Early mortality, quality of life and cost-effectiveness of palliative radiotherapy for bone metastases in the English NHS

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The candidate confirms that the work submitted is his/her own, except where work which has formed part of jointly-authored publications has been included. The contribution of the candidate and the other authors to this work has been explicitly indicated below. The candidate confirms that appropriate credit has been given within the thesis where reference has been made to the work of others.

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Chapter 6 and 8 contain sections included in 'Spencer K, Bojke C, Morris E, Henry A, Hall P. Outcome-based pricing of stereotactic radiotherapy for painful bone metastases. In: Summer 2019. Norwich; 2019.' I carried out the analyses for this paper and conceived the approach with support from my supervisors and Prof. Bojke. I wrote the manuscript with comments from co-authors prior to submission.

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Abstract

Introduction

Palliative radiotherapy is a standard of care for localised pain due to bone metastases. International guidance recommends single fraction treatment in preference to multiple fractions, but variation in practice exists. The cost-effectiveness of stereotactic radiotherapy in this setting is unclear. This study aimed to assess the quality of life benefits from response to treatment, cost-effectiveness and routine use of these treatments in the context of varying survival.

Methods

A mixed methods approach was used: A systematic review; secondary use of trial data to assess an alternative trial end-point and support multi-level regression modelling of treatment related quality of life benefits; a qualitative interview study to understand patients values and experiences of treatment; time-driven activity-based costing to determine radiotherapy cost; cost-utility analysis, to balance the quality of life benefits and cost of treatment in the context of varying survival and identify levels of 30-day mortality which reflect cost-effective care; and an analysis of the national radiotherapy dataset to provide insight into current practice and outcomes in the English NHS.

Results

With increasing proximity to death the quality of life benefits of palliative radiotherapy diminish markedly, to the extent that in the final months of life, treatment is unlikely to be cost-effective and may be associated with a net harm to the healthcare system. For those with longer survival, stereotactic radiotherapy may offer a cost-effective means to improve the quality and durability of pain control, once treatment costs have reduced beyond an initial learning-curve. Wide variation in fractionation pattern persists, with marked variation in 30-day mortality.

Conclusions

A value-based approach to the use of palliative radiotherapy for bone metastases offers an opportunity for improved decisions that avoid futile treatment and improve the cost-effectiveness of care. These analyses can form the basis of a novel approach to the commissioning of stereotactic radiotherapy.

Table of Contents

List of Tables

List of Figures

List of equations

List of abbreviations

AIC	Akaike information criteria
BSC	Best-supportive care
CR	Complete response
CEAF	Cost-effectiveness acceptability frontier
cEBRT	Conventional radiotherapy
CTE	Commissioning through evaluation
CUA	Cost-utility analysis
DBMS	Dutch Bone Metastasis Study
EoL	End of life
EQ-5D	EuroQOL- 5 Domain questionnaire
ESTRO-HERO	European society of therapeutic radiation oncology – Health economics in radiation oncology project
Gy	Gray (radiotherapy dose)
HPC	High performance computing cluster
HR-QoL	Health-related quality of life
HTA	Health technology appraisal
ICER	Incremental cost-effectiveness ratio
ICPRE	International consensus on palliative radiotherapy endpoints
IGRT	Image guided radiotherapy
IMRT	Intensity modulated radiotherapy
INHB	Incremental net health benefit
KPS	Karnofsky performance status
Linac	Linear Accelerator
MNAR	Missing not at random
MRI	Magnetic resonance imaging
MSCC	Malignant spinal cord compression

NCRAS	National Cancer Registration and Analysis Service
NHB	Net health benefit
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NR	No (pain) response
NSCLC	Non-small cell lung cancer
OBP	Outcome-based price
OBPM	Outcome based payment model
PHE	Public Health England
PMM	Predictive mean matching
PC	Pain control
PP	Pain progression
PR	Partial response
QALY	Quality adjusted life year
QIPP	Quality, Innovation, Productivity and Prevention programme NHS England.
RCT	Randomised controlled trial
SABR	Stereotactic ablative body radiotherapy
SRH	Self-reported health
TD-ABC	Time-driven activity based costing
VMAT	Volumetric arc therapy
VAS	Visual analogue score
VBP	Value-based price
WBRT	Whole brain radiotherapy
WHO	World Health Organisation
WTPT	Willingness to pay threshold
#	Fraction of radiotherapy

1 Introduction

It is estimated that 40-50% of cancer patients may benefit from radiotherapy at some point during their disease course.(1,2) Approximately 130,000 radiotherapy courses are delivered each year in England with half of these delivered with palliative intent. Palliative radiotherapy offers a quick, and relatively inexpensive way of reducing many of the focal symptoms of advanced, incurable cancer, whether these arise due to the primary tumour or metastatic deposits. It can improve quality of life whilst limiting treatment burden in terms of both hospital attendances and side-effects.(3)

1.1 Palliative radiotherapy

Palliative radiotherapy can improve a wide range of focal symptoms from advanced cancer. Indications for treatment include: painful bone metastases; locally advanced thoracic malignancies; malignant spinal cord compression; brain metastases; locally advanced head and neck cancers; advanced pelvic malignancies; and advanced/metastatic skin lesions. The evidence supporting these treatment indications is described in Table 1. Notably, palliative radiotherapy rarely improves overall survival, which is reported to be a median of 5.2 months in one observational study.(4) As such, careful consideration of likely prognosis is required when balancing the risks and benefits of treatment.

The treatment options and outcomes following palliative radiotherapy for bone metastases are particularly well documented. These treatments account for approximately 40% of all palliative radiotherapy episodes delivered. In addition, the potential role of novel, more costly, techniques for their delivery mean they provide an ideal focus for this study.

1.1.1 *Palliative radiotherapy for painful bone metastases*

Post-mortem studies have detected bone metastases in up to 70% of patients with advanced cancer.(5) Such metastases frequently cause localised pain and account for 35-40% of all palliative radiotherapy.(6) Pain may be constant or intermittent, can be neuropathic with a radiating dermatomal component and possible altered sensation and frequently limits activities of daily living.(7) If, despite weak opioids, patients have persistent pain or suffer side-effects of medication, radiotherapy can be considered.(8) This is associated with pain relief in a median of 2-3 weeks for 60% of patients (Table 1).(9,10) Where pain recurs, retreatment can be considered after at least 4 weeks to allow response.(11) Metastases in long bones have a risk of pathological fracture. Where this risk is assessed to be high, surgical stabilisation is often carried out prior to radiotherapy.(12–14)

In metastatic prostate cancer specifically, intravenous bisphosphonates offered equivalent pain relief to single fraction radiotherapy in a single randomised controlled trial (RCT).(15) This may

be an alternative option for patients with prostate cancer naïve to bisphosphonates, although its use in routine care is unclear.

Table 1. Indication for palliative radiotherapy. Gy = Radiotherapy dose in Gray.

Treatments assessed	Study	Sample size	Endpoints	Results
Pain due to bone metastases				
Single fraction radiotherapy vs longer, more fractionated courses.	Chow et al. 2012. (SR) (10)	n=5617 patients in 25 trials.	Pain response, re-irradiation rates and pathological fracture rate. Time point varied between trials	60.7% response rate (OR for single vs multiple fraction treatments 0.98 (95% CI 0.95-1.02)). 23.8% complete pain resolution. Re-irradiation higher following single fraction. OR 2.6 (95% CI 1.92-3.47) No significant difference in pathological fracture rates identified (overall 3.2%, OR 1.10 (95% CI 0.65-1.86)).
	Sze et al. 2004. (SR) (9)	n=3487 painful sites in 11 trials.	Pain response, re-irradiation rates and pathological fracture rate. Time point varied between trials.	59% response rate.(9) OR for single fraction vs multiple fractions 1.03 (95% CI 0.89-1.19). 33% complete pain resolution. Lower re-irradiation rates following fractionated courses (7.4% vs 21.5%, OR 3.44 (95%CI 2.67–4.43)). Pathological fracture rate 3% following single fraction vs 1.6% (OR 1.82 (95% CI 1.06 to 3.11)) following multiple fractions.
	Steenland et al.1999. (RCT) (16)	n=1157	Primary endpoint: Pain response in remaining life-span. Re-irradiation and pathological fracture rates. Assessed weekly	71% response rate. 35% complete resolution of pain. Median time to benefit was 3 weeks. Re-irradiation in 25% following single fraction vs 7% following multiple fractions (p<0.0001). 4% vs 2% pathological fractures after treatment (p<0.05).
Single 8 Gy fraction of radiotherapy vs Ibandronate infusion in metastatic prostate cancer	Hoskin et al.2015.(RCT) (15)	n=470	Primary endpoint: Pain response at 4 weeks. Crossover and pathological fracture rates. Assessed 4 weekly.	Response seen in 53.1% following radiotherapy vs 49.5% following Ibandronate (difference = 3.7% (90% CI -12.4%-5.0%, p=0.49). Crossover observed in 24% following Ibandronate vs 31% following radiotherapy. 3% pathological fracture rate following Ibandronate vs 2% following radiotherapy (p=0.31).
Locally advanced lung cancer				
Various palliative radiotherapy regimens for advanced lung cancer	Stevens et al 2015. (SR) (17)	n=3576 in 14 RCTs	Control of thoracic symptoms Time point varied between trials Overall survival	Pooled symptom response rates not reported due to study heterogeneity. Potential modest improvement in 1 year overall survival with higher dose regimens for good performance status patients (33.3% (11.4-46.2%) 1 year OS vs 25.6% (9.4-45.7%)) but unclear due to high study heterogeneity (n=1081, 8 trials).

				No survival improvement seen in poor performance status patients (RR 0.96 (0.91-1.02) (n=911, 7 trials).
Various palliative radiotherapy regimens for advanced lung cancer	Fairchild et al. 2008. (SR) (18)	n=3473 in 13 RCTs	Control of thoracic symptoms Time point varied between trials Overall survival	Complete resolution of haemoptysis was reported by 73.7% vs 68.9% following high and low dose regimens respectively (p=0.19), whilst 80.2% and 81.2% reported improvement. 48.2% vs 53.5% reported improved cough (p=0.04) and 57.5% vs 51.9% improved chest pain respectively (p=0.43 with significant heterogeneity between studies). Individual RCTs report improvement in shortness of breath in 35-40%.(19–21) One trial reported a median time to response of 5-7 weeks.(21) 1 year overall survival significantly higher (26.5%) following higher dose regimens than following lower doses (21.7%) (p=0.002), at the expense of significantly increased oesophagitis.
Locally advanced oesophageal and gastric cancer				
External radiotherapy (40 Gy in 20 fractions, twice daily).	Kassam et al. 2008 (Phase I/II) (22)	n=39	Dysphagia response at 56 days, survival and toxicity	Improved swallowing function reported in 69% of individuals with median time to benefit of 4 weeks and duration of response 5.5 months.
Oesophageal stenting with or without external radiotherapy.	Javed et al.2010 (RCT) (23)	n=84	Duration of dysphagia relief following stenting Overall survival	Duration of dysphagia relief increased with radiotherapy (7 vs 3 months (p=0.002). Median overall survival increased with radiotherapy (180 vs 120 days, p=0.009).
Oesophageal brachytherapy with or without external radiotherapy	Rosenblatt et al. 2010 (RCT)(24)	n=219	Dysphagia relief experience Overall survival	Improved duration of dysphagia relief with addition of external radiotherapy. At 200 days 69.6% had not experienced a dysphagia event vs 51.8% without external radiotherapy. p=0.014 in multi-variable modelling. No significant improvement in overall survival.
Palliative radiotherapy for advanced gastric cancer	Tey et al. 2017 (SR) (25)	n=122 (7 retrospective studies)	Reduction in gastric bleeding - response definitions varied	Gastric bleeding was reduced in 74% of patients (pooled analysis). Numbers reported for pain and obstruction responses were small (n=18 and 33).
Malignant spinal cord compression				
20 Gy in 5 fractions vs 30 Gy in 10 fractions radiotherapy	Rades et al. 2016. (RCT)(26)	n=203 (155 assessable)	Motor function at 1 month Local control Overall survival	No significant difference in mobility (p=0.86), local control (p=0.51) or survival (p=0.68) seen between the two regimens. 41.3% achieved an improvement in motor function following treatment with a further 47.1% remaining stable. Improvement in ambulation not reported. Median overall survival was 3.2 months.

8 Gy single fraction vs 16 Gy in 2 fraction radiotherapy	Maranzano et al. 2009. (RCT) (27)	n=327 (303 assessable)	Symptom control (pain, motor and sphincter function) at 1 month. Toxicity Duration of response Overall survival	No significant difference in response rates or duration observed (p=0.40). Median duration of response was 5 months and median overall survival 4 months. 53% (95% CI 47-58) achieved a pain response (25% complete resolution (95% CI 21-31.1)). 27% of non-ambulatory patients regained mobility following treatment (although this was only 4% for those with paraplegia prior to treatment). 27% with sphincter disturbance prior to treatment regained control. Acute side-effects were equivalent.
16 Gy in 2 fractions vs split course (total dose 30 Gy in 8 fractions)	Maranzano et al. 2005. (RCT) (28)	n=300 (276 assessable)	Symptom control (pain, motor and sphincter function) at 1 month. Toxicity Duration of response Overall survival.	No significant difference in response rates or duration observed. Median duration of response 3.5 months. Median overall survival 4 months. 56.9% (95% CI 51.1-62.7) achieved a pain response (33.3% (95% CI 27.7-38.9) complete resolution). 35% of non-ambulatory patients regained mobility (although this was not seen in anyone with paraplegia).14% with sphincter disturbance regained control. Acute side-effects were equivalent.
Radiotherapy (30 Gy in 10 fractions) with or without surgical decompression.	Patchell et al. 2005. (RCT) (29)	n=101 (study stopped at interim analysis)	Mobility (time point unclear), continence, corticosteroid use and pain control. Overall survival.	Post treatment ambulation rates were 84% in the surgical cohort and 57% in the radiotherapy cohort (OR 6.2 (95% CI 2.0-19.8), p=0.001). Continence was more likely following surgery and doses of corticosteroids (p=0.009) and opiates (p=0.002) were lower. Median survival was 126 days following surgery and 100 days following radiotherapy (On multi-variable analysis HR 0·60, 95% CI 0·38–0·96, p=0·033).
Brain metastases				
Whole brain radiotherapy (WBRT) (20 Gy in 5 fractions) vs dexamethasone alone in non-small cell lung cancer	Mulvenna et al. 2016. (RCT) (30)	n=538	Overall survival QoL (measured in QALYs) Use of steroids	All patients received dexamethasone. No difference in overall survival with or without WBRT (median survival 9.2 weeks vs 8.5 weeks, HR 1.06, 95% CI 0.90-1.26), overall QoL (mean QALYs 46.4 vs 41.7 days).
Effectiveness and adverse events following WBRT for adults with multiple brain metastases.	Tsao et al. 2012. (SR) (31)	n=10,835 in 39 trials.	Overall survival Cerebral disease control QoL and symptom control	Unable to recommend one WBRT regimen over others due to lack of QoL outcomes and no overall improvement in overall survival (n=3645, 8 trials). No improvement in survival (HR 1.08, 95%CI 0.98-1.18) or symptom control with the addition of radio-sensitizing drugs to WBRT. Toxicity increased. (n=2016, 6 trials). The addition of stereotactic radiotherapy to WBRT improved cerebral control (n=464, 3 trials). Improvement in overall survival only demonstrated in individuals with a single metastasis and good performance status in one trial (n=333) (6.5 months vs 4.9 months p=0.03).

				Significantly reduced steroid doses following stereotactic radiotherapy shown in one trial (n=333) (52% vs 33%, p=0.016). Addition of WBRT to stereotactic radiotherapy improved cerebral control (HR 2.61, 95% CI 1.68-4.06, p<0.001) in pooled analysis (n=577, 3 trials) but not overall survival (HR 0.98, 95%CI 0.71-1.35, p=0.88) (n=218, 2 trials).
Neurocognitive outcomes following stereotactic radiotherapy with or without WBRT.	Chang et al. 2009 (RCT)(32)	n=58 (trial stopped early after interim analysis)	Neurocognitive outcomes at 4 months Cerebral disease control	Addition of WBRT resulted in lower CNS recurrence at 1 year (73% recurrence free vs 27%, p<0.001). This was at the cost of a higher probability of significantly reduced total recall at 4 months (mean posterior probability 52% vs 24%). This difference persisted at 6 months. In practise, to avoid cognitive decline, regular MRI surveillance is often preferred over WBRT.(33)
Head and neck cancer				
30 Gy in 5 fractions radiotherapy delivered every 3 days.	Porceddu et al. 2007. (Phase II) (34)	n=37	Response rate. Symptom control, QoL, and toxicity. Overall and progression free survival.	80% had an objective response at 2 weeks following treatment. 67% reported improved pain control following treatment and 33% felt their ability to eat solids was improved. 62% reported improved overall QoL. 74% of patients experienced significant dysphagia during treatment, resolving by 4 weeks post. Median overall survival was 6.1 months (range 0.5–21) and PFS 3.9 months (range 0.5–21).
42 Gy in 12 fractions radiotherapy delivered twice daily in 4 fraction blocks repeated 4 weekly.	Corry et al. 2005. (Phase II) (35)	n=35	Response rate. Symptom control, QoL and toxicity. Overall and progression free survival.	53% objective response rate. Median overall survival 5.7 months (95% CI 3.4–9.3) and PFS 3.1 months (95% CI 2.2–6.1). 85% of patients experienced improved or stable dysphagia following treatment whilst 56% experienced improved pain control. Overall QoL improved in 44%.
Pelvic cancers				
Bladder cancer				
35 Gy in 10 fractions vs 21 Gy in 3 fractions radiotherapy	Duchesne et al 2000. (RCT) (36)	n=500 (272 assessable at 3 months)	Symptomatic improvement at 3 months. Overall survival.	No significant difference was seen between the arms for any endpoint (overall survival, HR =0.99 (95% CI 0.82-1.21, p=0.933)) 51.4% of patients reported symptom improvement at the end of treatment (p=0.421 for comparison between arms). In patients experiencing these symptoms initially; haematuria improved in 88%; urinary frequency in 82%; nocturia in 64% and dysuria in 72% of assessable patients at 3 months post treatment. Median overall survival was 7.5 months.
Rectal cancer				
30-39 Gy in 10-13 fractions	Cameron et al. 2016. (Prospective	n=51	Symptomatic improvement at 3 months.	Improvements in pain (77% (95%CI 54-100)), rectal dysfunction (90% (95% CI 0.71-100)) and bleeding (100%) observed following radiotherapy.

multicentre) (37)				
Gynaecological malignancies				
Any external radiotherapy or brachytherapy regimen delivered palliatively to the cervix.	van Lonkhuijzen et al. 2011. (SR)(38)	n= 476 (7 retrospective studies and 1 prospective study).	Symptomatic improvement	Wide heterogeneity in studies, with variable time points and poor reporting limited this analysis. Bleeding improvement ranged from 45-100% of patients whilst pain reduction ranged from 31-100% and discharge 15-100% between studies. Toxicity not consistently reported.
Locally advanced prostate cancer				
Any palliative radiotherapy regimen delivered to the prostate.	Cameron et al. 2014 (SR) (39)	n=315 (9 retrospective studies).	Symptomatic improvement, quality of life (QoL) and toxicity.	Pooled response rates were: 73% for haematuria, 80% pain, 63% bladder outlet obstruction and 78% rectal symptoms. Toxicity was mild/moderate although not systematically recorded. No reports of QoL or patient reported outcomes identified.

1.1.2 *Hypo-fractionation, novel techniques and technologies*

Radiotherapy is delivered on machines called linear accelerators in specialised cancer centres, generally located in large urban areas. High energy X-rays are targeted to the disease site, causing DNA damage and cell death. In the curative setting radiotherapy is routinely delivered over multiple small, daily doses (fractions of approximately 2 Gray (Gy) each) to reduce the risk of long-term, permanent, side-effects in adjacent normal tissues.(40) Palliative treatments require lower total doses, with the focus shifting to symptom control whilst minimising treatment burden both in terms of hospital visits and side-effects. This change underpins the routine delivery of palliative radiotherapy using much shorter courses of larger fraction size; hypo-fractionation. The equivalence of hypofractionated treatments has been demonstrated across a range of indications (41–43) with the strongest evidence in treatment to bone metastases.(10,11,43) These treatments make up 36-39% (4,6) of all palliative episodes and are the focus of this thesis.

Radiotherapy delivery has transformed over the last 20-30 years. Increasingly, advanced techniques are used to offer more precise treatment delivery, allowing increased dose and conformality to the tumour whilst maintaining limited dose to surrounding tissues (these are known as stereotactic radiotherapy). As a result the necessity to fractionate, even radical treatments, to spare late responding normal tissues is now, in part, circumvented in some groups (44,45) through the use of image guided radiotherapy (IGRT) combined with intensity modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT).(46) Randomised trial data to support these novel techniques has been relatively limited.(45,47,48) As described, however, late morbidity is not the focus of palliative treatments and in this setting hypo-fractionation is routine to reduce treatment burden where late morbidity is unlikely to occur due to short survival. The finding that single fraction courses for bone metastases are associated with higher rates of retreatment, however, leads many clinicians to conclude that higher doses (historically requiring longer courses), provide more durable disease and symptom control. This has given rise to the

hypothesis that dose escalation of hypofractionated treatments, using novel radiotherapy techniques, might offer benefit in terms of local control, and thus, symptom control without increasing toxicity or treatment burden. Figure 1 provides an example of the difference in radiotherapy dose distribution between the simple conventional palliative approach and a more complex, volumetric arc therapy (VMAT) technique with image guidance (stereotactic treatment) for isolated spinal bone metastases. This approach has been widely adopted in the United States on the basis of higher rates of pain control but there is no randomised data to support its use as yet; studies are ongoing.(49–51) The costs of SABR are, however, significantly higher than conventional external beam radiotherapy (cEBRT). Before routine adoption into NHS practice there is a need to consider to what extent, and for whom, these treatments might be cost-effective.

Figure 1. Differences in dose distribution between alternative radiotherapy treatment techniques.
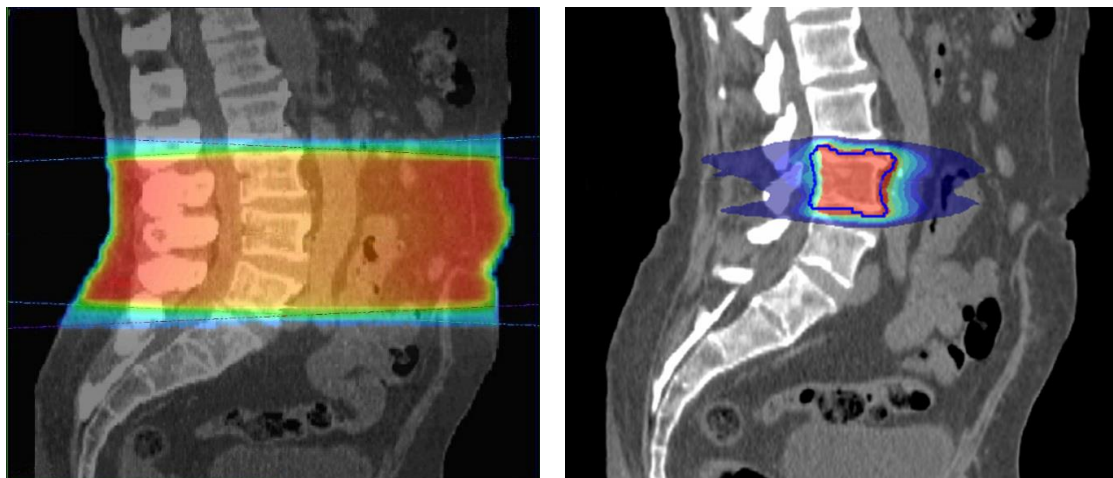
a) Simple, conventional palliative radiotherapy to the lumbar spine. The red region illustrates the area receiving 100% of the dose.

b) A stereotactic radiotherapy plan treating the same site and demonstrating the reduction in the proportion of dose being delivered to surrounding organs. This plan allows a dose of approximately 3 times greater biological effectiveness to the target with significantly lower dose to surrounding tissue.

1.1.3   *Cost-effectiveness, cost and commissioning in radiotherapy*

1.1.3.1   *Cost-effectiveness*

In stark contrast to the health technology assessment (HTA) process undertaken by NICE prior to funding agreements for the use of cancer medicines, health systems have for many years not required the same rigorous assessment of cost-effectiveness for planning radiotherapy services. As such, evidence of the effectiveness of incremental changes (47,52,53) in radiotherapy has rarely been the subject of HTA. This in part reflects the focus of decision-makers upon drug therapies, as opposed to devices. That radiotherapy is responsible for only 5% of spending on cancer care whilst contributing to 40% of cures has also, historically, contributed to the

justification for this.(54–56) In addition, as radiotherapy technology has progressed, relatively small incremental cost increases have accompanied small incremental improvements in effectiveness. These have not, however, been well quantified.(47) Given that approximately 50% of cancer patients are expected to require radiotherapy during their disease course, health care budgets in the UK have plateaued since 2008,(57) and significantly more costly radio-therapeutic interventions are now on the horizon (e.g. proton beam therapy and MRI linear accelerators), demonstrating the cost-effectiveness of novel radiotherapy treatments is vital.(47,58)

Whilst the radiotherapy community must recognise that previous attempts to robustly assess the cost-effectiveness of novel techniques and technologies have been extremely limited it should equally be recognised that a number of challenges exist in achieving this:

- Firstly, the assessment of any novel radiotherapy technique or technology requires significant investment not only to provide the equipment necessary but to deliver quality assurance and provide staff training. Once invested, this capital cannot be recovered and as such disinvestment is unlikely. Where uncertainty about treatment benefit exists this must be considered in the context of this capital investment.

- Radiotherapy treatment planning allows identification of potential dosimetric advantages from novel technologies which may improve the therapeutic ratio (the relationship between the probability of tumour control and normal tissue toxicity). To what extent these then result in improved clinical outcomes is often undocumented. Sometimes this is because the putative benefits are long-term outcomes which are difficult to capture within a standard trial follow-up period. This may also relate, however, to a lack of clinical equipoise and ethical concerns about randomisation due to the strength of the dosimetric evidence. This latter, contrasting with ethical concerns about expenditure in the face of uncertain opportunity cost to other, unidentifiable, patients.

- A single technological advance may have implications across a range of patient groups making assessment of cost-effectiveness technically complex.

- Finally, both costs and benefits may vary over time either due to learning curve effects or as a result of technological evolution and uncritical adoption of minor changes over prolonged periods. Given the time course of most clinical trials, and outcomes of interest, assessment of these minor changes might be outdated by the time studies are completed.

As a result of this, current radiotherapy practice has not always been subjected to trial based scrutiny and assessment of its cost-effectiveness is even more limited.(47)

1.1.3.2 Radiotherapy costs

Any assessment of cost-effectiveness requires accurate inclusion of treatment costs. Frequently provider reimbursement charges are used to represent the cost of healthcare within cost-effectiveness models. It is recognised, however, that these are not always a realistic reflection of provider cost or within-system opportunity costs.(59–61) In addition to this general recognition, specific issues arise in radiotherapy; provider reimbursement reflects the cost to the payer (NHS England) of treatment delivery, however, radiotherapy treatment delivery requires high levels of capital investment.(47) Once invested this resource cannot be released if treatment is forgone; it is a fixed cost.(62) As such, reimbursement, may not reflect realisable alternative health gain if treatment is forgone.(63)

Failure to recognise this may have a number of consequences both for delivering practice change and HTA. Where radiotherapy is delivered within a larger acute Trust, persistent fixed costs could result in resources being shifted from other services unless radiotherapy demand exceeds capacity such that when one treatment is forgone it is immediately replaced by an alternative. From an HTA perspective if fixed costs are not released, the opportunity cost of adoption will be over-estimated with consequences for the calculated cost-effectiveness of the interventions. Attempts to consider possible disinvestment in radiotherapy have recently been made by NICE without resolution.(64) To identify the fixed and variable costs of treatment a more in-depth assessment of the costs is required.

1.1.3.3 Radiotherapy commissioning

Since 2013 provider reimbursement for radiotherapy treatments has been defined nationally through the NHS England tariff system for treatments delivered in England.(54) This system provides reimbursement for planning and treatment separately on the basis of complexity and per fraction delivered.(65,66)

Considering a more global perspective, secondary care health services are financed in various ways internationally. Overall these fit along two main axes: Fixed versus variable and retrospective versus prospective.(63) Fixed payment defines the payment to a provider irrespective of activity whilst variable bases income on activity. This can then be carried out retrospectively (i.e. all the costs of treatment delivery are reimbursed after delivery has occurred) or prospectively (in which the reimbursement for delivering a given activity is defined ex ante). It is anticipated that activity based financing, particularly if retrospectively determined, may drive cost-escalation via providers increasing activity and hence income with no incentive to improve efficiency. In some situations this might also be expected to increase quality, for example, access to treatment might be improved.(63) Prospective variable payments provide fixed income on a per activity basis, effectively returning much of the financial risk to the payer, although incentivising activity.(67) Conversely fixed prospective payment systems (block funding) aim to reduce this cost escalation by shifting the financial risk of increasing activity back to the provider.

This might be expected to have a detrimental impact on access, waiting times and potentially, innovation.(63)

Reimbursement of radiotherapy in the NHS, predominantly, follows a prospective-variable system. Given the often fixed nature of radiotherapy costs there is a danger that this structure offers a perverse incentive to deliver treatment. Supplier induced demand could therefore result in more fractionated treatment delivery and increased likelihood of treatment with limited or absent marginal gains. Alternative mixed-models which encompass an element of pay-for-performance (either via rewards or penalties) could be considered in order to reduce this risk.(68,69) Such a system might recognise the fixed costs of treatment whilst also ensuring that services continue to innovate and deliver high quality, cost-effective care.(63)

1.2 Quality in healthcare

Donabedian recognised that in order to measure the quality of healthcare it is first necessary to define quality.(70) He also recognised that creating such definitions is not simple; "the definition of quality may be almost anything anyone wishes it to be, although it is, ordinarily, a reflection of values and goals current in the medical care system and in the larger society of which it is a part".(71) In this statement the fact that quality of care can be considered at both a patient and societal level is recognised alongside its normative nature. Donabedian also recognised the possibility of defining quality either from a maximalist or optimalist perspective.(70) If the latter, we must decide from whose perspective this optimum should be defined i.e. the patient or the society. If the former, it is necessary to define at an individual level what is valued such that the care received, and outcomes available, can be considered in the context of the individual's values and expectations. Donabedian states that clinicians will tend towards the maximalist approach; decision making always aiming to determine simply whether an additional intervention provides benefit for an individual patient. This is expected and not inappropriate given that the first duty of a doctor as defined by, for example, the General Medical Council is to "Make the care of your patient your first concern".(72) This approach, however, fails to recognise the opportunity cost of care and it is increasingly acknowledged that clinicians have a responsibility to use healthcare resources responsibly.(73–75) By considering optimal care at a population level the opportunity cost is recognised, ensuring maximisation of population health from finite resources.(70)

The World Health Organisation has subsequently defined quality in healthcare using a framework of six dimensions; effectiveness, efficiency, accessibility, acceptability/patient-centeredness, equity and safety.(76) The inclusion of effectiveness at a community level, efficiency, equity and accessibility suggests a need to assess quality at a population as well as patient level. That efficiency is considered to be an important element of quality once again recognises the opportunity cost of inefficient care. As Donabedian stated "lower quality and inefficiency coexist because wasteful care is either directly harmful to health or is harmful by displacing more useful care".(70)

1.2.1 *Health productivity and marginal gains*

In economic terms, the increase in an output delivered by an additional unit of input is termed the marginal gain. It is recognised, however, that the relationship between inputs and outputs is non-linear; as resource investment rises the marginal gains fall (diminishing marginal productivity) until the point at which further investment does not deliver increased output or indeed, this increased investment can result in reduced productivity. This is recognised within health economics and can be represented graphically as the health productivity function (Figure 2).

The health productivity function aims to consider investment in the wider healthcare economy. Parallels exist, however, between this and the use of treatment for a single indication where clinicians balance treatment burden and benefit, implicitly considering the marginal benefits for an individual patient in order to maximise their health; those with the strongest indication to receive treatment may be expected to be the most likely to do so, these individuals should experience the largest gains, increasing input by treating these individuals delivers high marginal gains. As individuals are treated with a weaker indication for intervention, however, it is likely that the benefit experienced will be smaller i.e. the marginal gain will reduce, eventually to zero. Finally, where treatment carries with it a risk of side-effects or burden we may see that towards the margins of a population with an indication for treatment it may be that this treatment detriment starts to out-weigh any marginal gain.(77)

Figure 2. Health productivity function. A and B demonstrate diminishing marginal gains with increasing input. C demonstrates the potential for reduced health outputs with overuse.
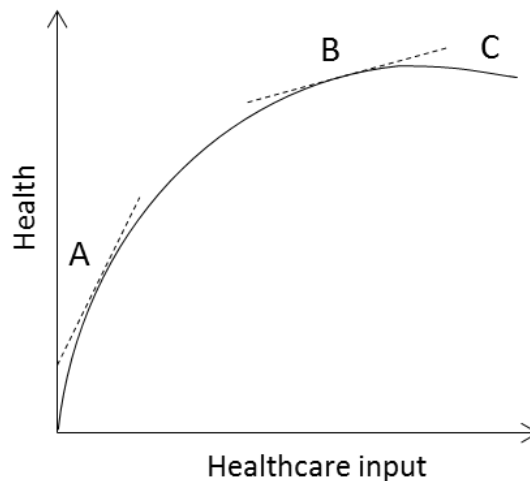
Hence, within a heterogeneous population as increasing numbers are treated the marginal gains will reduce and treatment may become futile or in fact harmful. The parallel with the wider population then rises to the fore as the use of these resources may deprive others of more effective care. As such, at a societal level, in a publically funded healthcare system, treatment at the margins may result in a net reduction in population health.

It has been increasingly recognised over the last decade that a significant proportion of the money spent on healthcare does not in fact deliver improvements in health. Estimates of the proportion of spending this represents vary; the OECD estimate that 20% of healthcare spending does not deliver any benefit, whilst others find lower and markedly higher estimates.(78–80) Wennberg and Olsen, separately, make the distinction between "effective care", "preference-sensitive care" and "supply-sensitive care".(63,81) Critically the latter two are unlikely to be delivered to 100% of individuals and for many interventions, increasing rates of delivery will be associated with reducing marginal health gains. Where supply is induced to include individuals where harm outweighs benefit, "overuse" is occurring.

1.2.2 *Quality in palliative radiotherapy*

The median survival of patients treated with palliative radiotherapy is 5.2 months.(4) With limited exceptions, palliative radiotherapy aims simply to improve quality of life by reducing the localised symptoms of advanced cancer. Despite the evidence, in a range of settings, supporting the equivalence of hypofractionated treatments to longer courses there is sometimes still a perception that more is better;(41,43,82–84) potentially increasing the duration of symptom control as measured by lower risk of re-irradiation, reducing the potential for late-toxicity and, rarely, increasing length of life.(17)

For bone metastases particularly, single fraction treatment has been shown to have equivalent efficacy to fractionated courses in terms of pain relief, all be it with associated higher retreatment rates.(10,43,85) Studies have shown, however, that this increase in re-irradiation is not simply a reflection of earlier recurrence of pain but reflects clinician willingness to re-treat in the absence of risk of late toxicity (due to lower initial radiotherapy dose) and reduced confidence of both patients and clinicians in the efficacy of single fraction treatments.(86) Pathological fracture rates following treatment have been reported to be higher following single fraction treatment, although the literature in this area is not consistent and the most recent systematic review demonstrates no increase.(10,87) On this basis, single fraction treatment is the recommended standard of care internationally.(88,89) This minimises toxicity, treatment burden and inconvenience for a patient population near the end of life, and also cost to the healthcare provider.(90) Implementation of this recommendation is not, however, uniform.(91)

Subgroup analyses of the DBMS have shown that individuals with longer survival have a greater chance of response (86% in those surviving >1 year versus 45% in those surviving <12weeks).(92,93) Similar differences in treatment effect with survival are seen in the treatment of non-small cell lung cancer (NSCLC); hypofractionated courses deliver equivalent symptom control to more fractionated regimens, however, in better performance status patients (performance status being a major predictor of prognosis)(94) more fractionated treatment can provide small improvements in overall survival.(95) Notably, observational data in NSCLC demonstrate that for poor performance status patients with advanced disease and thoracic

symptoms palliative radiotherapy may deliver side-effects with very limited symptomatic benefit.(77) Similarly Gripp et al demonstrate that in patients dying within 30 days of treatment only 26% achieved either stable or improved symptoms following palliative radiotherapy. The proportion gaining symptom benefit is not clear.(83)

Given the equivalence of hypofractionated treatments for symptom control, quality palliative radiotherapy could be expected to result in treatment being delivered which maximises the quality of an individual's remaining life whilst minimising inconvenience and toxicity. Indeed, in the case of individuals very close to the end of life the optimum decision might be not to deliver palliative radiotherapy but to move to holistic palliative care, recognising physical, emotional, social and spiritual concerns and managing these through practical help and support with pharmaceutical based interventions for physical symptoms where appropriate.(77) As such, decisions to fractionate, and indeed to treat at all, need to reflect prognosis.

A particular challenge in this setting is that inaccurate survival predictions and lack of information supporting expected treatment benefits may prevent prefect decision making.(96) Despite the development of models to predict prognosis their use in clinical practice is not routine.(97,98) Additionally, oncologists have been shown to be poor at predicting prognosis, tending to be overly optimistic.(99,100) This finding is echoed in studies with patients (96) and may result in the use of overly intensive treatment near the end of life (EoL) (83,96,100). In systemic therapy delivery of chemotherapy within 30 days of death is accepted to be an adverse outcome.(101) With this "aggressive" care having been suggested as a possible quality issue.(102,103) Key tenants of quality in healthcare, efficacy, efficiency and patient-centeredness all being in doubt if limited survival results in minimal potential for benefit;(76) reducing marginal benefits. Compounding the uncertainty about benefits and survival, many oncologists prescribing palliative radiotherapy do not have the opportunity to follow up all patients, reducing further their appreciation of these outcomes. Given the documented tendency towards overly optimistic estimation of predicted prognosis and knowledge that prescribing behaviours of oncologists can be influenced by feedback of early mortality outcomes such feedback in palliative radiotherapy may be beneficial.(104,105)

1.2.3 *Quality measures*

Ensuring that all NHS services deliver high quality care has become a key priority.(106,107) Despite the availability of routine data, radiotherapy in the NHS has adopted quality measures only to a limited degree. There is an increasing focus upon their use in this setting.(108)

As outlined above quality assessment in palliative radiotherapy should include, amongst other domains, recognition of two elements: 1) the role of hypo-fractionation in delivering symptom control without undue toxicity, inconvenience or cost. 2) The avoidance of treatments which provide minimal marginal benefit, or indeed, detriment, due most importantly to delivery in close proximity to death.

Whilst the extent to which hypofractionated regimens are used can be assessed using routine data, assessing the clinical benefit they deliver is more challenging. During the development of clinical indicators there has been considerable discussion around the optimal metrics in any given setting.(109–111) Early mortality is now a routinely used indicator in a number of healthcare interventions.(101,112,113) NHS England's Improving outcomes; A strategy for cancer document has suggested 30-day mortality as a possible quality indicator in palliative radiotherapy.(108) In considering the use of this metric the limited marginal benefit of treatment near the end of life is recognised. Small local assessments of this outcome have been carried out (6,114,115) but no large-scale analysis after palliative radiotherapy has been conducted. In addition, given that the benefits of treatment are quality of life outcomes, and treatment is by definition delivered in a population with limited prognosis, acceptable levels of early mortality are not known.(116)

1.2.4   *Cost-effectiveness as a measure of quality*

Increasing comorbidity, healthcare innovation, population growth and demographic changes are resulting in increasing financial demands on international healthcare systems whilst the available resources are failing to keep up. Health economics recognises that where resources are finite all expenditures result in an opportunity cost. By balancing the incremental costs and benefits of treatment the value of an intervention is assessed (its cost-effectiveness) and resources allocated accordingly to maximise population health outcomes.(61) In order to determine whether the benefits of a given treatment justify its cost to the healthcare system there is a need to use generic methods which support comparisons between treatments across the whole range of healthcare interventions.(117) Cost-utility analysis (CUA) aims to achieve this. In CUA the benefits and costs of alternative treatment strategies for a given indication are captured with benefits measured as a combination of both length and quality of life to provide a single comparable measure of outcome; the quality adjusted life year (QALY). The incremental QALY benefit is then assessed relative to the incremental costs and a cost per QALY defined for alternative strategies. If this cost per QALY falls below society's willingness to pay threshold an intervention is said to be cost-effective. This approach is routinely used by the National Institute of Health and Care Excellence (NICE) to inform reimbursement decisions for interventions.(118)

Since the inception of NICE, where the cost-effectiveness of interventions has been considered in the UK, this has focussed predominantly upon ensuring that novel technologies are cost-effective prior to their widespread adoption. Once treatments are established in routine use, cost-effectiveness is rarely considered.(119) Failure to assess all technologies prior to implementation, subsequent indication creep, violation of the assumptions underpinning cost-effectiveness analyses (e.g. expected survival and heterogeneous treatment effects), unstable costs (particularly true of radiotherapy implementation (120)) and failure to disinvest from low value technologies and techniques may all contribute to reduced efficiency in routine care.(119) These factors may

occur to differing degrees in different provider institutions with the treatments delivered for a given indication differing for varying reasons beyond individual patient need. For example, differing clinician preferences, variable access to technology and differing resource allocation. Variations in the treatment of cancer across the NHS are well documented, potentially contributing to the relatively poor cancer outcomes seen in the NHS compared to economically comparable nations.(121–124) Additionally, ensuring healthcare provision is efficient is a key priority in increasingly resource constrained healthcare systems.(125)

Whilst HTA typically precedes routine implementation there is an increasing interest in the use of health economics as a means of assessing efficiency of existing services.(119) It has been suggested that health economists need to increasingly focus upon the cost-effectiveness of delivered rather than available services.(119) The recent development of value-based healthcare, in part, reflects this.(126,127) This considers not only the evidence base behind the treatments delivered, but the variation in clinical practice which results in their sub-optimal utilisation. Value-based healthcare does not, however, formally recognise the opportunity cost of these treatments.

Hypofractionation of palliative radiotherapy is strongly supported by the available literature. Yet, anecdotally, variation in its use persists. The use of cost-utility analysis to appraise the cost-effectiveness of current palliative radiotherapy offers a method which can recognise both the opportunity cost of treatment, whilst also valuing the health-related quality of life (HR-QoL) it delivers, in the context of a population with varying survival. By encompassing this variation in survival beyond treatment this model can support recognition of heterogeneity in cost-effectiveness; optimising net benefits of treatment for proximity to death and, by combining the valuable balance a cost-utility analysis delivers with routine outcome data, assess and improve the cost-effectiveness of delivered services.

1.3   Aims

This study aims to assess to what extent the palliative radiotherapy delivered for bone metastases in the English NHS is cost-effective and how cost-effectiveness might be improved, including through improved patient selection for treatment and the use of stereotactic ablative body radiotherapy (SABR) in this setting.

1.4   Objectives

- To consider to what extent the conventional radiotherapy treatments delivered for bone metastases offer improvements in quality of life and whether these treatment effects are constant with proximity to the end of life.

- To determine the costs of delivering radiotherapy within a UK cancer centre and the extent to which these costs are fixed in order to consider the potential consequences of this for commissioning of treatments.

- To assess the cost-effectiveness of four possible strategies for bone metastases; single fraction treatment, hypofractionated conventional radiotherapy, stereotactic radiotherapy or best supportive care.

- To assess the extent to which palliative radiotherapy for bone metastases delivered within the English NHS is delivered using a single fraction regimen, the levels of 30-day mortality observed and if the treatment currently delivered reflect cost-effective care.

1.5   Outline methods

This thesis sits at the intersection between clinical oncology and palliative care and between health economics and epidemiology. As a consequence a number of methods were used to address the above objectives. In addition, the style of thesis sections vary depending upon the likely target audience e.g. clinicians, health economists, epidemiologists. What follows is an outline of the methods that were used and of how the thesis is structured:

Chapter 2 provides:
- A systematic review of the literature to ensure that the outcomes seen in the most recent meta-analysis of single fraction and hypofractionated, short course radiotherapy for bone metastases remain unchanged in light of any new data.

- A systematic review to assess the available evidence for pain response following stereotactic radiotherapy to bone metastases.

Chapters 3 and 4 provide:
- Two approaches to assess the treatment effects of palliative radiotherapy:

    o In order to assess the relationship between response to palliative radiotherapy and HR-QoL multi-level, multi-variable regression models were used. Incorporating time to death provided a fully conditional specification with a restricted cubic spine for this variable allowing flexibility in the relationship between pain response and HR-QoL.(128,129)

    o Net pain relief has previously been considered as a possible trial end-point in assessing palliative radiotherapy to bone metastases. This assesses the duration of remaining life for which palliative radiotherapy provides symptom relief, as

compared to the current outcomes which recognise response as a single, per patient, event.(130) As such, net pain relief provides an assessment of response durability; an end-point of significant interest when making comparisons between alternative radiotherapy regimens.(130) This chapter reports an analysis of the possible role of this outcome measure in future trials.

Chapter 5 provides:
- An analysis of the costs of delivering radiotherapy, using a time-driven activity-based costing (TD-ABC) approach, in line with work carried out within the European Society of Therapeutic Radiation Oncology – Health Economics in Radiation Oncology (ESTRO-HERO) project.(131)

Chapter 6 reports:
- The results of a cost-utility model which assessed the cost-effectiveness of the four treatment strategies detailed above. This model was informed in line with the NICE reference case and the model parameters reflect the outcomes of the previous chapters.(118) The impact of survival time upon the most cost-effective strategy was examined, alongside the challenges of assessing cost-effectiveness very close to the end of life. Finally, placing the cost-effectiveness analysis in the context of routine practice, a combined role for cost-utility analysis and routine data was developed. This informed both an estimate of the levels of 30-day mortality which reflect cost-effective care and a novel approach to ensuring the cost-effective diffusion of the stereotactic radiotherapy strategy into routine practice.

Chapter 7 presents:
- The results of a qualitative study which aimed to confirm that the outcomes valued by patients were captured in the model, using a small series of patient interviews. These were analysed using a framework analysis.(132)

Chapter 8 provides:
- An analysis of the fractionation patterns and 30-day mortality of palliative radiotherapy in the English NHS using the National Radiotherapy Dataset. Variation in 30-day mortality was assessed both with and without adjustment for co-variables using funnel plots. Finally, the results of the cot-effectiveness analysis were considered in the context of this routine outcomes data.

The following figure provides a diagrammatic representation of the whole project.
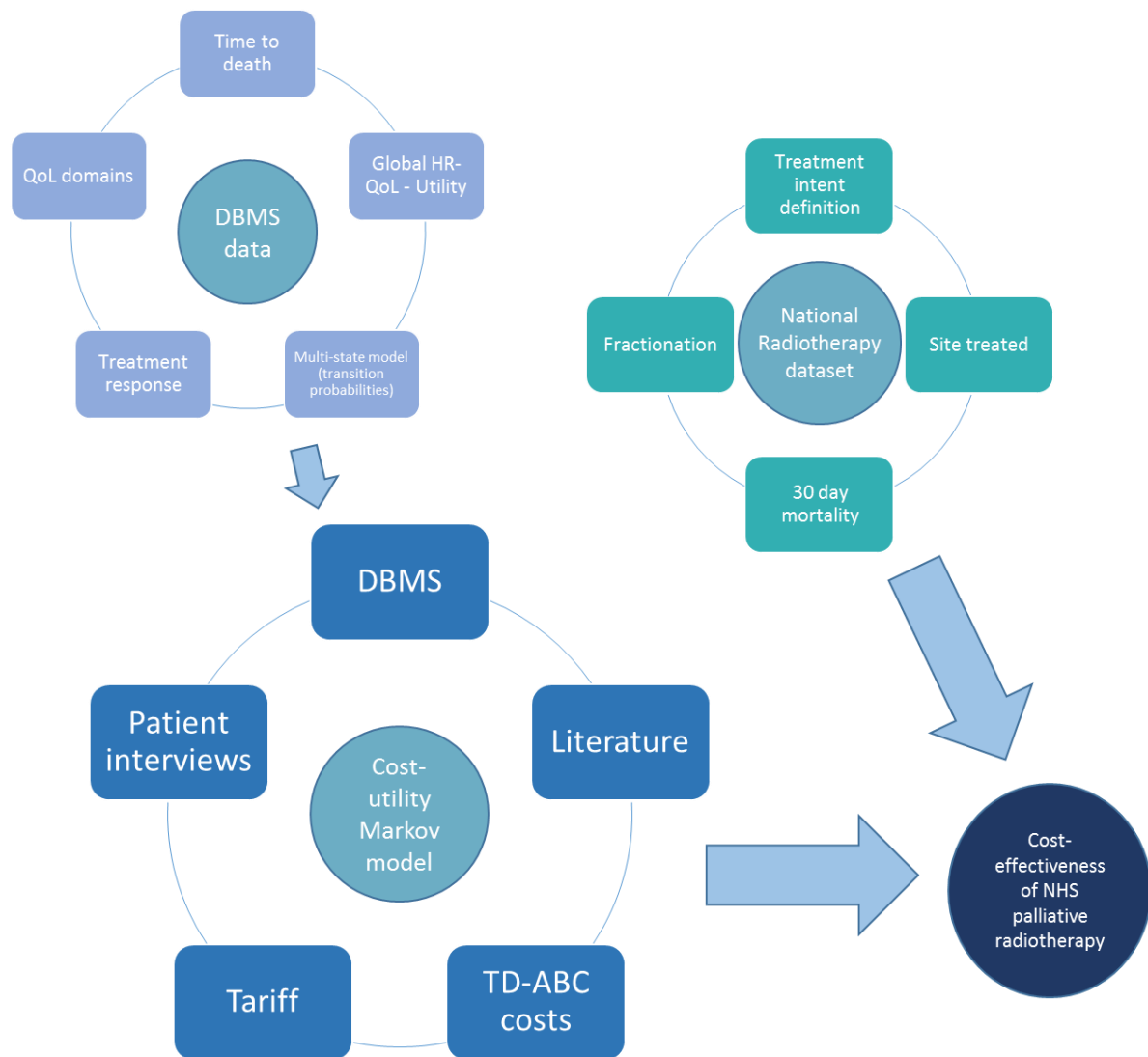
Figure 3. Diagrammatic representation of the study.

1.5.1 *Ethics approval*

This work received ethical approval from the Yorkshire and the Humber – South Yorkshire Research Ethics Committee (REC reference number 17/YH/0101).

2 Reviewing the evidence base supporting palliative radiotherapy for bone metastases

One of the principle aims of this thesis is to assess the cost effectiveness of palliative radiotherapy for bone metastases. Before that can be done, however, information on response rates following differing treatment strategies (conventional external beam radiotherapy (cEBRT), best-supportive care and high-dose highly conformal stereotactic ablative body radiotherapy (SABR)) are required. Raw data, from the Dutch Bone Metastasis Study (DBMS), were available to inform the cEBRT strategies.(16) There is a need, however, to confirm that this will provide a reasonable representation of the wider literature. In addition, no systematic review or meta-analysis of pain response outcomes following SABR is available. The following systematic reviews aim, therefore, to address these questions.

2.1 Assessing the impact of fractionation in palliative radiotherapy for bone metastases – update of a meta-analysis

The comparative efficacy of single fraction with multiple fraction radiotherapy treatments has been assessed previously in meta-analyses, conducted by the Cochrane collaboration (43) and subsequently updated by other teams. The most recent of these was published in 2012. (10,133,134) Given the time elapsed a further update was required so this review aimed to identify any more recent randomised studies addressing this question and consider the extent to which these new studies might change the results of the existing meta-analyses.

2.1.1 *Methods*

The searches detailed by the original Cochrane review were reproduced in Ovid Medline, EMBASE and Scopus (searching for studies referencing the original Sze et al. systematic review and allowing capture of conference abstracts) for all publications between 1st Jan 2010 and 3rd February 2017 to ensure all more recently published studies were captured.(10,43) De-duplication was carried out and studies screened by title and, where necessary, abstract or full text. Only randomised studies, comparing differing radiotherapy fractionation regimens, in patients with uncomplicated bone metastases from metastatic solid-organ tumours were included. The studies identified for inclusion were assessed for risk of bias using the Cochrane collaboration tool.(135) Pain response outcomes were extracted and response assessment was assessed relative to the International Consensus on Palliative Radiotherapy Endpoints (ICPRE).(130)

2.1.2 *Results*

Searches of Ovid Medline, EMBASE and Scopus, yielded 377, 894 and 204 results respectively, a total of 1475. De-duplication removed a total of 129 results. Subsequent screening identified only 6 new randomised studies published or presented since publication of the last systematic review. Figure 4 shows a PRISMA diagram detailing the searches and screening. The remaining studies were identified as not relevant on the basis of being non-randomised, investigating a different intervention (frequently systemic treatments for bone metastases, dose of single fraction

cEBRT or SABR) or considering the wrong patient population. Many of the studies identified fell into more than one category.

Figure 4. PRISMA diagram for systematic review to update previous systematic review of the impact of fractionated radiotherapy upon bone metastases.
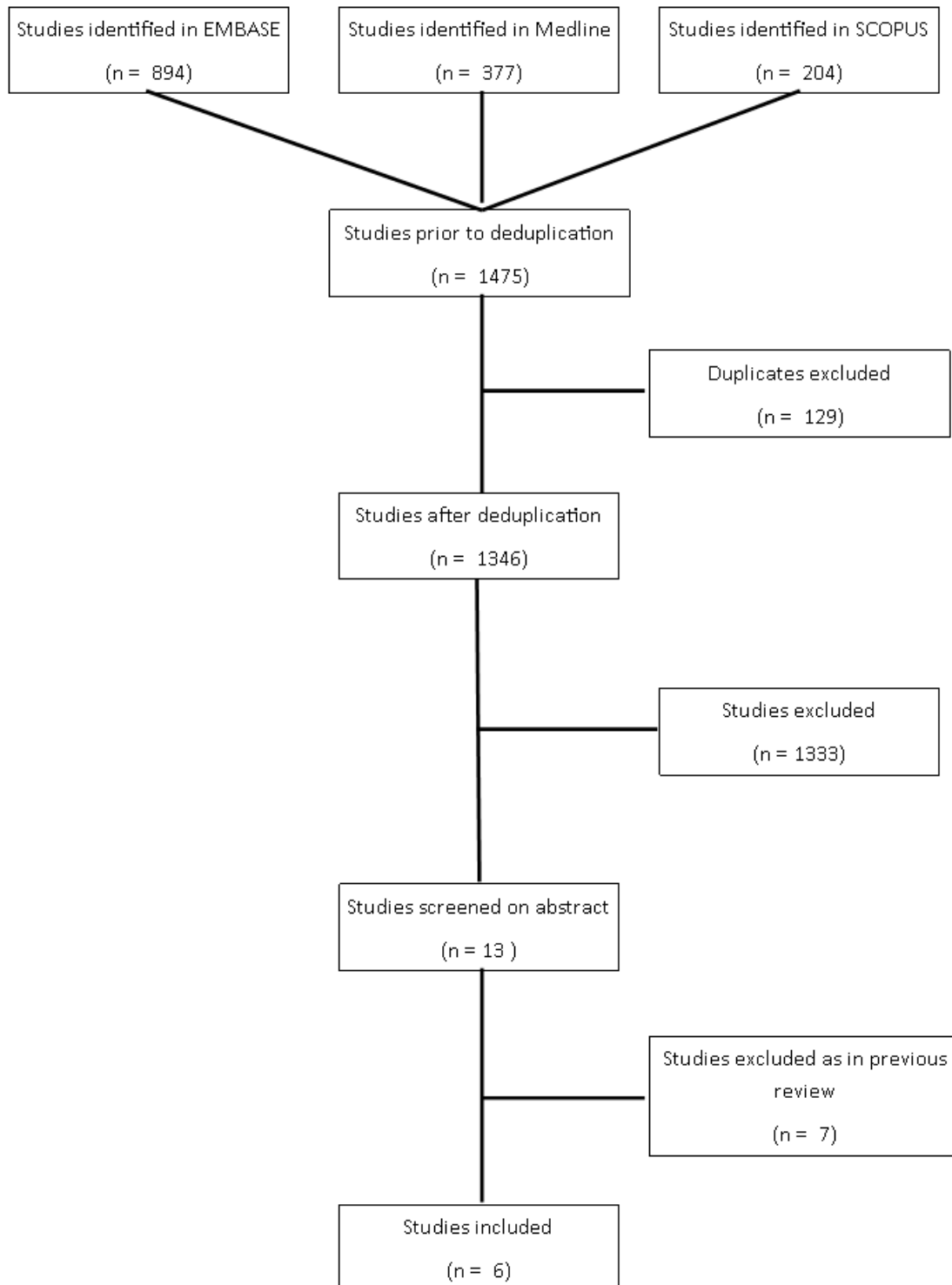
In total the 6 studies identified included 470 randomisations. 208 individuals received a single fraction of palliative radiotherapy (8Gy in all but 26 patients treated by Kumbhaj et al (136) who received 6.25Gy) and 262 received a fractionated course (104 received 20Gy in 5 fractions whilst 158 received 30Gy in 10 fractions).

Study	Year	Arms	Number randomised (*assessable*)*	Follow-up timing	Pain response assessments	Who assessed pain	Pain response definitions	Response rates	Re-irradiation rate **
Anter	2011-2013 (2015)	8Gy in 1# vs 20Gy in 5#	n=100 (51 vs 49) (*44 vs 44*)	12 wks	0-10 point numerical scale	Patient	CR – no pain, PR – reduction >1 pt. No adjustment for analgesia.	Overall rate 75% vs 74% (CR 18% vs 22%)	Not reported
El Hawwari et al.	2007-2009 (2012)	8Gy in 1# vs 20Gy in 5# vs30Gy in 10#	n=120 (40 vs 40 vs 40) (*28 vs 30 vs 28*)	12 mths (Unclear)	4 point graded scale (none, a little, quite a bit, very much)	Completed by physician at review	>25% decrease from initial score. Partial vs complete response not defined. No adjustment for analgesia.	Overall response rate 74%, 76% and 75% respectively.	15%, 12.5% and 7.5% respectively.
Gutierrez Bayard et al.	2005-2006 (2014)	8Gy in 1# vs 30Gy in 10#	n=90 (45 vs 45) (*45 vs 45*)	5 yrs (4 wks and 3 mths)	0-10 point VAS.	Unclear	CR – no pain, PR – reduced by >1 pt. No adjustment for analgesia.	CR – 17% vs 18%. PR – 62% vs 70%	26.6% vs 8.8% (assessable, ITT not reported)
Kumbhaj et al. (abstract only)†	2010-2013 (2013)	6.25Gy in 1# vs 30Gy in 10#	n=51 (26 vs 25)	1 mth (1 mth)	VAS	Unclear	Unclear	NR. Only aggregate pain scores reported.	NR
Majumder et al.	2010-2011 (2012)	8Gy in 1# vs 30Gy in 10#	n=64 (31 vs33) (*24 vs 29*)	Unclear (Unclear)	0-10 point VAS.	Unclear – single # telephone follow-up.	CR – no pain and no analgesia increase. PR reduced by >1 pt without analgesia increase. Pain progression increase >1.	PR – 77% vs 85%. All other patients had pain progression.	NR
Malik et al (abstract only)	(2012)	8Gy in 1# vs 20Gy in 5# vs 30Gy in 10#	n=45 (15 vs 15 vs 15)	Unclear (1 mth)	5 point verbal rating scale (0-4)	Unclear	Overall response – a decrease in pain by at least 1 point. CR – reduction to no pain. No adjustment for analgesia.	Overall response 71.4%, 73.3% and 73.3%. CR – 20% in all arms.	NR

Table 2 Summary of new studies included in updated systematic review of cEBRT fractionation. *Numbers randomised are the assessable individuals. Randomisation of unassessable individuals not reported. ** Re-irradiation rates are reported for the intention to treat population. † Included only patients with prostate cancer. NR – not reported. VAS – Visual analogue scale. CR – complete response. PR – partial response. ITT – Intention to treat.

2.1.2.1 Study quality

Risk of bias was either unclear or high for all six studies.(136–140) In none of the studies was a power calculation carried out, despite the non-inferiority question addressed. This may result in the trials delivering a misleading non-inferiority result due to a lack of statistical power. None of the studies reported that patients or clinicians were blinded to the treatment received and details were not provided about the randomisation procedure carried out. Non-standard response definitions were used by all six studies; Majumder et al adjusted for analgesia use but used a five point scale and did not recognise the possibility of no response, Kumbhaj et al. reported only average visual-analogue scale (VAS) scores before and after treatment, whilst Anter, Malik et al, Gutierrez Bayard et al. and El Hawwari et al. all failed to adjust for analgesia usage. It was unclear in all but two studies whether pain response was assessed by the patient or clinician; Anter used patient/carer reported pain scores and El Hawwari et al used clinician assessed pain response at clinical review. Anter, Gutierrez Bayard et al. and Kumbhaj et al. provide a clear definition of the timing of response assessment, this was unclear in the remaining three studies.

Only Anter provided adequate information regarding losses to follow-up. No other studies provided this information or raw numbers of responders, making it impossible to determine if the outcomes published reflect responses in assessable patients or on an intention to treat basis. Details of the six included studies are provided in Table 2.

2.1.2.2 Outcomes

The response rates reported in the six included studies are shown in Table 2. Overall response rates following single fraction treatment ranged from 71%-79% with complete response in 17-20%, multiple fractions showed response rates of 73%-88% with complete response in 18-22%. None of the studies demonstrated a significant difference between single fraction and fractionated treatments.

Only Gutierrez Bayard, L et al. and El Hawwari et al. report retreatment rates. Re-irradiation was seen in 27% and 15% of patients respectively following single fraction treatment and in 9% and 8% following 30Gy in 10 fractions.

2.1.3 *Discussion*

In the original review this work was based on, Chow et al reported a meta-analysis of 25 randomised controlled trials, including a total of 5,617 treatments (2,818 single fraction and 2,799 multiple fraction courses). Intention to treat response rates (60% and 61% for single and multiple fraction treatments respectively) and response rates in the assessable population (72% versus 74% respectively) were reported. With complete response rates of 23 and 24% on intention to treat analysis, compared to 28 and 30% for assessable lesions.

The response rates seen in the additional six studies included here are higher than those reported in the previous meta-analysis, more closely reflecting assessable response rates (overall response

rate 72% vs 74% respectively and 28% vs 30% for complete response).(10) As such, it is likely that the reported response rates represent responses in assessable patients only (although this is unclear in 3/6 manuscripts). In addition, failure to adjust for analgesia use may in part explain the discrepancy whilst the use of non-standard response definitions and times is also likely to have contributed. Only Majumder et al. adjusted pain assessments for analgesia use as per the ICPRE published in 2002.(141,130,140) The response rates seen in this trial are, however, difficult to interpret due to the definitions used failing to recognise the possibility of no response.

The previously demonstrated non-inferiority of single fraction radiotherapy compared to fractionated treatment is replicated in these studies. The included studies randomised a limited number of patients (470) in comparison to the number in the existing meta-analysis (5,617). Inclusion of these results is therefore unlikely to modify the overall results. Finally, the above listed methodological and reporting difficulties make direct comparison and synthesis of these new studies with the existing meta-analysis of limited value. The meta-analysis results were therefore not updated.

Subsequent to the completion of this review an update of the previous meta-analysis was published. This included five of the studies identified here (excluding Kumbaj et al as this was only available in abstract form). Notably the published outcomes of this meta-analysis demonstrate a 61% and 62% response rate following single fraction and multiple fraction treatments respectively (pooled odds ratio=0.98 (95%CI 0.95-1.01). The previous meta-analysis reports rates of 60% and 61% (pooled odds ratio = 0.98 (95%CI 0.95-1.02). As such the updated meta-analysis again does not change the conclusions of the previous study.

The data used to inform the economic model (Chapter 6) was collected in the Dutch Bone Metastasis Study (DBMS).(16,86) This was the single largest study included in the two meta-analyses discussed here and, as such, provides a significant component of the data included. Response rates are at the upper end of those included within the meta-analysis (overall response rates 68% following single 8Gy and 69% following 24Gy in 6 fractions). Re-irradiation was seen in 25% following an 8Gy dose and 7% following 24Gy in 6 fractions, comparable (although slightly higher following 8Gy) with the overall rates of 20% and 8% reported in the meta-analysis. Pathological fracture rates were found to be no different between the two arms (as replicated in the meta-analysis) and are therefore not included within the economic model.(87) As such, the outcomes of this study lie within the expectation of outcomes identified in the overall meta-analysis.

2.1.3.1   Alternative treatment strategies

The above studies do not provide evidence to support a comparison between palliative radiotherapy and best-supportive care, or indeed alternative treatment modalities. Given that eligibility for study recruitment in all of the above studies was determined by the presence of significant pain there is a risk that some of the responses attributed to palliative radiotherapy

represent response to increased analgesia after recruitment or indeed, regression to the mean.(142) The extent to which this is the case cannot be elucidated from these trials and no randomised placebo controlled trials are available. Other information which might help to confirm the role of palliative radiotherapy as compared to placebo would be evidence supporting the presence of a dose-response relationship and data informing comparisons to alternative treatment modalities.

2.1.3.1.1 The optimum dose of single fraction cEBRT

The comparisons between different single fraction doses provide the only evidence supporting a dose-response relationship in palliative radiotherapy for bone metastases.(143,144) These studies report that a 4Gy dose delivers inferior rates of pain response compared to a single 8Gy dose.

Hoskin et al published the first of these in 1992.(145) This study randomised 270 patients to receive either 8Gy or 4Gy for clinically diagnosed pain due to bone metastases. Patients with an estimated prognosis of less than 6 weeks were excluded. Pain was assessed by the patient at baseline, 2, 4, 8 and 12 weeks using a 4-level categorical scale (none, mild, moderate and severe). No adjustment was made for analgesic usage, in line with other studies at this time. 75% of patients returned the pain chart at the 4 week point. Response rates at this point were 69% following single 8Gy and 44% following 4 Gy (p<0.001). This was the time point at which separation between the two arms was maximal, by 8 weeks the response rate following 8Gy was 70%; stated to be only marginally superior to the 4Gy response rate. No difference in durability of response or proportion of complete responses was demonstrated. Re-irradiation was more frequent in the first 12 weeks following 4Gy (20%) than 8Gy (9%) although it is recognised that this may in large part reflect willingness to re-treat rather than a clear increase in the indication for re-irradiation following 4Gy. The study was unblinded resulting in a risk of bias.

At a similar time Jeremic et al conducted a second unblinded, randomised study comparing pain relief in 327 patients who received single 8, 6 or 4Gy treatments.(144) Again, this was conducted prior to the development of the ICPRE and pain response was assessed using a four point scale without adjustment for analgesic usage. Pain assessment was at 1, 2, 4, 8, 12 and 24 weeks. Pain scoring was not always patient-reported. Whilst potentially a limitation, this latter element ensured that 100% of pain response questionnaires were completed up to 8 weeks. No details are provided about the randomisation process. Pain response at 8 weeks was reported in 78% following 8Gy, 76% following 6Gy and 59% following 4Gy (p=0.002 for 8Gy versus 4Gy comparison). At no point is a significant difference between 6Gy and 8Gy treatments whilst the comparison between 4Gy and 6Gy is significant at all points except 1 week post treatment. Durability of response was found to be no different between the treatment arms. Extensive comparisons are made between treatment arms and at various time points, no correction for multiple testing is reported. Of note, Jeremic et al do not report outcomes beyond 8 weeks post treatment stating that response rates rose sharply at this point due to high rates of mortality, particularly in non-responders.

A further, larger and more recent study was published by Hoskin et al in 2015.(143) This international trial compared 8Gy and 4Gy single fraction treatments in patients with a prognosis of greater than 12 weeks. It used multiple different methodologies to assess response rates; a 4-level categorical scale and 100mm VAS (>10mm considered response)). Adjustment was made for analgesia, however, the outcomes presented are markedly different depending upon the method and time-point used to assess pain response. A Bonferroni correction for multiple testing is reported. Using the ICPRE VAS based definition of response no difference in response rates at individual time-points were demonstrated between the two regimens, excepting a comparison made between complete response rates at 4 weeks (in which the numbers are extremely small) and overall response rate at 52 weeks. Overall response, in assessable patients at four weeks, was seen in 86% following a single 8Gy dose and 82% following a single 4Gy dose (p=0.2) whilst across all follow-up this was 90% and 86% respectively (p=0.01). Using the categorical scale, response is reported in 88% following 8Gy and 80% following 4Gy across all follow-up points. At four weeks these were 83% and 71% respectively. These response rates are higher than previously, although more than 10% of patients in each arm were lost to follow-up and no analysis of the total treated population is reported, thus potentially explaining the high response rates. In terms of the response assessment, it is unclear which of the pain response measures is considered to be the primary end-point. In addition, pain appears to be clinician reported and given that the study was not blinded, this poses a significant risk of bias. The authors note that the endpoint measurement and definition has a marked impact upon the study interpretation; the more sensitive VAS measurement resulting in lessened or absent difference between the treatment arms. A further acknowledged limitation of this study was that its participants were predominantly recruited from a limited numbers of centres.

Jeremic et al report re-irradiation occurring in 42% of patients receiving single 4Gy dose and 48% following single 8Gy dose (p=0.71). Notably this study was carried out before single 8Gy treatments were accepted as being non-inferior to higher doses. Conversely, Hoskin et al. implemented strict criteria for re-irradiation and rates seen were lower than those in previous studies; 14% following 8Gy single dose and 22% following 4Gy treatments (p=0.01). Despite strict re-irradiation criteria the authors state that there remains potential for willingness to re-treat to influence the rates observed, particularly in the 4Gy arm. The findings in this study do support the possibility that re-irradiation rates are now lower following single 8Gy treatments than they were previously. This may be due to increased clinician confidence in the regimen or greater systemic therapy options. Unpublished data by van der Velden et al. supports the finding that re-irradiation in routine practice is now lower than has previously been reported.

None of the above studies were blinded. This is of particular concern where an outcome such as pain control is assessed, especially if clinicians may not have complete equipoise at an individual patient level. These studies all included a single fraction regimen so blinding would be technically feasible and, given the doses involved, patients would not need to be unblinded in order to receive re-irradiation with a single 8Gy dose.(11) In addition, the clear differences in outcome

demonstrated by Hoskin et al based upon response measurement and definition suggest further consideration of appropriate end-points is needed.(143)

2.1.3.1.2 Intravenous bisphosphonates

Only a single trial exists making the comparison between palliative radiotherapy and an alternative treatment modality.(15) This study by Hoskin et al investigated the comparison between a single intravenous bisphosphonate dose (6mg Ibandronate) and an 8Gy dose of radiotherapy in patients with prostate cancer and a prognosis of >3 months. Bisphosphonates had previously been shown to reduce skeletal events in patients with bone metastases and improve pain acutely.(146,147)

Median survival in this study was >12 months. Response rates for Ibandronate and radiotherapy were 49.5% and 53.1% respectively at 4 weeks and 56.1% vs 49.4% respectively at 12 weeks (using ICPRE definitions). Nausea and diarrhoea were more frequent following radiotherapy but with more frequent other (unspecified) toxicity following Ibandronate.

A meta-analysis by Wong et al. (carried out in 2000) examined the role of bisphosphonates in the management of malignant bone pain. They report a modest benefit with a number needed to treat of 11 for pain relief at four weeks and 7 at twelve weeks.(146) The authors state, however, that due to the small numbers of studies, of limited quality, with poorly defined, non-standard endpoints, robust conclusions cannot be drawn. Additionally, the bisphosphonates used in the included studies were first and second generation agents limiting interpretation in the context of third generation bisphosphonates and Denosumab.(148)

In addition to the above study Mannix et al developed evidence based guidelines in 2000 to inform the use of bisphosphonates in the management of metastatic bone pain.(149) The literature included within this review is similar to that of the meta-analysis. The review concludes that Pamidronate and Clodronate offer a significant reduction in bone pain within 14 days. Responses were seen in 50-60% of patients with a variety of malignancies, although the evidence was strongest for breast cancer and multiple myeloma.(150–152)

It is notable that the numbers reported in the above reviews are not hugely different to the intention to treat outcomes seen following palliative radiotherapy.(149) The quality of some of this literature, its limited scale and the lack of standardised outcome reporting make direct comparisons impossible.

2.1.4 *Conclusions*

The above radiotherapy studies, as reported, support the presence of a dose-response relationship in single fraction palliative radiotherapy for bone metastases. As discussed above, however, the evidence supporting this is at risk of bias and the optimum end-point measurement is unclear. Radiotherapy is the accepted standard of care for metastatic bone pain, however, no randomised,

placebo-controlled comparisons exist. Given the uncertainty and methodological concerns regarding the low-dose comparisons and evidence of the efficacy of bisphosphonates alone in this setting, this is a significant piece of missing information. The bisphosphonate study reported by Hoskin et al. starts to address the question of the comparability of radiotherapy and bisphosphonates in the relief of metastatic bone pain. Given that no difference in outcomes was observed in this population, other factors, such as patient preference and travel time to nearest radiotherapy centre, might reasonably be included in treatment decisions. The question of a dose-response relationship in single fraction treatments arguably remains an open one.

In addition, the studies conducted to date have actively avoided addressing the question of optimal bone pain treatment in a population very close to the end of life; all excluded patients with very limited prognosis. Subgroup analyses in the DBMS demonstrate lower response rates in those with short prognosis (45% in those surviving less than 12 weeks versus and 87% in those surviving >1 year).(92,93) The comparison between a single 8Gy and 24Gy in 6 fractions remained unchanged, however, as response rates drop the extent to which palliative radiotherapy improves pain control beyond what might be achieved through holistic palliative care or systemic bone-directed therapies is unclear and treatment burden through travel and toxicity in this population is relatively greater.

Further randomised studies in this area are needed. Before these are conducted the ICPRE should be re-visited. Subsequent trials should, ideally, include randomisation to bisphosphonates or alternative bone directed therapies and supportive care options. Such studies should prospectively recognise the heterogeneity of the treated population and assess the role of these treatments in patients very close to the end of life. In the absence of a clear dose-response relationship and placebo controlled trials, the true incremental benefit of palliative radiotherapy remains unclear.

2.2 Systematic review of the role of stereotactic radiotherapy for bone metastases

2.2.1 Introduction

The difference in re-irradiation rates observed between fractionated and single fraction conventional radiotherapy (cEBRT) for bone metastases appears to have resulted in a persistent belief amongst clinicians that higher biologically equivalent doses of radiotherapy may deliver more durable pain control.(82) As such, efforts are under way to improve the quality of pain relief delivered by palliative radiotherapy to bone metastases through the use of higher dose radiotherapy. With recent improvements in the availability of highly conformal, image-guided radiotherapy, the hypothesis has arisen that stereotactic radiotherapy (with much higher radiobiological doses to smaller conformal volumes) may offer improved local disease control and better, more durable pain relief. Early single arm studies have provided support for this hypothesis. No randomised data have been published to address this question, however, and no systematic review is available to formally assess the results of all available single arm series.

As such, this study aimed to determine pain response rates following SABR for bone metastases. It did this by systematically identifying all of the available literature informing the use of stereotactic radiotherapy for bone metastases from solid organ malignancies.

This work was carried out in collaboration with Dr Joanne van der Velden (JVDV, University Medical Center Utrecht) and her supervisory team in The Netherlands. This collaboration was set up after the study protocol submitted by JVDV was identified on PROSPERO prior to work commencing.(153) Initial searches and screening for the time period prior to April 2016 were carried out by the team previously. I updated these, carried out screening of all manuscripts identified, assessed study quality, completed data extraction and wrote the systematic review manuscript.

The study, initially developed by Dr van der Velden and published in collaboration, reported both local control and pain control outcomes. Only the outcomes for pain control are reported here as this is the more clinically relevant outcome, providing patients with improvements in HR-QoL. The results of this study were used to inform the response parameters of the subsequent health economic model (chapter 6).

2.2.2 Methods

This systematic review was carried out in line with PRISMA guidelines and the MOOSE checklist.(154,155)

2.2.2.1 Study inclusion criteria:

All original studies published in English, with full text available, reporting pain response or local control following SBRT to bone metastases from solid organ malignancies, using 1-6 fractions, were included. No time limit was placed on inclusion and non-randomised studies were included reflecting the lack of randomised data available to address this question. Studies could include patients with or without prior history of radiotherapy or surgery. It was not possible to exclude low dose SABR treatments as these were not reported separately. All studies were independently assessed by at least two authors for eligibility based on their title and abstract. Where uncertainty remained the full-text was reviewed. Where individual patients were included in multiple published series, the most complete or recent article was cited.(135) If less than 10 patients overlapped, both study populations were included. As such a small number of individuals will have been included twice.

2.2.2.2 Search strategy:

A structured search was conducted in PubMed, Embase, and Cochrane electronic databases on March 16th 2016. The search was updated on April 14th, 2017. Reference lists from included articles were cross checked to identify additional articles. Search terms used were:

"bone and bones" OR bone OR bones OR bony OR skeletal OR osseous OR spine OR spinal

AND

neoplasmata OR metastasis OR metastases OR metastatic OR neoplasm OR neoplasms OR cancer OR cancers OR carcinoma OR carcinomas OR tumor OR tumors OR tumour OR tumours

AND

radiosurgery OR "stereotactic body radiotherapy" OR "stereotactic body radiation therapy" OR "stereotactic body radiosurgery" OR "stereotactic radiosurgery" OR "stereotactic spinal radiotherapy" OR "stereotactic spinal radiosurgery" OR stereotaxis OR sbrt OR srs OR sbrs OR ssr OR sabr OR "stereotactic ablative"

2.2.2.3 Data extraction:

The primary outcome of interest was pain response reported on a per patient basis. The definition of pain response was that used in the original study. Where possible response rates were identified on both an intention to treat and assessable basis. If it was not clear which were reported it was assumed the results reflected assessable patients only (a conservative assumption). For every study, it was recorded whether the response was reported on a patient or lesion level. Pain response definition, response time-point, adjustment for analgesia, how pain response was collected (e.g. clinician or patient, 0-10 point numerical rating scale (NRS)), baseline patient and primary tumour characteristics, treatment dose and fractionation were extracted for all included studies. As most studies reported the Karnofsky performance score (KPS), if performance status was reported as WHO or ECOG performance status it was converted to the KPS.(156) Secondary endpoints were duration of pain relief, toxicity and quality of life.(157) Vertebral compression fracture (VCF) rates were not assessed as these have been considered elsewhere.(158) Many included articles did not report this outcome. Conversely, articles considering this outcome were excluded if they did not report the primary outcomes of interest. This prevented assessment of VCF in this study. All data were extracted by both JVDV and KS independently directly from the text or calculated independently using available information. Where reported the overall survival of the study population was identified.

2.2.2.4 Study quality:

Study quality was assessed using pre-defined criteria reflecting the STROBE criteria for reporting observational studies.(159) In addition, fields specifically relevant to the assessment of pain response for bone metastases were included. Specifically, the definition of response used was assessed relative to the International consensus guidelines including whether adjustment for analgesia was made, if pain was reported by patients using a 0-10 point numerical rating scale and how response was defined using this information.(130) Additionally, the time point for

response assessment and whether response was reported for assessable or intention to treat populations (recognising the extent of attrition and missing data) was determined.

Studies were separately assessed using the Institute of Health Economics, quality appraisal checklist for case-series studies.(160,161) This tool was developed using an initial Delphi methodology and subsequent principal components analysis to support the review of case-series literature for use in HTA. Studies are assessed across a range of domains. A total maximum score of 40 can be achieved and whilst this cannot be thought of as providing a precise estimate of study quality it does provide an indication of the relative risk of bias.

2.2.2.5   Quantitative synthesis:

The original protocol submitted to PROSPERO included a plan to carry out a meta-analysis.(153) Meta-analysis outcomes are not reported as the systematic review revealed marked heterogeneity and risk of bias in the included studies making quantitative synthesis inappropriate.

2.2.3   Results:

The initial search yielded 2619 articles. After screening of these articles on title and abstract, 343 studies proceeded to full-text screening, of which 290 were excluded (Figure 5). Exclusions were predominantly of conference proceedings, studies reporting duplicate data or not reporting bone metastasis outcomes separately in the context of a case-series reporting more general SABR outcomes. One additional article was included after cross-referencing since it used 'high dose' instead of 'stereotactic radiotherapy' in the title.(162) The search update yielded five more articles,(162–167) of which two articles provided updated information about already included studies replacing the earlier included ones.(165,168)

A total of 57 studies (reporting outcomes for 3995 patients) were included in the overall review. 38 reported pain control outcomes (at least 2185 patients and 2947 lesions) and 45 local control (at least 3455 patients and 4683 lesions). 26 studies reported both outcomes. Patient and lesion numbers are not certain due to reporting limitations in the included studies. Only five included pain control studies (169–173) reported outcomes for more than one hundred patients. The median number of patients per study was 47 in pain control studies.

Figure 5. PRISMA diagram of studies included in the systematic review.
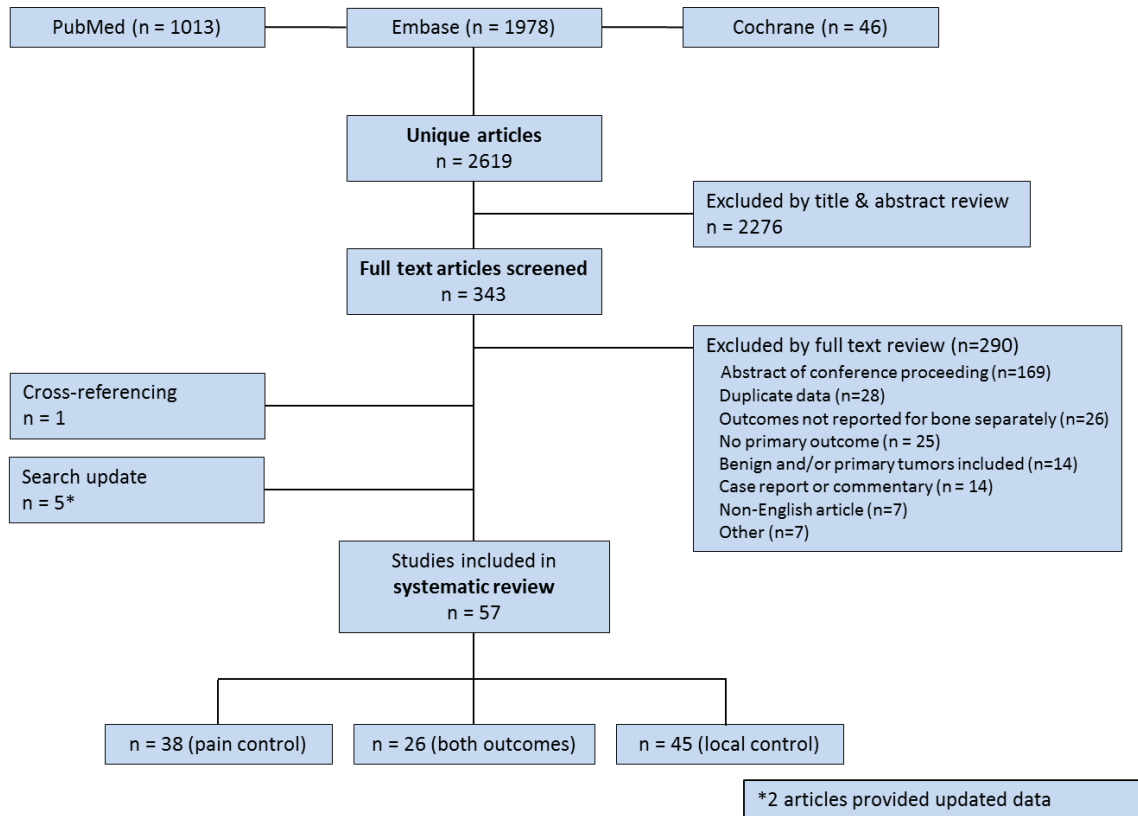
2.2.3.1 Risk of bias:

One of the 38 included pain control studies reported outcomes from a randomised phase two trial.(174) A further two non-randomised phase 1-2 trials were included.(169,175) Seven pain control studies reported a prospective design.(172,176–181) In the remaining 28/38 pain control studies a retrospective cohort design was used or the study design was not clearly reported. Given the increased risk of bias present with non-randomised data this is a significant limitation of the included literature.

When assessed using the IHE appraisal checklist the included studies scored between 14 and 34 out of 40, median score 24.(168,182) These scores were predominantly limited by the retrospective, single centre design of the majority of included studies. Further specific areas of concern for risk of bias or unclear risk were identified as outcome definition, lack of blinding, outcome timing and incomplete data availability. Detailed consideration of these and other areas at risk of bias are discussed below.

2.2.3.2 Study outcomes and heterogeneity:

Where the total treated population were considered (intention to treat (ITT)) the range of pain control (PC) outcomes varied from 27% (n=28)(183) to 98% (n=52)(184). Notably the extent of

this range is defined by the outcomes of smaller studies, potentially reflecting outlying results due to statistical chance.

2.2.3.2.1 Outcome measurement and definition:

The measurement and definition of PC varied widely between studies. Seventeen (44%) studies reported no information about measurement tools or response definition. In those where this information was included a majority used a 0-10 NRS or VAS for measurement of pain. Response definitions varied: four studies used the ICPRE (174,185–187), and a further two used the RTOG 0631 trial protocol definitions.(188,189) These studies report total treated population (ITT) PC of 60-77%. A further four studies reported adjusting response rates for analgesia.(172,190–192) ITT PC rates in these studies ranged from 65% (191) to 88%.(192) The largest of these series (n=336) reports long-term pain improvement in 86% of treated lesions.(172) In this study, however, it is unclear how adjustment for analgesia was made. Long-term pain improvement was defined as pain control at last clinical review although no protocol for follow-up frequency was reported. Unusually, Heron et al asked patients to classify their pain relative to baseline at 1-2 weeks and at intervals beyond this up to 12-24 months.(171)

In 16/38 studies (42%), patient-reported outcomes (PROs) were used.(169,172,174–180,185–187,193–196) In the remaining studies this was not clearly reported. Where PROs were reported the mechanism of collection was frequently not clear. In addition, the time-point used to report PR was unclear in a majority of studies (21/38).

A limited number of studies reported rates of attrition, due either to death or loss to follow-up. As such it was often unclear if outcomes were for assessable patients only or on a ITT basis. Where both are reported the ITT PC result was lower than for assessable patients only (62% vs 82%,(197) 47% vs 62%,(198) 60% vs 69%,(174) 77% vs 91%,(173) 61% vs 93%,(199) and 71% vs 88% (192).(10) Overall response rates for PC varied from 38% (n=28) (183) to 100% (n=18)(200)) in assessable patients.

Four studies reported the duration of response. Lee et al showed a median duration of pain relief of 3.2 months after SABR in 57 patients with spinal metastases.(192) A small study including 18 patients with bone metastases from renal cell cancer (RCC) found that 32% of patients who responded had a symptomatic recurrence after a mean of 2.3 months.(201) In two larger, mixed diagnosis studies, Hunter et al report durability of PC of 4.8 months following SBRT whilst in contrast, Ryu et al report a much longer median duration of PC of 13.3 months in 49 patients with a single isolated spinal metastasis.(179,189) Notably, the frequency of follow-up in these studies was not clearly reported,(189,201) reported to be flexible (179), or stated as every 1-3 months.(192)

2.2.3.2.2 Study population:

A majority of studies included patients with various primary cancer diagnoses (29/38 PC studies). The remaining studies focussed upon an individual diagnostic group (e.g. hepatocellular carcinoma (HCC) (TTP PC rate 64%‑92%),(186,202) breast (PC in assessable patients 100%),(203) prostate (ITT PC rates 83%‑92%),(176,204) and renal cell cancer (RCC) (ITT PC 62%‑78%, not all studies reported ITT outcomes).(187,194,197,201)

In a majority of studies treatment was delivered to spinal disease only (32/38 studies). Only eight studies included other sites of disease with ITT PC response rates of 60-88%.(174,176,177,197,201,204) 14/38 studies report outcomes only for patients with uncomplicated bone metastases demonstrating ITT PC rates of 60-92%. (171,172,174,175,177,178,185,187,189,193,194,201,204,205) Whilst a large proportion of other studies included this patient group (17/38 studies) the extent was not always clear (where reported this ranged from 20-47%), and outcomes were not reported separately for patients with malignant spinal cord compression (MSCC) with only regression model results presented. For example, Lee et al report that patients with MSCC at baseline were more likely, on multi-variable analysis, to experience pain recurrence after initial relief (p=0.001).(192) Anand et al report 95% improvement in PC in patients with epidural compression and 100% in those without. PC was defined as improvement in a 0-10 point VAS of >50%, no adjustment was made for analgesia usage, however, and no time-point was specified.(184)

Wide variation is seen in the overall survival of the study populations (median survival ranging from 8 to 30.4 months).(170,174,175,186) This is likely to reflect the variation in baseline characteristics of the study populations. For example, in many studies patients with predicted short survival or poor performance status were excluded (176,202) either from receiving treatment or, retrospectively, based on lack of follow-up data.(206) Lee et al 2012 demonstrate that poor performance status is a predictor of pain recurrence post response on multi-variable analysis (p=0.01).(192)

2.2.3.3 Treatment:

Dose schedules ranged from 6Gy to 52.5Gy in 1-6 fractions in the included studies and planning margins varied from 0 to 5 mm. A simultaneous integrated boost approach was used in 3 studies.(175,184,185)

Heron et al. report no difference in PC between fractionated (mean BED 35.7Gy) and single fraction (mean BED 43.2Gy) SABR (70% versus 71% at 12 months) in a mixed diagnosis population, although higher rates of pain progression were seen following fractionated treatments. Lee et al 2015 also report no significant difference in PC between treatments delivered using 1-4 fractions versus 10 fractions in an HCC population, although the hypo-fractionated group experienced superior outcomes.(202) Similarly, Ryu et al report no significant difference in PC

with SABR dose (<14Gy vs >=14Gy) in a mixed diagnosis population, although they stated a strong trend towards increased pain control was observed with dose >= 14Gy. The lack of numerical results mean it is not possible to comment on the magnitude of this possible effect.(179)

Two studies (180,193) reported outcomes for a cohort of patients undergoing combined modality treatment with surgery and stereotactic radiotherapy. In these patients ITT PC was reported to be 86% by Gertszten et al. A further 16/38 studies included variable proportions of patients who underwent surgical decompression or stabilisation prior to stereotactic radiotherapy. Reporting of both prior surgical decompression and concurrent systemic therapy was variable and other studies rarely reported outcomes for these groups separately. As such, it is not possible to draw conclusions about the impact of combined modality therapy or systemic therapy.

A limited number of studies reported outcomes for only those patients known to have received prior radiotherapy. Nikolajek et al report local failure in 12.9% of previously irradiated patients.(182) They do not report PC rates only reporting an improvement in median VAS post treatment in patients with pain prior to SABR (p=0.002). Mahadevan et al and Choi et al both report 65% ITT PC in a re-irradiation cohort (n=34 and n=23 patients respectively).(191,199) These three studies all included a mixed diagnostic cohort. Conversely, 11/38 PC studies excluded individuals who had received prior irradiation to the index site. ITT PC in these studies ranged from 47% to 92%.(198,204) In the remaining studies it was either unclear or a varying proportion of patients had undergone previous radiotherapy with limited reporting of outcomes by re-irradiation. Chang et al report PC at 6 months, 1 year or 2 years for patients who had or had not undergone previous radiotherapy to the index lesion, outcomes were superior in those not previously irradiated although this difference was not significant (n=54 re-irradiation and n=131 initial treatment).(173)

2.2.3.4 Toxicity outcomes:

Overall, 40 out of all 57 studies reported on toxicity. The largest prospective PC study (a non-randomised phase I-II trial) analysed toxicity in 149 patients using patient reported outcomes, and stated that toxicity was mostly mild including grade 1-2 transient numbness and tingling, nausea and vomiting.(169) Grade 3 toxicities included pain, gastrointestinal disturbance, fatigue and diaphoresis (overall 12 events, patient numbers unclear), although no radiation-related spinal cord myelopathy was reported.(169) Similarly, Garg et al reported a total of 48 grade 1-2 toxicity events (patient numbers unclear), two patients experienced grade 3-4 neurotoxicity.(175) Berwouts et al reported pain-flare was observed in 25% of patients undergoing 16Gy dose painting by numbers (DPBN) in their small randomised phase II study. Including these studies, overall ten studies, including 676 patients, recorded toxicity prospectively and reported grade 3 or 4 toxicity in 19 patients (0.03%).(169,175–178,185,193,199,207,208) All other grade 3–4 toxicities reported in prospective studies were treatment-related neurologic

toxicity.(175,178,199,208) Of the 28 studies evaluating toxicity retrospectively, five grade 3 or 4 toxicities (0.002%) were observed in 2033 patients.(163,165,166,170,171,173,183,184,186–188,191,194–198,201,203,204,209–216)

2.2.3.5 Within study comparisons to conventional radiotherapy:

Berwouts et al report a small randomised phase II trial in which 12 patients received cEBRT with a dose of 8Gy, 14 received 6.1-10Gy DPBN based on an FDG-PET-CT and 13 received a single 16Gy fraction using DPBN. The latter two arms were delivered using an IMRT technique. Overall response rates were 53%, 80% and 60% at 1 month respectively.(174) Hunter et al. compared pain control in 110 RCC patients treated with SABR (n=76) or cEBRT (8–30 Gy in 1–10 fractions, n=34). They report no difference in the proportion with PC (62% versus 68% respectively) although cEBRT was associated with higher partial response (56% versus 29%) and lower complete response (12% versus 33%). A non-significant increase in durability of pain response was seen (1.7 months vs 4.8 months, p=0.095) but the difference in FU between the cohorts makes this very difficult to interpret. No overall survival (OS) outcomes are reported although performance status was significantly higher (p<0.001) in the SABR group suggesting this group may be likely to have superior survival.(189)

Gagnon et al report no significant difference in PC between 18 breast cancer patients undergoing stereotactic radiotherapy (prior irradiation having been given to 17) with 18 matched patients undergoing cEBRT. Similarly, Sohn et al report outcomes for a matched cohort of 28 patients with HCC. The decrease in VAS was greater in the SABR cohort than the cEBRT cohort (3.7 versus 2.8, p=0.13) and the overall response rates higher (64% versus 57%) although neither of these differences were significant. No difference was observed in progression-free survival.(186) A similar analysis by the same group considered a cohort of 13 patients with RCC who received SABR. The decrease in VAS was significantly larger in the SABR cohort (p=0.04), although PC rates were again not significantly higher. Progression free survival was significantly higher in the SABR cohort (p=0.01).(187)

2.2.3.6 Model parameter studies:

Given the significant risk of bias in the included studies, marked heterogeneity and limited reporting of outcomes suitable to inform the health economic model it was necessary to identify a small number of studies to inform the model with both base-case and alternative scenarios.

Subsequent to the completion of the above review the first randomised comparison between cEBRT and SABR was published.(217) Given that this is the highest level of evidence currently available the outcomes of this study were used to inform the base-case model parameters. Berwouts et al provides another source of randomised outcomes, however, results are only

reported for 13 patients at 1 month, providing limited information.(174) The two other prospective phase II studies identified included insufficient detail of response rates to be used.(169,175)

Two further studies were identified to inform alternative model parameterisations.(168,185) Both of these studies scored comfortably above the median using the IHE tool to assess risk of bias. This indicates that they are at relatively lower risk of bias than many of the other included studies. They also provide adequate information to inform the economic model. One of these studies is not reported in the above review as the outcomes of the included cohort are reported in a larger, more contemporaneous study.(189) The information provided in this earlier report is more informative for the economic model and therefore is used here. The three studies used to inform the economic model all adjust for analgesia usage and include a limited proportion of patients who have undergone prior surgery or radiotherapy. They also exclude patients with spinal cord compression, therefore more closely reflecting the cEBRT trials.

The studies used to inform the health economic model are detailed below.

Randomized phase II trial evaluating pain response in patients with spinal metastases following stereotactic body radiotherapy versus three-dimensional conformal radiotherapy. Sprave et al 2018.

This small, single institution, non-blinded study, randomised 55 patients to single fraction SABR (24 Gy) or 3D planned, fractionated cEBRT (30Gy in 10 fractions). The primary study outcome was pain response of ≥2 points on a 0-10 VAS at 3 months following treatment (of note whilst the 0-10 scale is referred to a 0-100 scale is illustrated in the figures). Secondary endpoints were pain response at 3 and 6 months according to the ICPRE. Patients with neurological compromise, >2 vertebral bodies involved at the site or > 2 spinal sites, cervical disease, previous radiotherapy to the index site, contraindications to MRI, haematological malignancy and distance to the cord of <3mm were excluded. Notably 11 patients with a pain score of <20/100 at baseline were included, their balance between the treatment arms is unclear.

Pain response was reported to occur significantly more quickly following SABR then cEBRT (p<0.001), the analysis carried out to determine this is not clear. At 3 months following treatment the proportion of patients experiencing a response was 69.6% in the SABR arm and 47.8% in the cEBRT arm (p=0.134). At 6 months this difference had widened with 73.7% reporting pain response following SABR and 35% following cEBRT (p=0.015). Notably, at 6 months complete response was seen in 52.6% of patients undergoing SABR as compared to only 10% of those undergoing cEBRT. Whilst representing small patient numbers this study supports the possibility that SABR may offer superior quality and durability of pain control as compared to cEBRT.

Despite being the highest level of evidence available, however, this study has a number of limitations: 11 patients with no pain at baseline were treated within the trial, their distribution between the trial arms is unclear; this represents phase II data and as such is a small study, conducted in a single centre; finally, the assessment of pain was non-standard.

Stereotactic Body Radiotherapy with Helical Tomotherapy for Pain Palliation in Spine Metastasis. Kim et al 2013

This retrospective study reports pain control outcomes for a mixed diagnosis cohort of 22 patients (31 lesions) treated in Seoul, South Korea. The International consensus guideline definitions of pain response were used with pain symptom data collected during consultations.(130) They state that patients with MSCC were excluded, although in the analysis 6.5% of lesions are identified as being compressive. Only 6.5% had received prior radiotherapy whilst 16.1% of lesions had undergone prior surgery. The dose of SABR was relatively well standardised with 87% of patients receiving 24Gy in 3 fractions. Median overall survival was 10 months and the report includes the clearest information available on attrition and missing outcome data. Using the Institute of Health Economics quality appraisal checklist for case-series studies this study scored 29 out of 40, being limited by its single centre retrospective design but otherwise minimising risk of bias. Overall response rates for assessable and ITT lesions are provided at 2 weeks (PR 25.8% and CR 35.5%), 1 (PR 6.5% and CR 54.8%), 2, 3 (PR 19.4% and CR 51.6%), 6, 9 and 12 months (PR 0%, CR 38.7% and 58.1% deceased).

Single-fraction stereotactic body radiotherapy for spinal metastases from renal cell carcinoma. Balagamwala et al 2012.

This retrospective study reports pain control outcomes for 57 patients (67 painful lesions) with renal cell cancer treated at the Cleveland clinic, Ohio. The study excluded patients with MSCC or spinal instability although patients with neurological deficit not related to MSCC were included. Only 5% of patients had undergone prior radiotherapy to the index lesion. All patients underwent single fraction SABR to a median dose of SABR was 15Gy. Median overall survival was 11.7 months. Partial and complete pain response rates in assessable patients are reported at 2 weeks (PR 35.9% and CR 15.4%, n=39) , 1 (PR 45.8% and CR 43.8%, n=48), 2, 3 (PR 31.3% and CR 40.6%, n=32), 6, 9, and 12 months (PR 9.1% and CR 63.6%, n=11). It is unclear how many patients were deceased and how many were missing at each time point. This study scored 32/40 using the IHE appraisal checklist.

Re-irradiation rates were not reported in any of the studies identified to inform the cost-effectiveness model. Given the need to inform this parameter a pooled analysis of the rates of re-irradiation reported in the previously identified studies was used. In the 12 studies that reported re-irradiation rates 19 patients were re-irradiated following SABR from a total population of 610. An overall re-irradiation rate following SABR of 3.1% was therefore used.

2.2.4 *Discussion:*

This systematic review assessed the available literature reporting the effectiveness of SABR for bone metastases in patients with advanced cancer. More than half of studies reporting ITT PC outcomes demonstrate PC rates of above 75%. Reported toxicity was generally mild. As such, SABR appears to be a safe treatment for bone metastases with PC rates superior to those reported following cEBRT (ITT PC 61%).(10,43) Given the results detailed above, however, there is a need to be critical in interpreting these data as a number of aspects of the included studies may give rise to biased estimates of treatment effect.

2.2.4.1 *Outcome definition:*

The variable definition of PC used between studies is critical. Despite the ICPRE being published in 2002 to ensure comparable outcome reporting between trials the majority of the studies identified here did not incorporate these recommendations into their analyses.(130,141) Of particular concern are the failure of many studies to adjust for analgesia, retrospective designs and the use of clinician reported outcomes.(65) A number of studies reported only average pain scores pre- and post-treatment rather than response rates. This approach is widely discouraged, particularly in trials assessing pain response in patients recruited due to significant pain at baseline. This stems from concern about the potential effects of other interventions (e.g. analgesia) and regression to the mean.(142) Further, even in studies where SABR was reportedly delivered for PC, patients without pain at baseline were included.(169,178,179,212) Notably, those studies where response was assessed in line with consensus guidelines, report lower PC response rates (ITT PC 60-77%) much more in keeping with those seen in cEBRT.

In addition, in most studies it was unclear whether PC was reported for assessable or all treated patients; both are necessary in this fragile patient population where assessment of pain is complex and survival is limited. In studies carried out in palliative populations missing data are inevitable. These can be handled using multiple imputation,(218) however, at a simple level, recognition and reporting of the extent and potential consequences of missing data are required.(219) In many of the included studies it was unclear to what extent data were missing and the consequences of this were rarely recognised. Where both assessable and ITT results were reported, assessable PC was higher than ITT PC. As such, variable response definitions and reporting may explain some of the variation observed between studies and be contributing to the relatively high rates of PC reported.

The time points for outcome measurement were frequently not well defined. Rather than response rates reflecting the proportion experiencing a response at e.g. 1 or 3 months post treatment, any response during follow-up was accepted. This may result in the outcomes seen reflecting the impact of subsequent treatments rather than SABR and being higher than those demonstrated previously for cEBRT.

Finally, toxicity data were predominantly reported by clinicians and collected retrospectively, potentially leading to underestimation of the rates seen. In the prospective studies, however, severe toxicity (grade 3 or higher) was reported in only 0.03%, suggesting that severe toxicity is indeed rare. Although limited information was available to quantify low-grade toxicity this may still impact upon quality of life and, therefore, remains important in informing clinical decision-making.

2.2.4.2 *Heterogeneity and selection bias:*

In observational studies bias may result from a number of methodological and reporting limitations.(62,63) Whilst measurement error is discussed above, two further causes of bias warrant discussion; selection bias and confounding. These result from variation between treatment cohorts in observational studies. If the predictors of treatment allocation, or associated features (confounders), also influence outcomes, treatment effect estimates will be biased. Adjustment can be made for observed variation, however, unobserved variation persists. In this case, the variable inclusion, lack of separate outcome reporting and lack of adjustment for baseline co-variables, may all contribute to the estimated effect of SABR being biased.

The factor most likely to be having this affect is selection bias. It is notable that the median survival of patients included in these studies was significantly higher than that of individuals randomized in previous cEBRT trials (median 7 months)(16) or, indeed, in the routinely treated population (median 4.8 months).(220) In comparison, the studies included here report a median survival of 8–30.4 months. It has been previously demonstrated that patients with survival of over one year following treatment have superior response rates to single fraction cEBRT (85-87%) compared to those surviving less than 3 months (44-47%).(92,93) Within the included studies Garg et al demonstrate a correlation between pain response and survival, whilst in the only randomised study included here Berwouts et al report some of the lowest PC rates following SABR in a population with one of the shortest survival times.(174,175) The better survival of the included populations is likely to reflect exclusion of patients with limited follow-up or poor performance status.(176,206) In particular, patients in the included studies had predominantly good performance status. Performance status has previously been shown to predict pain response, (221,222) and Lee E et al report poor performance status predicts for a lower probability of pain response following SABR on multi-variable modelling (p=0.01).(192) As such, it is clear that the populations included in a majority of these studies were highly selected and this may have had a significant influence upon the observed outcomes.

Other sources of heterogeneity in the treated populations which may potentially impact upon the reported outcomes include the variable inclusion of patients with MSCC and prior irradiation. In contrast to the possible impact of prolonged survival on response rates these factors may result in reduced response rates as compared to previously published cEBRT studies in uncomplicated bone metastases. For example, Lee et al demonstrate that the presence of MSCC predicts for a

lower probability of pain response (p=0.001) on multi-variable modelling whilst prior irradiation was reported to be associated with a non-significant reduction in PC.(166,192) It is also possible, however, that the effect of MSCC and re-irradiation may be mediated through radiotherapy dose. If a dose-response relationship is present (as supported by Choi et al.)(199) and dose to the tumour is limited (by proximity to the spinal cord or previous radiotherapy) the inclusion of patients with MSCC and prior irradiation might result in poorer outcomes.(223) Conversely, it may be that tumours which result in MSCC or relapse after previous radiotherapy are inherently less likely to respond to SABR. The studies included here often included small patient numbers and multi-variable regression was frequently not attempted. Whilst a dose-response relationship is an intuitively appealing hypothesis, given the non-randomised nature of the studies, variable reporting and limited adjustment for baseline co-variables it is not possible to confirm this in the available studies.

Finally, heterogeneity is present in the considered studies as a result of varying treatment regimens. This may result from variation and evolution in the radiotherapy dose-fractionation schedules used, incorporation of surgery into the treatment pathway or concurrent and subsequent systemic therapy.(193,194)

The heterogeneity resulting from the above outlined study variation is clinically significant and likely to be resulting in biased estimates of treatment effect. Previous trials of dose fractionation in palliative radiotherapy have always focussed exclusively upon uncomplicated bone metastases or spinal cord compression and excluded patients undergoing prior radiotherapy or surgery to the index lesion. In addition, the populations reported in these studies are highly selected. Ideally, a meta-regression approach might allow investigation of how these factors impact upon outcomes, however, the quality of reporting in the included studies meant that this was not possible.(224)

The three studies identified to inform the subsequent cost-effectiveness model demonstrate relatively robust methodology and reporting. Specifically, the two non-randomised studies both adjust for analgesia usage and represent populations of patients with predominantly uncomplicated bone metastases. In addition, whilst the survival of the treated cohorts in these two studies is longer than that seen in routine practice it is not increased to the extent seen in many of the other included studies. Additionally, the results presented by these studies are better suited to informing the economic model as the degree of pain relief achieved is reported and multiple time-points are considered.

2.2.4.3   Future recommendations:

It is clear, from the above discussion that the outcomes reported in many of the included studies are not directly comparable to those which might be expected in a patient population with uncomplicated bone metastases. Indeed, where attempts have been made to provide a comparator cohort, either through randomisation of a small number of patients or through an observational matched cohort design, the differences in PC are markedly less than might be anticipated. Given

the clear challenges of selection bias in observational studies, risk of measurement bias and marked heterogeneity in the included studies further large randomised studies are required to assess the role of SABR in the management of bone metastases.

The emphasis of trials comparing SABR with cEBRT is likely to be on the potential for improved quality of pain control and greater durability. Yet very few of the studies included here have attempted to address these endpoints. A limited number of studies recognised and robustly reported complete and partial pain relief separately. Where durability of pain control has been considered it has been measured by "long-term pain control" or as a component of a composite progression free survival end-point.(172,204) These outcomes are not well defined and it is unclear if the methods used reflect the hoped for outcome; a greater proportion of remaining life spent with pain control. Net pain relief measures this outcome. It has, however, been reported in a limited number of studies, is not strongly recommended in the consensus guidelines and has limited information available to support its value as an outcome measure.(130,225,226) It may be argued therefore, that the ICPRE are not well suited to assessing the role of SABR for bone metastases. In order to support these trials the existing consensus guidelines should be reviewed. Their update and implementation will help to ensure that the patient group to be studied is clearly defined, the intervention and comparator are specified and that the outcomes measured are defined and measured robustly, reflecting the question to be addressed and critically, offering value to patients.

The studies included in this systematic review report higher rates of PC following SABR than have previously been reported following cEBRT, with limited toxicity. These outcomes may very well, however, be the result of study methodology and, more importantly, selection bias. Further work is required. Large randomized trials are needed to define, in patients with pain due to uncomplicated bone metastases, the incremental benefit of SABR over cEBRT, in improving pain control and quality of life. As such, this systematic review supports recruitment into the ongoing randomised trials of SABR for bone metastases and the need for further trials in this setting.

2.2.5 *Conclusions:*

The above literature review confirms that the outcomes of the previous meta-analyses are unchanged; pain response following single fraction palliative radiotherapy is no different to that seen following fractionated treatment. In addition, through systematic review of the literature three studies assessing pain response following SABR are identified in order to inform the parameters of the cost-effectiveness model.

More broadly, the presence of a dose response relationship remains unclear. Indeed, the systematic review of PC following SABR confirms the need for randomised studies to assess this, even with the markedly higher radiotherapy doses delivered using SABR.

3 Quality of life near the end of life in relation to palliative radiotherapy for bone metastases

3.1 Introduction

Multiple previous studies have demonstrated improved health-related quality of life (HR-QoL) in individuals responding to palliative radiotherapy for bone metastases.(221,227) The response rates of approximately 60% and reported median time to benefit of 1-4 weeks (86,228) have led some clinicians to suggest that treatment should be offered irrespective of expected survival. It is, however, well documented that HR-QoL deteriorates near the end-of-life (EoL) for patients with advanced cancer (229) and whilst individuals close to death have been shown to have lower potential to respond to radiotherapy it is not clear if the relationship between pain response and HR-QoL is maintained in this frail population.(92,93)

The EQ-5D-3L questionnaire was developed by the EuroQoL group as a generic measure of HR-QoL which could be used across all diagnostic groups. It consists of 5 domain measures coupled with a measure of the respondent's self-reported health using a 0-100 VAS (the EQ-VAS) where 0 represents the worst possible health state and 100 is the best possible health state.(230,231) The five domains relate to: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. To each domain, a response in 3 possible levels is provided: no problems, some problems, extreme problems.(232)

The responses to the EQ-5D-3L domain questions result in 243 potential health states, each represented by five digits (from 11111 being no problems in any domain to 33333 reflecting severe problems in all five domains). In order for the health-states captured by the EQ-5D to be incorporated into health economic analyses these states must be converted into a utility value; a single number representing the utility of each state on a scale anchored on zero and one (zero being equivalent to death and one perfect health). To achieve this a range of methodologies are used (e.g. time trade-off, standard gamble). These ask individuals to make comparisons between various health states. A tariff value-set is then derived from their answers and this can then be used to convert the domain scores into a utility value representing how the population studied value the reported health states. In NICE technology appraisals the value-set used was developed by Dolan in 1997,(233) in a UK population, using a time trade-off approach. The value-set, therefore, explicitly values HR-QoL from the perspective of the UK general public, a justifiable approach when healthcare is funded through general taxation.(117) Combining this utility value with length of life after treatment provides a measure of post-treatment health in quality adjusted life years (QALY). As such, multiple different HR-QoL outcomes can be considered using the EQ-5D responses; self-reported health via the EQ-VAS, specific domain responses and HR-QoL as measured by the utility derived from the combined EQ-5D domain responses.

Whilst the methods used to value HR-QoL for cost-effectiveness analyses aim to provide a fair and robust means to make comparisons across all interventions, concerns have been raised about

the use of the QALY to measure health of populations near the EoL.(234) Multiple arguments exist both for and against this. Of particular focus here, it is argued that the values placed upon the five domains of EQ-5D may change as people near the EoL. In that case, the tariffs, which are based on preferences of the general population, might be argued not to be appropriate for this population. In addition, the dimensions of health that are captured by the EQ-5D, may become less important or their value be supplemented by other domains not captured by the EQ-5D at the EoL. Assessing the relationship between self-reported health (as measured by the EQ-VAS) and the five domains of the EQ-5D-3L,(235) may provide insight into how these domains contribute to an individual's overall HR-QoL and how this may vary with proximity to death.

This chapter will examine the relationship between pain response following treatment and wider HR-QoL benefits and the extent to which this relationship is constant with proximity to death. This will inform both an assessment of the clinical benefits of treatment and deliver parameter values for the subsequent cost-effectiveness analysis of palliative radiotherapy for bone metastases. Specific questions to be addressed here are:

1. How does the relationship between pain response and other domains of HR-QoL vary with proximity to the EoL?

2. Is the influence of the EQ-5D-3L domains on self-reported overall health (as measured by the EQ-VAS) constant with proximity to death?

3. What EQ-5D based utility values should be used in the planned cost-effectiveness model and how do these vary with survival?

The data used to carry out these investigations was collected in the Dutch Bone Metastasis Study (DBMS).(16) Details of this study and the data captured will initially be provided. The methods to address the above questions will then be detailed separately.

3.2 Methods

3.2.1 *The Dutch Bone Metastasis Study (DBMS)*

The data used were kindly provided by Dr Yvette van der Linden of the DBMS group, Leiden University Medical Center, The Netherlands. Details of the DBMS methods have previously been published,(16) however, a brief summary is as follows. Patients were eligible for entry if they had painful bone metastases from solid organ malignancies and a clinical decision had been made to deliver palliative radiotherapy. Patients with pain of less than 2 on a 0-10 point numerical scale were excluded from the trial. The study recruited 1,157 patients from 21 out of 24 Dutch radiotherapy centres between March 1996 and September 1998. Patients were randomised to receive either 24Gy in 6 fractions or a single 8Gy fraction palliative radiotherapy to the painful site. Information about re-irradiation was collected on a three monthly basis from treating institutes. Survival was assessed from the start of radiotherapy.

3.2.1.1 Pain response and HR-QoL assessments

Baseline pain (using an 11-point numerical rating scale (NRS)), quality of life (using the EQ-5D-3L), analgesia, cancer and demographic characteristics were collected and individuals were asked to complete weekly follow-up questionnaires for the first 12 weeks beyond recruitment, followed by monthly questionnaires thereafter (to a maximum of 104 weeks). As questionnaire collection started at randomisation patients whose treatment was delayed a number of weeks after recruitment returned less than 12 weekly questionnaires, moving to monthly collection relatively more quickly.

The pain response status of the patient at each questionnaire was classified in line with ICPRE guidelines (130) to incorporate analgesia and thus categorised as pain progression (deterioration in pain score of ≥2 above baseline), partial response (an improvement in NRS of ≥2 below baseline without analgesic increase, or analgesic decrease without increase in pain), complete response (a reduction in NRS to 0 without concomitant increase in analgesia) or no response (any response not captured by the previous categories).

Where the EQ-5D-3L based utility was used this was defined using the 1997 UK value-set as applied to the observed EQ-5D domain scores.(196)

3.2.2 *Study cohort*

1,157 patients were treated within the DBMS resulting in a possible 20,727 questionnaires between treatment and death. Seven patients were excluded due to a lack of information regarding their treatment date and, in three cases, death so soon after radiotherapy that no response questionnaires could have been returned. 298 individuals were alive and censored at trial closure in December 1998. Consequently their survival beyond treatment was unknown. This group are excluded from the analyses within this chapter, leaving us with a study cohort of 849 patients with known survival time (a possible 12,135 questionnaires). Figure 6 shows how the study cohort was defined.

Figure 6. CONSORT diagram illustrating the study population and questionnaires. The number of questionnaires with missing response assessment is shown for the final cohorts.
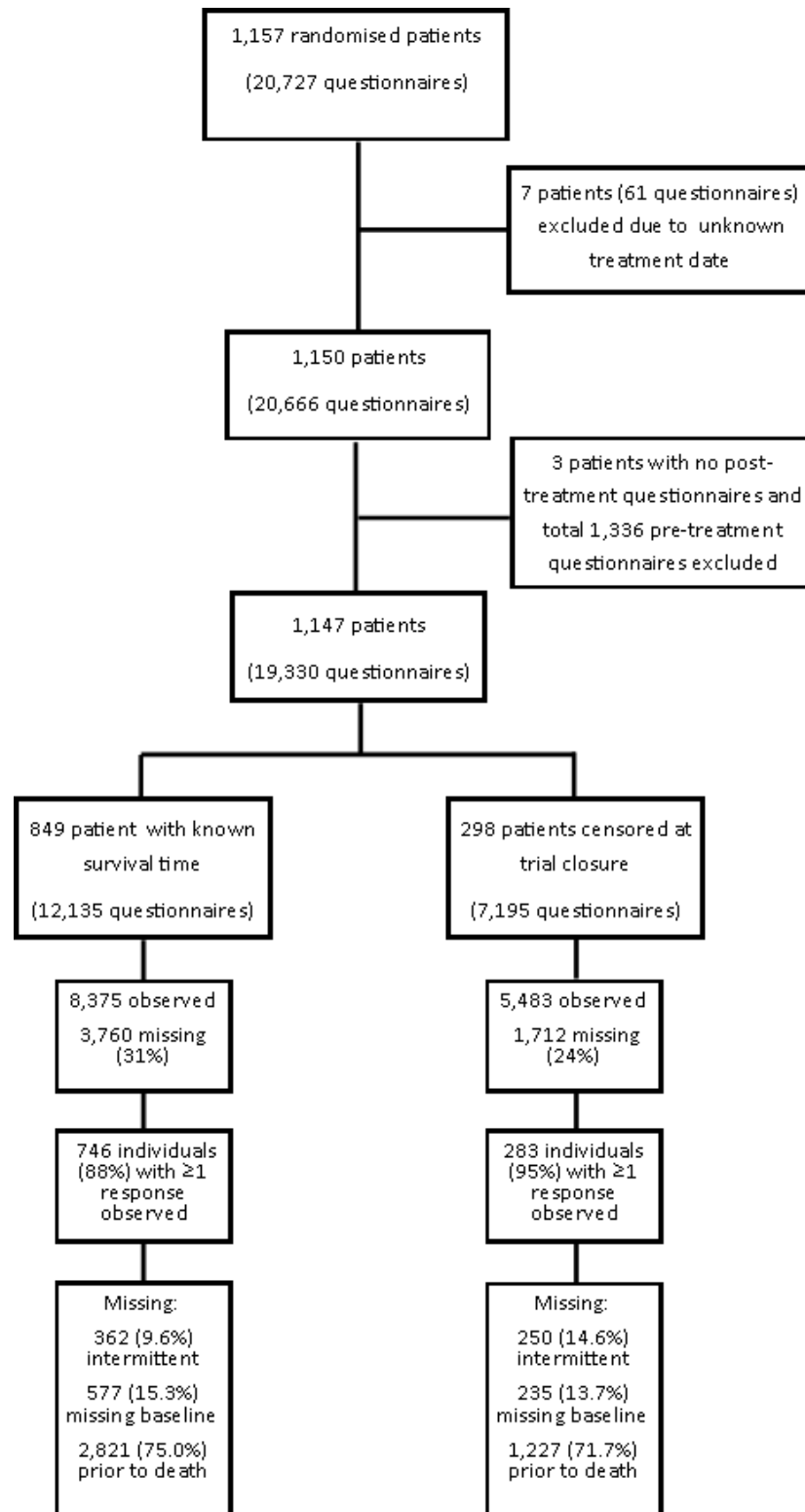
Baseline characteristics of the whole trial cohort and those with known survival time are described for the study population in Table 3. For analysis purposes, patients were grouped into four groups according to their primary tumour; breast cancer, prostate cancer, lung cancer and all other diagnoses.

Table 3. Base-line characteristics of the study population.

		Total cohort		Final study cohort	
		Number	**%**	**Number**	**%**
Age (range)		(32-89)		(32-89)	
	<55	239	20.8	169	19.91
	55-64	279	24.3	205	24.15
	65-74	402	35.1	300	35.34
	>74	227	19.8	175	20.61
Sex					
	Male	618	53.9	516	60.78
	Female	529	46.1	333	39.22
Primary diagnosis					
	Breast	449	39.2	261	30.74
	Prostate	266	23.2	199	23.44
	Lung	281	24.5	257	30.27
	Other	151	13.2	132	15.55
Treatment arm					
	6x4Gy	571	49.8	430	50.65
	1x8Gy	576	50.2	419	49.35
Performance status					
	WHO 0-1	504	43.9	317	37.34
	WHO 2	436	38.0	359	42.29
	WHO 3-4	170	14.8	155	18.26
	Unknown	37	3.2	18	2.12
Baseline pain score					
	2	16	1.4	7	0.82
	3	40	3.5	29	3.42
	4	71	6.2	47	5.54
	5	131	11.4	91	10.72
	6	125	10.9	87	10.25
	7	180	15.7	137	16.14
	8	330	28.8	257	30.27
	9	134	11.7	104	12.25
	10	117	10.2	88	10.37
	Unknown	3	0.3	2	0.24
Baseline analgesia					
	None	145	12.6	86	10.13
	Simple	415	36.2	276	32.51
	Weak opioids	214	18.7	157	18.49
	Strong opioids	306	26.7	273	32.16
	Unknown	67	5.8	57	6.71
Total		1,147	100	849	100

Response rates following treatment have previously been reported for this trial, however, for clarity maximum response rates by survival cohorts are reported in Table 4.

Table 4. Maximal response to palliative radiotherapy for bone metastases by survival cohort

		<6 weeks	6-12 weeks	12-24 weeks	24-52 weeks	>52 weeks	Total
Pain progression (n)		5	4	2	0	2	13
	%	*4.2*	*2.5*	*0.9*	*0.0*	*0.9*	*1.5*
No response (n)		50	41	50	23	35	199
	%	*42.0*	*25.6*	*22.9*	*16.4*	*16.5*	*23.4*
Partial response (n)		26	62	120	57	98	363
	%	*21.9*	*38.8*	*55.1*	*40.7*	*46.2*	*42.8*
Complete response (n)		4	26	29	55	62	176
	%	*3.4*	*16.3*	*13.3*	*39.3*	*29.3*	*20.7*
Unknown (n)		34	27	17	5	15	98
	%	*28.6*	*16.9*	*7.8*	*3.6*	*7.1*	*11.5*
Total (n)		119	160	218	140	212	849

3.2.3 *Missing data*

The subsequent analyses use the longitudinal data collected from patients recruited into the DBMS. As is anticipated in any study carried out in a palliative population, significant missing data are present.(236) Questionnaires were considered missing if it was not possible to define the pain response following treatment. This may reflect a lack of baseline information or absent pain or analgesia information during follow-up. As shown in Figure 6, 31% of pain response assessments were missing (3,760 out of 12,135) despite robust clinical trial design and resource invested in ensuring questionnaire completion wherever possible. Figure 7 demonstrates the proportion of missing questionnaire responses over sequential questionnaires (1-35 questionnaires post radiotherapy). The proportion of individuals who died prior to each questionnaire return is included to recognise attrition due to death as opposed to missing.

Figure 7. Proportion of missing questionnaires over the study duration.
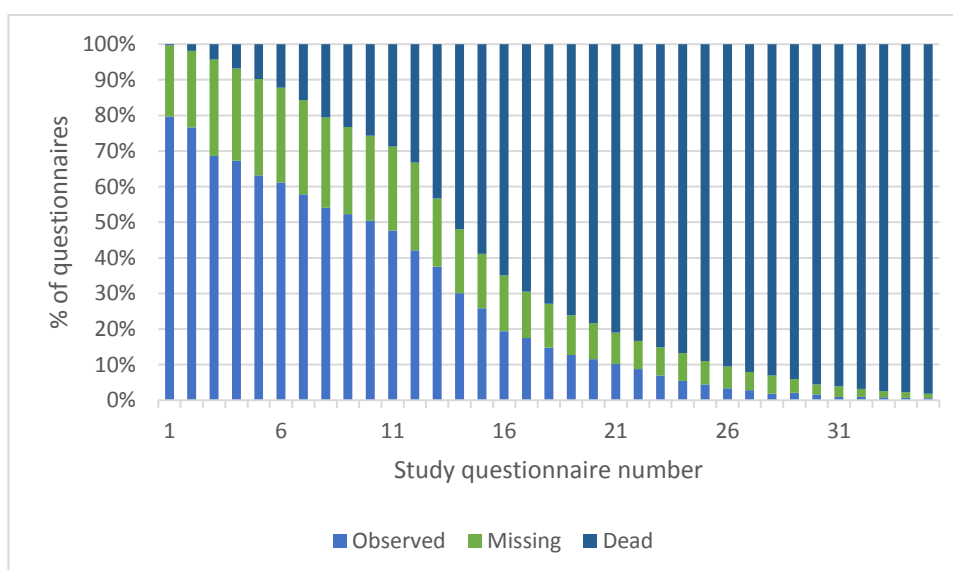
Subsequent analyses require information not only on pain response but also wider HR-QoL as reported using the EQ-5D-3L. Missing data may, therefore, reflect a completely unreturned questionnaire (missing response) or an incomplete individual question (missing item). Where the EQ-5D responses were included in the assessment of missing data the proportion of questionnaires with missing data rose to 35% (out of 12,135 questionnaires overall). In this study missing response was the predominant type of missing data (3,411 questionnaires (80.5% of the missingness)). Missing item questionnaires included 349 questionnaires with lack of pain response assessment information alone, 126 due to incomplete EQ-VAS and 353 due to incomplete EQ-5D domain information. This predominance of response missing was consistent with proximity to death.

The missing responses were assessed graphically to determine whether they followed an intermittent or a monotone pattern (Figure 8). Monotone missing occurs when an individual fails to return a questionnaire and all subsequent responses are also missing. Conversely intermittent missing represents the situation where a questionnaire is missing in isolation with subsequent responses being completed. It can be seen that during the first 6 questionnaires the proportion missing increases. A monotone missing pattern is predominantly, although not exclusively, seen; once missing patients do not then start to submit. It does, however, become challenging to interpret this beyond 6 weeks as questionnaires beyond an individual's death are removed entirely and, therefore, not considered missing so explaining the apparent return to questionnaire submission. It was not possible to illustrate missing separately to death in this graph.

Figure 8. Patterns of missing pain response assessment data in the first 12 questionnaires following treatment. The y-axis numbers represent the questionnaire number following treatment, each vertical column represents an individual patient. Missing questionnaires are represented in black and patients arranged according to their pattern of missing data.
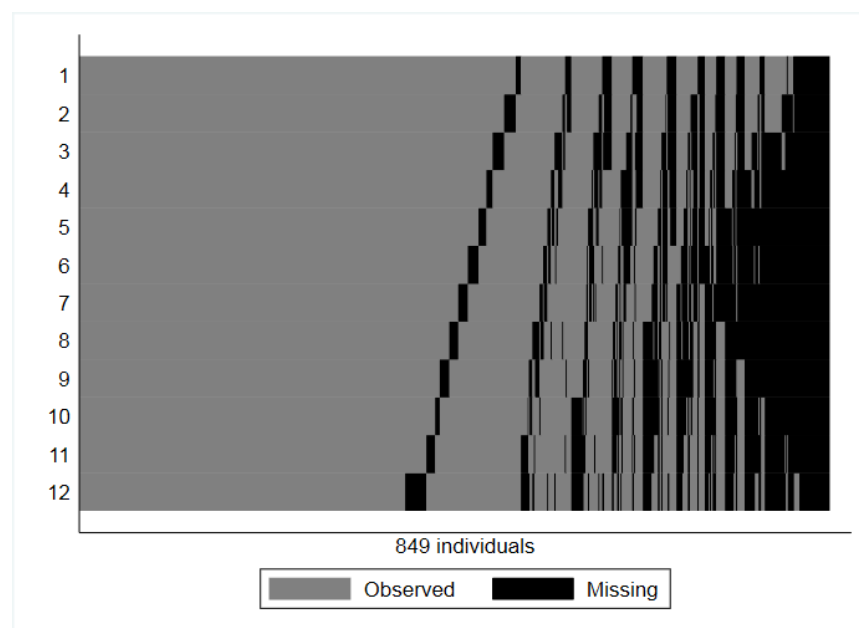
The amount of missing data increased from 19.9% in those who were within 6 to 12 months from the EoL up to 59.2% in those who were within the final 6 weeks of life (Table 5).

Table 5. Missing data with varying time to death.

	Total (n)	Observed (n)	% missing
<6 weeks	2,456	1,002	59.20
6 weeks - 3 months	2,093	1,334	36.26
3 - 6 months	2,727	1,873	31.32
6-12 months	1,881	1,506	19.94
>12 months	2,978	2,181	34.93
	12,135	7,896	34.93

Other possible predictors of missing data were assessed using a multi-level multi-variable random effects logistic regression model. The random effects model allows recognition of the clustering of observations within individuals whilst also allowing assessment of both patient level variables and time-varying variables upon the probability of missingness. Patient level co-variables included age, sex, diagnosis, baseline EQ-VAS, site treated, baseline performance status and site of other metastases whilst time-varying co-variables included time to death (TTD) and re-irradiation status (no re-irradiation, on re-irradiation, post re-irradiation). The model outcomes are shown in Table 6. Missing data are more likely to be observed with proximity to death. A primary cancer other than breast and prostate cancer reduced the likelihood of missing data whilst having received re-irradiation increased the likelihood of missing data.

Table 6. Predictors of missing questionnaire response on random-effects multi-variable logistic regression modelling.*$p \leq 0.05$, **$p < 0.01$, *** $p < 0.001$.

	Coef.	Std.err	z	p	L 95% CI	R 95% CI
Time to death (weeks)	-0.100***	0.004	-27.730	<0.001	-0.107	-0.092
Age (years)	0.015	0.010	1.450	0.146	-0.005	0.036
Sex						
Male	0.000	-	-	-	-	-
Female	0.198	0.405	0.490	0.624	-0.595	0.991
Baseline EQ-VAS	-0.002	0.005	-0.320	0.750	-0.012	0.009
Radiotherapy site						
Spine	0.000	-	-	-	-	-
Non-spine	0.156	0.247	0.630	0.527	-0.327	0.639
Primary diagnosis						
Breast	0.000	-	-	-	-	-
Prostate	-0.564	0.507	-1.110	0.266	-1.558	0.430
Lung	-1.479**	0.440	-3.360	0.001	-2.341	-0.616
Other	-1.107*	0.457	-2.420	0.015	-2.003	-0.212
WHO_PS						
WHO 3-4	0.000	-	-	-	-	-
WHO 2	0.231	0.313	0.740	0.460	-0.382	0.845
WHO 0-1	0.092	0.331	0.280	0.781	-0.557	0.740
Retreatment status						

No re-irradiation	0.000	-	-	-	-	-
On re-irradiation	-0.217	0.295	-0.740	0.461	-0.795	0.360
Post re-irradiation	0.909***	0.186	4.890	<0.001	0.545	1.273
Other metastases						
None	0.000	-	-	-	-	-
Visceral	-0.594	0.306	-1.940	0.052	-1.194	0.006
Brain	-0.796	0.706	-1.130	0.260	-2.179	0.587
Other bone mets	-0.028	0.280	-0.100	0.919	-0.578	0.521
Constant	-0.112	0.922	-0.120	0.903	-1.919	1.696
/lnsig2u	2.014	0.077			1.863	2.165
sigma_u	2.738	0.105			2.539	2.952
rho	0.695	0.016			0.662	0.726

The consequences and possible methods to address the challenges of missing data are discussed subsequently. Briefly, for the purposes for multi-level modelling, missing data are accommodated under an assumption that missing is predicted completely by the observed variables (missing at random (MAR)). In this situation models should remain unbiased. Where parameter values are required to inform a cost-effectiveness model missing data may result in biased parameter estimates. Multiple imputations can be considered in order to reduce this bias under an assumption of MAR. Missing not at random (MNAR, i.e. missing related only to unobserved co-variables) will remain a cause of bias after multiple imputations.

3.2.4   Statistical methods

Details of the data used and trial methods for the DBMS are provided in section 3.2. Only patients with known time to death (TTD) were included in this analysis. Two baseline HR-QoL assessments were used here, EQ-VAS and domain levels. The time between subsequent questionnaire responses and death was calculated providing TTD. Questionnaires were then allocated to cohorts by TTD for the purpose of descriptive analyses. Pain response following treatment was defined as detailed in section 3.1. The average EQ-VAS and EQ-5D domain responses were tabulated by pain response state for each TTD cohort separately.

Using the longitudinal data collected within the DBMS this study addressed the three questions outlined in section 3.1. The analyses were based on multi-variable multi-level regression modelling (for continuous or categorical dependent variables as appropriate). One of the underlying assumptions relied upon by a pooled regression analysis is that the expectation of the error at time t for variable x and unobservable time-constant individual level variation c is 0. If this assumption holds then the pooled regression may be unbiased. If however, c is correlated with any time-varying co-variable (i.e. unobserved patient-level variation is correlated with the co-variables over time) then the pooled regression is biased and inconsistent.(237) With repeated measures over time, it is possible to eliminate the time-constant unobservable, c. A multilevel model allows us to take into account the correlation between observations which results from repeated measures within individuals.(238) The need to recognise clustering within individuals

can be tested and was confirmed by the Breusch-Pagan Lagrange multiplier with a p<0.0001 in both assessing the relationship between time to death and EQ-VAS and the relationship between EQ-VAS with EQ-5D domain levels.

Co-variables included in the multi-variable models were time varying (pain response state, time to death (TTD) and re-irradiation) and time in-variate characteristics (baseline demographics, diagnosis, baseline performance status and EQ-VAS, delivered fractionation). Age was considered to be time invariant in all models as the survival of the population is sufficiently short that aging is unlikely to be associated with significant changes over the study period. Where pain response was considered it was simplified to a discrete binary variable; response vs no response (combining CR and PR versus NR and PP). The EQ-5D domains were modelled as discrete variables using level 1 (no problems) as the reference level. Whilst modelling these levels as a continuous variable would have been possible this leads to the strong assumption that the difference between level 1 and 2 of an individual domain is the same as the difference between level 2 and 3 and this is unlikely to be true.

The research question regarding whether the overall HR-QoL benefit, that is associated with pain response to radiotherapy is constant with proximity to death corresponds to estimating the following equation:

$$EQVAS_{it} = \beta_1 \, Pain \, response_{it} + \beta_2 X_{it} + \beta_3 X_i + \beta_4 EQVAS_{i0} + \beta_5 Pain \, response_{it} TTD_{it} + c_i + \mu_{it}$$

Equation 1.

$EQVAS_{it}$ represents the self-reported EQ-VAS of individual i at time t. *Pain response$_{it}$* represents pain response of individual i at time t, X_{it} and X_i are vectors of time-varying (including re-irradiation) and time-invariant independent variables respectively. $EQ\text{-}VAS_{i0}$ is the individual's baseline EQ-VAS. The terms μ_{it} and c_i are error terms and they respectively represent a time-dependent individual model error term and an individual specific time-independent error term; they are both assumed to tend to zero.

Subsequently five equations were successively estimated, for each of the EQ-5D health domains, to investigate the EQ-5D domain level probability associated with pain response at differing times in proximity to death. The following equation corresponds to this question:

$$DomainLevel_{it}^{K*}$$
$$= \beta_1 \, Pain \, response_{it} + \beta_2 X_{it} + \beta_3 X_i + \beta_4 EQVAS_{i0} + \beta_5 Baseline \, domain \, level_{i0} + \beta_5 Pain \, response_{it} TTD_{it} + c_i + \mu_{it}$$

Equation 2.

Here $DomainLevel_{it}^{k*}$ was considered, the latent domain level underlying the domain-related health of individual i at time t with $k=1,....,5$ (the domain of interest). The domain level was

assumed to be a function of *Pain response$_{it}$* (the pain response of individual *i* at time *t*), X_{it} and X_i (vectors of time-varying and time-invariant independent variables), *EQ-VAS$_{i0}$* (the individual's baseline EQ-VAS), *Baseline domain level$_{i0}$* (the individual's baseline EQ-5D domain level for the modelled domain) and *Pain response$_{it}$TTD$_{it}$* (which represents the interaction between the EQ-5D domains and TTD). The error terms μ_{it} and c_i (the were assumed to be probabilistically distributed).

Finally, how self-reported health, as proxied by the EQ-VAS, is associated with the EQ-5D domains and whether this is constant with proximity to death, was investigated. This was then replicated using the EQ-5D utility in place of the EQ-VAS. The equation is written as follows:

$$EQVAS_{it} = \beta_1 \, Mobility_{it} + \beta_2 Selfcare_{it} + \beta_3 Activity_{it} + \beta_4 Pain_{it} + \beta_5 Anxiety_{it} + \beta_6 TTD_{it} + \beta_7 Domain_{it}^k TTD_{it} + c_i + \mu_{it}$$

Equation 3.

Here *EQVAS$_{it}$* represents the self-reported EQ-VAS of individual *i* at time *t*. This is assumed to be a function of *Mobility$_{it}$, Selfcare$_{it}$, Activity$_{it}$, Pain$_{it}$* and *Anxiety$_{it}$* (the five EQ5D domains each for individual *i* at time *t*), *TTD$_{it}$* (the time to death of individual *i* at time *t*) and $Domain_{it}^k TTD_{it}$, an interaction between domain level and TTD which allows flexibility for the relationship between the domain levels and the EQ-VAS to vary with proximity to death. As in equation 1 the terms μ_{it} and c_i are error terms which are both assumed to tend to zero.

The Hausman test was used to guide whether a random or fixed effects specification was preferred.(237) This demonstrated inconsistency in the results both in the assessment of HR-QoL with pain response and in the relationship between the EQ-VAS and the EQ-5D domain levels ($p<0.001$ in both cases). On the basis of this result, and that the study aims to investigate the association between a number of time-varying co-variables (including pain response, TTD, re-irradiation) and two key dependent variables, namely EQ-VAS and utility, the presented results are restricted to those estimates in a fixed effects specification.

Within a linear regression model the assumption is made that the relationship between the EQ-VAS, for example, and TTD is linear. It has previously been shown that patients with cancer experience a period of relatively stable HR-QoL until the final few months of life, when HR-QoL rapidly declines.(90,221) Visual inspection of the Lowess plot confirmed the presence of a non-linear relationship between HR-QoL and TTD (Figure 9). Alternative specifications of TTD were considered including squared, logarithmic and restricted cubic splines (RCS) for TTD. RCS provided the optimum model fit on Akaike Information Criteria (AIC) and allowed flexibility in the relationship between TTD and the EQ-VAS.(239) Four knots were placed for the RCS within TTD using Stata's *mkspline2* command.(129) Knots were placed at 1, 6, 27 and 77 weeks. Greater numbers of knots and alternative positions did not improve the model fit by AIC and visual assessment of the model predictions for over-fitting. In addition, the Wald test was used to confirm the improvement in model fit with RCS ($p<0.001$ demonstrating a non-zero relationship between the EQ-VAS and 2nd and 3rd TTD splines).

Figure 9. Lowess plot for EQ-VAS with TTD by response to treatment. Modelling global quality of life and pain response with time to death.
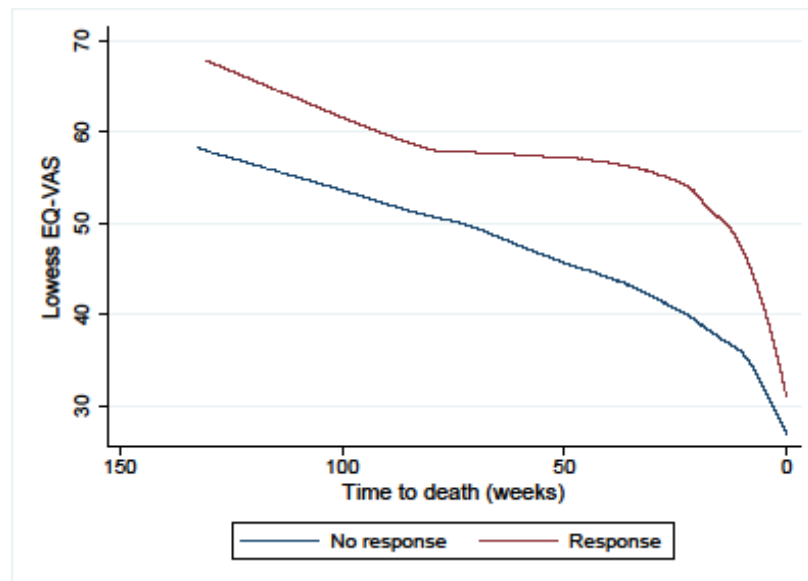
Interaction terms between the pain response, EQ-5D domain levels and TTD splines were included to recognise the potential for the effect of response/domain level to vary with proximity to death. This resulted in three interaction terms where the pain response and TTD were interacted (equations 1 and 2) and fifteen where the EQ-5D domains were interacted with TTD (equation 3). The addition of these interactions terms improved the model fit on AIC. By including TTD rather than survival, the models provided a fully conditional specification.(128) Regression diagnostics using quantile-quantile plots and residual-variable plots demonstrated normally distributed errors and no evidence of clinically significant systematic error in the predictions with time to death.

The modified Durbin-Watson test statistic was used to assess for auto-regressive correlation in the errors where continuous dependent variables were modelled, such as EQ-VAS or utility (equation 1 and 3). In the case of equation 1 the Durbin-Watson test statistic took a value of 1.15, well below the 5% significance level specified for a model with 250 individuals and 6 time points (lower bound 1.904 and a conservative estimate of the population considered).(240) For equation 3 the test statistic took a value of 1.287, again, well below the 5% significance level specified for a model (1.896) with 250 individuals and 6 time points. The final multivariable models for EQ-VAS and utility were therefore built using the *xtregar* command in Stata which fits a generalised least squares (GLS) model recognising this auto-correlation and accommodating unbalanced panels with unequal spacing over time.(241,242)

Figure 10. Assessment of the individual observation level residuals from the fixed effects model for the predicted EQ-VAS by response category. A) Q-Q plots (response and no-response) and B) Residual-variable plots with residuals plotted against time to death (weeks) are shown (response and no-response).
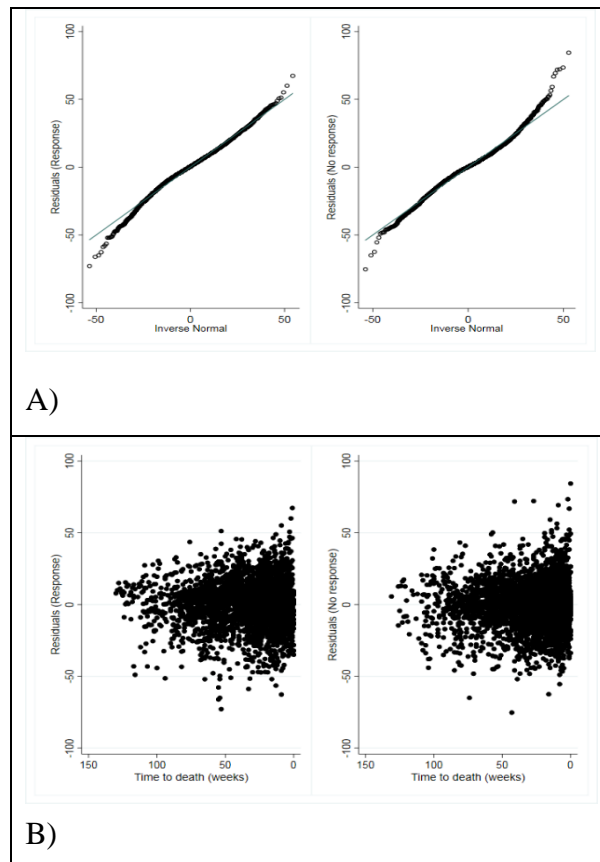
The Stata command *xtregar* incorporates all available data, not excluding those for which some questionnaires were unobserved.(241) Significant missing data are, however, present. Where data are missing completely at random (MCAR) this will not result in biased estimates in a pooled regression analysis. Within the multi-level framework, theoretically robust estimates will be provided in the presence of data missing at random (MAR) (i.e. where missing is conditional upon observed variables). Multiple imputation (MI) of the missing data (assuming MAR) can be considered, however, given the complexity of the multi-level model structure with auto-regressive correlation and ordered categorical variables this was not pursued here on the basis that the multi-level, fully conditional specification should produce robust results under an assumption of MAR. Neither multi-level models nor MI can adjust for missing not at random (MNAR), where missingness is non-random but unrelated to observed co-variables. In this study it might reasonably be anticipated that whilst overall health might reduce with proximity to death, failure to return a questionnaire might be indicative of worse health than is observed in returned questionnaires i.e. patients who didn't return a questionnaire had, on average, a worse health status than those who did return it. If this is the case, bias which is related only to unobserved variation, would be expected and should be borne in mind when interpreting the study outcomes.

After model fitting the average predicted EQ-VAS for response versus no response was calculated with varying TTD whilst assuming no re-irradiation. This was carried out using the *margins*

command in Stata.(243) Subsequent predictions of EQ-VAS based on observed domain levels were then made over TTD, again based on no-re-irradiation. These predictions were presented graphically with 95% confidence intervals. The minimally important difference in EQ-VAS for cancer patients has previously been defined as 8-12 points.(244) A reference line is placed on the predicted EQ-VAS graph to demonstrate the point at which the average predictions show this separation (8 points) with pain response (see Figure 15). Finally, the predicted EQ-VAS based on the observed EQ-5D domains was presented for cohorts with varying proximity to death, alongside predictions from a population undergoing elective surgery within the NHS.(235)

3.2.4.1 Robustness checks

There is a risk that small sample sizes at level 1 (questionnaires clustered within individuals) will result in biased estimates.(245) Within the study population the number of returned questionnaires ranged from 1 to 35. In order to assess the risk of bias due to the inclusion of those with a small numbers of observations the models were re-produced excluding individuals who had returned less than five questionnaire responses.(246) This resulted in an exclusion of 174 (20.5%) individuals. Notably, the survival following radiotherapy for these individuals was 6.857 weeks (95% CI 5.571-9.000) as compared to 25.000 weeks (95% CI 22.857 – 27.143) in those returning five questionnaires or more.

A final sensitivity analysis investigates the potential consequences of violating the assumption that the individual fixed effects are time-constant and uncorrelated with the time-varying co-variables by repeating the analyses represented by equations 1 and 3 in cohorts surviving more, and separately less, than six months beyond treatment. Where patients surviving less than six months only were considered the RCS knot positions were changed. Knots placed at 1 and 6 weeks were retained and a knot placed at 24 weeks as those at 27 and 77 weeks are not appropriate having excluded individuals with survival beyond 24 weeks. Where only patients surviving more than 6 months were assessed it became clear from the model predictions that the RCS was resulting in overfitting. As such the number of knots were reduced to three and placed automatically at 2, 17 and 62 weeks. Re-siting these knot positions manually offered no improvement in model fit on AIC.

3.2.4.2 Pain response and the EQ-5D-3L domains with proximity to death

The relationship between treatment response and the level probability of each of the five domains of EQ-5D over TTD was examined using ordered logistic regression models. The probability of Pareto improvement in HR-QoL was then considered, as measured by an improvement in at least one of the five EQ-5D domains in the absence of deterioration in any other. This latter was modelled as a discrete binary outcome.

As previously, multi-level model specifications were used to account for clustering within individuals. A RCS was again used to allow flexibility in the relationship between TTD and EQ-5D level and the benefit this approach was confirmed using the AIC. The knot positions and number were as in the previous analyses (4 knots at 1, 6, 27 and 77 weeks). The models were fitted using multi-level fixed-effects models. *meologit* (for the ordered categorical domain outcomes) and *melogit* (for the binary Pareto improvement outcome) commands in Stata.(247,248) In all domain models records with unknown response were excluded.

The average predicted level probability of EQ-5D domains and Pareto response with pain response following treatment were predicted for varying TTD assuming no re-irradiation using the *margins* post-estimation command.(243)

3.2.5 Results

3.2.5.1 The relationship between pain response and self-reported health with proximity to death

Baseline characteristics of the study population were shown in Table 3 (page 67).The mean baseline EQ-VAS in the study population was 44.278 (Standard error (SE) = 0.799) and equivalent baseline utility was 0.288 (SE = 0.013). The distribution of EQ-VAS and utility at baseline are illustrated in Figure 11. The baseline EQ-VAS of individuals who subsequently gained a pain response following treatment was 45.412 (SE 0.971) whilst for those who did not respond it was 41.912 (SE 1.396)(two sided Students t-test, p=0.040). This is in keeping with the known reduced probability of response in those with short survival and deteriorating HR-QoL with proximity to the EoL.(92)

Figure 11. Histograms demonstrating the distribution of baseline EQ-VAS (a) and tariff (b) in the study population.

a)   b)
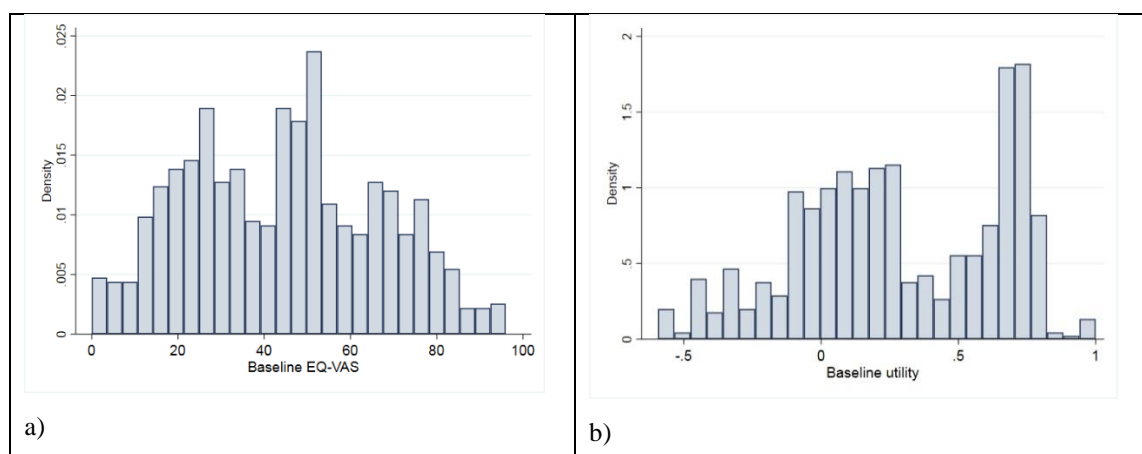
The mean EQ-VAS following treatment was 45.922 (SE 0.257) for all returned questionnaires. This ranged from 53.359 (SE 0.568) in questionnaires returned 24-52 weeks from the EoL, down to 33.148 (SE 0.681) in those returned <6 weeks from the EoL (see Figure 12). Individuals reporting a complete pain response reported mean EQ-VAS scores of 58.710 (SE 0.980), those with partial response 51.892 (SE 0.429), no response 41.406 (SE 0.363) and pain progression

35.663 (SE 0.708), illustrating a gradient in EQ-VAS with level of pain response. Figure 13 shows the average observed EQ-VAS by pain response and TTD category.

Figure 12. EQ-VAS histograms for varying TTD cohorts.
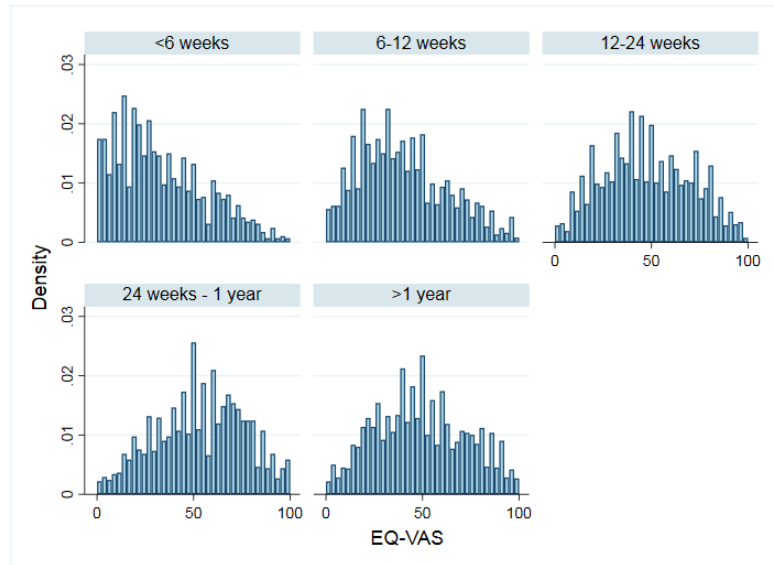
Figure 13. EQ-VAS following palliative radiotherapy for bone metastases by reported response to palliative radiotherapy and time to death.
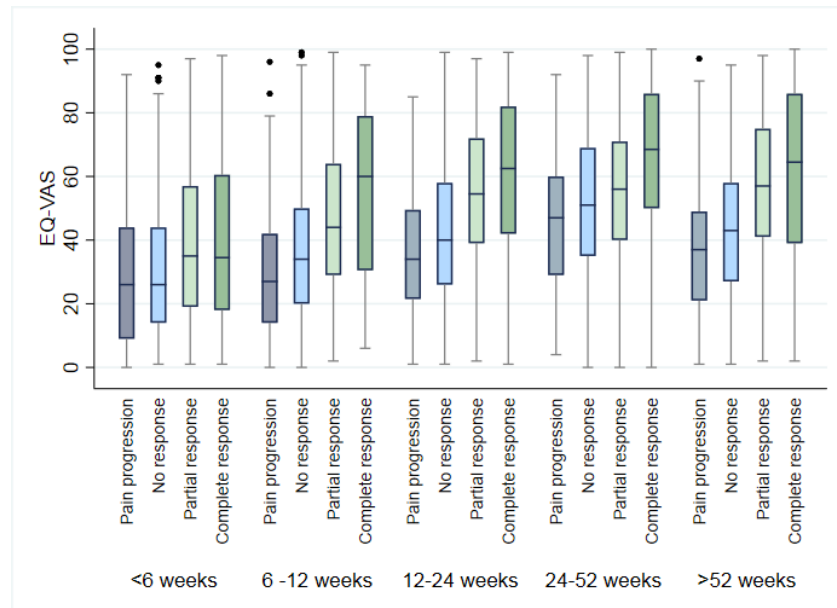
Where patients experienced a pain response following treatment the EQ-VAS was estimated to be 8.946 points higher than for those not experiencing pain response on univariable fixed-effects modelling. Pain response following treatment was significantly associated with increased general health as measured by the EQ-VAS as well as by the utility on multi-variable fixed-effects modelling (p=0.050 and p=0.001 respectively). The extent of the increase in the EQ-VAS with pain response was, however, attenuated to 3.835 (95% CI 0.004-7.666) points after adjustment for other time-varying co-variables (including TTD). Full model outcomes are shown in Table 7.

Table 7. Multi-variable fixed effects regression model for a) EQ-VAS and b) Utility with response to treatment over restricted cubic spline for time to death. *p≤0.05, ** p<0.01, *** p<0.001

a) R^2 = 0.1504 (within = 0.0804, between = 0.1688), n=7,470 observations in 710 individuals. Modified Durbin-Watson = 1.159.

	Coef.	Std.err	t	p	L 95% CI	U 95% CI
Spline 1	1.532***	0.194	7.880	<0.001	1.151	1.913
Spline 2	-20.818***	3.963	-5.250	<0.001	-28.586	-13.049
Spline 3	25.866***	5.043	5.130	<0.001	15.980	35.753
No pain response	0.000	-	-	-	-	-
Pain response	3.835*	1.954	1.960	0.050	0.004	7.666
No re-irradiation	0.000	-	-	-	-	-
On re-irradiation	-4.117**	1.537	-2.680	0.007	-7.129	-1.104
Post re-irradiation	-1.904	1.421	-1.340	0.180	-4.689	0.880
Response#Spline1	0.375	0.256	1.460	0.144	-0.128	0.877
Response#Spline2	-3.517	4.979	-0.710	0.480	-13.276	6.243
Response#Spline 3	4.031	6.305	0.640	0.523	-8.329	16.390
Constant	25.783***	0.838	30.750	<0.001	24.139	27.426
rho_ar	0.450					
sigma_u	17.180					
sigma_e	15.019					
rho_fov	0.567	(fraction of variance because of u_i)				

b) R^2 = 0.2041 (within = 0.1341, between = 0.2063), n=7,275 observations in 706 individuals. Modified Durbin-Watson 1.245.

	Coef.	Std. Err.	t	p	L 95% CI	U 95% CI
Spline 1	0.037***	0.003	14.170	<0.001	0.032	0.042
Spline 2	-0.473***	0.053	-8.880	<0.001	-0.577	-0.368
Spline 3	0.581***	0.068	8.580	<0.001	0.448	0.713
No pain response	1.000	-	-	-	-	-
Pain response	0.088**	0.027	3.290	0.001	0.036	0.141
No re-irradiation	1.000	-	-	-	-	-
On re-irradiation	-0.064**	0.021	-3.070	0.002	-0.105	-0.023
Post re-irradiation	-0.026	0.019	-1.370	0.172	-0.062	0.011
Response#Spline1	0.002	0.004	0.680	0.497	-0.005	0.009
Response#Spline2	-0.051	0.069	-0.750	0.455	-0.186	0.083
Response#Spline 3	0.065	0.087	0.750	0.456	-0.105	0.235
Constant	-0.110***	0.012	-9.130	<0.001	-0.134	-0.087
rho_ar	0.412					
sigma_u	0.294					
sigma_e	0.205					
rho_fov	0.673	(fraction of variance because of u_i)				

Increasing time from the EoL (TTD) was significantly associated with improved EQ-VAS although the relationship was non-linear; a more rapid decline in EQ-VAS being seen in the final few months of life (Figure 14a). In addition, the Wald test was used to assess the probability of all three splines/pain response interaction terms being zero. The Wald test supported rejection of the null hypothesis of all zero coefficients (p=0.003); there is a significant interaction between pain response and TTD. With increasing proximity to death the self-reported health benefit associated with pain response reduces as a result of this interaction. If eight points on the EQ-VAS are used as the minimally important difference, this is only observed with pain response where TTD is greater than 14 weeks (the vertical reference line on Figure 14a).(244)

Notably the interaction demonstrated between TTD and pain response in EQ-VAS was not demonstrated in utility. In this case the Wald test for combined zero values of the interaction terms did not reject the null hypothesis (p=0.805). The valuation of the EQ-5D domains is constant (as defined by the value-set),(233) as such the lack of interaction between TTD and pain response suggests there may be no interaction between TTD and the domain level probabilities. This will be assessed subsequently.

Undergoing re-irradiation with palliative radiotherapy was associated with a significant reduction in EQ-VAS (a reduction by 4.117 (95% CI -7.129 - -1.104)) and in utility (by 0.064 (95% CI -0.105 - 0.023)) in the week following re-irradiation compared to those not receiving re-irradiation. EQ-VAS and utility were both lower at subsequent points post re-irradiation although this difference was not statistically significant (a reduction of 1.904 (95% CI -4.689 – 0.880) in the EQ-VAS and a reduction of 0.026 (95% CI -0.062 – 0.111) in utility). Predictions of utility with response in proximity to death are shown in Figure 14b.

Figure 14. Average predicted EQ-VAS (a) and utility (b) with response over time to death. The dashed vertical reference line is placed at the point at which the minimally important difference (8 points) is seen with response to treatment (13 weeks).(244) No data is available to inform the placement of the minimally important difference in utility.
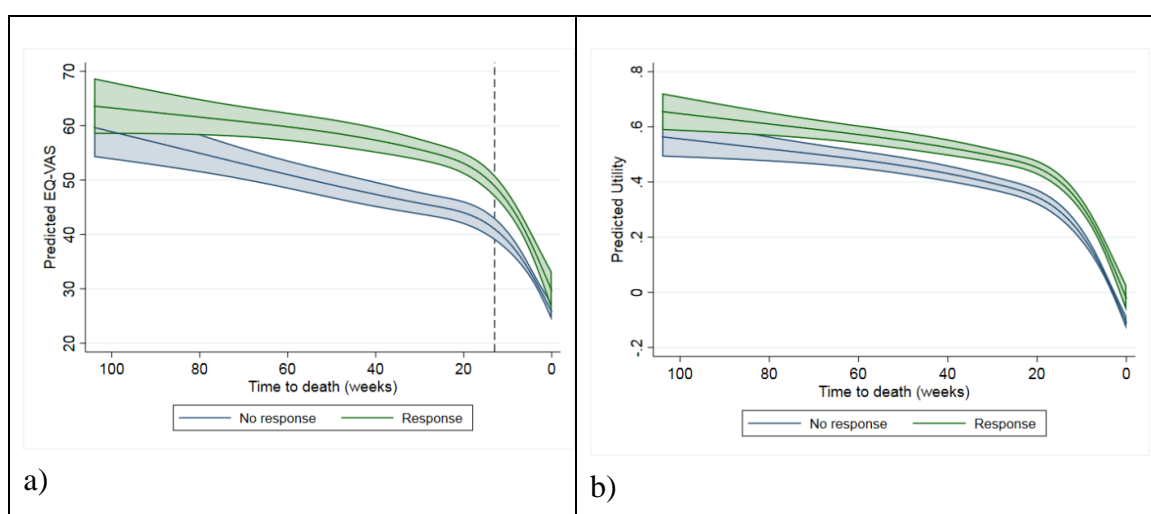
Re-fitting the multi-variable fixed-effects model excluding those individuals who returned less than five questionnaires resulted in some change in the model coefficients, particularly with regard to the TTD splines. Predictions based on this second model are shown in Figure 15a. Given the number of individuals excluded from this analysis and their shorter overall survival time it is difficult to draw conclusions from this analysis. Notably the model predictions remain fairly stable, although the point at which the minimally important difference occurs reduces from 14 weeks to 8 weeks.

Table 8. Multi-variable fixed effects model estimates with and without individuals with <5 questionnaire returns. *p≤0.05, ** p<0.01, *** p<0.001

	Including all observations	Excluding <5 observations
Spline 1	1.532***	1.244***
Spline 2	-20.818***	-14.284**
Spline 3	25.866***	17.588**
Pain response	3.835*	4.332
On re-irradiation	-4.117	-4.559*
Post re-irradiation	-1.904	-2.278
Response#Spline1	0.375	0.509
Response#Spline2	-3.517	-6.621
Response#Spline3	4.031	8.004
Constant	25.783***	26.748***

Figure 15. Predicted EQ-VAS with response at varying time to death based on fitted model a) excluding individuals with less than 5 questionnaire returns (b) for comparison including these individuals. The vertical reference lines on these graphs are placed at 8 weeks and 14 weeks to represent the minimally important difference.

a)   b)
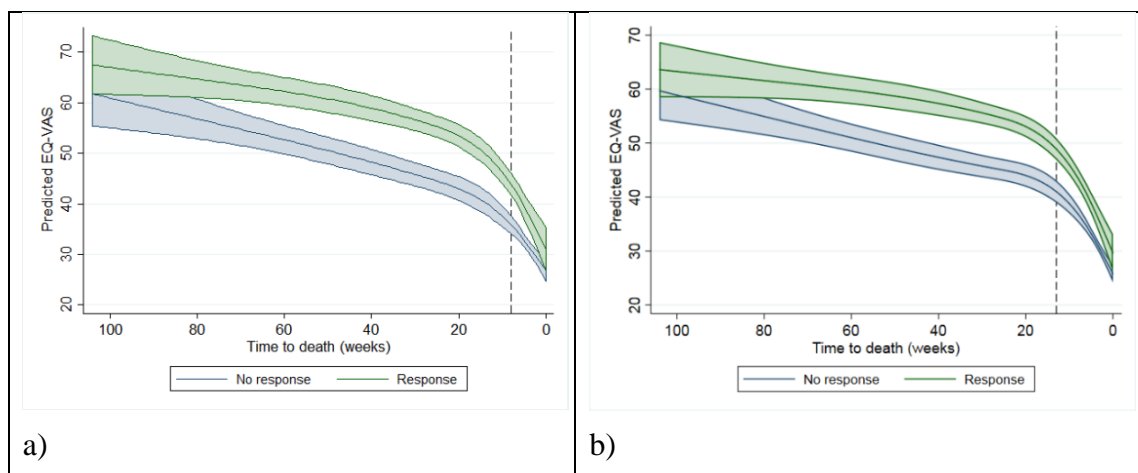
The average marginal prediction of EQ-VAS from a final sensitivity analysis assessing the impact of considering only individuals surviving more or less than 6 months beyond treatment are shown in Figure 16. The two cohorts appear to have very different outcomes; those surviving more than six months beyond treatment having a significantly higher EQ-VAS with pain response, even in

the final weeks of life. Conversely, in those surviving for less than 6 months beyond treatment the difference in EQ-VAS is much less marked, falling below the minimally important difference at all time points and reducing to show no significant difference in the average marginal prediction in the final 8 weeks of life irrespective of pain response. The marked separation in the average predicted EQ-VAS near the EoL for patients surviving more than 24 weeks is hard to explain. In the longer surviving cohort, relatively small numbers of questionnaires are available in the final months of life, potentially influencing this outcome (only 57 questionnaires in the final 6 weeks of life reflect pain response following treatment). Alternatively, this may be reflecting an imbalance in the panels where patients with short survival time are included; a consequence of the fixed effects specification (in which the fixed effect is constant across an individual's entire survival time) or, more simply, heterogeneity in the population. From a clinical perspective, the limited separation in EQ-VAS between those who respond to treatment delivered in the final 25 weeks of life is notable; the improvement in HR-QoL is markedly attenuated in this group. Conversely, the wider separation of EQ-VAS as death approaches in patients treated more than 24 weeks from the EoL is occurring a number of months after treatment, therefore, its relationship with the treatment itself cannot be determined.

Figure 16. Predicted EQ-VAS with pain response in those surviving a) more than 24 weeks after treatment and b) less than 25 weeks.
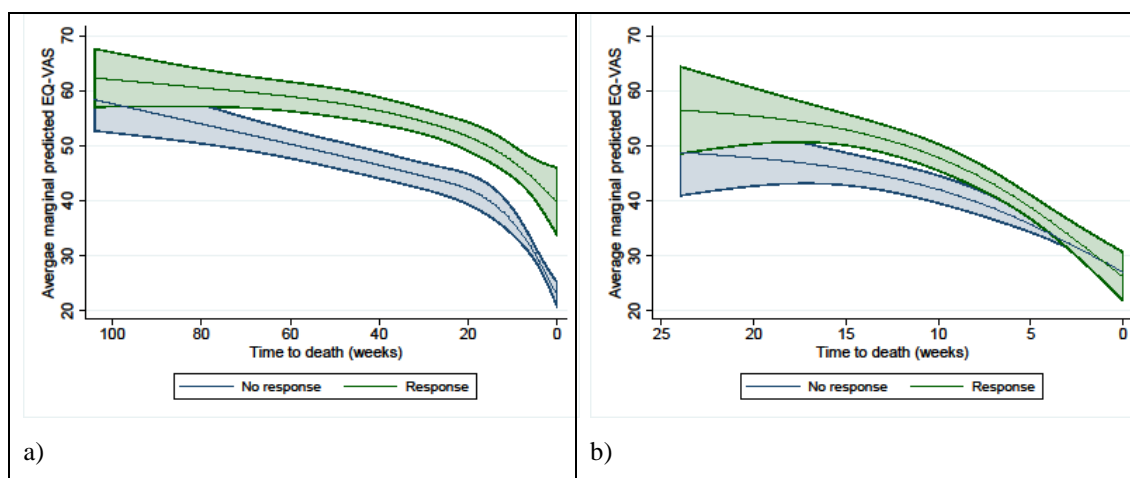
3.2.5.2 Treatment response and the EQ-5D-3L domains

In each domain of the EQ-5D-3L a large proportion of individuals reported some problems at baseline (Table 9).

Table 9. Baseline EQ-5D domain levels in the study population.

n	Mobility		Self-care		Usual activities		Pain		Anxiety	
	n	%	n	%	n	%	n	%	n	%
No problems	384	45.2	365	43.0	86	10.1	21	2.5	346	40.8
Some problems	307	36.2	333	39.2	325	38.3	471	55.5	379	44.6
Severe problems	92	10.8	95	11.2	370	43.6	301	35.5	67	7.9
Unknown	66	7.8	56	6.6	68	8.0	56	6.6	57	6.7

In post-radiotherapy follow-up 62.4% (n=1,669) of completed questionnaires in which the patient reported a pain response to treatment also reported a Pareto improvement in the EQ-5D domains. This Pareto improvement was seen less frequently where pain response was not experienced (2,045, 35.8%). On univariable multi-level fixed-effects logistic regression modelling the marginal predicted effect of pain response to treatment showed a 16.1% (95% CI 13.9-18.3) increase in the probability of Pareto improvement. Table 10 demonstrates the observed rates of Pareto improvement with pain response for varying TTD categories. On univariable fixed-effects modelling the marginal predicted probability of Pareto improvement was found to be significantly lower for individuals within the final 6 weeks of life (7.3% (95% CI 6.0 – 8.7) compared to those within 6-12 months (42.0% (95% CI 27.7-32.3).

Table 10. Pareto improvement with response by time to death category.

| | | Pareto improvement | | | | |
| | | Absent | | Present | | Total |
	Pain response	n	%	n	%	n
<6 weeks	No	612	88.6	79	11.4	691
	Yes	283	**72.4**	108	**27.6**	391
6 weeks - 3 months	No	708	80.1	176	19.9	884
	Yes	341	**63.4**	197	**36.6**	538
3 - 6 months	No	833	78.3	231	21.7	1,064
	Yes	501	**53.9**	429	**46.1**	930
6 - 12 months	No	565	71.4	226	28.6	791
	Yes	359	**44.7**	444	**55.3**	803
>12 months	No	938	76.2	293	23.8	1,231
	Yes	561	**53.3**	491	**46.7**	1,052

Multi-variable fixed-effects logistic regression modelling with RCS for TTD and interactions between pain response and TTD splines demonstrated that TTD and pain response retained a significant relationship with EQ-5D Pareto response after adjustment for re-irradiation. A significant interaction between pain response and TTD splines was, again, observed, suggesting that the effect of pain response upon Pareto improvement is not constant with TTD (Table 11). Average marginal predictions of probability of Pareto response with pain response over varying TTD are shown in Figure 17. After adjustment in the multi-variable model patients with approximately two years to the EoL had an average marginal predicted probability of Pareto improvement just under 20% higher with response than no response (18.94% at 104 weeks). This predicted benefit is sustained at six months from the EoL (18.15% at 24 weeks TTD). Within 16 weeks of death, the marginal benefit reduces steeply falling below 10% at five weeks from the EoL (Figure 17). Whilst reduced in magnitude this predicted difference remains significant (p<0.05) until the final two weeks of life but it is unclear, whether this predicted marginal effect is clinically meaningful.

A gradual decline in the probability of Pareto improvement with TTD is seen in both those with, and without, a pain response. This decline accelerates in the final months of life in those

responding relative to non-responders; with reducing TTD the relative benefit of pain response diminishes, as measured by the Pareto response.

Table 11. Fixed effects logistic regression model for Pareto response with pain response and time to death. 8,375 observations from 751 patients. Minimum observations per patient 1, maximum 35. *p≤0.05, ** p<0.01, *** p<0.001

	Coef.	Std.err	z	p	L 95% CI	U 95% CI
Spline 1	0.150***	0.033	4.590	<0.001	0.086	0.214
Spline 2	-1.784**	0.630	-2.830	0.005	-3.019	-0.548
Spline 3	2.192**	0.798	2.750	0.006	0.627	3.756
No pain response	0.000	-	-	-	-	-
Pain response	0.697*	0.351	1.990	0.047	0.009	1.386
No re-irradiation	0.000	-	-	-	-	-
On re-irradiation	-0.236	0.301	-0.780	0.433	-0.827	0.354
Post re-irradiation	-0.425*	0.199	-2.140	0.032	-0.814	-0.036
Response#Spline1	0.105*	0.045	2.340	0.019	0.017	0.193
Response#Spline2	-1.845*	0.857	-2.150	0.031	-3.525	-0.164
Response#Spline 3	2.310*	1.084	2.130	0.033	0.185	4.434
Constant	-4.229	0.279			-4.775	-3.682
Patient id						
var(_cons)	7.183	0.681			5.965	8.649

Figure 17. Predicted probability of Pareto improvement with response to treatment at varying proximity to death. Predictions based on fixed-effects model with restricted cubic spline for TTD.
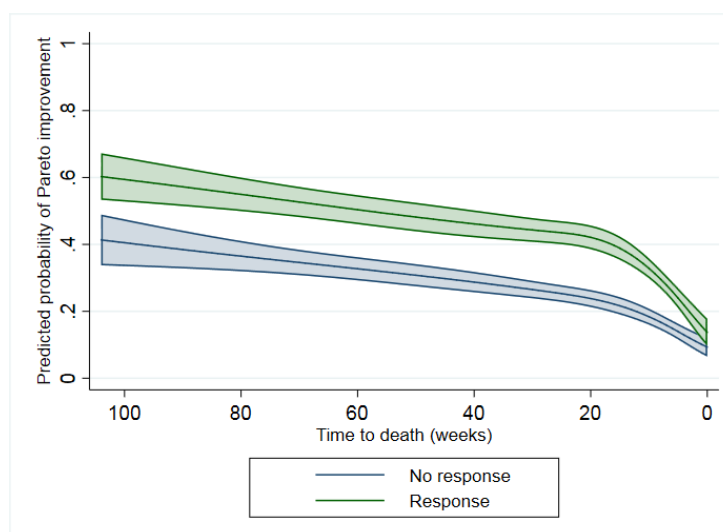
Across all five EQ-5D domains, the frequency of "no problems" was lower with no pain response following treatment. Conversely, "severe problems" were more frequently seen across all domains (Table 12). The observed difference was greatest in the pain domain ("no problems" being seen in 142 (3.0%) questionnaires reporting no pain response versus 626 (16.9%) reporting pain response. "Severe problems" were reported in 1,336 (28.7%) questionnaires reporting no response and 322 (8.7%) reporting pain response. These differences are illustrated graphically in Figure 18.

Table 12. EQ-5D domain responses with pain response to radiotherapy during follow-up.

	No response		Response		Unknown	
	n	%	n	%	n	%
Mobility						
No problems	1,917	**41.1**	1,925	**51.8**	132	3.5
Some problems	1,926	41.3	1,354	36.5	117	3.1
Severe problems	693	**14.9**	364	**9.8**	85	2.3
Unknown	125	2.7	71	1.9	3,426	91.1
Self-care						
No problems	1,779	**38.2**	1,833	**49.4**	101	2.7
Some problems	2,044	43.9	1,412	38.0	144	3.8
Severe problems	771	**16.5**	426	**11.5**	98	2.6
Unknown	67	1.4	43	1.2	3,417	90.9
Usual activities						
No problems	447	**9.6**	569	**15.3**	43	1.1
Some problems	1,692	36.3	1,457	39.2	105	2.8
Severe problems	2,403	**51.6**	1,597	**43.0**	190	5.1
Unknown	119	2.6	91	2.5	3,422	91.0
Pain						
No problems	140	**3.0**	626	**16.9**	26	0.7
Some problems	3,112	66.8	2,716	73.1	252	6.7
Severe problems	1,336	**28.7**	322	**8.7**	63	1.7
Unknown	73	1.6	50	1.3	3,419	90.9
Anxiety						
No problems	1,812	**38.9**	1,817	**48.9**	128	3.4
Some problems	2,310	49.6	1,654	44.5	177	4.7
Severe problems	466	**10.0**	198	**5.3**	32	0.9
Unknown	73	1.6	45	1.2	3,423	91.0

Figure 18. EQ-5D domain levels and treatment response status.
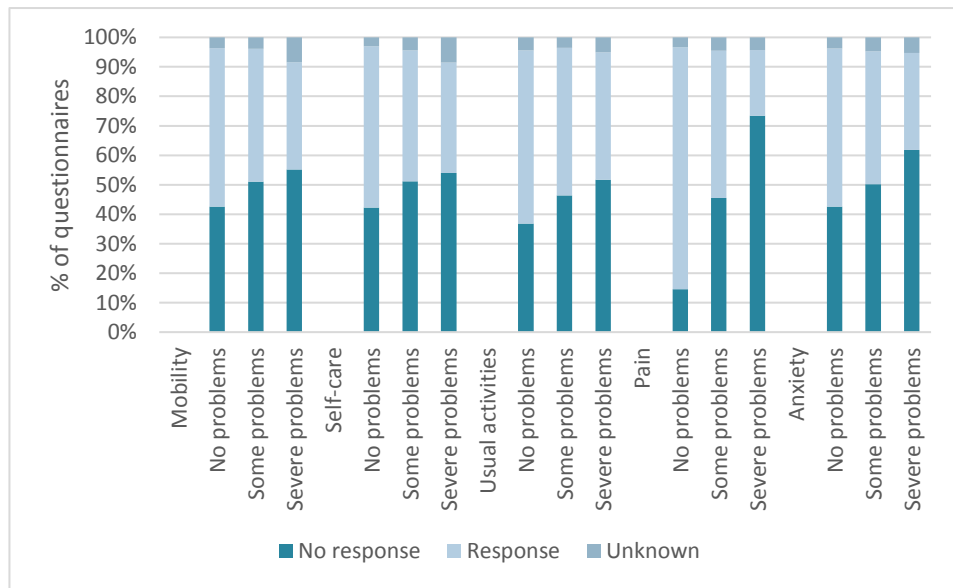
On univariable fixed-effects modelling there was a significant negative relationship (p<0.001) between pain response and domain level probability across all domains of the EQ-5D. For the pain domain this resulted in an average predicted marginal increase in the probability of "no problems" of 10.299% (95% CI 9.000-11.598) and reduced probability of "severe problems" of 21.446% (95% CI 23.234-19.658). The marginal effect of pain response was lower in the other EQ-5D domains; an 8.663% (95% CI 6.775-10.551) increased probability of "no problems" in the anxiety domain with pain response and 3.728% (95% CI 2.808-4.649) reduced probability of "severe problems", a 4.678% (95% CI 3.641-5.715) increased probability of "no problems" in the usual activities domain with pain response and 9.584% (95% CI 7.742-11.426) reduced probability of "severe problems".

On multi-variable, ordered logistic regression fixed-effects modelling pain response following treatment was associated with a significant reduction in problems reported in the EQ-5D pain and usual activities domains (p<0.001). This effect was not seen in the mobility, self-care and anxiety domains (Table 13).

Table 13. Multi-variable, ordered logistic regression, fixed effects model estimates for EQ-5D domains with response and TTD. *p≤0.05, ** p<0.01, *** p<0.001.

	Mobility	Self-care	Usual activities	Anxiety	Pain
Spline 1	-0.330***	-0.414***	-0.350***	-0.189***	-0.111***
Spline 2	4.629***	5.550***	4.357***	2.719***	1.528***
Spline 3	-5.727***	-6.853***	-5.328***	-3.374***	-1.905**
No pain response	0.000	-	-	-	-
Pain response	-0.488	-0.439	-1.337***	-0.144	-1.555***
No re-irradiation	0.000	-	-	-	-
On re-irradiation	0.647**	0.970***	0.397	0.474	0.463*

Post re-irradiation	0.756***	0.783***	0.611***	0.619***	-0.320*
Response#Spline1	-0.074*	-0.047	0.031	-0.056	-0.036
Response#Spline2	1.621*	0.747	-0.193	0.748	0.416
Response#Spline 3	-2.060*	-0.927	0.206	-0.915	-0.499
/cut1	-3.876	-5.363	-9.661	-2.535	-5.890
/cut2	0.459	-0.398	-4.679	3.090	0.083
upid					
var(_cons)	11.117	12.289	14.876	11.537	3.062

Figure 19 shows the predicted level probability of each EQ-5D domain with response to treatment across varying times to death. All predictions are made assuming a baseline EQ-5D response of "some problems" and no re-irradiation (the modal categories). The average predicted probability of "no problems", whilst increased with pain response across all domains, was increased markedly and across all TTD for the EQ-5D pain domain. In all other EQ-5D domains increases were small and statistically insignificant for most TTD.

Figure 19. Predicted probability of EQ-5D domain level with response to palliative radiotherapy over varying survival times beyond treatment. Predictions with response are shown in green and no response in blue. Predicted level probability for level 1 (no problems) is shown in darker shades and level 3 (severe problems) in brighter shades. All predictions are based on a multi-variable random-effects ordered logistic regression model with restricted cubic spline for TTD. Level 2 predictions are omitted here for ease of interpretation.
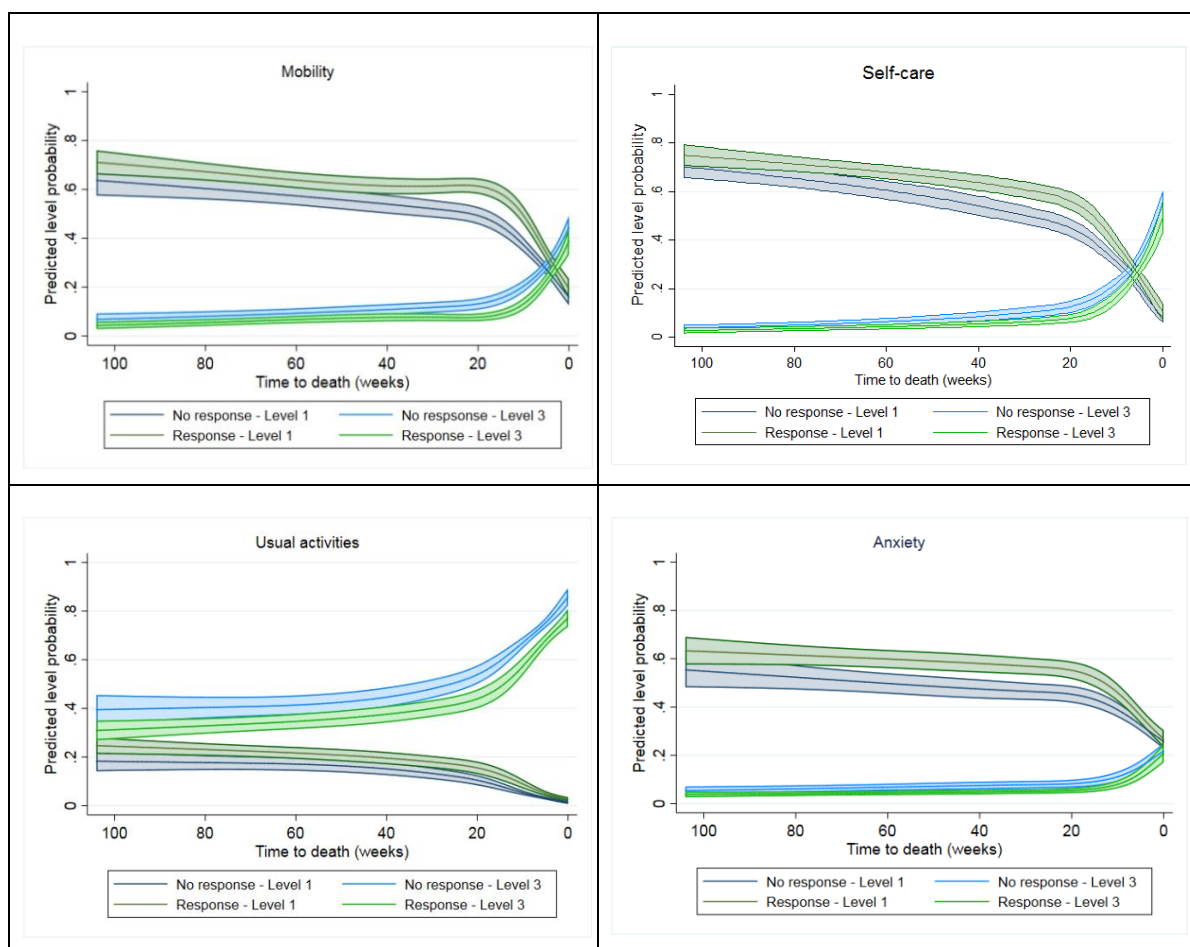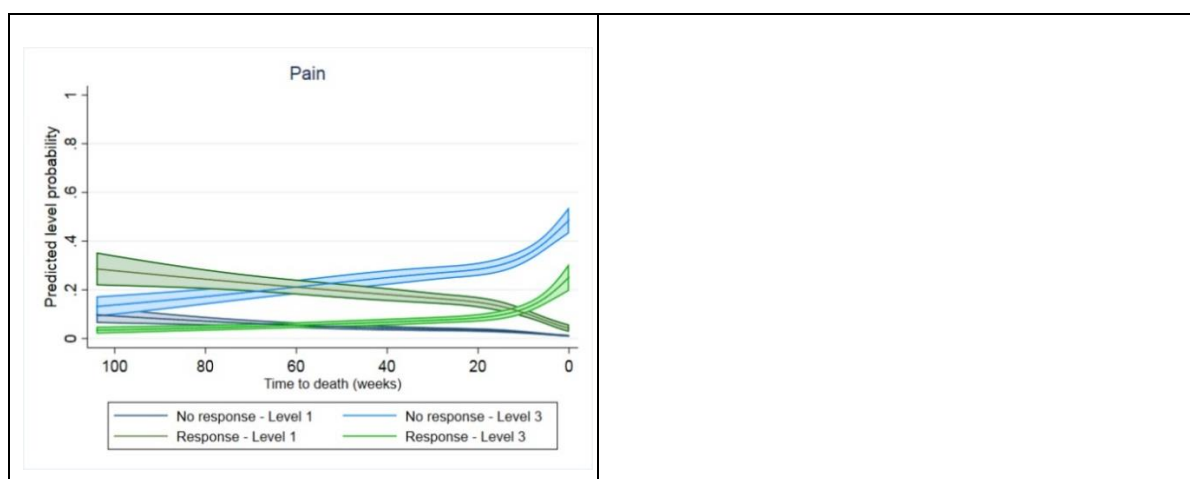
As suspected based on the absence of an interaction between TTD and pain response in modelling utility (equation 1), the multi-variable, ordered logistic regression, fixed-effects EQ-5D domain models (equation 2) demonstrate no interaction between TTD and pain response with regard to the level probability. The Wald test was used to test for combined zero coefficients in the pain response/splines interactions. Across all EQ-5D domains the Wald-test supported acceptance of the null hypothesis, that no variation in the relationship between pain response and TTD was observed. The resulting Wald test statistics for each domain model were: Mobility p=0.096, self-care p=0.505, activity p=0.140, anxiety p=0.090 and pain p=0.257. Only model results for pain and mobility are presented for brevity.

Table 14. Fixed effects ordered logistic regression for level probability with TTD a) EQ-5D Pain domain b) Mobility domain *p≤0.05, ** p<0.01, *** p<0.001

a)	Coef.	Std. err	z	p	L 95% CI	U 95% CI
Spline 1	-0.111***	0.022	-5.130	<0.001	-0.153	-0.069
Spline 2	1.528***	0.432	3.530	<0.001	0.680	2.375
Spline 3	-1.905**	0.549	-3.470	0.001	-2.981	-0.829
No pain response	0.000	-	-	-	-	-
Pain response	-1.555***	0.257	-6.060	<0.001	-2.059	-1.052
No re-irradiation	0.000	-	-	-	-	-
On re-irradiation	0.463*	0.214	2.170	0.030	0.044	0.882
Post re-irradiation	-0.320*	0.143	-2.230	0.026	-0.601	-0.039
Response#Spline1	-0.036	0.034	-1.040	0.300	-0.103	0.032
Response#Spline2	0.416	0.669	0.620	0.534	-0.895	1.727
Response#Spline 3	-0.499	0.847	-0.590	0.556	-2.160	1.161
/cut1	-5.890	0.192			-6.267	-5.513
/cut2	0.083	0.167			-0.245	0.411
Patient id						
var(_cons)	3.062	0.235			2.635	3.558

8,252 observations from 749 individuals. Minimum observations per patient 1, maximum 35.

b)	Coef.	Std. err	z	p	L 95% CI	U 95% CI
Spline 1	-0.330***	0.025	-13.340	<0.001	-0.378	-0.281
Spline 2	4.629***	0.491	9.430	<0.001	3.667	5.591
Spline 3	-5.727***	0.623	-9.190	<0.001	-6.948	-4.505
No pain response	0.000	-	-	-	-	-
Pain response	-0.488	0.280	-1.740	0.081	-1.035	0.060
No re-irradiation	0.000	-	-	-	-	-
On re-irradiation	0.647**	0.233	2.780	0.005	0.191	1.104
Post re-irradiation	0.756***	0.163	4.630	<0.001	0.436	1.077
Response#Spline1	-0.074*	0.037	-1.990	0.047	-0.147	-0.001
Response#Spline2	1.621*	0.731	2.220	0.027	0.188	3.053
Response#Spline 3	-2.060*	0.926	-2.220	0.026	-3.876	-0.245
/cut1	-3.876	0.219			-4.306	-3.446
/cut2	0.459	0.210			0.047	0.870
Patient id						
var(_cons)	11.117	0.860			9.553	12.938

8,179 observations from 749 individuals. Minimum observations per patient 1, maximum 35.

The average marginal predictions of level probability from the ordered logistic multi-variable, fixed-effects EQ-5D domain models demonstrate similar effects across the mobility, self-care and anxiety/depression domains (Figure 19). For each of these domains the predicted probability of "no problems" was high and stable across TTD from two years from the EoL until the final few months of life. At this point in all three domains the probabilities of "no problems" and "severe problems" converged. In the case of mobility and self-care the probability of "severe problems" then exceeded that of "no problems" in the final months of life irrespective of pain response. A similar convergence in the level probability of the anxiety domain; although at no point did the probability of "severe problems" exceed that of "no problems". The changes in level probabilities with TTD in the mobility and self-care domains are likely to reflect increasing physical frailty near the EoL. This also provides some rationale for the relatively lesser change seen in the anxiety/depression domain.

The usual activities domain has strikingly different outcomes to those discussed above; across all times to death "severe problems" are more likely than "no problems" with the "severe problems" markedly increasing in the final few months of life. The "no problems" level was predicted to occur in less than 20% of patients at any time point, irrespective of response to treatment. The wording of the EQ-5D usual activities domain may explain this marked difference. Usual activities are defined as "e.g. work, study, housework, family or leisure activities". EQ-5D usual activities level 2 states "I have some problems with performing my usual activities" whilst level 3 states "I am unable to perform my usual activities". Few patients undergoing palliative radiotherapy for bone metastases would be expected to state they have "no problems" and it is

arguably unsurprising in this patient group that level 3 is the predominant group. It has previously been found that patients receiving supportive or palliative care can find it difficult to interpret and answer the usual activities domain.(249)

Finally, the pain domain is the only one where a significant difference in level probability is seen with pain response following treatment; "no problems" is significantly more likely in those with a pain response across all TTD. Conversely, "severe problems" are significantly less likely. The difference in predicted probability of "no problems" reduces in the final few months of life despite pain response whilst the difference in "severe problems" is maintained across all TTD. Many patients with bone metastases will experience pain at multiple bony sites and, potentially due to other sites of disease. It is, therefore, possible that near the EoL pain response at an individual site is overtaken by symptoms related to disseminated disease.

3.2.5.3 *Relating the EQ-VAS to the five domains domains with proximity to death*

It has been shown above that in the prediction of EQ-VAS a significant interaction exists between pain response and TTD splines. This interaction was not seen where either utility or the EQ-5D domains were modelled, suggesting that the source of the interaction lies in the relationship between the EQ-5D domains and EQ-VAS; how individuals self-report overall health (using the EQ-VAS) relative to the experienced EQ-5D domains. This hypothesis was tested using equation 3 (pg 73). The results are shown in Table 15 and diagnostic plots (quantile-quantile and residual versus variable plots) for the model residuals in Figure 20.

Table 15. Fixed effects model of EQ-VAS with EQ-5D domains over varying proximity to death. *$p \leq 0.05$, ** $p < 0.01$, *** $p < 0.001$. The Wald test for joint non-zero coefficients in splines 1, 2 and 3 was $p < 0.0001$. 7,440 observations from 719 patients. Minimum observations per patient 1, maximum 35. $R^2 = 0.3420$ (within = 0.198, between = 0.4083). Modified Durbin-Watson = 1.287.

		Coef.	Std. Err.	t	P	Lower 95% CI	Upper 95% CI
Spline 1		4.546***	0.446	10.200	<0.001	3.673	5.420
Spline 2		-71.827***	8.720	-8.240	<0.001	-88.921	-54.732
Spline 3		89.469***	11.052	8.100	<0.001	67.804	111.134
Mobility							
	2	-2.217	2.875	-0.770	0.441	-7.854	3.420
	3	-2.698	3.271	-0.820	0.409	-9.109	3.713
Pain							
	2	6.406	3.405	1.880	0.060	-0.268	13.080
	3	-2.774	3.679	-0.750	0.451	-9.987	4.438
Activity							
	2	13.009**	4.324	3.010	0.003	4.532	21.486
	3	7.108	4.724	1.500	0.132	-2.153	16.369
Anxiety							
	2	-8.066***	1.971	-4.090	<0.001	-11.930	-4.202
	3	-9.673***	2.750	-3.520	<0.001	-15.064	-4.283
Self-care							
	2	-1.052	2.914	-0.360	0.718	-6.764	4.660
	3	-1.388	3.477	-0.400	0.690	-8.204	5.428

Pain#Spline1							
	2	-1.748***	0.427	-4.090	<0.001	-2.585	-0.911
	3	-1.809***	0.479	-3.780	<0.001	-2.747	-0.871
Pain#Spline2							
	2	31.681***	7.973	3.970	<0.001	16.051	47.310
	3	31.719**	9.186	3.450	0.001	13.713	49.726
Pain#spline3							
	2	-39.868***	10.061	-3.960	<0.001	-59.590	-20.145
	3	-39.852**	11.623	-3.430	0.001	-62.636	-17.068
Activity#Spline1							
	2	-1.993***	0.512	-3.900	<0.001	-2.996	-0.990
	3	-1.626**	0.568	-2.860	0.004	-2.740	-0.512
Activity#Spline2							
	2	32.925***	9.397	3.500	<0.001	14.504	51.345
	3	27.194*	10.565	2.570	0.010	6.484	47.905
Activity#Spline3							
	2	-41.044**	11.852	-3.460	0.001	-64.278	-17.810
	3	-34.006*	13.338	-2.550	0.011	-60.153	-7.858
Mobility#Spline1							
	2	0.241	0.368	0.660	0.512	-0.479	0.962
	3	0.040	0.454	0.090	0.929	-0.849	0.930
Mobility#Spline2							
	2	-5.745	7.029	-0.820	0.414	-19.524	8.035
	3	-5.804	9.337	-0.620	0.534	-24.107	12.498
Mobility#Spline3							
	2	7.332	8.896	0.820	0.410	-10.107	24.771
	3	7.620	11.889	0.640	0.522	-15.687	30.927
Anxiety#Spline1							
	2	0.320	0.260	1.230	0.219	-0.190	0.831
	3	-0.173	0.408	-0.420	0.671	-0.972	0.626
Anxiety#Spline2							
	2	-5.932	5.109	-1.160	0.246	-15.947	4.084
	3	3.731	8.472	0.440	0.660	-12.876	20.337
Anxiety#Spline3							
	2	7.528	6.478	1.160	0.245	-5.170	20.226
	3	-4.723	10.789	-0.440	0.662	-25.873	16.427
Self-care#Spline1							
	2	-0.290	0.370	-0.780	0.433	-1.014	0.435
	3	-0.873	0.475	-1.840	0.066	-1.804	0.058
Self-care#Spline2							
	2	3.106	6.954	0.450	0.655	-10.526	16.738
	3	15.890	9.474	1.680	0.094	-2.682	34.463
Self-care#Spline3							
	2	-3.724	8.784	-0.420	0.672	-20.943	13.494
	3	-20.166	12.030	-1.680	0.094	-43.748	3.416
Constant		25.621	2.147	11.930	<0.001	21.412	29.830
rho_ar		0.402					
sigma_u		14.641					
sigma_e		14.111					
rho_fov		0.518		(Fraction of variance because of u_i)			

Figure 20.Observation level residuals as both a quantile-quantile plot and residual-versus-variable plot
with TTD for fixed effects model of EQ-VAS with domains over TTD.
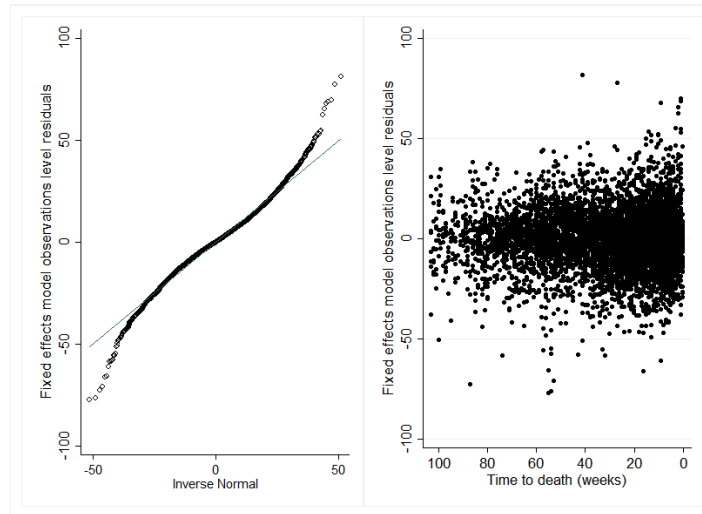
TTD is shown to be a significant independent predictor of EQ-VAS (p<0.001 for all three TTD splines); with reducing TTD the EQ-VAS deteriorates independently of the EQ-5D domains. Significant interactions between the five EQ-5D domains and TTD are seen on the Wald test for combined zero coefficients for the pain (p=0.002), usual activities (p=0.003) and mobility (p=0.045). This demonstrates variation in how these domains are valued by patients with proximity to the EoL (as measured by the EQ-VAS). No significant interaction was demonstrated in the anxiety (p=0.543) and self-care domains (p=0.147).

Interpretation of the coefficients associated with the cubic spline variables is challenging as the relationship between splines 2 and 3 with TTD is not intuitive. Additionally, the inclusion of interaction terms which incorporate the spline variables further complicates interpretation. In order to support this, average marginal predicted outcomes are provided and plotted graphically. Predictions are made at the average of the fixed effects. Predictions for each level assume all other domains are held at level 2 ("some problems")(Figure 21).

Comparisons between model specifications demonstrated that the modelled outcomes were relatively insensitive to the exclusion of individuals with less than 5 questionnaire responses (results not shown). The exclusion of patients with survival of more than 24 weeks beyond radiotherapy also did not affect the model conclusions. Specifically the independent effect of TTD was retained (p<0.001 for both splines) and the interactions previously demonstrated remained the same (Wald test results: pain p=0.045, usual activities p=0.017, mobility p=0.049, self-care p=0.615 and anxiety p=0.342).

Figure 21. Predicted average EQ-VAS in the final 2 years of life with differing domain levels and varying time to death. Fixed effects with restricted cubic spline over time to death (4 knots) and auto-regressive error correlation. No problems (blue), some problems (red), severe problems (green). Wald test for joint non-zero estimates of spline 2 and 3 p<0.0001.
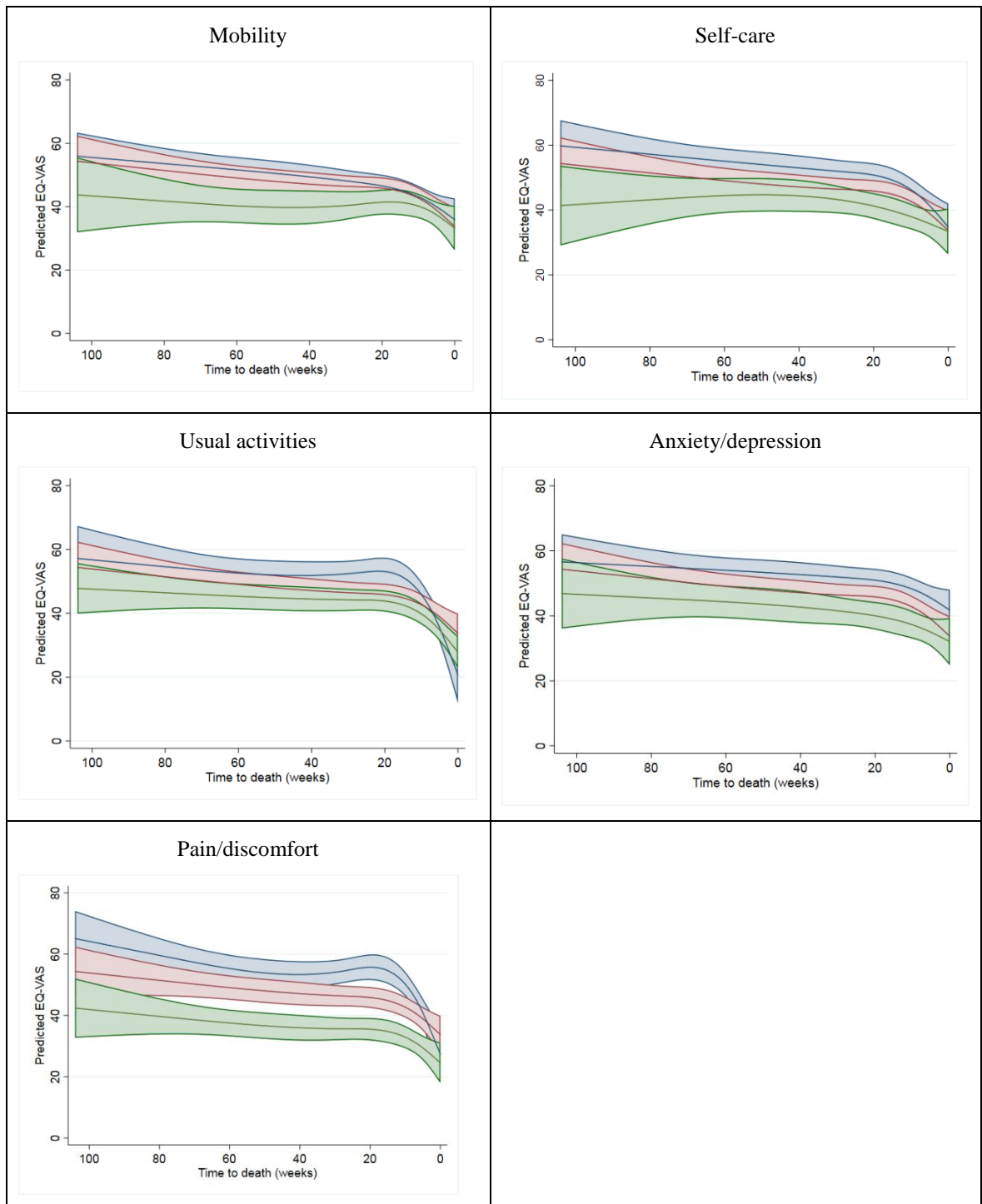
Figure 22 demonstrates the predicted EQ-VAS values for patients with varying proximity to the EoL. These predictions are presented alongside EQ-VAS predictions from a population of patients who have undergone routine surgical procedures in the NHS, the differential effects of TTD are illustrated compared to this standard population.(235)

Figure 22. Predicted EQ-VAS for varying EQ-5D domain levels following palliative radiotherapy for bone metastases with proximity to the end of life. In all predictions the four domains which are not the focus of the predictions are held at level 1. Comparator values are shown for a post-surgery outpatient population not expected to have a short prognosis. Green = no problems, blue = some problems and grey = severe problems.

3.2.6 *Discussion*

It has previously been shown that HR-QoL is better in patients who gain a pain response following palliative radiotherapy than in those who do not respond.(221,250) It has also been demonstrated that HR-QoL deteriorates with proximity to death.(90) This new study demonstrates that the relationship between pain response and HR-QoL is also not constant with proximity to death; as patients near the EoL the magnitude and likelihood of improved HR-QoL, as measured by the EQ-5D, reduces markedly. In addition a systematic difference in EQ-VAS relative to the domains of the EQ-5D occurs; the self-reported overall health reduces independently of the EQ-5D domains falls as patients near the EoL.

3.2.6.1 EQ-VAS with TTD and response

The improved self-reported health associated with pain response following palliative radiotherapy for bone metastases is, again, confirmed in this work. A gradient in HR-QoL is observed with the extent of pain response gained following treatment. Individuals with a complete response to treatment report greater EQ-VAS (mean 58.7) than those with partial response (mean 51.9) and this gradient continues through individuals who don't respond (mean 41.4) or indeed develop progressive pain (mean 35.7). This overall variation in EQ-VAS with pain response masks significant underlying heterogeneity with TTD as demonstrated by a significant interaction between pain response and TTD splines. The self-reported benefit associated with pain response of any kind reduces as patients near the EoL such that within 13 weeks of the EoL the HR-QoL benefit associated with pain response falls below a level which has previously been defined as a minimally important difference (MID).(244) Notably, where MID has previously been calculated a range of values has been identified, from 8 to 12 points on a 0-100 EQ-VAS.(244) The differences observed here in EQ-VAS are below 12 points at all time points, the maximal benefit seen being of approximately 10 points at 9 months from the EoL. For patients with more than a year to live the HR-QoL benefit of pain response again appears to reduce. This result is counterintuitive, as it might be anticipated that these are the patients who will derive the greatest benefit from treatment.

The interpretation of the results shown here for EQ-VAS are similar to those demonstrated for utility. In this population, utility was higher in those with response to treatment than without, although in contrast to the analysis with EQ-VAS, no interaction between pain response and TTD splines was demonstrated. The benefit of pain response as measured by utility is relatively consistent with TTD. Predicted utility deteriorates as patients near the EoL, utility at 104 weeks was 0.655 with response versus 0.564 with no response. This deteriorates gradually to 0.474 and 0.370 respectively at 24 weeks before a rapid deterioration to 0.057 and -0.036 respectively two weeks from the EoL.

McDonald et al. report that the relationship between pain and other HR-QoL domains is greater at 42 days than 10 days.(227) The assessment at these two different time points includes different patients, both due to attrition to death and, potentially, also to unobserved data as patients become increasingly frail near the end of life. The findings presented here provide some insight into why this difference is seen between the two time points; individuals with very limited survival being included in the first time point but not the latter. It may also be that improvements in HR-QoL domains lag behind pain responses, this was not assessed in the current study but would not change the conclusions given that those with limited survival are less likely to have the opportunity to derive maximum HR-QoL benefit if this is delayed beyond the point of pain response.

3.2.6.2   EQ-5D domain levels with pain response and time to death

Patients experiencing a pain response following palliative radiotherapy are more likely to report a Pareto improvement in the EQ-5D domains; HR-QoL has improved in at least one domain without deterioration in any other (Table 10). The likelihood of this improvement with pain response significantly increases with longer TTD from approximately a 1 in 4 chance in the final 6 weeks of life up to over a 1 in 2 chance for patients beyond six months from the EoL. Bearing in mind that response is only reported in 25% of patients in the final 6 weeks of life the likelihood of Pareto improvement becomes very small for patients in this cohort.

Patients experiencing a pain response are more likely to report "no problems" across all domains of the EQ-5D than those who report no pain response (Table 12). On univariable fixed-effects modelling there was a significant negative relationship ($p<0.001$) between pain response and domain level probability across all domains of the EQ-5D. For the pain domain this resulted in an average predicted marginal increase in the probability of "no problems" of 10.3% (95% CI 9.0-11.6) and reduced probability of "severe problems" of 21.4% (95% CI 23.2-19.7). The marginal effect of pain response was lower in other EQ-5D domains; an 8.7% (95% CI 6.8-10.6) increased probability of "no problems" in the anxiety domain with pain response and 3.7% (95% CI 2.8-4.6) reduced probability of "severe problems", a 4.7% (95% CI 3.6-5.7) increased probability of "no problems in the usual activities domain with pain response and 9.6% (95% CI 7.7-11.4) reduced probability of "severe problems". As can be seen from the marginal predictions of level probability (Figure 19) the distinction between those with and without pain response is, however, relatively small across all EQ-5D domains except pain (approximately 10% higher predicted probability of "no problems" versus approximately 20% in the EQ-5D pain domain). Similarly, "severe problems" are more likely in those reporting no pain response.

For patients in the final weeks of life "severe problems" in all domains except anxiety/depression become more likely than "no problems". In contrast where TTD is longer "no problems" are more likely. This is clinically unsurprising, the changing EQ-5D domain levels (particularly mobility, self-care and usual-activities) are likely to reflect increasing frailty. As demonstrated, this is unlikely to be influenced by an improvement in focal pain; the impact of TTD upon the domain level probability is more marked than the impact of pain response.

The lack of interaction between TTD splines and pain response in the EQ-5D domain level probability model is worthy of consideration. There are a number of possible explanations for this; it may reflect a lack of power to identify such an effect. As shown in Table 12, however, a large number of questionnaire returns were considered within this analysis, although numbers are not consistent across all TTD cohorts potentially influencing the study's power. Alternatively, this lack of interaction, may be the result of a lack of discrimination in assessing HR-QoL domain outcomes using the EQ-5D-3L. Whilst possible, a lack of discrimination might be expected to

increase any interaction rather than reducing it; individuals with longer TTD, potentially experiencing a greater magnitude of benefit and, therefore, being more likely to report an improvement than those near the EoL. Alternatively, the patient's interpretation of these domain levels may vary with proximity to death (a response shift being seen). Conversely, the EQ-5D-3L is clearly reflecting deterioration in domain levels with proximity to the EoL. Given it is able to discriminate changes with TTD, it is possible that the lack of interaction between pain response and TTD in terms of level probability does exist.

3.2.6.3   EQ-VAS with domains

With less problems in the EQ-5D domains a higher EQ-VAS is observed across all of the domains, although the distinction between levels is not marked. Similarities are seen in the relationship between each of the EQ-5D domains and proximity to death; all domains are associated with reduced EQ-VAS with proximity to death. A gradual decline is demonstrated between two years and six months from the EoL with a more rapid decline in EQ-VAS in the final few months of life independently of the five EQ-5D domains. This is illustrated graphically in Figure 21. In addition, across all domains, the EQ-VAS associated with on level 3 ("severe problems") remains relatively consistent across all TTD whilst that associated with levels 1 and 2 deteriorates more markedly with proximity to death. It maybe that individuals further from the EoL are adjusting to their condition, whilst increasing frailty and more rapid deterioration near the EoL mean this adjustment is no longer sufficient to compensate for their declining health. Conversely, the lack of precision in the EQ-5D-3L domains may mean that each level represents a broad range of self-reported health (measured here by the EQ-VAS) and that systematic variation within these levels maybe occurring with proximity to death resulting in variation in the EQ-VAS.

Differences between the individual domains are also worthy of consideration:

In this population, having "some problems in walking about" (Figure 21 a) was not associated with a significant reduction in the EQ-VAS as compared to having "no problems in walking about" (Table 15, Figure 21a). In contrast the reduction seen with confinement to bed was more marked, although the independent impact of the mobility domain level was not statistically significant. This relationship did not appear to be constant with proximity death; the predicted EQ-VAS with levels 1 and 2 fell towards the end of life to become minimally different to level 3. Whilst each individual domain level/spline interaction term was not significant the Wald test rejected the null hypothesis of all interaction terms having zero effect (p=0.045). The relatively consistent value placed on "severe problems" suggests that the impact of confinement to bed is marked and consistent across the final two years of life.

As seen in the mobility domain the predicted EQ-VAS seen with differing levels of the self-care domain varies with proximity to death. In this case the difference between predictions with levels 1 and 2 is more marked (although non-significant). Again, the difference between levels reduces with proximity to death although here the separation persists closer to the EoL. As with mobility,

the interactions observed between domain levels and proximity to death splines were not significant.

Considering the usual activities domain, level 2 demonstrates a significant independent relationship with EQ-VAS. In addition, a significant interaction between the domain level and TTD splines was found (p<0.02) and this resulted in a gradual decline in EQ-VAS with all levels across TTD until the final five months of life when all levels deteriorate markedly. The gradient of this decline being particularly marked for level 1 as compared to levels 2 and 3.

The anxiety domain is the only domain in which a significant relationship between the domain level and EQ-VAS is seen independently of TTD (p<0.001 for both level 2 and 3 compared to level 1). No significant interaction between domain level and TTD splines is seen and whilst a slight narrowing of the difference in average marginal predictions of level 3 and 2 is seen near the EoL the relative value of the three levels is consistent across all TTD.

In this cohort (as in other value sets) the pain domain demonstrates the widest separation in predicted EQ-VAS with domain level, independently of TTD. In addition significant interactions are seen with all domain level and TTD splines (p<0.001). As seen with the level 1 usual activities domain, however, the deterioration in predicted EQ-VAS with level 1 across TTD was more marked than that seen with level 2 or 3.

The comparisons made with EQ-VAS predictions based on Feng et al. are of interest in assessing how the self-reported health of this cohort differs to that of a patient cohort who have undergone surgical interventions within the NHS.(235) As might be expected the predicted EQ-VAS for health state 11111 in the surgical cohort (EQ-VAS=86.3) is greater than the predicted EQ-VAS in the current study cohort, even in those with TTD of 2 years (EQ-VAS=77.2). Differences between the cohorts also arise in the domain levels:

Levels one and two of the mobility domain demonstrate relatively little discrimination in the current cohort (across all TTD) although the impact of severe problems with mobility appear greater in patients with more than nine months to live than in the surgical cohort; The impact of pain level is greater in this cohort than in the surgical cohort with this difference being relatively sustained with TTD and only reducing markedly in the final few weeks of life; The separation of EQ-VAS with the usual activities and self-care domains is similar in both cohorts, although this is lost in the final months of life; The anxiety/depression domain presents markedly wider separation in the EQ-VAS predictions in the current population than seen in the surgical cohort. Notably this separation persists across all TTD.

As with all analyses carried out here, however, the most striking difference between the two cohorts is the independent impact of TTD upon EQ-VAS.

The EQ-5D domains only partially explain the observed variation in the EQ-VAS ($R^2 = 0.3420$). Notably the variation observed was predominantly attributable to variation between individuals

(R^2 for between variation = 0.4083), however, within variation was still marked (R^2 for within variation = 0.1980). Overall it is clear that the deterioration in EQ-VAS seen in this patient cohort near the EoL occurs independently of the domains of the EQ-5D ($p<0.001$).

3.2.6.4 Model specifications

Given the significance of the Hausman test result and the focus of this study on the time-varying co-variables, fixed-effects model specifications were used. Such specifications recognise, but do not quantify, the impact of patient level (time-invariant) co-variables. As such, the interpretation of the fixed effects model might be considered limited beyond the studied population. This is, however, a large sample of patients with bone metastases from solid organ tumours. As only those known to have died during the study period are included, the survival time for the study cohort is less than that observed routinely (4.3 versus 6.2 months).(4) Given the interest in the final months of life in this study, this difference should not have a detrimental impact upon interpretation.

In the fixed-effects model the time-varying effects reflect the average effects seen across all patients as the patient level variance is averaged out over the population.(251) The resulting model, by definition, provides no estimate of the patient level predictors. Debate exists in the literature as to the optimum way to model in the presence of correlation between the patient level and time-varying co-variables, such correlation potentially introducing heterogeneity bias. Li demonstrates when using simulation and real data that the fixed effects model should remain unbiased.(252) Conversely, Bell and Jones make a strong case for an alternative within-between random-effects specification, which incorporates a patient-level mean of the dependent variable in order to avoid the challenges of omitted level two variables in the random-effects specification whilst continuing to estimate the level two predictors.(253) They conclude that the two alternatives are equally unbiased. The fixed effects model specifications are presented here.

Where patients returning less than five questionnaires were excluded this resulted in a blunting of the reduction in the change in EQ-VAS seen with response near the EoL. Average marginal predictions from the fixed-effects models integrate out the fixed-effects i.e. effectively assuming each individual takes the population average. This average gives equal weighting to all individuals included in the analysis irrespective of the number of questionnaires included. Excluding those with less than 5 returned questionnaires predominantly excluded patients with short survival time and this meant that the predictions near the EoL reflect a population with longer survival beyond treatment i.e. whose whole disease trajectory can be observed. The marginal predictions modelled were shown based on models including and excluding individuals who returned less than 5 questionnaires; a slight reduction in the average marginal predictions of the EQ-VAS was seen when those with less than 5 questionnaires were included (comparing Figure 14 and Figure 15). These individuals had shorter survival time and were, therefore, closer to the EoL, with lower EQ-VAS. Other model coefficient estimates remain relatively consistent after exclusions (Table

8) although the effect of pain response is no longer significant. It is not possible to say to what extent this reflects reduced sample size as opposed to a difference in effect seen, notably the estimate of the effect of pain response was slightly higher after exclusions (3.835 versus 4.332) suggesting the lack of significance may reflect reduced sample size. Given that the fixed-effects model should be robust to correlation between the fixed and time-varying effects this should not result in significant bias or change the study conclusions.

Mis-reporting of subjective health has long been considered a potential source of bias when self-reported indicators are used as a measurement of health.(254–256) In addition, systematic variation in response styles may be the result of cultural differences,(257) age,(258) education level (259), sex,(260) and income.(261) All of these factors are time-constant and as such will be incorporated within the fixed effects specification of the models developed here. As such these factors are not expected to result in bias. If, however, these fixed effects were to interact with any of the time-varying co-variables (e.g. the effect of pain response were to vary with age), this heterogeneity would not be recognised in the fixed effects model; the predictions represent an average across the population.

The possibility that heterogeneity exists is demonstrated by the modelled average marginal predictions of EQ-VAS when individuals with less and more than six months are considered separately. Here the separation between the predictions of the EQ-VAS with and without pain response was reduced in those surviving less than six months, to the extent that the difference falls below a minimally important difference at all TTD. This heterogeneity does not change the study conclusions and, if anything, strengthens them further in a patient cohort, which is within six months of the end of life.

3.2.6.5   Limitations

This study has a number of limitations. Firstly, the population included were recruited into a single randomised controlled trial and may not, therefore be representative of a more routine population. Given the longitudinal nature of the data and the question studied, the observed difference in survival time between the study cohort and that seen in routine practice, may not be a problem.(4) Moreover there is an evident advantage with this trial based sample as there are resource invested in ensuring data completeness as far as possible and the sample size remains relatively large due to the size of the original study population.

In analyses relying upon the domains of the EQ-5D the potential insensitivity of the EQ-5D-3L to small changes in domains of HR-QOL is a concern. Given the extent of the variation of EQ-5D three levels seen with survival, however, it is unlikely that increased sensitivity in the instrument would contradict the conclusions drawn. It is possible, however, that smaller changes may be identified using the EQ-5D-5L. The changes seen in the EQ-5D-3L are likely to be clinically significant whilst smaller changes identified using other instruments, whilst statistically

significant, may not be clinically important. The consequences of using an alternative HR-QOL instrument cannot be investigated in the current dataset.

The challenges of modelling a change from baseline, as seen in the pain response outcome used here, must be recognised. Pain response is defined relative to baseline in line with the international consensus guidelines.(130) This approach is open to criticism; patients enter the study based on the presence of marked pain at the time and therefore, given the fluctuating nature of this symptom, regression to the mean may be contributing to response.(262) Given the focus of this study upon the relationship between pain response and HR-QoL this is not a major concern, however, it should be recognised that not all of the pain responses observed here are necessarily attributable to radiotherapy; analgesia, regression to the mean, systemic therapy and placebo effects all potentially playing a role. EQ-VAS was modelled in relation to pain response with adjustment for baseline EQ-VAS in order to avoid the challenges inherent in comparisons to baseline as have the individual domains of the EQ-5D.(262) The Pareto effect is the only other place where comparisons to baseline are used. Challenges exist in this; it is not possible either to improve from level 1 nor deteriorate from level 3, and this is potentially limiting the responsiveness of the measure (only 2.1% of patients reported no problems at baseline (Table 9)). Finally, the EQ-5D-3L pain domain and the radiotherapy pain response are different measures of the same outcome. It is, therefore, unsurprising that the relationship between the pain domain and radiotherapy pain response is stronger than that observed with the other domains.

A lack of responsiveness in the EQ-VAS at both very high and very low levels might limit the identification of varying self-reported health over time. If this were the case individuals with very poor or very good health might not accurately report deterioration or improvement (respectively) due to having reached a floor or ceiling beyond which they would not report; even in the final few weeks of life few patients report EQ-VAS values of less than ten. If present, however, this effect would be likely to reduce the variation with proximity to death and thus is unlikely to change the study conclusions.

This study focusses only upon self-reported health as measured by the EQ-VAS, therefore, whilst providing experience-based values it cannot determine the extent to which individuals value time spent in these states. These experience-based values are not decision utilities although some argue that they may provide preferences that more closely reflect those of patients receiving treatment than those derived based upon hypothetical scenarios.(263,264)

3.2.6.6   Study outcomes in context

3.2.6.6.1   Clinical context

Delivery of palliative radiotherapy near the EoL has been shown to lead to lower pain response rates than are seen with longer survival times; 45% of patients surviving less than 12 weeks experiencing a response as compared to 85% in those surviving over a year.(92,93) This study

demonstrates that not only is the likelihood of pain response reduced but the associated HR-QoL this results in is also less, whether measured by the EQ-VAS, Pareto response in the EQ-5D domains or EQ-5D domain probabilities. In addition, it is shown that the value, in terms of self-reported health, placed upon the domains of the EQ-5D changes with proximity to death. As such, the argument that high response rates and associated significant improvements in HR-QoL support treatment very close to the EoL is flawed by a failure to recognise that heterogeneity in the treated population results in systematic variation in treatment benefit.

Clinicians should be mindful of these results when considering the role of palliative radiotherapy near the EoL. These results do not mean there is no role for palliative radiotherapy in this population, however, careful consideration of patient values and expectations are required. Pain response is less frequent near the EoL but the value of "some problems" relative to "severe problems" is relatively consistent. Conversely, near the EoL the probability of reporting a level 3 in all other EQ-5D domains becomes more likely than reporting a level 1 and the incremental value placed upon these domain levels is reduced. The lower probability of reporting level 1 irrespective of response is unsurprising in a population who will be increasingly frail as a result of their disease burden. This should be borne in mind when considering what it is that patients hope to gain from treatment.

3.2.6.6.2   Health economic context

The health economic arguments about the suitability of the QALY in assessing cost-effectiveness near the EoL are ongoing.(234,265–267) According to Round, who asks "Is a QALY still a QALY at the end of life?" one must acknowledge that the QALY framework is imperfect but that the need for equitable decision making has resulted in its adoption in the absence of superior methods.(117,268) He argues that the QALY framework is not the problem but that improvements in the measurement tools (to reflect the relevant evaluative space), and valuation are needed to ensure its appropriate use in the EoL setting. Further empirical evidence is recommended. Specifically, Round identifies a need to assess the extent to which preferences are constant over time, particularly near the EoL.(265)

The outcomes of this study can help to inform these discussions; with varying proximity to death the reported EQ-VAS is not constant relative to the EQ-5D domains. The importance of this instability is limited from the perspective of cost-utility analyses if it is accepted (as it currently is) that societal values are used to value outcomes and that health states are valued consistently irrespective of when, or indeed who, they effect. These valuations, however, rely on the assumption that individual's valuation of hypothetical states will reflect their revealed preferences. Empirical evidence suggests that this assumption is unrealistic in both health and other areas of public spending.(263,269)

The finding that the relationship between the reported EQ-VAS and the EQ-5D domains changes with proximity to death, aligns with the recognition that the EQ-VAS is measuring a broader underlying construct of HR-QoL than that of the EQ-5D domains and therefore utility. Other, unmeasured, factors are having a greater impact near the EoL. With recognition of the finitude of life it has been shown that individuals preferences shift away from future-orientated goals to more emotionally orientated goals.(270,271) The consequence of this is a preference for time spent with emotionally close social partners and reduced attendance to emotionally negative stimuli. This has principally been demonstrated with aging,(272) although is also seen in other populations known to have finite survival time. For example, symptomatic HIV positive young men, prior to the widespread availability of combined anti-retroviral therapies, showed similar social preferences to older people.(273) Carstensen argues that it is an individual's time horizon that determines their preferences with regard to social interactions and emotional stimuli rather than chronological age per se.(272,274) It is unclear to what extent the patients included in the current study were aware of their prognosis. Patient's preferences for prognostic information vary and, therefore, an explicit explanation of prognosis may not have occurred in all cases.(275) Deteriorating HR-QoL may provide an indication to the patient themselves of reduced prognosis where explicit discussions have not occurred.(276) If we assume awareness of a reducing time horizon exists in this cohort, this might provide an explanation for the systematic changes seen in the value placed upon the domains of the EQ-5D with proximity to the EoL.

Sutton and Coast have demonstrated that the domains of HR-QoL which were considered most important to patients near the EoL include freedom from physical and emotional suffering.(277) The analysis here provides some quantitative support for these findings; with proximity to death the EQ-VAS associated with higher levels of the anxiety and pain domains remains relatively consistent, in contrast to that observed in the mobility, usual activities and self-care domains. Notably, the pain domain provides greater discrimination between levels, no pain carrying the highest relative value compared to the other EQ-5D-3L domains, at least until the final weeks of life.

The development of a preference-based measure (PBM) for outcomes near the EoL is in progress, such that appropriate domains are captured and valued.(249,278) A further challenge arises, however, in defining for whom and when such a PBM would be used. The variation observed here suggests systematic change with proximity to death may occur, however, identifying a single time point at which this happens is unlikely to be possible. In addition, Coast et al. found that even in a hospice population there was variation in patient's preferred measurement tool.(249) Longitudinal data in an end-of-life population is needed, including alternative measures of HR-QoL and wellbeing. It would then be possible to explore individual's experienced preferences for the different domains included and how these vary between instruments with proximity to death. Identification of this transition might help to better align the interventions we deliver very close

to the EoL with outcomes which are valued by patients and their loved ones; The expected benefits of palliative radiotherapy may be captured by the EQ-5D domains, however, if these domains are both unlikely to improve and no longer as valuable to patients, maybe we should reconsider both the treatment and the measurement tool in this population?

From a clinical perspective there is a welcome and increasing drive to deliver HR-QoL outcomes from randomised trials. These outcomes are often poorly reported, or may not reflect patient's values.(279) The line "an acceptable toxicity profile", may reflect a medical judgement of acceptability rather than a patient judgement.(280) A number of studies have started to address this by including the QALY as a clinical end-point.(30,281,282) A note of caution is, however, required when using the QALY in this way. The studies assessing this to date have calculated the QALY outcome based on the EQ-5D domains reported by patients, however, it is important to underline that the mapping from EQ-5D answers to a utility uses valuations based on tariffs, which reflect societal values. These may be appropriate for cost-effectiveness analyses but, where outcomes are being reported as clinical benefits, this must be questioned. Whilst systematic bias may be introduced if utility is measured using the EQ-VAS this might in fact be valuable when systematic differences in patient's occur over time.

The current study adds to the literature demonstrating that the value placed upon the HR-QoL domains vary systematically, not only *between* individuals but, as demonstrated here, *within* individuals, especially over time. If QALY outcomes are to be used to inform clinical decisions and patient choices, the domains considered and values used should reflect how the patients themselves define HR-QoL. Any other value set has the potential to drive clinical decisions which do not reflect the values of the patients undergoing treatment. The EQ-VAS offers a simple means to achieve this. The increasing interest in assessment, reporting and use of HR-QoL as a trial outcome should be welcomed, however, for the information produced to be meaningful to patients, recognition is required of the underlying assumptions about value that underpin these analyses.

Finally, this study demonstrates a strong relationship between HR-QoL and TTD. Here HR-QoL is considered as the dependent variable, however, there is increasing recognition that HR-QoL is a strong predictor of prognosis.(283–285) The ability to predict short survival may be valuable in clinical practice. Recognition of very limited prognosis might offer a number of advantages clinically: this information could contribute significantly to shared-decisions about the use of anti-cancer treatments, potentially reducing their use near the EoL and hence their deleterious effect upon EoL outcomes.(286,287) It can act as a trigger for engagement with palliative care services, potentially improving EoL outcomes and supporting carers.(288–291) Finally, in itself this information can help patients, their loved ones and carers to understand and prepare for the EoL, uncertainty around prognosis being associated with greater levels of anxiety and depression.(276,292)

In summary, palliative radiotherapy can improve focal pain due to bone metastases for a significant proportion of cancer patients. Treatment in close proximity to death is associated with lower rates of pain response and this study demonstrates response is associated with reduced HR-QoL improvement near the end of life, both in terms of global HR-QoL (as measured by the EQ-VAS) and other domains of HR-QoL (measured by the EQ-5D questionnaire). It can also be seen that the value placed on these domains, in terms of self-reported health, also changes near the EoL. This provides empirical evidence that experienced preferences may not be constant with proximity to death and supports further work to ascertain when alternative instruments for measuring outcomes near the EoL might be more appropriate.

That patients prioritise domains related to anxiety about future deterioration and hope for pain relief may well justify the use of palliative radiotherapy very near the end of life. Pain response may still be seen in patients with very limited survival, however, it is less frequent and unlikely to be associated with improvement in other domains of HR-QOL in the EQ-5D-3L. On this basis we must be honest about the expected benefits of treatment, enquire about and recognise patient's individual priorities and offer treatments which are able to improve the things which patients value most. The analysis provided here can help to inform these conversations. The use of prognostic tools, potentially based on patient reported HR-QoL outcomes, might help to inform these complex decisions.

4 Net pain relief

4.1 Introduction:

As presented in chapter 2, in attempting to quantify response durability, studies have routinely reported re-irradiation rates in the absence of difficult to collect longitudinal response data. 20% re-irradiation rates are seen following single fraction treatment compared to 8% following multiple fraction regimens.(10,103) The re-irradiation end-point, however, is a composite one, encompassing recurrence of pain but also patient and clinician perception of treatment efficacy, and willingness to re-irradiate.(103) Willingness to re-irradiate is lower following higher dose treatments, reflecting, in part, a lack of clinical confidence in the efficacy of lower dose treatments and, reduced willingness to re-irradiate after higher doses, due to toxicity concerns.(86) Re-irradiation rates do not, therefore, provide a simple representation of response durability. As a consequence, whilst no clear dose response relationship has been demonstrated using cEBRT, the suggestion has remained that a higher biologically effective dose, potentially delivered using stereotactic radiotherapy, might provide superior levels of pain relief with greater durability.(203,239,240) Given the challenges to the use of re-irradiation as a measure of response durability, alternative measures to assess this are clearly needed.

The potential of net pain relief (NPR) as a possible outcome measure to assess response durability has been recognised in the ICPRE.(130) NPR after palliative radiotherapy is defined as the proportion of remaining life for which pain is improved and was originally reported by Salazar et al in 1986.(225) NPR may offer an outcome measure of clear value to patients, informing not simply the probability of response its durability. This may be particularly relevant in studies assessing the role of stereotactic treatments. NPR reporting remains rare due to limitations of data collection and concern about the influence of subsequent treatments upon NPR (as raised by the consensus working party). Where reported, it was approximately 70%,(226,293) but, these studies have not specifically assessed the role of NPR as an outcome.

This chapter will use the longitudinal data collected in the DBMS to 1) assess NPR by treatment regimen, diagnostic group and survival cohorts, and 2) carry out sensitivity analyses to assess the consequences of missing data, considering the impact this may have upon NPR as an outcome measure.

4.2 Methods:

The details of the DBMS trial methodology and data were outlined in section 3.2.1. This analysis incorporates data from all 1,157 study participants.

The patient's pain response at each questionnaire was classified in line with the ICPRE,(130) incorporating changes in opioid intake (pain progression (PP), no response (NR), partial response

(PR) or complete response (CR)). Each patient's overall best response was then defined. Unlike in previous reports, only questionnaire responses after treatment were considered, rather than those beyond randomisation. No exclusions were made for individuals with missing data in order to ensure the subsequent sensitivity analyses encompassed all individuals. At each questionnaire, time since treatment or last possible questionnaire response was calculated and the questionnaire assumed to represent this whole period. Given the fluctuating nature of pain, it was accepted that patients could move between response states, experiencing initial response, followed by NR and subsequent return to response. Adjustment for analgesia was made so allowing for the fluctuating nature of pain an individual may experience whilst also recognising if any pain improvement was the result of increased analgesia. NPR was then calculated as the sum of time spent with pain response divided by the total time represented by observed questionnaires (including those beyond re-irradiation) and multiplied by 100 to give a percentage (complete questionnaire analysis NPR (cqaNPR)). Calculation of mean cqaNPR was carried out in the following cohorts:

- Initial analyses included only individuals with known survival time who were known to have responded to treatment. This determines observed NPR in responders. This was assessed by survival cohorts (<6 weeks, 6-12 weeks, 12-24 weeks, 24-52 weeks and >52 weeks), diagnosis and by treatment regimen.

- Subsequently, this analysis was reproduced including patients with known survival time but who were not known to have experienced a response to treatment. This provides overall expected NPR for all patients.

- Those individuals censored at trial closure and known to have responded were then considered separately as their response duration beyond trial closure was not known.

Mean cqaNPR for different treatment regimens was compared using two-sided Student's t-test in individuals with known survival time.

Studies investigating interventions in patients near the EoL often have significant amounts of missing data.(236) This does not imply poor study design or conduct.(294,295) Where complete case analysis is carried out, however, it must be recognised that the act of completing a questionnaire may not be independent of the patient's health state and, therefore, may result in biased inference.(236) Sensitivity analyses were conducted to determine maximum and minimum possible outcomes accounting for missing data. These analyses were carried out by survival cohorts, separately excluding and including those not known to have responded. This ensures that the sensitivity analyses represent the full range of possibilities. Alternative scenarios considered were:

- cqaNPR) assumes that response in unobserved questionnaires was as seen in the observed questionnaires (as detailed above). This includes response beyond re-irradiation.

- NPRa) all unreturned questionnaires were assumed to represent a no response state (worst case estimate),

- NPRb) unreturned questionnaires were assumed to represent response (an anticipated overly-optimistic scenario).

- NPRlv) a last value carried forward approach was used to replace the missing values. In this analysis an individual's last known pain state was assumed to persist until the next known state or death. No response is assumed prior to the first known response following radiotherapy.

Finally, the consequences of excluding all responses beyond re-irradiation were assessed (i.e. assuming these represent response to re-irradiation rather than the original treatment)(NPRc). The exclusion of these responses provides an assessment of response durability in the absence of re-irradiation.

4.3   Results:

The baseline characteristics of the study cohort are provided in section 3.2.

4.3.1   *Complete questionnaire analysis NPR outcomes:*

Patients responding to radiotherapy with known survival time had a mean cqaNPR of 56.6% (std err 1.34)(n=539), including all responses beyond re-irradiation. cqaNPR was higher in those known to have experienced a complete pain response compared to partial response (70.2% versus 49.9% respectively). cqaNPR appeared higher in those with very limited survival, namely 66.4% (<6 weeks survival (n=30 patients)) versus 54.4% in long term survivors (survival >52 weeks (n=160)), although significantly more data were missing in the short survival cohort making these results difficult to interpret (Figure 23 a and b). Where response beyond re-irradiation was included, no significant difference was seen in cqaNPR between the two treatment regimens (55.4% (single 8Gy) vs 57.7% (24Gy in 6) in responders) (p=0.191)(Table 16a and Figure 24). Patients with breast or prostate cancer responding to treatment experienced higher cqaNPR (59.4%) than those with lung or other cancers (cqaNPR 52.2%)(Table 17).

In patients alive at trial closure and responding to treatment cqaNPR was 66.3%, higher than in those with known survival time (56.6%)(Figure 23 a and b). The proportion of breast and prostate cancer patients was higher in those censored at trial closure (85.5% vs 54.2%), potentially contributing to this higher cqaNPR (Table 3).

Figure 23. Net pain relief a) complete questionnaire analysis in all patients and b) responders only by survival cohort. Survival cohorts shown with overall average provided both with and without those censored at trial closure. The range of sensitivity analyses is represented by the grey bar (NPRa-NPRb) with the cqaNPR shown by the black dot.
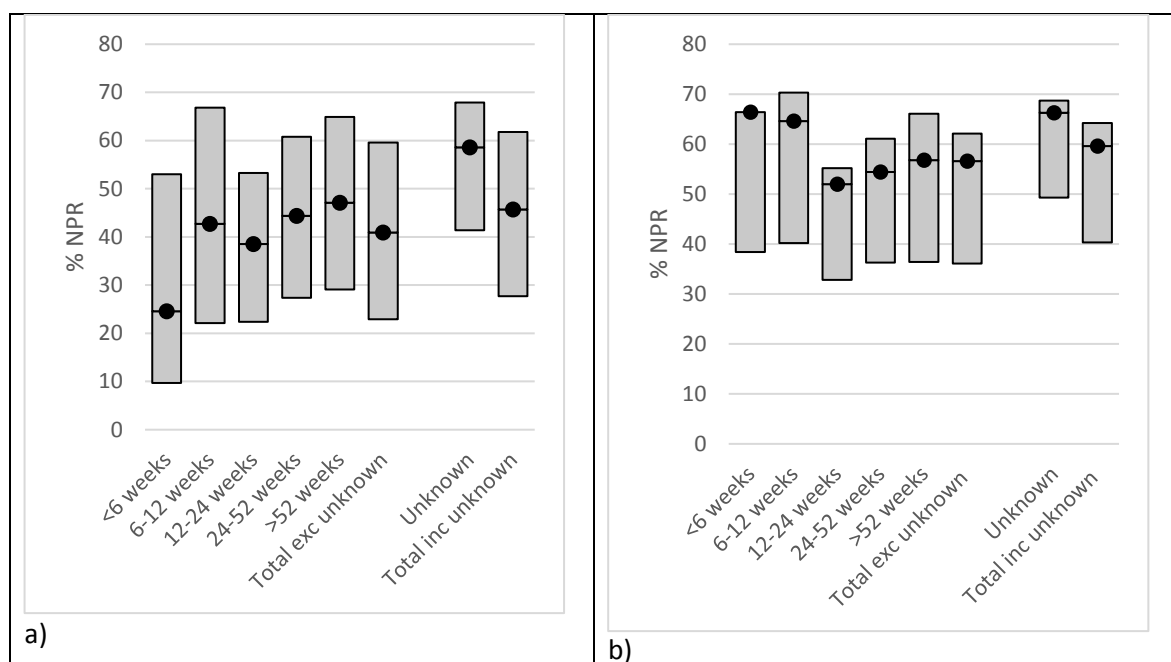
Table 16. Complete questionnaire analysis of NPR by radiotherapy regimen received. a) cqaNPR values including response beyond re-irradiation, (p=0.3863) b) excluding responses beyond re-irradiation (p=0.008). Missing questionnaires accounted for 29.6% and 32.4% in the single 8Gy and 4 x 6Gy groups respectively. Re-irradiation occurred following 26.0% of single 8Gy treatments and 7.9% of 4x6Gy treatments.

Arm	% NPR in responders		
a)	n	Mean (%)	Std error
1 x 8 Gy	269	55.4	1.95
4 x 6 Gy	270	57.7	1.84
b)			
1 x 8 Gy	269	49.0	1.88
4 x 6 Gy	270	56.5	2.08

Table 17. Complete questionnaire analysis of NPR by primary diagnosis in patients with known survival time. All patients and those with known pain response considered separately.

Primary diagnosis	All patients			Responders		
	n	Mean (%)	Std error	n	Mean (%)	Std error
Breast	236	46.1	*2.42*	183	59.4	*2.33*
Prostate	177	48.6	*2.71*	145	59.3	*2.56*
Lung	215	33.3	*2.41*	134	53.4	*2.63*
Other	118	32.6	*3.18*	77	49.9	*3.52*

4.3.2 *Missing data and sensitivity analyses:*

103 (12.1%) patients had no observed response assessment following treatment. Median survival of this group was 7.86 weeks (95% CI 6.57-11.14)). In the population who were observed until death 3,760 questionnaires were missing (31.0%). Missing data were more common for patients with limited observed survival (49.4% missing (<6 weeks), and 26.5% missing (>52 weeks)). In individuals who returned at least one post-treatment questionnaire, 38.7% of questionnaires were missing in non-responders whilst 21.6% were missing in responders. Less data were missing following single 8Gy treatment (29.6% versus 32.4% (chi-squared p=0.001)).

The outcomes of sensitivity analyses by survival cohorts are shown in Figure 24 a and b. The range of possible outcomes for NPR was 36.1%-62.1% in responders (cqaNPR 56.6%) and 22.9-59.6% (NPRa-NPRb) in all patients (cqaNPR 40.9%). Last value carried forward resulted in outcomes between cqaNPR and the lower limit of sensitivity analyses (52.8% (responders) and 38.1% (all patients)).

Only 115 individuals (13.5%) with known survival time returned enough questionnaires to allow assessment of more than 90% of their remaining life. The median survival of this group was 33.0 weeks, 101 individuals (87.8%) were responders, of which 48 (41.7%) complete responders (as compared to 17.4% CR in those with <90% time observed) and mean cqaNPR was 55.7% in responders.

In patients with known survival time, re-irradiation occurred in 26.0% in the single 8Gy arm and 7.9% in the 24Gy arm. Only when all questionnaires beyond re-irradiation were assumed to reflect no-response was NPRc greater following 24Gy than 8Gy (56.5% versus 49.0% in responders (p=0.004)) (Figure 24 b and c).

Figure 24. NPR by treatment arms, sensitivity analyses shown in the grey bars with cqaNPR the black dot, sensitivity analyses in grey (NPRa-NPRb), (a) All patients, b) Responders, c) NPRc - excluding response beyond re-irradiation. Individuals censored at trial closure were excluded.
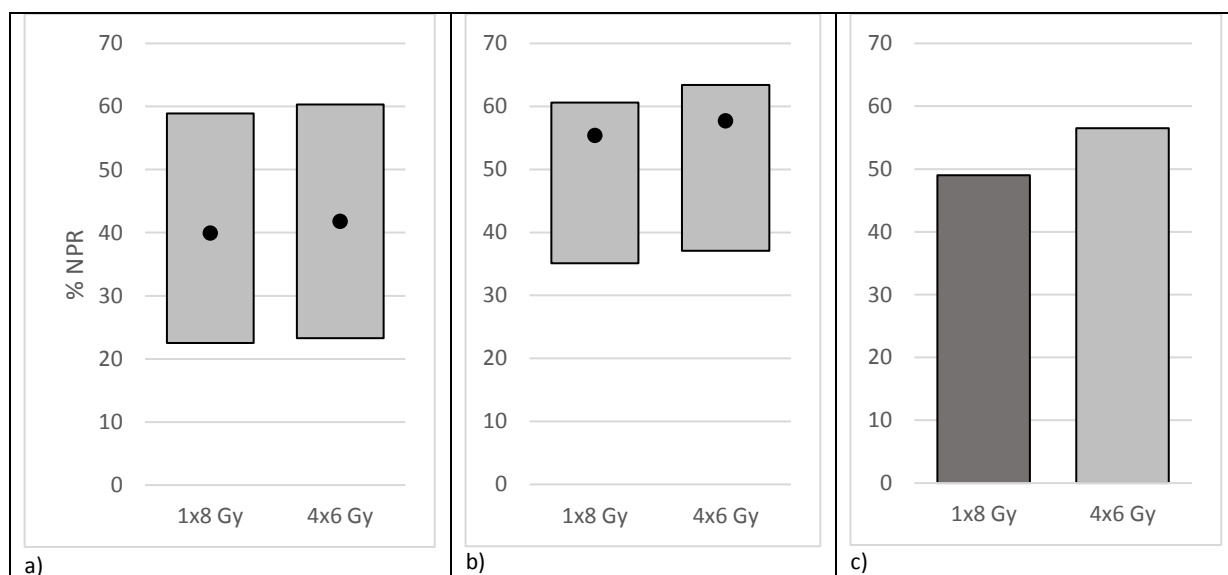
4.4   Discussion:

Durability of pain control is an important outcome to patients undergoing palliative radiotherapy for bone metastases.(82,296) ICPRE guidelines recommend reporting responding proportion, however, this method does not provide information on response durability. Re-irradiation rates, however, are not a simple representation of response durability given differing willingness to re-irradiate between the two interventions considered here.(86) Net Pain Relief (NPR) reflects the time spent in response divided by the actual survival time and has potential to provide this information.

In this study, patients who responded to palliative radiotherapy gained improved pain control for 56.6% of their remaining life (cqaNPR). No difference was seen in cqaNPR following single and multiple fraction palliative radiotherapy in responders (55.5% vs 57.5%), although a significant difference was seen when response beyond re-irradiation was excluded (49.0% versus 56.5% respectively). Whilst statistically significant, it is unclear if this latter difference is of sufficient scale to be clinically significant given the recognition that re-irradiation is not a simple reflection of pain and therefore this outcome is likely to be confounded by differential willingness to re-irradiate between the treatment arms.(86).

Challenges to NPR as a trial outcome measure:

Whilst appealing in its potential to offer valuable information about response durability this study demonstrates that challenges exist in the use of NPR as an outcome measure:

Despite the DBMS being well conducted, significant numbers of questionnaire responses are missing. Complete questionnaire analysis (cqaNPR) assumes that the proportion of time spent in response in observed questionnaires reflects the proportion in unobserved questionnaires. This assumption is questionable if patients whose clinical condition is below average are less likely to return questionnaires; that more missing data is seen near the end of life reinforces the likely violation of this assumption. As a consequence cqaNPR is likely to represent an optimistic estimate of true NPR. Those with known survival time and >90% of their remaining life observed (n=115) provide the greatest certainty in NPR outcomes. In this group cqaNPR was 55.9%, although the higher proportion of CR in this cohort means this too may be an optimistic estimate. As such, those who gain a pain response after palliative radiotherapy for bone metastases can expect improved pain control for approximately half of their remaining life with patients with prostate and breast cancer experiencing better outcomes than those with other cancers.

By reporting both intention to treat and assessable responses, existing studies recognise the impact of missing data upon response rates (due to death and incomplete data).(10,11,85) A range of possible outcomes can be derived based on Chow et al 2013; Response in assessable individuals (complete case analysis) was 72%, possible range 60-76.7%. As such, the uncertainty around

NPR outcomes (36.1-62.1%) is greater than that seen in overall response rates. NPR was similar in the two treatment groups considered here (8Gy and 24Gy), however, if interventions with markedly different outcomes are compared the potential for systematic bias due to missingness must be acknowledged. Multiple imputation (MI) of missing data can be considered in order to probabilistically replace missing data with reference to observed data, thus allowing valid inference.(297) This process still relies upon the data being missing at random and, therefore, the missing observation values being conditional upon the observed values, it is unclear if this assumption is justified here and, therefore, sensitivity analyses are presented as an alternative means to recognise the consequences of missing data.

NPR, as measured here, recognises that patient's symptoms may fluctuate,(298) accepting all pain response beyond first recurrence of pain as reflecting this fluctuation. Importantly, where response beyond further treatment (such as re-irradiation) was included the distinction, between response due to the initial treatment and response due to subsequent treatment, was not made. This is, potentially, a limitation. It is, however, notable that even where response beyond re-irradiation is excluded the difference between the two treatment arms is 7.5% of remaining life in responders. Re-irradiation following single 8Gy treatment was observed in 26% of patients with a known date of death in this study (compared to 7.9% following 24Gy in 6 fractions). More contemporaneous studies have demonstrated markedly lower re-irradiation rates following single 8Gy treatments (as low as 14%).(299) Given that the decision to re-irradiate is not a simple reflection of pain control the exclusion of responses post-re-irradiation risks introducing the same bias as is present when re-irradiation itself is used as an end-point.(86) Conversely, inclusion of these responses is questionable when assessing response durability. Overall, the proportion of remaining life spent with pain response was the same for patients receiving these two regimens. For a proportion of patients, undergoing single fraction treatment, re-irradiation may be contributing to this. Notably, 74% of patients in the single fraction arm did not require re-irradiation and were saved a further five treatment attendances. Reporting of NPR, both including and excluding response beyond re-irradiation, may therefore be appropriate. In addition, future studies should ensure clear protocols to ensure that the re-irradiation end-point is as unbiased as possible.(299)

Patients who responded and were alive at trial closure experienced higher NPR than those observed until death (cqaNPR 66.3% vs 56.6%). It is not possible to determine if this difference reflects the nature of the censored group (greater proportion of breast and prostate cancer, longer survival times) or the fact that the observations included were relatively closer to treatment, possibly not including the point of pain recurrence. With well-balanced treatment arms this may not be a problem but differing follow-up periods with variable time points for response assessment will limit comparability of NPR between studies. This has implications for the use of NPR in

stereotactic radiotherapy studies as benefit may be anticipated to be greatest in patients with longer survival, more likely to be censored at trial closure.

A further limitation of the NPR outcome is that a returned questionnaire is assumed to be representative of the entire period since the previous questionnaire. Questionnaires, however, specifically focussed upon an individual's worst pain experienced over the preceding week as robust capture of experienced pain can only be achieved over short time periods in cancer patients. (16,300,301) As such these outcomes rely upon the untestable assumption that symptoms remain stable between questionnaires. Notably, Foro Arnalot et al report NPR of 68% whilst Salazar et al report NPR of 71%, possibly reflecting the limited longitudinal data collected.(226,293) Longer periods between questionnaires will increase uncertainty in NPR outcomes.

NPR, as measured here, recognises that patient's symptoms fluctuate,(298) making no assumptions about the cause of pain control beyond first recurrence of pain. This may be viewed as a weakness of the measure, potentially incorporating response to subsequent treatments. In a well-balanced clinical trial this should not be a problem unless treatment decisions are influenced by the prior treatment received in an unblended study.

Implications for the use of NPR in future bone metastases trials:

Unfortunately, missing data during follow-up are inevitable in this patient population and will remain a limitation of NPR as an outcome measure, particularly in subgroups where missing data are more prevalent (e.g. those with very limited prognosis). Caution is required in interpreting outcomes in these groups. These uncertainties should not, however, prevent the use of NPR as an outcome measure in future trials although they have implications for trial conduct and reporting:

- Specific efforts, beyond those already in place, are required to minimise missing data (e.g. ensuring complete collection of baseline data, increasing questionnaire completion and balancing questionnaire burden with adequate follow-up).(236)

- The collection of outcomes using digital platforms has been shown to be feasible and beneficial in advanced cancer and might enable capture of weekly outcomes to reduce the uncertainty in the measurement of NPR.(302)

- The use of cohort multiple randomized controlled trial designs could be considered to aid recruitment and gain follow-up information for those receiving standard treatment. The challenges of this in a populations with high attrition may, however, be significant.(303,304)

- Robust reporting of the extent of missing data, and sensitivity analyses, will be required to allow comparisons of NPR both within and between trials.(219)

- Whilst assessing NPR in all patients (both responders and non-responders) provides an important sensitivity analysis, the increased uncertainty introduced by including non-responders can be

avoided by assessing this outcome only in responders. The question answered by these two results differs and given the overall aim, of comparing treatment efficacy, it may be necessary to accept (and recognise) this uncertainty.

Despite comparable response rates following fractionated and single dose treatments for patients with painful bone metastases the justification offered for fractionated radiotherapy is often response durability, as measured by re-irradiation rates.(82) Yet re-irradiation is not simply a function of pain recurrence,(86) and no measure of durability of pain control has been routinely reported in studies. In addition, if we are to make the case for stereotactic radiotherapy, with higher total doses, on the basis of durability of pain control, measures which are able to evaluate this outcome are required.

NPR might address these concerns, however, given the inevitability of missing data in palliative care studies, variable frequency of pain assessment and practicalities of trial duration, uncertainty in the measurement of NPR is significant. Consensus guidelines should consider its incorporation and provide methodological and reporting recommendations, to minimise these limitations. If this can be achieved, NPR may provide valuable within trial information about an outcome of clear importance to patients.(296,305) Comparison between trials can be improved by consensus but may remain a limitation.

5 Time-Driven Activity Based Costing of UK radiotherapy

5.1 Introduction

When considering the cost-effectiveness of healthcare interventions there is a clear need to accurately identify the treatment costs. One possible source of this information is the tariff system.(306) All treatments delivered within the NHS in England are reimbursed through the tariff system. This is based on Health Resource Groups (HRGs) with all inpatient, outpatient, emergency and unbundled services (including radiotherapy and chemotherapy) costed using HRG codes.(307,308) These HRGs allow clinically meaningful grouping of patients on the basis of procedure (OPCS-4) and diagnosis (ICD-10) codes.(308) Within the HRGs, the tariff for external beam radiotherapy is separated into planning and treatment costs. The costs of each component reflecting the complexity of the procedure undertaken (for example, single field palliative radiotherapy planned using a simulator and with simple 2D online-imaging versus VMAT treatment, planned using 4D-CT and with cone-beam CT based online-imaging).

The process by which NHS England determines the tariff prices requires reference costs to be submitted by provider institutions.(309) Historically, these have been based upon top-down calculations. Total hospital or departmental costs are taken and allocated to a lower (patient or treatment) level, before being weighted by patient and treatment complexity.(309) This approach will limit the granularity of information available about the costs of varying complexity. In addition, the differential between simple and complex treatments that is incorporated into this process was defined ten years ago and the methods used to achieve this are unclear.(309) Given the changes in technology and techniques over the last decade and lack of clarity on the methods used to determine the differential costs of complexity, it is unclear if the weightings used remain appropriate.

5.1.1 *Alternative costing methodologies*

Micro-costing aims to attribute costs to an individual patient pathway through direct observation of the resources used and the unit costs of each resource.(61) This provides a granular bottom-up cost but is very labour intensive and has limited value in terms of transferability between different treatments. This contrasts with studies which capture only the average costs of intervention using more readily available data and top-down methodologies. Activity-based costing (ABC) involves identifying the resources used to deliver an activity, often through in depth surveys of those undertaking the processes. This determines the proportion of time individuals spend on various activities and assigns costs to processes accordingly using a top-down approach.(310) It has been criticised for tending to over-estimate treatment costs, however, ABC is, a form of absorption costing in which overheads are more fairly distributed through full absorption in line with reference cost guidelines in the English NHS.(307) Time-driven Activity-Based Costing (TD-

ABC) extends upon ABC providing a middle ground between very granular micro-costing and the more top-down standard ABC approach.

In radiotherapy a number of previous studies have been carried out investigating the costs of treatment.(311–314) The European Heath Economics in Radiation Oncology (HERO) project (131) in now building upon work undertaken in Belgium using the TD-ABC approach, to further develop understanding of the cost of radiotherapy delivery in countries across Europe.(315) Treatment processes (e.g. radiotherapy planning) are divided into activities (e.g. CT simulation scanning, contouring, planning) and the resources required to deliver these activities are identified (e.g. CT simulator, radiographer time, doctor time, physicist time, space). The cost per minute of the required resources is then determined, and by combining the resources required to deliver the necessary activities with the time needed to deliver them, a cost per treatment is identified. This approach is appealing in costing radiotherapy treatments; these are complex but predictable interventions which can be readily modelled in this way acknowledging the varying complexity of each activity as reflected by both time taken and resources used.(316)

5.1.2 *Fixed and variable costs*

Many of the costs of radiotherapy are fixed. Linear accelerators (linacs) and specialist buildings require significant capital investment. Linacs have a life expectancy of approximately 10 years whilst the buildings these are housed in are assumed to have a life expectancy of at least 30 years and in both cases alternative uses are limited so disinvestment cannot easily be achieved.(47) In health technology assessments (HTA) mechanisms to handle disinvestment from technologies with high fixed costs are unclear. NICE considered this issue during its appraisal of Intrabeam™ but reached no resolution.(64) Not only does this have implications for HTA but also for the implementation of recommendations. If it is determined that a treatment, or part thereof, is no longer cost-effective and should therefore not be delivered the opportunity cost is released to the payer (NHS England) who no longer reimburses the provider. The opposite is true for the provider organisation; the costs of equipment and space persist irrespective of treatment delivery. Thus, introducing a perverse incentive for treatment to be given.

To allow reduction in fraction activity over time the linac fleet in a provider institution might be reduced, however, a single machine is expected to deliver over 6000 fractions per year and, therefore, disinvestment is only possible after the number of treatments has dropped significantly or at the end of a linac's life expectancy. Linac costs are thus typical of stepped-costs.(62) Notably, this only becomes a concern if capacity outstrips demand. Historically national linac capacity has been lower than modelled estimates suggested were necessary, i.e. demand was likely to be greater than capacity, resulting in waiting times and potentially inadequate availability of treatment.(2) New indications for treatment are evolving (e.g. oligo-metastatic disease), however, with an increasing move towards more highly conformal, hypo-fractionated treatments

or, indeed, a reduction in indications, the possibility of capacity outstripping demand may become real and the challenges of disinvestment more acute.(45,317–319) The consequences of this for the costs of treatment delivery are unclear. How the risks of investment and disinvestment are split within the commissioning process must recognise these fixed costs to avoid introducing perverse incentives to pursue treatment.

Finally, it is recognised that the costs of delivering care may demonstrate learning curve effects.(61) This has previously been demonstrated for Intensity Modulated Radiotherapy delivery in head and neck cancer and might reasonably be anticipated for other complex radiotherapy interventions.(120) This increase in initial costs in part reflects capital investment but also time invested in safe implementation and increased quality assurance processes which may be used until a provider becomes confident in the quality of the treatments being delivered. This time-varying element of the costs of treatment must also be recognised in commissioning structures if these are to appropriately reimburse novel techniques over time.

5.1.3 *Aims*

This study aims to identify the costs of differing radiotherapy treatments delivered for bone metastases using a TD-ABC approach.(131,314,320) The differential costs of varying treatment complexity will be assessed and cost drivers considered. The costs derived will then be used as alternative parameterisations in the subsequent cost-effectiveness model (Chapter 6) and are therefore fully absorbed.(307) It will go on to assess the extent to which these costs are fixed and variable, in order to assess the consequences of disinvestment from treatments delivered within the provider institution. Finally, for the SABR treatment strategy, the impact of the learning curve on treatment costs will be assessed.(120)

5.2 Methods:

5.2.1 *Structure of TD-ABC model*

TD-ABC breaks down each procedure into its constituent activities, each of these activities requiring resources for a defined time period. Costs were defined as directly attributable to the activity (i.e. patient specific costs which are either discrete material costs or time-driven resources) or indirectly attributable (e.g. department wide administration team, waiting areas, planning spaces, the review clinic nursing team). In addition, for novel techniques it is recognised that investment may be required both in terms of time and equipment and this was considered indirectly attributable. Finally, in the context of radiotherapy delivered within an NHS Trust, further Trust level overheads were allocated. A diagrammatic representation of this cost allocation is shown in Figure 25.

Whilst some department level costs were used to inform this model, the costs reported were those relating to the delivery of palliative radiotherapy to bone metastases using one of four strategies: a single non-computer planned fraction with 2D online-imaging; a non-computer planned multiple fraction course with 2D online-imaging; a 3D computer planned multiple fraction course with 2D online-imaging; stereotactic treatment course (SABR) delivered with a VMAT technique and online cone-beam CT imaging. Costs reported pertain to radiotherapy delivery in the Leeds Teaching Hospitals NHS Trust. This model will incorporate all costs (fully absorbed) in order to capture the full cost to the NHS of treatment, in line with NHS reference costs guidance.(307)

Figure 25. Diagrammatic representation of the TD-ABC model.
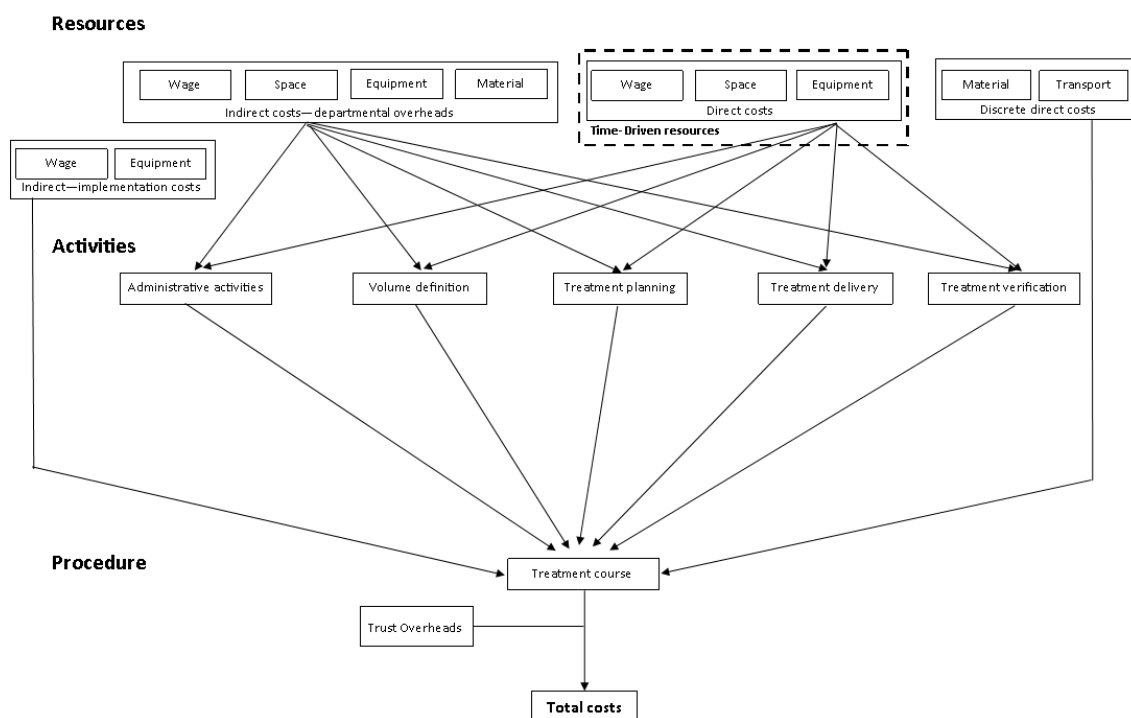
The patient pathways and activities for each technique were defined through consultation with experts within the radiotherapy department, Leeds Teaching Hospitals NHS Trust (LTHT) to ensure they reflect routine practice (senior radiographers, physicists and doctors). The resources required to deliver each activity were similarly defined with appropriate team members and allocated using a time-driven approach for all resources except materials. Figure 26 shows the agreed pathways in LTHT, including the staff members involved in the delivery of each activity. The overall activity costs were calculated based on a combination of all the resources required and time taken for delivery of the activity (see Equation 4).

Equation 4. Calculation of the total treatment cost.

$$Total\ activity\ cost$$
$$= \left(\left(Cost_{Staff\ per\ minute} + Cost_{Equipment\ per\ minute} + Cost_{Space\ per\ minute}\right)x\ Time\right) + Cost_{Materials}$$

The TD-ABC model was developed in Excel and follows the methodology outlined by Lievens et al.(314) All costs are for the 2016/17 financial year and capacity reflects the 2016 calendar year. A more detailed description of the identification and allocation of costs is given below.

5.2.2   *Activity timings*

All treatment activities required to deliver the radiotherapy treatment process were identified (see Figure 26) and the time each took assessed. For the treatment planning process this was carried out using a department wide survey of the time taken to deliver each element of the planning process over a 2 month period in March-April 2017. Clinicians were asked to record basic details of the site, treatment intent, planning technique, use of contrast and the time taken for each component of the planning pathway (e.g. CT simulation, contouring and physics planning). The average of all recorded activities was used to inform the TD-ABC model. Specific elements of the planning process (SABR multi-disciplinary team (MDT) review and MRI fusion) were defined under discussion with senior members of the MDT.(314)

The timings for the treatment delivery pathway were defined using the booked appointment times, a previously conducted departmental evaluation of both imaged and un-imaged fraction delivery times and discussion with senior treatment radiographers.

5.2.3   *Resource costs*

Resource costs per minute were defined based upon the total annual cost of the resource divided by its practical capacity in minutes (providing fully absorbed costs). Details of how capacity and resource costs were identified are provided below.

5.2.3.1   Capacity

The practical capacity of the linacs and CT simulators was defined as the total delivered activity in 2016 (a usage approach, ensuring all machine/space/staff costs are allocated using a time-driven approach as far as possible). This information was extracted from the Centre's oncology management system by the department's data manager (Mosaiq®).

For treatment radiographers the practical capacity of the treating linac team was considered to be the total linac activity in a year. The practical capacity of other staff members was defined as 80% of their theoretical capacity in order to account for annual leave, study leave and other down time.(315) For medical staff this was defined based on a standard NHS job plan of ten weekly sessions with a commitment that this be delivered 42 weeks of the year (thus allowing for study and annual leave).(321)

5.2.3.2   Staff costs

Staff were assessed for the following groups: radiographers, physicists, doctors, radiotherapy technologists, radiotherapy nurses and administrative staff. The pay demographics of each staff

group were determined through discussion with senior MDT members and cross-checked against finance data. This defined the number of staff in each group, banding and associated on-costs (reflecting cost to employer). For all groups (excluding doctors for whom much time is spent outside of the radiotherapy department) the proportion of time spent undertaking direct clinical care (i.e. care for an individual patient), indirect clinical activities (e.g. administrative activities), departmental management and maintenance (e.g. physics machine quality assurance (QA) or departmental management functions) and implementation projects was determined through discussion with senior members of the MDT.(314)

Staff costs for the planning process were attributed to an individual's care on a per staff member per minute basis (TD) (dividing the average cost for the staff member by the practical capacity in minutes). Conversely, staff costs for the treatment process were allocated on a team basis, ensuring all staff costs are captured.

In order to support the fitting of immobilization devices a mould room is used. This is staffed by a limited number of radiographers and dosimetrists. The total costs of these staff members were identified and divided by the number of mould room attendances per year. Staff costs were then allocated on a per course basis as the proportion of patients requiring immobilisation (an estimated 5% based on discussion with senior clinicians).

5.2.3.3   Equipment costs

Radiotherapy equipment has high capital costs. Capital resources included were linacs, CT simulators and software. Previous studies have amortized the capital costs by dividing by the life expectancy of the equipment (10 years in the case of a linac).(320) The LTHT equipment was purchased with the building in 2007. The building and equipment costs are all included within the private finance initiative (PFI) contract.(322) The PFI agreement commits the department to monthly payments over a 30 year period which, in the first half, includes the replacement of the linac fleet after ten years. As such the equipment costs for radiotherapy in LTHT were identified as the relevant component of the monthly unitary payment (UP). By using the annual costs taken from the UP the costs of equipment incorporated here are annuitized recognising both discounting and inflation over the expected 10-year life expectancy of the equipment.(61) Linac and simulator costs were TD by dividing the annual UP cost by the annual number of minutes of activity delivered. Linacs and CT simulators maintenance is carried out by engineering/physics staff and costs for this were incorporated indirectly.

The software maintenance and licensing costs were identified through discussion with senior physicists and the finance department. Software costs related to all treatments, planned treatments or VMAT only were identified and allocated on a per attendance (Oncology management system) or per course basis (planning software).

The proportion of physics and engineering time spent on ongoing maintenance and quality assurance of the linac fleet was identified. This excluded time spent in the brachytherapy and gamma knife facilities. 77% of physics time (FTE) is spent in external beam radiotherapy. The incremental increase in maintenance time required for linacs with VMAT capability was identified through discussion with the lead physicist for online-imaging (25-30% more time). A total departmental maintenance/QA budget was identified by combining physics/engineering staff, space and equipment budgets. This was included in the linac costs, weighted to reflect the greater intensity of QA required for VMAT capable machines.

The base-case scenario in LTHT recognises a 10 linac fleet (the fleet purchased within the PFI agreement). Two further linacs were purchased using charitable funds. These linacs are not used routinely in the department but provide capacity for research and support for planned and unplanned linac down time within the full time fleet. The additional capital costs of these two linacs were considered in sensitivity analyses. Similarly, four CT simulators are available in the department although only two or three are in use at any time. Given this variable usage the costs of all four are included and split between the scanning activity.

5.2.3.4 Space

The total space available in the Bexley wing in m^2 was determined from finance data and architectural plans. Corridors, lifts and staircases were excluded to give a total number of m^2 available for use (the costs of these unused areas are therefore incorporated in the final cost per m^2 and allocated TD). The cost per m^2 per year was then calculated by dividing the total unitary payment per year (excluding radiotherapy specific costs) by this area. Additional costs are added on a per m^2 basis to include the costs of utilities, cleaning, security, maintenance, insurance etc. The directly attributable space used by a linac bunker or CT simulator was calculated from finance data, cross-referenced with architectural plans of the building. Combining the space (m^2) and costs information gives an annual resource cost (e.g. per linac bunker) which was then divided by the total annual activity in minutes per linac (practical capacity) to provide a cost per minute. Using the unitary payment as the basis to define space costs ensures that the capital and maintenance costs are annuitized recognising inflation, discounting and the expected life of the building (30 years).(61)

5.2.3.5 Materials

A limited number of resources are required on a per patient basis. An estimated 5% of bone metastases patients will require a 5 point thermoplastic shell for treatment to the head or neck. The cost for this is directly attributed. Reusable immobilization devices were included in departmental overheads as the per patient costs of these is extremely small (<£2/patient). In addition all patients receiving spinal SABR (approximately 50% of bone metastases) require an

MRI scan to allow fusion and accurate delineation of tumour and OARs (spinal cord). Costs for this reflect the tariff charged by the radiology department.

Patient transport and interpreter services were considered as material costs and allocated to the same proportion of patients in each treatment strategy. These costs are not part of NHS tariff but are a component of the overall pathway and as such were included here.

5.2.4 *Indirectly attributable resource costs*

Indirect costs are those which cannot be attributed to an individual treatment course either as materials or in a TD manner. These included, for example, room costs for areas not directly attributable to individual treatments, and material costs and software system costs not directly attributable. These costs were weighted to reflect the variable costs of complexity. The weighting applied was determined by discussion with senior radiographers, physicists and clinicians.

5.2.4.1 Staff

Staff costs relating to non-specific clinical activities were allocated as departmental overheads. This included administrative staff, review clinic nursing staff and MDT helpers. These are likely to be stable across all levels of complexity and were allocated on a per attendance basis.(78)

The radiography workforce includes a large proportion of women of child-bearing age and within a large department like LTHT approximately five maybe off on maternity leave at any time. The costs of maternity leave are indirectly allocated on a per attendance basis.

Radiographer and dosimetrist time spent on routine departmental management was calculated. Radiographer time being allocated on a per attendance basis and dosimetrist on a per course basis in line with their different roles. Indirect dosimetrist costs were weighted for complexity.

5.2.4.2 Equipment

Within the department small items of equipment are purchased to support ongoing management, maintenance and quality assurance. Disposable items related to nursing and medical care are also required within the review clinic. The costs of these over a one year period were included (in addition to costs of training courses funded by the department). Equipment used for maintenance and QA was identified and included in the linac costs while other expenses were divided by the total departmental attendances and allocated on a per attendance basis.

5.2.4.3 Space

The indirect space costs were calculated based on the space used but not attributable to an individual patient in a TD manner. The costs of the area used by physics for planning was allocated to all planned courses, whilst space used for maintenance was allocated within the linac costs. The space used by mould room was identified and an annual cost derived and divided between all mould room attendances in the year and allocated on a per course basis to the

proportion of patients requiring mould room involvement for immobilization. The cost of departmental space used only for management functions was allocated on a per course basis.

5.2.4.4 Implementation

Bonastre et al. demonstrated that 42% of the variation in the cost of delivering IMRT for head and neck cancer related to learning effects.(120) Novel techniques when implemented within the department require MDT input to deliver class solutions, QA, standard operating procedures and, in the case of SABR for spinal treatments, purchase, setup and training in the use of new equipment.(120) To avoid cost shifting from novel, complex, treatments to simpler more routine treatments the costs associated with this process were identified. Physicist, radiographer, dosimetrist and doctor time allocated to implementation was determined. 10% of the resulting annual budget was then allocated to the implementation of spinal SABR after discussion with senior MDT members.

New immobilization equipment (HexaPOD™) was required to support the implementation of SABR for spinal treatments. The HexaPOD™ system's life expectancy is expected to be 10 years although it's use is currently limited to indications within NHS commissioning through evaluation (CTE) scheme. The staff and equipment implementation costs for SABR were combined. The assumptions used within the CTE process were used to determine an appropriate amortization period of 3 years. The total costs were then split between the estimated number of individuals to be treated in the first 3 years (150 patients) and allocated to individuals undergoing SABR. This assumption was tested in sensitivity analyses considering varying numbers of patients treated per year.

5.2.5 NHS Trust level overheads

The wider NHS Trust in which the radiotherapy department is based provides a number of critical services supporting the running of the radiotherapy department. These include human resources, finance, senior management, informatics and portering functions. These costs are complex to identify, however, under discussion with the finance team an overhead of 15.4% on all other costs was applied.

5.2.6 Cost drivers

In order to assess the major drivers of treatment costs sensitivity analyses were carried out. Major input parameters were identified and their value systematically increased and decreased by 10% whilst holding all other parameters at their base-case values. Where number of fractions delivered per year was considered it was assumed that the fractions not delivered were spread equally across the whole linac fleet and that fraction delivery time was 13 minutes.

5.2.7 *Disinvestment consequences*

In order to consider the consequences of disinvestment the fixed and variable costs of radiotherapy were assessed in line with WHO definitions.(62) This allows an assessment of the extent to which treatment costs will be released if a treatment is forgone. Having assessed the proportion of costs released the potential impact disinvestment may have upon the cost of other remaining treatments was assessed by reducing the total number of delivered fractions per year with and without disinvestment from semi-variable and stepped costs. Subsequent sensitivity analyses considered the consequences of reducing the number of courses delivered for bone metastases.

5.3 Results

5.3.1 *Activities*

The activities contributing to the delivery of radiotherapy are detailed in Figure 26.

5.3.2 *Timings*

Over the 2 month period of the study 526 surveys were returned. Compliance was variable and only a limited number of returned questionnaires contained all of the required items. A total of 52 surveys reporting the activity timings for the bone metastasis planning pathway were returned. These provided a maximum of 46 results for each time point requested. Due to the prescribing practises within the department, however, only four returned surveys referred to fractionated bone metastases treatments. As the results of these were within the range observed for single fraction treatments it was assumed that these required no additional time (a clinically plausible assumption). Appropriate timings for a putative computer planned palliative bone treatment reflected those for a palliative chest treatment as no surveys included a relevant treatment (Table 18).

Finally the time taken to plan a SABR treatment to bone metastases was reported in only one survey. Clinician contouring, physics planning time and data prep time were returned, however, scan time was not. The average from the other two returned palliative SABR treatments to other disease sites was used under discussion with treating clinicians.

Figure 26. Radiotherapy treatment pathways for bone metastases. a) using non-computer planned treatment (single fraction and fractionated regimens).
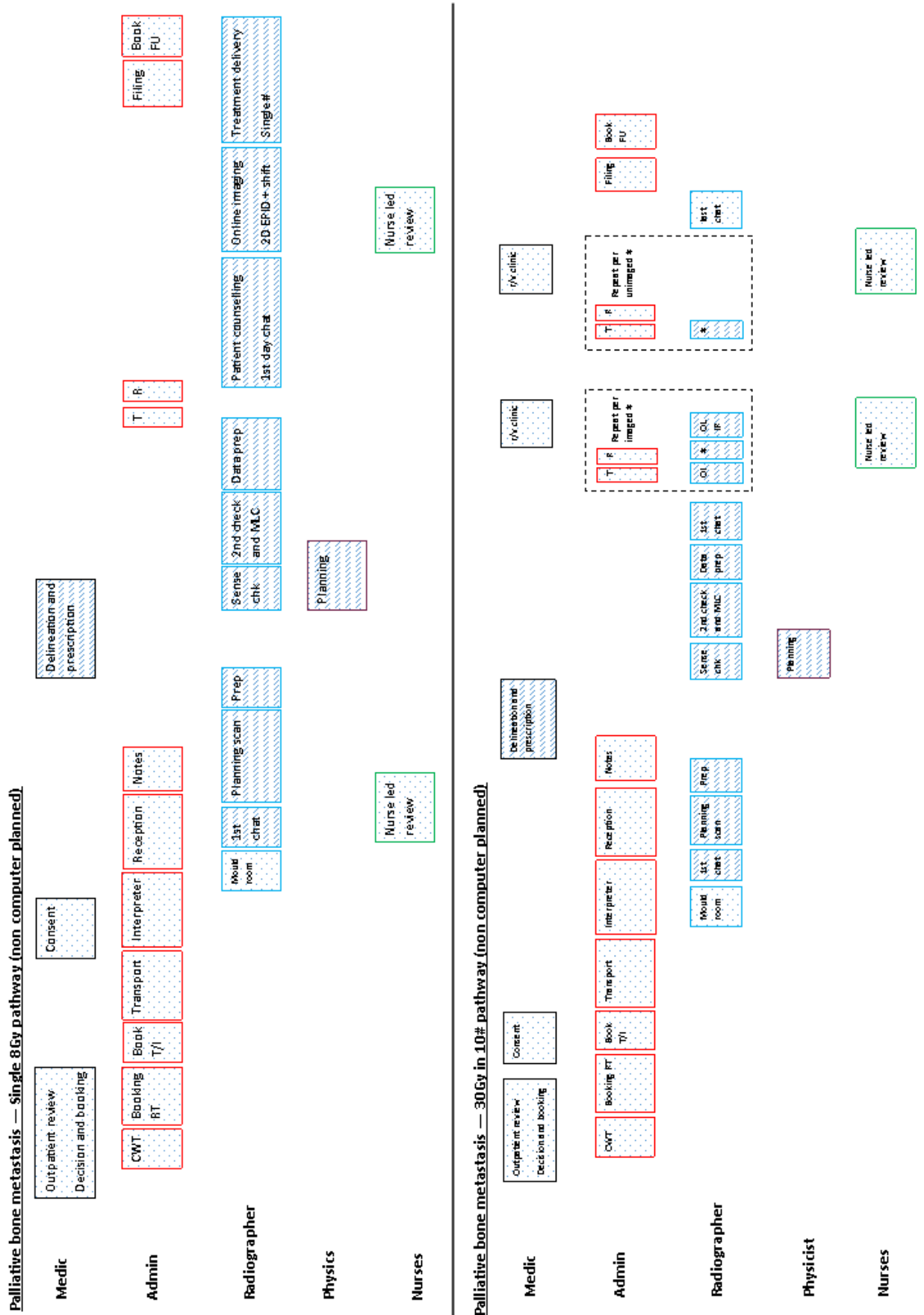
b) Radiotherapy treatment pathways for bone metastases using computer planned treatment or stereotactic radiotherapy.

Palliative bone metastasis — 30Gy in 10# pathway (3D planned)
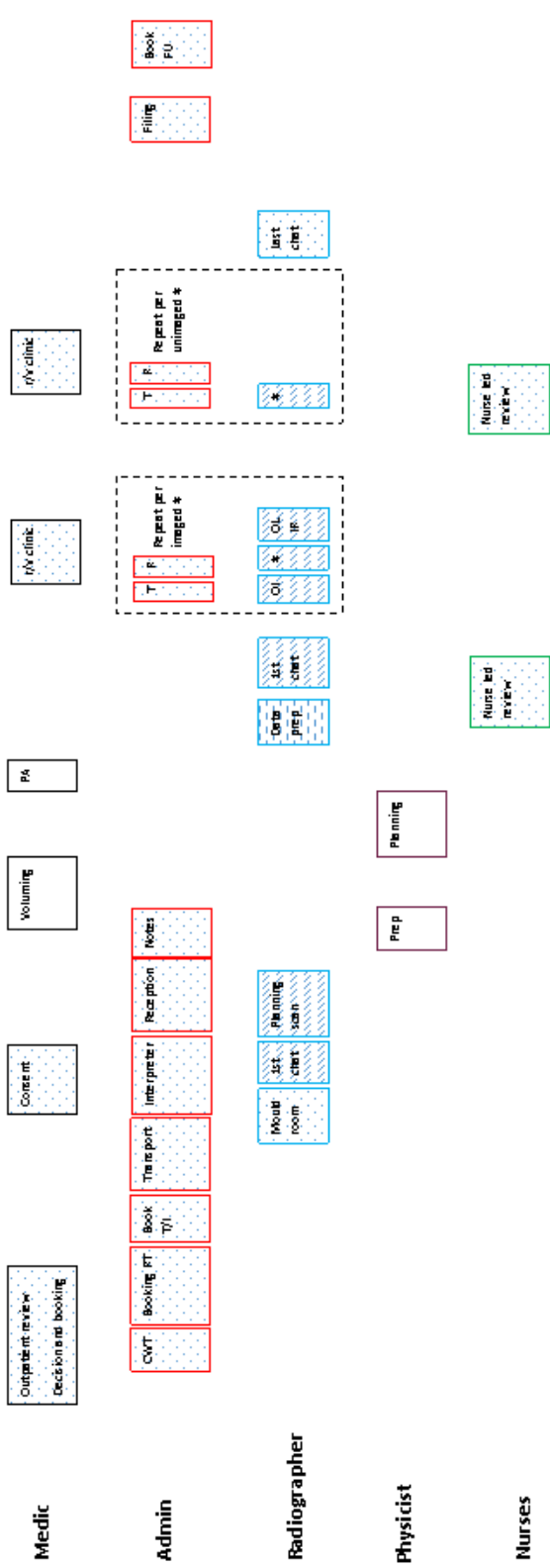
Palliative bone metastasis — SABR (VMAT technique with CBCT)
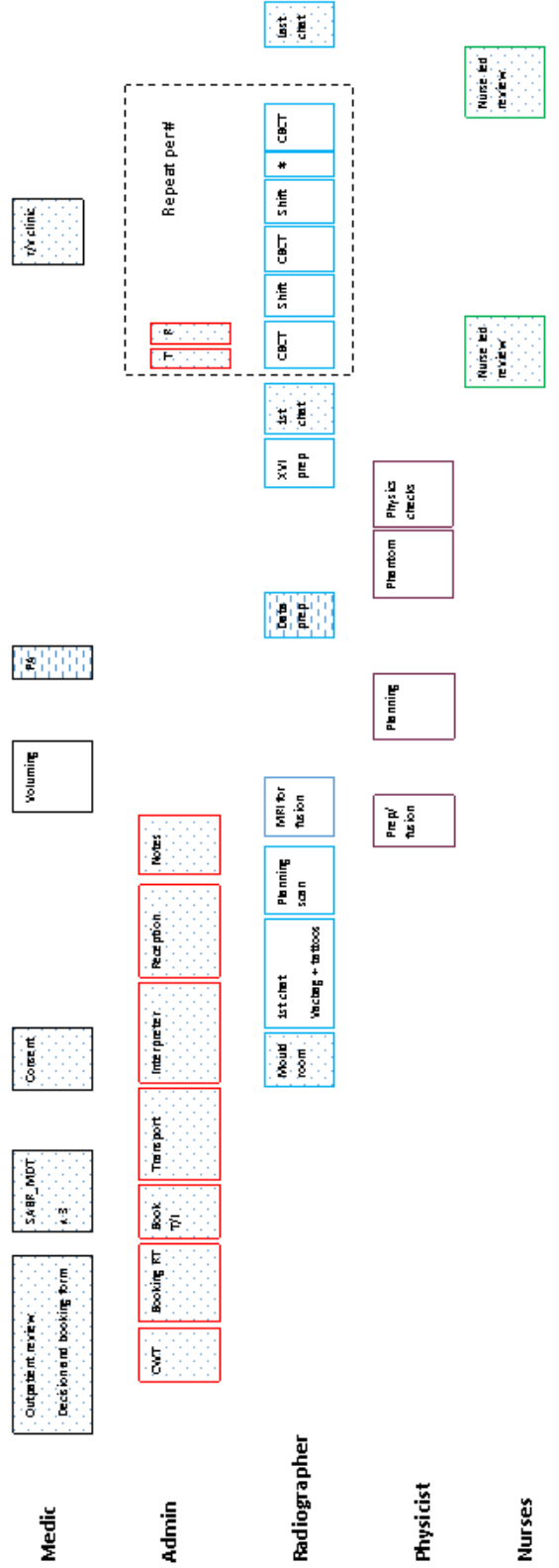
Table 18 Activity timings for palliative radiotherapy pathways

	Time (mins)	Source/ n if survey	Staff
Consent	10	Appointment	Consultant x 1
MRI for fusion	60	Appointment	Radiographer (B7) x 2
Pre-plan patient discussion	9	45	Radiographer (B6) x 1
Planning CT			
Conventional RT	15	46	Radiographer (B5) + Radiographer (B6)
SABR	30	1	Radiographer (B5) + Radiographer (B6)
Preparation time			
Physics preparation time (3D planned only)	10	2	Dosimetrist (B6) x 1
Physics preparation time (SABR only)	30	1	Physicist (B7) x 1
Radiographer preparation time (non-computer planned only)	7	35	Radiographer (B5) x1
Volume delineation/field placement			
Single non-computer planned	16	41	Consultant x 1
Computer planned	30	9	Consultant x 1
SABR	150	2	Consultant x 1
Planning			
3D Computer planned	55	5	Physicist (B6) x 1
SABR	120	1	Physicist (B7) x 1
Plan approval			
3D computer planned	10	3	Consultant x 1
SABR	20	1	Consultant x 1
Sense check			
Non-computer planned	17	28	Radiographer (B5) + Radiographer (B6)
Treatment preparation			
Non-computer planned (3 separate checks)	17,13,11	46,44,29	Radiographer (B5) x 2 + Radiographer (B6)
Computer planned (2 separate checks)	11,10	4,5	Radiographer (B5) + Radiographer (B6)
SABR (2 separate checks)	28,10	1	Radiographer (B7) x 2
Individual phantom QA (SABR only)	45	Appointment	Physicist (B7) x 2
Physics checks (SABR only)	20	1	Physicist (B7) x 2
XVI checks (SABR only)	10	1	Radiographer (B7) x 2
Treatment delivery			
Imaged fraction	16	Appointment	MLC linac team
Unimaged fraction	10	Appointment	MLC linac team
SABR fraction	30	Appointment	Agility linac team

5.3.3 *Capacity and resource costs*

The costs used to inform the base-case TD-ABC model are shown in Table 19. All costs are 2016/17 values and capacity reflects the 2016 calendar year.

Table 19. Base-case costs in LTHT radiotherapy department.

	Value	Source
Capacity:		
Total activity per year treated (mins)	1155687	
Total average per Agility linac (mins)	99693	
Total average per MLC linac (mins)	131444	
Total average per linac (mins)	115569	Oncology management system
Average per CT simulator per year (mins)	80328	
Total planned treatment courses per year	3263	
Total number of courses per year	6597	

Total fractions per year	76412	
Total attendances per year	83009	
Total courses having at least 1 CBCT	1904	
Total patients attending mould room per yr	1168	
Teams:		
Average linac staff costs per minute (£)	1.64	
MLC linac staff cost per minute (£)	1.60	Finance, Senior MDT members, Oncology management system
Agility linac staff cost per minute (£)	1.68	
SABR MDT team cost per minute (£)	4.28	
Mould room staff cost per patient (£)	125	
Equipment:		
Linac cost per year (£) (inc maintenance and physics space)	391,893	Finance capital team, Senior MDT members, Finance
Linac cost per year (£) (inc maintenance)	328,488	
Linac cost per year (£) (exc maintenance)	285,000	
CT simulator cost per year (£)	273500	
Space:		
Cost per metre squared per year (£)	680	Finance capital team
Utilities cost per metre squared per year (£)	49	
Linac bunker space (m²)	88	
Simulator space (m²)	90	
Physics planning space (m²)	200	
Physics and engineering space (exc planning)	546	Finance and Architectural plans
Mould room space (m²)	110	
Indirect space (m²)	2158	
Materials:		
MRI fusion material costs (£)	175	NHS tariff
Interpreter costs (£)	50	Senior MDT members
Patient transport costs (£)	29	Clinical commissioning group
Implementation:		
Total annual implementation budget (exc doctors) (£)	681675	Senior MDT members, finance
Implementation cost per SABR course (£)	195	
Treatment planning process:		
Initial outpatient consultation (mins)	30	Senior MDT members
Proportion using transport (%)	40	Oncology management system - for all treatments
Proportion requiring interpreter (%)	1	Oncology management system - for all treatments
MRI fusion staff costs (£)	61.63	Senior MDT members, finance
SABR MDT costs (£)	64.20	Senior MDT members, finance
Consent (£)	11.36	Senior MDT members
Trust overheads:		
Total percentage applied as Trust level overheads (%)	15.4	Reference costs team, finance, finance capital team

5.3.4 *Treatment course costs*

The total costs of the different treatment regimens for bone metastases are shown in Table 20, broken down into external costs, direct staff, equipment, space and material contributions (separately for treatment planning and delivery), indirect costs, departmental overheads and Trust

Table 20. Total radiotherapy treatment costs in LTHT.

	External costs	Direct planning costs				Direct delivery costs			Indirect departmental costs	Trust overheads	Total
		Staff	Equipment	Space	Materials	Staff	Equipment	Space			
Single 8Gy											
(£)	58.23	90.90	51.07	15.62	1.91	28.85	51.76	8.80	86.09	51.59	386.60
(%)		**41.26**				**23.13**			**22.27**	**13.34**	
30Gy in 10# non-computer planned											
(£)	177.60	83.92	51.07	15.62	1.91	201.98	362.34	61.58	441.59	188.96	1415.94
(%)		**10.77**				**44.20**			**31.19**	**13.34**	
30Gy in 10# computer planned											
(£)	177.60	119.09	51.07	60.13	1.91	230.83	414.10	70.37	549.45	230.53	1727.50
(%)		**13.44**				**41.41**			**31.81**	**13.34**	
SABR - 3 #											
(£)	82.23	542.26	407.42	120.66	89.54	151.24	366.33	57.99	680.30	372.03	2787.78
(%)		**41.61**				**20.65**			**24.40**	**13.34**	
45 Gy in 25# computer planned											
(£)	391.68	119.09	51.07	60.13	1.91	574.70	1392.07	220.37	1083.16	539.39	4041.90
(%)		**5.75**				**54.11**			**26.80**	**13.34**	

level overheads. The proportional contribution of planning costs is markedly higher for hypofractionated treatments (41% vs 6-19%).

In LTHT the extent to which the tariff reflects the modelled treatment costs varied. Tariff is <1% higher than the calculated treatment costs of a single fraction non-computer planned treatment, Discrepancies exist, however, between other regimens; the tariff is 19% higher than the calculated cost of delivering a three fraction SABR treatment. Conversely, simple more fractionated treatment is relatively under-reimbursed being up to 11% lower than the calculated costs of delivering a simple 10 fraction treatment. The extent to which delivery of a planned 25 fraction course is reimbursed is heavily dependent upon the reimbursement tariff claimed; assuming a complex tariff for delivery, reimbursement is 1.8% above treatment costs (as shown below). Minimal changes to this can result in marked under reimbursement (3.6% below if planning is assumed to be simple, or 23% if treatment delivery is also assumed to be simple). The comparison between the TD-ABC modelled costs and NHS reimbursement tariff is shown in Figure 27.

Figure 27. TD-ABC cost of treatment compared to NHS reimbursement tariff (2016/17 tariff prices).
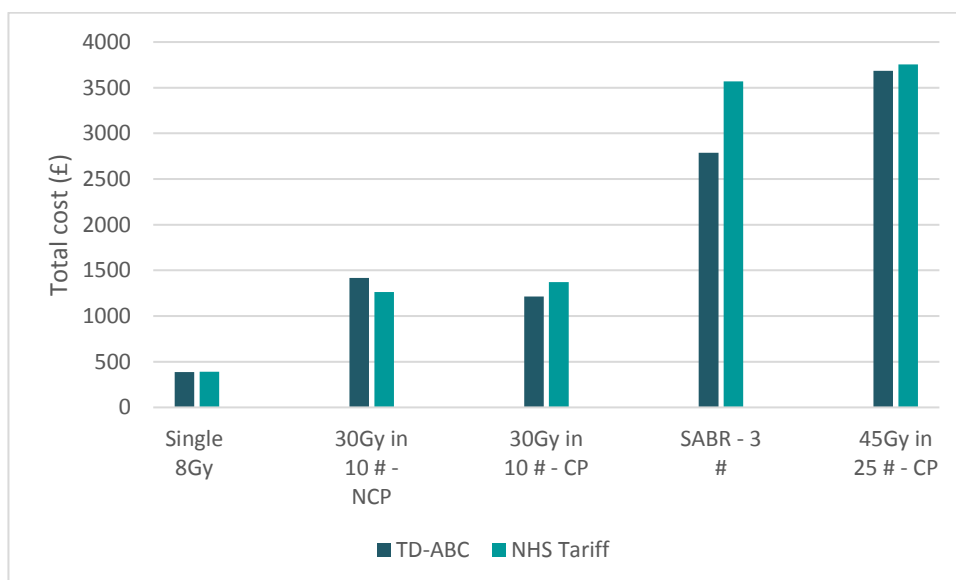
In order to assess the appropriateness of the relative weighting allocated to different treatments in tariff the ratios between these, using tariff and TD-ABC values, were examined. Considering specifically the costs of treatment delivery, the ratio between the reimbursement for delivering a fraction of complex, adaptive treatment (£163 (2016-17 tariff)) and a simple fraction (£97) was 1.68. In comparison using the TD-ABC model (excluding overheads) and assuming a delivery time of 18 minutes (with 2D online-imaging) for both treatments, recognising the greater complexity of the treatment machines the ratio modelled here is 1.29 i.e. the difference between the costs of delivering these different strategies appears to be over-estimated by tariff. Where the planning process is considered, the ratio between the tariff provided for a treatment plan with dosimetry (£403) and one with a simple calculation (£293) was 1.38. Where the TD-ABC model costs were considered this ratio was similar at 1.46.

The proportion of the total costs falling into different cost types (as defined by the WHO as variable, semi-variable, stepped and fixed) are shown in Table 21. The proportion of costs related to stepped and fixed investments is greater for fractionated treatment courses than hypofractionated (76-80% versus 64-68%).

Table 21. Proportion of cost types by radiotherapy treatment regimen.

	Variable (%)	Semi-variable (%)	Stepped (%)	Fixed (%)
Single 8Gy	0.57	35.75	30.70	32.99
30Gy in 10# non-computer planned	0.16	23.43	33.89	42.52
30Gy in 10# computer planned	0.13	23.38	31.07	45.42
SABR - 3 #	3.71	28.71	32.03	35.56
45Gy in 25# computer planned	0.05	19.81	41.20	38.93

Tornado plots illustrating the percentage change in total treatment costs resulting from varying the resource costs and departmental activity are shown in Figure 28. The parameter with the greatest influence upon treatment costs is departmental fraction activity; a 10% reduction in this resulted in a 4.28-8.67% increase in treatment course costs. This change was greater for fractionated than unfractionated courses (8.67% for a 25 fraction course versus 4.28% for a SABR course).

A 10% increase in departmental wages and equipment costs was associated with a cost change of at least 3% across all treatments except SABR (range across treatment regimens 2.28-3.31% and 3.07-4.12% respectively). Space costs were associated with lesser changes in treatment costs (10% increase resulting in 1.28-2.57% change in costs). Finally, recognising the cost of the charitably funded linacs resulted in a cost increase of 1.4-3.3% (including the bunker space occupied by these two linacs).

The principal cost drivers for SABR differ to those of more fractionated treatments; fraction activity, departmental wages and equipment costs remain important, although their effect is lessened, conversely doctor wages and implementation have a greater impact than is seen following conventional treatments (10% increases resulting in 0.99% and 1.56% cost increases respectively). Implementation costs are influenced by the expected number of treatments delivered over the first 3 years. A decrease in patient numbers from 150 to 90 over 3 years increased costs by 10.43%. An increase up to 200 only reduced the costs by 3.91%.

Figure 28. Tornado plots demonstrating cost-drivers in radiotherapy treatment using a) Non-computer planned single 8Gy or b) 30Gy in 10#, c) computer planned 30Gy in 10# d) SABR and e) 25 fraction course. All input parameters were varied by a 10% in both directions.

Cost elements shown from top to bottom are:

- Fraction activity,
- Departmental staff wages,
- Equipment,
- Space,
- Trust overheads,
- Number of planned courses,
- Doctors wages,
- Mould room activity,
- Software costs
- Implementation costs.
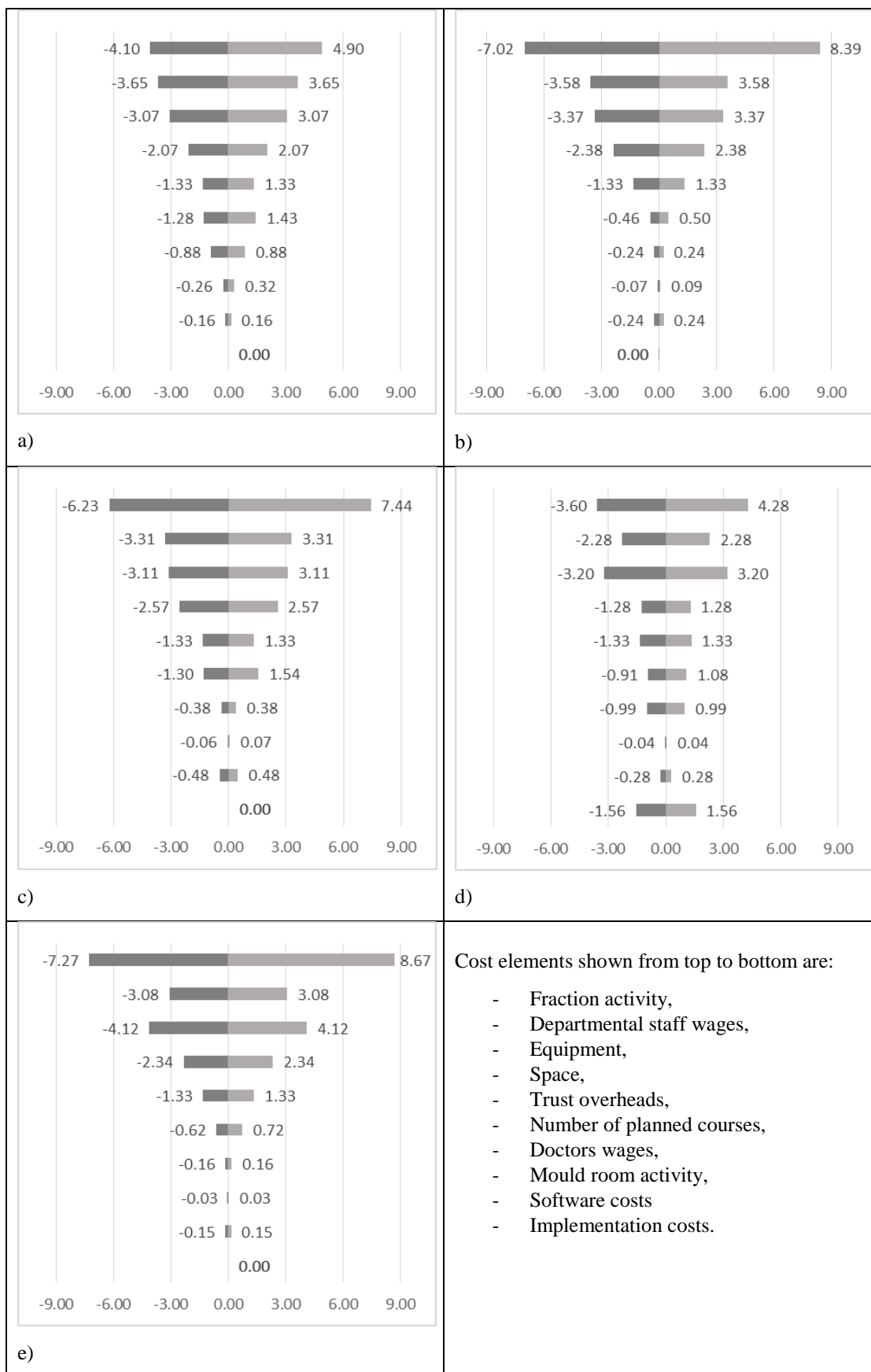
5.3.5 *Learning curve effects in SABR*

The modelled impact of the learning curve upon the costs of delivering SABR is presented in Figure 29. The costs beyond year 6 are expected to remain stable although there is potential for some further reductions in the planning process costs these are likely to be relatively limited.

Figure 29. TD-ABC estimates of the impact of learning curve effects on the costs of SABR delivery. 3 fraction SABR is shown in dark blue, single fraction in light blue.
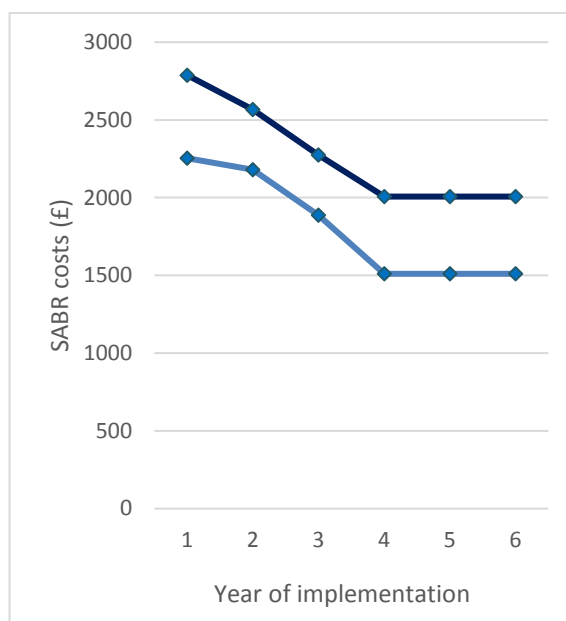
5.3.6 *Disinvestment*

Sensitivity analyses assessing the consequences of disinvestment from treatments demonstrate increased costs for remaining treatments, in line with the finding that departmental fraction activity is a major driver of costs. Figure 30 illustrates these results. Notably the stepped nature of the linac costs mean that even if linac disinvestment can be achieved this can only occur when its entire capacity is no longer required (or can be transferred to other machines within the department without consequential staff cost increases due to e.g. extended working). In LTHT the point at which this occurs is likely to be at approximately 8% activity reduction. In a smaller department a 10% reduction in activity is unlikely to be adequate to allow disinvestment from a whole linac. Given that the percentage at which disinvestment might be possible will vary between providers step changes are not illustrated here.

A final sensitivity analysis examining the consequences of reducing the number of single 8Gy courses delivered suggests that even when 200 single 8Gy courses are forgone the consequences for the costs of other treatments remains limited (0.25% increase in the costs of SABR, 0.36% for a prolonged fractionated course and 0.6% for the remaining single 8Gy fraction courses). Disinvestment from staff has limited impact upon these increases, reducing them to 0.24%, 0.31% and 0.58% respectively. It must be noted, however, that disinvestment from the resources required

to deliver such a small number of treatments is unlikely to be realistic. Particularly as these treatments will be spread over a whole year.

Figure 30. Consequences of fraction reduction upon treatment costs by treatment regimen a) single 8Gy, b) 30Gy in 10 fractions non-computer planned, c) 30Gy in 10 fractions computer planned, d) 3 fraction SABR e) 25 fraction planned treatment. The three lines on each graph represent the cost consequences given varying disinvestment from resources; Blue) all departmental resources remain the same, Green) treatment delivery staff are disinvested from, Red) treatment delivery staff and linacs are disinvested from.
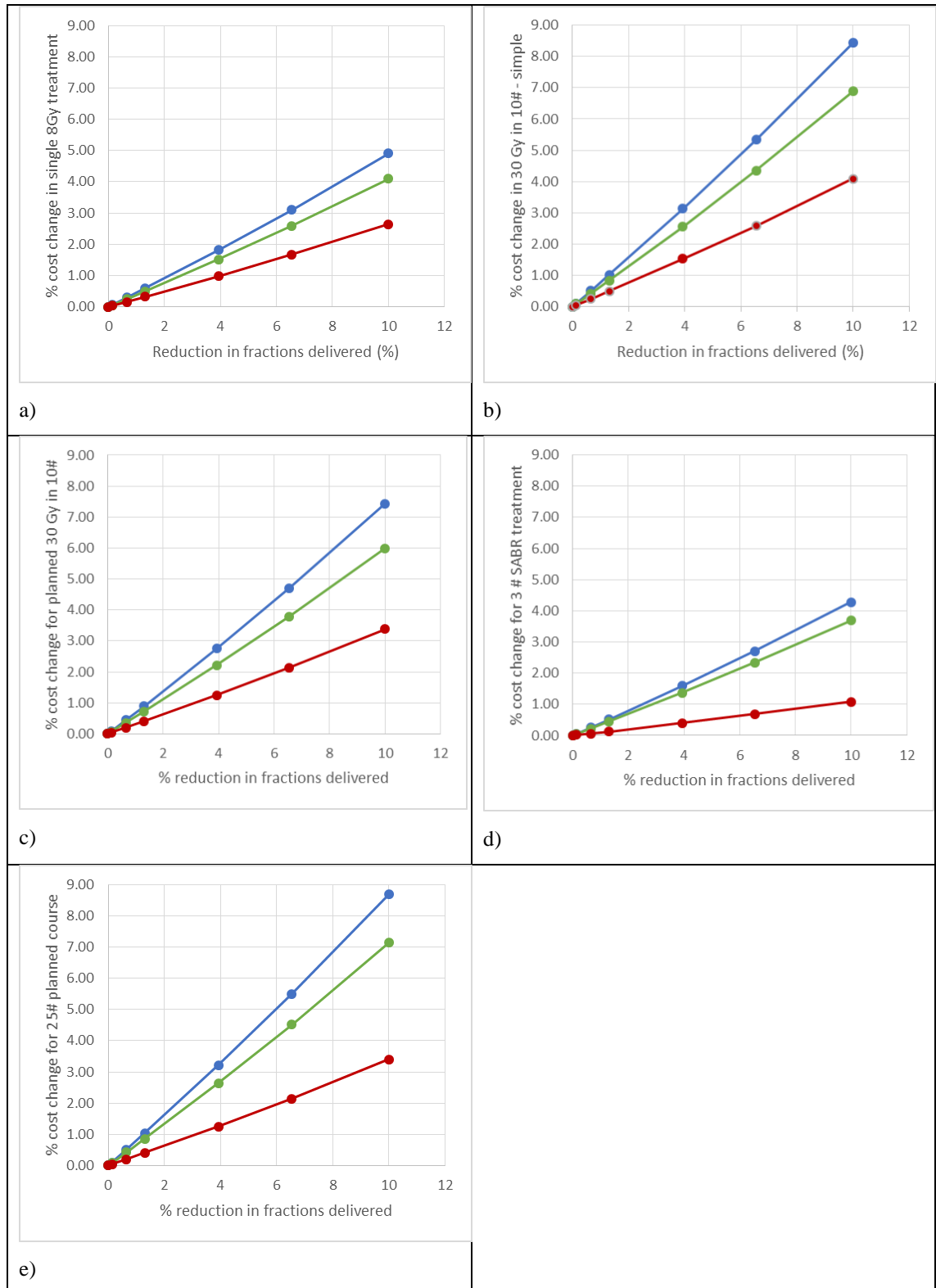
5.4 Discussion

This TD-ABC model demonstrates that the reimbursed tariff paid by NHS England to LTHT is, overall, a reasonable representation of the costs of radiotherapy treatment delivery. Discrepancies between the two arise predominantly in relation to the costs of treatment delivery whilst the alignment with planning costs appear closer. Specifically, more complex treatment delivery appears relatively appropriately reimbursed (or indeed over reimbursed in the case of SABR) whilst less complex treatment delivery appears to be under-reimbursed. Whilst it is possible that this reflects cost-shifting (where costs relating to complex treatment are inappropriately allocated to simpler techniques) within the TD-ABC all possible efforts were made to avoid this.(314) Given that all treatments are delivered on similar machines it is plausible that this is a feature of modern radiotherapy delivery; simple treatments are delivered using similar equipment to more complex ones, thus increasing the costs of their delivery. It is not possible to comment upon the extent to which this discrepancy might result in a deficit or surplus at the departmental level. The relatively superior reimbursement for complex treatments may, however, incentivise delivery of more complex treatments, potentially beyond those where evidence of clinical benefit supports their use. The tariffs used are independent of treatment intent and given the lack of evidence for clinical benefit with more conformal treatment plans in the palliative setting, incentivising a move towards these is hard to justify.(323)

In addition to these more general discrepancies, the cost of delivering the novel SABR treatment techniques appears to be over-estimated by tariff. It could be argued that reimbursement above the cost of treatment may be necessary to drive uptake and implementation of novel treatment techniques. In addition, as demonstrated here and in previous studies, the costs of delivering a novel radiotherapy technique are subject to learning curve effects.(120,324) In light of this, reassessment of tariff may be required once treatments are established. It must be recognised, however, that this learning curve is likely to be replicated in all departments implementing a novel technique; reducing tariff to all providers once early adopters have successfully embedded a novel technique may dis-incentivise the further dissemination of this technique and thus introduce geographical inequities in treatment access. The variation in treatment costs with implementation phase should also be recognised where cost-effectiveness analysis is employed (see chapter 6).

5.4.1 *Cost drivers*

The cost drivers of hypofractionated treatments (single 8Gy fractions and SABR) are different to those of more prolonged treatments. This is explained by the relative proportion of costs attributable to planning and treatment delivery for these treatments (41% of all costs being planning related in SABR and single fraction as compared to 5-13% in more fractionated courses).

The strongest driver of costs across all treatment regimens was departmental fraction activity (4.28-8.67%). These economies of scale are unsurprising given the knock-on effects of variation

in this parameter to other resource costs; staff, equipment and space costs are all calculated based upon departmental activity.(325) Notably fraction activity has a markedly greater impact upon the costs of fractionated treatments than hypofractionated treatments; the treatment planning costs making up a greater proportion of the total cost of these treatments and will be much less affected by variation in fraction activity.

Previous studies have demonstrated that costs vary significantly between providers; a treatment course being 50% more expensive in a centre treating 400 patients a year as compared to one treating 1600 patients per year.(325,326) This study demonstrates the role of economies of scale and may result in larger centres having a relative financial advantage over smaller ones if tariff is constant across all providers. The impact of fraction activity will also have a marked impact upon treatment costs when delivered using specialised equipment with limited indications. Increasingly, linac based solutions are available for the delivery of all highly conformal photon treatments which might previously have required specialised equipment. Where limited numbers of patients require such treatments the equipment, space and maintenance costs will be spread across a smaller cohort resulting in increased treatment costs. More flexible equipment may therefore offer greater cost efficiency.

When considering the possible financial advantages offered by economies of scale the inverse relationship between distance to a radiotherapy treatment provider and likelihood of undergoing radiotherapy must be recognised.(327–329) In recognition of this relationship there has been a increase in the number of smaller providers providing services for more dispersed populations. These findings would suggest that these may be delivering treatment at a higher cost due to the limited economies of scale available. Satellite centres, staffed by a larger central unit which undertakes the planning process and provides maintenance staff and equipment might allow greater flexibility in terms of staffing and reduce departmental overheads.(320) It is likely, however, that delivering care to geographically dispersed populations will increase costs to an extent.

In the context of assessing the costs of delivering SABR for bone metastases it is important to note that the cost drivers of novel interventions may differ to those in more routinely delivered treatments. Specifically, the learning curve effect is demonstrated here. The costs associated with this are sensitive to the underpinning assumptions. Most importantly, the expected patient numbers treated in the initial period; overestimating the number of treated patients will markedly, and inappropriately, reduce the estimated costs below those seen in reality. As with overall fraction activity, economies of scale are seen in the implementation of novel techniques and must be recognised when these novel interventions are commissioned across a range of providers of varying sizes.

5.4.2 *Disinvestment challenges*

Disinvestment from treatment is an increasingly recognised challenge.(330) The potential cost released through disinvestment from palliative radiotherapy for bone metastases, based upon current fractionation patterns and early mortality, is likely to be small. Disinvestment from these treatments will reduce departmental income but the modelling here demonstrates this is unlikely to have a marked impact upon the cost of remaining treatments delivered within the department (up to 0.6% increase if 200 treatments were forgone in LTHT). Conversely, the potential consequences of disinvestment from larger numbers of fractions would be more significant; future changes in the delivery of treatments for breast and prostate cancer may result in a marked drop in fraction activity.(331)

Modelling here relates simply to the number of fractions no longer delivered and as such the outcomes must be interpreted as the change in costs associated with the final reduction in activity after any unmet need has been fulfilled; a 10% reduction in fractions delivered in this model resulted in a 4.3-8.7% increase in remaining treatment costs. Providers may feel unable to deliver this reduction in activity, in the face of stepped and fixed costs, if the reimbursement for remaining treatments doesn't reflect these increased costs.

A number of potential challenges to disinvestment should be noted from this model:

- Within an organisation such as the NHS, in line with employment contracts, disinvestment from staff cannot be achieved in the short-term.(321) Radiotherapy departments do, however, experience significant staff turnover and this might allow staged disinvestment from staff over a number of years.(54)

- Disinvestment from buildings is not readily achieved; the buildings used for radiotherapy delivery are purpose built generally requiring large capital investment. Re-purposing could be considered although the potential for this has not been explored.

- Equipment disinvestment might be achieved to varying extents but, given the stepped nature of linac costs, this will depend upon a sufficiently large drop in fractions to allow removal of a whole linac. In addition, where equipment has been purchased using capital this can only be disinvested from at the end of the machine's life expectancy (approximately 10 years). Linacs purchased via lease arrangements may have greater flexibility in terms of disinvestment before the end of a machine's life expectancy, however, fixed lease terms and commissioning/de-commissioning costs may make this infeasible. LTHT is one of the largest radiotherapy providers in the country, as such, a 10% drop in delivered fractions would be sufficient to justify decommissioning of a linac and the staff required to run it. This is unlikely to be true in smaller centres and therefore the potential for disinvestment from linacs would be much more limited.

Throughout the sensitivity analyses assessing the consequences of disinvestment an assumption is made that capacity and demand are currently perfectly matched; fractions not delivered for one indication are not delivered for any indication. Multiple attempts to model radiotherapy demand have been made by international teams.(332–334) Measured UK activity has always fallen below these modelled estimates.(2,335) It is unclear, however, to what extent this reflects over-estimation in the models versus under-utilisation in practice; it remains unclear if demand is such that drops in activity will be filled by this unmet need. In this context it should also be noted that cancer diagnoses are predicted to rise over the coming decades.(336) There are also a small number of new indications for radiotherapy which might, to a degree, offset any reduction in currently delivered treatments.(337) It is likely, therefore, that any fall in fraction activity will only be temporary. Any temporary reduction in departmental income may, however, act as a dis-incentive to disinvestment.

5.4.3 *Limitations of the TD-ABC model:*

The TD-ABC model developed here has a number of limitations:

The cost of delivering radiotherapy treatments is likely to vary between providers. This variation may be in line with the cost-drivers identified here, however, as a single large centre, with a PFI contract the costs of treatment may differ to those in other centres. Staff costs are likely to be relatively stable within the NHS with geographical variation determined by workforce demographics rather than differing salaries. Equipment costs will, however, vary based upon the purchase price (potentially higher in small centres with lower buying power) but also funding arrangements. It is unclear how the PFI costs included here compare to other centres. Space costs do appear to drive costs to some extent, however, given the PFI arrangement these are likely to be higher in LTHT than elsewhere.(338) Further work to compare costs between multiple centres is required.

- A potential limitation of the costing of space is that all space is considered equivalent in this model. This is probably not an unreasonable assumption in terms of ongoing costs as cleaning etc is unlikely be higher for linac bunkers for example. Conversely, the cost of building will have been increased by the need for shielding the linac bunkers and, as such, their costs may be underestimated. Given the high space costs seen here it is unclear that this would have had a significant impact upon the overall costs.

- Provider level overheads are modelled as an additional percentage on top of departmental costs rather than as a direct function of complexity or attendances. This approach seems reasonable given that the direct and indirect costs will already capture variation with complexity and attendances. An alternative method is to derive an overall sum for Trust overheads to be allocated across all treatments on the basis of complexity and the number of fractions delivered. The previous Belgian analyses carried out by Prof Lievens team have used this

approach, splitting the provider overheads between fractions and courses.(314) This strategy requires further data which were not available and, given the detailed assessment of departmental overheads undertaken, is likely to add limited additional information.

- Accounting for all Trust level overheads is challenging without double counting any departmental costs. The principal costs of treatment relate to departmental expenditure (13.4% resulting from Trust overheads) and are therefore well captured. If Trust level overheads were to vary more widely this would be a more major cost-driver and some uncertainty remains around this value.

- This model focusses upon the cost of delivering outpatient radiotherapy treatments, as is clinically appropriate for palliative bone metastases treatments. It must be acknowledged that a proportion of patients will require an inpatient stay. These costs are reimbursed separately within the NHS and are, therefore, excluded from this analysis.

- The costs of Clinical Oncologist time is incorporated based on the time spent on specific activities within the treatment process. This reflects the nature of Clinical Oncology in the UK as a specialty where a large proportion of a clinicians time may be spent delivering systemic therapy. This approach may, however, result in underestimation of the costs of clinician time although the extent of this at a departmental level cannot be determined here. This may contribute to the relatively low proportion of costs attributable to staff wages.(338)

- In the costing of SABR treatments, assumptions were made regarding the anticipated number of treatments delivered over the initial 3 year period with overall SABR costs highly sensitive to these assumptions and the total number of patients treated is, as yet unknown.

- The extent to which tariff reflects delivered costs depends heavily upon the specific tariff reimbursed. Treatment definitions in tariff are extremely limited, resulting in significant uncertainty around the extent to which measured costs will align with the reimbursement tariff.

- There is a risk of cost shifting occurring within the model. This has been minimised as far as possible, however, it is notable that simple treatment delivery is relatively poorly reimbursed as compared to more complex treatments. Given that all treatments are delivered using the same equipment and space it is possible that any cost shifting observed is not an artefact of the model but a reality of modern radiotherapy practice; simple treatments are delivered on more complex machines and thus this shift in costs may not be avoidable.

- The ESTRO-HERO project has recently developed a TD-ABC tool to aid departments and countries in determining the regional and national costs of radiotherapy services. The model developed here is not able to inform these whole department, regional or national analyses. It is, however, better placed to provide a more detailed and transparent analysis of the costs and

cost-drivers in a single UK department and provide increased flexibility in sensitivity analyses. This information can then be used to inform service planning within the treating department and local commissioning discussions.

5.4.4 *Potential consequences:*

In light of the analysis carried out here valuable information is available to guide the commissioning process. In particular a number of potential consequences of failure to align reimbursement to costs, to understand cost drivers and to manage disinvestment risks can be considered:

- If providers are not fully reimbursed for all treatments delivered they may actively seek to maximise income by identifying treatments where income more closely reflects (or indeed exceeds) costs. This may be advantageous if these treatments offer superior outcomes and are, therefore, cost-effective. There is a risk, however, that the treatments which are incentivised do not maximise the health outcomes delivered and thus tariff may introduce perverse incentives.

- Reduction in fraction activity, whilst continuing to reimburse on a per fraction basis and without recognition of the fixed costs of treatment, may further widen the gap between costs and reimbursement. Implementing lower fraction courses, whilst clinically justified and preferable to patients, will exacerbate any discrepancies between costs and reimbursement. Again, introducing a perverse incentive to deliver more fractionated treatments in order for providers to cover their fixed costs.

- Clear definitions for the varying levels of treatment complexity do not exist. As such, providers may interpret the available definitions differently in order to maximise reimbursement. This may increase the overall budget without changing the treatments delivered. In addition, the available data informing how treatments are delivered may be affected, thus preventing appropriate monitoring and regulation.

- It is likely that the costs of delivering radiotherapy are not fully reimbursed by income from tariff for all providers, particularly given the economies of scale available in this large centre and close alignment to tariff. As many provider institutions are acute Trusts and, as demonstrated many of the costs of radiotherapy are fixed, this may result in other clinical departments effectively subsiding radiotherapy provision. The opportunity costs of this will be geographically isolated to the provider institutes, potentially resulting in geographical inequities.

- The introduction of novel techniques and technologies is challenging in radiotherapy; without investment, assessment of benefit is not possible.(47) There is a danger, however, that given the irrecoverable costs of implementation, once investment is committed treatments will

continue to be delivered and, indeed, integrated into routine care in the absence of evidence of benefit. These irrecoverable costs will be replicated as each provider implements a new technique and will not be markedly lower in later adopters, which will often be smaller providers.(339) Managing the diffusion of these techniques as evidence accrues, recognising the implementation costs in late adopting centres and ensuring equitable access to beneficial treatments requires careful consideration if geographical inequities in access to beneficial care are to be avoided.

- The use of specialised equipment, for limited indications may result in higher treatment costs than would be achieved through the use of more flexible linac based solutions. Previous studies have reached mixed conclusions in this setting.(340) Such equipment is often purchased from charitable funds, however, the space, maintenance and staffing costs remain significant. This model does not specifically incorporate any such equipment and further work to consider the costs of treatment in this setting would be valuable.

- Given the extent to which both equipment and space costs drive overall treatment costs, the financing of these large capital investments may have a significant impact upon treatment costs. PFI has been a major source of capital investment in the NHS for the last two decades, however, it remains controversial with suggestions it is not a cost-efficient approach to capital funding.(341) The extent to which individual PFI agreements are cost-efficient will vary and is unclear in this case.

- Finally, whilst cost-effectiveness modelling in radiotherapy has been limited to date, this is unlikely to remain the case given ongoing pressures on healthcare budgets and high incremental cost increases with novel radiotherapy technologies. The variation in costs seen during and beyond implementation require recognition in these analyses.

In conclusion, the cost of treatment identified here broadly align with current reimbursement tariffs. This study demonstrates, however, that less than 5% of treatment costs are variable and that marked variation exists in the expected cost of treatment delivery over the first five years beyond the implementation of a new technique. These findings should be recognised in cost-effectiveness analyses of novel radiotherapy techniques and can help to inform the commissioning of these interventions.

6 Cost-effectiveness modelling of palliative radiotherapy for bone metastases

6.1 Introduction

As discussed in chapter 2 novel radiotherapy techniques have the potential to offer improved clinical outcomes for patients with bone metastases, both in terms of the quality and durability of pain control achieved. These treatments are, however, significantly more expensive and it is unclear if they could be cost-effective within the NHS, particularly given the lack of previous analysis looking at the cost-effectiveness of the intervention in this context. One previous study has considered the cost-effectiveness of SABR for bone metastases, however, the model was developed from the perspective of the US healthcare provider and its relevance in the UK is unclear given the differences between the healthcare systems.(342) In addition this study has a number of limitations: Post-treatment response is considered either present or absent rather than aligned to the International Consensus endpoints. Given that one of the key benefits of SABR may be higher rates of complete pain response this is a significant limitation, potentially reducing the QALY gain which might be delivered by SABR; How the model that forms the basis of this analysis is parameterised is unclear from the published manuscript. Specifically, it is unclear if appropriate conversions between observed overall rates and monthly transition cycles in the underpinning state transition model have been carried out; The probability of pain relief after cEBRT re-irradiation is significantly higher (80%) than is reported in a randomised study assessing this outcome.(11) Following SABR this is parameterised as 95%; The costs incorporated in the model are limited to opioid analgesia and radiotherapy treatment costs and informed by a normal distribution. This study does, however, recognise that the survival of the treated population has a critical influence over the cost-effectiveness of the SABR strategy.

Health economic technology appraisals have historically been conducted during the development phase of new technologies. As a consequence, once a technology has been approved for reimbursement and released into the healthcare system its use has not been subject to health economic analysis.(119) This can mean that when carried into routine practice the assumptions underpinning cost-effectiveness analyses may no longer hold; the population treated may differ, resulting in heterogeneity of treatment efficacy and cost-effectiveness;(343) indication creep may occur; adoption may precede full HTA (as is routine in radiotherapy technology implementation); costs may be unstable; and superior technologies may evolve without appropriate, timely disinvestment from older treatments (either due to clinician reticence or failure to implement). The implementation of novel radiotherapy technologies and techniques faces many of these challenges. Addressing these may, therefore, help to optimise the cost-effective use of these treatments in routine care.

If cost-effective in the NHS, it is possible that SABR will only offer cost-effective care for patients with more prolonged survival, measured in long months or, indeed, years. The median survival following palliative radiotherapy in routine practice is 5.2 months.(4) As such, for many patients undergoing palliative radiotherapy survival beyond treatment is measured in weeks to short months. The median time to benefit following cEBRT for bone metastases is 2-4 weeks with documented response rates of 45% in those surviving less than 12 weeks.(92) In chapter 3 it was shown that near the EoL the self-reported HR-QoL benefit associated with pain response reduces significantly. The use of palliative radiotherapy in individuals with very limited survival might, therefore, be expected to offer only very limited benefits. Indeed, if survival is very short the balance between treatment burden and benefit may tip in favour of active symptom management and palliative care, delivering a holistic approach, potentially closer to the patient's home and minimising treatment burden near the end of life. 30-day mortality has been suggested as a possible measure to assess the appropriateness of palliative radiotherapy, however, in a palliative population it is unclear what acceptable levels of early mortality are.(116) A method to assess this would need to balance the expected treatment benefits and side-effects alongside the costs. A cost-utility model to assess the levels of 30-day mortality which reflect cost-effective use of these treatments was, therefore, used as this provides such an approach.

On the basis of the above, a cost-utility model was developed with the aim of addressing the following questions:

- Can stereotactic radiotherapy for pain due to bone metastases be cost-effective in the English NHS?
- If not, are there clinically plausible scenarios under which treatment might be cost-effective?
- What is the most cost-effective strategy for treating patients with differing survival duration beyond treatment?
- Recognising that the most cost-effective strategy may vary with survival, could combining cost-effectiveness modelling with routinely captured healthcare data support the commissioning of cost-effective care?

6.2   Methods

The cost-effectiveness model was developed in line with NICE methods for technology appraisal and detailed following the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines.(118,344) A Markov model was used to assess the cost-utility of four potential strategies for a cohort of patients undergoing their first palliative treatment for pain due to bone metastases from solid-organ malignancies. The four considered strategies were single fraction cEBRT, multiple fraction cEBRT, SABR and best-supportive care. Re-irradiation was only considered as a subsequent event. Given the palliative nature of this cohort a lifetime horizon

was used and the model run until <5% of the cohort remained alive (approximately 3 years in the base-case model). Alternative scenarios were considered to reflect outcomes for subgroups of patients with short (less than 12 weeks) and longer (over 9 months) survival times.

The model was developed from a payer (NHS England) perspective using English NHS costs for treatment and the subsequent health states. Both costs and health states were discounted at a rate of 3.5% per year.(118) All prices were captured in 2016 pounds sterling for health state costs and 2015/16 for treatment costs.

6.2.1   *Model structure*

The primary outcome of interest was pain response, with its associated quality of life. This outcome measure and the modelled health states were defined based on the ICPRE.(130) Details of the definition of these four response states are available in section 3.2.1.1. Re-irradiation rates were considered within the model as these are associated with costs and a utility decrement. Pathological fracture risk was not included, however, as it has been shown to be independent of fractionation pattern in cEBRT, predominantly reflecting the extent of underlying bony abnormality.(85,87) The model structure and five modelled health states are illustrated in Figure 31. Death was a consuming state which which could be reached from any pain response state and all other states were conditional upon survival with respect to transition probabilities, utility and cost. A parallel re-irradiation health state was included to model the probability of re-irradiation conditional upon survival and persistent pain (i.e. re-irradiation is not possible from the complete response state). This parallel design allowed the instantaneous capture of costs and utility decrement (for re-irradiation) whilst respecting the finding from previous studies that re-irradiation probability is not entirely related to pain state but varies depending upon the previous radiotherapy delivered and clinician confidence in its success.(16)

Figure 31. Health states and transitions within the proposed model. Death can be reached from any pain response state and is consuming.
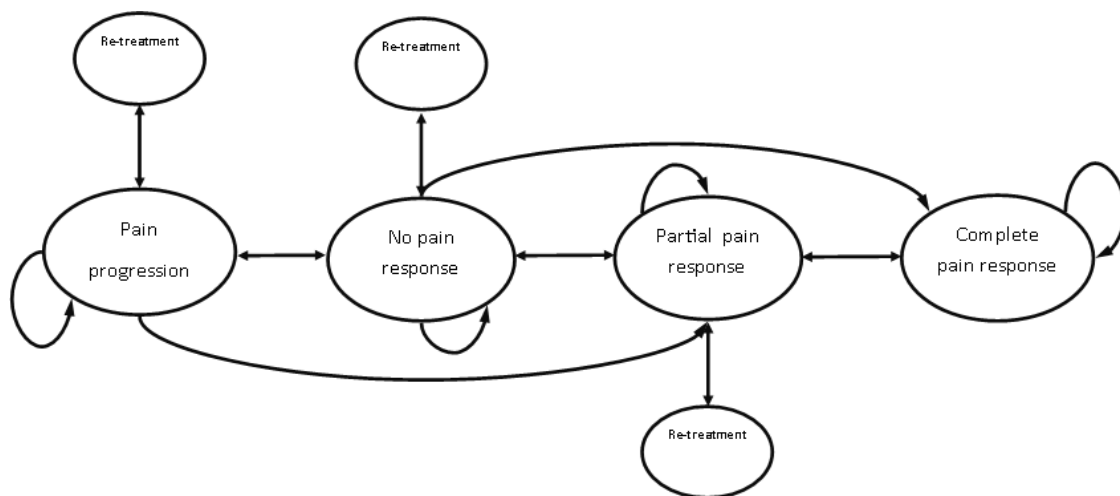
- Assumption – In line with Sande et al. dose fractionation of radiotherapy does not impact upon pathological fracture or spinal cord compression rates.(345)

Markov models provide a means to follow a treated population over time and through fluctuating health states of varying duration. A cycle length was first defined and the probability of movement from one state, to any other state, during each cycle, was used to predict the proportion of individuals in each health state at each cycle following treatment. The total quality adjusted life years (QALYs) associated with a given strategy can then be calculated by combining the proportion of the cohort in each state per cycle with the utility associated with these states.(346) Patients entered the model at the time of treatment and a cycle length of 1 week was used. This cycle length was selected on the basis that the median time to treatment benefit is reported to be 2-4 weeks and the model aims require recognition of the short time periods involved in populations with short survival.(10,16)

- Assumption – The Markov assumptions are met i.e. transition probabilities are independent of the time spent in the previous state.

A half-cycle correction was applied in order to recognise that patients do not transition at the end of each weekly cycle, effectively providing a calculation of QALYs and costs which reflects an average transition in the middle of each cycle.

In the metastatic setting there is no expectation that palliative radiotherapy improves survival. Where oligo-metastatic disease is identified the potential for survival benefit remains the subject of randomised trials.(337,347,348)

- Assumption – Palliative radiotherapy for bone metastases offers no survival advantage.

6.2.2 *Modelling treatment effectiveness*

Having defined the health states of the Markov model the probability of transition between states must be identified in order to inform the effectiveness of the four modelled strategies in delivering pain response. This was achieved in different ways for the four strategies.

Conventional radiotherapy transition probabilities

The outcomes of randomised studies assessing the impact of fractionation on pain control and re-irradiation rates have been assessed within meta-analyses previously.(10,43) The searches for this comparison were updated (see section 2.1) and demonstrated that no significant change to the overall outcome has occurred since the prior update. The DBMS was the largest trial ever carried out in this setting. As such it's results have a significant impact upon the meta-analysis outcomes and are representative of the response rates seen.(16)

- Assumption – The DBMS outcomes are representative of wider outcomes following conventional palliative radiotherapy for bone metastases.

The transition probabilities, between response states, were informed using a multi-state model fitted to the DBMS data, using the *msm* package in R.(349) This approach manages the competing

risk of being in alternative response states whilst also providing the flexibility of a bidirectional model; allowing patients to move back out of a response state when pain recurs. In Markov cost-effectiveness models a semi-parametric approach is routinely used (e.g. Kaplan-Meier) with parametric extrapolation beyond the available data. This type of analysis is able to handle censored events, relying upon the assumption that those censored have the same risk as those remaining in the risk set; the non-informative censoring assumption.(160) Censoring may be; administrative (trial closure), at loss to follow-up (missing data or lost to follow-up) or due to a competing risk (an alternative event preventing the event of interest from being observed). Administrative censoring can reasonably be assumed to maintain the non-informative censoring assumption, however, both loss to follow-up and competing risks are likely to significantly violate this; patients entering a competing state being at zero risk of entering the state of interest. The consequence of violation of this assumption is that the hazard of transition to the state of interest is overestimated.(350) In this case, all response states are competing risks and failure to recognise this will result in a gradual increase in the size of the cohort over time; an implausible outcome.

The *msm* package in R supports identification of time-inhomogeneous (piece-wise constant) transition probabilities and inclusion of co-variables e.g. trial treatment arm, primary diagnosis.(161) For each observed questionnaire from 1,150 patients treated in the DBMS the time since treatment start (in weeks) was identified and those questionnaires returned prior to treatment and by patients with less than 2 post-treatment questionnaires excluded (see Figure 6 for details). All questionnaire responses were defined as reflecting one of the four response states (as per the ICPRE). Patients were censored when missing or dead. This latter was done in order to allow the survival probability in the model to be independent and constant across all treatment strategies and preventing the inadvertent introduction of a survival advantage were one treatment to deliver superior pain control. Initial clinically plausible values were estimated in order to support model fitting by maximum likelihood. In addition, it was assumed that transition between non-consecutive states was impossible (e.g. complete response and pain progression).

A time-inhomogeneous, piece-wise constant multi-state model was fitted and the transition probabilities between states extracted. Transition intensities were allowed to change at 2, 6, 12, 24 and 52 weeks. The improvement in model fit with the piece-wise constant model compared with a time-homogeneous model and alternative model specifications with fewer change points was assessed using the likelihood ratio test (p<0.001). The model fit was then confirmed visually by comparing the observed prevalence with the modelled outcomes. Initially only trial intervention (single 8Gy vs 24Gy in 6 fractions) was included as a time-constant co-variable. Notably this did not have a significant impact upon model fit although was retained in the model to inform the cost-utility model (likelihood ratio test for the comparison between models p=0.437). Subsequent alternative scenarios adjusted for a further co-variable for diagnostic group

(p<0.001). Weekly transition probabilities were extracted from the model. The base-case transition matrices for single and fractionated cEBRT are shown in Table 22.

Table 22. Transition probabilities between pain response states for conventional radiotherapy treatment arms.

	Multiple fractions				Single fraction			
1-2 weeks								
	NR	PR	CR	PP	NR	PR	CR	PP
NR	0.618	0.240	0.020	0.122	0.618	0.248	0.016	0.118
PR	0.266	0.609	0.054	0.071	0.264	0.628	0.050	0.058
CR	0.074	0.331	0.577	0.018	0.065	0.303	0.619	0.013
PP	0.409	0.087	0.006	0.498	0.435	0.096	0.005	0.464
3-6 weeks								
	NR	PR	CR	PP	NR	PR	CR	PP
NR	0.680	0.213	0.017	0.090	0.678	0.218	0.014	0.090
PR	0.182	0.724	0.080	0.014	0.181	0.731	0.074	0.013
CR	0.032	0.247	0.720	0.002	0.028	0.221	0.750	0.001
PP	0.398	0.066	0.004	0.532	0.424	0.073	0.004	0.499
7-12 weeks								
	NR	PR	CR	PP	NR	PR	CR	PP
NR	0.745	0.140	0.023	0.092	0.749	0.143	0.016	0.092
PR	0.131	0.805	0.056	0.009	0.130	0.810	0.051	0.009
CR	0.018	0.210	0.771	0.001	0.015	0.187	0.797	0.001
PP	0.352	0.034	0.005	0.609	0.380	0.038	0.004	0.578
13-24 weeks								
	NR	PR	CR	PP	NR	PR	CR	PP
NR	0.880	0.057	0.016	0.048	0.884	0.058	0.010	0.049
PR	0.078	0.888	0.027	0.007	0.077	0.893	0.025	0.005
CR	0.005	0.104	0.891	0.000	0.004	0.092	0.904	0.000
PP	0.175	0.006	0.002	0.818	0.192	0.006	0.001	0.800
25-52 weeks								
	NR	PR	CR	PP	NR	PR	CR	PP
NR	0.881	0.053	0.011	0.055	0.882	0.055	0.007	0.056
PR	0.059	0.909	0.026	0.006	0.059	0.913	0.023	0.005
CR	0.002	0.066	0.932	0.000	0.002	0.058	0.940	0.000
PP	0.149	0.005	0.001	0.846	0.163	0.005	0.001	0.831
>52 weeks								
	NR	PR	CR	PP	NR	PR	CR	PP
NR	0.909	0.054	0.009	0.028	0.911	0.056	0.006	0.028
PR	0.056	0.917	0.024	0.004	0.055	0.920	0.022	0.003
CR	0.002	0.071	0.927	0.000	0.002	0.062	0.936	0.000
PP	0.093	0.003	0.000	0.903	0.103	0.003	0.000	0.894

One-way sensitivity analyses from these transition matrices are challenging to deliver due to their complexity. An alternative means to model upper and lower extreme values from this data is to include a further co-variable. In this case primary diagnosis was used. Here the cohort was split into patients with breast/prostate cancer and those with lung cancer or other diagnoses. It has previously been demonstrated that breast and prostate cancer patients have a higher probability of pain response than other patients.(222) This is in keeping with the results shown in Table 17.

Including this co-variable improved the msm piece-wise constant model fit (log likelihood test p =2.55x10e-12). Using predicted transition probabilities for these separate patient groups provided a means to deliver this one-way sensitivity analysis. Figure 32 demonstrates the response state prevalence predictions for these two diagnostic groups. Breast and prostate cancer patients are more likely to gain, and remain, in partial or complete response than those with other primary cancer diagnoses.

Figure 32. Health state prevalence by primary diagnosis a) breast or prostate cancer b) all other diagnoses. The overall population prevalence is illustrated by the blue line, the predicted prevalence for the diagnostic cohorts by the red dotted lines.
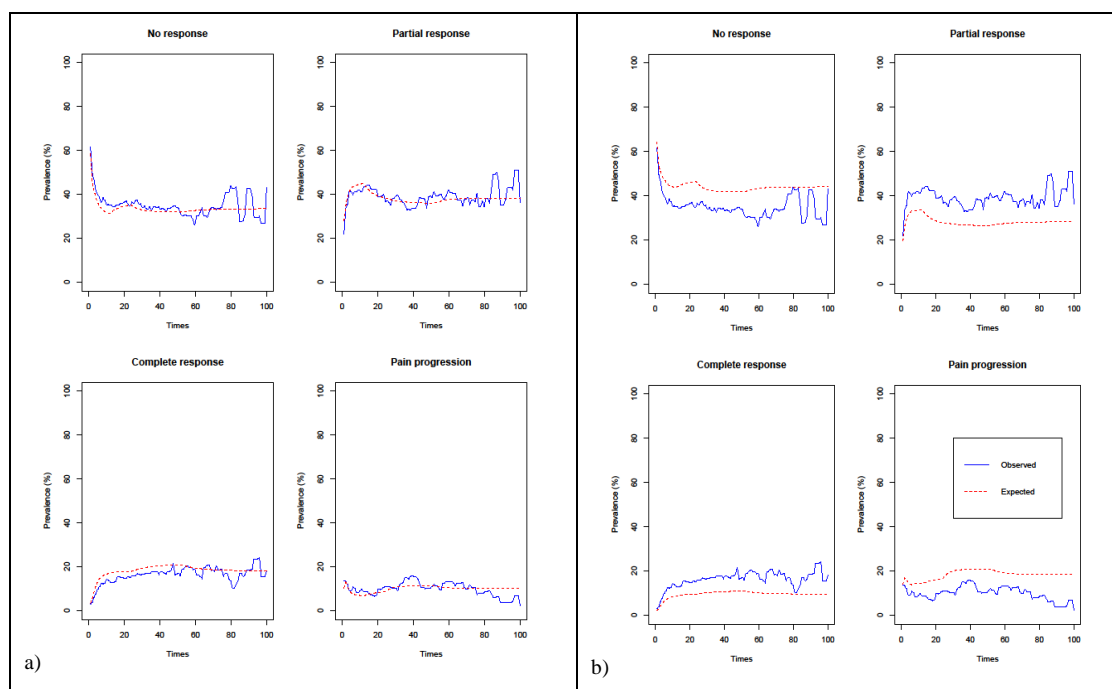
In order to recognise the uncertainty around the modelled transition probabilities, non-parametric bootstrap resampling was undertaken using *msm.boot.* Using this method adjacent pairs of observations (from within an individual) are randomly drawn from the sample with replacement. The model is then re-fitted repeatedly for each bootstrapped sample in order to provide a distribution of transition probability estimates. In order to inform 10,000 simulations in the cost-utility model 10,000 bootstrapped samples and their models were required. This is very computationally intensive and, as such, was carried out using the high-performance computing (HPC) cluster in the University of Leeds.(351) This allows the bootstrap samples to be drawn and the model re-fitted simultaneously, using multiple computer cores, and thus markedly expedites the process from one which is likely to take weeks to run to one which runs overnight.

The technical aspects of modifying the *R* scripts and submitting them to the HPC were supported by Dr Alastair Droop. Dr Droop developed a script using *qsubsec,* his Python based mini-language.(352,353) This template mini-language and interpreter provides separation of the core *msm* function from the data to support submission to the HPC. Modifications to the *R* script to

support this also ensured that the returned bootstrapped transition matrices were complete (i.e. there are no missing values due to model failure). The *qsubsec* script included the necessary metadata (e.g. maximum iteration numbers, total bootstraps required, number of cores) required and incorporated this information into the *msm* function at the point of submission to the HPC, bringing in the appropriate data for model fitting. This allows submission of many alternative models/iterations with ease. Prior to use on the HPC the relevant DBMS data were fully anonymised. All output files from the HPC were reviewed to confirm no missing values and transition matrices were within a plausible range (i.e. sum to 1).

The resulting 10,000 transition matrices provide the transition probabilities required to inform the subsequent probabilistic sensitivity analyses for the single and multiple fraction strategies of the cost-utility model.

Best-supportive care transition probabilities

As detailed in Chapter 2 there are no randomised studies to inform the comparison between palliative radiotherapy and best-supportive care. As such informing the transition probabilities for pain response in this cohort is challenging. Within the DBMS, 307 patients returned more than one questionnaire prior to undergoing radiotherapy. 81 of these returned three questionnaires and 21 returned four prior to treatment commencing. The transitions seen in this population can provide some indication of the expectation of response in the absence of radiotherapy. As detailed above, for the conventional radiotherapy strategies, an *msm* model was fitted using R to identify transition probabilities from this data.(349) A simple time-homogeneous model was used as introduction of a piece-wise time-point at two weeks did not improve the model fit using the likelihood ratio test, probably reflecting the very limited data available. The model fit is illustrated in Figure 33 and transition probabilities shown in Table 23.

As previously, non-parametric bootstrapping was used to support the probabilistic sensitivity analysis. The simplicity of this *msm* model meant that the HPC was not required. Given the limitations of the data, predictions beyond the first three weeks were felt to be unjustified. As such, the base-case model assumed that the cohort transitions according to the pre-irradiation DBMS for the first 3 weeks and then remains in these states throughout the model, conditional upon survival.

- Assumption – Response in the absence of radiotherapy is possible and reflects the response rates seen prior to treatment in the DBMS. Responses gained in this period are assumed to be maintained subsequently.

Figure 33. Pain response state prevalence conditional upon survival.
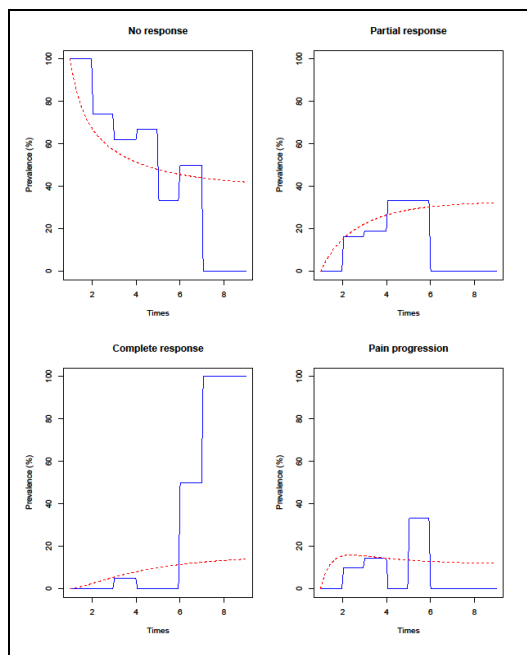
Table 23. Weekly transition probabilities for best supportive care.

	NR	PR	CR	PP
NR	0.672	0.150	0.024	0.154
PR	0.187	0.692	0.060	0.061
CR	0.026	0.202	0.763	0.009
PP	0.573	0.090	0.070	0.268

One-way sensitivity analyses of this parameter assumed that, at the lower extent of the plausible range, no response is possible in the absence of radiotherapy and at the upper limit, response is possible in the absence of radiotherapy and that this aligns with response rates seen in lung/other cancer patients following cEBRT in the DBMS.

SABR transition probabilities

As reported in section 2.2 the available published literature to inform the transition probabilities for the SABR strategy are at significant risk of bias, predominantly due to case-selection. As detailed, a limited number of studies were therefore identified which were acceptable in terms of both their methods and reporting. The probabilities incorporated into the base-case model reflect the post-SABR response rates reported in the small, randomised study by Sprave et al, on the basis that this is the highest level data available to inform the model. Alternative scenarios were then used reflecting the results reported by Kim et al and Balagamwala et al.

In order to incorporate the reported probability of pain response into the cost-utility model weekly transition probabilities are required. This was achieved using sequential dirichlet distributions. The Dirichlet distribution is routinely used to provide probabilistic estimates from a multinomial distribution e.g. where patients within a cohort are able to transition to more than two health states, as seen here.(354) A probability of health state occupancy at e.g. two weeks is then produced

before converting this to a weekly transition probability (see Equation 5).(346) In this case a bi-directional model was required; pain can deteriorate after initial response or vice versa. In order to achieve this, sequential Dirichlet distributions were constructed providing piece-wise constant transition probabilities. Draws from these sequential Dirichlet distributions were constructed using the *rdirichlet* function in R. The data to inform these transition probabilities were limited and, therefore, the resulting health state prevalence plots were reviewed and manually calibrated to the reported outcomes (seeFigure 34). This allowed replication of the reported outcomes, recognition of appropriate levels of uncertainty (through including the reported low numbers in the Dirichlet draw) and the bi-directional model necessary to respect the clinical scenario. The base-case transition probabilities informing this strategy are shown in Table 24.

Equation 5. Conversion between a) a rate and a probability and b) vice versa. In the case of the sequential Dirichlets this allows conversion to a rate per week and subsequent reversal back to a weekly transition probability.

$$a) \quad p = 1 - \exp\{-rt\}$$

$$b) \quad r = -[\ln(1 - P)]/t$$

Figure 34. Trace illustrating the prevalence of varying pain response states. Calibrated to Sprave et al.
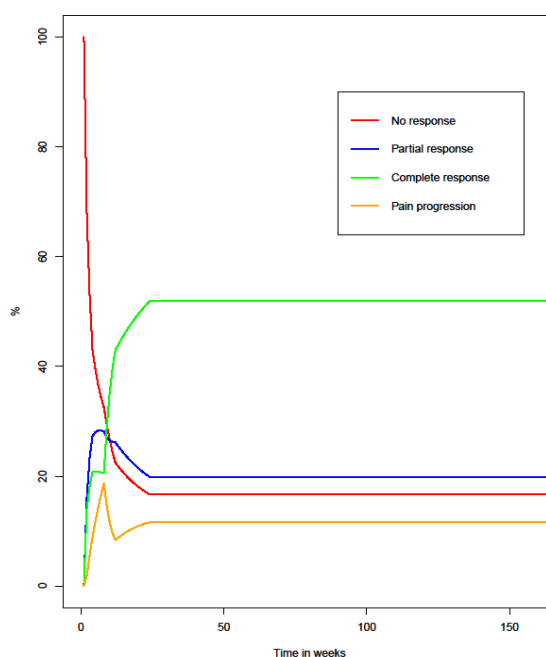
Table 24. Base-case transition probabilities for pain response following SABR. Derived from Sprave et al.

1-2 weeks	NR	PR	CR	PP
NR	0.681	0.161	0.139	0.019
PR	0.000	1.000	0.000	0.000
CR	0.000	0.000	1.000	0.000
PP	0.000	0.000	0.000	1.000
3-4 weeks				
NR	0.736	0.134	0.087	0.043

PR	0.095	0.763	0.095	0.047
CR	0.099	0.134	0.767	0.000
PP	0.000	0.000	0.000	1.000
5-8 weeks				
NR	0.834	0.085	0.026	0.054
PR	0.096	0.846	0.029	0.029
CR	0.029	0.061	0.910	0.000
PP	0.033	0.000	0.000	0.967
9-12 weeks				
NR	0.817	0.069	0.045	0.069
PR	0.054	0.834	0.085	0.026
CR	0.015	0.065	0.920	0.000
PP	0.054	0.000	0.331	0.614
13-24 weeks				
NR	0.934	0.033	0.000	0.033
PR	0.015	0.929	0.056	0.000
CR	0.006	0.006	0.989	0.000
PP	0.018	0.018	0.000	0.963
25-52 weeks				
NR	1.000	0.000	0.000	0.000
PR	0.000	1.000	0.000	0.000
CR	0.000	0.000	1.000	0.000
PP	0.000	0.000	0.000	1.000
>52 weeks				
NR	1.000	0.000	0.000	0.000
PR	0.000	1.000	0.000	0.000
CR	0.000	0.000	1.000	0.000
PP	0.000	0.000	0.000	1.000

Survival probability

The probability of death was informed using a Weibull parametric survival function fitted to the observed survival of the 1,150 patients with known radiotherapy treatment dates in the DBMS.(355) The Gompertz model provided superior fit on Akaike's information criteria (AIC), however, this resulted in the implausible long-term survival of some patients within the model and so was considered inappropriate. In contrast, the Weibull model provided acceptable model fit both by AIC and on visual examination (Figure 35) and did not result in implausible long-term survival. Median survival from the Weibull model was 34 weeks; longer than that reported in the DBMS (30 weeks).(16) This is unsurprising as the median is the point at which the Weibull adheres least closely to the observed data (Figure 35).

Equation 6. Weibull model for the hazard at time t. λ represents the scale parameter and γ the shape parameter with β representing the hazard ratio.

$$h_i(t) = exp(\beta x_i)\, \lambda \gamma t^{\gamma - 1}$$

Figure 35. Weibull proportional hazards model fitted to DBMS survival data. The observed DBMS outcomes are shown in black and the fitted Weibull function in red.
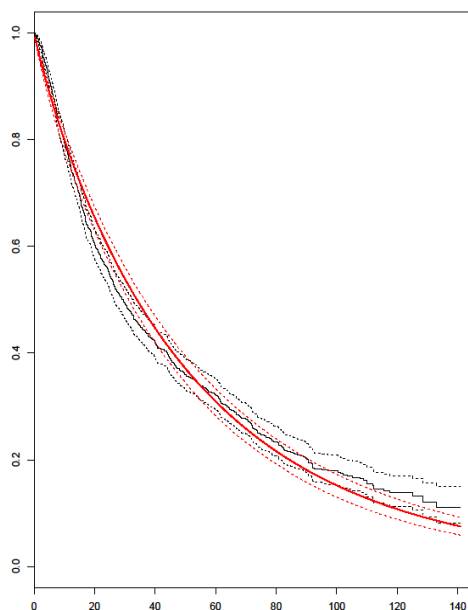
Survival is not expected to increase with SABR, whilst pain response may. Modelling survival probability as conditional upon response state might, therefore, introduce a survival advantage following SABR treatment (where higher response rates are seen). In the oligo-metastatic setting this is possible, although far from certain, and is the subject of ongoing randomised studies.(337,347,348) This model was not investigating the potential role of SABR for disease control in the oligo-metastatic setting and, therefore, improved survival with SABR was implausible. It was avoided by informing the transition probabilities independently of survival. Response state was then conditional upon survival in all treatment strategies.

- Assumption - The probability of death is the same from all response states.

- Assumption – SABR is not associated with a survival advantage.

The probabilistic sensitivity analysis draws the shape and scale parameters of the Weibull model from the multi-variate normal distribution respecting the variance-covariance matrix. These parameters inform the hazard over time (a rate) which is then converted to a weekly probability of death (see Equation 5 a)).(346)

Re-irradiation probability

To inform the cost-utility model a Gompertz parametric survival curve was fitted to the observed re-irradiation data from the DMBS with patients censored at death and trial closure. Treatment arm was considered a co-variable (Figure 36). This supports modelling beyond the observed trial period. The rate, shape and coefficient for the single fraction treatment arm (natural log of the hazard ratio) parameters were then used to inform a Gompertz survival function and subsequent

transition probabilities for re-irradiation following cEBRT (Equation 7). Probabilistic sensitivity analysis was carried out by drawing these parameters from the multivariate normal distribution recognising the variance-covariance matrix from the fitted model.

Equation 7. Gompertz proportional hazards parametric survival function for the hazard of individual i at time t. λ represents the scale parameter, θ the shape parameter and β the hazard ratio.

$$h_i(t) = \exp(\beta x_i)\lambda e^{\theta t}$$

Figure 36. Fitted Gompertz parametric survival model for re-irradiation following cEBRT. Observed DBMS outcomes shown in black and fitted Gompertz function in red.
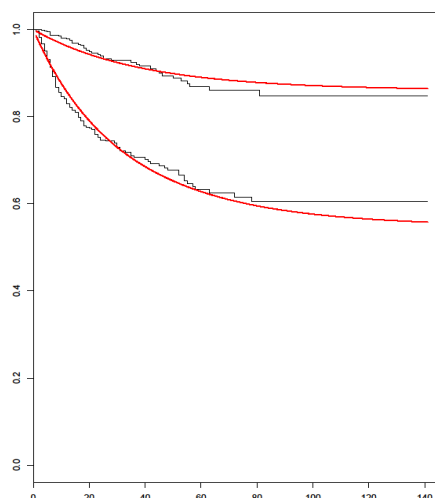
As detailed in chapter 2, re-irradiation following palliative radiotherapy for bone metastases is more frequently seen after single fraction treatments than following multiple fractions.(85) It has, however, also been shown that this increase in re-irradiation is not dependent upon pain progression rates in the single fraction cohort. A number of factors may be contributing to this: in trial populations clinicians may have doubted the efficacy of single fraction relative to multi-fraction treatments, whilst in addition there is greater willingness to re-treat when lower previous dose means lower risk of long-term spinal cord toxicity after re-irradiation.(356) In light of the difficulties with assuming a direct causal relationship between pain response and re-irradiation the probability of re-irradiation was modelled in parallel to the pain response transitions and conditional upon survival in all the radiotherapy treatment strategies. In this way re-irradiation was not related to response status, however, re-irradiation rates were incorporated allowing accrual of costs and utility decrement. In line with clinical trials in palliative radiotherapy for bone metastases a minimum time to re-irradiation of 4 weeks following completion of initial radiotherapy was included for all strategies.(11,130)

- Assumption – Re-irradiation is conditional upon survival and persisting pain but is independent of degree of pain response.

- Assumption – A simplifying assumption is made that response after re-irradiation is captured within the observed outcomes of the DBMS and SABR studies.

- Assumption – Re-irradiation rates in UK practice reflect those observed in the DBMS.

- Assumption – The parametric survival function fitted to the cEBRT data is an acceptable representation of the distribution of re-irradiation following SABR.

As seen previously, for response states, failure to recognise competing risks (in the case of re-irradiation the competing risk of death) will result in overestimation of the probability of re-irradiation due to violation of the non-informative censoring assumption.(350,357) An illustration of this is shown in Figure 37 in which the overall probability of re-irradiation can be seen to be significantly overestimated by the Kaplan-Meier method whilst being accurately estimated by the cumulative incidence function based on a Fine and Gray competing risk analysis (with death considered a competing risk). Notably the Cox proportional hazards modelled hazard ratio and Fine and Gray sub-distribution hazard ratio are reasonably consistent (HR = 4.023 vs SHR 4.048). Incorporation into the Markov model, acknowledging that re-irradiation is conditional upon survival and, crucially, persisting pain, resulted in re-irradiation rates in keeping with the DBMS results. Conditioning on survival alone resulted in persistent over-estimation.

Figure 37. Observed re-irradiation probability over time by a) Kaplan-Meier survival and b) cumulative incidence in competing risks framework. The horizontal reference lines represent the total observed proportion of individuals undergoing re-irradiation in each treatment arm.
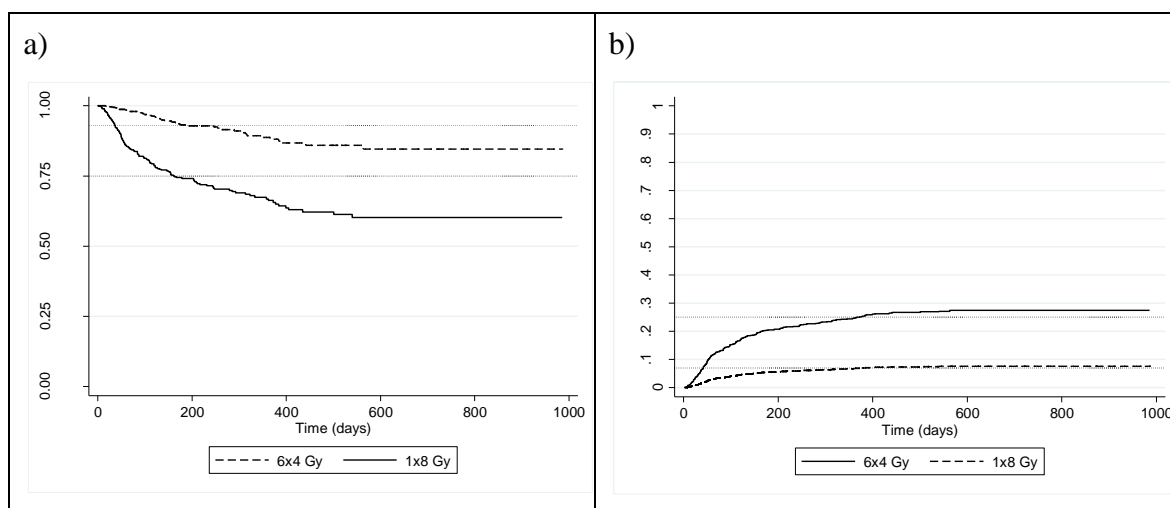
In order to inform the SABR strategy the proportion of patients undergoing re-irradiation was identified from the studies included in chapter 2. Where re-irradiation rates were reported these were pooled to provide an overall re-irradiation rate of 3.1% (19 patients out of 610 in the included cohorts).(171,174,176,178,183,186,187,194,198,202,204,212,215) Using the baseline hazard from the fractionated treatment strategy a hazard ratio of 0.82 was identified by manual calibration to provide this rate at 3-years post-treatment. Probabilistic values for this parameter were then drawn from the lognormal distribution. The standard error of the mean was estimated to be 0.4,

reflecting the wide uncertainty around this parameter. Whilst the rate incorporated here was taken from a large sample there is significant risk of bias in this estimate as discussed in chapter 2. In addition, high rates of surgical intervention in US based institutions (relative to UK practice) may reduce re-irradiation rates.

- Assumption - Re-irradiation following SABR reflects reported rates in US practise.

6.2.3 *Measurement and valuation of preference-based outcomes:*

Response state utilities

The response state utility values for the model were informed based on the outcomes presented in chapter 3. These used the HR-QoL data collected using the EQ-5D-3L in the DBMS. Valuation of the reported domain levels in each questionnaire used the UK value set published by Dolan in 1997.(233) The base-case model was informed by the mean utility for each response state from all returned follow-up questionnaires. The means for complete, partial, no response and pain progression response states were 0.633, 0.531, 0.360 and 0.256 respectively (Table 25 pg. 159). These outcomes were used for the base-case model with the standard errors used to inform a probabilistic draw from the normal distribution. The normal distribution of the mean is accepted based on the central limit theorem which demonstrates that the distribution of the mean is normal when based upon an appropriately large population (as seen in the DBMS dataset).(358) As the mean values are well separated from the upper bound of 1.0 and the lower bound of -0.594 and the standard errors are small, 10,000 simulated draws from the normal distribution resulted in no parameter values outside the acceptable range.

- Assumption – EQ-5D domain responses, in relation to pain following palliative radiotherapy, are the same in Dutch and UK populations.

- Assumption – In the base-case model it is assumed that missing data do not result in bias.

Utility decrement of treatment

Palliative radiotherapy is associated with side-effects which may be anticipated to reduce overall HR-QoL and hence utility following treatment. In order to identify the magnitude of this decrement the fixed effects model developed in chapter 3 was used with an additional co-variable included to represent the first weeks after treatment. Dummy variables were included to represent the first three weeks after either a single or fractionated treatment course (both following initial treatment or subsequent re-irradiation). The period over which the decrement was applied was assessed with models fitted incorporating 2, 3, and 4 week decrements. The model incorporating a 3 week decrement provided optimal model fit by AIC. The estimated utility decrement of single fraction treatment was -0.00816 (se = 0.0113), whilst for fractionated treatment it was -0.0254 (se = 0.010). This decrement was independent of pain response state. Given the limited toxicity

reported following SABR the utility decrement associated with a single fraction was used to inform the SABR strategy.

- Assumption – the utility decrement of SABR is equivalent to that seen following an 8Gy single fraction

Recognising the consequences of missing data on response state utilities

It is clear from chapter 3 that there are significant amounts of missing data in the DBMS (overall 27.98%). Different causes of missing data are well recognised as having varying consequences for outcomes. Where data are missing completely at random (MCAR) (e.g. a returned questionnaire was lost in the post) this will not result in bias in parameter estimates. Truly MCAR missing data are, however, uncommon. More frequently data are missing at random (MAR) or indeed, not at random (MNAR). Where data are MAR the probability of the being missing is independent of the value of unobserved data, conditional on the observed data. Predictions of the value the unobserved data takes can therefore be made based upon the observed data.(359) In the case of MNAR, however, the value of the unobserved data is conditional not only upon the observed data i.e. predictions of the unobserved value based upon surrounding observed values will be biased. Whilst the fixed-effects model in chapter 3 was expected to be robust to bias introduced by MAR, the mean utility values used to inform the model parameters will be biased even under MAR. This results from the finding that individuals closer to the end of life are more likely to have missing questionnaires whilst also having poorer HR-QoL. As such the observed mean health state utility values will systematically overestimate the true utility values and potentially bias the results of the cost-utility model.(360)

A range of possible methods exist to replace missing values. Last value carried forward and mean imputation are simple methods of replacement but in the context of terminal decline are unlikely to adequately reflect the changing patterns of utility, indeed these methods result in biased estimates even when data are missing completely at random (MCAR).(361) In addition these fail to recognise the uncertainty around the replacement of missing values, resulting in underestimation of uncertainty.(362) Inverse probability weighting (IPW) can be used where a monotone missing pattern is observed i.e. once a patient drops out they remain missing permanently. This approach weights the observed observations by the inverse probability of being observed i.e. if a value is observed when it was highly likely to be missing it will be weighted heavily. This can result in biased estimates if some individuals have very low probability of being observed, in this context it might be anticipated that those in the final weeks of life are extremely likely to have missing observations and thus where these results are available they will be heavily weighted, potentially introducing bias. In addition, whilst monotone missing is the predominant pattern observed here intermittent missing is also observed. The patterns of missingness observed were illustrated in Chapter 3.(362)

Multiple imputation (MI) is a regression technique which uses the available observed data to produce probabilistic predictions of the missing values based upon the distributions of the observed variables under an assumption of MAR.(360) Unlike single imputation (where a single full dataset is produced) MI produces multiple datasets in which each dataset contains a single value for each missing item taken from the posterior distribution. The datasets are then combined using Rubin's rules, thus maintaining the uncertainty in the predicted values (the standard errors being inappropriately reduced if the results from the multiply imputation datasets are simply combined).(359,363)

MI techniques traditionally assume the observed data follow a multivariate normal distribution. Where utility tariff values are considered this assumption is not justified; the range of values being -0.594 - 1.0 and the distribution of utilities non-normal.(364) As such, two challenges arise when carrying out multiple imputation with the DBMS dataset; the multi-level structure of the data must be recognised and the distributions of the variables respected. In addition it is possible to impute either the individual domains or the combined utility. It has previously been demonstrated that where the predominant pattern of missingness is unit non-response and a large sample size (>500) is available it is acceptable to impute the utility value directly rather than domains.(365)

In order to carry out multiple imputation within the DBMS whilst respecting the outlined concerns the *mice* package in R was used.(366) This supports MI by chained equations in a multilevel framework, using predictive mean matching (pmm)(to respect the non-normal distribution of the parameters), with categorical level 1 variables and in the presence of interactions and non-linear terms in the imputation equation.(365) Pmm is a method for multiple imputation which is based upon a linear regression model. Rather than the predicted values coming directly from the regression model, however, the coefficients of this model are drawn from the posterior predictive distribution. A predicted value for both observed and unobserved data items is produced and the predicted value of the unobserved missing data item is then replaced with the observed value from one of the five closest matches from the predicted data (i.e. k=5).(362,367) Here the pmm method was used to impute the pain response, pain score, utility and EQ-VAS scores based on baseline characteristics, observed HR-QoL outcomes, time from treatment and the restricted cubic spline (RCS) for time to death (TTD) identified in section 3.2.4. In order to provide a fully conditional model specification and to avoid imputing survival time (which was felt to be beyond the scope of this study and remains a limitation of the data), MI was only carried out for patients who were observed until death within the trial. Multiple imputation using *mice* was carried out recognising the clustering of observations within patients. 25 imputed datasets were created (see Figure 38) and the observed data for those censored at trial closure were then appended to each imputed dataset.(368) Whilst not providing a complete dataset this reduced the percentage missing from 27.98% to 8.39% with the aim of reducing bias as far as reasonably possible whilst retaining all observed data. Finally, imputed datasets were combined using Rubin's rules to determine the

combined mean and standard error of the response state utilities from the imputed datasets. The multiply imputed utility values were used to inform an alternative scenario in the cost-utility model.

Figure 38. Utility distributions for patients with known survival time within the DBMS a) 24Gy in 6 fraction arm, b) single 8Gy fraction arm. The blue line demonstrates the distribution of observed utility values, the red lines each represent a set of multiply imputed values (using pmm).
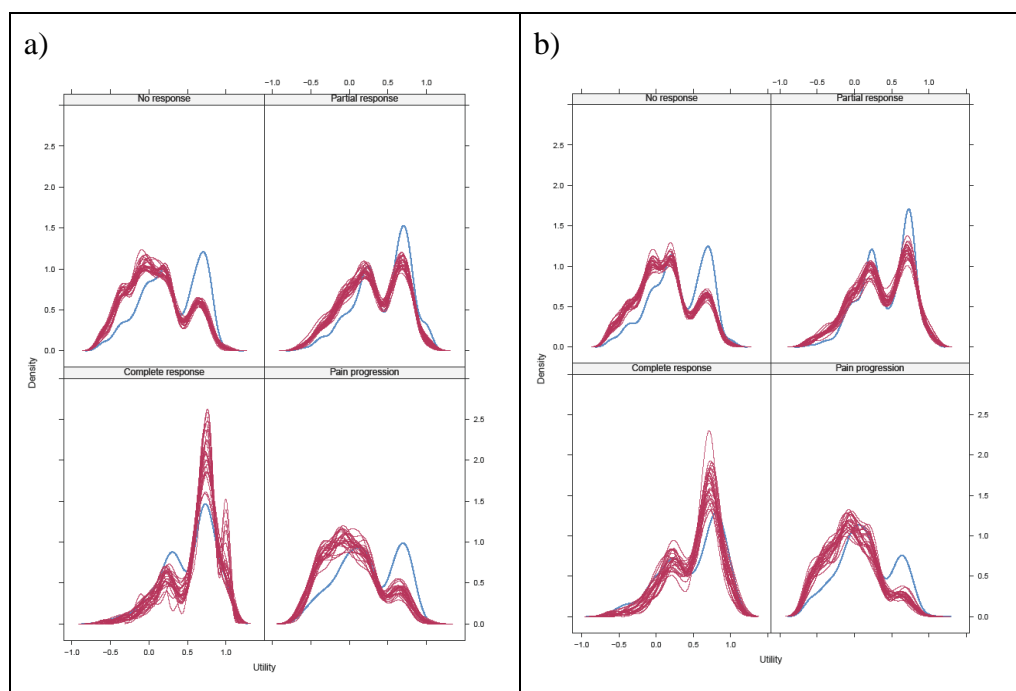
Finally, it was demonstrated in chapter 3 that the relationship between QOL and pain response is not constant with time to death. Given the interest here was modelling cost-effectiveness across populations with varying survival times further alternative scenario analyses were carried out to consider the impact of this heterogeneity of treatment effect. These analyses used utility values from patients with survival of less than 12 weeks and more than 9 months separately. Where those surviving less than 12 weeks were considered the multiply imputed utility values are used given the significant missing data seen in this population. Conversely where survival is over 9 months this is based on observed data due to the challenges of imputing outcomes beyond the trial period in a population with unknown survival time. Notably, less missing data were observed in this cohort. The utility values used are shown Table 25.

Table 25 Utility values. Mean (standard error).

	Observed	Observed <12 weeks	Observed >9 months	MI overall	MI <12 weeks
No response	0.360 (0.005)	0.065 (0.017)	0.452 (0.006)	0.303 (0.005)	0.011 (0.014)
Partial response	0.531 (0.004)	0.132 (0.021)	0.588 (0.005)	0.504 (0.005)	0.140 (0.020)
Complete response	0.633 (0.009)	0.065 (0.038)	0.685 (0.010)	0.615 (0.009)	0.260 (0.048)
Pain progression	0.256 (0.011)	-0.003 (0.031)	0.339 (0.013)	0.185 (0.012)	0.044 (0.040)

6.2.4 *Estimating costs*

Treatment costs

The costs of initial radiotherapy in the base-case model will be informed by a combination of the submitted NHS reference costs, supplemented by specialist commissioning tariff information for the stereotactic treatment arm (for which no reference costs are available yet).

The base-case model scenario uses the NHS reference cost prices for radiotherapy from 2015-16 to inform the cEBRT treatment strategies and outpatient appointment costs.(369) Radiotherapy costs are separated into treatment and delivery costs with complexity reflected in each element separately. The cost of planning an intensity modulated treatment plan with technical support is included in the reference costs and was used for the base-case model as the closest approximation of SABR planning costs. SABR treatment costs are not included in the reference costs, which pre-date the introduction of commissioning through evaluation (CTE). Tariff prices are, however, available for SABR delivered within CTE. As such, the costs of SABR delivery were accepted as the CTE tariff, minus the planning costs for IMRT with technical support, divided by the fraction numbers (three fractions in the base-case model, in line with that delivered within CTE). In this way both the costs of planning and treatment are incorporated separately. Uncertainty around the cEBRT, SABR planning and outpatient appointment costs were informed using a random draw from the lognormal distribution (based on the lower and upper quartiles of the NHS reference costs). This is not possible for the SABR treatment costs. Given the uncertainty around this value the interquartile range was intentionally wide (calculated average £697, IQR £300-£900). The number of centres providing costs is assumed to be the same as for the planning process (n=14).

- Assumption – SABR planning costs are the same as IMRT with technical support planning costs.

Alternative costing information to inform the one-way sensitivity analyses was included based on the TD-ABC model presented in chapter 5. In all cases the cost of the initial outpatient appointment (and therefore best-supportive care) was included based on the NHS reference costs.

Re-irradiation costs

Re-irradiation costs were again based upon NHS England tariff. It is assumed that re-irradiations are delivered using a single 8Gy fraction.(11)

- Assumption – Re-irradiation to the index site is carried out using a single 8Gy cEBRT treatment.

Health state costs

Costs associated with the modelled health states are required to estimate the costs resulting from varying treatment response probabilities. The health state costs were initially taken from the

DBMS. These were captured for only 166 patients in the study. Captured costs were in Dutch Guilders as the study ran from March 1996 to September 1998. In addition, costs questionnaires were completed by patients alongside alternate HR-QoL questionnaire. It is, therefore, challenging to relate the weekly costs to the reported response states. Given the different jurisdiction, prolonged time elapsed since the study period and the limited data available it was not possible to use the DBMS to determine health state costs. A logistic regression model was used to assess the relationship between health state and admission probability, however, the overwhelmingly driver of admissions was the use of chemotherapy. As such, the health state costs were estimated based on information from multiple data sources.

It has previously been demonstrated that individuals with pain due to cancer incur healthcare costs as a consequence of their pain.(370) In one US study 5% of inpatients with cancer reported a previous admission because of cancer pain.(371) Of an outpatient population with known cancer related pain, 8% of patients required hospitalization, 12.7% emergency department attendance and 44.7% a medical visit due to pain. Higher pain intensity predicted higher healthcare costs.(370) In this study despite analgesic requirements being the most frequently experienced driver of direct costs, hospitalizations accounted for 71% of all pain-related healthcare costs.

As such the major driver of costs in this population is likely to be inpatient admissions due to pain progression. Given the limited data, no further conclusions could be drawn. On this basis expert opinion was sought from three oncologists working within the NHS with the aim of identifying the expected proportion of individuals with pain progression who would be expected to require an inpatient admission. These experts estimated that pain progression would be associated with a 20% likelihood of admission with admissions in other response states more likely to reflect inter-current events. This estimate is in keeping with the results from Fortner et al. although slightly higher, a reasonable expectation given the progressive pain experienced by those in this health state.(370) The costs of these admissions were taken from PSSRU's Unit costs for health and social care.(372) Admissions were assumed to be of short duration and require inpatient palliative care review on two occasions. The total cost was multiplied by 0.2 (to recognise the proportion of individuals undergoing this event) and then divided by 2.6 to give a cost per week (the average (sojourn) time spent in the pain progression state in the *msm* model was 2.6 weeks (SE = 0.124)).

Fortner et al also identified higher costs resulting from opioid prescriptions in those with ongoing pain. The proportion of individuals on strong opioids for each of the four response states was determined using the DBMS dataset. The analgesia used within the trial is, however, not standard within UK practice and, therefore, not suitable to inform the economic model. Zeigler et al assessed the use of opiate based analgesia in cancer patients in the final year of life in the UK.(373) This provides information to inform the type of oral strong opiate analgesia used. Monthly costs of each type of analgesia were taken from the British National Formulary (BNF) online and converted to weekly costs.(374)

Uncertainty around the response state costs was defined using the interquartile range from PSSRU costs to provide a log-normal distribution, standard error of the sojourn time to define a normal distribution, beta distribution for the proportion of patients requiring strong opiates in each response state and Dirichlet distribution for the proportion of patients on different types of opiates.

- Assumption – Health state costs are independent of treatment strategy.

- Assumption – Admission for pain control is only seen where patient's pain deteriorates from baseline.

An alternative model scenario incorporates health state costs based on the IMPACTT study (personal communication D Meads 2019). The health states recognised in the IMPACCT model represent varying levels of pain (rather than response categories). The utilities associated with these states were available (No/mild pain – 0.525, Moderate pain – 0.423, Severe pain – 0.148). These align to an extent with those observed in the DBMS study although with no state equivalent to the complete response state reported in the DBMS. The health state costs of the partial response, no response and pain progression states are therefore taken from these data and an estimate of the complete response state costs made based on the moderate pain costs minus the no/mild pain state costs. Given the differing populations and health states considered these estimates are to be considered indicative only, supporting assessment of the consequences of variation in the health state costs.

6.2.5 *Parameter estimates*

Table 26. Base-case parameter values and probabilistic sensitivity analysis distributions

Parameter	Base-case estimate	Distribution	Distribution parameters	Source
Survival (median weeks)	34	Weibull (proportional hazard)	Shape = 0.927 Scale = 0.026	Fitted to DBMS data
Mean utility				
Complete response	0.633	Normal	se = 0.009	DBMS data
Partial response	0.531	Normal	se = 0.004	DBMS data
No response	0.360	Normal	se = 0.005	DBMS data
Pain progression	0.256	Normal	se = 0.011	DBMS data
Utility decrement				
Single fraction	-0.008	Normal	se = 0.011	DBMS data
Multiple fraction	-0.025	Normal	se = 0.010	DBMS data
SABR	-0.008	Normal	se = 0.011	As per single fraction decrement
Transition probabilities				
Single 8Gy cEBRT (% response at 6 months)	CR = 14 PR = 35	Bootstrapped from multi-state model	-	DBMS data
Fractionated cEBRT (% response at 6 months)	CR = 15 PR = 35	Bootstrapped from multi-state model	-	DBMS data
SABR (% response at 6 months)	CR = 52 PR = 20	Sequential Dirichlet distributions	-	Calibrated to Sprave et al.
Best supportive care (% response at 6 months)	0	Bootstrapped from multi-state model	-	DBMS – data pre-cEBRT

Proportion re-treated

Fractionated cEBRT (% at 6 months)	3.3	Gompertz - Multivariate- normal	Theata = -0.025 Lambda = -5.596 Coef = 1.388	DBMS data
Single 8Gy radiotherapy (% at 6 months)	13.8	Gompertz - Multivariate- normal	Theata = -0.025 Lambda = -5.596 Coef = 1.388	DBMS data
SABR (% at 6 months)	2.1	Lognormal	mu = -1.139 sigma = 0.668	Calibrated to Chapter 2 results
Best supportive care (% at 6 months)	-	-	-	-
Radiotherapy costs				
Outpatient appointment	£168	Lognormal	LQ = 122, UQ = 216, n = 92	NHS reference costs
Planning costs - simple calculation	£324	Lognormal	LQ = 198, UQ = 464, n = 13	NHS reference costs
Treatment costs - unimaged	£107	Lognormal	LQ = 82, UQ = 127, n = 14	NHS reference costs
Planning costs - SABR	£1,548	Lognormal	LQ = 934, UQ = 2376, n = 14	NHS reference costs, Tariff 2016-19
Treatment costs - SABR	£697	Lognormal	LQ = 300, UQ = 900, n = 13	NHS reference costs, Tariff 2016-20
Health state costs				
Cost of short admission	£628	Lognormal	LQ = 425, UQ = 733, n = 10000	PSSRU
Cost of specialist palliative care input per day	£104	Lognormal	LQ = 53, UQ = 119, n =10000	PSSRU
Morphine costs per week	£5.67	-	-	BNF
Oxycodone costs per week	£19.06	-	-	BNF
Fentanyl costs per week	£15.71	-	-	BNF
Probability of opiate prescription				
Complete response	9.3	Beta	α = 148, β = 1440	DBMS data
Partial response	16.7	Beta	α = 902, β = 4506	DBMS data
No response	37.9	Beta	α = 2101, β = 3442	DBMS data
Pain progression	41.8	Beta	α = 551, β = 768	DBMS data
Opiate analgesia type (morphine, oxycodone, fentanyl)		Dirichlet	αs = 2231, 681, 632	Zeigler et al.

6.2.6 *Analytic methods:*

Cost-effectiveness was assessed using the Incremental Net Health Benefit (INHB) and, for the two-way comparison between single fraction cEBRT and SABR, the Incremental Cost-Effectiveness Ratio (ICER). The ICER represents the amount which would need to be spent on a treatment to deliver one extra QALY, whilst the INHB is the additional QALYs gained by delivering this treatment at a specified willingness to pay threshold (WTPT). The base-case WTPT was £30,000/QALY. The interpretation of the ICER is complex, particularly where treatment is associated with reduced costs or QALYs, and hence only being presented in limited analyses.

An initial deterministic estimate of the NHB associated with each treatment strategy was produced and the INHB assessed for each strategy compared to the single fraction cEBRT standard of care.(375)

6.2.6.1   One-way sensitivity analyses

Comparing each strategy to the single fraction cEBRT standard one-way sensitivity analyses were used considering a range of deterministic parameter values to investigate which had the greatest influence over cost-effectiveness.(346) All input parameters were varied to reflect an extreme but plausible range of values. In the case of cost parameters, these were the lower and upper quartile values. For normally distributed and survival parameters these reflected the upper and lower 95% confidence intervals. Plausible ranges for the response state transition probabilities were informed in different ways for the four strategies: In the cEBRT strategies these were based on alternative scenarios incorporating the primary diagnosis co-variable in the *msm* model (lung/other primary vs breast/prostate cancer providing the lower and upper values respectively); in the best-supportive care strategy no response without treatment represents the lower value, whilst response informed by the fitted *msm* model for lung/other primary cancer patients undergoing cEBRT provides the upper value; finally calibration to the other published outcomes identified in section 2.2.3.6 was used to inform the range of possible values following SABR.(168,185) The variation in cost-effectiveness, as measured by the INHB relative to the single 8Gy cEBRT strategy, was then illustrated using tornado plots.

Table 27. Parameter values to inform one-way sensitivity analysis.

Parameter	Base-case estimate	Lower limit	Upper limit
Survival (median weeks)	34	22	52
Mean utility			
Complete response	0.633	0.61536	0.65064
Partial response	0.531	0.52316	0.53884
No response	0.360	0.3502	0.3698
Pain progression	0.256	0.23444	0.27756
Utility decrement			
Single fraction	-0.008	-0.02956	0
Multiple fraction	-0.025	-0.0446	-0.0054
SABR	-0.008	-0.02956	0
Transition probabilities (% response at 6 months)			
Single 8Gy cEBRT	CR = 14 PR = 35	CR = 9 PR = 28	CR = 15 PR = 37
Fractionated cEBRT	CR = 15 PR = 35	CR = 10 PR = 27	CR = 17 PR = 37
SABR	CR = 52 PR = 20	CR = 38 PR = 19	CR = 68 PR = 0
Best supportive care	CR = 5 PR = 22	0	CR = 9 PR = 28
Proportion re-treated (% at 6 months)			
Fractionated cEBRT	3.3	2.20%	5.20%
Single 8Gy cEBRT	13.8	10.00%	19.00%
SABR	2.1	1.30%	2.60%
Best supportive care	-	-	-
Radiotherapy costs (£)			

single 8Gy cEBRT	587	402	807
Fractionated cEBRT	959	730	1315
SABR	3785	1956	5292
Best-supportive care	214	122	216
Health state costs (per week) (£)			
Complete response	1.074	0.576	1.729
Partial response	1.923	1.153	3.458
No response	4.369	2.306	5.764
Pain progression	69.123	22.074	171.002

Given the marked impact of SABR costs upon the modelled cost-effectiveness of this strategy further one-way sensitivity analyses investigating the consequences of varying these costs were considered. Multiple approaches to considering these costs were taken to inform one-way sensitivity analyses. These represent values base on the 2015/16 reference costs and tariff prices in addition to incorporating costs derived from the TD-ABC model in chapter 5. These latter estimates recognise the impact of the learning curve on costs of treatment as the treating department becomes more confident in their abilities to safely deliver these treatments.(120) For this analysis the costs of the initial outpatient appointment remained constant for all strategies (£214).

- The consequences of varying the number of SABR fractions was assessed based on the 15/16 reference costs and tariff prices (Single fraction SABR = £2,459, five fractions = £5,247).

- Anticipated long-term treatment costs derived from the current reference costs were then used. These assume the planning costs reflect those of an IMRT adaptive treatment whilst the treatment costs drop to reflect the current tariff for adaptive complex treatment delivery. The total deterministic cost for a three fraction SABR treatment in this scenario being £2,055.

- Base-case TD-ABC: single fraction cEBRT = £386.60 and three fraction SABR = £2788. In the case of SABR this reflects the costs in the first two years following implementation, assuming the implementation costs (both staff and capital) are shared between 150 patients over the first 3 years.

- The marginal costs of treatment were derived from the TD-ABC values. These were the costs which would be released if treatment were forgone. These were extremely limited in the case of single fraction cEBRT (initial outpatient costs and immobilisation devices), however, in the case of SABR reflected capital and staff investment costs in addition to individual level phantom-based QA and extra online-imaging to confirm accuracy of treatment setup.

- SABR costs in the third year following implementation (assuming phantom-based individual quality assurance is no longer required and the time on the treatment machine is reduced to reflect reduced online-imaging requirements): £2,171.

- SABR costs beyond the three year implementation period: £1,793.

The incremental QALYs and costs of each parameterisation were then tabulated alongside the ICER (for SABR compared to single fraction cEBRT) for each parameterisation.

6.2.6.2   Probabilistic sensitivity analyses

Probabilistic sensitivity analysis (PSA) was carried out incorporating the parameters and distributions detailed in Table 26 for the four treatment strategies. Incremental comparisons between strategies with increasing QALY gain were than tabulated alongside two-way comparisons between single fraction cEBRT and all other strategies. The cost-effectiveness plane for all strategies compared to single fraction cEBRT was then produced. Cost-effectiveness acceptability frontiers (CEAFs) were then produced to illustrate the outcomes of the PSA analysis for all four strategies.

6.2.6.3   Expected value of perfect information (EVPI) analysis

The limited information available to inform the SABR treatment arm parameters is a significant limitation of the current model. Limited randomised data exists and as such it was important to understand the possible consequences of this lack of information, what the value of future research in this area may be and which parameters are of greatest priority to the decision-making process. In order to achieve this a 'value of information' analysis was completed via the Sheffield Accelerated Value of Information online tool.(376) Parameters, QALYs and costs for 10,000 simulations of the single fraction and SABR strategies were uploaded to the SAVI website. Two alternative assumptions of cost were considered recognising both the currently commissioned price and expected long-term treatment costs once SABR is embedded in routine practice. For the purposes of this analysis it was estimated that the decision will impact upon 2,500 patients per year nationally.

6.2.6.4   Alternative PSA model parameterisations

A number of alternative parameterisations were considered using PSA. These aimed to more fully characterise the consequences of variation in the input parameters of the model. As previously, the ICER is only presented for the single fraction cEBRT vs SABR comparison with all other outcomes reported using the INHB. The following analyses were carried out:

1) Missing utility data

In order to assess the consequences of missing utility data, on the cost-effectiveness outcomes, the multiply imputed utility values were used to inform the model (Table 25). The impact of this alternative parameterisation was considered for two-way comparisons between best-supportive care and SABR with single fraction cEBRT.

2) Alternative SABR response probabilities

Given the variation in the ICER for SABR compared to single fraction cEBRT on one-way sensitivity analysis, alternative parameterisations of the response probabilities for the SABR strategy were used. These reflect calibration of the transition probabilities to the other two studies identified in chapter 3 and provided a range of outcome estimates.(168,185,217) Base-case SABR and anticipated long-term SABR costs were then incorporated for each parametrisation of the transition probabilities. The INHB associated with each parameterisation was presented graphically.

3) Alternative health state costs

Given the significant uncertainty in the parameterisation of the health state costs alternative costs were used reflecting those collected in the IMPACTT study and taken from a log-normal distribution. The impact of this upon the two-way comparisons between best-supportive care and SABR with single fraction cEBRT were reported.

4) Exploring Heterogeneity

The published literature to date would suggest that the likelihood of response to palliative cEBRT is significantly affected by subsequent survival time.(92,93) Given this finding and the results demonstrated in chapter 3 the consequences of this heterogeneity were further investigated. The model was used to assess the outcomes in two additional cohorts:

The first cohort considered had a median survival time of 53.3 weeks (37% of patients in this cohort were deceased before 36 weeks and 95% by 3.18 years). The survival probability was modified using the addition of a hazard ratio to the Weibull parametric survival function. The transition probabilities and utilities for this cohort were informed using the observed utility values from those treated in the DBMS with a survival of more than 9 months and an *msm* model fitted to this cohort's response data.

The second cohort modelled had a median survival time of 6.2 weeks, 75% of this cohort died by 12 weeks and 95% by 38 weeks. The response probabilities (from a fitted *msm* model) and utilities for this cohort were informed based on those of patients treated in the DBMS with a survival time below 12 weeks. Given the extent of missing data in this population (51% of questionnaires) and availability of time to death data for the whole population, in this scenario the multiply imputed

utilities were incorporated; for completeness a further analysis in the cohort with very limited survival was carried out incorporating the observed utility values from the DBMS. Finally, recognising the possible consequences of alternative parameterisations of the health state costs the two-way comparison between single fraction cEBRT and best-supportive care was further assessed incorporating the costs collected within the IMPACCT study for this population with very short survival time.(377)

Given the finding that there is a high likelihood that best-supportive care represents the most cost-effective treatment option in a patient group with very short survival further EVPI analysis was carried out to investigate this analysis. Single fraction radiotherapy remains the standard of care for this group with some authors suggesting that given the QoL benefits and time to response, palliative radiotherapy should be used irrespective of prognosis. The EVPI analysis was carried out assuming 2000 patients per year were affected in England. Initially a WTPT of £30,000/QALY was incorporated, however, in order to investigate the expected value of perfect parameter information (EVPPI) further this threshold was raised to £300,000/QALY (the QALY gain was very small in this cohort). EVPPI results are presented at this latter WTPT.

6.2.6.5 Impact of equity weighting for End of Life populations

There is much discussion in the Health Economics literature about the "QALY problem" in the context of palliative care.(265,378) One possible means to address what some consider to be a limitation of the current cost-effectiveness methods is to incorporate an equity weight. This allows greater value to be placed on some QALYs than others e.g. QALYs gained within the final months of life might be more highly valued than those gained by patients with longer survival. This is explicitly accepted by NICE for treatment delivered in the final two years of life with an associated improvement in survival of at least 3 months through the acceptance of the £50,000/QALY threshold. The relevance of this threshold for the current intervention is questionable given the lack of survival advantage.

Given the finding that, compared to BSC, single fraction cEBRT was not cost-effective in a cohort with very short survival, further investigation was carried out. In order to assess the extent to which this result was a reflection of the reduced clinical effectiveness of treatment in this cohort the model was parameterised based on the transition probabilities and utilities of patients with survival of more than nine months from the DBMS but maintaining the short survival time.

In light of the possibility that QALYs near the EoL may be considered to have greater value than at other times a further analysis was carried out in order to investigate the impact of equity weights upon the cost-effectiveness of cEBRT in the final 12 weeks of life. The NHB of each intervention was plotted at a WTPT of £30,000/QALY after incorporating incrementally increasing equity weights between 0 and 10 (at increments of 0.1). This was presented graphically to illustrate the equity weight required to make treatment in this EoL population cost-effective.

6.2.6.6   Re-framing the CEAF in the context of survival time

In routine practice the population receiving palliative radiotherapy for bone metastases shows marked heterogeneity, particularly in terms of their survival time. Clinicians recognise this heterogeneity in the treatment decisions they make; the 30-day mortality of patients receiving a single 8Gy fraction is markedly higher than that of patients receiving more fractionated treatment.(6) In order to assess the cost-effectiveness of the varying treatment strategies in the context of differing survival times, a further probabilistic sensitivity analysis was carried out. This model incorporated the anticipated long-term costs of SABR treatments alongside base-case parameters for all other inputs. A threshold sensitivity analysis was used to vary the survival probability of the treated cohort via the addition of a hazard ratio (incorporated at increments of 0.01 in the range from 0.05 to 10). 10,000 simulations per hazard ratio were used. The probability of each strategy being the most cost-effective was then presented graphically relative to both the populations 30-day mortality and median survival, at a WTPT of £30,000/QALY.

6.2.6.7   Outcome based pricing of SABR for bone metastases in the English NHS

Given the demonstration that the strategy most likely to be cost-effective varies widely with population survival, whilst the treatment costs of SABR will also vary during implementation, a means to incorporate this into commissioning was sought. Using the same threshold sensitivity analysis outlined above the costs and QALYs associated with the SABR and single fraction cEBRT were identified using 1,000 simulations at each hazard ratio. Rearranging the NHB formula provided an outcome-based price (OBP) for SABR based upon a WTPT of £30,000/QALY (Equation 8). The OBP was then presented graphically against its associated 30-day mortality and median survival with 5th, 25th, 75th and 95th quantiles to demonstrate uncertainty around this value. Using the varying costs of SABR derived from the TD-ABC model the 30-day mortality/median survival of the treated population which would be associated with the cost-effective delivery of these treatments was identified.

Equation 8. Calculation of the outcome based price of SABR. λ (WTPT) is defined separately wherever this formula is used. hs represents the ongoing health state costs following treatment.

$$C_{SABR} = C_{cEBRT+cEBRT(hs)} - C_{SABR(hs)} + (\Delta E \times \lambda)$$

6.2.6.8   Clinical outcomes

Finally, given the demonstration of a lack of cost-effectiveness from single fraction cEBRT in a population with a median survival of 6.2 weeks, the Markov model was used to provide an expectation of clinical benefit for patients with survival times of less than 12 weeks. This aims to provide more clinically meaningful predictions of benefit in this population. For the purposes of this model the EQ-VAS was used to assess HR-QoL as this provides a measure of overall health based on the patient's own perception rather than the societal valuation of the EQ-5D-3L. As

previously, given the extent of missing data in this population, this model was informed using multiply imputed EQ-VAS values (in this case the MI model incorporated the interaction between the TTD RCS and pain response). Response state transition probabilities were informed by the *msm* model fitted to the observed outcomes for a population with survival of less than 12 weeks. Survival time was fixed, incrementally, as two to twelve weeks post-treatment.

Two outcomes were reported from this model: The expected cumulative number of VAS points per week gained over the patient's remaining life; and the absolute increase in probability of response on a weekly basis following single fraction cEBRT as compared to best-supportive care. As previously, the possibility of pain response in the absence of treatment was acknowledged in the best-supportive care strategy based on the *msm* model fitted to the reported outcomes prior to treatment in the DBMS. This analysis included only 1000 simulations as a means to provide an illustration of outcomes. Uncertainty in this analysis was represented by the 2.5[th] and 97.5[th] quantiles of the simulated estimates of each outcome.

6.3   Results

As outlined above the cost-effectiveness model developed here provides the opportunity to address a number of questions. The results of the these analyses are presented in the order outlined within the analysis section.

6.3.1   *Base-case Incremental costs and outcomes*

In comparison to BSC, single fraction cEBRT offered an INHB of 0.028 QALYs (incremental QALYs 0.046 and costs £551), whilst fractionated cEBRT offered an INHB of -0.011 compared to single fraction cEBRT (incremental QALYs -0.037, incremental costs £303). The SABR strategy was associated with an incremental QALY gain of 0.055 QALYs and incremental costs of £3,066 compared to single fraction cEBRT. The ICER for this scenario was £56,230/QALY with an INHB of -0.048 QALYs at a WTPT of £30,000/QALY.

6.3.2   *One-way sensitivity analyses*

One-way sensitivity analyses to investigate the factors influencing the cost-effectiveness of SABR compared to single fraction cEBRT revealed the parameters with the greatest impact upon the cost-effectiveness of SABR were the median survival of the population (INHB range -0.048 - -0.010), response rates to treatment (INHB range -0.057 - -0.015 in the case of complete response following SABR) and costs of radiotherapy (INHB -0.089 - -0.048 for SABR costs). The utility value associated with the complete response state also had a modest effect (INHB range -0.053 - -0.043). Conversely where the comparison with best-supportive care was made the costs became less important, whilst survival time and response rate retain their impact. Tornado plots

illustrating the impact of one-way sensitivity analyses for each of the three strategies in comparison to single fraction cEBRT are shown in Figure 39.

Figure 39. Tornado plots displaying one-way sensitivity analyses for a) SABR vs single 8Gy comparison, b) Best-supportive care vs single 8Gy comparison and c) Fractionated vs single 8Gy comparison.

a)

b)

c)
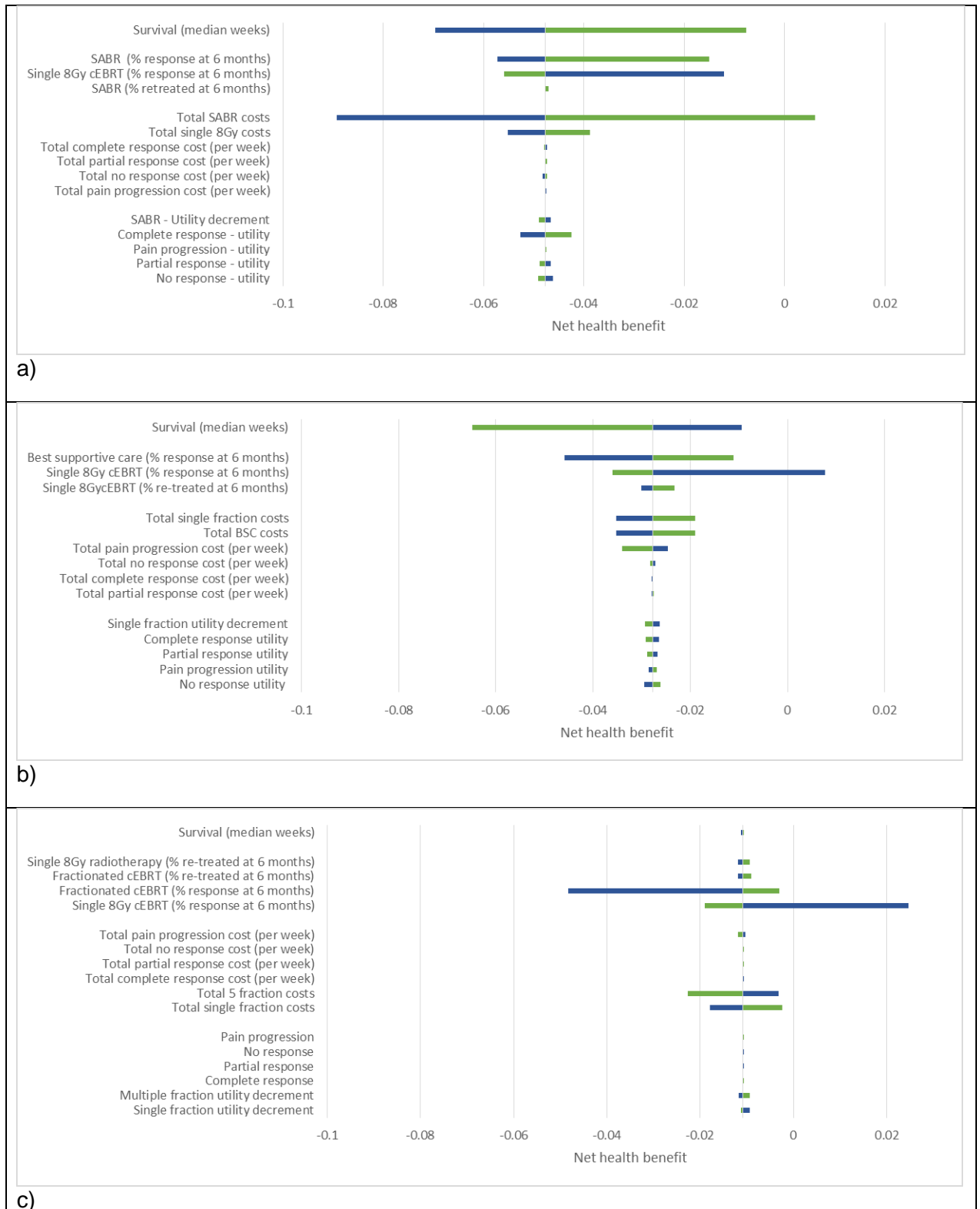
Based on the differing assumptions of the TD-ABC model the cost-effectiveness of SABR was determined at varying points over time following implementation (see Table 28). It can be seen

that if the assumptions of the TD-ABC model are met (most importantly the numbers treated over the first 3 years) the SABR treatment strategy becomes cost-effective beyond the 3 year implementation period with an expected ICER of £23,325 /QALY. Similarly, recognising that the tariff price paid for each treatment is likely to reduce in future (to more in line with those currently reimbursed for adaptive IMRT treatment delivery) reduces the ICER markedly (from £56,230 to £28,431, or even £22,231 if single fraction treatment is delivered).

Table 28. One-way sensitivity analysis of the consequences of varying SABR costs. *Anticipated long-term treatment costs based on current IMRT adaptive tariff cost per fraction. † Base-case costs. ** Marginal costs derived from the TD-ABC values (i.e. those which would be released if treatment were forgone).

	Treatment costs (£)	QALYs	Costs (£)	Incremental QALYs	Incremental costs	ICER (£ /QALY)
Single fraction base-case†	373	0.401	1185	-	-	-
Single fraction (TD-ABC - total)	387	0.401	1201	-	-	-
Single fraction (TD-ABC - marginal)	2	0.401	737	-	-	-
SABR 1 fraction (BC) †	2245	0.456	2925	0.05	1740	**31,915**
SABR 3 fraction (BC) †	3571	0.456	4251	0.05	3066	**56,230**
SABR 5 fractions (BC) †	5033	0.456	5713	0.05	4528	**83,039**
SABR 1 fraction (long-term costs)*	1717	0.456	2397	0.05	1212	**22,233**
SABR 3 fractions (long-term costs)*	2055	0.456	2735	0.05	1550	**28,431**
SABR TD-ABC 3 fraction (Marginal costs only)	995	0.456	1664	0.05	927	**16,993**
SABR TD-ABC 3 fractions (Long-term costs)*	2007	0.456	2473	0.05	1272	**23,325**
SABR TD-ABC 3 fractions (Year 3 costs)	2385	0.456	2851	0.05	1666	**30,556**
SABR TD-ABC 3 fractions (Years 1-2 costs)	2788	0.456	3468	0.05	2267	**41,575**

6.3.3 *Incorporating uncertainty - Probabilistic sensitivity analysis*

SABR was associated with mean QALYs of 0.458 (95% CI 0.407-0.509) and mean costs of £4,336 (95% CI £3,255 - £5,772). In comparison, single fraction cEBRT was associated with 0.401 QALYs (0.370-0.435) and costs of £1211 (95% CI £811 - £1972). This resulted in an incremental cost-effectiveness ratio (ICER) of £55,592 per QALY for SABR compared to single fraction cEBRT in the base-case scenario.

The fractionated cEBRT strategy delivered 0.400 QALYs (95% CI 0.369-0.434) with associated costs of £1525 (95% CI £1139 - £2215). As such, fractionated treatment was dominated by single fraction in the base-case scenario.

Table 29 shows the incremental costs and QALYs of each strategy at the base-case. In 89% of simulations single fraction cEBRT was the most cost-effective strategy with fractionated cEBRT (6%), SABR (4%) and best-supportive care (0.1%) being unlikely to be the most cost-effective at

a WTPT of £30,000/QALY. Figure 40 and Figure 41 illustrate these results as both a cost-effectiveness plane and cost-effectiveness acceptability frontier (CEAF).

Given that fractionated cEBRT was dominated at the base-case and best-supportive care was associated with negative incremental QALYs and costs, all subsequent results for these strategies will be presented using net health benefit; the expected net health benefit (in QALYs) delivered by the treatment given the specified WTPT. The ICER will continue to be used for SABR; the question of reimbursement of this strategy remains an open one and with the expected ICER being in the North-East quadrant the ICER provides meaningful information.

Table 29. Incremental QALYs and costs of differing treatment strategies. For INHB calculation λ=£30,000/QALY. Initially demonstrated as incremental comparisons between all four treatments (A) and then with comparison of each alternative strategy to the single fraction strategy (B).

	Incremental QALYs			Incremental costs			ICER	Mean INHB
A)	Mean	L95%CI	U95%CI	Mean	L95%CI	U95%CI		
Best-supportive care	-	-	-	-	-	-	-	-
Fractionated treatment	0.047	0.029	0.064	725	275	984	15,507	0.023
Single 8Gy treatment	0.001	-0.011	0.013	-314	-445	-143	Dominates	0.012
SABR	0.056	0.016	0.092	3125	2087	4404	55,211	-0.048
B)								
Single 8Gy treatment	-	-	-	-	-	-	-	-
Fractionated treatment	-0.001	-0.013	0.011	314	143	445	Dominated	-0.011
SABR	0.056	0.016	0.092	3125	2087	4404	55,211	-0.048
Best-supportive care	-0.048	-0.066	-0.030	-411	-657	9	10,972	-0.034

Figure 40. Cost-effectiveness plane illustrating the incremental costs and QALYs of the differing treatment strategies compared to single fraction cEBRT based on base-case parameter values. λ=£30,000/QALY. Light blue = fractionated cEBRT, dark blue = best-supportive care and purple = SABR.
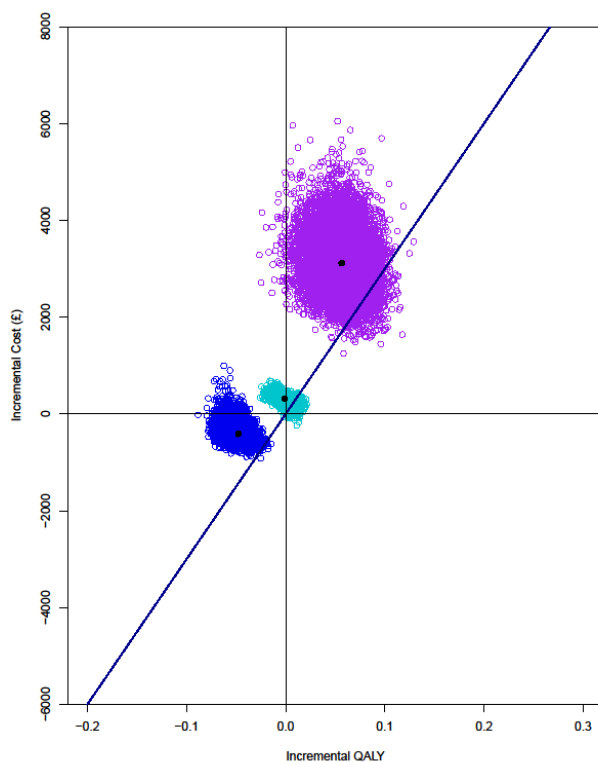
Figure 41. Cost-effectiveness acceptability frontier for single fraction cEBRT, fractionated cEBRT, best-supportive care and SABR. All parameters set to the base-case. Light blue = fractionated cEBRT, green = single fraction cEBRT, dark blue = best-supportive care and purple = SABR
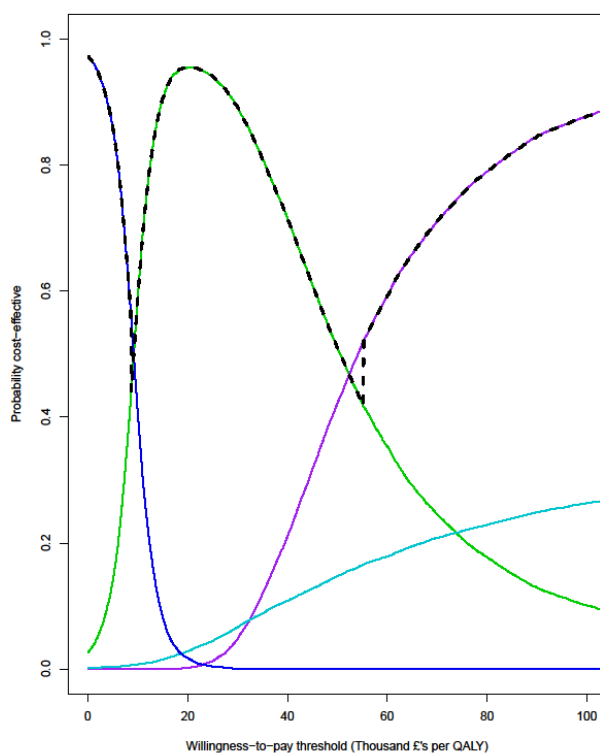
6.3.3.1 Expected value of perfect information (EVPI) for SABR versus single fraction cEBRT

The EVPI was heavily dependent upon the SABR treatment costs. Assuming base-case costs of SABR, with 2,500 patients affected by the decision each year and a WTPT of £30,000 the overall EVPI was £36,410 per year. Conversely, assuming that the costs of SABR reflect the anticipated long-term costs of treatment delivery the uncertainty in the model parameters had a much greater influence with the overall EVPI rising to £525,265 per year. The parameters having the greatest influence over this outcome were the response rates at 6 months post SABR (totalling £297/year in the base-case scenario and £607,000/year assuming anticipated long-term costs) and costs of SABR (£142/year and £112,500/year). Expected value of perfect parameter information (EVPPI) outcomes are presented in Table 30.

Table 30. Expected value of perfect parameter information based on either anticipated long-term costs and base-case costs separately.

	Anticipated long-term costs			Base-case costs		
	Per Person EVPPI (£)	SE	Indexed to Overall EVPI = 1.00	Per Person EVPPI (£)	SE	Indexed to Overall EVPI = 1.00
Pain progression 6mths SABR	125.78	2.84	0.6	0	0	0
Partial response 6mths SABR	0	0	0	0	0	0
Complete response 6 mths SABR	117	2.75	0.56	0.12	0.03	0.01
Cost - SABR	45.01	2.7	0.21	0.06	0.06	0
Cost - single fraction cEBRT	0	0	0	0	0	0
Pain progression 6 mths cEBRT	1.27	0.57	0.01	0	0	0
Partial response 6 mths cEBRT	0	0	0	0	0	0
Complete response 6 mths cEBRT	0.04	0.08	0	0	0	0
Re-irradiation at 6 months - cEBRT	0.95	0.74	0	0	0	0
Re-irradiation at 6 months - SABR	0.95	0.72	0	0	0	0
30 day mortality	0	0	0	0	0	0
Utility of no response	0	0	0	0	0	0
Utility of complete response	0.08	0.1	0	0	0	0
Utility of partial response	0	0	0	0	0	0
Utility of pain progression	0	0	0	0	0	0
Utility decrement of treatment	0	0	0	0	0	0
Cost - No response	0	0	0	0	0	0
Cost - Partial response	0	0	0	0	0	0
Cost - complete response	0	0	0	0	0	0
Cost - pain progression	0	0	0	0	0	0

6.3.3.2   Alternative probabilistic scenario analyses:

6.3.3.3   Assessing the consequences of missing utility data

Recognising the potential impact of missing data, upon the estimated NHB of the modelled strategies, had limited impact upon the modelled cost-effectiveness of fractionated cEBRT or best-supportive care. This analysis did not result in a change of the overall model conclusions. In these strategies the inclusion of multiply imputed utility parameters resulted in an INHB of -0.012 for fractionated cEBRT compared to single fraction cEBRT (95%CI -0.029 -0.006 and probability of being most cost-effective 7% in the four-way comparison) and -0.042 for best-supportive-care compared to single fraction cEBRT (95% CI -0.070 - -0.018 and probability of being most cost-effective 0.2% on four-way comparison). The INHB of SABR increased to -0.037 (95%CI -0.105 - 0.022) (with the ICER falling to £46,799) with a 12% probability of SABR being the most cost-effective of the four modelled treatment strategies at a WTPT of £30,000 /QALY.

6.3.3.4   Alternative treatment response assumptions following SABR

Given the limitations of the available literature demonstrated in section 2.2, alternative scenarios were modelled to reflect varying response probabilities following SABR. Incorporating response rates calibrated to these alternative studies had a significant impact upon the cost-effectiveness of SABR. The INHBs of SABR, assuming varying response and cost scenarios, are illustrated in Figure 42. At a WTPT of £30,000/QALY this ranged from -0.057 (95% CI -0.112 --0.005), assuming base-case costs and response rates in line with Balagamwala et al, to 0.0394 (95% CI -0.013-0.090), assuming anticipated long-term costs and response rates in line with Kim et al.(168,185)

Figure 42. Incremental NHB of SABR compared to single 8Gy fraction cEBRT based on varying assumptions of efficacy and costs. λ=£30,000/QALY
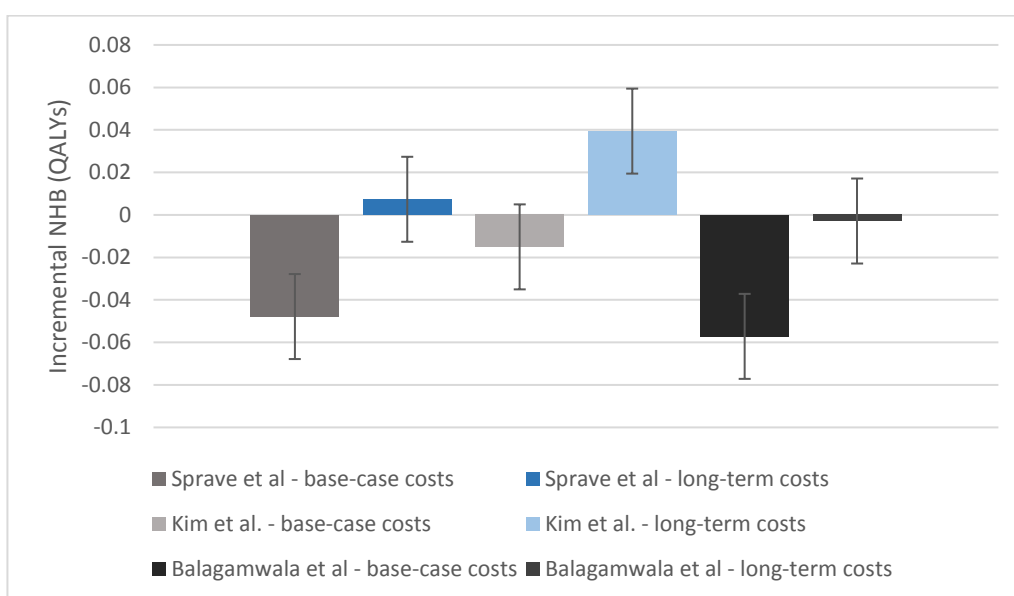
The probability that SABR was more cost-effective than single 8Gy cEBRT also varied widely. Both response rates and cost impacted upon this, although, as demonstrated in Figure 42 it was the cost which had the greatest influence. Scenarios incorporating anticipated long-term costs showed a positive INHB (excepting those where transition probabilities reflect those seen in Balagamwala et al. (-0.003 (95% CI -0.047 - -0.042). The probability of being cost-effective in these scenarios at a £30,000/QALY WTPT ranged from 45% to 93% depending upon the transition probabilities used. Conversely, irrespective of response parameters, SABR delivered a negative average INHB when current CTE reimbursement costs were accepted; the probability of cost-effectiveness at a WTPT of £30,000/QALY was only 2-32%.

6.3.3.5 Alternative health state costs

An alternative parameterisation of the health state costs was carried out, incorporating the costs collected in the IMPACCT study. This change in health state costs resulted in an expected INHB for SABR compared to single fraction cEBRT of -0.021 (95% CI -0.099- 0.073) with SABR having a 27% probability of being the most cost-effective strategy at a WTPT of £30,000/QALY. The CEAF for this scenario is shown in Figure 43. The ICER for SABR in this scenario was £41,413/QALY. Notably, the inclusion of the health state costs derived from the IMPACCT study results in single fraction cEBRT remaining the most cost-effective strategy at almost all thresholds up to the point where SABR becomes cost-effective. Where the two-way comparison between single fraction cEBRT and best-supportive care was considered, best-supportive care resulted in an INHB of -0.051 (95%CI -0.103 - -0.020).

Figure 43. Cost-effectiveness acceptability frontier for the overall treated population incorporating costs taken from the IMPACCT study. Dark blue = best supportive care, green = single fraction cEBRT, purple = SABR, light blue = fractionated cEBRT.
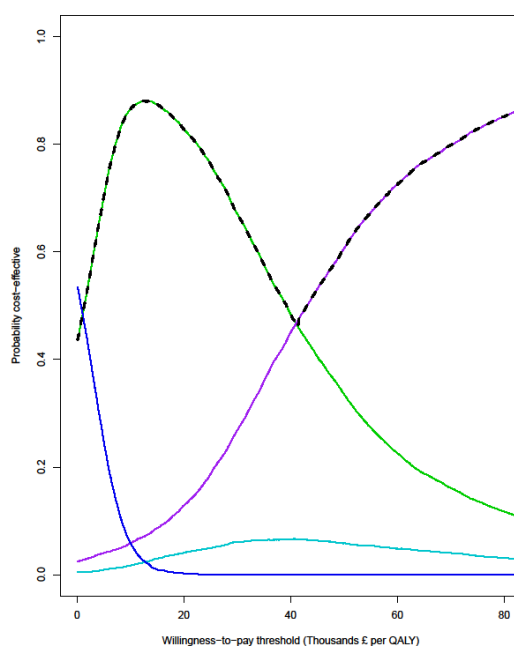
6.3.3.6   Heterogeneity with cohort survival:

Considering alternative scenarios reflecting cost-effectiveness in populations with varying survival times reveals significant heterogeneity in the cost-effectiveness of the modelled treatment strategies.

In the base-case scenario the INHB following SABR compared to single fraction cEBRT at a WTPT of £30,000/QALY was -0.048 (95% CI -0.111 – 0.004) with a probability of delivering the highest NHB of the four strategies of 4%. This increased in the population with a median survival of 53.5 weeks, to an INHB (WTPT = £30,000/QALY) of -0.022 (95% CI -0.109 – 0.057) (ICER=£38,218), although in this case the probability of SABR delivering the highest NHB of the four rose to 25%. Conversely, in a population with median survival time of 6.2 weeks the INHB fell to -0.098 (95%CI -0.139 – -0.064) (ICER=£363,119) with SABR being the most likely to deliver the highest NHB in 0% of simulations.

The INHBs of the three alternative strategies are illustrated in Figure 44 for these differing cohorts. For the overall population the INHB of best-supportive care compared to single fraction cEBRT was -0.034 (95%CI -0.059 – -0.012). This INHB fell to -0.056 (95%CI -0.098 - -0.018) in those with a median survival time of 53.5 weeks, whilst rising to 0.014 (95%CI 0.008-0.020) in those with median survival time of 6.2 weeks. In this population with very short survival time best-supportive care is expected to be the most cost-effective strategy in 99.9% of simulations.

Figure 44. Incremental NHB of varying treatment strategies in two-way comparisons compared with single 8Gy fraction for populations with differing survival times. λ= £30,000 per QALY.
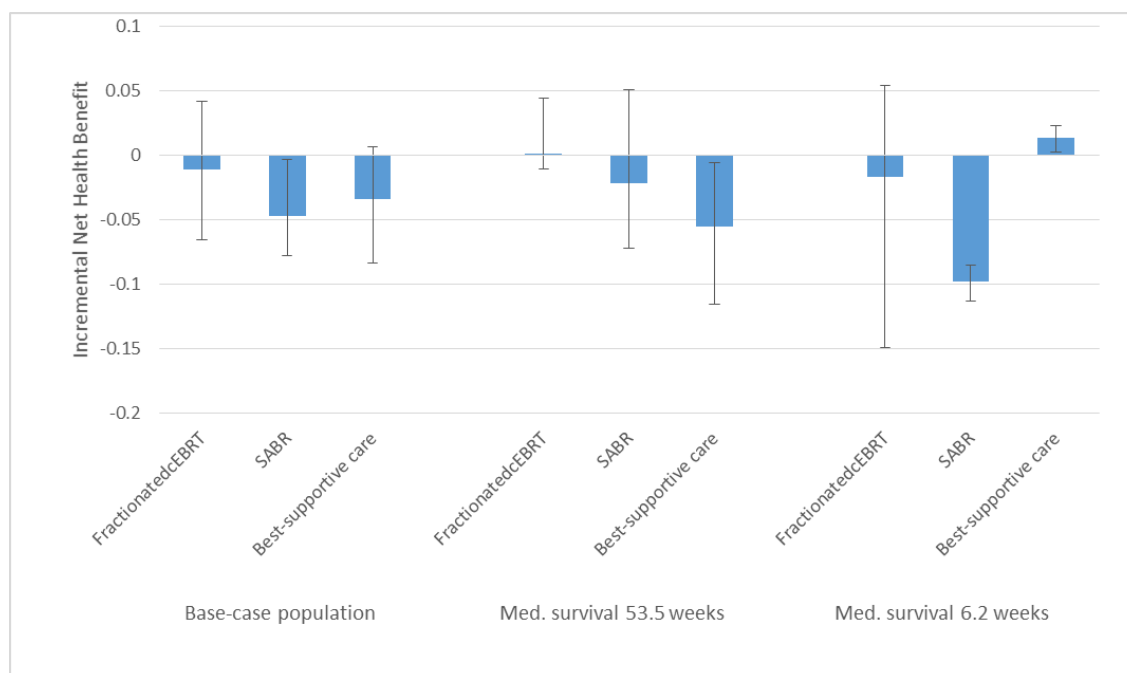
The uncertainty around the optimal treatment strategy in each scenario is better illustrated by the cost-effectiveness acceptability frontier shown in Figure 45. This demonstrates that across all plausible values of the WTPT the probability that best-supportive care is the most cost-effective strategy, in a population with a median survival of 6.2 weeks, is nearing 100%. Of note, the

modelled strategy here assumes that patients can improve in the absence of palliative radiotherapy.

For a population with more prolonged survival (median 53.5 weeks) the INHB of fractionated cEBRT compared to single fraction cEBRT was <0.001 (95%CI -0.031 - 0.033) with a probability of being the most cost-effective strategy of the four of 37%. Using current SABR costs, this strategy can be seen to become the most likely of the four strategies to be cost-effective those with longer survival times at a WTPT of £39,200/QALY. Below this, fractionated cEBRT is the most likely strategy to be cost-effective between thresholds of £29,800 and £39,200/QALY. With single fraction cEBRT most likely to be the most cost-effective option for a range of WTPT which encompass all thresholds from £8,600 to £29,800/QALY. This pattern is not observed when the parameterisation of SABR costs reflects anticipated long-term costs. In this final scenario, for a patient population with a median survival of 53.5 weeks, SABR is associated with an ICER of £17,889/QALY with a probability of being the most cost-effective treatment of 80.6% at a WTPT of £30,000/QALY.

Figure 45. Cost-effectiveness acceptability frontier using treatment effectiveness parameters (utilities and transition probabilities) for varying population subgroups a) patients surviving less than 12 weeks, b) overall population and c) patients surviving over 9 months. d-f) use the same treatment effectiveness parameters and incorporate anticipated long-term SABR costs. Dark blue = Best supportive care, green = single fraction cEBRT, purple = SABR and light blue = fractionated cEBRT.

d)   e)   f)
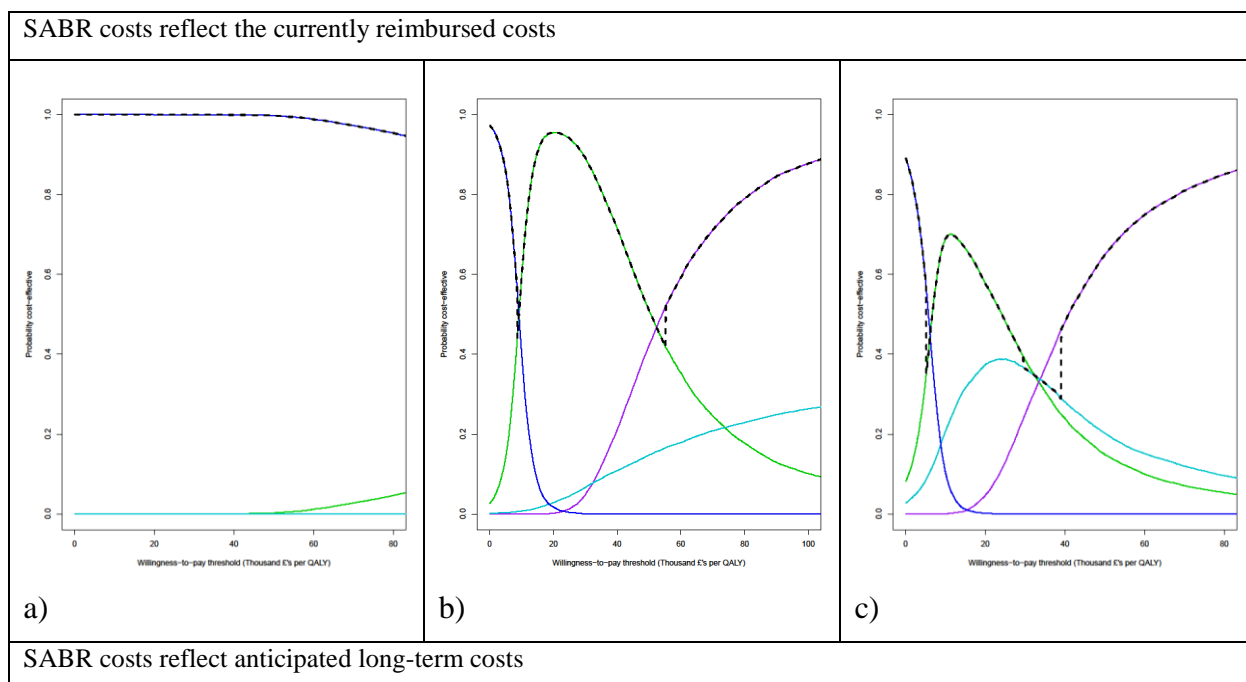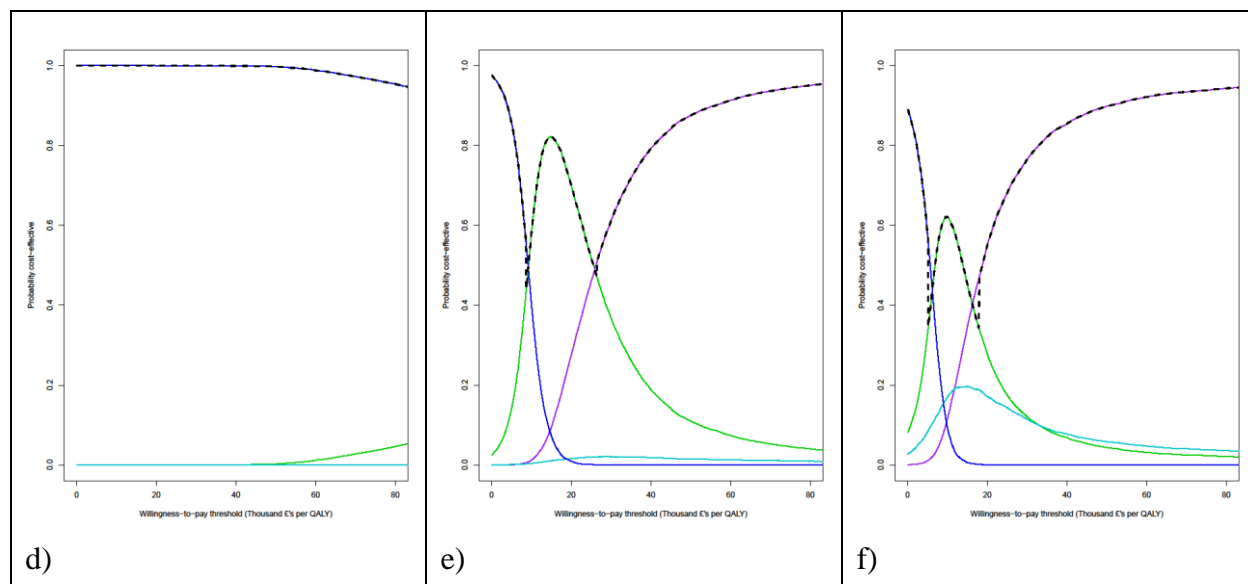
Modifying the utilities for the population with very short survival time, to reflect those reported in the DBMS (rather than the multiply imputed values used above) the INHB for best-supportive care compared to single fraction cEBRT in this model rose slightly to 0.016 (95% CI 0.010 – 0.024) (at a WTPT of £30,000/QALY). The probability of best-supportive care being the most cost-effective strategy in this cohort remained 100%. This probability did not change markedly (99.97%) if the threshold was increased to £50,000/QALY. This does not alter the conclusion that best-supportive care is the most likely strategy to be cost-effective in this cohort.

Given the finding that where the IMPACCT health state costs were considered the single fraction cEBRT strategy was most likely to be the most cost-effective strategy across all acceptable WTPT values the IMPACCT health state costs were incorporated into the model assessing a cohort with median survival of 6.2 weeks. This alternative parameterisation of the health state costs results in a marked change in cost-effectiveness. The INHB of best-supportive care is now reduced to 0.009 (95%CI -0.014 – 0.027). Best-supportive care remains the most cost-effective strategy of the four in 82% of simulations at a WTPT of £30,000/QALY.

6.3.3.7   Expected value of perfect information in a short surviving population

Under the base-case parameterisation for this cohort (which acknowledges pain response can occur in the absence of radiotherapy) the total EVPI for England over 10 years was £61.27. Recognising an alternative parameterisation, in which without treatment patients are unable to gain a pain response, this rose to £6747.41. Recognising a WTPT of £300,000/QALY allowed consideration of the parameters with the greatest influence over this outcome. Response probability and the utility decrement of treatment have the greatest EVPPI. These results are presented in Table 31.

Table 31. Expected value of perfect parameter information at WTPT of £300,000 for illustrative purposes. PR = partial response, CR = complete response, PP = pain progression, BSC = Best supportive care. This parameterisation assumes pain response occurs in the absence of radiotherapy in line with that reported prior to treatment in the DBMS.

	Per Person EVPPI (£)	Standard Error	Indexed to Overall EVPI = 1.00	EVPPI for England Per Year (£)	EVPPI for England over 10 years (£)
30-day mortality	0	0	0	0	**0**
PR at 6 weeks - BSC	7.53	1.32	0.05	15,070	**150,700**
CR at 6 weeks - BSC	23.81	2.38	0.15	47,610	**476,100**
PP at 6 weeks - BSC	0.25	0.32	0	500.1	**5,001**
PR at 6 weeks - Single #	15.47	2.02	0.1	30,940	**309,400**
CR at 6 weeks - Single #	2.34	1.04	0.01	4679	**46,790**
PP 6 weeks - Single #	1.8	0.63	0.01	3591	**35,910**
Utility - NR	0.09	0.11	0	176.3	**1,763**
Utility - PR	0	0.03	0	0	**0**
Utility - CR	4.67	1.05	0.03	9,342	**93,420**
Utility - PP	0	0	0	0	**0**
Utility decrement – Single #	26.71	2.05	0.17	53,420	**534,200**
Cost – NR	0	0	0	0	**0**
Cost - PR	0	0	0	0	**0**
Cost - CR	0	0	0	0	**0**
Cost - PP	0	0	0	0	**0**
Cost - Single #	0.76	0.37	0	1,523	**15,230**
Cost - BSC	0	0	0	0	0

6.3.3.8 Incorporating QALY equity weights for patients with very short survival

The base-case model for a population with a median survival time of 6.2 weeks demonstrated that best-supportive care was the most cost-effective strategy at a WTPT of £30,000 per QALY for 100% of simulations (Figure 46a). In order to assess the extent to which this was the result of reduced clinical efficacy in this cohort the transition probabilities and utility values used for the prolonged survival cohort were used. As demonstrated in Figure 46b this improved the cost-effectiveness of single fraction cEBRT although the threshold at which it became the most likely strategy (£61,400/QALY) to be cost-effective remains well above the NICE threshold of £30,000/QALY and even above the £50,000/QALY threshold. A similar outcome is seen when a parameterisation that assumes no response can be achieved without treatment is used (Figure 46c). As such, the lack of cost-effectiveness is not simply a reflection of the reduced clinical efficacy; the WTPT at which single fraction cEBRT becomes cost-effective remains well above any which might be acceptable within the NHS.

Figure 46. Cost-effectiveness acceptability frontiers for a population with median survival of 6.2 weeks. a) Base-case parameters. b) Transition probabilities and utilities for a patient population with median survival of 54 weeks c) Alternative parameterisation where without treatment no response is seen. Green = single fraction cEBRT, dark blue = best-supportive care.
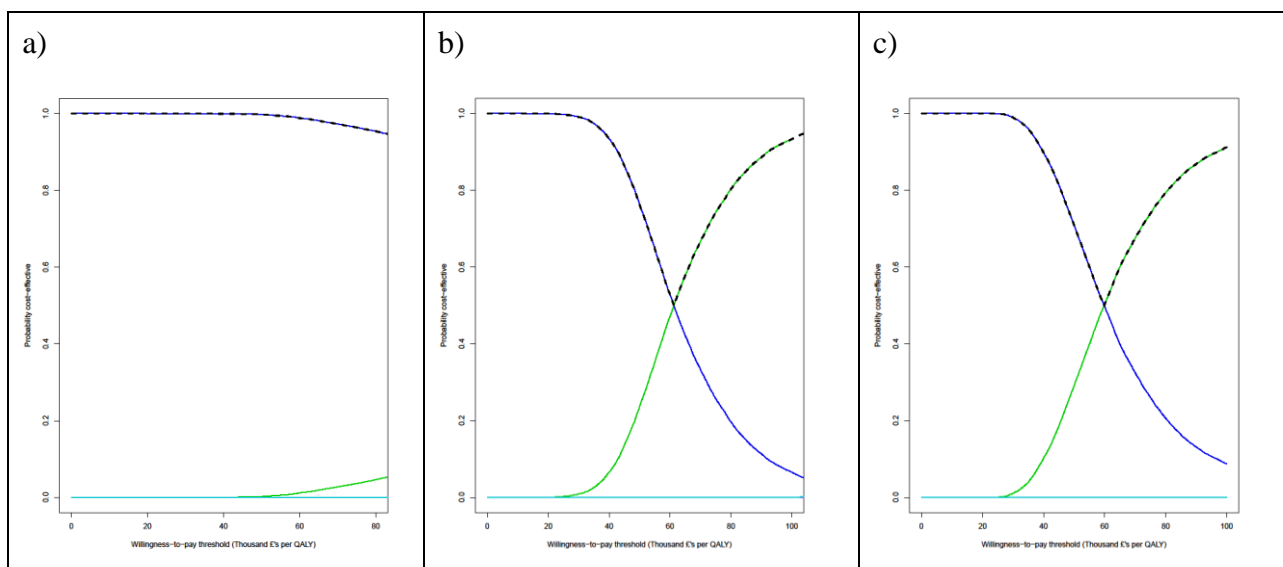
Returning to a parameterisation which recognises the response probabilities and multiply imputed utilities of patients surviving less than 12 weeks, a range of equity weights for the modelled population was incorporated. This showed that an equity weight of 7.3 was required for single fraction cEBRT to be the most likely strategy to be cost-effective at a WTPT of £30,000/QALY (see Figure 47 a). Replication of this analysis using the health state costs from the IMPACCT study showed a lower equity weight of 7.0 was required (Figure 47b). Only where the parameterisation reflects an assumption that without treatment no response can be achieved does the equity weight required to make treatment cost-effective fall to 2.1 (£30,000/QALY WTPT) (Figure 47c). In keeping with the WTPT seen in Figure 47c.

Figure 47. Threshold analysis assessing the necessary equity weight required for single fraction cEBRT to be the most likely strategy to be cost-effective in a population with median survival time of 6.2 weeks. a) assuming base-case parameters, b) assuming costs captured in the IMPACCT study and c) Alternative parameterisation where without treatment no response is seen. Green = single fraction cEBRT, dark blue = best-supportive care.
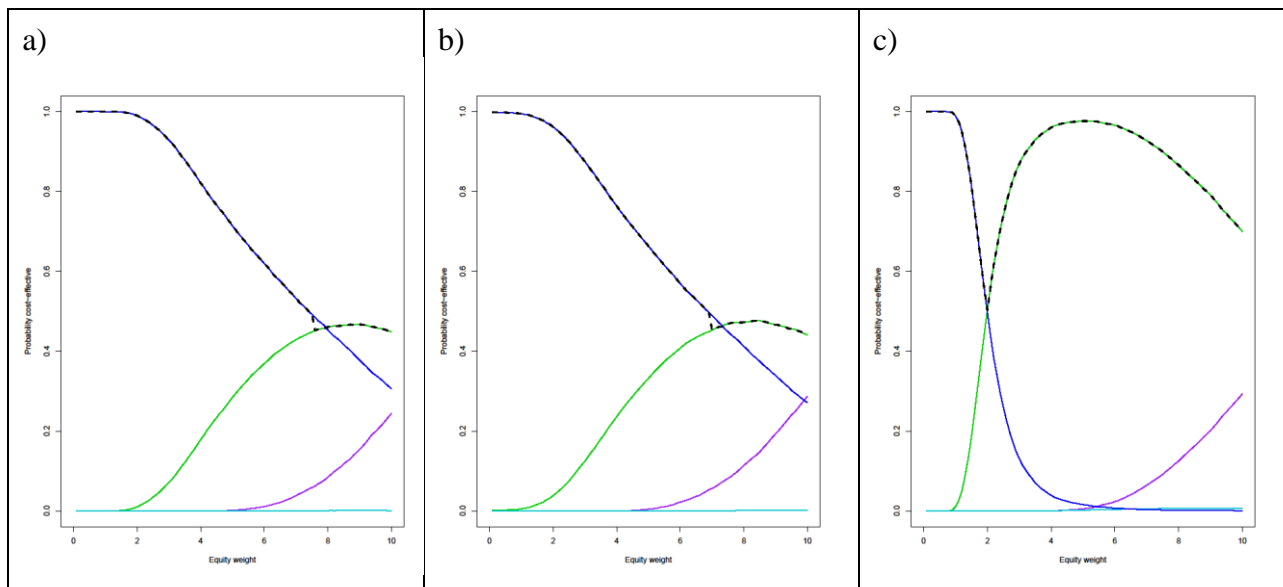
6.3.3.9 Re-framing the CEAF in the context of survival time

As illustrated in Figure 45 the cost-effectiveness of interventions varied widely with the survival of the treated cohort. Assuming base-case model parameters for the whole treated population, Figure **48** illustrates the probability of each strategy being the most cost-effective for cohorts with differing survival probabilities. The outcomes are shown relative to 30-day mortality and median survival. These again demonstrate the variation in the most cost-effective treatment strategy in relation to survival probability. Where the anticipated long-term treatment costs of SABR are considered, at a WTPT of £30,000/QALY, the threshold at which SABR becomes most likely to be cost-effective was at a median survival of 31 weeks (Figure 48 b). Incorporating the base-case cost parameterisation and a NICE WTPT of £30,000/QALY, SABR becomes the strategy which is most likely to be cost-effective only when the median survival of the cohort is greater than 58 weeks. Conversely, at a WTPT of £30,000/QALY, single fraction cEBRT becomes the strategy most likely to be cost-effective at a median survival of 11 weeks (30 day mortality of 24%).

Figure 48 Cost-effectiveness survival frontiers illustrating the probability that each treatment strategy is cost-effective for a cohort with varying survival probability. Base-case parameters are used for treatment effectiveness, anticipated long-term (lower) SABR costs and varying cohort survival probability. Cost-effectiveness at £30,000 per QALY WTPT against population a) 30 day mortality and b)Median survival (weeks). Purple = SABR, green = single fraction cEBRT, dark blue = best supportive care and light blue = fractionated cEBRT.
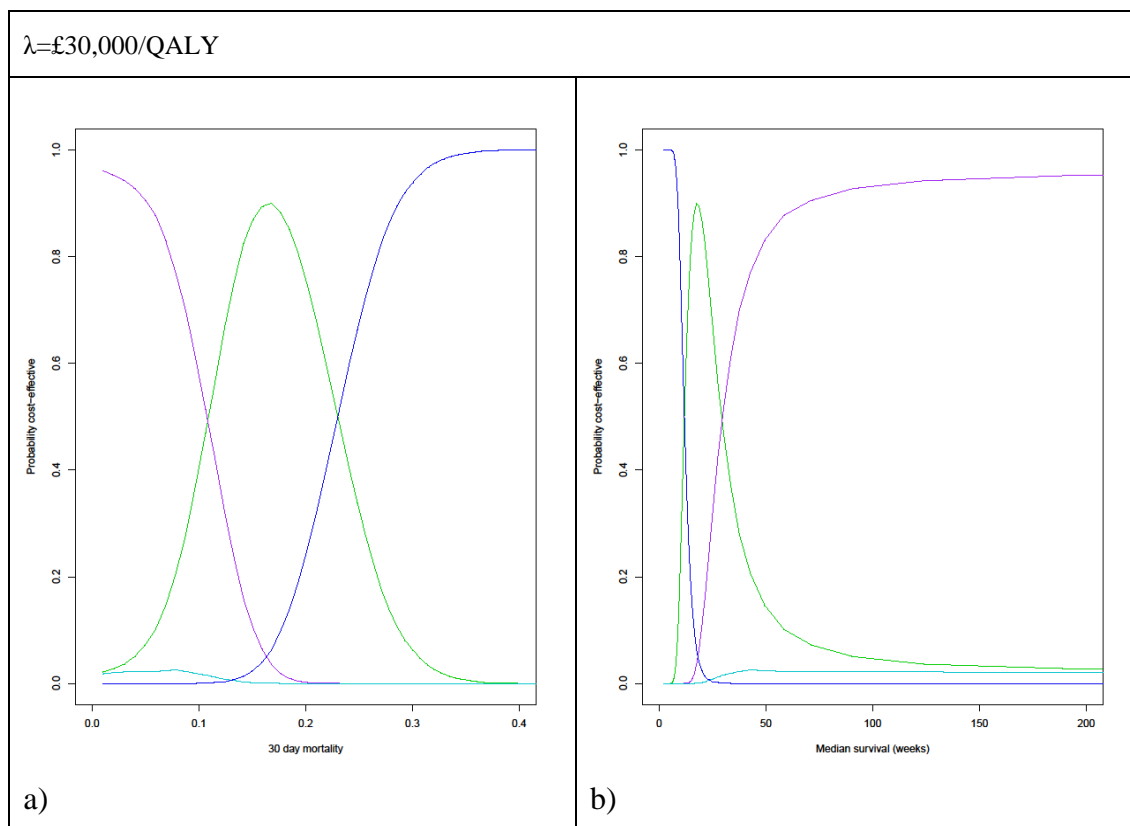
6.3.3.10 Outcome-based pricing

Re-arranging the ICER formula and incorporating these varying outcomes with survival allows the production (Equation 8) of an outcome-based price relative to the 30-day mortality or survival of the treated cohort. Figure 49 illustrates the results of this analysis. It can be seen that at a WTPT of £30,000/QALY the current treatment costs (£3571) of SABR would be associated with cost-effective treatment delivery if the 30-day mortality of the treated population were under 5.9% (Upper 95% CI 9.7%) with a median survival of over a year. This rises to 11.5% (upper 95% CI 16.8%, median survival 27 weeks) where the anticipated long-term SABR treatment costs are considered (£2055). These values will be compared to those observed in routine care in chapter 8.

Figure 49. Outcome-based price of SABR relative to a)30 day mortality and b) median survival of the treated population. The horizontal reference lines are placed at the currently commissioned price of SABR and a realistic expectation of anticipated long-term SABR treatment costs. The 2.5th, 25th, 75th and 97.5th quantiles of simulations illustrate the uncertainty around the estimated OBP.
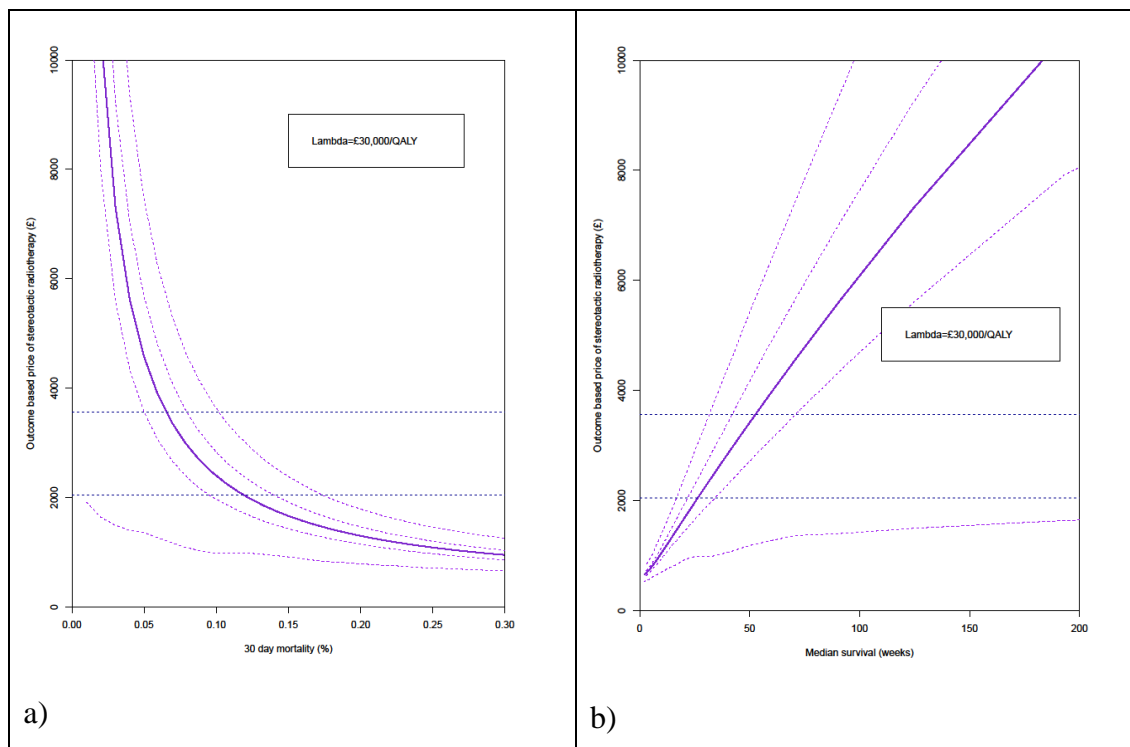
6.3.3.11 Markov modelling of treatment benefit

In order to consider an outcome with greater direct clinical relevance, the Markov model was repurposed to assess the expected HR-QoL benefit of palliative radiotherapy very close to the EoL. The comparison between single fraction cEBRT and best-supportive care was focussed upon in a population surviving less than 12 weeks. Response following best-supportive care is assumed to reflect that seen prior to radiotherapy delivery in the DBMS. The estimated absolute increase in pain response probability each week following treatment and the expected cumulative gain in HR-QoL (measured as EQ-VAS points gained each week) were estimated. The results of this analysis are presented in Figure 50. At 4 weeks following treatment the estimated mean cumulative gain in EQ-VAS was 9.8 points (95%CI 6.63-13.13). These were accumulated over the four week period and, therefore, the incremental benefit per week is anticipated to be an average of 2.5 EQ-VAS points, well below the minimally important difference identified in chapter 3. From the perspective of the incremental improvement in pain response, an absolute improvement of 13.3% to 26.2% was seen. On average this translates to a number needed to treat (NNT) to deliver an improvement in pain (of two or more points on a 0-10 NRS) of 5.7; for every 5.7 patients treatment with palliative radiotherapy in the final twelve weeks of life, it is estimated one will gain a pain response. For comparison these figures are reproduced recognising the transition probabilities and multiply imputed EQ-VAS values for the whole treated population (Figure 50 b and d).

Figure 50. Expected benefit of palliative radiotherapy (single 8Gy) compared to best-supportive care under varying assumptions of short survival time. The upper panels demonstrate the incremental lifetime gain in VAS points given varying survival times a) assuming parameters derived from a population with survival of less than 12 weeks and b) based on overall study population. The lower panels illustrate the absolute increase in response rates each week. c) population with less than 12 weeks survival d) overall study population.
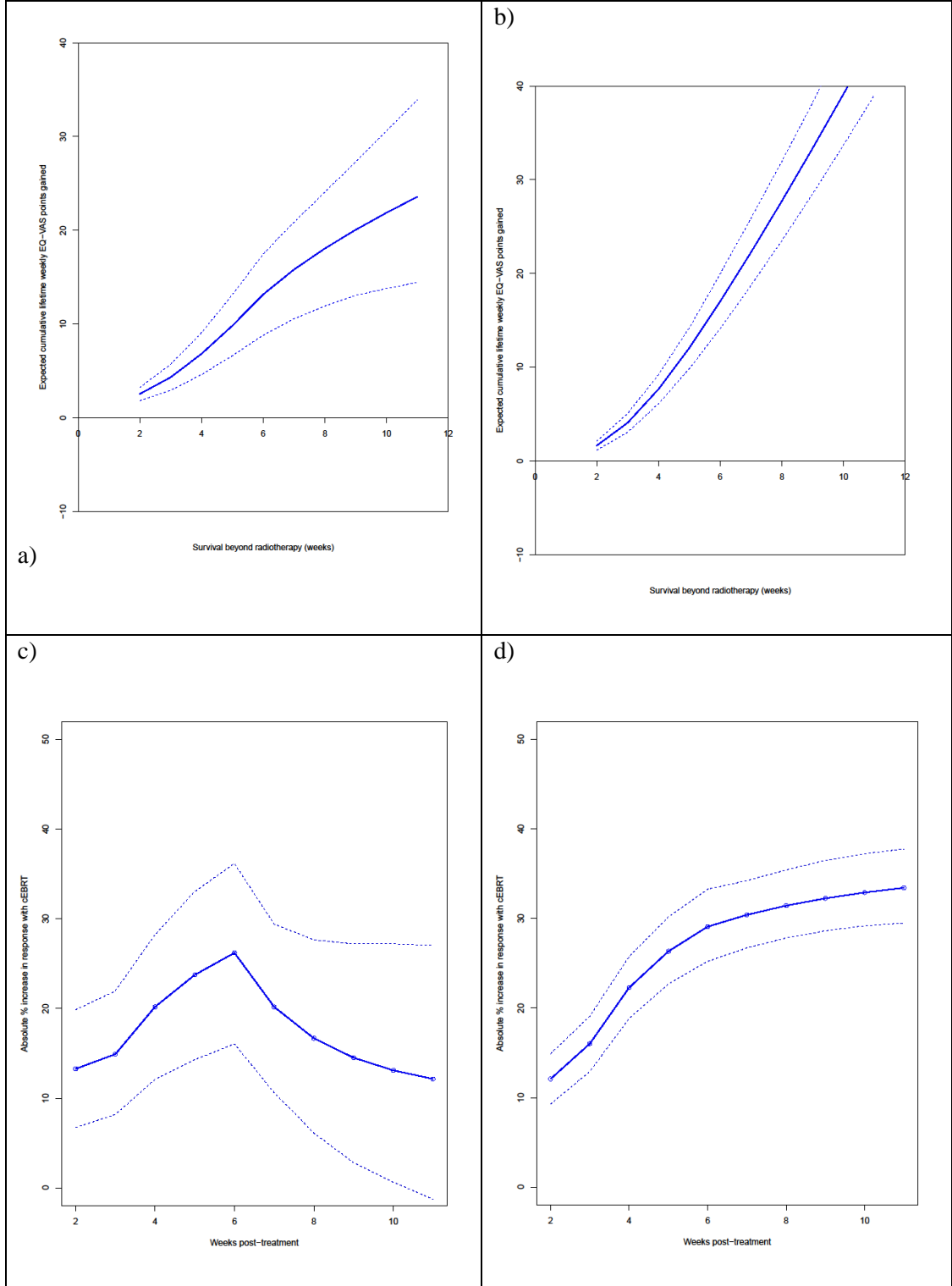
6.4 Discussion

This study demonstrates that SABR for pain due to bone metastases is unlikely to be cost-effective in the NHS at the currently commissioned price, irrespective of response probability (base-case ICER = £55,592/QALY). Given the recognised learning curve demonstrated in radiotherapy costs,(120) which is likely to result in lower long-term treatment costs, the need to deliver further certainty in the clinical-effectiveness of SABR gains greater importance. Where the anticipated long-term costs of SABR are considered these treatments may offer a cost-effective intervention if the outcomes reported by Sprave et al are replicated in larger, randomised studies (ICER = £26,225/QALY). Conversely, incorporating an analysis of the expected consequences of heterogeneity, this study demonstrates the possibility that SABR may offer a cost-effective improvement in pain control for patients with more prolonged survival, even where current costs are considered. This finding is further supported by the outcomes of the VOI analysis which demonstrate that reducing uncertainty around the response rates following SABR is a key outcome for a future trial. Notably, where SABR costs remain high the VOI analysis suggests that future studies are unlikely to be cost-effective.

Focussing upon patients very close to the EoL, this study attempted to identify levels of 30-day mortality which are consistent with the cost-effective use of palliative radiotherapy. The outcomes presented here provide interesting insight into this question. On the one hand, it is clear from the analysis of cost-effectiveness in a cohort with median survival of 6.2 weeks that single fraction cEBRT for this cohort is highly unlikely to be cost-effective at any plausible threshold. This, in part, reflects the relatively reduced efficacy of cEBRT in this cohort (Figure 46b). It also, however, raises important questions about the value placed upon improvements in HR-QoL near the EoL. It is notable, however, that where the cost-effectiveness of the four strategies are considered for populations with varying survival probabilities single fraction cEBRT remains the strategy most likely to be cost-effective up to a 30-day mortality of 24% (at a WTPT of £30,000/QALY). Markedly higher than that which has previously been reported in NHS practice.(6) A key limitation of this latter analysis is that the modelled treatment benefit represents the expectation of the average from the overall population and does not recognise the reduced efficacy in those near the EoL resulting from the heterogeneity demonstrated in chapter 3. Incorporating the parameters for a population with short survival into a model including patients with longer survival, in order to address this question, would be questionable and, therefore, this was not carried out.

Where decision-making occurs at an individual patient level, it must be acknowledged that cost-effectiveness may not be the ideal way in which to determine acceptable levels of 30-day mortality, even if this supports recognition of the opportunity cost to the wider healthcare system. This approach has clear appeal as it has the ability of balance benefit and costs. Where an individual dies within 30 days of treatment, however, the incremental benefit is highly unlikely

to be clinically meaningful and for a large proportion of patients treatment will deliver no benefit. In fact, without incorporating treatment burden and disruption to the patient and family any harm may be underestimated; for those who do not respond (the majority in this cohort) a net harm is likely. Within the overall cost-utility analysis, however, this futility, or even harm, is balanced by the higher benefit derived by the population surviving for longer. As a consequence, this approach raises questions about the metric itself; harm is experienced at an individual level, but the metric balances these individual harms with the greater gains at a population level. Additionally, this analysis does not consider the potential detrimental consequences of aiming to reduce 30-day mortality. This might reduce harm to those individuals who would otherwise be inappropriately treated, however, if the consequence of this were to reduce access to beneficial care for others, this should be considered extremely carefully. As such, the approach presented here is of value in assessing cost-effectiveness at a population level. It does this by balancing the harm to a small number of individuals with the benefit to others and, therefore, cannot be used to guide individual clinical decisions. Further analysis to assess the extent to which 30-day mortality may relate to access to treatment should be carried out to determine the extent to which reducing the use of treatment very close to the EoL might have a detrimental impact upon access to care.

6.4.1 *Outcome-based pricing*

If further studies are able to provide greater certainty in the measurement of expected pain response following SABR there is potential for these treatments to be approved for reimbursement in routine practice on the basis of empirical data, rather than opinion, anecdote and in response to lobbying. Once implemented routinely, however, it is possible that treatment is delivered to patient groups where it is unlikely to be cost-effective. In order to recognise this possibility and, conversely, to allow recognition of the varying costs of SABR after implementation the outcome-based price (OBP) analysis presented here was carried out. This relates the modelled cost-effective price of SABR to the survival of the treated cohort, presented as the 30-day mortality and median survival. This provides an opportunity to retrospectively assess the cost-effectiveness of delivered services, potentially modifying the future commissioned price to reflect outcomes. Alternatively, an agreed price might be commissioned with recognition that treatment will be delivered to a population whose expected survival aligns with the commissioned price. How this might be implemented and where such a model fits beside previously conducted studies will be discussed below.

6.4.1.1 *Price discrimination*

Price discrimination describes the way in which a monopolistic provider varies the price of goods provided to two separate markets by maintaining their separation.(379) This allows the provider to maximise profit by capturing the greatest amount of consumer surplus. Price discrimination can be achieved in a number of ways. First degree discrimination exists if the price charged varies by one-unit increments, thus maximising profit by capturing the full consumer surplus and

perfectly matching supply and demand. Second degree price discrimination exists where a monopolist places minimum blocks of units on the market at the maximum attainable price with subsequent blocks priced successively downwards. Finally, third degree price discrimination occurs where the provider maintains full separation of two markets, maintaining differing prices in the two markets to match the elasticities of demand in each market.(379,380) Whilst in business economics the maximand is profit given consumer surplus, in the healthcare setting the maximand is population health given a finite healthcare budget. As such, population health can be maximised through price discrimination with the outcome-based price presented here providing an example of first degree price discrimination if implemented at an individual patient level. It is notable, however, that the outcome-based price presented here differs in some ways from those implemented elsewhere and therefore should be considered in the context of other pricing and commissioning structures.

6.4.1.2   Alternative commissioning models

Outcome-based pricing (OBP) has been defined previously as where the price paid for a healthcare intervention is linked to the real-world outcomes it achieves for individual patients. OBP has been used, predominantly in the reimbursement of pharmaceuticals, as a means to manage uncertainty, supporting the early use of novel interventions in the absence of mature randomised trial outcomes.(381,382) This has been advanced by some as a means to ensure timely access to promising novel agents despite immature trial data resulting in uncertainty. In delivering this access the risk related to uncertainty is split between the payer and, in the case of pharmaceuticals, the manufacturer.(382) This may be achieved by the manufacturer only receiving payment where treatment is successful; by no or proportional reimbursement being delivered where no/reduced response is seen; or through a reduction in the price if the desired outcomes are not observed.

Multiple challenges to implementing OBP have, however, been identified. These include both challenges around selecting appropriate outcomes, linking these outcomes to the reimbursed price and more practical concerns around the need for detailed longitudinal patient data and the substantial financial, human and infrastructure resources associated with this.(381,382) As a result of these challenges, OBP models remain relatively infrequently used in practise. In a review of managed access schemes Lu et al identified an extensive range of schemes in Asia-pacific, of which only a limited number incorporated an outcome-based pricing element where reimbursement was formally tied to either intermediate of final clinical endpoints.(381) Hybrid models which incorporated both financially-based models and OBP models were also seen where reimbursement was conditional upon response with a pricing arrangement coupled to this. Of note, the schemes identified were principally involved in the commissioning of novel pharmaceutical agents and in addition it was highlighted that the extent to which these models ensured appropriate access, for all patients with the potential to benefit, was unclear.(381)

OBP contrasts with value-based pricing, where the reimbursed price of an intervention is linked to its known efficacy.(383) Whilst OBP supports commissioning in uncertainty, value-based pricing aims to maximise health by ensuring that the reimbursed price of an intervention reflects the known value it delivers, i.e. the benefits of treatment delivery exceed those of the any treatment forgone due to displacement. It has been suggested that using value-based pricing within stratified cost-effectiveness analyses might offer the potential to maximise population health. This would allow access to beneficial treatments to be broadened whilst ensuring that the reimbursed price of treatment is appropriately reduced in subgroups for whom treatment is less cost-effective.(383) This might be achieved by identifying a negotiated price which maintains cost-effectiveness in a subgroup where cost-effectiveness is reduced whilst increasing patient access and thus also manufacturer income.(384) Alternatively, through second degree price discrimination, differing prices might be agreed for treatments delivered to patient subgroups in order to ensure both increased access and maintained cost-effectiveness.

In contrast to the individual patient level price variation delivered by OBP, healthcare commissioning using a pay for performance (P4P) approach has been widely used with a view to improving the quality of healthcare, reducing costs and thus increasing cost-effectiveness. P4P commissioning links provider level payments to predefined quality targets. These relate, predominantly, to process and structure indicators due to the challenges of capturing outcome data. As more outcome indicators have been incorporated these models have developed into outcome-based payment models (OBPM).(385) These models have been defined as aiming to improve quality of care and reduce healthcare costs by linking provider payments to the outcomes of care. Vlaanderen et al separate these OBPMs into "narrow" and "broad" categories, with narrow, relating to the commissioning of a single provider or clinical area and broad relating to the commissioning of a wider multidisciplinary provider group with payment encompassing the entire provider payment. These OBPMs contrast with the OBP models discussed above; OBPMs focus on improving quality and cost across a clinical area, whilst in the previously discussed OBP the focus was predominantly upon reducing the payer exposure to risk relating to uncertain treatment outcomes. The OBP model outcomes presented here might form part of a "narrow" OBPM. Evidence informing the effectiveness of OBPMs was reviewed by Vlaanderen et al, however, who found that their effectiveness was variable with narrow OBPM appearing to be less effective. Their effects were more short lived with a greater tendency towards ceiling effects than was seen with broad OBPM.(385)

The model presented here provides a mechanism to support the identification of suitable prices for patients with differing survival times and painful bone metastases in the English NHS. How these prices are then implemented is an important question.

6.4.1.3 Implementation options

If further randomised controlled trial data supports the improved efficacy of SABR over conventional radiotherapy the principle challenge in implementing this treatment will be in

ensuring cost-effective delivery despite uncertainty in prognostication. This would be particularly challenging, given that limitations to ensure treatment is delivered just to those with the best prognosis might, inappropriately, prevent those with slightly poorer prognosis from accessing a beneficial intervention. A secondary challenge is the variable treatment costs over time once treatment is implemented. Multiple potential ways in which the model presented here could be implemented will be considered in the context of the commissioning frameworks outlined above.

Using OBP the uncertainty of prognostication might be managed using retrospective, patient-level data. A patient would be treated and their survival time observed. This known survival time could then be used to define a reimbursement price. In this context survival time is a surrogate for cost-effectiveness, with the two being inextricably linked. OBP has been carried out using surrogates on many occasions previously; the reimbursement of Velcade based on para-protein levels or Imatinib based upon bone marrow analyses being just two examples. Notably these surrogate outcomes can reasonably be considered to be intermediate clinical outcomes whilst in SABR for bone metastases survival is not an intermediate outcome being a surrogate for cost-effectiveness but not clinical effectiveness. Whilst the data to support such an approach exist, this level of first degree price discrimination would require significant resource to deliver due to the need to define a different price for each individual treated. Such an approach is unlikely to be practical given the resource requirements.

An alternative approach might see treatment commissioned using a value-based price for a defined population, over a finite period of time (years), with a plan to reconsider reimbursement pricing after this initial period. The reimbursed price could then be modified based upon the survival of patients treated within the initial period. Ongoing monitoring would then allow commissioning to maintain cost-effective treatment delivery through regular monitoring and price modification. This approach might offer some appeal given the demonstrated variation in treatment cost over time following implementation. The national level of the analysis would be a significant limitation, however, as late-adopters might then be expected to commission this novel treatment at markedly lower reimbursement prices than early adopters had benefited from despite the expected higher initial provider cost. Potentially acting as a disincentive to adoption.

Given this variation between providers in the timing of implementation and the known variation in practise between centres nationally, a model which considers outcomes at a national level has some limitations. In particular it would not recognise variation in the cost-effectiveness of treatment between centres, potentially resulting in a reduction in reimbursement prices in all centres, including those where treatment delivery was already cost-effective and risking reducing access. Using patient-level data the outcomes for individual treatment centres could be assessed after an initial implementation period and the reimbursed price varied in line with local treatment patterns and cost-effectiveness. Survival could either be considered using a time-to-event analysis or based upon mortality at a fixed point following treatment e.g. 90 day mortality. Given the low numbers included this latter might not allow discrimination between provider organisations. If patient numbers were sufficient this could maintain cost-effectiveness through a narrow OBPM,

although in line with Lu et al, the consequences of this for access to beneficial treatment would require careful consideration and monitoring. In addition, despite the relatively simple approach, this might still require significant resource to deliver.

Finally, a VBP approach could be adopted. This would rely upon the use of a validated prognostic model to support the commissioning of SABR only in subgroups of the population where it delivers cost-effective outcomes at an agreed reimbursement price. In this way the population eligible to receive treatment could be extended through identification of an appropriate VBP. Prognostic models have been developed in this setting but none are in routine use.(97,386) One simple model includes only the patient's primary diagnosis, performance status and presence of visceral metastases to allocate patients to one of three prognostic categories.(ref Chow) Primary diagnosis and performance status are routinely used in the commissioning of pharmaceutical based treatment for advanced incurable cancer and might, therefore, provide the basis of a VBP approach. Subsequent monitoring of survival outcomes, using routine data, could then be used to ensure ongoing cost-effective treatment delivery.

Overall it can be seen that multiple approaches to implementation exist within different frameworks. If further RCTs confirm the benefit of SABR in painful bone metastases consideration of these results will be required to inform the cost-effective commissioning of this intervention. The availability of routine data can then provide a valuable opportunity to ensure cost-effective treatments are delivered.

6.4.2 *Model strengths and limitations*

The flexibility of the model presented here provides an opportunity to investigate the consequences of varying parameterisations which reflect heterogeneity in the treated population. The model incorporates the available literature and is clinically plausible. The multi-state modelling approach taken also provides clear value in a setting where failure to recognise the competing risk of death would have resulted in marked overestimation of the risk of re-irradiation and health state occupancy. There are, however, a number of limitations some of which relate to the specification of the model itself, others to the broader methodologies used. These are discussed below:

6.4.2.1 *Pathological fracture and malignant spinal cord compression (MSCC) rates*

This model assumes that the likelihood of pathological fracture and malignant spinal cord compression are equivalent for all strategies. The lack of data to support this parameter is a significant limitation. Vertebral compression fracture (VCF) rates are reported to be higher following SABR than single fraction cEBRT (11-39%), however, data supporting pathological fracture rates at other sites are limited and the consequences of this outcome for patient's quality of life and costs are not well quantified.(158,387) In addition, the studies reported represent practice in North American centres. Given the very different treatment and follow-up in these jurisdictions and the non-randomised nature of the data available, incorporation into the cost-

effectiveness model was not felt to be appropriate. Conversely, VCF rates following single fraction cEBRT are not well defined. Pathological fracture rates more generally have been shown not to be significantly different following single fraction and fractionated treatment with cEBRT with rates broadly equivalent at around 3%.(133) These rates are markedly lower than those reported following SABR, however, these reflect fractures identified during clinical follow-up and not regular imaging follow-up as is seen in the SABR series. As such they cannot be considered comparable. If rates of VCF (and indeed pathological fracture more widely) are confirmed to be higher following SABR this would be expected to reduce the QALY gain associated with treatment and increase costs, both of which will reduce the cost-effectiveness of these treatments. Equally, it is clinically plausible to think that MSCC rates may be reduced following SABR with consequent marked reduction in costs and increase in QALYs. Further randomised data to inform these outcomes and their consequences are urgently needed.

6.4.2.2   Re-irradiation rates

Re-irradiation rates following SABR are informed based on the limited case series data available in the published literature and identified in chapter 2. The uncertainty around this outcome is, therefore, significant. In addition, further clarification of re-irradiation rates following cEBRT in a UK population are required. The systematic review of randomised studies reports re-irradiation rates of 20% in the single fraction arms versus 8% in those receiving multiple fractions.(10) A more recent international trial assessing different single fraction doses showed a re-irradiation rate of only 14% following a single 8Gy fraction.(143) Notably this study included clear criteria for re-irradiation, unlike in previous studies, although it included patients recruited from a range of jurisdictions making interpretation challenging. As such, there remains uncertainty around this parameter. In addition, such analyses may be better informed using routine data, in order to better reflect practice in the UK. There are, however, significant limitations to confirming re-irradiation is delivered to the index site when using routine data. The result of a reduction in re-irradiation rates following cEBRT might be to reduce the cost-effectiveness of SABR by increasing the incremental costs of this treatment strategy. Whilst the expected value of perfect parameter information (EVPPI) for re-irradiation was low (£0.95 per patient for both SABR and single fraction cEBRT) the potential for rates in the single fraction cEBRT strategy to reduce markedly below those observed in the previous trials would increase this and greater certainty around this parameter should therefore be sought in future studies.

6.4.2.3   Health state costs

Whilst health-state costs were found not to be a significant driver of cost-effectiveness in the base-case model, incorporation of the costs derived from the IMPACTT study increased the probability of SABR being the most cost-effective treatment strategy from 4% to 31%, reducing the ICER to £41,043/QALY from £55,592/QALY. The patient cohort treated within the IMPACTT study had a shorter survival time than those included here (1-year survival was 3% in IMPACTT) and the

health states reported do not map exactly to those modelled here. The potential for a differential effect of pain status on costs is, however, plausible in a longer surviving population with the health states considered here. This was not demonstrated in the DBMS data, however, the small number of questionnaires available and limitations of identifying the related health state mean this finding should be interpreted with significant caution. Given the marked impact of this variation in the health state cost parameterisation future studies should ensure this information is captured.

6.4.2.4   Utility decrement estimates

The utility decrement of palliative radiotherapy was found to be very small. This is plausible given that adjustment was made for pain flare. It might, however, still be expected to be higher than the modelled values here. The potential for an interaction between the utility decrement and proximity to death was not assessed and could further impact upon the modelled outcomes in the population with very short survival time.

6.4.2.5   Parametric model fit

The fitted Weibull parametric survival model provided the optimum compromise between a clinically plausible model and model fit both graphically and on AIC. The consequences of violation of the resulting structural assumption have not been examined. The median survival of the population appears slightly increased by this parameterisation, conversely the long-term survival may be reduced. The impact of this on the two-way comparison between SABR and single fraction cEBRT could be assessed in a future randomised trial. This would also be anticipated to impact upon the relationship between the 30-day mortality and median survival of the treated cohort with a consequent impact upon the use of an outcome-based price. Once more certainty about clinical effectiveness has been delivered and if this approach were to be implemented the most appropriate means to model the survival of the cohort would need to be considered using routine data to ensure a realistic representation of patients treated in routine practice.

6.4.2.6   Simulation numbers

The probabilistic sensitivity analyses carried out here contained 10,000 simulations. This aligns with the principle that with an adequately high number of simulations the estimated ICER of the means will be consistent.(388) It has been suggested that this number of simulations may not be adequate to fully characterise uncertainty where this is marked. Due to the computational expense of the model, in particular the transition probabilities, the impact of further simulations was not explored.

6.4.2.7   Uncertainty in the transition probabilities

The specific limitations of the SABR model should be addressed within a future study: response rates must be clarified, re-irradiation rates (and their distribution) assessed and pathological

fracture and cord compression rates determined, given the likely bias resulting from case-selection in the single arm series reported in chapter 2. It is notable that the outcomes reported by Sprave et al at 6 months following 30Gy in 10 fractions cEBRT are relatively poor; 35% of patients experiencing a response at this time-point, lower than the 49% in the base-case parameterisation for single fraction cEBRT modelled here. If replicated in a larger randomised study this result might significantly influence the cost-effectiveness of SABR by increasing the incremental QALY gain.

Similarly transition probabilities derived from the DBMS pre-irradiation population provide some insight into response rates without radiotherapy but significant uncertainty persists as follow-up in this cohort was extremely limited. Additionally, patients returning more than one questionnaire before treatment might well have had their radiotherapy delayed due to a need to improve pain control ahead of treatment. If this is the case the observed data may overestimate response in the absence of treatment due to medical management of pain and regression to the mean.

6.4.3 *Methodological limitations*

6.4.3.1 *Missing data*

A further source of uncertainty in this analysis is missing data. Whilst incorporating multiply imputed utility data did reduce the ICER for SABR this was not sufficient to for it to be considered cost-effective at a WTPT of £30,000/QALY. The limitations of the multiple imputation carried out here must also be recognised: the imputation model is developed in the whole population, the incorporation of the RCS for TTD, along with the interaction term should ensure that the utility values for longer surviving patients do not have significant influence over the imputed outcomes for those with short survival time. Given the high levels of variation in the survival and attrition seen, alongside lower response rates near the EoL, this cannot be excluded due to the significant imbalance in the panels; The possibility that data are MNAR cannot be excluded, again the RCS for TTD addresses the influence of increasing frailty, however, the possibility of worse than predicted quality of life being systematically related to missingness cannot be excluded; Additionally, imputation was not carried out in patients surviving beyond the end of the trial period as time to death was unknown for these individuals. As such, there is a risk that the combined utility values following imputation more strongly reflect the population with shorter survival. It was not possible to identify to what extent these factors might balance each other. Missing data remains a challenge in this setting and future studies should focus upon minimising this as far as possible. This could also address any potential concerns regarding the possibility of a systematic variation in the utility parameterisation based upon the non-UK population reporting the original EQ-5D domain outcomes.

6.4.3.2 *Lack of precision in the QALY estimates*

One of the most significant limitations of this model, particularly in those very close to the EoL, is a possible lack of precision in the assessment of QALY gain; the incremental QALY gain so

close to the EoL is extremely small (<0.001 QALYs). Equally, the very small QALY values involved, result in extremely small confidence intervals suggesting high levels of certainty.

It is unclear to what extent the EQ-5D-3L and valuation methods used here are able to inform the small changes seen. Uncertainty in this outcome is captured in the PSA, however, measurement imprecision and uncertainty in the valuation coefficients has not been addressed and might further increase the uncertainty around the cost-effectiveness of treatment.(389) The EQ-5D-5L would offer greater precision in the measurement of domain outcomes, although, paradoxically this might reduce the QALY gain (and cost-effectiveness) further as the differences in utilities between the reported health states would be reduced.(390)

6.4.3.3 Heterogeneity in outcomes

It is clear from this analysis that heterogeneity of survival in the treated population can have a major influence upon cost-effectiveness. A significant limitation of the OBP model and analysis of cost-effectiveness relative to survival time, is the acceptance of the base-case parameterization for all input parameters except survival time. Given the clear variation in response rates and utilities with survival time this is challenging and the consequences of failure to capture this are unclear, particularly given the limited data informing the SABR strategy. This limitation aligns with the challenges of recognising correlations between the input parameters; currently not addressed in this model. The result of this latter limitation might be to inappropriately increase uncertainty, given the clear need for further randomised data to address these questions this is unlikely to significantly alter the conclusions drawn. An alternative modelling method would be required to address incorporate this correlation; a discrete event simulation informed by a joint longitudinal survival model would allow predictions of all response parameters in line with an individual's survival probability. This approach would be computationally extremely intensive, would require robust data to inform the SABR treatment strategy and was beyond the scope of the current study.

6.4.3.4 Value of Information limitations

VOI analysis aims to provide an upper limit of the value of future research to reduce uncertainty in model parameterisation; what might a decision maker be willing to spend on reducing the risk of an inappropriate decision with consequent opportunity cost. Whilst the Sheffield Accelerated Value of Information online application provided a swift and computationally inexpensive means to assess the partial EVPI a specific limitation of this approach was the number of included parameters and the correlations between them.(376) The relatively small number of parameters included in the bone metastases model, and the simulations provided to inform these, should go some way to ameliorating this. More broadly, however, the VOI analysis has methodological and structural limitations which reflect those of the cost-effectiveness model. This is pertinent because VOI does not capture structural uncertainty without more sophisticated analysis such as model averaging approaches. Specifically, the structural uncertainties include MSCC and pathological

fracture rates, and measurement and valuation challenges in utility. Alternative model parametrisations may result in marked changes in the EVPI outcome, as illustrated by the difference seen when SABR costs are incorporated at both base-case and anticipated long-term values. In addition, the WTPT used would also result in marked differences in the EVPI outcomes whilst the possible role of equity weights is not considered in the VOI analysis. As such the EVPI analysis is valuable in directing the key parameters to be captured in future research but must be considered in the context of the limitations of the model already outlined and other factors which might influence the decision makers prioritisation of future research. For example, in radiotherapy specifically, trials of novel techniques can be a means to support diffusion into routine practice. In this case if current research assessing the role of SABR for oligo-metastatic disease demonstrates benefit, a trial of palliative treatment for bone metastases might provide an opportunity to support the wider implementation of these treatments, beyond those centres commissioned within existing trials and CTE, whilst also providing valuable information to inform the role of these treatments in the management of pain due to bone metastases.

The results of the EVPI analysis comparing single fraction cEBRT with best-supportive care in the short surviving population are worthy of note here. The very small QALY gains involved have similar consequences for the total EVPI as for the cost-effectiveness analysis; the total EVPI for England over 10 years was below £10,000 under either parameterisation of response in the absence of treatment and with a WTPT of £30,000/QALY. Research in this area would be hard to justify based on this analysis. If the equity weight identified above (7.3) is incorporated into the analysis (WTPT £219,000) the EVPI rises steeply to £3,276,000 over 10 years. Whilst the factors driving the EVPI will vary between interventions, and those treatments of relevance to greater numbers of people will accrue a higher total EVPI, this analysis suggests that interventions in an EoL population may struggle to accrue adequate QALY gains to justify the necessary resources required to support clinical trials. The possibility arises then that patients near the EoL could continue to travel for and receive palliative radiotherapy in the absence of evidence to support its value if the EVPI were interpreted as the maximum amount that could be justifiably spent on a trial to address this question.

6.4.4 *Equity concerns*

Equity weighting of QALY gains provides the opportunity to lend greater weight to some QALYs over others; a QALY is no longer a QALY. Great care is required in delivering this as evidence is required to support the identification of groups eligible for greater weights and subsequently means the value of these weights must be robustly identified. In doing this, the finite nature of resources should be remembered; weights will not be allocated to everyone and thus an increased opportunity cost will fall to those who are not eligible for an equity weight.

In this analysis, the consequences of equity weighting of QALY gains for patients very close to the EoL was considered. Where the model was informed based on a parameterisation for a

population with median survival of 6.2 weeks, Figure 47 demonstrates that a QALY would need to be valued 7.3 times more highly in this population than in others in order to make single fraction cEBRT cost-effective at a WTPT of £30,000/QALY (i.e. the WTPT is effectively raised to £219,000/QALY). Even parameterising the health state costs based on those collected within the IMPACTT study the equity weight required would be 7.1. Rowen et al. carried out a discrete choice experiment aiming to determine the possible increased value of a QALY near the EoL. They report that where the QALY gain was less than 0.05, the marginal rate of substitution (MRS) for QALYs at the EoL was -2.17.(391) It should be noted that, in line with NICE guidance, this study specifically identified EoL treatments as those delivered with a survival benefit of at least 3 months in a population within 2 years of the EoL. Therefore extrapolation to the current population, in whom no survival advantage is expected, is questionable. In addition, the equity weight required here is far higher than the estimate identified by Rowen et al. Notably, however, Rowen et al demonstrate a significant negative coefficient for a QALY squared term; with increasing QALY gains there is diminishing marginal value for additional QALYs. The population studied here have extremely limited QALY gain and, therefore future work to assess such small gains should be considered.

The approach taken here to incorporate equity weights was relatively simplistic; the weighting was allocated after QALY calculation within the model. An alternative strategy would identify the individuals within the cohort for whom an EoL equity weight were appropriate and incorporate this within the model. Whilst unlikely to be a concern in the short surviving cohort (where less than 5% survive over 2 years), this could be a challenge in a population with longer survival where patients move into an eligible state over the course of the model.

The possible inclusion of equity weights also raises other significant questions. These have been discussed elsewhere, however, specifically with regard to measurement and valuation of QoL near the EoL a number of issues arise:

- Are the EQ-5D domains used to derive utility as relevant in this population? Coast et al have carried out work to assess this in populations near the EoL, demonstrating that emotionally orientated goals may be of greater importance to this population.(249,277) It would seem perverse to place greater weight on an outcome of relatively reduced valued to the recipient.

- NICE's explicit equity weight (by approving a £50,000/QALY WTPT near the EoL) assumes that all QALY gains are equivalent, irrespective of how they are achieved i.e. through prolongation of life or improved QoL. There is some evidence that this may not be the case and that individuals place differing value upon QALYs derived in varying ways across the life-course.(392) The QALY gains here are small, reflecting their origin in utility improvement alone in a population with very short survival time.

- The results shown in chapter 3 suggest that the relative values placed upon these domains by the patients experiencing them may not be sustained near the EoL. Therefore as with the measurement of appropriate domains, this should be addressed before equity weighting can be considered. It is notable that the change in value placed on the domains occurs only in the final 4-6 months of life in contrast to the two year threshold NICE use to define EoL.

- In equity weighting the outcomes of the assessment of a novel technology will result in resources being diverted from other areas. It is, however, possible that this opportunity cost will fall to individuals who themselves might be eligible for an equity weight. As with most health economic analyses the methodology recognises the opportunity costs generically but cannot identify where they fall. Therefore, individuals whose health outcomes might be similarly prioritised could potentially bear this cost.(393)

- Equity weights for a population very close to the end of life might well result in a cost per equity weighted QALY gain that supports reimbursement. In the current model, however, it is clear that much of the lack of cost-effectiveness here reflects reduced efficacy in this population. As such, it would be necessary to ensure recognition of this heterogeneity of treatment effect. The finding then that treatment very close to the EoL was deemed cost-effective despite being of reduced efficacy would be hard to justify, unless other unmeasured but valuable outcomes could be shown to be affected.(393) Hope, for example, is not valued within cost-effectiveness analyses but as shown in Chapter 7 patients may value this in the absence of treatment efficacy. To what extent this value is shared at a societal level is unknown. This again raises the question of ensuring that the state that is measured, valued and weighted is also valued by the individuals experiencing it.

In addition to the above challenges arising from the incorporation of equity weights near the EoL a number of other potential challenges arise in the use of cost-effectiveness analyses for populations near the EoL. Some of these may have a significant impact upon decision-making:

- Non-health effects of interventions are explicitly excluded from the NICE reference case, (268) however, the health outcomes of carers can be incorporated where appropriate. Holistic palliative care aims to treat both the patient and their loved ones. As such, failure to recognise and measure this benefit may impact upon the cost-effectiveness of interventions near the EoL. It is not clear to what extent this is relevant to the current analysis, however, there is some evidence to support a relationship between patient quality of life and carer quality of life near the EoL.(394) How the health benefits to carers might be incorporated within the cost-effectiveness model, particularly in the context of equity weighting, is not clear.

- A further possible health benefit to carers might also require recognition; benefits to carers might accrue beyond the point of the patient's death and through the bereavement process. There is some evidence that palliative care interventions may reduce pathological grief and major depression in bereaved caregivers.(394,395) If present in relation to treatments delivered in the final weeks of life, failure to recognise and measure these benefits might underestimate the value of interventions at this time. Equally, in the context of oncological care near the EoL, which might in fact be counter-productive, failure to recognise this may result in decisions which drive a net reduction in health within a wider evaluative framework.

Burden of illness (BOI) has been suggested by NICE as a possible characteristic which might be eligible for equity weighting. This aims to provide a measurement of the effects of disease by its impact upon both QoL and life expectancy. Rowen et al assessed the value associated with BOI and found a small, but significant, positive impact upon the value of QALY gains; the greater the BOI the greater the value of QALYs gained. This result was, however, less consistent than that seen for EoL.(391) Were a BOI equity weight included here many of the patients within the cohort would be eligible, however, the challenges of implementing this are significant in this setting; the QALY loss associated with the disease state for this patient cohort will be extremely variable. Patients enrolled in the DBMS varied in age from 32 to 89.(16) Any BOI equity weight must therefore incorporate variation in lost life-expectancy alongside the significant variation in baseline QoL. The challenges to incorporating such a weight are therefore arguably greater even than that of incorporating an EoL weight.

6.4.5 *Conclusions*

Single fraction cEBRT remains the most cost-effective treatment option across a range of WTPTs for the overall population eligible for treatment. If pain response rates and durability can be replicated in larger, randomised studies, however, there may be a role of SABR for pain due to bone metastases in the English NHS. Further work is now required to better inform the clinical efficacy of SABR for pain due to bone metastases. The OBP of SABR, presented here, provides a novel and potentially valuable means to guide the commissioning of this technique as it diffuses into routine practice, ensuring that resources are allocated in a cost-effective way.

The results presented also raise questions about the likely cost-effectiveness of single fraction cEBRT in a population very close to the EoL. Greater certainty is required over the efficacy of single fraction cEBRT as compared to holistic palliative care for this population. Studies aiming to better predict prognosis in this setting are also critical to ensuring that patients can be identified with acceptable levels of accuracy to help optimise treatment for this frail population. The incorporation of such a model into the cost-effectiveness model presented here could help to guide

appropriate thresholds for treatment. Beyond, the specific treatment considered here, however, further investigation of how best to measure and value outcomes in this population is required in addition to clarification of the appropriate evaluative space in terms of spillover effects. Equity weighting might then be justified if appropriate weights and methods for their incorporation can be identified.

It is clear from these results that heterogeneity in the treated population has a significant impact upon cost-effectiveness. Indeed, the extent of this is a significant limitation to the attempts made here to consider cost-effectiveness in the context of survival probability. Incorporating baseline heterogeneity, alongside knowledge of its impact upon treatment effects, would offer improvements in the estimation of cost-effectiveness in this setting. Two options to achieve this could be considered:

Should SABR be found to provide superior quality and durability of pain and quality of life in larger randomised studies, cost-effectiveness will need to be confirmed. The use of trial-based data to support investigation of heterogeneity in cost-effectiveness should be considered focussing upon relevant sub-groups. Stratification based on predicted prognosis at trial recruitment would support this analysis allowing commissioning in populations where treatment is expected to be cost-effective. If an outcome-based pricing approach is felt to be appropriate, however, integration of regression based predictions into the model might better support incorporation of heterogeneity into the model. This approach can ensure that the treatments delivered in routine practice offer a cost-effective intervention, not extending onto the flat of the health productivity curve where the marginal gains delivered are not adequate justification for the high incremental increase in costs.

7 Patient experiences and values in relation to palliative radiotherapy for bone metastases

7.1 Introduction

The cost-effectiveness model developed in chapter 6 assesses the incremental costs relative to benefits of various treatment strategies for the management of bone metastases. The methods used are in line with the NICE reference case and the model is clinically plausible. It is important, however, to ensure that the model aligns with the experience of patients undergoing these treatments. This can help to ensure that the preferences of patients are incorporated and contextualise the results of the cost-effectiveness analysis.(396)

The use of qualitative methods in health economics is increasing and provides an opportunity to supplement and enhance quantitative cost-effectiveness models by better understanding the patient experience.(397) This can be achieved by both ensuring that the modelled parameters and pathway are aligned to those experienced by patients and by identifying elements which are not currently incorporated in the model. This latter may provide valuable information to place the model in the context of routine practice. Given the variation in EQ-VAS in relation to the EQ-5D domains demonstrated in chapter 3 with proximity to the EoL this context may be of particular importance in analyses of treatment near the EoL.

This study aimed to use a qualitative framework approach to provide improved understanding of the patient experience of radiotherapy. This supports an assessment of the appropriateness of the parameters incorporated in the cost-effectiveness analysis and allows consideration of emergent themes which may also influence the decision to pursue palliative radiotherapy.

7.2 Methods

7.2.1 *Interview study design rationale*

Given the frailty of the population treated with palliative radiotherapy a patient focus group was felt to be inappropriate, requiring both travel and time commitment resulting in an overall burden which was hard to justify. In addition, it would potentially result in the selective recruitment of a cohort with relatively good survival time, who were less frail and not generally representative of the relevant population. As such, after initial discussion with patient representatives, a small number of one-to-one patient interviews were carried out with patients who attended the Leeds Cancer Centre for palliative radiotherapy to bone metastases.

7.2.2 *Participant recruitment and interviews*

Patients were identified by members of the treating team using a purposive sampling framework recognising sex, age and prognosis as key factors potentially impacting upon the responses (see

Table 32). This sampling approach aimed to ensure patients were included with varying prognoses beyond palliative radiotherapy. Patients were recruited until data saturation was reached in the interview analyses. Eligible patients were approached face-to-face by a research radiographer and provided with written information about the study on the day they attended for their radiotherapy planning appointment. The patient information sheet detailed the nature of the study and its aim to ensure that in assessing and improving the value of palliative radiotherapy the outcomes in the model are indeed those valued by patients. If they agreed to consider study entry they were contacted a minimum of 24 hours later by the researcher. At this point they either declined study entry or agreed a suitable time for an initial interview to coincide with their attendance for radiotherapy treatment. In this way disruption to the patients was minimised. Patients provided written consent prior to being interviewed and agreed for the researcher to contact them over the telephone subsequently. The interview could be terminated at any point at the patient's request.

Table 32. Purposive sampling framework.

	Male		Female	
	<70	>70	<70	>70
Prostate	1 or 2	1 or 2		
Breast			1 or 2	1 or 2
Lung	1 or 2	1 or 2	1 or 2	1 or 2
Other	1 or 2	1 or 2	1 or 2	1 or 2

In line with the framework approach a priori themes were initially identified to assess patient perspectives on themes already captured in the cost-effectiveness model in addition to emergent themes recognised as potentially important but not well captured. As such, themes relating to costs and QALYs (for the patient and carers) were incorporated a priori in addition to patient experience of the treatment process. Further details of these a priori themes are provided below. Semi-structured interviews were carried out in line with a pre-specified topic guide (Appendix 11.1). This guide incorporated all of the a priori themes and also allowed exploration of the decision making process in order to support identification of other emergent themes. The topic guide was reviewed by a patient representative prior to submission for ethics approval. As the interviews progressed these emergent themes were incorporated into the interview process in line with qualitative methodology. Although family members were not excluded from the interviews they were not specifically invited and with patients were free to keep their relatives with them if they felt this was helpful. Interviews were recorded in the radiotherapy department.

A subsequent follow-up telephone interview was recorded approximately six weeks after treatment was delivered. All interviews were transcribed verbatim by an experienced independent typist. Manuscripts were reviewed for accuracy prior to analysis.

7.2.3 *Data analysis*

A framework approach was used in order to allow a mixed deductive/inductive approach to data analysis. Microsoft Excel was used to support data indexing and theme identification. The framework approach incorporated themes already included within the cost-utility model for deductive analysis (a priori themes) whilst allowing further, emergent themes, to be identified inductively during interview conduct and analysis.(132) Interviews were initially read and re-read to provide familiarity.

A priori themes were those that reflect 1) EQ-5D domains, 2) side-effects of treatment, 3) comfort during the treatment process/travel, 4) financial costs of attending, 5) possible non-financial costs of attending for treatment, 6) wider societal costs of treatment if the patient, or their care, incurred costs related to employment. Interviews were re-read and indexed allowing inductive identification of further themes to provide the final thematic framework. Patients were not asked to check the themes identified as the duration of the study was beyond the expected survival time of the participants and the work aimed to minimise the burden upon participants in order to allow recruitment of as wide a range of people as possible. These study outcomes are reported in line with the consolidated criteria for reporting qualitative studies (COREQ).(398)

1.1. Reflexivity

7.2.4 *Researcher background and experience*

As a researcher new to qualitative methods the process of carrying out this study was a learning experience. Equally, as a clinical oncologist I have extensive experience of interviewing patients and discussing treatments. I undertook a week long course in qualitative methods early on in the PhD period, however, this focussed more on the analysis of qualitative data and less on the interview process. Early on in the interview series I was very conscious that my approach to the interviews was much more aligned with my clinical practice than with the qualitative methodology. Having read the initial interview transcripts I modified my interview style to include more open questions and to probe for more information where patients commented on important themes. Over the course of the study there was a noticeable change in the structure of the interviews with patients providing longer, more in depth answers to more open questions. After discussion with Dr Laura Ashley (Qualitative researcher, Leeds Beckett University) I also felt increasingly able to probe patient's responses and encourage them to provide more detail. This undoubtedly strengthened the later interviews, allowing me to bring in discussions of themes arising from previous interviews.

None of the patients I interviewed knew me in a clinical context and I endeavoured to always introduce myself as a researcher. The staff on the radiotherapy treatment machines, however, know me well and I may have been introduced as a doctor by them. The extent to which this may have modified patients responses to me is unclear. One patient says "what you've done for me". This might suggest I was considered as part of the wider treating team, or may simply reflect this patient's language use.

The qualitative interview process is said to be relatively easy for clinicians to undertake as our background training and daily experience working with patients is perceived to be not far removed from this process. Certainly I did not find the interviews uncomfortable or challenging in terms of their content at the time I conducted them, revisiting them repeatedly during the analysis was, however, more challenging. I realised, the extent to which a clinical consultation is often focussed upon the necessary information to inform the current decision process, probably at the expense of exploring wider concerns. This is not the case in qualitative interviewing. I found it initially hard to probe into specific issues and ask suitably open questions. Having read the interview transcripts many times now I realise I have developed significantly in terms of my ability to conduct these interviews and found them refreshing in allowing the freedom to better explore the patients experiences and values.

7.2.5   *Initial perceptions of the research*

I started this study as a clinician with a recognition that the processes and decisions about undergoing palliative radiotherapy were more complex than can be captured in the cost-effectiveness model. Specifically, in my clinical practice, I tend towards a more hypofractionated approach whenever possible and think I am generally perceived (rightly or wrongly) to be pragmatic and relatively unlikely to encourage the use of marginally beneficial treatments. This perspective must be acknowledged in carrying out this qualitative study; I recognise I am probably more likely to identify and focus upon elements which might support this perspective and possibly avoid conflicting views. Being aware of this bias, however, has allowed me to try to remain open minded and conscious of the need to identify themes and sub-themes which support alternative perspectives.

By its nature reflexivity recognises that the analysis conducted is influenced by the researcher. This is counter to expectations in quantitative research. My influence upon the data collection process cannot be ignored. I have carried out the quantitative work presented in the rest of this thesis and therefore have an a priori belief that it is a robust and complete assessment of the reality. This qualitative analysis provides an opportunity to challenge and enhance this.

7.2.6   *Effect of the interviews on the researcher*

As clinicians we potentially don't appreciate the simple elements of getting through the day with symptoms of advanced cancer. In part this may be as a means of self-preservation, in part a lack

of time and probably also a wish to avoid acknowledging the impotence of therapeutic failure. Analysing these interview transcripts brought home to me how patients experience pain and an advanced cancer diagnosis. Specifically, this has highlighted the consequences for daily living, particularly the psychological consequences which are potentially not well captured by routine measures of HR-QoL. This experience may change my clinical practice but it's likely I'll relax back into a more standard clinical approach due to the pressures outlined above. It will undoubtedly influence my academic work and motivation to contribute to improvements in the measurement and valuation of HR-QoL near the EoL.

7.2.7   *The patient information leaflet*

It was clear during the interviews that different patients interpreted the patient information leaflet differently. Some focussed heavily upon the practicalities of treatment and provided feedback which could potentially improve care within the department. Others were clearly very aware of the financial side of the analysis and concerned about the costs of the treatment they were receiving. It's hard to know to what extent this reflects the information sheet and to what extent this is inevitable; individuals will always focus upon specific elements of importance to them. The interviews did not specifically ask about patient's views of cost-effectiveness and value of treatments. All interviews contained all elements of the topic guide although with variation in the structure dictated by patient's responses.

7.3   Results

7.3.1   *Study population*

A total of nine patients were recruited to the study. Having recruited six individuals it became clear that the patients recruited in this way were predominantly of good prognosis and as such specific efforts were made to identify patients with poor prognosis through discussions with treating consultants. All patients recruited to this study underwent a single 8Gy fraction of palliative radiotherapy in line with local protocols.

17 patients were approached to consider entry into the study. 9 agreed to take part. For the other 8 patients the reasons for non-participation varied; predominantly this was a reflection of feeling that they had enough to cope with at the time without the additional burden of study entry, others were simply reluctant to take part with reasons reflecting both a broader reluctance to participate in research and specific reluctance to enter this study. 14 interviews were conducted; in four cases the follow-up telephone interview was not conducted due to the patient's deteriorating clinical condition or death.

The interviews carried out within the radiotherapy department lasted 20-45 minutes and relatives were present during three of the nine interviews.

Table 33. Characteristics of the final qualitative study population (*Patient study ID*, Age in years, Survival time in months).

	Male		Female	
	<70	>70	<70	>70
Prostate	**1** (*2*, 69yrs, 6.1)	**0**		
Breast			**0**	**2**
				(*3*, 75yrs, >14.8)
				(*5*, 76yrs, >8.4)
Lung	**1** (*4*, 56yrs, >8.4)	**0**	**0**	**1** (*6*, 74yrs, 2.0)
Other	**1** (*1*, 48yrs, 9.0)	**1** (*8*, 76yrs, 2.6)	**1** (*9*, 57yrs, 2.3)	**1** (*7*, 75yrs, 0.9)

7.3.2 *Patient interview results*

Content analysis of the interview transcripts identified a number of themes and sub-themes resulting in the framework presented in Table 34.

Table 34. Thematic framework of patient's experiences of and expectations for palliative radiotherapy and its benefit.

Themes	Sub-themes	Description
A priori themes		
EQ-5D HR-QoL domains	Pain	Patient's experience of pain
	Mobility	Patient's experience of their ability to mobilise
	Self-care	Patient's experience their ability to self-care
	Activities of daily living	Patient's experience of their ability to carry out routine activities of daily living e.g. work, leisure activities, housework.
	Anxiety/depression	Patient's experience of anxiety/depression
Side-effects		The side-effects experienced and those which raise concerns for patients undergoing radiotherapy.
Treatment process	Comfort during planning and treatment	Patient's physical experience of undergoing the radiotherapy treatment process.
	Physical comfort travelling	Patient's experience of travelling for treatment.
	Financial cost of attending	The financial costs experienced in attending for radiotherapy.
	Emotional aspects of attending	Any emotional responses to the radiotherapy treatment process.
	Social aspects of attending	How patient's experience attending for treatment in relation to those around them e.g. whether

		attending for treatment impacts upon their ability to spend time with loved ones.
Impact on others	Financial and time impact on relatives/friends	How attending for treatment impacted upon a patient's friends and family in terms of financial costs and time.
	Emotional impact upon relatives/friends	What, if any, emotional impact attending for treatment had on friends and family.

Emergent themes

Capabilities	Enjoyment	A patient's ability to enjoy the activities they are able to undertake.
	Preparedness	A patient's ability to prepare for the end of life.
	Independence	Being able to remain independent of others and therefore able to maintain autonomy and choice.
Adaptation and coping	Recognition of changing expectations	Patient's awareness of how they have adapted to accommodate their changing physical condition.
Impact on others	Burden of disease upon relatives/friends	Feelings of being a burden to friends and family as a result of their disease.
	Opportunity cost to others	The possible opportunity cost of the patient receiving treatment in terms of others healthcare.
Factors impacting upon decision making	Confidence in advice from the treating clinician	The role of trust and confidence in the treating clinician in the treatment decision-making process.
	Psychological benefits of receiving ongoing treatment	Psychological benefits of undergoing treatment which do not relate directly to the relief of pain.
	Expectations of family and friends	Any expectations from family/friends which might influence a patient's decision to undergo treatment.
	Trade-offs	The balance between the treatment burden and side-effects which might be expected and the potential benefits of treatment.
	Hope and uncertainty	How uncertainty in the expected outcomes of treatment and disease are handled and the role of hope in managing this uncertainty.
Study participation	The wish to give something back	Patient's altruistic desire to give something back for the treatments they have received.

7.3.3   *A priori themes*

7.3.3.1   EQ5D Quality of life domains

7.3.3.1.1 Pain

All patients reported that they hoped radiotherapy might relieve their pain.

   "...at the moment it's just pain relief, because at the moment I'm getting a lot of lower back

   pain, so I'm hoping and that the treatment will dampen that pain down." (1a)

"Well, if it relieves the pain then it's worth having it, you know, to relieve the pain." (3a)

"I'm doing it because I want to get rid of the pain" (6a)

"the pain gone, like I said, once the pain goes I'll be fine." (7a)

"that it's going to help with the pain, we hope." (8a)

"I'm just grateful for any assistance to ease that pain. " (9a)

7.3.3.1.2 Mobility, usual activities and self-care

Multiple patients stated that pain relief was hoped for, however, there was immediate recognition that this was a means to an end, their principle hope being improvement in mobility, activities of daily living and self-care.

"I can't walk very far before I start getting a cramp-like pain" "I mean my hobby, before I became ill, was fell walking, would you believe, and I do really miss getting out on my own, just being me and the world, you know, the fresh air and, yeah. I miss that, but I can't do it now," (2a and b)

"I mean, try and get this leg going again, you know, it'll solve lots of problems but at present it's causing a lot." (8a)

"there's lots of things I don't do because I know it's going to hurt. " (7a)

"Well, lifting things. Any sort of use, I'm left-handed and it's on the left side" (5a)

"by teatime I were absolute agony and I had to take morphine and go to bed."(4a)

"Well I can walk farther now so I mean there's silly little things like going to shopping centres and walking round"(2b)

"Getting socks on and things is worse because I can't get down."(8a)

7.3.3.1.3 Anxiety/depression

For one individual a wish that treatment might slow the tumour growth was expressed alongside the desire for pain relief. It is unclear if this effect would be captured by the anxiety domain of the EQ-5D.

"Yeah, to stop it from sort of forming any bigger and also to help with the pain I'm getting from it, yeah."(5a)

The wider impact of pain relief was also expressed with two patients reporting that the pain was resulting in reduced enjoyment in other areas of life and had emotional consequences. These might potentially align with the anxiety and depression domain of the EQ-5D.

"if I can relieve that pain so that more of the time is focused on the pleasurable things in seeing friends and family and I can relax and enjoy that," "even if I can't do a great deal, but if I can be with people and be able to enjoy that, that's what really matters." (9a)

"even watching the television I'm not enjoying it, because of the pain."(6a)

7.3.3.2   Side-effects

Side-effects of treatment were a concern for many of the patients. For some this manifested as uncertainty and anxiety about how the treatment would affect them. One commented on the reassurance they'd received from their doctor, although this had not completely resolved their worries.

"I'm just wondering how much, whether they're going to give me a much stronger dose this time than they have before."(3a)

"the thought of that the pain might be worse afterwards before it gets better, because I'm not really settled with any particular pain medication, sometimes it works, sometimes it doesn't."(6a)

"I am nervous about the level of pain it's going to give me before it all settles down, yes" "Diarrhoea is one that concerns me. And again, that again had to do with the having confidence to go out and about."(9a)

"Well, yes, that's one thing that I do worry about. But from what I've been told, I'll be alright." (5a)

In follow-up interviews patient's views differed about the side-effects experienced as is expected given the wide variation expected in side-effects with site treated. For some there was uncertainty expressed about the origin of the symptoms they were experiencing with acknowledgement these might not have been entirely attributable to the radiotherapy.

"Well I were quite ill for a good week or 12 days, after I'd had the radiotherapy" "the days following I was just weak and wobbly and feeling generally unwell" "I think because, you know, I had the bout of illness or whatever it was and thinking it was the radiotherapy, it was a shock for me, because I thought just having one lot I wouldn't get any symptoms" (5b)

"I wasn't too bad actually, I expected to have a lot more pain than what I had, but I didn't have a right lot of pain either, so no, I'm chuffed to ten!"(2b)

"I think I was feeling a bit sickly and of course I'd lost me appetite before but, I don't know, every time I seemed to be enjoying a meal and then it wanted to come back up again."(8b)

"I do fight this tiredness but it's, you know, you just can't work out, really, whether it's just the radiotherapy or whether, you know, it's just old age" (3b)

One patient expressed some conflicting views. Having previously expressed a willingness to trade-off benefits and side-effects they reported feeling "fed up" that the side-effects of treatment

had limited their activity for a number of days. It is difficult to interpret this, the patient expressed understanding of the side-effects and their potential to lead to limitations but the reality of this trade-off was still unpleasant.

"just after radiotherapy and I just slept and slept and slept every day" "No, just a bit fed up I was missing half the days. In my position, yeah, in my position I don't want to be missing out on a right lot to be fair" (4b)

7.3.3.3   Treatment process

The experience of undergoing treatment was associated with a number of consequences not readily considered as either HR-QoL or side-effects but which relate to the treatment process and were broadly identified within this theme.

7.3.3.3.1   Comfort during planning and treatment

For some the treatment process itself was associated with discomfort, although this was by no means universal. Many patients reflected upon how much staff had worked to ensure they were comfortable.

"They got me all prepared, and then I suddenly thought, "I always get cramp on my left leg", so I moved a tiny little bit and, of course, it all had to be set up again"(3a)

"longer you lay down, certainly with lung cancer where the sputum on your chest, laying flat's quite, it just starts to make you want to cough,"(4a)

"That was very hard. Right up to the point where, I don't know, I don't know how long I'd been laid there, and my arm, elbow were pressing on some metal"(5b)

"It really were quite scary, because they show you a photograph of the machine but it doesn't let you into the thing whereas when you walk in that room and look at it all and think, ooh"(4b)

"Yeah, no problems at all, it's very quick." [discomfort during treatment] (4b)

"and made me comfy which is important to me because me back was really hurting me"(1a)

"Oh that's fine, that's lovely, in fact I could doze off."(7a)

7.3.3.4   Travelling and attending for treatment

Various sub-themes relating to the need to travel and attend for treatment were identified.

7.3.3.4.1   Physical comfort travelling

For some patients travel was reported to be uncomfortable, although they coped with this in various ways adapting to their situation as well as possible.

"It's not nice because if I sit on seats like this for long, I get pain."(8a)

"you learn to put the cushion in the right place and generally then, yeah I'm quite happy."(9a)

"a collar and cuff, and since she got me that, driving in the car has been so much easier, because it cushions"(7a)

"I took painkillers on the way back home, but, you know, it's fine."(3a)

7.3.3.4.2 Financial costs of travelling

Generally, patients were not concerned about financial costs of coming for treatment although this varied with personal circumstances. Some reported that using hospital transport meant their personal costs were minimal and the stress of attending was reduced.

"picking me up with the car and bringing me, took all the stress out of any travelling because I'd never have found it if I'd been driving"(8a)

"If it costs, it costs money, you have to pay."(7a)

"No, no, nothing, no, nothing at all, but if there was any cost it wouldn't really bother me, you know, I'd be happy to pay it."(2b)

"the only cost that occurs is I have to come by taxi if I haven't got a friend or a relative that's bringing me…But my son's brought me today, yeah." (5a)

"So, yeah, cost is an issue and especially because I've had to give up work and had to go onto benefits, it does create problems but you get over it."(4a)

"no, it's been alright, well fortunately I'm still working but I'm on, I've got really good sick pay, so financially I'm in a good position which is more than most people, so that that's fine."(1a)

7.3.3.4.3 Emotional aspects of attending

Anxiety in relation to attending for treatment was present for many patients. Patients expressed this in terms of the feelings associated with spending time in the hospital. In some cases this related to anxiety about attending a previously unknown hospital, conversely, others reported the experience of spending time in a known hospital was associated with distress.

"It was me, I got a bit worked up and I was halfway down the corridor and I forgot which machine it was, so I had to go back again"(3a)

"Apprehensive, apprehensive about today" "hell of a walk love, and it's daunting because the ambience, the highness and the largeness, again overpowering."(7a)

"Yeah, well, there was one thing this week worrying about the weather, although I wouldn't be driving so it's a less of a worry but, yeah, getting here is..."(2a)

"If you're sat in here for hours on end, they just, they're just not nice places to sit and be really at the end of the day and all it does is remind you of what you're sat here waiting for."(4a)

"towards the end of my last treatment, I'd had 30 days solid, one day after the other, and I were quite ill towards the end, so I walked back in this morning and it's all a bit like visual association. So I nearly felt ill when I walked in, it were quite bizarre,"(4a)

For one patient anxiety was expressed in relation to the need to remain still throughout treatment. The patient had experienced pain whilst trying to maintain the treatment position and was concerned about the impact her struggling to remain still have upon the treatment,

"it's so vital they get it right."(3a)

7.3.3.4.4 Social aspects of attending

Concern about possible social costs of attending varied between patients; predominantly patients reported that treatment did not feel like a burden, that they could work around it or that the benefits were sufficient to out-weigh this burden. For two patients, tiredness was a specific factor mentioned in relation to attending for treatment. One patient expressed both a lack of concern about time spent attending whilst more holistically reflecting that their time was precious as a result of their incurable diagnosis.

"*don't bother me because everybody's out at work.*" (4a)

"*No, not really, I mean, if I wasn't travelling or coming, I would only be at home.*"(8a)

[what you would be doing otherwise] "*Nothing, probably trying to think about doing some craft or tidy up, which I'm not doing very well, but…*"(6a)

"*I just work round them socially. You know, to me, this is more important and I'm sort of…*"(4b)

"*I would never think that, not if I was having treatment, it's for my benefit int it.*"(2a)

"*I would rather be lying down and having an hour*"(7a)

"*but sometimes you think you're coming for an hour appointment and it turns into three hours, that can be a bit frustrating and tiring because once you come home from here you're like shattered.*"(1a)

"*I'm used to that, because I'm going through palliative care so I've got loads of time*" "*that seemed like a waste of me time and when you're on palliative care every hour counts*"(1a)

For two patients the social costs of coming for treatment were considered relative to other treatments they'd seen or experienced and they, therefore, felt the burden of palliative radiotherapy was small.

"because of the way it is and I'm only coming for one or possibly two, depending how it goes, treatments, that's not really an issue for me when I consider what we needed to do for chemotherapy but that doesn't seem a big deal"(9a)

"I mean, I'm lucky because it's always one that I'm having, I'm not having to come every day and have three weeks of it, so I'm thankful for that"(5a)

Finally, in some cases positive interactions were reported. These occurred with other patients, with staff and with family members. These potentially reflect a benefit of the treatment process which is beyond those routinely measured.

"But the whole thing was just, in a way, actually, it was a day out [laughs]. I know it might sound strange to you to say that, but it was just nice to have some company, you know, and everybody was kind there"(3b)

"in fact I met, I actually met an old friend and he was going there virtually every day"(2a)

"And his face went from this, like that to actually brightening up a little bit and all them little things help. The surroundings are nice, it's nice to sit out there," (4a)

"apart from I'm seeing more of me son now, than I have done in the past, you know?"(6a)

7.3.3.5   Consequences of treatment for others

Patients were asked about the impact of treatment upon those around them. For some this related predominantly to impacts upon their loved ones. These consequences could be separated into sub-themes reflecting the more physical and financial consequences of treatment (often relating to employment) and the broader emotional consequences of the disease and treatment.

"Yeah, well, he booked down to work at home and he's brought his laptop but he can't get it up and running in this department, so"(5a)

"My husband drives. And my daughter's come, yes, for the support. It's her day off today"(7a)

"I rely on me son having the time off work to take me," (8a)

"I think it's just the stress of waiting and not understanding and also being in a room where everybody's ill, really the waiting room it's, it brings back the reality that your husband's really poorly, and I think that upsets her"(1a)

"Obviously it's just the anxiousness of them, of me being OK for me to get here and get home."(4a)

7.3.4   Emergent themes

7.3.4.1   Capabilities

The capabilities framework was originally described by Amartya Sen as a means to inform the outcomes of economic development.(399) This approach has more recently been adopted as the basis for the development of alternative measures of wellbeing in health economics.(234,277,400) Sen's approach takes the perspective that life "is seen as a set of "doings and beings" that are valuable". He suggests that by identifying and measuring these "functionings" a picture can be

developed of the individual's capability to function. From this perspective many of the domains measured by the EQ-5D can be perceived as resources; the means to support a patient in functioning but not of themselves the ends. A number of patients expressed elements which might be considered more holistically within a capability framework. This does not suggest they are ignored by the EQ-5D measurement but that they might be more fully incorporated by recognising them as elements of capability functions.

Examples of this follow, with reference both to the EQ-5D domains they reflect most closely and the capability functions which may go beyond theses EQ-5D domains:

The ability to enjoy time spent with loved ones was reported to be important to patients. This might reflect a combination of the anxiety/depression and usual activities domains of the EQ-5D. It is unclear if these domains will adequately capture this outcome although the statements below have been considered in both contexts.

> *"even if I can't do a great deal, but if I can be with people and be able to enjoy that, that's what really matters." (9a)*

> *"even watching the television I'm not enjoying it, because of the pain."(6a)*

For some patients the reduction in autonomy and independence was a significant concern. Again, this might be expected to relate to the activities of daily living and self-care domains of the EQ-5D, however, again might be more readily accommodated by a capability framework which explicitly recognises and values the overall function.

> *"I mean my hobby, before I became ill, was fell walking, would you believe, and I do really miss getting out on my own, just being me and the world, you know, the fresh air and, yeah. I miss that, but I can't do it now,"(2b)*

> *"and it's so frustrating when I want to get up and do it meself you see and I can't"(6a)*

> *" I can't, because of the pain I can't push myself up with that side, so every time I want, if I'm with Michael and he has to come and pull me up with my good arm,"(7a)*

> *"I'm that used to popping into the car and into [town], now I've got to rely on other people doing these things."(8a)*

Having prepared and being able to prepare was also reported by two patients. This preparedness is unlikely to be captured fully by the EQ-5D usual activities domain but has been identified as important to patients nearing the EoL.(277)

> *"So I'm hoping that I'll have a bit more freedom for a short while anyway if the treatment works"*
> *"I think, probably, if it just gives me a year to sort of sort my life out a bit more, it will be a great help," (3a)*

> *"No, I mean, I even moved house to, I lived out in a little village out, a long way from Leeds and I even moved house and came back to live in Leeds, to live near one of my sons and, so that I were here for this"(5a)*

7.3.4.2 Adaptation and coping

Broader concerns about the effect of deteriorating health were also expressed.

"This year, a year last September I was as fit as a butcher's dog, nothing wrong with me at all"(8a)

"loss of confidence in what I'm able to achieve has really limited me even wanting to try those anymore."(9a)

"so I think the loss and potential loss of the mobility was a big issue for me, I'm very active, swimming and golfing and walking and that, really a big problem." "but I was doing quite a lot of exercise to keep myself fit and I've not been able to do much of that because I've spent longer in bed" (1a)

Two patients expressed recognition that they had modified their behaviours and expectations to adapt to their increasing physical frailty. Activities which might previously not have been considered enjoyable were now more pleasurable. This is likely to reflect "response shift". This phenomenon is seen in the measurement of HR-QoL where individuals adjust their internal standards and values to accommodate their deterioration.(401) It is notable that both these individuals died before a second interview could be carried out and were, therefore, within weeks of the end of life at the time of their treatment.

"So, the day was cosying up in a lovely chair watching a lovely view, which is not us, it's not us, we've never been people to go to a place and sort of stay in. We've always been out and about."(9a)

"So yes, I do quite enjoy that, which I never thought I would've done years ago, but there you go." (7a)

Two patients mentioned awareness of their deteriorating health, how this had already affected them and uncertainty about how it might affect them in future.

"when people used to say to me, yeah do it while you can, I used to think, what do they mean? Now I know what they mean"(9a)

"I just would like to know what's ahead, but nobody seems to want to tell me, but I like to know. I don't dwell on it, but I like to be prepared," "I'll become sort of really housebound and rely upon people with drugs that I've got to take, I'd rather not prolong that stage."(3a)

7.3.4.3 Consequences of treatment for others

Predominantly patients focussed upon the practical and financial impact of treatment upon their loved ones, however, two patients reflected upon a wish not to place more of a burden upon their relatives. This sentiment goes beyond the more practical aspects of treatment burden to a broader construct.

"I don't like upsetting all their life really but unless it's, you know, really necessary."(8a)

"I put enough on him, he does more than enough for me."(7a)

One older patient, possibly in recognition of the information provided about the study, commented on the trade-off between her treatment and care for others. She felt she would not have raised this but given the limited funding available and the context of the interview she expressed some concern about this.

"because I think a young person should have priority over an old, well it's very difficult, it's personal"(3a)

"But, you know, if it wasn't, if you weren't short of money then I wouldn't bring this discussion up"(3a)

7.3.4.4 *Influences on decision-making*

Multiple sub-themes were identified relating to the decision to undergo palliative radiotherapy. These recognise influences upon decision making coming from others and from the patient themselves in addition to incorporating trade-offs and uncertainty about expected outcomes.

7.3.4.4.1 Confidence in advice from the treating clinician

The relationship between the patient and their doctor was mentioned in multiple ways. This may be interpreted as an expression of trust and confidence in the doctors judgement, although at times the impression given is of a passive role for the patient in accepting recommendations from their doctor.

"Well that was from an Oncologist, so I took her word for it […] To take, yeah, that's why she's in that position." (7a)

"I came to see the consultant and so they suggested that I have this palliative radiography" "anything that they think will be beneficial to me, you know, I'll sort of say thank you very much, yeah"(5a and b)

"if you said to me, you know, "You need to have that again," then yes I would be doing it again"(4b)

"I've also got a referral to see a back specialist to see whether I need potentially an operation to alleviate that pain, so I've been, I'm hoping that I don't need that, and I'm hoping that the radiotherapy will just dampen down the pain"(1a)

When asked about how they might feel about the need for a more prolonged treatment course patients expressed mixed views. For many the confidence they had in their treating clinician was reflected in their willingness to pursue more prolonged treatment if this were felt necessary.

"I'd accept it, definitely, you know, I sort of accept whatever's offered to me because I want to sort of, well, fight it, I know I can't beat it, but fight it, yes"(5b)

"I'd be fed up because that means coming all that way again every day and back. But if that's what it needs, that's what it needs." "You need to have that again," then yes I would be doing it again."(4a and b)

"Probably heavy going I think, coming in here every day. But saying that I've had 50 lots of chemotherapy, so it's take it in its stride."(1a)

Conversely, for one patient who derived significant benefit from treatment, regret was expressed that treatment had not been offered sooner to enable him to return to his previous level of function for longer.

"The only thing I would say about the radiotherapy, I wish I'd have had it eighteen month ago, because at least the last year I could have done a lot more than what I've been able to do, so on that score I'm disappointed, you know, that I didn't get it earlier."(2b)

7.3.4.4.2 Psychological benefits of undergoing treatment

Many patients expressed a feeling of reassurance just to be receiving treatment, irrespective of the benefit it delivered. Placing this in the context of the patient's broader experience, one patient expressed recognition of the psychological impact of their diagnosis.

"...actively trying to do something about it, it makes you feel better, even if it isn't working." "If we weren't doing anything, then I'd feel very forlorn because then, you know, it's very, very bad news then."(4a)

"So yeah, it's just knowing there's something happening too..."(9a)

"Positive that I knew something was happening, I was having a treatment plan which is really important,"(1a)

"more peace of mind, to think that you're having something done about it other than popping pills, do you know what I mean, do you understand?"(5a)

"But I'm really grateful that, you know, I had the chance to try and have some relief,"(3b)

"I can't understand people who would say no [to treatment], just can't understand." (7a)

"And yes, for a great deal of the time what your head is doing to you is worse than what the disease is doing to you at that time physically."(9a)

When asked how their family felt about them coming for treatment, patients often expressed similar feelings of reassurance for their family to those they expressed for themselves.

"and so I think me coming for radiotherapy they think, oh that's good, go and see a back surgeon, oh that's good, so they feel as if I'm doing something myself rather than just saying, no, I've had enough and see what happens."(1a)

"so anything that will help and prolong my life, you know, the family wish me to do it and grateful that it's provided"(3a)

"Oh she's pleased but obviously she's worried about the future."(2b)

"very much of the fact that we're actually doing something."(4a)

7.3.4.4.3 Incorporating the expectations of others

Patients reported that they felt their relatives were in favour of their having more treatment, with this view conflicting with that of the patient themselves in two cases. For one patient this extended further and a feeling of not wishing to disappoint the treating team was expressed.

"Well I think he's more for it, you know, when I've said, "Oh I don't know about that," and he's said, "Go, you need to go,"(6a)

"I don't know how they feel genuinely, well yes, I do know how they, they genuinely feel, that I should have it, so yes, I suppose it does affect them really."(7a)

"I mean, part of me would like to give in and not to have it and not to prolong the agonies of dying ahead, but my family don't want that, and I can't, it's a responsibility for being alive and for what you've done for me and, you know, I'll just go ahead and have treatment." "I cannot, as a Christian and as a mum of three daughters, I can't not have it, it sounds double Dutch..." (3a)

7.3.4.4.4 Trade-offs

The decision making process was recognised by some patients to involved trade-offs. These were expressed in terms of trading off between benefits and side-effects or time spent attending. Patients were largely willing to accept to these trade-offs.

"I'm expecting to be not so well over this next sort of, maybe a week, so I've got a couple of things planned in the next two days then I've got nothing planned in at all and expect to be maybe laid up."(4a)

"Well there's always a price to pay isn't there [laughs], there's always a price to pay. Again, as long as it's, you know, it's not making your life that miserable that you can't get on with it,"(4b)

"I would never think that, not if I was having treatment, it's for my benefit int it."(2a)

"sit there all day if they're going to help me and if, you know, provided I get the treatment, I'll just sit and wait, I wouldn't complain" (3a)

For some the possibility of a more prolonged treatment course prompted recognition of the trade-offs being made. For these individuals a single treatment was acceptable whilst a longer course might have been too great a burden. It isn't clear if these patients would, none the less, have accepted more prolonged treatment.

"I wouldn't have felt very good, to be quite honest. That's one of the things I was dreading, if I had to come sort of every week or whatever for eight or ten or whatever, that would have played on my mind quite a bit, you know, it would have worried me."(8a)

"but I'd probably find it very tiring but obviously it's something that has to be done, so yeah, you get on with it."(2b)

"She said it'd be a one-off dose, and I accepted that, and so if she asked me to come back for more, I think I'd have to think three times."(7a)

"Well I was hoping it was just a one-off"(6a)

7.3.4.4.5   Hope in the face of uncertainty

In discussions around the side-effects and benefits a number of patients recognised the uncertainty present in decision making. These comments were often made with recognition that whilst uncertain there was potential for benefit and treatment was therefore worth pursuing.

"Nobody can explain to you the side-effects of what's going to happen because I'm sure everybody's quite different"(4a)

"because I have been a little bit iffy about this, you know, and I'm thinking shall I not bother, you know, thinking I can't stand it if the pain gets any worse"(6a)

"doing something is better than not doing something, even if it might look a little bit futile sometimes, or the result's not as great as you might have thought it would be."(4b)

"Yes, well, if they said it most likely won't work, then I would have said, well, you know, I won't bother but if there's any hope, while there's hope there'll have it done."(8a)

"Because you'd… you… because of your diagnosis, you know, you just clutch at anything that's offered to you, because in the hope that, you know, it is going to make you well again."(5b)

7.3.4.5   Patient responses to the study

For three patients participation in the study was expressed as being positive. For one this provided an opportunity to give something back, in return for the treatment they had received.

"As I say I will sort of say yes to any sort of trial or anything that's offered to me, you know, I've… sort of my way of giving back to what I'm sort of getting from them, you know, so yes."(5b)

"And again if you ever need any help for meself on that sort of thing,"(4b)

"I'd just like to help if I could, you know"(3b)

In one case, the experience of undergoing the interview was reported to be a positive one, despite the patient reporting that they don't usually like to discuss the issues raised within the interviews.

> *"I'm grateful that you've asked me the questions that's led me into sort of talking about it,"*
> *"I don't like talking about it, I don't, I just get on with it and sort of keep it to myself I suppose, yeah" (5b)*

7.4   Discussion

This study aimed to assess both the extent to which the parameters incorporated in the cost-effectiveness model presented in chapter 6 align with patients' experience and values, and determine if other elements exist which might influence the decision to pursue palliative radiotherapy. Overall, patient's reported priorities and expectations aligned well with the a priori themes and sub-themes identified from the parameterisation of the cost-effectiveness model. Specifically:

- The domains of the EQ-5D were of high-priority: Pain, usual activities, mobility and self-care were all reported to be important. The anxiety/depression domain was not focussed on a widely, although it's relevance was recognised and the reassurance gained from undergoing treatment might fit into this domain.

- The payer perspective of the model is justified. patients reported limited concern about the financial costs of attending for treatment, in part due to the availability of hospital transport, funded by the NHS.

- Side-effects were a concern and therefore, their capture within a utility decrement in the health economic model is appropriate.

In addition to the themes relating to the cost-effectiveness parameterisation discussed above the additional a priori themes relating to the treatment process were supported. For example, patients expressed manageable discomfort when travelling, although this was not universal with one experiencing significant problems on the journey home. Some reported anxiety about attending for treatment and found the process stressful. For a small number of patients, attending for treatment provided a positive social experience, giving them an opportunity to spend time with others, including family. All patients in this study received a single fraction of radiotherapy. It is unclear if the offer of more prolonged treatment would have been refused. Given the perspective of patients expressed here, it seems probable this might well have been accepted, particularly if the information given and received is not adequate to reflect realistically the available options, including single fraction treatment.

Due to the very short-term impact of these process factors, however, they are not well captured in the cost-effectiveness model. Such factors are recognised as being relevant within the NICE

reference case, although they are not explicitly parameterised within the cost-effectiveness model and are instead accepted as qualitative data.(268)

7.4.1 *Capabilities as outcome measures*

It is notable that whilst many of the patients' priorities are well captured by the EQ-5D some might potentially be better represented in a capability wellbeing framework.(277,399,400) As described above, this focusses upon functioning; what a person is able to be and do. A number of elements expressed by patients in these interviews are suggestive of important outcomes which might, in part or whole, fall beyond the scope of the EQ-5D. Specific examples of this were: enjoyment of life; independence, autonomy and burden to others; preparedness. Falling independence might be captured within the EQ-5D self-care and usual activities domains, however, the broader consequences of this in terms of autonomy and burden to others are unlikely to be so well captured. Ability to prepare for death may reflect combined physical and mental attributes but it is unclear that this can be well defined by the domains of the EQ-5D. Finally, the ability to enjoy activities will not be measured by the EQ-5D; if a patient is able to be with loved ones and this is felt to be a usual activity, then from the perspective of the EQ-5D this is success. That the activity was not enjoyable due to physical or emotional suffering may not be well captured.

Measures of capability are explicitly aiming to assess outcomes beyond health in order to deliver a broader measure of wellbeing. As generic measures of capability well-being the ICECAP modules may support this. The Adult (ICECAP-A) module and Supportive Care Module (ICECAP-SCM) being of specific relevance. ICECAP-A incorporates five domains; stability, attachment, autonomy, achievement and enjoyment.(400) All of these align with the themes identified here, with the exception of achievement, possibly due to the palliative nature of the cohort. The ICECAP-SCM is specifically developed for patients very close to the EoL and so incorporates other relevant domains: Choice (being able to have a say); love (being able to be with people who care about you); freedom from physical suffering; freedom from emotional suffering; dignity (being able to maintain dignity and self-respect); support (able to have help and support); and preparation (having the opportunity to make preparations). ICECAP-A might well provide a good measure of wellbeing for many patients treated with palliative radiotherapy. For some, however, based on these interviews and previous studies, the ICECAP-SCM may be more relevant, particularly as patients near the EoL.(249) This study supports the ongoing development and assessment of the role of capability based measures as means to assess outcomes for patients near the EoL. These consider domains beyond those currently captured in routinely used HR-QoL measures and might provide greater insight into domains of high importance to patients.

7.4.2 *Decision making*

Notably the patients interviewed here largely expressed a feeling that the treatment burden (both process and side-effect related) they were aware of was justified by the potential benefits on offer.

On further questioning, however, there was widespread recognition that the process of undergoing treatment was, of itself, beneficial from a psychological perspective even if the medical benefits were small and uncertain. This psychological benefit was expressed as being "reassuring" and "really important". A number of patients went as far as to recognise that even were treatment "futile" it would still be preferable to be "doing something" and that "any treatment's better than no treatment". This has been reported in previous qualitative studies where it is suggested that this allows "some semblance of control" and "avoiding confrontation with the little efficacy that the physician has to offer".(402) It does, however, raise significant challenges in attempts to reduce the use of palliative radiotherapy very close to the EoL in line with the findings of the cost-effectiveness model (chapter 6).

Limited ability to predict outcomes, both in terms of survival and quality of life, may hamper fully informed decision-making. Equally, the delivery of unfavourable, cold, numerical expectations has been reported to be damaging to hope.(403) Conveying necessary information to support informed decision-making whilst maintaining hope is, therefore, recognised to be challenging.(404) Studies have identified that clinicians underestimate the information needs of their patients.(405–407) Indeed, other qualitative evidence, has found that where information is provided by oncologists about the survival gains of palliative chemotherapy this was often unclear, and that discussions about both chemotherapy and radiotherapy are often overly optimistic.(408–410) It has been shown that aside from a desire to protect their patients from bad news, this over-optimism may, in part, reflect clinicians need for self-preservation (overly optimistic predictions also being shown to be more likely with increasing duration of clinical relationship) or a failure to recognise a gradual decline.(411) Conversely, it has been found in other settings, that patients who are fully informed about their treatment decisions may pursue less aggressive treatment, whilst those whose beliefs about their prognosis are less realistic may be willing to pursue interventions more likely to damage their HR-QoL.(412,413) Ensuring adequate information is available to make an informed decision is, undoubtedly, not a simple undertaking.

It has previously been shown that patients may be willing to hand responsibility for decision making to clinicians, as is illustrated in this study.(402) This has been said to provide a number of advantages to the patient: unpleasant information may be avoided; information asymmetry and lack of understanding is then perceived not to impinge upon an appropriate decision being made and the burden of responsibility for the outcome of a given decision is avoided.(402) This, however, raises significant challenges as information asymmetry may be two-sided; the clinician having a better understanding of the disease and its treatment, the patient having knowledge of their lived experience, priorities and values. If the desire to avoid unfavourable information giving and relieve patients of decision making burden results in a failure to address the clinician's lack of information about the patients values, this might limit the clinician's ability to recommend

treatment which is aligned to these. Aggarwal et al suggest that clinicians use "Nudge" techniques in routine clinical conversations to guide patients away from reasoning failures. They acknowledge that whether this is ethical remains open to debate but that it is undoubtedly happening and that transparency and self-awareness amongst clinicians are needed.(414) A further factor which might support the ethical use of "Nudges" in the clinical consultation is ensuring that the clinician has a thorough understanding of their patient's preferences. In this way decisions which might be thought to reflect reasoning failures by the clinician may be demonstrated to be rational from the patient perspective. "Nudges" might then be more justified if these reasoning failures are identified as running contrary to the patient's own expressed priorities and values.

This study also identifies the additional recognition from patients that where benefits and outcomes were uncertain there was always hope for a positive result; hope is predicated on uncertainty, with certainty there is no need for hope. Again, this aligns with the findings of previous studies.(402,403) This further highlights the challenges of communication in this setting; prognostication and prediction of outcomes is inevitably uncertain and where uncertainty remains the patients interviewed here expressed a wish to pursue treatment, even if the potential for benefit was small. This will favour treatment very close to the EoL as a means to maintain hope, as has been demonstrated in modelling studies previously.(415) It is clear that this maintenance of hope is of high importance to patients, however, how it might and if it should, be incorporated into decision-making at a population level is unclear.

Shared decision-making might ensure that treatment decisions reflect not only the optimal treatment for the cancer or symptom but better alignment with each individuals values and priorities. This has been recommended by NICE in the English NHS and aims to ensure that both the clinician's and patient's expertise are represented in the decision making process. It is, however, not without its challenges.(416) These have previously been identified within the MAGIC programme and include challenges from both a clinician and patient perspective (including a perception that it is already done, that the tools and time to deliver it are not available and that patients don't want it).(417) Given the views expressed by patients here, specifically their willingness to entrust decision-making to their treating clinician and to pursue treatments of uncertain and marginal benefit the need for a shared decision making approach is clear. This does not mean the patient is forced to make every decision but that the individual doing so is fully informed of their perspective.(418) In addition, more robust means to predict both survival time and response probability might offer a valuable improvement on current clinical estimation and support for the shared decision making process.(412)

7.4.3 *Limitations*

This study has a number of limitations. It has previously been recognised that the identity of the person who asks a patient about their treatment outcomes is known to impact upon patient

reporting of outcome in pain control for example.(419) It is unclear to what extent patients considered me an independent researcher or a Clinical Oncologist. I am certainly well known within the department and may, therefore have been introduced as a Doctor. This might have influenced patient's responses and expression of their feelings about coming for treatment, particularly if, as expressed by one person, the patient felt that they needed to pursue treatment to in some way meet the expectations of the medical team. A further limitation is my limited experience undertaking qualitative research. This may have resulted in limitations to the conduct and interpretation of the interviews. Support was provided by an experienced qualitative researcher, however, a second researcher analysing the interview transcripts would have helped to ameliorate this. This was not available within the current study period.

Finally, whilst data saturation was reached during the interview process it is notable that there were no younger women interviewed and, equally, only one man over the age of 70 was interviewed. The perspective of these groups may differ from those of the included patients. More broadly, all the patients in this study underwent palliative radiotherapy; all had been offered and accepted treatment at the time the interviews were carried out. It is, therefore, not possible to know to what extent their reflections on the value of treat might reflect a reluctance to consider the possibility of therapeutic failure. This is a significant limitation to the generalisability of these findings to a population who have never been offered treatment.

7.5   Conclusions

Economics at its base assumes rational behaviours from individuals. It is demonstrated here that the cost-effectiveness model presented in chapter 6 captures many of the factors which are important to patients and which are valuable from a medical perspective. It also, however, highlights other factors which might influence decision making by patients and clinicians. Some of which might not at first sight appear to represent rational perspectives; in particular the sentiment that even if futile, undergoing treatment is better than not undergoing treatment does not appear rational from a medical or cost-effectiveness perspective. This qualitative work highlights key themes of importance to patients, enhancing the quantitative work presented previously.

Treatment decisions near the EoL are complex, conversations supporting them are often challenging and uncertainty supports hope beyond what may realistically be achieved. There is a need, therefore, to better inform these treatment decisions. Individualised predictions of treatment outcomes are needed and these predictions must then be placed in context using a shared decision making approach. This will help to ensure that the treatments delivered can reasonably be expected to provide outcomes aligned with each patient's values and priorities.

8   Analysis of the National Radiotherapy Dataset (RTDS) to assess early mortality following palliative radiotherapy in routine practice.

8.1   Introduction

Variation in practice and outcomes has been demonstrated across a range of cancer diagnoses and treatments.(122,124,420–423) Anecdotal evidence also suggests variation in the appropriate use of hypofractionation in palliative radiotherapy across the English NHS. The extent to which variation exists in early mortality following palliative radiotherapy is not known.

Early mortality is frequently used to assess quality of care across many healthcare interventions and 30-day mortality (30DM) has been suggested as a possible measure of quality in palliative radiotherapy.(108) There are limited occasions when palliative radiotherapy might be expected to improve survival, equally, the extent to which toxicity due to palliative radiotherapy would be expected to result in mortality is extremely limited. Conversely, as demonstrated in chapters 3 and 6, for patients treated near the EoL the HR-QoL benefits of treatment diminish significantly, to the extent that within the final weeks of life, palliative radiotherapy may well deliver an overall net harm in HR-QoL. The potential role of 30DM in palliative radiotherapy is, therefore, a means to assess the extent to which treatments delivered within the English NHS are futile, or indeed harmful, when benefit is minimal and treatment burden and toxicity remain.

Beyond a population with very short prognosis, as detailed in chapter 6, early indications suggest a possible role for stereotactic radiotherapy (SABR) in the management of bone metastases. The cost-effectiveness of this treatment is heavily dependent upon the survival time of the treated population and an outcome-based pricing approach to maintaining cost-effectiveness in routine practice was presented previously. This chapter will examine the extent to which it may be possible to use routine data to implement this approach.

This study will use routinely collected, national, cancer diagnosis and treatment data to:

- Assess the variation in fractionation patterns used in palliative radiotherapy for bone metastases across the English NHS.

- Provide an analysis of 30-day mortality outcomes and factors associated with this. Use these outcomes to consider the extent to which these treatments are cost-effective as currently used in routine practice.

- Consider the role of this routine data in ensuring the delivery of cost-effective SABR for bone metastases should further trial-based data confirm the early indications of benefit.

8.2 Methods

Analyses using the National Radiotherapy Dataset (RTDS) face a number of challenges: linkage between relevant datasets; robustly identifying the cancer diagnosis for which the treatment was delivered; ensuring the treatment regimen details are clearly recorded and episodes are not fragmented; identifying the clinical intent of treatment delivery (e.g. palliative, curative); identifying the site a palliative treatment to metastatic disease was delivered to; and finally, calculating survival outcomes whilst respecting the sensitive nature of the data which means that all dates have been removed prior to transfer to the researcher. Overall study methods, including those used to address each of these points, will now be detailed.

All radiotherapy treatments delivered to patients over the age of 17, within the English NHS, between 1st January 2014 and 31st December 2015 were included within the study population. Datasets required to support this analysis were the national cancer registration dataset, national radiotherapy dataset (RTDS), hospital episode statistics (HES) dataset and the office for national statistics mortality data. These data are routinely collected, linked and held in Public Health England's (PHE) Cancer Analysis System (CAS).(424) Treatments delivered to individuals with no known cancer diagnosis were excluded.

These data were extracted from CAS in the form of multiple separate data tables and held within the secure electronic environment for data within the University of Leeds. All data were de-identified within PHE prior to extraction with all patients allocated a pseudo-identification number and all treatment episodes and prescriptions allocated numbers similarly. In this way the separately extracted tables could subsequently be linked to provide the final dataset for analysis.

The separately extracted tables were as follows:

- Radiotherapy treatment episodes table - this included the pseudo-episode and pseudo-patient identification numbers, the interval (in days) between the first attendance associated with this episode and the most recent cancer diagnosis, treatment priority (emergency, urgent, routine, elective delay), clinician defined treatment intent (palliative, anti-cancer, other), diagnosis for which the treatment was delivered (as documented by the treating team), patient age at treatment start and travel time from the patients recorded residence at the time to treatment to the provider institution.

- Radiotherapy providers table - detailing the centre delivering the radiotherapy treatment and linked via the pseudo-episode identification number.

- Radiotherapy prescriptions table – this included the treated region (primary, primary and regional nodes, regional nodes, metastasis, prophylactic and non-anatomically specific primary site), the anatomical site (in the case of palliative prescriptions not delivered to the primary or regional nodes), prescribed and actual radiotherapy dose and fractionation,

treatment modality (external beam or brachytherapy) and the interval between the last attendance for the previous prescription and first attendance for this prescription. Linked via the pseudo-episode identification number.

- Radiotherapy attendances table, providing details of all attendances for radiotherapy, if the attendance fell on a bank holiday or was delivered within 1 week of an inpatient spell. Linked via the pseudo-episode identification number.

- Patient and cancer table, which includes patient sex, ethnicity, vital status, interval between most recent cancer diagnosis and vital status, cancer diagnosis and staging information. Linked via the pseudo-patient identification number to the radiotherapy episodes table.

- Hospital episodes table, detailing information available through the Hospital Episodes Statistics dataset for patient co-morbidities (defined using the Charlson comorbidity index)(425) and major resections. Linked via the pseudo-patient identification number.

8.2.1 *Definition of cancer diagnosis*

Two separate cancer diagnosis fields are available within the data; that defined by the treating centre within the RTDS and that defined within the cancer registration dataset. All diagnoses are included using their International Classification of Diseases (ICD-10) codes.(426) Given the complexity of this coding system and number of separate cancer diagnoses these codes were categorised into clinically meaningful groupings. For example, head and neck cancer included 20 individual ICD-10 codes reflecting the range of primary epithelial cancers found within the head and neck. The full diagnostic groupings are shown in appendix 11.2.

Whilst the RTDS defined diagnosis is entered at the time of treatment delivery, and should reflect the diagnosis for which the treatment was delivered (excepting errors of data entry) the cancer registry records all cancers a patient has been diagnosed with. In many cases more than one cancer will be listed and it is possible that the most recent diagnosis will not be the one for which treatment was delivered. A separate field was created to identify if an individual had more than one malignant diagnosis. Subsequently, in order to define the cancer registry diagnosis for which treatment was most likely to have been delivered, an algorithm was developed:

Cancer diagnoses were placed in order with the most recent diagnosis first. If this diagnosis was a malignant one ("C" diagnosis within ICD-10)(426) this was accepted as being the diagnosis for which the treatment was delivered. In addition if this diagnosis was a benign or in-situ tumour diagnosis for which radiotherapy is routinely used (e.g. ductal carcinoma in-situ, pituitary adenoma) this was accepted as the treated diagnosis. If neither of these were the case then the patients second diagnosis was considered and the same rules applied. This was repeated through to the third diagnosis. At this point the most recent "D diagnosis" was accepted if no other

diagnosis was identified. In this way a registry defined diagnosis was derived. As with the RTDS diagnoses these ICD-10 codes were then grouped as per appendix 11.2. The extent to which the algorithm defined registry based diagnosis matched with that of the RTDS defined diagnosis was assessed.

8.2.2 *De-fragmentation*

A number of challenges exist in using the RTDS data for this analysis. Principle amongst these is uncertainty about the ascertainment and veracity of the treatment intent field and the site treated information. There is also, however, recognised to be an element of fragmentation in the submitted data with some treatment episodes being fragmented into multiple prescriptions. Knowledge of the total delivered dose and fractionation is key to defining the intention of treatment and, therefore, initial work was carried out to de-fragment the radiotherapy prescriptions delivered within each recorded episode to ensure curative treatments could be identified as such. This de-fragmentation was initially carried out by combining the delivered doses and fraction numbers for all prescriptions with a dose per fraction of less than three Gray. These treatments, with smaller dose per fraction, are more likely to be delivered over longer treatment courses and, therefore, more likely to be fragmented due to treatment duration and possibility of treatment being delivered via a multiple-phase plan (this predominantly occurring in curative treatments). Further de-fragmentation focussed specifically upon ensuring stereotactic treatments to primary lung cancer and hypofractionated treatments to primary prostate and breast cancer, were not split across multiple prescriptions. Having created a total delivered dose and fractionation the included prescriptions were, therefore, condensed into a single record for each episode. By de-fragmenting the data in this way the total delivered dose and fractionation was calculated and this total used to define treatment intent. Prescriptions delivered using a dose of 0.1Gy were dropped, these may reflect total body irradiation test doses or simply erroneous data entries. Treatments delivered using brachytherapy were also excluded, these were (almost) exclusively delivered with curative intent and are, therefore, not the focus of this analysis.

8.2.3 *Intent allocation*

The treatment intent was defined using a clinically determined algorithm. Treatments delivered with curative intent (either where radiotherapy was the principal curative treatment modality or where this was delivered in the peri-operative setting) were first identified. A pragmatic approach was taken to achieve this which incorporated the total delivered dose and fractionation, RTDS defined diagnosis, region treated and, where, these fields alone were unable to determine intent, the intent as defined by the treating clinician. The Royal College of Radiologists dose-fractionation guidelines were used to support the development of this algorithm in addition to discussion with senior Clinical Oncologists.(427) Examples of where the treatment intent recorded by the treating clinician was incorporated included; treatments of 40Gy in 15 fractions to the primary/nodes for breast cancer, a dose which may in some cases reflect high-dose

palliation and can only be defined as such based upon the clinicians reported palliative intent; five fraction treatments to the primary and nodes for rectal cancer, which may be delivered either in the peri-operative setting or palliatively. Additionally, a number of regimens were identified as curative where the timing and dose/fractionation pattern reflected delivery within a clinical trial e.g. the Fast-Forward trial in breast cancer and PATHOS trial in oropharyngeal cancer.(428,429)

Using this approach 4.9% of palliative prescriptions were delivered with more than 14 fractions. Accepting that if the treating clinician had defined the intent as curative this was indeed the case, the proportion of palliative prescriptions delivered over more than 14 fractions fell to 1.6%.

Treatments delivered for prophylaxis were defined as curative unless the treating clinician defined them as being delivered palliatively or they were delivered to the breast, in prostate cancer (breast bud treatments to limit the side-effects of systemic anti-androgen therapy).

8.2.4 *Identification of site treated*

The target tissue for each palliative prescription was then identified based upon the combined information available from the treatment region and anatomical site. In order to define the site treated a "target tissue" was identified as the chest, skin, soft-tissue, head and neck, brain/base of skull, bone, spine (a sub-set of bone), total-body irradiation and hemi-body irradiation. Where the primary tumour or nodes were treated (as defined by the treatment region in the RTDS) this was taken as treatment to soft-tissue for pelvic malignancies, primary breast cancers and sarcomas, treatment to the chest for lung and oesophageal primaries, to the skin for primary non-melanomatous skin cancers and to the brain for primary brain tumours. Where a metastatic site was treated the target tissue was defined based upon the recorded Operations, Interventions and Procedures anatomical Z-code (OPCS).(430) All Z-codes included within the data were reviewed and allocated to a target tissue based on their OPCS definition.

It is not possible to separate treatments to uncomplicated spinal metastases and malignant spinal cord compression (MSCC) based upon the currently used OPCS Z-codes. Emergency treatments are more likely to represent treatments to MSCC given the NICE guidance recommending treatment within 24 hours of identification.(431) While there is no clear randomised evidence to support fractionated treatment for this indication there are no guidelines to the contrary and fractionated treatment remains an accepted standard of care.(427) Excluding these treatments from the analysis of bone metastases provides a pragmatic solution to identifying and excluding MSCC. There remains uncertainty, however, due to the documentation of treatment urgency. It is possible that some patients considered to have uncomplicated bone metastases using this approach have, in fact, received treatment for MSCC but the urgency has not been accurately recorded whilst conversely, some emergency spinal treatments may not have MSCC. From a pragmatic perspective this is the best identification of all bone metastases possible.

The total number of distinct sites treated within each treatment episode was identified based upon the number of distinct Z-codes recorded on prescriptions delivered within that episode. In addition, the total number of prescriptions contributing to each episode was calculated.

After initial analyses to number of sites treated and fractionation patterns delivered to these sites the separate prescriptions were combined into a single episode record. This record included new fields to recognise if any treatment was delivered to bone, spine, brain and soft tissue within the episode. The fractionation (and dose) delivered in this episode were accepted as the highest one within the episode; this reflecting the most significant clinical decision.

8.2.5 *Calculation of survival time*

As all dates are considered potentially identifiable, date of diagnosis, date of death or date of radiotherapy (in the form of day, month and year)were not available. Instead, to assess early mortality the interval in days between the last recorded vital status/death and the most recent cancer diagnosis was used.

8.2.6 *Analysis*

8.2.6.1 *Baseline patient and treatment characteristics*

An initial analysis assessed the extent to which the split between curative and palliative treatment episodes varied between radiotherapy providers across the English NHS. Comparison between the registry and RTDS cancer diagnoses were then made, followed by an assessment of the extent to which the treatment intent identified by the algorithm developed here matched that reported by the treating centre.

All subsequent analyses focussed upon treatments delivered with palliative intent. The number of separate anatomical sites treated within a treatment episode were counted and the total number of separate prescriptions allowing identification of the total number of treated sites and the proportions delivered to different target tissues. The proportion of patients receiving treatment to multiple sites within a single episode could, therefore, be identified.

The baseline characteristics of the patient population receiving palliative radiotherapy and of the prescriptions delivered with palliative intent were identified. Patient characteristics assessed were age, sex, socio-economic status, ethnicity, comorbidity and travel time to the radiotherapy provider from the patient's home address. Characteristics of the delivered prescriptions considered were cancer diagnosis, fractionation pattern and target tissue treated. Socio-economic status was included as the rank quintile of the index of multiple deprivation ((IMD) from the Office for National Statistics 2010 version)(432) score for the Lower Super Output Area (LSOA),(433) population defined geographical region of approximately 1500 people) of the patient's postcode of residence at most recent cancer diagnosis. SES quintiles from one to five represent the least to most deprived areas in the country. Ethnicity was defined as white/non-white due to the limitations of the recorded data. Comorbidity was incorporated using the

Charlson comorbidity index for all diagnoses identified in HES in the year prior to the most recent cancer diagnosis and categorised into scores of 0, 1, 2 and ≥3.(425,434) The travel time variable used represents the value held by NCRAS. This is the modelled time between the patient's postcode and provider postcode. Data for this field were provided in 10 minute time bands.

The fractionation patterns delivered to bone metastases by individual provider organisations were then assessed. This was replicated for prescriptions delivered to spinal metastases and finally, for all treatments delivered to bone or spine in a non-emergency setting.

8.2.6.2   Survival and 30-day mortality

The median survival of all patients following their first treatment within the cohort was assessed using the Kaplan-Meier method, censoring at last known vital status. This was replicated for patients undergoing a first episode to bone/spine in the non-emergency setting and separately for patients undergoing emergency treatment to the spine for comparison.

The 30DM observed following palliative radiotherapy was assessed and variation with baseline patient characteristics, diagnosis, fractionation and travel time to treating centre considered. It must be recognised that many patients will undergo more than one treatment episode during the cohort period. In contrast, death can only occur once. As such, descriptive outcomes are presented for all palliative treatment episodes within the cohort and separately for only the first treatment episode each patient underwent within the cohort. In line with previously published work, only the first treatment episode within the cohort was considered within regression analyses.(6) Univariable and multivariable logistic regression models were used to assessed the factors associated with 30DM (e.g. fractionation, primary diagnosis, delivery of treatment during an inpatient stay). These results were presented for both all palliative treatments and only those delivered to bone/spine metastases (excluding emergencies). Factors considered within the regression models were age, sex, IMD, Charlson comorbidity score, travel time to provider, number of sites treated during the episode, target tissue, fractionation, urgency of treatment (excluded from bone/spine model were emergency treatments were excluded), and, in the case of the bone/spinal model, whether treatment was delivered to a spine or other bony site.

8.2.6.3   Funnel plots

Funnel plots were then produced to illustrate the variation in 30DM by provider institutions. These were presented for all palliative treatment and bone/spinal treatments separately. Unadjusted funnel plots are presented alongside funnel plots adjusted for fractionation pattern and travel time to provider institution. Only these two factors were considered within the adjusted funnel plots on the basis that both of these will result in variable levels of treatment burden (either through varying treatment attendances and toxicity or travel time) reduction is desirable in populations very close to the end of life. Conversely, it is unclear that any of the other factors will be associated

with greater treatment efficacy or indeed, lower treatment burden. Factors predicting response are also strong prognostic predictors.(222) As such, adjustment was not made for these factors.

8.2.6.4 Incorporating the routine outcomes and health economic analysis

In chapter 6 it was shown that treatment to bone metastases in the final 12 weeks of life is expected to be associated with minimal overall benefit, in terms of HR-QoL; is highly unlikely to be cost-effective, even when delivered using a single 8Gy fraction; and for many patients will be associated with a net harm. Using the routine data, the number of treatment episodes delivered to patients who died within 12 weeks of treatment was assessed and the fractionation patterns delivered to this group determined. The potential savings associated with all of these treatments being delivered with a single fraction were then calculcated. The levels of 30DM observed in routine practice were then incorporated with the previously presented OBP model and the levels of 30DM observed following single fraction and ten fraction treatments were plotted to provide an estimation of the extent to which SABR might be cost-effective in these treated populations in light of differing costs assumptions.

Finally, the extent to which the Weibull proportional hazards model used within the decision-analytic model was a reasonable representation of survival probability in routine practice was assessed. The fitted Weibull proportional hazards parametric function provided the optimum compromise between a clinically plausible model and fit both graphically and on AIC using the trial data on which this model was developed. Parametric functions were fitted to the survival outcomes of the routinely treated population.

8.3   Results

The study population consisted of a total of 251,498 prescriptions delivered over 237,839 treatment episodes to 213,660 individual patients. Of these 139,427 patients received curative treatment and 77,788 palliative treatment. These patients received 141,274 and 96,565 episodes respectively. 3,555 patients received both curative and palliative treatments.

Across the 52 provider institutions in the English NHS the number of treatment episodes delivered ranged from 398 to 14,541 with the proportion of treatment episodes per provider delivered with palliative intent ranging from 32.1% to 51.7% (Figure 51).

Figure 51. Variation in the proportion of palliative and curative treatment episodes delivered across radiotherapy providers in the English NHS.
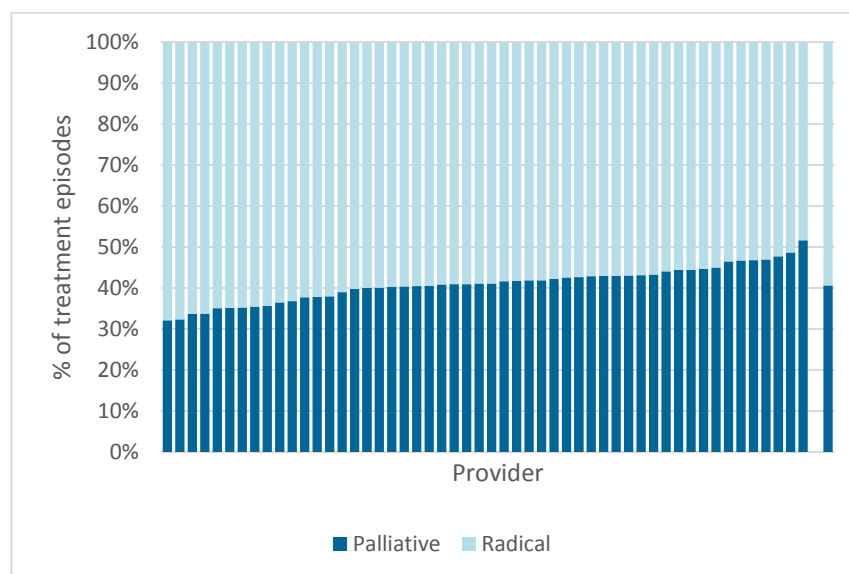
All subsequent results will focus only upon the treatment episodes delivered with palliative intent. Figure 52 illustrates the derivation of the final cohort which includes only treatment episodes delivered with palliative intent. This final cohort includes 96,535 treatment episodes, delivered to 77,762 patients using 108,473 prescriptions.

8.3.1 *Data quality*

For the treatment episodes included within the whole treated population the RTDS and cancer registry diagnoses matched in 91.8% of episodes. This level was higher amongst episodes delivered with curative intent (94.1%) than in those delivered with palliative intent (88.7%). Where the diagnoses were not matched 31.1% of episodes were delivered to an individual with more than one malignant cancer diagnosis, reflecting the challenges of identifying the treated cancer diagnosis from those recorded in the registry. Notably those with a mismatch between the two diagnostic sources were more likely to have a diagnosis of non-melanomatous skin cancer (13.9%) than in the total treated episodes (1.2%). Historically there has been wide variation in the extent to which non-melanomatous skin cancer is recorded by cancer registries around the country. These variations in ascertainment potentially explain this discrepancy.

Considering the classification of treatment intent, 8,873 (8.2%) prescriptions classified as palliative here were reported to be delivered with curative intent by the treating clinician. Of these 2,058 (23.2%) prescriptions were delivered using a single fraction. 641 (31.1%) of which had a recorded dose of 8Gy. 955 (10.8%) were prescribed a dose of more than 10Gy suggesting these treatments may reflect stereotactic treatment e.g. to oligo-metastatic or cerebral disease. 771 (8.7%) prescriptions delivering 20Gy in five fractions were recorded as being delivered with curative intent with a further 546 (6.1%) prescriptions delivering 30Gy in 10 fractions and 869 (9.8%) delivering 36Gy in predominantly 6 (540) or 12 (279) fractions. These are likely to reflect

erroneous coding of clinician intent within the RTDS given that these doses are not considered to be curative beyond limited diagnostic groups which have been specifically identified within the allocation algorithm defined here (e.g. lymphoma and testicular cancer).

Figure 52. CONSORT diagram illustrating the derivation of the study population
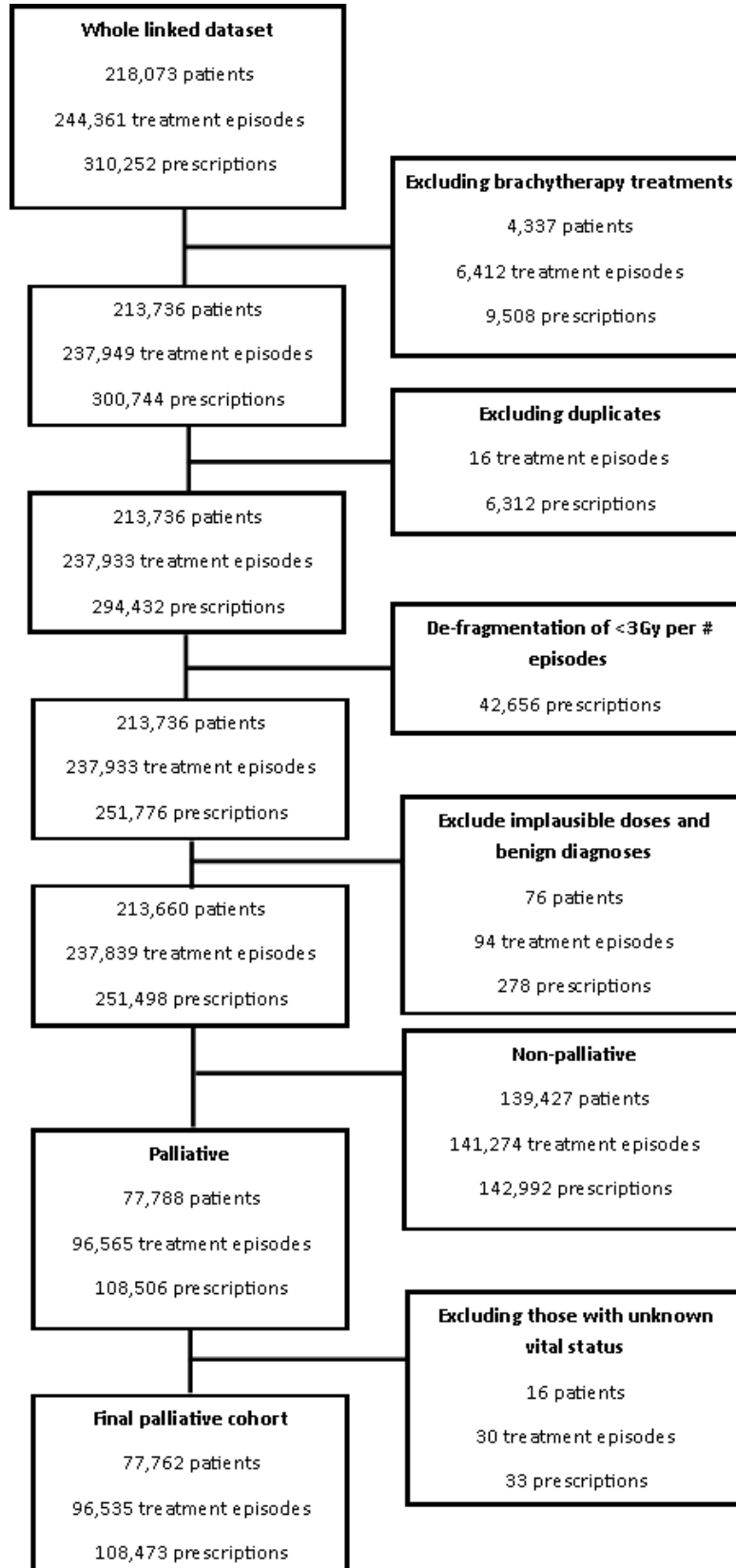
8.3.2 *Treatment numbers and baseline characteristics*

Focussing upon the palliative treatment episodes, these 96,535 episodes were delivered to a total of 77,762 patients with a total of 108,473 individual prescriptions. Baseline characteristics for all patients receiving radiotherapy are presented in Table 35, split by intent of treatment. Of the 108,473 prescriptions delivered with palliative intent 3,393 (3.1%) had no anatomical site recorded. Table 36 details the diagnostic case-mix, sites treated and fractionation patterns delivered in these prescriptions.

Table 35. Baseline characteristics of the patient population treated with palliative and non-palliative radiotherapy.

	Palliative		Non-palliative	
	Number	**(%)**	**Number**	**(%)**
Age (median)	70	IQR(78-103)	64	IQR(56-73)
Sex				
Male	43,529	56.0	58,006	41.6
Female	34,233	44.0	81,421	58.4
Index of Multiple deprivation				
1 (least deprived)	15,599	20.1	30,819	22.1
2	16,515	21.2	31,323	22.5
3	16,328	21.0	28,630	20.5
4	15,006	19.3	25,452	18.3
5 (most deprived)	14,314	18.4	23,203	16.6
Charlson				
0	57,623	74.1	117,776	84.5
1	12,402	16.0	14,383	10.3
2	4,460	5.7	4,434	3.2
≥3	3,277	2.6	2,834	2.0
Ethnicity				
Non-white, including unknown	9,217	11.9	19,516	14.0
White	68,545	88.1	119,911	86.0
Travel time (minutes)				
<20	27,843	35.8	49,225	35.31
20-29	21,396	27.5	39,743	28.5
30-39	13,778	17.7	25,500	18.29
40-49	6,989	9.0	13,119	9.41
50-59	3,508	4.5	5,775	4.14
≥60	4,248	5.5	6,065	4.35
Total	77,762	100	139,427	100

The cancer diagnosis, site treated and fractionation pattern delivered at each prescription event is shown in Table 36.

Table 36. Characteristics of the delivered palliative radiotherapy prescriptions.

	Number	(%)
Diagnosis		
Head and neck	2,596	2.4
Oesophageal	4,842	4.5
Colorectal	6,240	5.8
Anal	514	0.5
Lung	28,545	26.3
HPB	1,168	1.1
Sarcoma	3,124	2.9
Melanoma	2,113	2.0
Skin	568	0.5
Breast	15,139	14.0
Gynae	3,136	2.9
Prostate	16,735	15.4
Renal	2,737	2.5
Bladder	4,339	4.0
CNS	1,540	1.4
Lymphoma	4,167	3.8
Other haem	4,604	4.2
Other	5,739	5.3
Unknown	627	0.6
Site treated		
Spine	25,767	23.8
Bone	19,297	17.8
Soft tissue	24,018	22.1
Chest	17,899	16.5
Brain/base of skull	11,303	10.4
Head and neck	3,174	2.9
Skin	2,225	2.1
Total body irradiation	1,371	1.3
Hemibody radiotherapy	26	<0.1
Unknown	3,393	3.1
Fractionation		
1	40,973	37.8
2-4	10,401	9.6
5	36,131	33.3
6-9	5,086	4.7
10	10,792	10.0
>10	5,090	4.7
Total	108,473	100

The RTDS data collection during the study period was carried out by an independent company called NATCANSAT. This company defined a limited set of anatomical Z-codes to simplify the collection of treatment site data. They specify Z879 as being "wholebody" radiotherapy and as such, within the algorithm developed here this was assumed to reflect total body irradiation. It is notable, however, that one provider appears to have delivered 35.7% of their palliative treatments to anatomical Z-code Z879 (accounting for 99.7% of all such treatments delivered with palliative intent). Given that the OPCS definition of Z879 is "Musculoskeletal NEC" it is plausible to think

that these treatments may reflect treatments to bone or spinal metastases. This could not be confirmed within this study.

8.3.3 *Patterns of care*

8.3.3.1 Variation in fractionation patterns for bone metastases

The fractionation patterns used by different provider institutions to deliver treatments to bone metastases (excluding spine) are illustrated in Figure 53a, those delivered to spine are shown in Figure 53b.

Figure 53. Variation in fractionation patterns delivered to bone (a) and spine (b) sites between provider organisations. The right hand most bar represents the total national fractionation patterns prescribed.
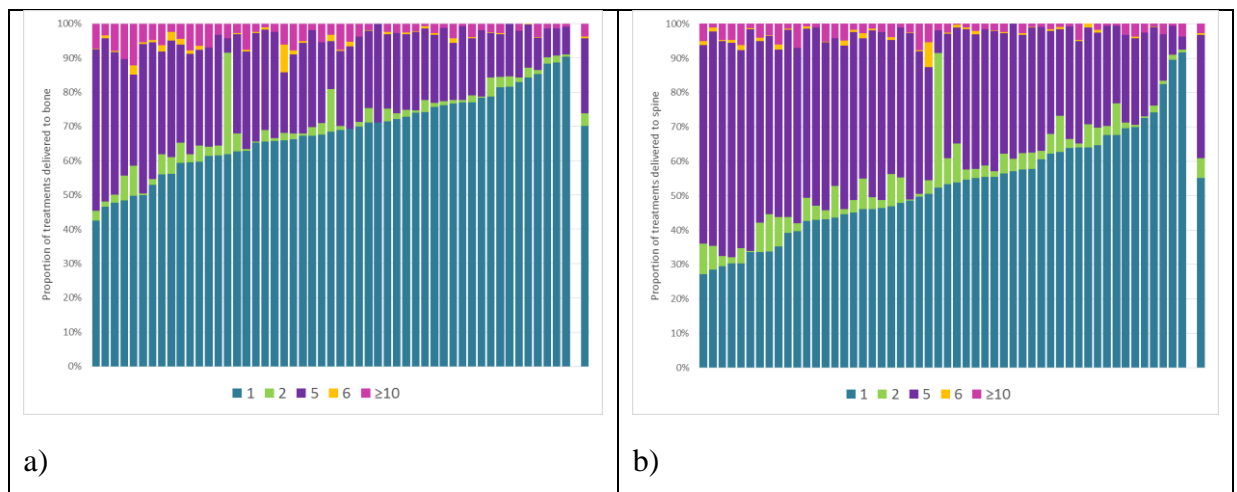
Of all treatment episodes delivered to the spine 5,152 (22.8%) were reported to have been delivered as an emergency treatment. This proportion varied between provider institutions between 0% and 59.0%, suggesting that not all providers are accurately submitting this data to the RTDS. As such, this number is likely to be an under-estimate of the proportion of emergency treatments delivered.

The fractionation patterns delivered to bony and spinal lesions when emergency treatments were excluded are shown in Figure 54. Overall 65.1% of these treatment episodes were delivered using a single fraction treatment with the variation between providers ranging from 37.7% to 90.3%. It is notable from Figure 54 that two providers appear to be delivering unusual patterns of care which are markedly different to those observed elsewhere and not supported by the clinical guidelines.(427) In one provider organisation four fraction treatments appear to be being used in place of five fraction treatments. In a second a large number of 8 fraction treatments delivering a total dose of 8Gy appear to be being delivered. It is likely this latter represents an error in the data submission. The former requires further assessment as this approach lies outside of accepted guidelines and appears prominent in this provider institution.

Figure 54. Variation in fractionation patterns by provider institutions for palliative radiotherapy delivered to bone or spine in non-emergency episodes.
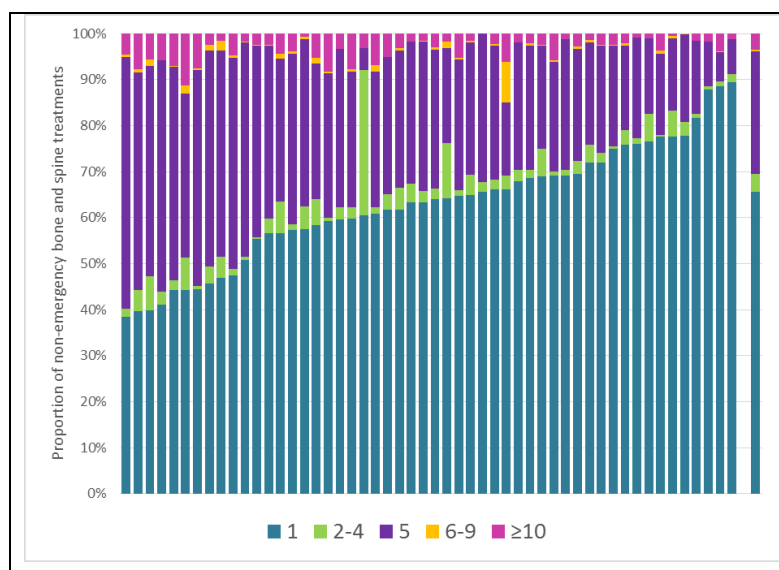
8.3.3.2 Survival and 30-day mortality outcomes

On Kaplan-Meier analysis the median overall survival of all patients undergoing a first palliative radiotherapy episode within the cohort was 28.1 weeks (95% CI 27.7-28.6). This was slightly higher in those receiving a first treatment to bone/spinal metastases in the non-emergency setting at 29.3 weeks (95% CI 28.6-29.9) and markedly lower in those receiving a first treatment to spine in the emergency setting at 11.7 weeks (95% CI 11.1-12.4).

Across the NHS, over the two year period considered, 10,756 patients died within 30 days of commencing palliative radiotherapy. This resulted in an overall 30DM of 11.1% where all treatment episodes were considered and 10.4% if only the first treatment delivered to each patient within the cohort was considered. Table 37 shows the levels of 30DM observed by differing patient and treatment characteristics. Considering all treatment episodes in the cohort where treatment was delivered to a bony lesion the 30DM was 9.8% overall, whilst treatment to spine was associated with 30DM of 15.7% (higher amongst those treated as emergencies at 23.4%). Treatment to the brain was associated with 30DM of 12.6% with soft tissue treatments having 30DM of 8.8%.

Table 37. 30-day mortality following palliative radiotherapy delivered to any site. a) For all treatment episodes within the cohort b) for only the first treatment episode per patient within the cohort.

		All delivered episodes			**First treatment episode only**		
		Alive	Dead	30DM	Alive	Dead	30DM
Age							
	<50	7,131	754	9.6	5,426	483	8.2
	50-59	12,177	1,427	10.5	9,388	979	9.4
	60-69	23,359	3,061	11.6	18,623	2,236	10.7
	70-79	25,789	3,436	11.8	21,189	2,660	11.2
	≥80	17,323	2,078	10.7	15,041	1,737	10.4

Sex						
Male	48,008	6,560	12.0	38,617	4,912	11.3
Female	37,771	4,196	10.0	31,050	3,183	9.3
Charlson						
0	65,384	7,584	10.4	52,054	5,540	9.6
1	12,851	1,888	12.8	10,941	1,475	11.9
2	4,438	726	14.1	3,871	595	13.3
≥3	3,106	558	15.2	2,801	485	14.8
Index of multiple deprivation						
1 (least deprived)	17,782	1,995	10.1	14,137	1,462	9.4
2	18,436	2,269	11.0	14,828	1,687	10.2
3	17,971	2,290	11.3	14,621	1,707	10.5
4	16,432	2,071	11.2	13,450	1,556	10.4
5 (most deprived)	15,158	2,131	12.3	12,631	1,683	11.8
Travel time (minutes)						
<20	30,584	4,062	11.7	24,802	3,017	10.8
20-29	23,370	2,973	11.3	19,138	2,253	10.5
30-39	15,338	1,831	10.7	12,394	1,381	10.0
40-49	7,689	927	10.8	6,292	712	10.2
50-59	3,873	462	10.7	3,156	356	10.1
>60	4,925	501	9.2	3,885	376	8.8
Fractionation						
1	29,327	5,077	14.8	20,998	3,511	14.3
2-4	7,200	879	10.9	5,900	664	10.1
5	29,995	3,926	11.6	24,846	3,126	11.2
6-9	4,602	236	4.9	4,314	215	4.7
10	9,852	473	4.6	8,987	419	4.5
>10	4,803	165	3.3	4,622	160	3.3
Urgency						
Non-emergency	80,457	9,143	10.2	65,556	6,906	9.5
Emergency	5,322	1,613	23.3	4,111	1,189	22.4
Total		85,779	10,756	11.1	69,667	8,095	10.4

Focussing upon treatments delivered to bone metastases in the non-emergency setting the variation in 30DM across fractionation patterns is shown in Figure 55. Overall, 3,901 (11.6% of all delivered episodes) such treatments were delivered within 30 days of death. In patients receiving their first episode within the cohort period, the 30DM varied widely from 12.5% following single fraction treatment to 3.2% following 10 fraction treatments. Where all non-emergency treatment episodes delivered to bone or spine are included, 3,901 episodes were delivered within 30 days of the EoL.

Figure 55. 30-day mortality following palliative radiotherapy to bone metastases by fractionation pattern. a) all treatments delivered within the cohort b) only the first treatment episode for the patient within the cohort.

a)

b)
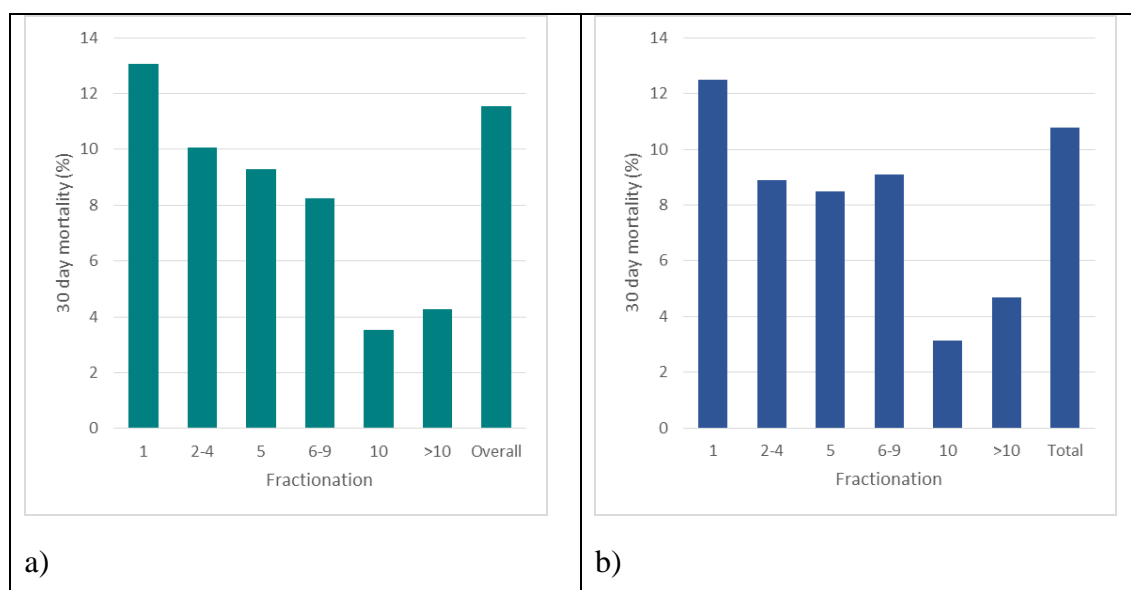
8.3.3.3 Factors associated with 30-day mortality

In order to assess the variation in outcomes further, univariable and multivariable logistic regression was carried out for all first palliative radiotherapy episodes within the treatment cohort (Table **38**) and, separately, non-emergency first treatments delivered to bone or spine (Table 39). Factors associated with significantly higher levels of 30DM were increasing socio-economic deprivation (IMD 5 vs 1, OR 1.16 (95% CI 1.07-1.25)), increasing comorbidity (Charlson score ≥3 vs 0, OR 1.28 (95% CI 1.15-1.42)), two treatment sites, as compared to one (OR 1.14 (95% CI 1.04-1.24)), and treatment being delivered as an emergency (OR 2.58 (95% CI 2.39-2.77)). Whilst factors associated with significantly lower levels of 30DM were female sex (OR 0.86 (95% CI 0.81-0.91)), travel time of more than an hour (OR 0.84 (95% CI 0.75-0.94)) and increasing fractionation pattern (ten vs single fraction, OR 0.23 (95% CI 0.20-0.25)).

Table 38. Univariable and multivariable logistic regression models assessing the relationship between various patient and treatment related variables and probability of death within 30 days.

	Univariable				**Multivariable**			
	OR	p	Lower 95% CI	Upper 95% CI	OR	p	Lower 95% CI	Upper 95% CI
Age	1.005	<0.001	1.003	1.007	1.003	0.002	1.001	1.005
Sex								
Male	1.000	-	-	-	1.000	-	-	-
Female	0.806	<0.001	0.769	0.845	0.855	<0.001	0.809	0.904
Index of multiple deprivation								
1 (least deprived)	0.000	-	-	-	0.000	-	-	-
2	1.100	0.011	1.022	1.184	1.069	0.085	0.991	1.153
3	1.129	0.001	1.049	1.215	1.084	0.036	1.005	1.170
4	1.119	0.003	1.038	1.206	1.029	0.473	0.952	1.112
5 (more deprived)	1.288	0.000	1.196	1.387	1.160	<0.001	1.073	1.254

Charlson comorbidity index								
0	1.000	-	-	-	1.000	-	-	-
1	1.267	<0.001	1.192	1.346	1.042	0.208	0.977	1.111
2	1.444	<0.001	1.319	1.581	1.183	0.001	1.076	1.301
≥3	1.627	<0.001	1.472	1.799	1.282	<0.001	1.153	1.424
Diagnosis								
Lung	1.000	-	-	-	1.000	-	-	-
Head and neck	0.783	0.001	0.680	0.901	0.961	0.589	0.830	1.112
Oesophageal	0.786	<0.001	0.708	0.872	0.903	0.064	0.811	1.006
Colorectal	0.630	<0.001	0.570	0.697	0.589	<0.001	0.531	0.653
Anal	0.288	<0.001	0.183	0.451	0.405	<0.001	0.257	0.640
HPB	1.323	0.001	1.115	1.569	1.096	0.306	0.919	1.307
Sarcoma	0.608	<0.001	0.525	0.704	0.628	<0.001	0.540	0.730
Melanoma	0.865	0.070	0.739	1.012	0.868	0.088	0.738	1.021
Skin	0.654	0.014	0.467	0.916	0.661	0.019	0.469	0.933
Breast	0.344	<0.001	0.314	0.378	0.349	<0.001	0.316	0.386
Gynae	0.499	<0.001	0.430	0.579	0.645	<0.001	0.552	0.754
Prostate	0.382	<0.001	0.350	0.417	0.256	<0.001	0.233	0.281
Renal	0.657	<0.001	0.561	0.769	0.554	<0.001	0.471	0.651
Bladder	0.887	0.027	0.798	0.986	0.854	0.005	0.765	0.953
CNS	0.472	<0.001	0.384	0.579	0.854	0.156	0.687	1.062
Lymphoma	0.489	<0.001	0.421	0.569	0.518	<0.001	0.444	0.604
Other haem	0.307	<0.001	0.261	0.361	0.221	<0.001	0.188	0.261
Other	1.113	<0.001	1.017	1.218	0.891	0.016	0.811	0.979
Unknown	0.881	0.408	0.653	1.189	0.720	0.036	0.530	0.979
Fractionation								
1	1.000	-	-	-	1.000	-	-	-
2-4	0.675	<0.001	0.618	0.737	0.568	<0.001	0.518	0.622
5	0.753	<0.001	0.715	0.793	0.606	<0.001	0.574	0.640
6-9	0.300	<0.001	0.260	0.345	0.286	<0.001	0.246	0.332
10	0.280	<0.001	0.252	0.310	0.227	<0.001	0.204	0.252
>10	0.207	<0.001	0.176	0.243	0.153	<0.001	0.130	0.181
Number of sites within single episode								
1	1.000	-	-	-	1.000	-	-	-
2	1.272	<0.001	1.166	1.388	1.135	0.006	1.037	1.242
3	1.575	0.002	1.184	2.095	1.464	0.011	1.090	1.966
4	1.371	0.512	0.534	3.520	1.265	0.632	0.484	3.308
Urgency								
Non-emergency	1.000	-	-	-	1.000	-	-	-
Emergency	2.748	<0.001	2.565	2.945	2.575	<0.001	2.393	2.770
Travel time (minutes)								
<20	1.000	-	-	-	1.000	-	-	-
20-29	0.968	0.266	0.913	1.025	0.980	0.508	0.923	1.040
30-39	0.916	0.011	0.856	0.980	0.928	0.036	0.866	0.995
40-49	0.930	0.100	0.853	1.014	0.948	0.238	0.867	1.036
50-59	0.927	0.202	0.826	1.041	0.927	0.217	0.823	1.045
>60	0.796	0.000	0.711	0.890	0.838	0.003	0.746	0.941

Where only treatments to bone or spinal lesions in a non-emergency setting were considered, similar findings were noted. Factors associated with significantly higher rates of 30DM on multivariable logistic regression were increasing age (OR 1.010 (95% CI 1.007-1.014)), greater

comorbidity (OR 1.581 (95% CI 1.293-1.934)), greater socio-economic deprivation (IMD 5 vs 1 OR 1.254 (95% CI 1.091-1.440)), spinal treatment as compared to bone (OR 1.584 (95% CI 1.451-1.728)) and increasing number of sites treated in a single episode (two vs one site, OR 1.230 (95% CI 1.081-1.399)). Conversely, factors associated with a significant reduction in 30DM were female sex (OR 0.803 (95% CI 0.724-0.892)), increasing treatment fractionation (ten vs a single fraction, OR 0.187 (95% CI 0.129-0.272)) and travel time to the treating centre of more than an hour as compared to less than 20 minutes (OR 0.807 (95% CI 0.653-0.998). With the exception of hepatobiliary and "other" cancers, 30DM was significantly higher in patients receiving palliative radiotherapy with a diagnosis of lung cancer than in all other diagnostic groups.

Table 39. Univariable and multivariable logistic regression models assessing factors associated with 30-day mortality following palliative radiotherapy for bone or spinal metastases delivered as the first episode within the cohort.

	Univariable				Multivariable			
	OR	p	Lower 95% CI	Upper 95% CI	OR	p	Lower 95% CI	Upper 95% CI
Age	1.007	<0.001	1.003	1.010	1.010	<0.001	1.007	1.014
Sex								
Male	1.000	-	-	-	1.000	-	-	-
Female	0.826	<0.001	0.759	0.899	0.803	<0.001	0.724	0.892
Index of multiple deprivation								
1 (least deprived)	1.000	-	-	-	1.000	-	-	-
2	1.160	0.023	1.021	1.318	1.117	0.102	0.978	1.275
3	1.186	0.009	1.044	1.348	1.094	0.187	0.958	1.249
4	1.084	0.238	0.948	1.240	0.941	0.397	0.818	1.083
5 (more deprived)	1.539	<0.001	1.351	1.754	1.254	0.001	1.091	1.440
Charlson comorbidity index								
0	1.000	-	-	-	1.000	-	-	-
1	1.609	<0.001	1.441	1.796	1.107	0.086	0.986	1.244
2	1.795	<0.001	1.514	2.129	1.242	0.018	1.038	1.486
≥3	2.460	<0.001	2.037	2.972	1.581	<0.001	1.293	1.934
Diagnosis								
Lung	1.000	-	-	-	1.000	-	-	-
Head and neck	0.834	0.256	0.609	1.141	0.931	0.661	0.675	1.283
Oesophageal	1.053	0.641	0.847	1.311	1.139	0.258	0.909	1.426
Colorectal	0.565	<0.001	0.470	0.679	0.640	<0.001	0.531	0.772
Anal	0.259	0.024	0.080	0.835	0.372	0.104	0.113	1.224
HPB	1.164	0.230	0.908	1.491	1.110	0.417	0.862	1.430
Sarcoma	0.633	0.002	0.474	0.845	0.896	0.469	0.665	1.207
Melanoma	0.846	0.279	0.624	1.145	1.033	0.840	0.756	1.411
Skin	0.583	0.219	0.246	1.378	0.593	0.241	0.248	1.420
Breast	0.188	<0.001	0.160	0.220	0.235	<0.001	0.197	0.279
Gynae	0.570	<0.001	0.430	0.756	0.924	0.603	0.687	1.244
Prostate	0.214	<0.001	0.188	0.244	0.188	<0.001	0.163	0.217
Renal	0.376	<0.001	0.296	0.477	0.462	<0.001	0.363	0.589
Bladder	0.792	0.014	0.657	0.954	0.890	0.237	0.735	1.079
CNS	0.568	0.198	0.241	1.343	0.811	0.640	0.338	1.949

Lymphoma	0.430	<0.001	0.280	0.659	0.522	0.003	0.338	0.807
Other haem	0.181	<0.001	0.138	0.237	0.175	<0.001	0.133	0.230
Other	0.753	0.001	0.640	0.887	0.821	0.020	0.695	0.970
Unknown	0.518	0.014	0.306	0.877	0.569	0.038	0.334	0.971
Fractionation								
1	1.000	-	-	-	1.000	-	-	-
2-4	0.705	0.004	0.557	0.894	0.619	<0.001	0.485	0.790
5	0.651	<0.001	0.592	0.717	0.557	<0.001	0.504	0.616
6-9	0.696	0.254	0.374	1.297	0.533	0.052	0.283	1.005
10	0.227	<0.001	0.157	0.328	0.187	<0.001	0.129	0.272
>10	0.303	0.002	0.142	0.646	0.223	<0.001	0.104	0.480
Number of sites within single episode								
1	1.000	-	-	-	1.000	-	-	-
2	1.327	<0.001	1.172	1.501	1.230	0.002	1.081	1.399
3	1.678	0.007	1.152	2.443	1.512	0.039	1.022	2.238
4	2.864	0.115	0.775	10.587	3.402	0.078	0.870	13.304
Bone vs Spine								
Bone	1.000	-	-	-	1.000	-	-	-
Spine	1.541	<0.001	1.417	1.675	1.584	<0.001	1.451	1.728
Travel time (minutes)								
<20	1.000	-	-	-	1.000	-	-	-
20-29	0.965	0.492	0.870	1.069	0.969	0.564	0.870	1.079
30-39	0.947	0.361	0.842	1.065	0.968	0.607	0.856	1.095
40-49	0.882	0.102	0.759	1.025	0.906	0.220	0.774	1.061
50-59	0.836	0.092	0.679	1.030	0.868	0.200	0.699	1.078
>60	0.691	<0.001	0.564	0.848	0.807	0.047	0.653	0.998

8.3.3.4   Funnels

In order to assess the extent to which the observed variation in 30DM by provider reflects statistical chance as opposed to significant variation which might warrant further investigation funnel plots were produced. Figure 56 demonstrates the variation in 30DM seen across all treated sites where treatment was the first within the cohort period. It can be seen that both where no adjustment for co-variables is made (a) and where adjustment for fractionation pattern and travel time is made (b) a number of provider organisations can be seen to lie outside the 95% confidence interval with a limited number outside the 99.8% limit. Similar results are seen when only treatment to bone metastases were considered (Figure 57).

Figure 56. Funnel plots illustrating the variation in 30-day mortality between provider institutions for all palliative radiotherapy delivered as the first treatment within the cohort a) unadjusted rates and b) adjusted rates (adjusted for fractionation and patient travel time to treating institution).
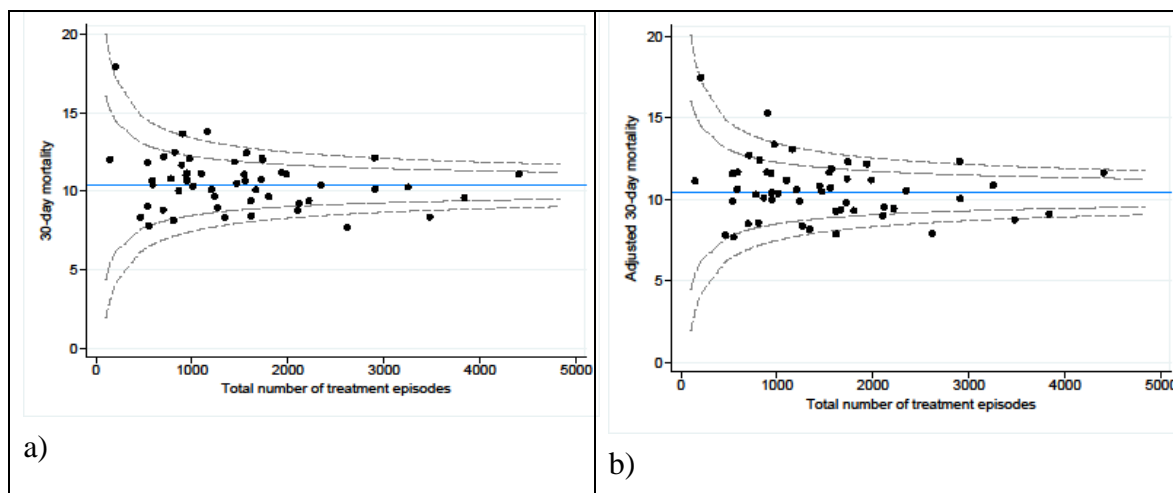
Figure 57. Funnel plots illustrating the variation in 30-day mortality between provider institutions for all palliative radiotherapy delivered to bone or spine sites as the first treatment within the cohort a) unadjusted rates and b) adjusted rates (adjusted for fractionation and patient travel time to treating institution).
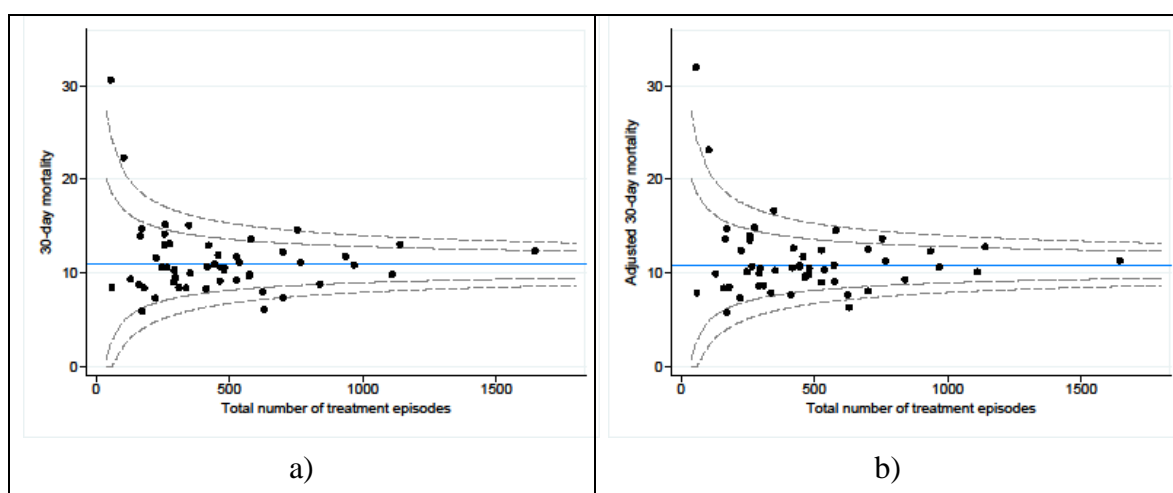
8.3.4 Integrating routine data and cost-effectiveness analysis; implementation of an outcome-based price for SABR treatment to bone metastases

During 2014-15, 10,516 non-emergency treatment episodes to bone metastases were delivered to patients who died within twelve weeks (31.2% of all such treatment episodes). As shown for 30DM in Figure 55, death occurred more frequently in patients undergoing a single fraction treatment than in those undergoing more prolonged courses. It is notable, however, that 2,658 five fraction episodes were delivered to bone metastases within twelve weeks of death. Overall, patients dying within twelve weeks attended for a total of 23,240 fractions, delivered over 10,516 episodes. 3,901 of these episodes being deliver to patients who died within 30 days. At 2014-15 tariff prices, and making a conservative assumption that all treatments were delivered using a

simple approach (£88 per fraction) and planned with a simple dose calculation (£263 per episode), the total cost of treatments delivered within the final twelve weeks of life was £4,810,828. Of this, £1,118,988 was attributable to the delivery of greater than single fraction treatment. In the context of the wider NHS budget this is a relatively small sum, however, given the clear evidence to support the non-inferiority of single fraction treatment for uncomplicated bone metastases it is extremely hard to justify the additional treatment burden and cost associated with a fractionated treatment course in a population with such short survival. In addition, given the marginal benefit of treatment in this population a significant proportion of both fractionated and single fraction treatments are likely have delivered a net harm.

Conversely, 8,713 treatments were delivered to patients surviving for longer than a year beyond receiving a first episode of palliative radiotherapy to a bone metastasis. The number of patients in this group varied between providers, in line with the wide variation in activity, from 35 to 527 individuals. Of these patients, 58.2% underwent a single fraction treatment, in line with internationally accepted guidelines whilst 30.9% underwent five fraction and 5.8% ten fractions. For patients surviving for less than 30 days these proportions were 61.4%, 30.1% and 4.2% respectively. Whilst the 30DM of patients undergoing a ten fraction treatment is lower than following single fraction treatment, these figures suggest that the treatment patterns delivered are not markedly different between patients with short versus more prolonged survival.

Placing these outcomes in the context of the OBP estimations from chapter 6 it can be seen that for a population with the same 30DM as is seen following single fraction treatment in routine practice (12.5%) there is a greater than 50% probability that SABR will not be cost-effective, even where the anticipated long-term costs are considered. Conversely, where 30DM is in keeping with that currently seen following ten fraction courses (3.2%) there is a markedly greater than 75% probability that treatment will be cost-effective, even at the currently commissioned price (Figure 58).

Figure 58. Estimated outcome-based price for SABR to painful bone metastases based upon the 30DM of the treated population. Horizontal dotted lines represent the currently commissioned price of SABR (upper line) and anticipated long-term treatment costs (lower line). Vertical lines represent the observed 30DM following ten fraction palliative radiotherapy to bone metastases (left) and single fraction treatment (right). The 2.5th, 25th, 75th and 97.5th quantiles of simulation values are illustrated by dotted purple lines.
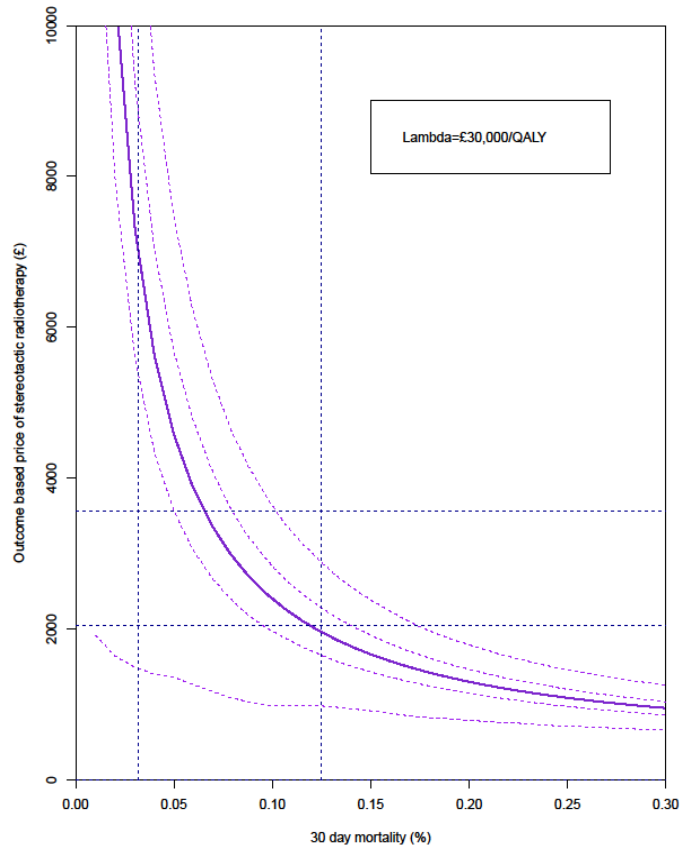
The fit of the Weibull proportional hazards function to the routine outcomes data was inferior to that of the lognormal function (Figure 59). The AIC for the Weibull model was 115,600 reducing to 112,929 for the lognormal model.

Figure 59. Parametric survival functions fitted to routine outcomes data. A)Weibull and B) Lognormal.
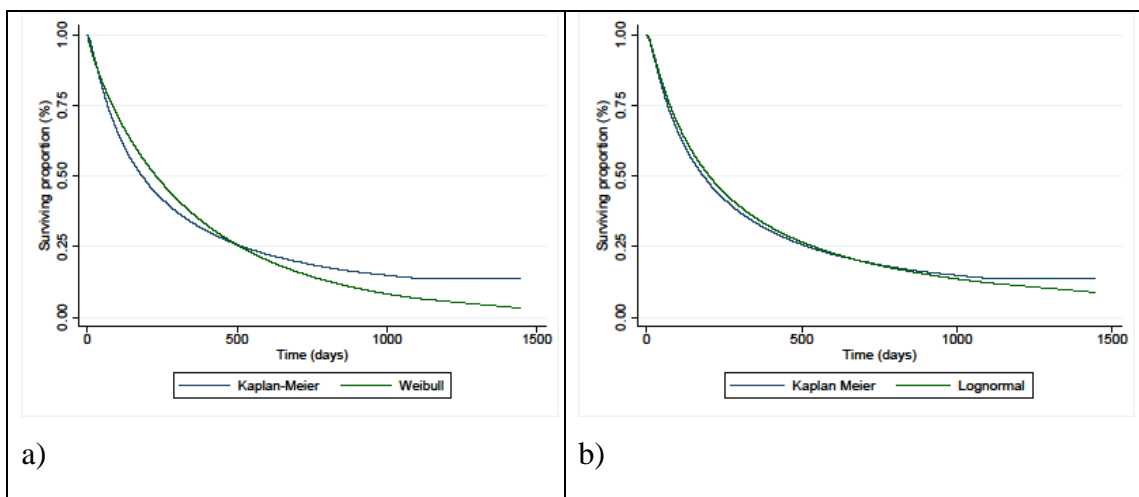
8.4   Discussion

Despite clear evidence of non-inferior pain response outcomes following single fraction palliative radiotherapy to bone metastases there remains wide variation in the use of single fraction treatment across the English NHS. The use of single fraction treatment varied from 37.7% to 90.3% between provider organisations. Treatment delivered using fractionated courses are not justified by the available randomised literature and are highly unlikely to be cost-effective (chapter 6).(90) Targets for the delivery of single fraction treatment already exist, with NICE recommending single fraction treatment for uncomplicated bone metastases in breast and lung cancer and NHS England's Quality, Innovation, Productivity and Prevention program (QIPP) requiring that 70% of treatments to uncomplicated bone metastases should be delivered using a single fraction.(375) This latter figure recognises that it is not always possible to define a treatment as being delivered to an uncomplicated bone metastasis given the available data and, in addition, some treatments may be fractionated due to inclusion of large volume soft-tissue disease within the field. Although, there is no randomised evidence to support this latter approach it remains accepted practice. Given the extent of variation in fractionation patterns delivered it is not realistic to suggest that all of observed variation simply represents variation in disease patterns. Anecdotally, some poorly performing centres have improved since the time period included here and analysis of more up to date data are required to assess the extent to which the variation observed has reduced. In addition, feedback of the unusual patterns observed in individual providers might ensure that subsequent data submissions are improved and, where necessary, treatment protocols modified to better reflect currently accepted guidelines. These data can support feedback to treating centres to guide practice change where appropriate.

Work to deliver this feedback is now required in collaboration with appropriate stakeholders; PHE, the Royal College of Radiologists and NICE. This will require validation of the algorithms used here to identify treatment intent and site treated. Specific focus should be given to ensuring the separation of MSCC from bone metastases is robust. This is critical to assessing the appropriate use of single fraction treatments for uncomplicated bone metastases.

In light of the limitations of the available data to accurately identify the treatment site/urgency it is possible that some of the treatments included here may have been delivered for MSCC. Evidence of benefit from fractionation in this setting is, however, lacking. Indeed, in 2017 a randomised trial, presented in abstract form, demonstrated non-inferiority in ambulatory status at eight weeks following a single 8Gy treatment as compared to 20Gy in five fractions.(435) The median survival in this study population was approximately 13 weeks, in keeping with that observed here in the routine data (11.7 weeks). In the trial no survival benefit was observed from fractionated treatment. Once published this trial might support a move towards the use of single fraction treatments in MSCC, however, concerns will remain about the potential for heterogeneity of treatment effect and the possibility that in those with a better prognosis more fractionated treatment may be beneficial. The presence of MSCC as a justification for delivering fractionated

treatment very close to the EoL is, however, no longer valid and future analyses of more contemporaneous data must recognise this, highlighting not only 30DM but particularly focussing upon ensuring the number of fractionated treatments delivered to patients near the EoL is minimised.

A further area in which the data collection process should be reviewed is in the categorisation of treatment intent. In limited instances fractionated palliative radiotherapy may offer improved survival,(17,20) however, good local control may also offer benefits in terms of long-term symptom control and a more prolonged interval to subsequent treatment with its associated side-effects. This is particularly relevant as the use of stereotactic radiotherapy for oligo-metastatic disease and progression becomes more prevalent.(348,436) This type of disease-modifying treatment, whether with SABR or otherwise, is undoubtedly being delivered by clinicians currently, however, the dichotomy between palliative and curative intent definition does not support collection of this more nuanced information. Modification of the treatment intent field to allow capture of a "disease modifying" intent might help to better align the algorithm defined treatment intent seen here with the clinical reality, thus potentially increasing the confidence clinicians can have in future analyses.

Treatment close to the EoL is less likely to be associated with pain response and, as shown in chapter 3, where response is seen the associated HR-QoL benefits are diminished. Beyond this, as shown in chapter 6, the overall impact upon HR-QoL is expected to be minimal for those treated in the final twelve weeks of life. In 2014-15, however, 10,516 non-emergency treatments were delivered for bone metastases in patients in the final twelve weeks of life, many of these being fractionated. These treatments are undoubtedly delivered with good intentions and optimism in the face of uncertainty.(100,437,438) Beyond the risk that a significant propoprtion of these treatments will have resulted in a net harm, however, in chapter 6 it was shown that in a cohort of patients with a median survival of 6.2 weeks palliative radiotherapy was highly unlikely to be cost-effective; the opportunity cost of these treatments is not insignificant. Whilst this subgroup analysis of the cost-effectiveness of treatment highlights the limitations of delivering treatment in a population with increasingly marginal benefit, or indeed harm, is it notable that when the threshold sensitivity analysis is used it is not until the 30DM rises above 24% that treatment to the entire cohort is unlikely to be cost-effective. Levels of 30DM this high are not seen in any provider institution here (excepting in one where data quality is poor and likely to be limiting the analysis), although this level of 30DM has been reported internationally.(439) This reveals a significant challenge in the use of a health maximisation approach in identifying acceptable levels of 30DM in palliative radiotherapy in an unselected population; the harm experienced by patients with very short survival times is readily offset by those with more prolonged survival.

The extent to which a net harm may be delivered near the EoL must, however, be addressed and multiple approaches will be required to support this change.

Firstly, treating clinicians often do not have the opportunity to follow-up all patients and given the recognised tendency of clinicians to be optimistic in their estimation of prognosis there is now a pressing need to deliver feedback to clinicians of these outcomes.(100,437) This can support a greater awareness of the extent to which the treatments delivered will be expected to deliver a net harm. Feedback of outcomes must be carried out sensitively. Beyond the validation of the algorithms used here, providers whose 30DM is outside of expected limits on the presented funnel plots must have the opportunity to assess these data, confirm the extent to which these outcomes are realistic and consider mechanisms by which to improve. This is particularly true of those outlying above the funnel (higher than expected 30DM). It should be noted, however, that in the overall analysis three providers are outlying below the funnel, whilst in the bone metastases analysis two are. This may reflect high levels of hypofractionated treatment use. The extent to which the rates of utilisation of palliative radiotherapy among the whole at risk population is low in these centres compared to elsewhere should also be considered. It may be that a balance exists between utilisation rates and early mortality. Equally, maintaining utilisation whilst delivering relatively low levels of early mortality might suggest appropriately early treatment of symptoms and maximisation of benefit to patients. Further work is needed to assess the extent to which this might be occurring as the data to support this analysis were not available here. This will need to include analyses of both those patients who have undergone palliative radiotherapy and those who have not, but might potentially have had an indication.(440) Providing feedback to clinicians recognising both of these outcomes might ensure a balanced approach to feedback, minimising the risk of unintended consequences.

The challenge to the use of a health maximisation approach in identifying acceptable levels of 30DM is an important one. The decision-analytic model used here to identify acceptable levels of 30DM was completely naïve to any prognostic estimation (insufficient information about the treatment effect of SABR being available). It is clear from the variation in 30DM seen between different fractionation patterns that clinicians are not so naïve; 30DM is markedly lower following fractionated courses than single fraction treatments (3.2% vs 12.5%). This might explain why the 30DM observed in routine practice is so much lower than the acceptable level estimated by the cost-effectiveness model. That such large numbers of treatments are delivered so close to the end of life, however, suggests that these estimations of prognosis are not sufficient currently. Two approaches to improving this could be considered. Firstly, given the evidence demonstrating the non-inferiority of single fraction treatment for bone metastases and, more recently, for MSCC, the approach to clinical decision making should change. Where treatment is planned for a painful bone metastasis or MSCC the question the clinician asks themselves should not be "can I get away with a single fraction?" but "can I justify fractionation?"; the standard of care must be single fraction treatment. In this way fractionated courses in those with very limited prognosis can be (largely) avoided.

Beyond the decision to fractionate, however, is a need to better determine if treatment should even be delivered. This will require the use of prognostic models. A number of candidate models

have been developed by various international groups.(441–444) These models use a range of clinical, biochemical and patient-reported variables to predict short survival with varying levels of success. The Prognosis Research Strategy project (PROGRESS) has highlighted the extent to which prognostic modelling studies preferentially develop novel prognostic models, failing to validate and implement existing work.(445) Systematic identification of appropriately simple, accurate and relevant models from the available literature should be a priority. Once completed a small number of candidate models should be validated in routine NHS practice and their ease of implementation assessed. The most appropriate model can then be identified and its use recommended whenever palliative radiotherapy is considered. Incorporation of such a model into the existing decision-analytic model might then support the identification acceptable levels of 30DM in routine practice recognising the improved ability to predict prognosis. In this way, treatment delivery can be optimised to reduce the risk that those very close to the EoL undergo disruptive treatments with minimal benefit. The incorporation of such a model into the cost-effectiveness analysis would provide an opportunity to better optimise treatment delivery. The challenges highlighted in chapter 6 regarding equity weights would then, however, come to the fore.

Until this work is completed simple strategies to improve outcomes should be implemented. All treatments delivered within 30 days of death should be reviewed by treating clinicians. These reviews should focus not only upon the final treatment decision but also more widely upon the whole treatment pathway; many patients will arrive in the radiotherapy clinic with an expectation that treatment will be offered and be beneficial. Ensuring that referring clinicians understand the limitations of treatment is likely to be a greater challenge but, wherever possible, through multi-disciplinary team working, feedback to referrers should be provided and a system wide approach taken to reducing the number of treatments delivered near the EoL. This might also have the potential to increase the delivery of treatment earlier in a patient's disease trajectory and thus maximise benefit at an individual level. As seen for one patient in chapter 7, his one regret was not having undergone this beneficial treatment sooner. Combining this individual level review with feedback of both 30DM and fractionation patterns can support appraisal of fractionation patterns and referral pathways by providers. This can then contribute to maximising patient benefit through earlier treatment and the avoidance of treatment very close to the EoL, whilst also minimising burden through hypofractionation.

At the other end of the prognostic spectrum these routine data suggest that outcome-based pricing of SABR, using a survival outcome, is practically possible in this setting. Assuming the response outcomes used in the model are accurate, SABR is likely to be cost-effective in patients currently treated with ten fraction palliative radiotherapy to bone metastases, given the low levels of 30DM observed (3.2%). It is notable, however, that 8,713 individuals survived more than one year beyond their first palliative radiotherapy to a bone metastasis. Of these 58.2% received a single fraction treatment whilst 5.8% received a course of at least 10 fractions. These treatments are delivered in the context of existing guidance recommending single fraction treatment, therefore,

whilst clinicians are currently reasonably reliable at identifying those with prolonged survival for fractionated treatment, it is unclear to what extent further patients might be accurately identified if a clinically superior, alternative, treatment strategy were recommended. Given the uncertainty of prognostication, tendency of clinicians to be optimistic in their estimates and potential for indication creep beyond routine commissioning this OBP approach provides a novel means by which to ensure that the treatments delivered in routine practice are cost-effective through changes to the reimbursed price to reflect previous 30DM outcomes. The risk that the OBP approach might increase inequities in access to treatment, as individual clinicians and providers became wary of the risk of reimbursement below the cost of treatment delivery, must be borne in mind. This might be signalled by relatively low levels of 30DM amongst patients treated by individual providers. Caution will be required in interpreting this, however, as the treated population is likely to be small, particularly in smaller providers, thus making the identification of significant deviation from acceptable limits challenging. The small numbers of patients who might be eligible to receive these treatments in smaller provider institutions might also limit the extent to which 30DM can be used in this setting. Further work to assess this would be required, should future randomised studies replicate the findings of those used to parameterise the decision-analytic model. In addition, further assessment of the fit of the parametric survival function would be required if the OBP approach outlined here were adopted for routine commissioning. The fit of the of the parametric function will be critical to ensuring the relationship between the modelled QALY outcomes and 30DM is a good reflection of outcomes in routine practice and, as such, modifications to the decision-analytic model may be required to incorporate this.

Palliative radiotherapy for bone metastases remains the standard of care for the relief of focal pain due to bone metastases. Wide variation in the fractionation patterns used and outcomes delivered are demonstrated here. In addition, significant numbers of patients are undergoing treatment so close to the EoL that treatment unlikely to be cost-effective and for many may be delivering a net harm. Feedback of these outcomes to treating clinicians is now urgently required, deaths within 30 days should be reviewed critically and future work should focus upon validating and implementing simple, prognostic models able to support clinicians and patients in identifying appropriate treatments and thus not only improving patient outcomes but also the cost-effectiveness of care.

9 Discussion and further work

This study aimed to assess to what extent the palliative radiotherapy delivered for bone metastases in the English NHS is cost-effective and also determine how cost-effectiveness might be improved. A range of methods were used to address this question considering outcomes from a patient perspective, clinical perspective, health economic perspective and commissioning perspective.

9.1 Findings

The results of each chapter are summarised below:

- In chapter 2, the literature review confirmed that single fraction palliative radiotherapy remains the standard of care, although questions about the benefit of treatment in comparison to best-supportive care remain. Similarly, it demonstrated that SABR for painful bone metastases shows promise, however, the routine implementation of these treatments currently seen in North America is not justified in light of the very limited randomised data currently available.(446)

- Chapter 3 demonstrated that with increasing proximity to the end of life the HR-QoL benefits of treatment diminish to a level below which they are no longer clinically significant. In addition, the outcomes currently used to assess response to treatment fail to capture durability of response. Chapter 4, considered the use of a net pain relief outcome to better support this. Given the demonstrated variation in HR-QoL with proximity to the end of life a QALY measure might provide a more meaningful outcome and effectively answer the key question – which treatment delivers the greater benefit in terms of HR-QoL.

- Chapter 5 showed that the costs of delivering radiotherapy are largely fixed at a provider level and, as a consequence, disinvestment from fractions may have an impact on the costs of remaining treatments. This is unlikely to have a significant effect where the number of treatments disinvested from is small, as seen here in palliative radiotherapy. Conversely, the impact of the learning curve upon the costs of SABR is demonstrated, supporting the need to recognise this when commissioning these treatments in routine care.

- Incorporating the outcomes from all of the preceding chapters, the cost-effectiveness modelling in chapter 6 demonstrates that the cost-effectiveness of all radiotherapy strategies is heavily dependent upon the survival time of the treated population; treatment in the final 12 weeks, even with a single fraction, is unlikely to be cost-effective. Indeed, in this cohort, an equity weight of 7.1 is required for treatment to be considered cost-

effective; a level well above any estimated in previous studies assessing societal preferences. Conversely, where median survival was over a year, SABR is likely to be cost-effective where the anticipated long-term costs of treatment (beyond the initial learning curve) are incorporated.

- In chapter 7 the qualitative interviews demonstrated support for the importance of the HR-QoL domains captured by the EQ-5D and incorporated into the cost-effectiveness model. Importantly, however, other domains, not currently captured were highlighted. These included: the patient experience of attending for treatment; psychological benefits of receiving palliative radiotherapy; ability to enjoy time sent with family or participating in hobbies; and relationships with loved ones. All of which are beyond the current evaluative space.

- Finally, in chapter 8, it was shown that despite clear evidence of the non-inferiority of single fraction treatment there remains wide variation in the fractionation patterns delivered. Additionally, large numbers so of patients are receiving treatment so close to the end of life that minimal benefit is anticipated from treatment. Conversely, whilst identifying patients for SABR prospectively would be ideal, an alternative approach to commissioning, using an outcome-based price based upon the survival of the treated cohort, is shown to be potentially feasible in this setting.

Feedback to clinicians and improvements in prognostication are urgently needed to support optimisation of treatment decisions both for the patients undergoing treatment and those upon whom the opportunity costs of these treatments may fall.

9.2   Strengths and limitations

This thesis has taken a mixed-methods approach to considering the cost-effectiveness of palliative radiotherapy services thus considering the services delivered from multiple perspectives. This holistic approach recognises the benefits of treatment to patients and the opportunity costs to the wider-healthcare system. The strengths and limitations of each chapter have been discussed in detail within this thesis. A number of key challenges are, however, highlighted here.

- Significant amounts of missing data are inevitable in studies assessing palliative radiotherapy and this was clearly evident in the DBMS dataset (as addressed in chapters 3, 4 and 6). The consequences of this have been ameliorated, as far as possible, through the multi-level modelling of HR-QoL and sensitivity analyses conducted in the analysis of both net pain relief and cost-effectiveness. Whilst the sensitivity analysis in NPR makes no assumption about the causes of missingness both other analyses rely on an, untestable, assumption of Missing At Random. The consequences of violation of this

assumption are, to a degree, unpredictable, although the multiple imputation used within the cost-effectiveness analysis provides clarification of the likely effects on this outcome.

- The time-driven activity-based costing study carried out here provides valuable information not only about the overall costs of treatment but also details the extent to which treatment costs are fixed and vary over time. These results will support the commissioning of services, although a note of caution is required, given that the data were collected from a single large provider with capital investment supported by a Private Finance Initiative contract. The extent to which these two factors will balance out in the assessment of total costs is unclear, however, this should be borne in mind when interpreting these data.

- The cost-effectiveness analysis carried out here has a clinically plausible structure and incorporates clinically appropriate parameters. Two key limitations are recognised: the data this model is based upon are non-randomised from the perspective of the comparisons with SABR and best-supportive care. Randomised data are now required and the model should be updated to reflect these outcomes. Secondly, where the model is used to assessed variable cost-effectiveness with population survival it was not possible incorporate heterogeneity of treatment response. Through the use of alternative parameterisations the consequences of heterogeneity were assessed; cost-effectiveness of treatment may be over-estimated in both patients with very short and very long prognoses. Once randomised data are available these should be incorporated into the model. Regression based techniques to assess cost-effectiveness can also be considered to handle the heterogeneity of treatment effects.(447)

- The qualitative work presented in chapter 7 provides an opportunity to better understand the treatment process and outcomes from a patient perspective. It must be recognised, however, that only patients who underwent treatment were interviewed. The study did not, and cannot, observe the counterfactual. Patients interviewed are likely to report from this single perspective and the perception that treatment is of value irrespective of its benefits must be considered acknowledging the nature of the interviewed population. The identification of domains of value to patients and beyond those currently captured in cost-effectiveness modelling, is unaffected by this and remains an important outcome.

- Finally, the analysis of routine data presented in chapter 8 presents the first national assessment of 30-day mortality in palliative radiotherapy. The challenges of data access limited the time available to conduct this component of the study and as such the algorithms used have not been validated. The analysis presented here uses clinically robust algorithms, implemented across all providers and thus delivers a strong analysis

of fractionation and 30DM. Future work to validate the algorithms used is now required ahead of feedback to treating clinicians.

30DM has been suggested as a possible quality measure in palliative radiotherapy. One element of this study aimed to identify acceptable levels of 30DM from a cost-effectiveness perspective. This method provides a means to incorporate the HR-QoL benefit of treatment, duration of benefit and costs. An acceptable level of 30DM of up to 24% was identified, with some caveats around the incorporation of heterogeneity. The limitations of this result warrant further consideration.

Palliative radiotherapy to bone metastases offers benefits in quality of life but not survival. As such the QALY detriment experienced by patients with very limited survival time is, by definition, extremely small and readily offset by the benefit experienced by those with more prolonged survival. This will be seen in any economic evaluation where treatment can result in harms and benefits, particularly if the benefits result in significant QALY gain. For example the use of immunotherapy in metastatic melanoma may result in prolonged survival for some individuals whilst having a treatment related mortality of 0.4%.(448) Where the potential benefit may extend to years of additional survival time the risks of treatment related mortality may be justified. Whether the benefits of palliative radiotherapy very close to the end of life can be considered sufficient to justify this trade-off is to a great extent an individual decision, albeit one which is not well informed by the available literature currently.

In this setting, the trade-off between detriment and benefit is hard to justify. In addition, the evaluative space considered is limited to health gains as measured by the EQ-5D. It is unclear how patients might weight the available benefits, however, in this analysis no weighting is applied. As such, the health maximisation approach used here, to identify an acceptable level of 30DM, is seen to be inappropriate. It remains unclear what an acceptable level of 30DM is. There is, however, value in the use of the 30DM measure to provide feedback to treating clinicians, even in the absence of a defined acceptable level as a better understanding may help to guide improvements in care, reduce the use of treatment very close to the end of life and support hypofractionation.

It is notable that bone metastases are the most frequently treated target-tissue using palliative radiotherapy.(4,6) As outlined in chapter 1, the available literature would also suggest it is more likely to deliver swift symptom control than palliative radiotherapy used for other treatment indications. As such, higher levels of early mortality in other treatment groups are highly unlikely to be justified.

9.3   Research in context and future directions

It is clear that the challenge of optimising palliative radiotherapy use across the NHS is complex; multiple stakeholders are involved and will need to collaborate to deliver the improvements needed. The implications of this work, how change in practice might be implemented, the barriers

to this and future directions for research will now be considered from a number of perspectives; the delivery of palliative radiotherapy services and clinical trials, valuation of treatments both near the end of life and in the context of heterogeneity and, finally, combining the two and considering these outcomes from the perspective of shared-decision making.

9.3.1 *Radiotherapy delivery*

9.3.1.1 *Clinicians*

The implications of this work for radiotherapy service delivery can be considered from the perspective of multiple different stakeholders. From a clinical perspective the outcomes presented here are challenging; the benefits of treatment diminish markedly near the end of life with treatment increasingly likely to deliver a net harm. Yet large numbers of treatments are delivered each year in the final few months of life and many of these are fractionated. There is now a pressing need to address this. The limitations of clinicians' ability to anticipate prognosis are well documented,(83,100,437) however, the challenges of changing practice are complex and will go well beyond the prognostication skills of the individual doctor.

The referral pathway many patients follow to receive radiotherapy may be a significant challenge to delivering change; for many the meeting with a clinical oncologist to discuss palliative radiotherapy may be perceived to simply be confirmatory if the patient has already received a recommendation from a known and trusted clinician. Prospect theory highlights that, under uncertainty, people are loss averse; we feel losses more strongly than gains.(449) Where the delivery of treatment might have been initially framed as a benefit, subsequent withdrawal might then be a loss. As such, both patients and clinicians may prefer to pursue treatment even where benefit might have been recognised to be minimal. Additionally, communication with patients near the end of life is complex with the balance between maintaining hope and ensuring understanding being very finely balanced.(436–438) This may contribute to a willingness to offer a treatment which is perceived to have limited toxicity and where the fact of delivery alone may be perceived to be beneficial.

The challenge of reducing the use of palliative radiotherapy very close to the end of life may be exacerbated by the increasingly sub-specialised nature of care delivered for patients with advanced incurable cancer. Clinical oncologists, medical oncologists, palliative care physicians and a range of other colleagues may be involved in an individual's care. In many cases, however, only one of these will lead care delivery at any one time. This may be a significant determinant of when, and indeed if, a patient receives palliative radiotherapy; a patient may receive radiotherapy under a clinical oncologist, intravenous bisphosphonates under a medical oncologist or modification to their analgesics under a palliative care physician. Early palliative care has been shown to be beneficial in other healthcare jurisdictions, although how such an approach might be delivered in the NHS and whether treatment being delivered by multiple different specialists in parallel can be cost-effective is unclear.(289,450,451) If we are to maximise the benefits and

efficiencies of the care delivered near the end of life, we must ensure that the balance between alternative treatment options is optimised with individuals receiving the care which can provide the maximum possible benefit at any given time point. It maybe that this cannot be delivered by oncologists and if this is the case alternative options must be sought. One limitation to the delivery of such an approach might be the availability of appropriately trained healthcare professionals. Trial-based evidence in the NHS is needed to clarify the potential benefit and, thus, support practice change if appropriate.

Once in the radiotherapy department the use of fractionation in palliative radiotherapy will, in part, be determined by the individual clinician's assessment of the patient. This assessment and the subsequent treatment decision are not made in isolation. Local treatment protocols will have a significant influence upon the decision to fractionate and should be modified accordingly for all treatments delivered to bone metastases or, indeed, spinal cord compression. Clinicians would then be encouraged to justify their decision to fractionate rather than considering the option to deliver single fraction treatment.

The development of a learning healthcare system is an increasing policy priority.(452,453) The analysis of fractionation patterns and 30DM presented here can form an element of this in clinical oncology practice. Feedback of these data to treating teams, supported by key external stakeholders (such as the Royal College of Radiologists and PHE), could help to ensure a focus upon delivering appropriately hypofractionated treatments and so appropriately reduce the use of treatment very close to the end of life.

Finally, the decision to pursue treatment and then to fractionate incorporates the patient's expected prognosis.(6,83) Patients and clinicians have been shown to be overly optimistic in their estimation of prognosis and this may impact upon their treatment decisions.(96,99,100,454) A range of prognostic models have been developed for patients with advanced incurable cancer with some authors suggesting their implementation might significantly reduce 30DM.(386,443,455) There is a pressing need to identify an optimum model, validate it within the NHS and then implement it in routine practice to guide decision making. This would help to support not only decision-making in the clinic but also, importantly, multi-disciplinary discussions about the appropriateness of treatment where patients have not yet been referred. The use of predicted prognosis as a surrogate for likelihood of response is supported by the available literature.(92,93,222) The ability to predict prognosis alongside response probability would, however, offer greater clinical value in informing the decision-making process. Joint longitudinal survival modelling of HR-QoL and survival might offer this potential.

9.3.1.2   Clinical trials

This thesis identified a number of gaps in the trial-based literature informing the clinical-decision making process. Studies conducted to assess the role of fractionation in palliative radiotherapy

for advanced NSCLC assessed differing treatment strategies in patient groups with varying prognosis based upon their baseline performance status.(20,456) Given the findings demonstrated here there is a clear need to replicate these studies in the analysis of treatment for bone metastases, entering patients to appropriate treatment randomisations based upon predictions of prognosis from a validated prognostic model might support this whilst also providing further valuable validation of the prognostic model.

The systematic review presented in chapter 2 and cost-effectiveness analysis support a possible role for SABR in the management of uncomplicated bone metastases. The literature to date is predominantly non-randomised with the published randomised studies being small in size and single centre. There is now an urgent need to replicate these studies in larger, multi-centre randomised trials to define the clinical efficacy of SABR. Such studies should aim to randomise patients with a prognosis of at least six months to better assess this intervention in a population for whom it might potentially be commissioned in future. Endpoints in these studies should be considered with care; the standards set out in the ICPRE are not sufficient to assess the key benefits of SABR. Net pain relief offers an opportunity to assess the extent to which these treatments can improve pain control over a patients remaining life, not simply at a single time point. As demonstrated in chapter 7 patients hope for improvements in a range of HR-QoL end-points, not simply pain response. As such, the potential role of the QALY as a clinical end-point, which can capture both the improvement in HR-QoL and duration over which this is delivered, should be considered. In measuring this for the purposes of clinical decision-making chapter 3 supports the use of the EQ-VAS as a self-reported measure of overall health, independent of the health-state values defined by a societal tariff. Health economic end-points in these studies should also be collected in line with those highlighted by the expected value of perfect parameter information in chapter 6.

In patients with a limited prognosis SABR is unlikely to be cost-effective and the delay to treatment which would be introduced by the complex planning process would be hard to justify clinically. For this patient group the response rate following palliative radiotherapy (45% in those surviving less than 12 weeks) is below that observed following intravenous Ibandronate treatment (49.5% response at 4 weeks).(15,92) It is worth noting, however, that the median survival of this latter population was markedly longer. In addition, the challenges in interpreting the outcomes of studies assessing the role of 4Gy versus 8Gy single fraction treatments leave open the possibility that, in those with very short survival, palliative radiotherapy may offer no significant benefit over alternative treatment strategies. These alternatives could be delivered closer to home and result in lower treatment burden, an important consideration in this patient group. This requires further investigation. Future studies in this setting should incorporate robust plans to minimise and address missing data. Initially a comparison between 4 and 8Gy could be made, ideally in a randomised double-blinded setting to minimise the potential for bias caused by awareness of the reduced dose delivered. Subsequent studies, examining alternative strategies, including intravenous bisphosphonates and best-supportive care could then be conducted depending upon

the outcome of this initial study. The outcomes of these studies, which should also validate the use of an appropriate prognostic model, could then have a significant impact upon clinical decision-making near the end of life.

9.3.1.3   Commissioners

Further work is now underway to extend the TD-ABC analysis to other treatment centres and provide an indication of treatment costs across other provider institutions. This would support an assessment of not only the costs implications of implementing novel techniques but also the workforce resource implications. Combined with the results presented in chapter 8 this provides key information about anticipated treatment numbers and resource requirements. This should be provided at a national, regional and local level to support commissioning decisions. It may be that, if appropriate, commissioning of SABR for bone metastases could best be achieved through commissioning in a limited number of centres. Issues of access for patients living further from a treating centre would need to be addressed, however, the data provided here can support an assessment of the extent to which commissioning in smaller centres might be cost-effective given the small number of patients who might be eligible for treatment. The potential consequences of the large capital investments required to implement a novel treatment, where significant uncertainty exists about its efficacy, can also be more robustly examined using this data.(1)

Whilst the observed levels of 30DM are well within the limits identified from a cost-effective perspective the number of patients dying within a short period of radiotherapy remains significant. In combination with the demonstrated variation in fractionation patterns there is now a need to deliver feedback of these outcomes to clinicians. The current move towards the development of a learning healthcare system will require support from commissioners if it is to be successfully implemented.(452,453)

Finally, whilst potentially providing clinically meaningful and cost-effective improvements in pain control, for a limited cohort of patients with bone metastases, the implementation of SABR for bone metastases in routine practice maybe challenging. Particularly as the intervention gains acceptance and diffuses into routine use. The risk that it is then adopted in populations where it cannot be cost-effective is significant. The extent to which the significant increase in the human resource required to deliver the treatment may ameliorate this is unclear. The ability to modify the reimbursed price of treatment to reflect the treated population provides an opportunity to support cost-effective implementation whilst also having the flexibility to accommodate the initial learning curve costs of a novel technique. Commissioners will need to overcome the current tension between financial constraints and value in order to achieve this; SABR is unquestionably more costly, but if it is shown to deliver a clinically meaningful improvement in pain control and HR-QoL it may still offer better value than conventional radiotherapy.

9.3.2 *Value near the end of life*

The societal valuation of health states to derive utility values has a number of important advantages: adaptation to a health state is not incorporated; the potential influences of demographic and socio-economic factors on individuals valuations is avoided; and this offers a degree of social legitimacy in a healthcare system funded by taxation. There is much discussion, however, amongst health economists about the most appropriate way in which to value health very near to the end of life and in particular where the duration of life can no longer be extended. Specifically, it has been argued that the QALY is an inappropriate measurement tool in this population. Reasons for this include: the argument that it is not possible to trade HR-QoL for time when death is imminent; failure of the assumption that all time is equivalent irrespective of proximity to death (the assumption of constant proportional trade-offs); variation in preferences near the EoL; variation in domains of importance (potentially beyond the currently accepted evaluative space);(457) and, finally, that some interventions deliver benefits not adequately captured within a QALY framework when time is so short. All of these have been discussed previously by other authors.(234,265,378)

The results presented here contribute to this debate:

The analysis presented in chapter 3 provides empirical evidence of systematic variation in the relationship between the domains of HR-QoL and global self-reported health with proximity to death, not previously demonstrated.(458) That this relationship is not constant contrasts with the valuation used in cost-effectiveness analyses. The EQ-VAS is recognised to capture a broader construct of health than is captured by the EQ-5D domains. The extent to which the variation observed here reflects the nature of this broader construct, differing values for the measured domains or simply an inability to adapt to a rapidly changing health state is unclear. Identifying which domains should be included in the measurement of health is, however, critical. The qualitative study presented here adds to the existing qualitative literature informing the nature of these "missing domains"; the ability to prepare for death, not to be a burden on loved ones, to sustain hope and to enjoy their remaining time are all identified by patients as important in the decision to pursue palliative radiotherapy. Coast and others have carried out significant work in this area identifying key domains of importance to patients near the end of life.(459) Once the appropriate domains are identified valuation can then be undertaken with consideration given to the extent to which variation exists in the valuation of these outcomes between patients, carers and wider society.(458)

As outlined previously in section 6.4.4, there is ongoing discussion about the role of equity weights in cost-effectiveness analysis near the EoL. Discrete choice studies have demonstrated some societal support for a greater weight being allocated to health benefits near the EoL, although results are conflicting.(391,460) Some particular results are also notable; there appears to be some support for greater weight being allocated to those with a newly diagnosed short prognosis than to those who have known of their diagnosis for some time.(460) This study also

demonstrated value for quality of life gains, although not at the expense of larger health gains elsewhere, supporting the health maximisation approach taken currently. Others have, however, shown societal support for greater weight being allocated to patients near the end of life.(391) What is unclear from these studies is the extent to which the respondents understood the quality of life construct being valued.

It is shown in chapter 6 that palliative radiotherapy is highly unlikely to be cost-effective in a population very close to the EoL at currently accepted willingness to pay thresholds. Indeed, the QALY would need to be valued 7.1 times more highly for this population than in others; a finding unlikely to gain support from a societal perspective.(391,460) It is questionable, however, if such support would be desirable. Equity weights are attempting to address the numerical issue that near the end of life, where survival cannot be increased, sufficient QALYs cannot be gained to deliver a cost-effective outcome. Equity weighting assumes that were we to be able to value the currently measured QALYs appropriately we would see cost-effectiveness. It has, however, been suggested that the current weights might, to an extent, be a recognition of concerns about the measurement and valuation of outcomes near the EoL.(460) Equity weighting might only emphasise any discrepancies between patient and societal values in terms of both the appropriate domains to be measured and their relative value. This may mean that by valuing QALYs near the EoL as we do,(461) we might support the use of costly interventions which deliver limited benefits, potentially to the detriment of other interventions (for example high quality palliative care) with greater potential to improve outcomes of greater value to patients. Improved understanding is needed of what and how patients value outcomes near the EoL before any such weighting can be justified. Finally, if alternative measures are developed, with domains of importance identified, measured, and valued appropriately, further work should then also focus upon identifying when this alternative measurement should be used.

In summary, there is a need to identify what matters near the EoL, reconsidering the evaluative space if necessary. Valuation can then be undertaken and only then can consideration of equity weights be made based on assessment of societal preferences for the outcomes that matter to patients.

9.3.3 *Shared decision-making*

Economic theory of choice is based upon the premise that individuals make rational choices in order to maximise their personal utility.(63) Whilst appealing as the basis for decision-making in healthcare a number of critical assumptions are, in practice, not met. Principally, in order to make perfect choices which maximise utility individuals require perfect information. In healthcare this is almost never possible; patients lack the knowledge and experience of their situation to support these decisions and hence rely upon clinicians to inform them, resulting in information asymmetry.(462) It might be assumed that doctors will act in their patients best interests and, therefore, maximise their patients utility. In order to achieve this, however, doctors must

understand the relative value of various outcomes to the individual patient, have perfect information on the likelihood of these and make decisions based purely upon this information without personal bias. Such decision making would reflect the behaviour of a "perfect agent" in economic terms. It is, however, unlikely to ever occur; values are often not known, information is not perfect and finally doctors may act to maximise their own utility rather than that of their patients.(462)

Shared decision making might address many of these challenges to a degree, however, imperfect information will remain an issue.(418,463) Prior to this study it had previously been demonstrated that the probability of pain response following palliative radiotherapy is reduced for patients near the EoL as compared to those with more prolonged survival. This thesis demonstrates that even where pain response is seen the wider benefits of this, as measured by HR-QoL, reduce with proximity to death; patients are more likely to experience severe problems across all EQ-5D domains and the difference in EQ-VAS with pain response falls below a minimally important difference. These findings are important in informing the decision to pursue palliative radiotherapy for bone metastases. Beyond the population studied here, however, the use of large, complex, routinely collected datasets to personalise decision support, beyond the guidelines and protocols we currently rely upon, may offer benefits in this area over the next decade.(452) Individualised predictions of prognosis, the likelihood of response and associated HR-QoL benefits following palliative radiotherapy will potentially offer significant value.

The challenges of presenting this information are not insignificant. Qualitative studies have identified honesty about expected prognosis and maintenance of hope as high priorities in communication.(464) In one survey of incurable cancer patients 98% of patients agreed with the statement that they would like their cancer specialist to be realistic about their likely future.(465) The same proportion wanted to be acknowledged as an individual, suggesting individualised prognostication may have more support than population-based statistics. Studies considering the presentation of statistical information have found conflicting results; a survey study of US cancer patients found that whilst 80% wanted to receive a qualitative prognosis only 50% wanted to receive a quantitative prognosis,(466) a similar Australian study demonstrated equal preference for words and numerical descriptors although graphical representations varied in their acceptability to different patient groups. In qualitative studies some individuals express a strong desire not to receive statistical information whilst others require detailed prognostic information to support shared decision making.(464) Given this information it is clear that preferences for how information is delivered will vary and significant uncertainty remains about how best to present prognostic information. Further work will, therefore, be required to better understand the information that patients and doctors need and want to inform their decisions and how this information may best be presented.(464,465,467)

Turning these predictions of treatment benefit into predictions of personal utility, however, requires a further step; one which has parallels with the challenges of valuation in health economics. The valuation of health states in a non-welfarist cost-effectiveness analysis is by

definition an expectation of the average societal values. The advantages of this in decision-making at a population level were outlined above. All of these are, however, less relevant when an individual patient-clinician pair make a treatment decision, if the opportunity cost of the treatment under consideration is acceptable at a societal level. For the individual patient the value placed upon life-extension, pain relief, mobility, preparation for death etc. will differ from the societal average. These differences are not captured in health-economic analyses currently and it is questionable if this would be desirable. As individual clinicians, however, we should not mirror this in clinical practice; we should seek better understanding of our patient's values and priorities. This, combined with improved prediction of outcomes of importance to patients, recognising heterogeneity, can support the implementation of shared-decision making. In this way we may be able to ensure that the treatments we deliver in the NHS are, within the confines of wider societal value, offering the best possible value to each individual patient.(416–418)

9.4 Conclusions

It is clear that palliative radiotherapy for bone metastases near the end of life is associated with lower response rates, a reduction in the HR-QoL benefit associated with response and is highly unlikely to be cost-effective. Indeed, in the final few months of life limited response rates, reduced HR-QoL benefits and treatment burden may combine to deliver a net harm for many patients; as treatment use extends into a population closer to the end of life the peak of the health productivity curve is passed. The harm delivered to the individual is mirrored at a population level through the opportunity cost of treatment delivery. Conversely, if the benefits identified in early studies are replicated, SABR may offer cost-effective improvements in HR-QoL for patients with more prolonged survival time. There is a clear need, however, to better personalise the use of these treatments. This already happens to some extent in routine practice, however, improvements are urgently needed. Prognostic models should be validated and implemented in order to better inform clinicians and patients and support the shared-decision making process. Further randomised trials are needed to better define the benefits of treatment in differing populations and finally, commissioning structures need to support clinicians in deciding not to pursue treatment. This value-based approach can help to optimise treatment delivery to the benefit of both the patients undergoing these interventions and the wider healthcare system.

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11 Appendices

11.1 Interview topic guide for patient interviews.

1. Explanation of the proposed project:
   Example:
   > We plan to find out if the radiotherapy treatments used to treat bone pain in the NHS currently are good value for money in terms of helping patients to feel better whilst considering the costs to the NHS and patient. We hope that if possible we will be able to improve this, possibly with newer techniques which might work better. We know about many of the effects of radiotherapy but it's really important that we understand these from a patient's point of view so that we value them as well as possible.

2. Opening question:
   Example:
   > Using your notes I'll be able to find out about your cancer and the treatments you've had for it in the past so I'd like to focus on the treatment that you're having now. Finding out how this treatment has been for you is really important so if you could tell me in your own words about coming for radiotherapy that would be really helpful.
   > Prompts:
   - Have you had to visit hospital a number of times in the run up to this appointment?
   - How long have you been waiting for treatment?
   - How long has it taken you to get here today?
   - Has anyone come with you?
   - How did you travel here?

3. Patient experience of the process:
   Example:
   > People have told me about what coming for treatment feels like. I wonder how you've found it? Is there anything particularly difficult about coming for treatment? Anything particularly positive?
   > Prompts:
   - How did you find travelling here?
   - How did you find lying still for the scan and treatment?
   - How did you feel about having to come back again to receive the treatment?

4. Costs of coming for radiotherapy:
   Example:
   > Some people say that coming for treatment can have cost implications, have you found this?
   > Prompts:
   - How much has it cost you to come here today? Maybe you've had to pay for transport, parking or food and drink when attending.
   - What would you have been doing today if you weren't coming here? Would you have been at work?

- Has someone brought you here today? Would they have been at work if they weren't coming here?

5. Social costs of coming for radiotherapy:
   Example:

   > Some people have said there are other costs from coming for treatment and that these can't be measured in pounds. Is this something you've thought about?

   Prompts:
   - Maybe you feel this is taking time up which you could be spending with your family or friends.
   - How has coming for radiotherapy affected your family?
   - Maybe the opportunity to spend time with family when coming here is helpful.
   - How would you have felt if you'd been told you needed to come for 10 treatments instead of 1?
   - Treatment side-effects might mean you feel less able to do things for a while after treatment, is this something you've thought about?

6. Patient expectations of treatment:
   Example:

   > As doctors we read about the effects of radiotherapy and try to explain these to our patients. Sometimes we don't have the same expectations and priorities as you do though. Are you able to tell me what you're hoping the radiotherapy will do?

   Prompts:
   - Which of these is the most important?
   - Are there other benefits that maybe doctors don't think about so much?
   - We know radiotherapy can reduce pain, if your pain improves are there things you can't do now that you would hope to be able to do?
   - Which of the things you're hoping for do you think is the most important.
   - You've said you would like this treatment to …. How important is that to you?
   - Sometimes people need a second treatment at some point in the future. How would you feel about this?
   - Radiotherapy has some side-effects, I'm not sure what's been discussed with you but wonder if you've had any thoughts about these.

7. Valuing hope:
   Example:

   > Can you tell me a little bit about why you decided to have this treatment now?

   - Is there anything else that's influenced your decision to have treatment?
   - What do your family think about it?
   - If a friend or relative was in this position would you suggest they go ahead with this?
   - What do you think has helped keep you going through all of this?

8. Other comments:
   Example:

We've discussed lots of different things about the treatment you're having and how you feel about it. Is there anything we've not covered?

- Is there any advice you might give someone else coming for treatment?

Follow-up interview topic guide

1. Patient experience of treatment and side-effects:

   Example:

   When we spoke in the department you were only just receiving your treatment. Tell me about how you've been since then.
   Prompts:

   - Is your pain any better?
   - Has your mobility improved?
   - Are you finding it any easier to dress yourself etc?
   - Have you felt tired since having the treatment?
   - Did you notice you felt particularly tired at all after the treatment?
   - You mentioned feeling a burden to others before, has this changed at all?
   - Did you notice any side-effects from the treatment? e.g. pain getting worse, tiredness, sickness, pain swallowing, bowel disturbance.

2. Patient expectations:
   Example:
   Given your experience of the last 6-8 weeks, do you feel that the radiotherapy was worthwhile for you?
   Prompts:
   - Would you recommend this treatment to other people?

3. Patient experience of the process:

   Example:

   Looking back, how did you find the experience of coming for treatment?
   Prompts:

   - Did you find the travel tiring?
   - Was lying still for the scan uncomfortable for you?
   - How did you feel about having to come back again to receive the treatment?

4. Costs of coming for radiotherapy:
   Example:
   We discussed how coming for treatment can cost money and you told me about the costs at the time you received it. Now that you've finished your treatment can you think of any other things you've had to spend money on?
   Prompts:
   - Maybe you had to pay for transport or parking or food and drink when attending.

5. Social costs of coming for radiotherapy:
   Example:

We also talked about other possible costs of having treatment. Since your treatment has finished and you've been through many of the side-effects and benefits is this something you've thought about?

Prompts:
- Maybe you feel this is taking time up which you could be spending with your family or friends.
- Treatment side-effects might have meant you felt less able to do things for a while after treatment, is this something you're worried about?
- How has coming for treatment affected your family? How would you have felt if you had needed to come for 10 treatments instead of 1?

6. Other comments:
   Example:
   Is there anything else you'd like to add?

11.2 Categorisation of cancer diagnoses

***Head and neck

replace RTdx = 1 if rte_dx_icd == "C 3" ///

| rte_dx_icd == "C 4" ///

| rte_dx_icd == "C 5" ///

| rte_dx_icd == "C 6" ///

| rte_dx_icd == "C 8" ///

| rte_dx_icd == "C00" ///

| rte_dx_icd == "C01" ///

| rte_dx_icd == "C02" ///

| rte_dx_icd == "C03" ///

| rte_dx_icd == "C04" ///

| rte_dx_icd == "C05" ///

| rte_dx_icd == "C06" ///

| rte_dx_icd == "C07" ///

| rte_dx_icd == "C08" ///

| rte_dx_icd == "C09" ///

| rte_dx_icd == "C10" ///

| rte_dx_icd == "C11" ///

```
            | rte_dx_icd == "C12" ///

            | rte_dx_icd == "C13" ///

            | rte_dx_icd == "C14" ///

            | rte_dx_icd == "C30" ///

            | rte_dx_icd == "C31" ///

            | rte_dx_icd == "C32" ///

            | rte_dx_icd == "C320" ///

            | rte_dx_icd == "C39"
```

***Oesophageal

```
replace RTdx = 2 if rte_dx_icd == "C15"
```

***Colorectal

```
replace RTdx = 3 if rte_dx_icd == "C17" ///

            | rte_dx_icd == "C18" ///

            | rte_dx_icd == "C19" ///

            | rte_dx_icd == "C20" ///

            | rte_dx_icd == "C26"
```

***Anal

```
replace RTdx = 4 if rte_dx_icd == "C21" | rte_dx_icd == "C210"
```

***Lung

```
replace RTdx = 5 if rte_dx_icd == "C33" | rte_dx_icd == "C34" | rte_dx_icd == "C341"
```

***Hepatobiliary

```
replace RTdx = 6 if rte_dx_icd == "C22" ///

            | rte_dx_icd == "C23" ///

            | rte_dx_icd == "C24" ///

            | rte_dx_icd == "C25"
```

***Sarcoma

```
replace RTdx = 7 if rte_dx_icd == "C40" ///

            | rte_dx_icd == "C41" ///

            | rte_dx_icd == "C411" ///

            | rte_dx_icd == "C45" ///
```

| rte_dx_icd == "C46" ///

| rte_dx_icd == "C47" ///

| rte_dx_icd == "C48" ///

| rte_dx_icd == "C49"

***Melanoma

replace RTdx = 8 if rte_dx_icd == "C43" | rte_dx_icd == "C437"

***Skin

replace RTdx = 9 if rte_dx_icd == "C44" | rte_dx_icd == "C443" | rte_dx_icd == "C444"

***Breast

replace RTdx = 10 if rte_dx_icd == "C50"

***Gynae

replace RTdx = 11 if rte_dx_icd == "C51" ///

| rte_dx_icd == "C52" ///

| rte_dx_icd == "C53" ///

| rte_dx_icd == "C54" ///

| rte_dx_icd == "C55" ///

| rte_dx_icd == "C56" ///

| rte_dx_icd == "C57" ///

| rte_dx_icd == "C541"

***Prostate

replace RTdx = 12 if rte_dx_icd == "C61"

***Renal

replace RTdx = 13 if rte_dx_icd == "C64"

***Bladder

replace RTdx = 14 if rte_dx_icd == "C65" ///

| rte_dx_icd == "C66" ///

| rte_dx_icd == "C67" ///

| rte_dx_icd == "C68"

***CNS

replace RTdx = 15 if rte_dx_icd == "C70" ///

| rte_dx_icd == "C71" ///

| rte_dx_icd == "C72"

***Lymphoma

replace RTdx = 16 if rte_dx_icd == "C81" ///

| rte_dx_icd == "C82" ///

| rte_dx_icd == "C83" ///

| rte_dx_icd == "C84" ///

| rte_dx_icd == "845" ///

| rte_dx_icd == "C85"

***Other haem

replace RTdx = 17 if rte_dx_icd == "C88" ///

| rte_dx_icd == "C90" ///

| rte_dx_icd == "C900" ///

| rte_dx_icd == "C902" ///

| rte_dx_icd == "C91" ///

| rte_dx_icd == "C92" ///

| rte_dx_icd == "C93" ///

| rte_dx_icd == "C94" ///

| rte_dx_icd == "C95" ///

| rte_dx_icd == "C96" ///

| rte_dx_icd == "C42"

***Other

replace RTdx = 18 if rte_dx_icd == "C17" ///

| rte_dx_icd == "C16" ///

| rte_dx_icd == "C37" ///

| rte_dx_icd == "C38" ///

| rte_dx_icd == "C60" ///

| rte_dx_icd == "C62" ///

| rte_dx_icd == "C63" ///

| rte_dx_icd == "C69" ///

| rte_dx_icd == "C73" ///

| rte_dx_icd == "C74" ///

| rte_dx_icd == "C75" ///

| rte_dx_icd == "C76" ///

| rte_dx_icd == "C77" ///

| rte_dx_icd == "C78" ///

| rte_dx_icd == "C79" ///

| rte_dx_icd == "C80" ///

| rte_dx_icd == "C97"

*** C17 - Small bowel, C16 - Gastric, C37 - Thymus, C38 - Mediastinum

*** C60 - Penis, C62 - Testis, C63 - Other male genitals, C69 - Eye

*** C73-75 - Endocrine, C76-80 – Other haem inc Langerhan's, C97 Multiple

***Benign

replace RTdx = 19 if rte_dx_icd == "E05" ///

| rte_dx_icd == "E07" ///   ***Thyrotoxicosis

| rte_dx_icd == "E23" ///   ***Hypopit

| rte_dx_icd == "E22" ///   ***Acromegaly

| rte_dx_icd == "E24" ///   ***Cushing's

| rte_dx_icd == "E34" ///   ***Endocrine disorder

| rte_dx_icd == "G50" ///   ***Trigeminal neuralgia

| rte_dx_icd == "G95" ///   ***syringomyelia

| rte_dx_icd == "H06" ///   ***Proptosis, lacrimal gland, eyelid

| rte_dx_icd == "H93" ///   ***Tinnitus

| rte_dx_icd == "K11" ///   ***Salivary gland

| rte_dx_icd == "K22" ///   ***Oesophageal ulcer

| rte_dx_icd == "L41" ///   ***Parapsoriasis

| rte_dx_icd == "L91" ///   ****Hypertrophic disorder of skin

| rte_dx_icd == "L98" ///   ***Skin disorder

| rte_dx_icd == "M61" ///   ***Myositis ossificans

| rte_dx_icd == "M72" ///   ***Plantar fasciitis

```
        | rte_dx_icd == "M82" ///      ***Osteoporosis

        | rte_dx_icd == "M89" ///      ***Disorder of bone

        | rte_dx_icd == "N62" ///      ***Hypertrphy of breast

        | rte_dx_icd == "N64" ///      ***Mastodynia

        | rte_dx_icd == "N89" ///      ***Inflammatory diagnosis of vagina

        | rte_dx_icd == "N99" ///      ***Post-procedural complications GUS

        | rte_dx_icd == "Q27" ///      ***AVM

        | rte_dx_icd == "Q28" ///      ***Cerebral AVM

        | rte_dx_icd == "R19" ///      ***Introabdominal swelling/mass

        | rte_dx_icd == "R22" ///      ***Localized swelling or mass unspecified

        | rte_dx_icd == "R23" ///      ***Unspecified skin changes

        | rte_dx_icd == "R79" ///      ***Abnormal blood test!

        | rte_dx_icd == "R90" ///      ***Abnormal finding on CNS diagnostic imaging

        | rte_dx_icd == "Z42" ///      ***Breast reconstruction

        | rte_dx_icd == "B21"          ***HIV


label define RTdx 1 "Head and neck" 2 "Oesophageal" 3 "Colorectal" 4 "Anal" ///

5 "Lung" 6 "HPB" 7 "Sarcoma" 8 "Melanoma" 9 "Skin" 10 "Breast" 11 "Gynae" ///

12 "Prostate" 13 "Renal" 14 "Bladder" 15 "CNS" 16 "Lymphoma" 17 "Other haem" ///

18 "Other" 19 "Benign"
```