐ (5)

2) **ALTERED PIN-PRICK THRESHOLD**

Determine the pin-prick threshold by comparing the response to a 23 gauge (blue) needle mounted inside a 2 ml syringe barrel placed gently on the skin in a non-painful and then painful areas.

If a sharp needle prick is felt in the non-painful are, but a different sensation is experienced in the painful area e.g. non/blunt only (raised PPT) or a very painful sensation (lowered PPT), an altered PPT is present.

If a pinprick is not felt in either area, mount the syringe onto the needle to increase the weight and repeat.

a) NO – equal sensation in both areas ..... ☐ (0)

b) YES – altered PPT in painful area ..... ☐ (3)

SCORING:

Add values in parentheses for sensory description and examination findings to obtain overall score.

TOTAL SCORE (maximum 24) ..... ☐

If score <12, neuropathic mechanisms are **unlikely** to be contributing to the patient's pain
If score >12, neuropathic mechanisms are **likely** to be contributing to the patient's pain

DATE *(dd/mon/yyyy)* _____ INVESTIGATOR'S SIGNATURE _____

HOSPITAL ANXIETY AND DEPRESSION SCALE (HADS)

Initials (forename, surname): ___ ___ **Today's Date:**____/____/_____

This 14 question score has been used extensively in cancer studies and validated thus. It can be completed either by the patient or with the assistance of study staff. A combined score of 20 or more suggests a diagnosis of depression.

Instructions:

This questionnaire is designed to assess how you feel. Read each item and tick the box of the reply which comes closest to how you have been feeling **in the past week.** Please tick only one reply for each item.

Don't take too long over your replies: your immediate reaction to each item will probably be more accurate than a long thought out response.

I feel tense or 'wound up':

- Most of the time
- A lot of the time
- Time to time, occasionally
- Not at all

I still enjoy the things I used to enjoy:

- Definitely as much
- Not quite so much
- Only a little
- Not at all

I get a sort of frightened feeling like something awful is about to happen:

- Very definitely and quite badly
- Yes, but not too badly
- A little, but it doesn't worry me
- Not at all

I can laugh and see the funny side of things:

- As much as I always could
- Not quite so much now
- Definitely not so much now
- Not al all

I feel as if I am slowed down:

- Nearly all of the time
- Very often
- Sometimes
- Not at all

I get a sort of frightened feeling like 'butterflies in the stomach':

- Not at all
- Occasionally
- Quite often
- Very often

I have lost interest in my appearance:

- Definitely
- I don't take as much care as I should
- I may not take quite as much care
- I take just as much care as ever

I feel restless as if I have to be on the move:

- Very much indeed
- Quite a lot
- Not very much
- Not at all

Worrying thoughts go through my mind:

- A great deal of the time
- A lot of the time
- From time to time but not too often
- Only occasionally

I feel cheerful:

- Not at all
- Not often
- Sometimes
- Most of the time

I can sit at ease and feel relaxed:

- Definitely
- Usually
- Not often
- Not at all

I look forward with enjoyment to things:

- A much as I ever did
- Rather less than I used to
- Definitely less than I used to
- Hardly at all

I get sudden feelings of panic:

- Very often indeed
- Quite often
- Not very often
- Not at all

I can enjoy a good book or radio or TV programme:

- Often
- Sometimes
- Not often
- Very seldom

NUMERIC RATING SCALES FOR DYSPNOEA AND NIGHT SWEATS

Initials (forename, surname): ___ ___ Today's Date:____/____/_____

DYSPNOEA
ON A SCALE OF FROM 0-10
INDICATE HOW MUCH SHORTNESS OF BREATH YOU ARE HAVING RIGHT NOW
0= NO SHORTNESS OF BREATH
AND 10= SHORTNESS OF BREATH AS BAD AS CAN BE
CIRCLE THE NUMBER:

0	1	2	3	4	5	6	7	8	9	10

NIGHT SWEATS
ON A SCALE OF FROM 0-10
INDICATE HOW SEVERE YOUR NIGHT SWEATS ARE
0= NO NIGHT SWEATS
AND 10= NIGHT SWEATS AS BAD AS CAN BE
CIRCLE THE NUMBER:

0	1	2	3	4	5	6	7	8	9	10

CTU Version 1: 12.07.12
Please return completed form to: CRUK Clinical Trials Unit, Level 0, The Beatson West of Scotland Cancer Centre, 1053 Great Western Road, Glasgow, G12 0YN.

FATIGUE SEVERITY SCALE

Initials (forename, surname): ___ ___ **Today's Date:**____/____/_____

Below are a series of statements regarding your fatigue. By fatigue we mean a sense of tiredness, lack of energy or total body given-out. Please read each statement and choose a number from 1 to 7, where 1 indicates you completely disagree with the statement and 7 indicates you completely agree. Please answer these questions as they apply to the past two weeks.

		Completely Disagree						Completely agree
1.	My motivation is lower when I am fatigued	1	2	3	4	5	6	7
2.	Exercise brings on my fatigue	1	2	3	4	5	6	7
3.	I am easily fatigued	1	2	3	4	5	6	7
4.	Fatigue interferes with my physical functioning	1	2	3	4	5	6	7
5.	Fatigue causes frequent problems for me	1	2	3	4	5	6	7
6.	My fatigue prevents sustained physical functioning	1	2	3	4	5	6	7
7.	Fatigue interferes with carrying out certain duties and responsibilities	1	2	3	4	5	6	7
8.	My fatigue is disabling	1	2	3	4	5	6	7
9.	Fatigue interferes with my work, family or social life	1	2	3	4	5	6	7

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: |_|_|_|_|
Your birthdate (Day, Month, Year): |_|_| |_|_| |_|_|_|_|
Today's date (Day, Month, Year): 31 |_|_| |_|_| |_|_|_|_|

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

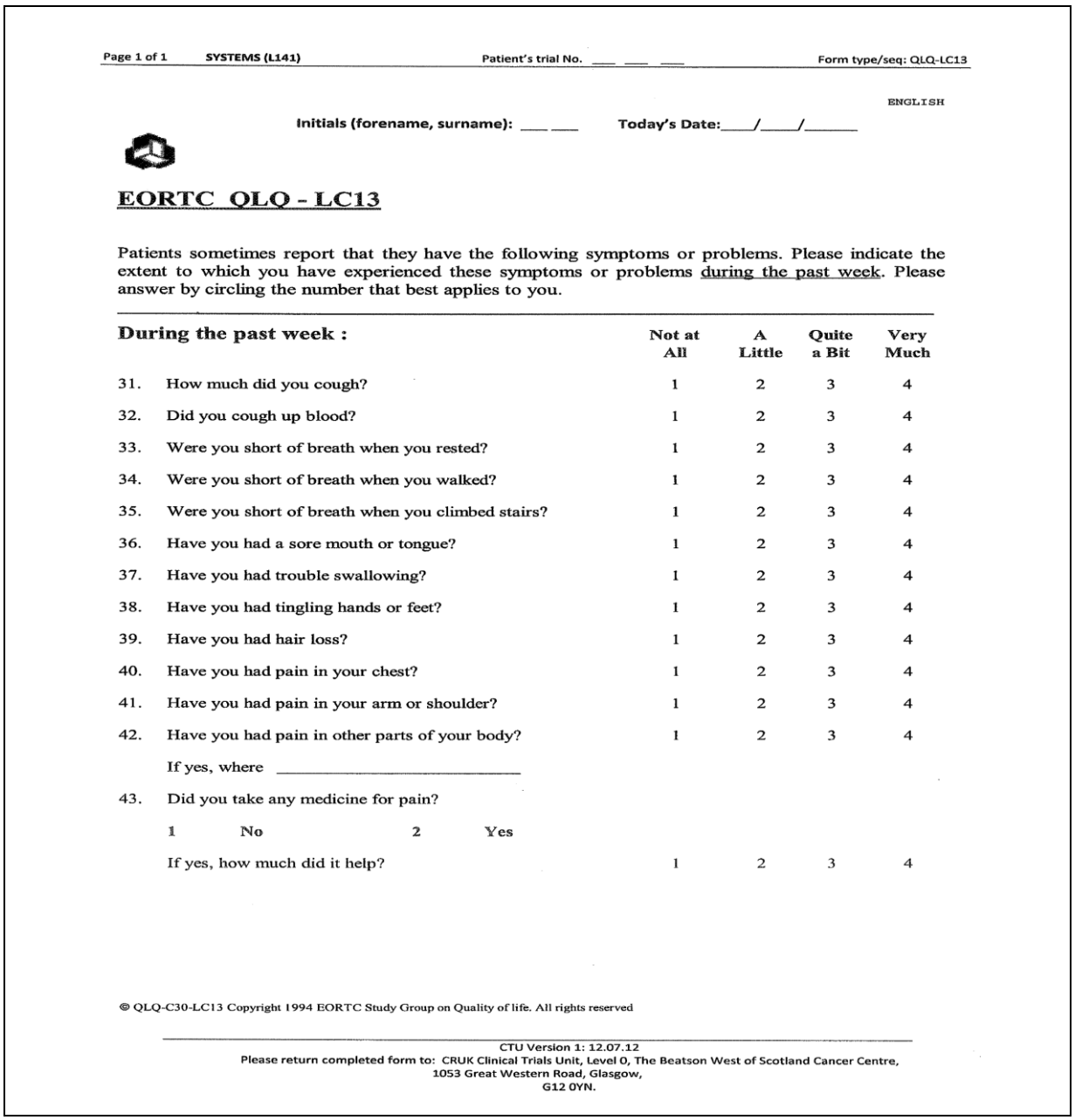
For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent



Page 1 of 1 SYSTEMS (L141) Patient's trial No. ___ ___ ___ Form type/seq: QLQ-LC13

ENGLISH

Initials (forename, surname): ___ ___ Today's Date:____/____/_____

EORTC QLQ - LC13

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week :	Not at All	A Little	Quite a Bit	Very Much
31. How much did you cough?	1	2	3	4
32. Did you cough up blood?	1	2	3	4
33. Were you short of breath when you rested?	1	2	3	4
34. Were you short of breath when you walked?	1	2	3	4
35. Were you short of breath when you climbed stairs?	1	2	3	4
36. Have you had a sore mouth or tongue?	1	2	3	4
37. Have you had trouble swallowing?	1	2	3	4
38. Have you had tingling hands or feet?	1	2	3	4
39. Have you had hair loss?	1	2	3	4
40. Have you had pain in your chest?	1	2	3	4
41. Have you had pain in your arm or shoulder?	1	2	3	4
42. Have you had pain in other parts of your body?	1	2	3	4
If yes, where _____				
43. Did you take any medicine for pain?				
1 No 2 Yes				
If yes, how much did it help?	1	2	3	4

CTU Version 1: 12.07.12
Please return completed form to: CRUK Clinical Trials Unit, Level 0, The Beatson West of Scotland Cancer Centre, 1053 Great Western Road, Glasgow, G12 0YN.

Please go to the following website to access the CTCAE Version 4.0.http://ctep.info.nih.gov/protocolDevelopment/electronic_applications/ctc.htm