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Extended Research Article

Rational treatment selection for primary Merkel Cell Carcinoma: a Rational MCC RCT comparing surgery and radiotherapy with parallel observational study

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Abstract

Background: Merkel cell carcinoma is a rare locally invasive skin cancer of older people. Standard management for primary Merkel cell carcinoma is surgery and/or radiotherapy, with no standard of care or unity of practice, based on retrospective experience without randomised trials.

Objectives: Feasibility objectives were to determine whether Rational Compare was likely to deliver on its objectives to influence individual treatment decisions and clinical practice, and to determine operational adaptations to reduce variation between patients and in non-randomised components of the management pathway.

If the feasibility objectives were met, then the primary objective of the overall trial was to determine if surgery or radiotherapy as first definitive treatment for primary Merkel cell carcinoma results in better loco-regional disease control.

Design: Rational Merkel cell carcinoma was a multicentre, two-arm, randomised Phase III, adaptive trial with integrated feasibility phase (Rational Compare) plus observational study (Rational Review) designed to produce probabilities that wide local excision or radiotherapy as first treatment for primary Merkel cell carcinoma was at least as good or better than the other in terms of loco-regional control. In the observational protocol (Rational Review), definitive treatment was allocated by regional Specialist Skin Cancer Multidisciplinary Teams to maximise data on this rare cancer.

Setting: National Health Service hospitals with Specialist Skin Cancer Multidisciplinary Teams.

Participants: All patients with newly presenting histologically proven Merkel cell carcinoma considered for radical loco-regional control without distant metastases, capable to consent, were eligible for the trial. Randomisation occurred using a bespoke computer randomisation system developed by the Cancer Research UK Clinical Trials Unit employing a stratified minimisation method. Those with primary Merkel cell carcinoma that could be treated with margins of ≥ 1 cm by either surgery or radiotherapy for which the Specialist Skin Cancer Multidisciplinary Team was in equipoise were eligible for Rational Compare.

Interventions: Wide local excision or radiotherapy as first definitive treatment for primary Merkel cell carcinoma.

Main outcome measures: Time from randomisation to loco-regional treatment failure.

Rates of registration and randomisation.

Marginal excision and macroscopic disease at the time of definitive treatment.

Results: Sixty-four patients were recruited, of whom five were randomised. The trial did not meet its feasibility target for randomisation and closed.

The five randomised patients all underwent their allocated treatment (three radiotherapy and two surgery, one with adjuvant radiotherapy following surgery), and none experienced loco-regional failure. Twenty-six loco-regional failure events were reported in 59 observational patients (8 had radiotherapy, 27 had surgery, 18 had surgery with adjuvant radiotherapy, 5 had regional Merkel cell carcinoma without known primary and 1 unknown treatment). About a quarter of patients had macroscopic disease, and a majority likely had microscopic involvement at the primary site at the time of definitive treatment.

Conclusions: Both wide local excision and radiotherapy are offered as first treatment for primary Merkel cell carcinoma in UK practice, but it remains uncertain whether one should be prioritised.

Implications for health care: As Merkel cell carcinoma is a rare cancer, the challenge for healthcare systems has been that no specific management strategy currently exists. Merkel cell carcinoma requires a more definitive guideline with optimised referral pathways and interhospital working, which could accelerate and clarify treatments and thus allow better comparison and improvement of outcomes.

Limitations: Major logistic challenges meant randomisation targets were not met, so the trial closed without answering the primary objective.

Future work: The design and outcomes of Rational Merkel cell carcinoma will inform design of future studies for rare cancers. Readouts of circulating immune cells and analysis of the immune microenvironment in the Merkel cell carcinoma primary will be explored in relation to the clinical data set and outcomes.

Study registration: This study is registered as ISRCTN16290169; Clinicaltrials.gov number NCT05253144.

Funding: This award was funded by the National Institute for Health and Care Research (NIHR) Efficacy and Mechanism Evaluation programme (NIHR award ref: 12/205/36) and is published in full in *Efficacy and Mechanism Evaluation*; Vol. 12, No. 12. See the NIHR Funding and Awards website for further award information.

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List of abbreviations

CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CSR	clinical study report
CT	computerised tomography
CTV	Clinical Target Volume
CT-PET	computerised tomography-positron emission tomography
DMC	Data Monitoring Committee
EORTC-QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EQ-5D-5L	EuroQol-5 Dimensions, five-level version
FDG	fluorodeoxyglucose
HBRC	Human Biomaterials Resource Centre
HR	hazard ratio
ITT	intention to treat
MCC	Merkel cell carcinoma
MCPyV	Merkel cell polyomavirus
PET	positron emission tomography
PIS	patient information sheet
PPI	patient and public involvement
QoL	quality of life
REC	Research Ethics Committee
RFS	relapse-free survival
SAEs	serious adverse events
SLNB	sentinel lymph node biopsy
SSMDT	Specialist Skin Cancer Multidisciplinary Team
TSC	Trial Steering Committee
UICC	Union for International Cancer Control
WLE	wide local excision

Plain language summary

Merkel cell carcinoma is a skin cancer affecting only 250–300 people in the United Kingdom each year. Its rarity means clinicians advise patients on available treatments based on their experience of past cases rather than on the basis of evidence from past clinical trials.

Merkel cell carcinoma starts on the skin (known as the primary), grows quickly and often spreads to nearby lymph nodes in the neck, armpit or groin. It must be treated effectively or it quickly regrows. The primary Merkel cell carcinoma is removed by specialist surgeons who can remove the lesion with a good margin of healthy tissue and who can decide on the possibility of accurate staging. To get a good clearance, large areas of tissue may need to be removed. These patients often need specialist repair after surgery, as well as the consideration of sentinel node staging at the time of surgery, and then possibly radiotherapy. Some patients are instead treated by radiotherapy right away, reducing the need for repair, allowing delivery of radiotherapy sooner.

The Rational Merkel cell carcinoma trial was designed to fairly compare surgery or radiotherapy for primary Merkel cell carcinoma so the trial results could help patients and doctors make the best decision for treatment, taking into account other issues for that person, such as which bit of the body the Merkel cell carcinoma was on, their age and fitness, and preferences.

People with Merkel cell carcinoma are typically elderly and are referred to travel long distances to specialist centres. Treatment requires co-ordination between specialists. Unfortunately, we found that the trial was not feasible with only five patients entered. We recognised this risk of failure in advance and stopped the trial. The patients all underwent their allocated treatment (three had radiotherapy and two surgery, one with radiotherapy following surgery), and after 2 years, the Merkel cell carcinoma has not come back in these patients. However, it was not possible to say with certainty from these small numbers whether surgery or radiotherapy should be offered as the first treatment. An additional 59 patients, concurrently treated for Merkel cell carcinoma but not entered into the comparison, still contributed data on the patient, tumour, treatment and disease control. This meant the trial still collected useful data along with immune measurements and tumour samples from this rare group of patients for further study.

Information on the experience of running this trial and use of a novel trial design may help with design of future research to help people with rare cancers.

Scientific summary

Background

Merkel cell carcinoma (MCC) is a rare locally invasive skin cancer of older people associating with impaired immunity. First treatment of primary MCC is commonly wide local excision (WLE), often necessitating reconstruction and sometimes adjuvant radiotherapy. Some patients instead proceed from biopsy to radiotherapy accelerating start of this modality, but potentially with macroscopic or microscopic disease at the primary site. The evidence base is confounded by being retrospective without trials, often with poor data on margins and disease status at the time of treatment.

Design

Rational MCC was a programme of work consisting of two strands.

The first, Rational Compare, was a multicentre, two-arm, randomised Phase III, adaptive trial comparing WLE versus radiotherapy as first treatment for primary MCC, with integrated feasibility phase. The sample size for Rational Compare was 250 randomised at 5 years using a Bayesian approach to provide evidence on the likelihood of whether each treatment was better/as good as/worse than the other in terms of loco-regional control, thus informing individual treatment decisions.

The second, Rational Review, was an observational study whereby definitive treatment was allocated by regional Specialist Skin Cancer Multidisciplinary Teams (SSMDTs). The planned sample size for Rational Review was 150 patients recruited in years 1–3.

For both Rational Compare and Review, the primary outcome measure was time to loco-regional failure. A key feasibility outcome measure was that 20 patients must have been randomised by month 24 of accrual.

Objectives

The primary objective was to determine if WLE or radiotherapy as first definitive treatment for primary MCC results in better loco-regional disease control.

Methods

Patients newly presenting with histologically proven MCC considered for radical loco-regional control without distant metastases were eligible for the Rational MCC trial. Those with primary MCC that could be treated with margins of ≥ 1 cm by either surgery or radiotherapy for which the SSMDT was in equipoise were eligible for Rational Compare. In Rational Compare, consenting patients were randomised 1 : 1 to either WLE or radiotherapy as first definitive treatment for primary MCC. Additional components of management pathways, such as sentinel lymph node biopsy (SLNB), post-operative adjuvant radiotherapy for the primary and treatment of regional nodes were determined by SSMDT.

Consenting non-randomised patients were registered for data, blood and tumour sample collection in Rational Review.

Results

Sixty-four patients were recruited, of whom five entered Rational Compare and were randomised. Patients on Rational Compare were randomised in a 1 : 1 ratio between Prioritise Radiotherapy and Prioritise Surgery arms using a bespoke

computer randomisation system developed by the Cancer Research UK Clinical Trials Unit employing a stratified minimisation method. The remaining patients, *N* = 59, entered Rational Review. The trial did not meet its feasibility target for randomisation and closed.

In Rational Compare, the five randomised patients all underwent their allocated treatment (three radiotherapy and two surgery, one with adjuvant radiotherapy), and none experienced loco-regional failure. In Rational Review, 26 loco-regional failure events were reported in 59 observational patients (8 had radiotherapy, 27 surgery, 18 surgery with adjuvant radiotherapy, 5 had regional MCC without known primary and 1 unknown treatment). About a quarter of patients had macroscopic disease, and a majority had likely microscopic involvement at the primary site at the time of definitive treatment.

Discussion

Both WLE and radiotherapy are offered as first treatment for primary MCC in UK practice, but it remains uncertain whether one should be prioritised. Blood and tumour samples are available for further research on immunity in MCC.

Study registration

This study is registered as ISRCTN16290169; Clinicaltrials.gov number NCT05253144.

Funding

This award was funded by the National Institute for Health and Care Research (NIHR) Efficacy and Mechanism Evaluation programme (NIHR award ref: 12/205/36) and is published in full in *Efficacy and Mechanism Evaluation*; Vol. 12, No. 12. See the NIHR Funding and Awards website for further award information.

Chapter 1 Introduction

Scientific background

The natural history of Merkel cell carcinoma

Merkel cell carcinoma (MCC) is a high-grade, locally invasive, highly metastatic neuroendocrine skin cancer generally diagnosed in older people (median age 76 years with 62% between 50 years and 80 years and 34% > 80 years).[1] It is very rare: 1515 cases reported centrally in England in the decade to 2008, but with incidence rising from 0.1 to 0.2/100,000 across that time.[2]

Merkel cell carcinoma typically presents on sun-exposed skin, and ultraviolet light exposure is a risk factor. MCC associates with immune suppression,[3] including coincidental chronic lymphocytic leukaemia,[4] organ transplantation,[5] human immunodeficiency virus (HIV) infection[6] and autoimmune disease.[7] Immune suppression or leukaemia/lymphoma also appear to predict a more aggressive clinical course.[5,8,9] Most MCC have the skin commensal, Merkel cell polyomavirus (MCPyV), integrated in the malignant cell genome.[10,11]

Two-thirds of patients present with primary lesions only (stage I and II), one-quarter have clinical or radiological evidence of regional nodal involvement (stage III) and fewer than 10% present with disseminated disease (stage IV). Primary MCC can be controlled with surgery, and there is evidence that it is also a radioresponsive tumour. Recurrence rates are high, with relapse-free survival (RFS) at 5 years for stage I–III patients reported as 48%, median time to recurrence 9 months and > 90% recurrences manifest within 2 years.[12]

The management of loco-regional Merkel cell carcinoma in the United Kingdom

Diagnosis of MCC is often unsuspected and commonly only made after biopsy or excision in a non-specialist centre. Patients should be rapidly referred to a Specialist Skin Cancer Multidisciplinary Team (SSMDT) for definitive management. Currently, treatment of the primary is diverse, including wide local excision (WLE), WLE plus adjuvant radiotherapy or radiotherapy without prior wide surgical margins.[13–15]

The management of patients presenting with primary Merkel cell carcinoma

Evidence for the treatment of primary MCC is confounded by there being few prospective or randomised trials. Scanty data are offered on attempted surgical margins. The consistent use of defined WLE, for example, 20-mm margins with clearance to the next fascial plane, has not been tested. Lewis[16] undertook a systematic review of case series and reports, comprising 418 patients in stage I–IV undergoing various surgical modalities with 1- and 5-year local relapse-free survival 70.5% and 60.5%, respectively. This is supported in more recent case series, for example, a 64% local RFS reported for 49 surgically treated cases treated in 17 centres in 1988–2009.[17]

Merkel cell carcinoma is known to be a radioresponsive tumour. Radical radiotherapy for primary MCC is variably defined and may include treatment after either limited local resection or just a biopsy, but in any case, without prior extensive surgical intervention to obtain wide margins. Most reports of radical radiotherapy are of patients who had been deemed medically or surgically unfit for surgery or those in relapse, that is, a poorer prognosis group. There is a signal that high rates of disease control can be achieved. Parvathaneni reported on just 26 patients receiving radiotherapy alone from a retrospective review of 547 MCC cases, with median tumour size 25 mm (range 3–110 mm) and 92.3% local control rate.[18] Other series report a local control in 25/25 patients with median primary size 20 mm[19] and in 17/18 patients.[20] Veness reported results of radiotherapy as definitive management resulting in in-field control rates of 75% in a mixed group, including inoperable primary MCC on initial diagnosis or relapse[21] and 85% in the extended data set, including both macroscopically present primary lesions and primaries excised with narrow margins.[22] Harrington reported on 42 patients given definitive radiotherapy for macroscopic primary MCC, 37 after biopsy only and 5 after failed excision, with 90% local RFS at 5 years similar to that for the 122 who had at least resection of local macroscopic disease.[23] Field margins were generally ≥ 3 cm around the tumour, and the importance of doses exceeding 50 Gy to achieve local control was emphasised.[23]

The use of surgery and adjuvant radiotherapy is associated with high-reported local disease control rates. The largest prospective trial of MCC to date (for a randomised comparison of adjuvant regional radiotherapy) used as inclusion criteria completion of WLE to defined standards, local radiotherapy starting within 6 weeks of surgery, good performance status, no immune suppression and no other cancers. This trial population included people with MCC on the lower limbs and on the head and neck, and an excellent local disease control rate of 96.4% was observed.[24] While giving a signal of efficacy for WLE plus adjuvant radiotherapy, it does not tell us both modalities are required for all patients, and the applicability is questionable because the eligibility criteria may have selected a population with favourable prognosis. A systemic review of retrospective series reported 1- and 5-year local RFS of 90.5% and 87.9%, respectively, for 169 patients undergoing mixed surgical modalities plus adjuvant radiotherapy to the tumour bed,[16] with similarly high local control rates in more recent series.[19,25] One retrospective series included patients undergoing radical radiotherapy after either surgical excision (n = 105) or biopsy (n = 13) with a 93% local RFS.[17] This paper distinguished between patients with uninvolved (R0) or involved (R1) margins, including those not undergoing excisional surgery (R2) and reported outcomes for surgery with or without adjuvant radiotherapy. Local disease control was 96% (R0, radiotherapy), 71% (R0, no radiotherapy), 87% (R1 or R2, radiotherapy) and 47% (R1 or R2, no radiotherapy). Both margin status and radiotherapy independently associated with local recurrence risk in multivariable analysis. Although outcome is worse for patients whose primary has not been cleared surgically prior to radiotherapy, it is unclear whether requiring further surgical clearance prior to radiotherapy for such patients would improve or worsen outcome. There is a risk that local disease may progress post surgery in patients awaiting adjuvant radiotherapy.[26]

In summary, at the time of trial design and set-up, it was uncertain (1) whether, if radiotherapy is also given, simple excision is as good as or better than WLE; (2) whether primary radiotherapy without prior excision (i.e. biopsy only) is as effective as with excision; (3) conversely, whether the consistent use of quality-controlled WLE, for example, surgical margin 20 mm and to the next fascial layer and with clear pathological margins, is sufficient treatment without adjuvant radiotherapy, in particular, for patients with smaller primary tumours.

Given the uncertainties about optimal management at multiple steps in the treatment pathway, this trial compares treatments for the primary, while collecting additional data on patient, tumour and other treatment variables to inform the design of successor trials.

Trial rationale

Justification for patient population

The primary question in the Rational Compare component of the Rational MCC trial tested two radical first-line strategies for newly presenting primary MCC. MCC is a rare cancer, which has compromised the development of clinical evidence underpinning treatment decisions. Selecting a question that was broadly applicable across the population maximised the probability of an informative result. The integrated Rational Review observational component, which was intended to recruit patient ineligible for or declining entry into the Rational Compare randomised trial, maximised data collection from this rare cancer population. This meant that the combined data from Rational Compare and Rational Review could be analysed to investigate putative prognostic factors detectable at presentation and the value of routine imaging in follow-up. This would generate a bank of clinical data, fixed tissue, viable peripheral blood mononuclear cells, serum and plasma coupled to clinical baseline, treatment and outcome data for future research to be funded separately.

In designing a randomised trial for a rare cancer population, there is a tension between conflicting imperatives, maximising accrual versus minimising heterogeneity in the randomised population to ensure the trial results can be interpreted for defined treatments in a defined group of patients. In the Rational MCC study, accrual was prioritised and a pragmatic approach adopted to minimise restrictive eligibility criteria and permit flexibility in non-randomised components of the treatment pathway. These areas of expected diversity included (1) the completeness of excision in initial biopsy prior to radical treatment, (2) the presence of immune compromise or other malignancies, (3) whether staging investigations prior to study entry included sentinel lymph node biopsy (SLNB), (4) whether adjuvant radiotherapy was planned for the primary or to clinically uninvolved regional nodes following definitive treatment for the primary and (5) the planned management of clinically involved regional nodes. The permissive approach to recruitment was intended to avoid the unintended consequence of slowing existing treatment pathways which might

otherwise arise by the trial constraining clinical decision-making in the absence of high-quality evidence or national consensus on best practice. The trial incorporated a feasibility phase to determine operational adaptations to design that will address the variation between patients and in non-randomised elements of treatment, based on data on UK practice and outcomes.

Justification for design

Rational MCC was a pragmatic trial for a rare cancer population. The aim was to maximise the information collected to inform rational clinical decision-making for patients first presenting with MCC, for whom the intent is to achieve loco-regional disease control. In the Rational Compare randomised trial, a frequentist approach to sample size suggested a sample size of 3000 patients, which was not feasible in this rare disease group, and therefore a Bayesian approach was chosen, which aimed to provide probabilities relating to whether either each treatment is better/as good as/worse than the other. This trial was designed statistically to enable clinical interpretation that either radical radiotherapy or surgery has a high probability of being better than or at least as good as the alternative and, conversely, that the probability was very low of making a disastrously wrong choice. This approach, offered varying probabilities for a range of effect sizes, could be achieved with a sample size of a few hundred patients.

Rationale for the interventions

The primary question of Rational Compare compared two radical first-line strategies to achieve clearance of biopsy-proven primary MCC and adjacent microscopic satellites.

The first strategy was termed 'Prioritise Surgery', that is, radical surgery was used as the first and principal treatment modality to achieve pathological marginal clearance of the primary. The trial required a consistent surgical policy of including clearance to the next fascial layer and a planned margin on the skin that generally exceeds 2 cm or, if limited by specified anatomical considerations, must at least exceed 1 cm. In many or most patients, healing requires a skin flap or graft.

The alternative strategy was termed 'Prioritise Radiotherapy', that is, radical radiotherapy was used as the early and principal treatment, aiming to eliminate malignant cells within the primary tumour bed without delay for radical surgery and healing. This represents a wholly different radiotherapy strategy compared to its delayed adjuvant use after healing following radical surgery.

The management pathway should be structured to start definitive local treatment as rapidly as possible because MCC is known to be an aggressive cancer. Screening procedures between consent and randomisation were kept to a minimum, mainly using data already collected upstream in the management pathway. It was intended that the SSMDT begin mapping the pathways to surgery and to radiotherapy early, even before consent, so that treatment-time targets can be achieved.

Patients randomised to prioritise WLE could subsequently be offered adjuvant radiotherapy to the primary site at the discretion of the SSMDT. This reflects the uncertainty and variation in practice around this issue and published guidance elsewhere supporting adjuvant radiotherapy after WLE but sparing patients with small primary MCC.[27] Note that risk factors guiding the selection of patients for adjuvant radiotherapy have not been validated. This issue was to be addressed by adapting the trial design following the review of data collected in the feasibility phase.

Sentinel lymph node biopsy was neither a study procedure nor a requirement for eligibility. SLNB was to be made available for patients for whom the SSMDT considered this to be appropriate, providing this did not slow the pathway to starting definitive treatment. The use of SLNB offers prognostic data: most but not all studies show patients with negative nodes on SLNB have better outcomes than those staged clinically as node negative or with positive operative staging.[1,8,9,28,29] SLNB can bring forward the time of detection of regional recurrence.[9,29,30] Studies of retrospective incomplete data sets show an association between undergoing SLNB and better disease-specific survival, though it is uncertain whether this is a direct causal link.[30,31] SLNB requires general anaesthetic. It, therefore, puts patients at risk, and some patients may be suitable for radical treatment but not for general anaesthetic. Regional nodal adjuvant radiotherapy could be offered to patients without clinical or radiological evidence of regional nodal involvement and who did not undergo SLNB. During the feasibility phase, Rational Compare offered no recommendation on this issue

because although adjuvant radiotherapy might plausibly result in a gain in progression-free survival, there is no evidence suggesting a survival gain.[24] Both issues were to be addressed by adapting the trial design following the review of data collected in the feasibility phase.

Treatment for patients registered on Rational Review was wholly at the discretion of the SSMDT.

Routine imaging in follow-up

The primary outcome for the trial, loco-regional failure, was based on 3-monthly clinical review and clinically directed imaging as appropriate.

It was considered reasonable to undertake cross-sectional imaging at the end of the first year after primary treatment as a standard part of routine follow-up in patients in whom loco-regional or distant recurrence had not already occurred, because more than half of recurrences were expected to occur in that time. The Rational MCC trial required routine imaging, at the end of both the first and second years to maximise the timely detection of treatment failure.

Computerised tomography-positron emission tomography (CT-PET) scanning using the glucose analogue 18F-fluorodeoxyglucose (FDG) CT-PET was to be employed as the principal routine modality to detect regional and distant metastases at 1 and 2 years. FDG CT-PET is sensitive in MCC and can detect dissemination missed by conventional CT scanning and SLNB (reviewed in Beylergil and Carrasquillo[32]), although it does not replace SLNB in detection of microscopic regional nodal disease.[33] FDG CT-PET scanning is increasingly recognised as contributing to decision-making in MCC,[27] but at this stage, there is no evidence that FDG CT-PET surveillance is associated with improved outcomes in patients with MCC.

Conventional CT scanning is widely available, but access to FDG CT-PET scanning may be more limited. Therefore, SSMDTs were allowed to use conventional CT scanning rather than FDG CT-PET, at least during the trial feasibility phase. At the end of the feasibility phase, the routine annual imaging will be re-evaluated centrally to provide a consistent, standardised report to a template, in order to explore the additional contribution of annual imaging to detection of loco-regional progression in the context of a clinically driven follow-up strategy.

Biological profiling of patients with Merkel cell carcinoma

Variables related to the primary MCC tumour are already components of the Royal College of Pathologists' core data set.[34] Irradiation and cancer immunity may interact (reviewed in Durante *et al.*[35]). MCC is a virus and immune-associated malignancy, and both factors appear to interact with outcome. Therefore, immune variables in the history and on analysis of peripheral blood, intratumoural infiltration by CD3+ and CD8+ T lymphocytes and detection of MCPyV genomes were to be assessed to provide a profile of patients to be factored into interpretation of outcomes.[36–40] Note that these are all factors which might feasibly assessed during the initial assessment of a patient newly presenting with MCC.

Future work is likely to include examination of circulating immune responses and further dissection of functional immune and inflammatory components within MCC tumours, to understand mechanisms of immune effect and evasion and identify targets for immune therapeutic intervention.

Chapter 2 Methods

Trial title

Rational treatment selection for Merkel Cell Carcinoma (MCC): a randomised, Phase III, multicentre trial comparing radical surgery and radical radiotherapy as first definitive treatment for primary MCC with an observational study for patients ineligible for the randomised trial.

Overview

Rational MCC was a pragmatic trial. It aimed to allow every patient newly diagnosed with MCC and suitable for radical treatment to contribute to a prospective data set. The overall ambition of this trial was to establish a national framework to deliver research to improve outcomes for patients with this rare aggressive cancer. Rational MCC had an adaptive design, and operational adaptations were informed by the results of the initial integrated feasibility phase.

Trial aims

- Provide evidence from a multicentre, randomised, two-arm, Phase III trial that will enable clinicians and patients to select rationally between two currently used interventions to treat the primary MCC.
- Provide evidence from a multicentre prospective study, including of patient, tumour and treatment variables in relation to outcomes to improve the quality of clinical practice and support the development of future clinical trials.
- To establish a UK-wide data and tissue bank supporting future research in MCC.
- The aim of the feasibility phase is to demonstrate that a sufficient number of eligible patients can be identified and recruited over the course of the randomised trial, and to monitor and inform the design of the randomised trial.

Trial design

Overview

All patients newly diagnosed with MCC suitable for radical treatment for newly presenting MCC were able to contribute to the UK-wide Rational MCC clinical study, which was made up of two components:

- **Rational Compare:** a national, multicentre, two-arm, randomised Phase III trial.
- **Rational Review:** a prospective multicentre observational study over 3 years which collected patient, tumour and treatment data from patients with new presentation of MCC, including those ineligible for randomisation in the Rational Compare trial. Rational Review included patients ineligible for Rational Compare.

The randomised trial: Rational Compare

This Phase III, multicentre, randomised, two-arm component of the Rational MCC trial was referred to as Rational Compare. The main aim of the trial was to compare surgery and radiotherapy as definitive treatments for the primary MCC tumour. The two arms, randomised 1 : 1, were:

Arm A – Prioritise Surgery – WLE of the primary site with radiotherapy reserved for later adjuvant treatment in selected patients.
Arm B – Prioritise Radiotherapy – early use of radical radiotherapy to the primary site without prior radical surgery.

Due to the nature of the interventions, it was not possible for the clinicians or participants to be blinded to the treatment allocation.

Rational Compare had an adaptive design, and an initial integrated feasibility phase informed operational adaptations to the trial.

During the first 3 years of the trial, data from the feasibility phase of Rational Compare was to be used to monitor, inform and adapt the design of the trial. Patients randomised during the feasibility phase are included in the final efficacy analysis.

The prospective observational study: Rational Review

Patients suitable for radical treatment for newly presenting primary MCC could instead be registered onto the observational study referred to as Rational Review. Reasons for entry to Rational Review rather than Rational Compare included that there was no primary tumour at presentation, that the SSMDT was not in equipoise between radiotherapy versus surgery as definitive first treatment for the primary or that the patient declined randomisation.

Patients on Rational Review received treatment determined by the SSMDT and the same follow-up schedule as participants in Rational Compare. Rational Review was intended to for 3 years.

Sample size

Up to 400 patients were to be recruited to the Rational MCC trial as a whole.

Rational Compare aimed to recruit at least 250 randomised patients after 5 years of accrual.

The sample size for Rational Review was up to 150 patients across years 1–3.

At least 20 patients must have been randomised after 24 months of accrual, and at least 40 patients must have been randomised after 30 months of accrual; otherwise, the Data Monitoring Committee (DMC) and Trial Steering Committee (TSC) were to review continuation of the Rational MCC trial.

Trial schema

The trial schema is given in *Figure 1*.

Sample size

Using conventional frequentist statistics, we estimated that a sample size of nearly 3000 patients would be required to falsify the null hypothesis that neither arm outperforms the other with conventional error rates using a two-sided log-rank test, assuming an event rate of 20% at 2 years (i.e. proportion of patients free of loco-regional failure at 80% at 2 years) and that the true hazard ratio (HR) for loco-regional progression for one arm compared to the other is 0.8 (power 80%, significance 5%). This sample size would not be feasible, even with international collaboration.

The scenarios in *Table 1* indicate that if 50 events were observed (with estimated sample size of 250), an observed HR of 0.8 for loco-regional failure comparing the two treatments would inform the clinician that there was a 79% probability that the superior treatment was truly better, a 50% probability that the superior treatment was a much better intervention (true HR < 0.8) and only 8% probability that the treatment was a much worse intervention (true HR > 1.2). The SSMDT and the patient would be able to use these probabilities to make a rational individualised therapeutic decision, alongside the patient's preferences and data on the quality-of-life (QoL) impact of the two treatments.

Table 1 also shows that even a smaller sample size, for example, 150 patients (with 30 events), could still inform decision-making for an individual patient, accepting a greater level of uncertainty. An observed HR of 0.8 would still mean a nearly 75% chance that the treatment was truly better, and a less than one in seven chance that it was truly much worse. Of course, if the observed effect size was larger, for example, a HR = 0.6, there was greater certainty regarding the better treatment, even at lower sample sizes.

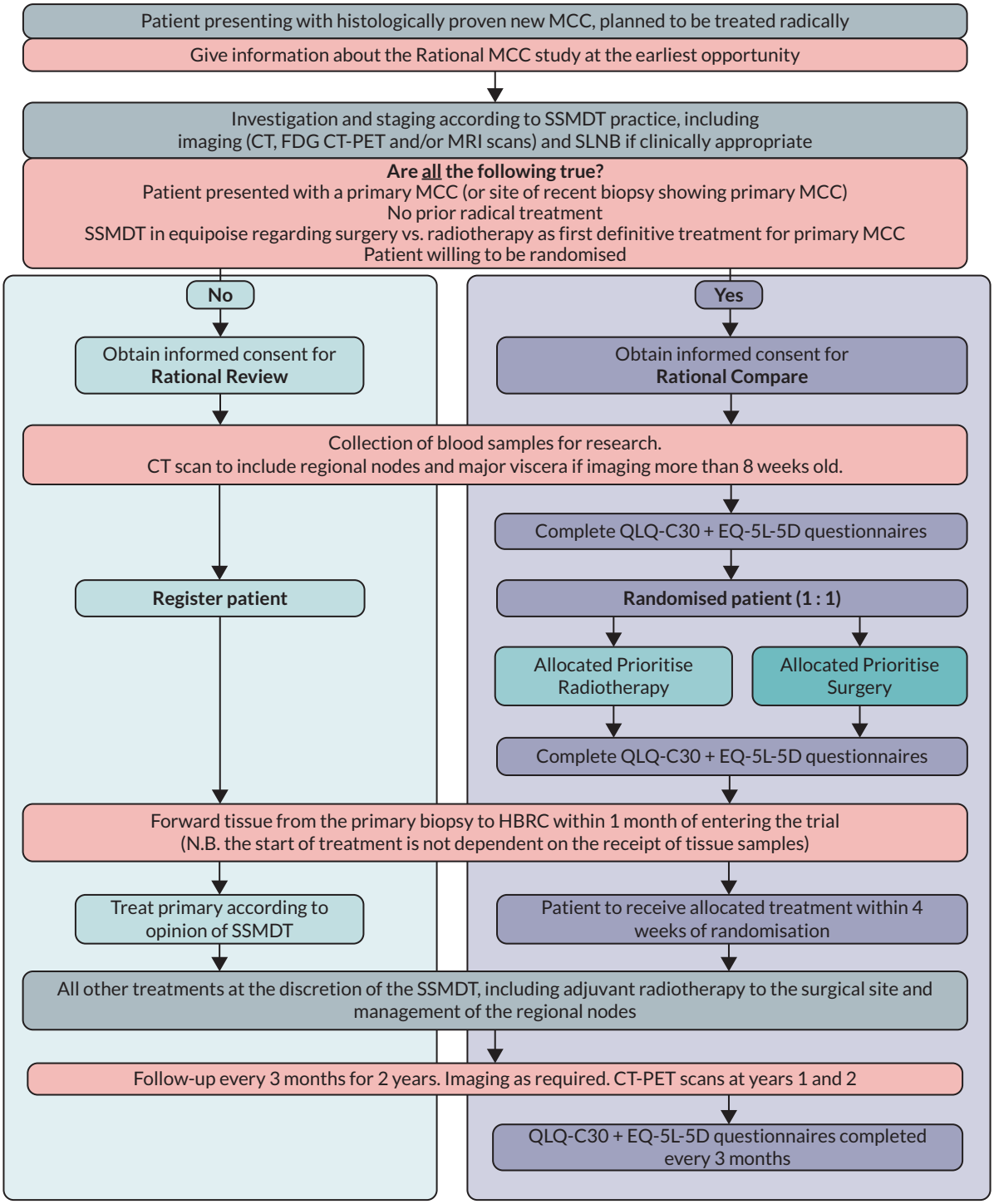

FIGURE 1 Rational MCC trial schema. HBRC, Human Biomaterials Resource Centre.

In considering the use of the trial in guideline development and in making policy decisions, we should be aware of the limitations of sample size. We can use a decision criterion to aid us in making a decision on the level of certainty required to determine if one treatment was indeed superior to the other. This would be based on the Bayesian posterior probability given the observed data from the trial, $p(\text{HR} < \eta^*/\text{data}) > \pi^*$, where η^* is the upper limit and π^* is the cut-off of the lower level of certainty. The design parameters η^* and π^* were calibrated on the basis of the operating characteristics of the trial design (and the ease of clinical interpretation), which were be examined in simulation studies. A preliminary simulation of 100,000 replications with $\eta^* = 1$, $\pi^* = 0.7$ and number of events = 50 gives a 77% chance

TABLE 1 Scenarios used to assess the posterior probability that a treatment is truly much better (true HR < 0.8), or better (true HR < 1), or worse (true HR > 1.2) based on different observed HR, with different number of events and sample sizes, using a non-informative prior

Total sample size		100			150			200			250	
Number of 2-year loco-regional failure events		20			30			40			50	
Observed HR		0.6	0.8	1.0	0.6	0.8	1.0	0.6	0.8	1.0	0.6	0.8	1.0
Posterior probability (%) that the true HR is:	< 0.8	74	50	31	78	50	27	82	50	24	85.0	50	22
Posterior probability (%) that the true HR is:	< 1.0	87	69	50	92	73	50	95	76	50	96.0	79	50
Posterior probability (%) that the true HR is:	> 1.0	6	18	34	3	13	31	1	10	28	0.7	8	26

of making a right decision that one treatment was superior to the other when true HR = 0.7, and a 30% of incorrectly concluding a treatment was superior when it is not (true HR = 1). If an arm was truly very inferior (true HR = 1.3), there would be a 7% chance of incorrectly concluding that it was superior.

Eligibility

Population

All patients with newly presenting with histologically proven MCC and who were being considered for radical loco-regional control were potentially eligible for entry to the Rational MCC trial.

General inclusion criteria for all patients

- Patients newly diagnosed with histologically proven MCC (either primary and/or regional nodal disease).
- Completion of clinical and radiological staging investigations, including CT imaging (or other modality) of regional nodal basin(s) and major viscera (and SLNB if clinically appropriate) to identify regional and distant metastases.
- No distant metastases beyond the regional nodal basin (i.e. not stage IV disease).
- Being considered for radical treatment to achieve disease control.
- Able to give valid informed consent.
- Consent for collection of data and tissue samples and follow-up.
- Life expectancy of 6 months or greater in relation to general fitness and comorbidities.

Additional inclusion criteria for Rational Compare

- Patients newly diagnosed with histologically proven primary MCC.
- In the opinion of the SSMDT, the primary MCC can be encompassed both within a wide surgical margin and within a radiotherapy field, and the SSMDT is in equipoise regarding WLE or radiotherapy as first treatment.
- A minimum margin of 1 cm surrounding the MCC achievable by either radiotherapy or surgery.
- Consent for randomisation into Rational Compare.

Exclusion criteria for Rational Compare

- The primary MCC has already been treated radically with WLE (surgical margins > 10 mm) or radiotherapy.
- Intended use of regional or systemic chemotherapy (including molecularly targeted agents and immunotherapy).

Intervention

Registration and randomisation

Patients were either randomised onto Rational Compare or registered onto Rational Review via telephone call to Cancer Research UK Clinical Trials Unit by research nurse or other delegated member of site staff.

Patients on Rational Compare were randomised with 1 : 1 ratio between Prioritise Radiotherapy and Prioritise Surgery arms using a bespoke computer randomisation system developed by the Cancer Research UK Clinical Trials Unit employing a stratified minimisation method. Patients were stratified by Union for International Cancer Control (UICC) version seven stage (IA, IB, IIA, IIB, IIIA and IIIB/C), intent to undertake adjuvant regional radiotherapy for stage I or II disease (no, yes), primary status at randomisation (macroscopic disease, locally excised with or without marginal clearance) and clinical history of current immunosuppressive illness or treatment (no, yes). Owing to the nature of the treatments, it was not possible to blind the treatment allocation.

Purpose of treatment

The purpose of either radiotherapy or surgery for primary MCC was to achieve complete excision of all MCC with confidence that there was no local residual disease. Compromise on volumes or margins were permitted for anatomical reasons.

Prioritise Radiotherapy

Patients on Rational Compare allocated Prioritise Radiotherapy received radiotherapy as their definitive treatment for MCC, including if macroscopic tumour was present during screening, but the SSMDT was in equipoise between radical surgery and radical radiotherapy. The Clinical Target Volume (CTV) was intended as the tumour and/or the pre-excision tumour area plus a margin of 3 cm and depth to the underlying aponeurosis of the muscle or periosteum of bone. The intended treatment dose was 60 Gy in 30 fractions over 40 days.

Prioritise Surgery

Patients on Rational Compare allocated Prioritise Surgery received surgery as their definitive treatment for MCC. The recommended minimum surgical margin is ≥ 2 cm, and the aim was to achieve an optimal 3-cm surgical margin and depth of excision to the next clear tissue plane.

Postsurgical adjuvant radiotherapy to the tumour bed could be offered for patients at the discretion of the SSMDT, for example, because of tumour size ≥ 2 cm, involved pathological margins, satellite or microsatellite tumour nodules, lymphovascular invasion, chronic immune suppression or no potential for further surgical management in the event of recurrence.

Rational Review

In Rational Review, treatment was according to the decision of the SSMDT.

Data were collected on definitive treatment for primary MCC for all patients on both Rational Review and Rational Compare.

Objectives and outcome measures

Rational Compare objectives

Primary objectives:

- To determine if radical surgery or radical radiotherapy as first definitive treatment for the primary MCC results in better control of loco-regional disease.

Secondary objectives

To compare between the trial arms:

- survival with current loco-regional control
- local, in-field, in-transit and regional nodal treatment failure and distant progression
- progression-free survival
- overall survival, and
- QoL.

Feasibility phase objectives (years 1–3)

- To determine whether Rational Compare is likely to deliver on the trial objectives such that the results will influence individual treatment decisions and international clinical practice, and
- To determine operational adaptations to Rational Compare design to reduce variation between patients and in non-randomised components of the management pathway.

Exploratory objectives (all patients in Rational Compare and Rational Review)

- To determine the additional value of routine FDG CT-PET at 1 and 2 years in identifying recurrence in patients undergoing clinical assessment and symptom-directed imaging.
- To identify clinical, pathological and treatment variables associated with good outcome from MCC and select for further investigation variables at presentation as possible prognostic and predictive biomarkers of MCC.

Rational Compare primary outcome measure

Time to loco-regional failure

The time to loco-regional failure for all patients was the time from randomisation to loco-regional treatment failure. Loco-regional failure was defined as macroscopic progressing or recurrent MCC between and including the tumour site and regional nodes during or after initiation of definitive loco-regional treatment. Persistence of macroscopic disease at a treated site such that additional treatment was required also counted as progression.

For patients undergoing radical surgery, loco-regional failure included (but was not limited to) failure to resect all macroscopic disease, macroscopic recurrence after WLE but before adjuvant radiotherapy, or any pattern that required additional treatment after surgery to control macroscopic disease at the surgical site but did not include demonstration of disease only on pathological examination, such as involved margins on the WLE pathological specimen or detection of microscopic nodal involvement on SLNB, if this was carried out during WLE.

For patients undergoing radical radiotherapy, loco-regional failure included (but was not limited to) recurrence or progression during the radiotherapy course, persistence of disease after radiotherapy, or any pattern that required additional treatment to control macroscopic disease at the site treated with radiotherapy but did not include detection of microscopic nodal involvement on SLNB if this was carried out after randomisation but prior to radiotherapy.

It could have occurred that patients received separate treatments for the disease at different sites, that is, the local disease (the primary and adjacent satellites) and regional disease (in transit metastases or regional nodes). If there was a delay between local and regional treatments, documented new disease or increase in disease volume would count as failure, whereas the fact that macroscopic disease persisted before treatment was initiated at that specific site would not count as progression.

Rational Compare secondary outcome measures

- The proportion of patients alive and free of loco-regional disease (irrespective of whether loco-regional failure has been previously demonstrated)
- Time to local failure (including in-field and in-transit metastases)
- Time to regional nodal failure
- Time to distant progression
- Progression-free survival
- Survival
- QoL

Feasibility phase outcome measures

- Number of recruiting sites
- Rate of registration to Rational Review and rate of randomisation to Rational Compare

- Time from randomisation to start of definitive treatment of the primary (WLE or radiotherapy)
- Proportion of randomised patients undergoing the allocated treatment
- Surgical and pathological margin for WLE
- Clinical treatment volume, planned treatment volume, dose and fractionation for definitive radiotherapy
- Proportion undergoing adjuvant radiotherapy post WLE
- Time from randomisation to start of adjuvant treatment of the primary site post WLE
- Proportion of patients at the point of randomisation with macroscopic disease (R2) or involved

Exploratory outcome measures

Assessment of the additional value of routine cross-sectional imaging, including loco-regional failure and distant progression first detected by routine FDG CT-PET [or CT scan if positron emission tomography (PET) scan is unavailable] at 1 and 2 years.

Assessment of prognostic and predictive variables for loco-regional failure-free survival time from the date of randomisation (or study entry for patients in Rational Review study), the proportion of patients alive and free of loco-regional disease, overall survival.

Decision criteria/stopping rules

The trial was to be reviewed against pre-set targets at four stop/go decision points which the Trial Management Group, TSC and DMC were to consider. A summary of the targets is given below:

12-month time point	5 eligible patients identified
18-month time point	At least 10 centres active
	At least 10 patients registered
24-month time point	At least 20 patients randomised
30 months	At least 20 patients randomised
	A monthly randomisation accrual rate of > 3/month
	Definitive treatment routinely started within 4 weeks of randomisation in both arms. Suitable margin sizes routinely achieved in both arms

Statistical analyses

Time-to-event outcomes

Time-to-event outcomes are analysed using the Kaplan–Meier method. Life tables and plots are to be produced. Time-to-event estimates at 1 and 2 years and, if appropriate, median times are presented with 95% confidence intervals (CIs) for each treatment arm and overall, for the primary outcome and other time-to-event outcomes. Cox regression analysis adjusted by the stratification factors are performed. The observed HR for loco-regional failure, obtained from the Cox model, is calculated and probabilities for various values of true HR estimated. These are presented in the context of clear clinical guidance regarding their use in making both policy and individualised treatment decisions.

If there are substantial number of patients who experience a competing risk (e.g. death) without experiencing the outcome of interest (e.g. loco-regional failure), additional competing risk analyses were conducted to demonstrate that the results are not biased.

Rate outcomes

Rate outcomes are presented as a numerator (number of events) and a denominator (number of subjects), and as a percentage, for each treatment arm and overall. CIs are presented using the Wilson method. To compare the rates between the arms, odds ratios are presented with CIs.

Quality of life

Data from questionnaires are used to compare the different impacts of the randomised interventions on QoL. EuroQol-5 Dimensions, five-level version (EQ-5D-5L) consists of five brief questions, which provide a simple descriptive profile describing the overall health status of a patient and a single index value for the QoL of the patients. European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) is a questionnaire developed to assess the QoL of cancer patients. In particular, the Global Health Status Score derived from it provides a descriptive measure of QoL ranging from 0 (the worst score) to 100 (the best score).

Following completion of the trial, the changes in QoL over the period following treatment are compared between the treatment arms. To model the trend in QoL over time, a linear mixed-effects model (taking into account within subject correlation) using linear and quadratic polynomials and more flexible semi-parametric models, such as cubic splines, was considered. Goodness-of-fit tests were used to compare the different models. The aim is to obtain the most parsimonious trend of QoL by considering simple parametric forms (if possible) to facilitate understanding, interpretation and use of the model by clinicians. We evaluated if QoL changes over time and, if so, what the pattern of change was, as well as if the pattern differs between arm A and B. If the observed death rate was high (which will result in missing QoL data that are not missing at random and not ignorable), we were to assess changes in QoL, taking into account non-random dropout of death (using joint modelling techniques).

Chapter 3 Trial overview

Trial status	Closed to recruitment and follow-up
Total recruitment	64 patients, constituting of 5 patients entered to the randomised study, and a further 59 enrolled to the registration cohort
Date trial opened to recruitment	1 June 2016
Date trial closed to recruitment: Follow-up complete	Rational Compare closed to recruitment on 6 July 2018
	Rational Review closed to recruitment on 1 December 2018
	29 October 2020
Date of database lock	21 February 2022
Protocol version	Version 4.0 (version date 11 January 2019)
SAP version	Version 1.0 (version date 1 June 2017)
Primary outcome	Time to loco-regional failure

All statistical analyses for the RCT within Rational MCC trial (Rational Compare) are carried out on the intention-to-treat (ITT) basis, whereby all patients are analysed in the treatment groups to which they are randomised, regardless of received treatment. Analysis of Rational Review is performed according to the sequence of treatment received.

Trial CONSORT diagram

Figure 2 shows the trial flow diagram.

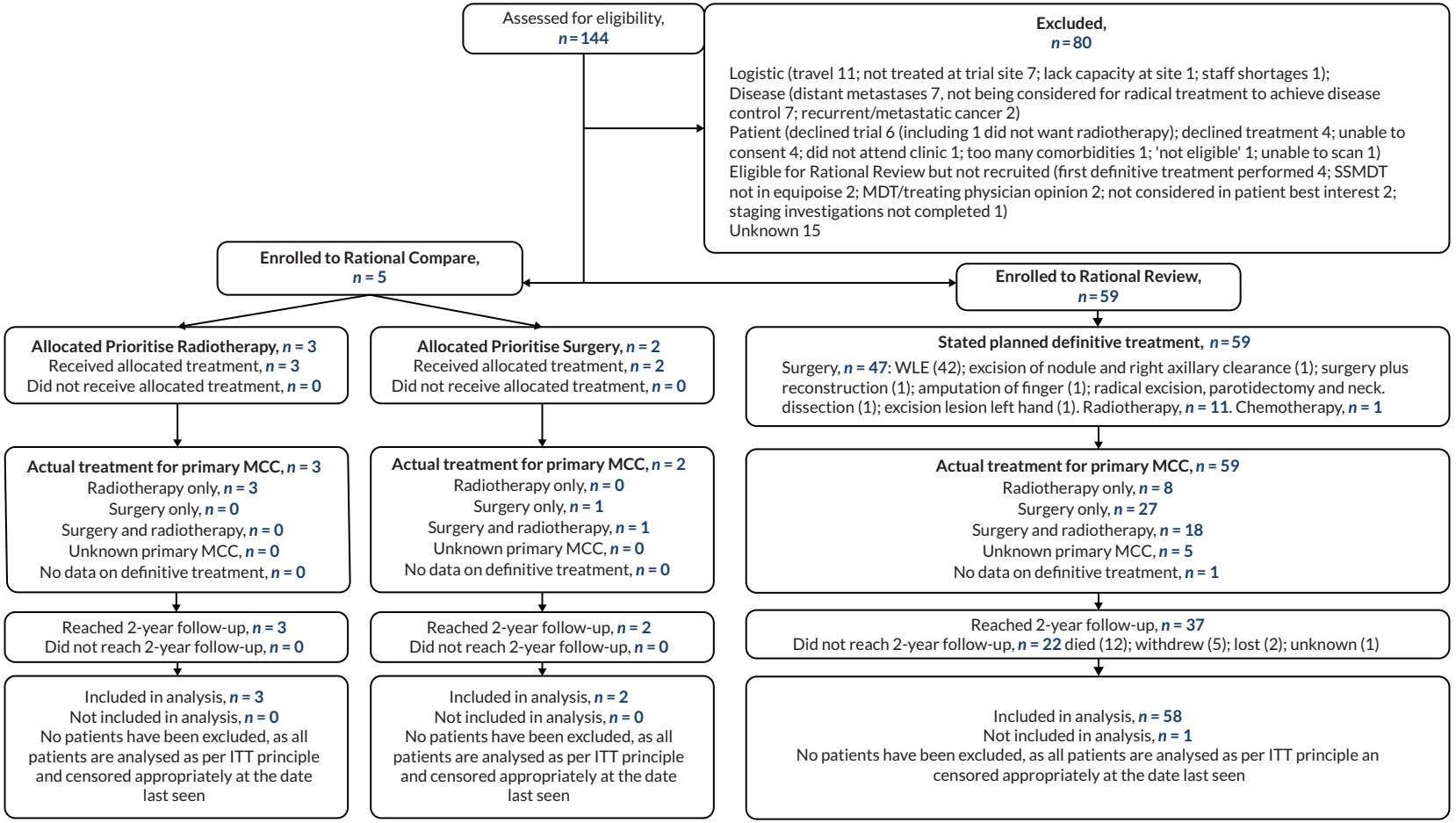

FIGURE 2 Consolidated Standards of Reporting Trials (CONSORT) diagram for the Rational MCC Trial. Note that there is one patient who had no definitive treatment or follow-up.

Chapter 4 Trial participants

Trial recruitment

Overview

Five patients were enrolled to Rational Compare, and 59 patients registered to Rational Review. The Rational MCC trial did not proceed to complete the full trial because of low recruitment to Rational Compare.

The risk of this outcome had been recognised in the trial development, because this was a trial recruiting a rare and elderly population for whom treatment strategies had been developed on low-quality evidence and clinician belief. This was the reason for the design whereby all patients presenting with stage I–III MCC managed with curative intent could be recruited, at least to an observational study, if not randomised. Had Rational Compare recruited to completion, the final trial analysis would have focused on comparison of the randomised populations.

Trial sites

Of the 31 NHS sites approached, 14 opened to recruitment to the Rational MCC trial, with the first site opening to recruitment on 1 June 2016.

Twelve sites opened to both Rational Compare and Rational Review parts of the trial, and two opened only to Rational Review. The issue for both sites was that surgery and radiotherapy services took place in different NHS trusts, creating contractual difficulties in trial set-up that were still being resolved when Rational Compare closed.

The full list of sites opened to recruitment was:

Rational Compare and Rational Review:

- St Bartholomew's Hospital (Barts Health NHS Trust)
- Addenbrooke's Hospital (Cambridge University Hospitals NHS Foundation Trust)
- Christie Hospital (Christie NHS Foundation Trust)
- Royal Preston Hospital (Lancashire Teaching Hospitals NHS Foundation Trust)
- Ninewells Hospital (NHS Tayside)
- Norfolk and Norwich University Hospital (Norfolk and Norwich University Hospitals NHS Foundation Trust)
- Nottingham City Hospital (Nottingham University Hospitals NHS Trust)
- Churchill Hospital (Oxford University Hospitals NHS Trust)
- Royal Cornwall Hospital (Treliske; Royal Cornwall Hospitals NHS Trust)
- Weston Park Hospital (Sheffield Teaching Hospitals NHS Foundation Trust)
- The Queen Elizabeth Hospital (University Hospital Birmingham NHS Foundation Trust)
- Royal Stoke University Hospital (University Hospital of North Midlands Trust)

Rational Review only:

- St Helens Hospital (St Helens and Knowsley Hospitals NHS Trust)
- Southmead Hospital (North Bristol NHS Trust)

Recruitment to Rational Compare

Table 2 and *Figure 3* show recruitment to Rational Compare by site. No other sites recruited to Rational Compare.

Recruitment to Rational Review

Table 3 and *Figure 4* show recruitment to Rational Review by site.

TABLE 2 Recruitment to Rational Compare by site

	N = 5
Site [n (%)]	
Addenbrooke's Hospital	1 (20.00)
Churchill Hospital	2 (40.00)
Norfolk and Norwich University Hospital	1 (20.00)
St Bartholomew's Hospital	1 (20.00)

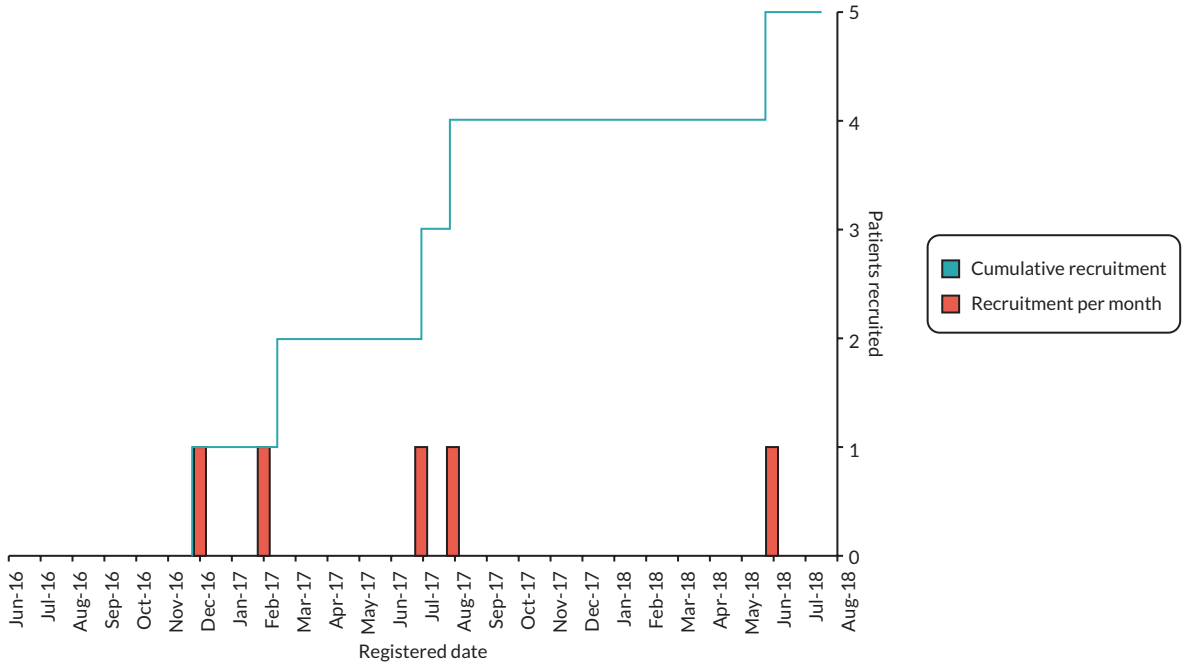

FIGURE 3 Cumulative recruitment to Rational Compare by calendar month.

TABLE 3 Recruitment to Rational Review by site

	N = 59
Site [n (%)]	
Addenbrooke's Hospital	7 (11.86)
Churchill Hospital	2 (3.39)
Ninewells Hospital	1 (1.69)
Norfolk and Norwich University Hospital	1 (1.69)
Nottingham City Hospital	6 (10.17)
Royal Cornwall Hospital (Treliske)	2 (3.39)
Royal Preston Hospital	1 (1.69)
Royal Stoke University Hospital	1 (1.69)
Southmead Hospital	1 (1.69)
St Bartholomew's Hospital	2 (3.39)
St Helens Hospital	11 (18.64)
The Queen Elizabeth Hospital	24 (40.68)

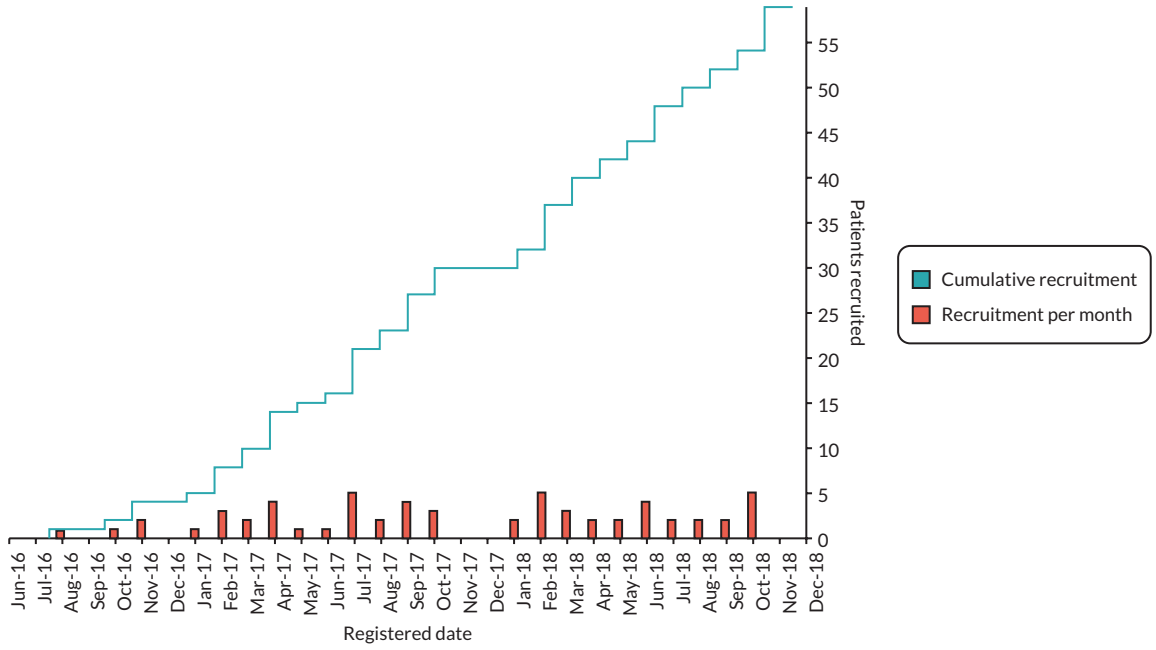

FIGURE 4 Cumulative recruitment to Rational Review by calendar month.

Trial populations

Overview

The data are presented categorising patients according to whether they were recruited to Rational Compare (also termed the 'Randomisation cohort') or Rational Review (the 'Registration cohort').

Statistical analyses were carried out on an ITT basis, retaining patients within Rational Compare or Rational Review, and for Rational Compare, within their randomised treatment groups. These included patients who were protocol deviations and ineligible patients. No patients were found to be ineligible post recruitment.

Why did patients not enter Rational Compare?

The following data (*Table 4*) were derived from trial management records and by comparing the date of registration with the date of first treatment. Post hoc exploration of the primary reason for failure to recruit to Rational Compare will be presented in the clinical study report (CSR) and subsequent manuscripts using data from the eligibility case report form (CRF) and narrative data from sites. Of note, registration appears to have been deprioritised once a clinical or patient decision had already been made not to randomise the patient. For this reason, registration after first treatment is not a complete or main explanation of why patients were not randomised.

Registration and randomisation

The registration form asked the question 'What is the planned definitive treatment for the primary?' The options were radiotherapy, WLE, chemotherapy or other with free-text narrative data. This information is summarised in *Table 5*.

Patient baseline information

Baseline data are drawn from the Baseline, Registration (Rational Review only) and Randomisation (Rational Compare only) data collection forms. The Randomisation form asked additional questions not included on the Registration form. These related to tumour stage, macroscopic disease and intent to offer adjuvant radiotherapy and are included in this section. The following tables show patient characteristics, including demographics and comorbidities.

TABLE 4 Possible reasons for patients not entering Rational Compare

	Rational Review patients (*N* = 59)
Registered after Rational Compare closed [n (%)]	
False	48 (81.36)
True	11 (18.64)
Site not open to Rational Compare [n (%)]	
False	47 (79.66)
True	12 (20.34)
Recruited after definitive treatment [n (%)]	
False	30 (50.85)
True	29 (49.15)

TABLE 5 Intended treatment for patients entering Rational Review

	Rational Review patients (*N* = 59)
Intended treatment [registered, n (%)]	
Amputation of the finger	1 (1.69)
Chemotherapy	1 (1.69)
Excision of lesion, left hand	1 (1.69)
Excision of nodule and right axillary clearance	1 (1.69)
Radical excision, parotidectomy and neck dissection	1 (1.69)
Radiotherapy	11 (18.64)
Surgery	42 (71.19)
Surgery plus reconstruction	1 (1.69)

Table 6 presents all relevant medical histories and baseline characteristics for all patients at trial for patients who entered Rational Compare (stratified according to whether they were randomised to Prioritise Surgery or Prioritise Radiotherapy) and Rational Review.

Empty entries in the first column indicate that such information was missing. This will carry true for all subsequent tables in this document.

Some questions were asked only on the randomisation form for purpose of stratification (shown by *). Full clinical pathological stage for all patients is reported in a later table.

TABLE 6 Summary baseline characteristics across all patients recruited to Rational Compare and Rational Review

	Rational Compare			Rational Review
	Prioritise Radiotherapy (*N* = 3)	Prioritise Surgery (*N* = 2)	Total (*N* = 5)	Registration (*N* = 59)
Age (years)				
n	3	2	5	59
Mean (SD)	79.67 (3.51)	77.5 (0.71)	78.8 (2.77)	77.2 (9.4)
Median	80	77.5	78	78
IQR	(78–81.5)	(77.25–77.75)	(77–80)	(72–84)
Range	(76–83)	(77–78)	(76–83)	(53–97)
Age [years, n (%)]				
≤ 60	0 (0.00)	0 (0.00)	0 (0.00)	3 (5.08)
61–70	0 (0.00)	0 (0.00)	0 (0.00)	8 (13.56)
71–80	2 (66.67)	2 (100.00)	4 (80.00)	25 (42.37)
81–90	1 (33.33)	0 (0.00)	1 (20.00)	21 (35.59)
≥ 91	0 (0.00)	0 (0.00)	0 (0.00)	2 (3.39)
Sex [n (%)]				
Female	2 (66.67)	0 (0.00)	2 (40.00)	26 (44.07)
Male	1 (33.33)	2 (100.00)	3 (60.00)	33 (55.93)
Clinical, radiological and pathological stage [n (%)][a]				
Stage IA/stage IIA	1 (33.33)	1 (50.00)	2 (40.00)	
Stage IB/stage IIB	2 (66.67)	1 (50.00)	3 (60.00)	
Stage IIIA	0 (0.00)	0 (0.00)	0 (0.00)	
Stage IIIB/C	0 (0.00)	0 (0.00)	0 (0.00)	
Intent to undertake adjuvant regional radiotherapy for stage I or II disease [n (%)][a]				
No	1 (33.33)	0 (0.00)	1 (20.00)	
Yes	2 (66.67)	2 (100.00)	4 (80.00)	

continued

TABLE 6 Summary baseline characteristics across all patients recruited to Rational Compare and Rational Review (*continued*)

	Rational Compare			Rational Review
	Prioritise Radiotherapy (*N* = 3)	Prioritise Surgery (*N* = 2)	Total (*N* = 5)	Registration (*N* = 59)
Primary status at randomisation [n (%)][a]				
Locally excised with or without marginal excision	3 (100.00)	1 (50.00)	4 (80.00)	
Macroscopic disease	0 (0.00)	1 (50.00)	1 (20.00)	
Clinical history of current immunosuppressive illness or treatment [n (%)][a]				
No	3 (100.00)	2 (100.00)	5 (100.00)	
Yes	0 (0.00)	0 (0.00)	0 (0.00)	
Eastern Cooperative Oncology Group status [n (%)]				
0	3 (100.00)	2 (100.00)	5 (100.00)	31 (52.54)
1	0 (0.00)	0 (0.00)	0 (0.00)	22 (37.29)
2	0 (0.00)	0 (0.00)	0 (0.00)	4 (6.78)
3	0 (0.00)	0 (0.00)	0 (0.00)	1 (1.69)
Missing				1 (1.69)
Other malignancies within 5 years [n (%)]				
No malignancies	3 (100.00)	0 (0.00)	3 (60.00)	42 (71.19)
Chronic lymphocytic leukaemia	0 (0.00)	0 (0.00)	0 (0.00)	1 (1.69)
Other	0 (0.00)	2 (100.00)	2 (40.00)	16 (27.12)
Autoimmune of chronic inflammatory conditions [n (%)]				
No conditions	3 (100.00)	1 (50.00)	4 (80.00)	53 (89.83)
Polymyalgia rheumatica	0 (0.00)	1 (50.00)	1 (20.00)	
Auto-immune overlap syndrome				1 (1.69)
Rheumatoid arthritis				4 (6.78)
Wegener's granulomatosis				1 (1.69)

TABLE 6 Summary baseline characteristics across all patients recruited to Rational Compare and Rational Review (*continued*)

	Rational Compare			Rational Review
	Prioritise Radiotherapy (*N* = 3)	Prioritise Surgery (*N* = 2)	Total (*N* = 5)	Registration (*N* = 59)
Immune suppression medication [n (%)]				
No medication	3 (100.00)	2 (100.00)	5 (100.00)	50 (84.75)
Corticosteroids	0 (0.00)	0 (0.00)	0 (0.00)	2 (3.39)
Other	0 (0.00)	0 (0.00)	0 (0.00)	7 (11.86)
Organ transplant [n (%)]				
No	3 (100.00)	2 (100.00)	5 (100.00)	58 (98.31)
Yes	0 (0.00)	0 (0.00)	0 (0.00)	1 (1.69)
HIV positive [n (%)]				
No	3 (100.00)	2 (100.00)	5 (100.00)	59 (100.00)
Yes	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Other immunosuppressing condition [n (%)]				
No	2 (66.67)	2 (100.00)	4 (80.00)	59 (100.00)
Yes	1 (33.33)	0 (0.00)	1 (20.00)	0 (0.00)
Absolute lymphocyte count (×109/l)				
n	2	2	4	54
Mean (SD)	2.25 (0.07)	1.45 (0.21)	1.85 (0.48)	1.92 (1.14)
Median	2.25	1.45	1.9	1.6
IQR	(2.22–2.28)	(1.38–1.53)	(1.53–2.22)	(1.4–2.1)
Range	(2.2–2.3)	(1.3–1.6)	(1.3–2.3)	(0.3–6.4)

IQR, interquartile range; SD, standard deviation.
a Stratification variable in Rational Compare and therefore only pertinent to this comparison.

Chapter 5 Diagnostic and staging data for Merkel cell carcinoma

Data source

Data on the primary MCC, lymph nodes and imaging were derived from the baseline and 3-month data collection forms and from central data extraction from the pathology report source data. Data are presented according to the allocation in the trial. The data from the CRF were prioritised for inclusion in these tables. Anomalies were resolved with reference to the original pathology report source data.

Primary site

Primary site was missing from the baseline CRF for 45/64 patients, including all 5 patients randomised into Rational Compare. Therefore, primary site was determined from the pathology report source data.

Diagnostic biopsies

Data on diagnostic biopsies include all listed diagnostic procedures from the baseline CRF, including multiple procedures on the primary and diagnostic tests on the regional nodes.

Primary size

Primary size was reported on the baseline CRF. As reported, data were missing for a proportion of patients. CRF data were supplemented by report of primary size from the diagnostic biopsy report. Both data are here presented. Combined data were used in assessing stage of MCC.

Biopsy margins

Biopsies were undertaken with diagnostic, not therapeutic, intent. Nonetheless, CRF data on biopsy type, combined with data acquired from the source pathology reports, enabled documentation whether the tumour had been excised with clear margins prior to definitive treatment or not.

Regional node metastases

The baseline CRF required cross-sectional imaging and asked the question 'Did the patient have clinical evidence of regional nodal metastases apparent on examination or imaging at trial entry?'.

Table 7 provides a summary of the diagnostic and staging information for all patients recruited to Rational Compare and Rational Review.

TABLE 7 Summary diagnostic and staging information across all patients recruited to Rational Compare and Rational Review

	Rational Compare			Rational Review
	Prioritise Radiotherapy (*N* = 3)	Prioritise Surgery (*N* = 2)	Total (*N* = 5)	Registration (*N* = 59)
Site of the primary MCC [n (%)]				
Face/eye/ear/nose	2 (66.67)	1 (50.00)	3 (60.00)	13 (22.03)
Head and neck				8 (13.56)
Upper limb	1 (33.33)	1 (50.00)	2 (40.00)	17 (28.81)
Trunk				3 (5.08)
Lower limb				12 (20.34)
Unknown primary				5 (8.47)
No data				1 (1.69)
All listed diagnostic biopsies [n (%)]				
Skin shave biopsy				1 (1.79)
Punch biopsy				6 (10.71)
Incisional biopsy	0 (0.00)	1 (50.00)	1 (20.00)	2 (3.57)
Core biopsy				5 (8.93)
Core biopsy and incisional biopsy				1 (1.79)
Core biopsy and node biopsy				1 (1.79)
Excision biopsy	2 (66.67)	1 (50.00)	3 (60.00)	33 (58.93)
Excision biopsy and incisional biopsy				1 (1.79)
Excision biopsy and open lymph node biopsy				1 (1.79)
Excision biopsy and SLNB				3 (5.36)
Core biopsy and excision biopsy	1 (33.33)	0 (0.00)	1 (20.00)	2 (3.57)
Longest diameter reported [CRF, n (%)]				
True	3 (100.00)	2 (100.00)	5 (100.00)	38 (64.41)
False	0 (0.00)	0 (0.00)	0 (0.00)	21 (35.59)

continued

TABLE 7 Summary diagnostic and staging information across all patients recruited to Rational Compare and Rational Review (*continued*)

	Rational Compare			Rational Review
	Prioritise Radiotherapy (*N* = 3)	**Prioritise Surgery (*N* = 2)**	**Total (*N* = 5)**	**Registration (*N* = 59)**
Longest diameter (CRF, mm)				
N	3	2	5	38
Mean (SD)	20.67 (9.29)	14.5 (0.71)	18.2 (7.4)	24.05 (24.14)
Median	25	14.5	15	17.5
IQR	(17.5–26)	(14.25–14.75)	(14–25)	(10.25–25)
Range	(10–27)	(14–15)	(10–27)	(5–136)
Biopsy primary size (pathology, mm)				
N	3	2	5	49
Mean (SD)	20 (10.44)	10.5 (6.36)	16.2 (9.58)	14.68 (11.9)
Median	25	10.5	15	13
IQR	(16.5–26)	(8.25–12.75)	(8–25)	(6–18)
Range	(8–27)	(6–15)	(6–27)	(0–50)
Biopsy, peripheral margin [n (%)]				
> 5 mm	1 (33.33)	0 (0.00)	1 (20.00)	5 (8.47)
≥ 1 mm, ≤ 5 mm	1 (33.33)	1 (50.00)	2 (40.00)	20 (33.90)
< 1 mm	1 (33.33)	0 (0.00)	1 (20.00)	3 (5.08)
Not measured clearance uncertain				1 (1.69)
States margin involved	0 (0.00)	1 (50.00)	1 (20.00)	9 (15.25)
Non-excisional biopsy				13 (22.03)
Not reported/no data				3 (5.08)
No primary				5 (8.47)
Biopsy, deep margin [n (%)]				
> 5 mm				1 (1.69)
≥ 1 mm, ≤ 5 mm				16 (27.12)
< 1 mm	1 (33.33)	0 (0.00)	1 (20.00)	11 (18.64)

TABLE 7 Summary diagnostic and staging information across all patients recruited to Rational Compare and Rational Review (*continued*)

	Rational Compare			Rational Review
	Prioritise Radiotherapy (*N* = 3)	Prioritise Surgery (*N* = 2)	Total (*N* = 5)	Registration (*N* = 59)
Not measured clearance uncertain				1 (1.69)
States margin involved	1 (33.33)	1 (50.00)	2 (40.00)	9 (15.25)
Non-excisional biopsy				13 (22.03)
Not reported/no data	1 (33.33)	1 (50.00)	2 (40.00)	3 (5.08)
No primary				5 (8.47)
SLNB performed [n (%)]				
No	3 (100.00)	2 (100.00)	5 (100.00)	50 (84.75)
Yes	0 (0.00)	0 (0.00)	0 (0.00)	9 (15.25)
SLNB result [n (%)]				
Negative – no microscopic nodal disease				8 (88.89)
Positive – microscopic nodal disease				1 (11.11)
Indeterminate				0 (0.00)
Did the patient have clinical evidence of regional nodal metastases apparent on examination or imaging at trial entry?				
Yes	0 (0.00)	0 (0.00)	0 (0.00)	12 (20.34)
No	3 (100.0))	2 (100.00)	5 (100.00)	46 (77.97)
Question not answered				1 (1.69)
Local satellite nodules [n (%)]				
No	3 (100.00)	2 (100.00)	5 (100.00)	57 (96.61)
Yes	0 (0.00)	0 (0.00)	0 (0.00)	2 (3.39)

Chapter 6 Definitive treatment for the primary Merkel cell carcinoma and loco-regional metastases

Overview

The data in this section are the definitive treatment for the primary MCC, treatment for regional nodes and skin metastases. These are based on data coded in the CRF and supplemented with source data from the pathology reports.

Treatment for the primary Merkel cell carcinoma

Data identifying the definitive treatment for the primary MCC were derived from the Definitive Surgery and Definitive Radiotherapy CRFs. The definitive treatment CRFs matched treatment given for randomised patients. For the purpose of *Table 8* summarising treatments given, seven anomalies in Rational Review were addressed by central monitoring involving three investigators: excluding as invalid three Definitive Surgery and one Definitive Radiotherapy CRFs for patients who had no primary MCC, categorising one patient as having surgery for the second excision of the MCC primary without submission of a Definitive Surgery CRF, and resolving first definitive treatment for primary MCC categorisation for two patients with both Definitive Surgery and Definitive Radiotherapy CRFs submitted.

'Surgery and Radiotherapy' for the primary MCC denotes all patients who had surgery for primary MCC that was followed by radiotherapy for the primary reported on the 3- or 6-month CRFs and/or (for two patients) on a Definitive Radiotherapy CRF. A single patient who had surgery and radiotherapy reported on a subsequent CRF after a progression event was excluded from these data.

Complete data, including all the submitted Definitive Surgery and Definitive Radiotherapy CRFs, are given in the subsequent sections.

Data on regional nodal treatments were derived from the categories listed on 3-monthly CRFs throughout the follow-up period. For the purpose of this table, there are no post hoc exclusions of data. Therefore, these categories include nodal interventions undertaken as part of initial treatment, alongside management of the primary if applicable, as well as interventions undertaken following progression events.

Macroscopic disease present at the primary site, after biopsy

Macroscopic disease was a question on the Definitive Surgery and Definitive Radiotherapy CRFs. In these data, we verified the CRF data with that reported on the pathology report source data for both the initial biopsy and the surgical specimen if applicable.

Staging

Merkel cell carcinoma staging at presentation was a CRF category. However, this was incompletely recorded. Furthermore, staging changed from UICC version 7 to UICC version 8 across the time of the trial, and it became clear that centres applied the UICC version 8 for some patients although the protocol was based on UICC version 7. For this reason, staging was reassessed using the current UICC version 8 categories and based on the CRF data and data drawn from the pathology report source data. These data were the largest recorded diameter of the primary, whether SLNB was undertaken, and the detection of regional nodal disease on SLNB, or clinically or radiologically as reported on the baseline CRF.

TABLE 8 Summary intervention information across all patients recruited to Rational Compare and Rational Review

	Rational Compare			Rational Review
	Prioritise Radiotherapy (*N* = 3)	Prioritise Surgery (*N* = 2)	Total (*N* = 5)	Registration (*N* = 59)
Intervention for primary MCC after first biopsy [n (%)]				
Radiotherapy	3 (100.00)	0 (0.00)	3 (60.00)	8 (13.56)
Radiotherapy and surgery	0 (0.00)	1 (50.00)	1 (20.00)	18 (30.51)
Surgery	0 (0.00)	1 (50.00)	1 (20.00)	27 (45.76)
No data on definitive treatment for MCC				1 (1.69)
Unknown primary MCC				5 (8.47)
Macroscopic disease present at the primary site at the time of definitive treatment [n (%)]				
Absent	1 (33.33)	1 (50.00)	2 (40.00)	31 (52.54)
Present	0 (0.00)	1 (50.00)	1 (20.00)	13 (22.03)
Apparent but not MCC				2 (3.39)
Uncertain				2 (3.39)
No data	2 (66.67)	0 (0.00)	2 (40.00)	6 (10.17)
Not applicable				5 (8.47)
Intervention for regional nodes [n (%), not mutually exclusive]				
Lymph node dissection	0 (0.00)	0 (0.00)	0 (0.00)	9 (15.25)
Adjuvant regional nodal irradiation without proven nodal involvement	1 (33.33)	1 (50.00)	2 (40.00)	5 (8.47)
Adjuvant regional nodal irradiation after surgical resection of regional node	0 (0.00)	0 (0.00)	0 (0.00)	12 (20.34)
Definitive regional nodal irradiation for proven lymph node involvement	0 (0.00)	0 (0.00)	0 (0.00)	5 (8.47)
Other				2 (3.39)
UICC version 8 staging, after WLE [n (%)]				
I	1 (33.33)	2 (100.00)	3 (60.00)	29 (49.15)
IIA	2 (66.67)	0 (0.00)	2 (40.00)	11 (18.64)
IIB				
IIIA				5 (8.47)
IIIB				9 (15.25)
III				4 (6.78)
Missing data				1 (1.69)

Data tables

Table 8 shows the definitive treatment patients in Rational Compare and Rational Review received for their primary MCC and any loco-regional metastases.

Details of definitive radiotherapy for the primary Merkel cell carcinoma

Table 9 shows a summary of data derived from all the Definitive Radiotherapy CRFs submitted. Note, in Rational Review, there were three Definitive Radiotherapy CRFs submitted for patients who were categorised as having 'unknown primary MCC' (i.e. patients presenting with regional nodal MCC without a clinically detectable primary). Two patients in Rational Review for whom a Definitive Radiotherapy CRF was submitted had had surgery for the primary MCC prior to radiotherapy documented on the CRFs so their radiotherapy is better interpreted as being adjuvant therapy.

TABLE 9 Summary of definitive radiotherapy details according to whether patients entered Rational MCC through randomisation (into Rational Compare) or registration (into Rational Review)

	Randomisation	Registration
Duration of radiotherapy (days)		
n	3	13
Mean (SD)	40.33 (1.15)	30.92 (8.32)
Median	41	32
IQR	(40–41)	(28–35)
Range	(39–41)	(11–43)
Planned total fractions		
n	3	13
Mean (SD)	30 (0)	22.31 (5.63)
Median	30	25
IQR	(30–30)	(20–25)
Range	(30–30)	(10–30)
Delivered total fractions		
n	3	13
Mean (SD)	30 (0)	22.31 (5.63)
Median	30	25
IQR	(30–30)	(20–25)
Range	(30–30)	(10–30)
Planned total fractions		
n	3	13
Mean (SD)	30 (0)	22.31 (5.63)
Median	30	25
IQR	(30–30)	(20–25)
Range	(30–30)	(10–30)
Delivered total fractions		
n	3	13
Mean (SD)	30 (0)	22.31 (5.63)

TABLE 9 Summary of definitive radiotherapy details according to whether patients entered Rational MCC through randomisation (into Rational Compare) or registration (into Rational Review) (*continued*)

	Randomisation	Registration
Median	30	25
IQR	(30–30)	(20–25)
Range	(30–30)	(10–30)
Delivered total dose (Gy)		
n	3	13
Mean (SD)	60 (0)	49.88 (5.73)
Median	60	50
IQR	(60–60)	(50–50)
Range	(60–60)	(40–60)
Percentage of planned dose delivered (%)		
n	3	13
Mean (SD)	100 (0)	100 (0)
Median	100	100
IQR	(100–100)	(100–100)
Range	(100–100)	(100–100)
Modality used [n (%)]		
Electrons	1 (33.33)	6 (46.15)
Photons	2 (66.67)	7 (53.85)
Experienced radiotherapy interruption [n (%)]		
No	2 (66.67)	9 (69.23)
Yes	1 (33.33)	3 (23.08)
Data missing	0 (0.00)	1 (7.69)
Planning imaging modality used [n (%)]		
CT	2 (66.67)	8 (61.54)
CT-PET	0 (0.00)	0 (0.00)
Magnetic resonance imaging	0 (0.00)	0 (0.00)
Ultrasound	0 (0.00)	0 (0.00)
No planning imaging	1 (33.33)	5 (38.46)
CTV margins (mm)		
n	3	8
Mean (SD)	23.33 (11.55)	95.75 (191.22)
Median	30	15
IQR	(20–30)	(8.75–54.5)
Range	(10–30)	(5–558)
Planning target volume margins (mm)		
n	3	9
Mean (SD)	6.67 (2.89)	28.89 (36.95)
Median	5	10
IQR	(5–7.5)	(10–30)
Range	(5–10)	(5–111)

Information regarding radiotherapy treatment interruptions and reasons for smaller-than-intended radiological margins are given in *Tables 34* and *35* in *Appendix 2*.

Details of definitive surgery for the primary Merkel cell carcinoma

Definitive Surgery CRFs were submitted for 52 patients. There were no anomalies affecting patients randomised to surgery in Rational Compare. In Rational Review, two patients had two Definitive Surgery CRFs each submitted for sequential procedures. Three patients were identified as presenting with regional nodal MCC without a clinically identifiable primary, and the Definitive Surgery CRF documented treatment of the regional nodes. Therefore, of the total, 47/52 Definitive Surgery CRFs document the first definitive treatment of the primary MCC.

Table 10 summarises relevant data on surgery. *Table 36* in *Appendix 2* then presents a line listing of reasons why a larger WLE surgical margin was not achieved.

TABLE 10 Summary of definitive WLE surgery details according to whether patients entered Rational MCC through randomisation (into Rational Compare) or registration (into Rational Review)

	Randomisation (*N* = 2)	Registration (*N* = 50)
Surgeon grade [n (%)]		
Consultant	1 (50.00)	44 (88.00)
Junior specialist doctor	0 (0.00)	1 (2.00)
Registrar	0 (0.00)	2 (4.00)
Registrar (specialist)	1 (50.00)	0 (0.00)
Surgeon	0 (0.00)	1 (2.00)
Unknown	0 (0.00)	2 (4.00)
Surgeon specialty [n (%)]		
Burns and plastics	0 (0.00)	4 (8.00)
Consultant plastic and reconstructive surgeon	0 (0.00)	3 (6.00)
Dermatology	0 (0.00)	7 (14.00)
Ear, nose and throat (ENT)	0 (0.00)	1 (2.00)
Maxillofacial	0 (0.00)	1 (2.00)
Ophthalmic	0 (0.00)	1 (2.00)
Plastic surgeon	2 (100.00)	29 (58.00)
Plastic surgeon and skin	0 (0.00)	1 (2.00)
Plastic, reconstructive, trauma, skin cancer and hand surgeon	0 (0.00)	1 (2.00)
Skin	0 (0.00)	1 (2.00)
Surgery	0 (0.00)	1 (2.00)
Type of anaesthetic [n (%)]		
General	1 (50.00)	27 (54.00)
Local	1 (50.00)	23 (46.00)

TABLE 10 Summary of definitive WLE surgery details according to whether patients entered Rational MCC through randomisation (into Rational Compare) or registration (into Rational Review) (*continued*)

	Randomisation (*N* = 2)	Registration (*N* = 50)
Deepest excision plane [n (%)]		
Subcutaneous fat	0 (0.00)	6 (12.00)
Superficial fascia	0 (0.00)	8 (16.00)
Deep fascia	0 (0.00)	17 (34.00)
Muscle	2 (100.00)	12 (24.00)
Bone/cartilage	0 (0.00)	5 (10.00)
Unknown	0 (0.00)	2 (4.00)
Surgical excision margin (mm)		
n	2	45
Mean (SD)	5.5 (6.36)	18 (8.93)
Median	5.5	20
IQR	(3.25–7.75)	(10–25)
Range	(1–10)	(2–30)
Peripheral margin of first surgery (in pathology report)		
No residual disease	1 (50.00)	24 (50.00)
> 5 mm	0 (0.00)	10 (20.83)
≥ 1 mm, ≤ 5 mm	1 (50.00)	3 (6.25)
< 1 mm	0 (0.00)	3 (6.25)
Not measured clearance uncertain	0 (0.00)	2 (4.17)
States margin involved	0 (0.00)	1 (2.08)
Other	0 (0.00)	1 (2.08)
Not categorised	0 (0.00)	4 (8.33)
Deep margin of first surgery (in pathology report)		
No residual disease	1 (50.00)	24 (50.00)
> 5 mm	0 (0.00)	6 (12.503)
≥ 1 mm, ≤ 5 mm	0 (50.00)	8 (16.67)
< 1 mm	1 (50.00)	0 (0.00)
Not measured clearance uncertain	0 (0.00)	3(6.25)
States margin involved	0 (0.00)	2 (4.17)
Not reported	0 (0.00)	1 (2.08)
Not categorised	0 (0.00)	4 (8.33)
Reasons why a larger margin was not achieved [n (%)]		
Anatomical consideration	1 (50.00)	21 (65.62)
Other	1 (50.00)	9 (28.12)
Data missing	0 (0.00)	2 (6.25)

continued

TABLE 10 Summary of definitive WLE surgery details according to whether patients entered Rational MCC through randomisation (into Rational Compare) or registration (into Rational Review) (*continued*)

	Randomisation (*N* = 2)	Registration (*N* = 50)
Reconstruction type [n (%)]		
None	1 (50.00)	17 (35.42)
Local flap	0 (0.00)	6 (12.50)
Full-thickness skin graft	0 (0.00)	2 (4.17)
Split skin graft	1 (50.00)	14 (29.17)
Local flap and local flap	0 (0.00	1 (2.08)
None and full-thickness skin graft	0 (0.00)	1 (2.08)
Full-thickness skin graft and other: contralateral tarsoconjunctival graft, orbicularis oculi myocutaneous propeller flap	0 (0.00	1 (2.08)
Other: direct closure	0 (0.00)	2 (4.17)
Other: dermal/fat graft	0 (0.00)	1 (2.08)
Other: free tarsal graft from fellow (left) upper lid and right upper lid advancement flap (local flap)	0 (0.00)	1 (2.08)
Other: hatchet flap	0 (0.00)	1 (2.08)
Other: local glabellar flap reconstructions	0 (0.00)	1 (2.08)

Adjuvant radiotherapy treatment for the primary Merkel cell carcinoma

The 3-monthly CRF included a line listing for 'Adjuvant radiotherapy to the primary tumour site following definitive WLE'. There were 28 entries for 23 patients. For one patient randomised into Rational Compare, there were no anomalies. In Rational Review, for three patients, the same treatment had been entered twice on two sequential CRFs. For four patients, there was a concurrent Definitive Radiotherapy CRF for treatment to the primary MCC with the same dates; in other words, the data submission had been duplicated. For one patient, it was evident that data had been submitted for adjuvant radiotherapy to the primary tumour after a progression event. Therefore, for those with data submitted on 'Adjuvant radiotherapy to the primary tumour site following definitive WLE', there were 18 with valid postoperative radiotherapy treatment data. *Table 11* shows all submitted data.

Nodal disease intervention

Table 12 gives a listing of all treatments to regional nodes.

Timing of interventions

Data are presented in *Table 13* for randomised patients on whether disease had progressed between randomisation and start of first definitive treatment.

Times are presented from first biopsy to first definitive treatment for the primary, and from trial registration or randomisation to first definitive treatment for the primary in *Table 14*.

TABLE 11 Summary of all adjuvant radiotherapy details

	Primary (*N* = 28)	Nodes (*N* = 7)	Post events (*N* = 14)	All (*N* = 49)
Time from surgery to adjuvant radiotherapy (days)				
n	23	3	13	39
Mean (SD)	83.65 (36.38)	71.67 (5.69)	196.23 (177.93)	120.26 (117.21)
Median	76	70	135	78
IQR	(57.5–105)	(68.5–74)	(80–257)	(66–133)
Range	(42–167)	(67–78)	(45–698)	(42–698)
Time from biopsy to adjuvant radiotherapy (days)				
n	28	7	13	48
Mean (SD)	131.71 (59.3)	79.57 (33.39)	267.77 (175.26)	160.96 (121.06)
Median	126	69	225	126
IQR	(90–168.75)	(60–101)	(182–314)	(84.5–192)
Range	(47–271)	(40–126)	(72–749)	(40–749)
Modality used [n (%)]				
Electrons	15 (53.57)	1 (14.29)	3 (21.43)	19 (38.78)
Other: HVX 250X	0 (0.00)	0 (0.00)	1 (7.14)	1 (2.04)
Photons	13 (46.43)	6 (85.71)	10 (71.43)	29 (59.18)
Total of fractions				
n	28	6	14	48
Mean (SD)	21.61 (5.78)	22.5 (4.18)	19.29 (6.75)	21.04 (5.92)
Median	20	25	20	20
IQR	(20–25)	(21.25–25)	(16.25–20)	(20–25)
Range	(10–30)	(15–25)	(5–30)	(5–30)
Total dose (Gy)				
n	28	6	14	48
Mean (SD)	49.82 (10.23)	49.17 (2.04)	49.34 (8.16)	49.6 (8.89)
Median	50	50	50	50
IQR	(48.75–55)	(50–50)	(45.75–50)	(47.25–50)
Range	(5–60)	(45–50)	(27.8–60)	(5–60)

TABLE 12 Listing of all procedures to regional nodes, one row per patient

Procedure	Other details	Site
Adjuvant regional nodal irradiation after surgical resection of regional node		
Adjuvant regional nodal irradiation after surgical resection of regional node		
Adjuvant regional nodal irradiation after surgical resection of regional node		
Adjuvant regional nodal irradiation after surgical resection of regional node		

continued

TABLE 12 Listing of all procedures to regional nodes, one row per patient (*continued*)

Procedure	Other details	Site
Adjuvant regional nodal irradiation after surgical resection of regional node		
Adjuvant regional nodal irradiation after surgical resection of regional node		
Adjuvant regional nodal irradiation after surgical resection of regional node		
Adjuvant regional nodal irradiation after surgical resection of regional node		
Adjuvant regional nodal irradiation without proven nodal involvement		
Adjuvant regional nodal irradiation without proven nodal involvement		
Adjuvant regional nodal irradiation without proven nodal involvement		
Adjuvant regional nodal irradiation without proven nodal involvement		
Adjuvant regional nodal irradiation without proven nodal involvement		
Adjuvant regional nodal irradiation without proven nodal involvement		
Definitive regional nodal irradiation for proven lymph node involvement		
Lymph node dissection		Regional nodes
Lymph node dissection		Regional nodes
Other (please state)	Axillary block dissection	Regional nodes

TABLE 13 Information regarding the progression of MCC between randomisation and start of definitive treatment, Rational Compare only

MCC progressed	Prioritise Radiotherapy (*n* = 3) (%)	Prioritise Surgery (*n* = 2) (%)	Total (*n* = 5) (%)
No	3 (100.00)	2 (100.00)	5 (100.00)
Yes	0 (0.00)	0 (0.00)	0 (0.00)

TABLE 14 Summary of time (days) from biopsy and from trial entry (either randomisation or registration) to start of definitive treatment

	Rational Compare			Rational Review
	Prioritise Radiotherapy (*N* = 3)	Prioritise Surgery (*N* = 2)	Total (*N* = 5)	Registration (*N* = 59)
Time from biopsy to start of definitive treatment (days)				
n	3	2	5	57
Mean (SD)	62.33 (22.01)	72 (18.38)	66.2 (18.83)	64.82 (44.1)
Median	63	72	63	57.5
IQR	(51.5–73.5)	(65.5–78.5)	(59–84)	(46.75–73)
Range	(40–84)	(59–85)	(40–85)	(0–314)
Time from trial entry (either randomisation or registration) to start of definitive treatment (days)				
n	3	2	5	57
Mean (SD)	22.33 (5.69)	26 (16.97)	23.8 (9.6)	−12.16 (38.76)
Median	24	26	24	−1
IQR	(20–25.5)	(20–32)	(16–27)	(−32–7)
Range	(16–27)	(14–38)	(14–38)	(−157–104)

Chapter 7 Withdrawals and discontinuations

Withdrawals

During the trial, there were five reported withdrawals of consent. None of the withdrawals occurred in patients randomised to Rational Compare, and five occurred in patients registered to Rational Review.

Chapter 8 Follow-up

Rational Compare: randomised patients

Table 15 and *Figure 5* summarise the data and show a Kaplan–Meier plot of the length of patient follow-up (in months) over the months post-trial enrolment of patients in the randomised part of the trial.

Table 16 shows a summary of Rational Compare patients lost to follow-up status at the point of trial closure.

TABLE 15 Summary information regarding length of follow-up (months) for patients in enrolled and randomised in Rational Compare

	Prioritise Radiotherapy	Prioritise Surgery	Total
Length of follow-up (months)			
n	3	2	5
Mean (SD)	46.02 (6.85)	40.26 (11.18)	43.72 (8.04)
Median	48.74	40.26	48.16
IQR	(43.48–49.92)	(36.31–44.21)	(38.23–48.74)
Range	(38.23–51.1)	(32.36–48.16)	(32.36–51.1)

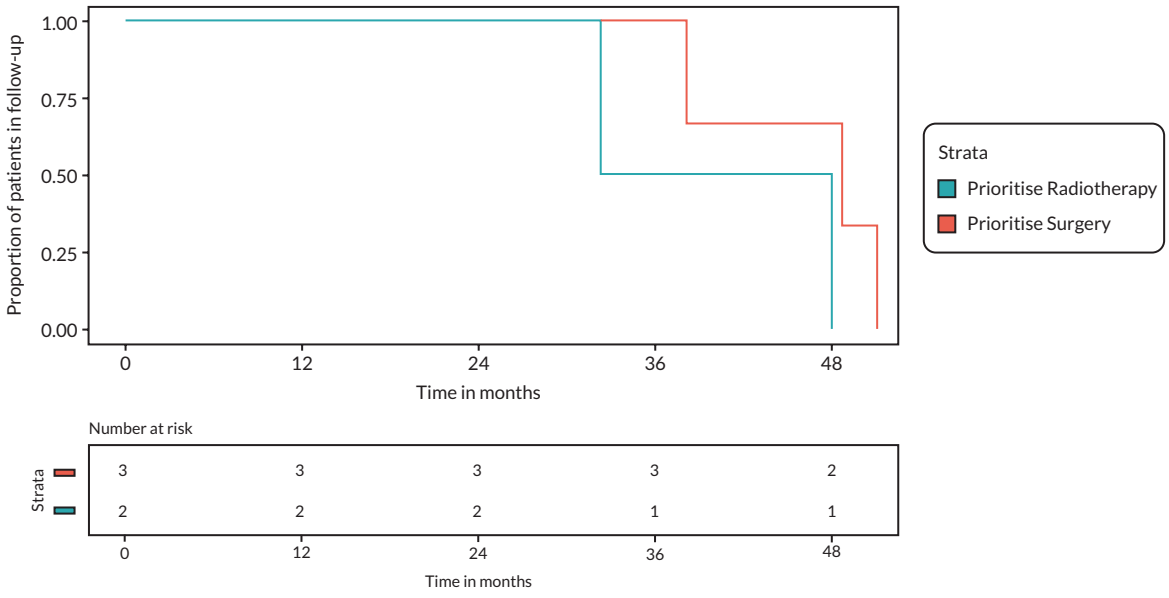

FIGURE 5 Length of patient follow-up (months) by treatment arm in Rational Compare.

TABLE 16 Summary information regarding patients lost to follow-up status for those randomised to Rational Compare

	Prioritise Radiotherapy	Prioritise Surgery	Total
Lost to follow-up [n (%)]			
False	2 (66.67)	2 (100.00)	4 (80.00)
True	1 (33.33)	0 (0.00)	1 (20.00)

Loss to follow-up is defined as not having been seen within 12 months' date of trial closure.

Rational Review: recruited patients

Table 17 and *Figure 6* summarise the data and show a Kaplan–Meier plot of the length of patient follow-up (in months) over the months post-trial enrolment of patients in the registration part of the trial.

TABLE 17 Summary information regarding length of follow-up (months) for patients in enrolled and recruited in Rational Review

	Recruited patients
Length of follow-up (months)	
n	59
Mean (SD)	30.88 (14.81)
Median	35.45
IQR	(18.96–38.38)
Range	(0.45–57.1)

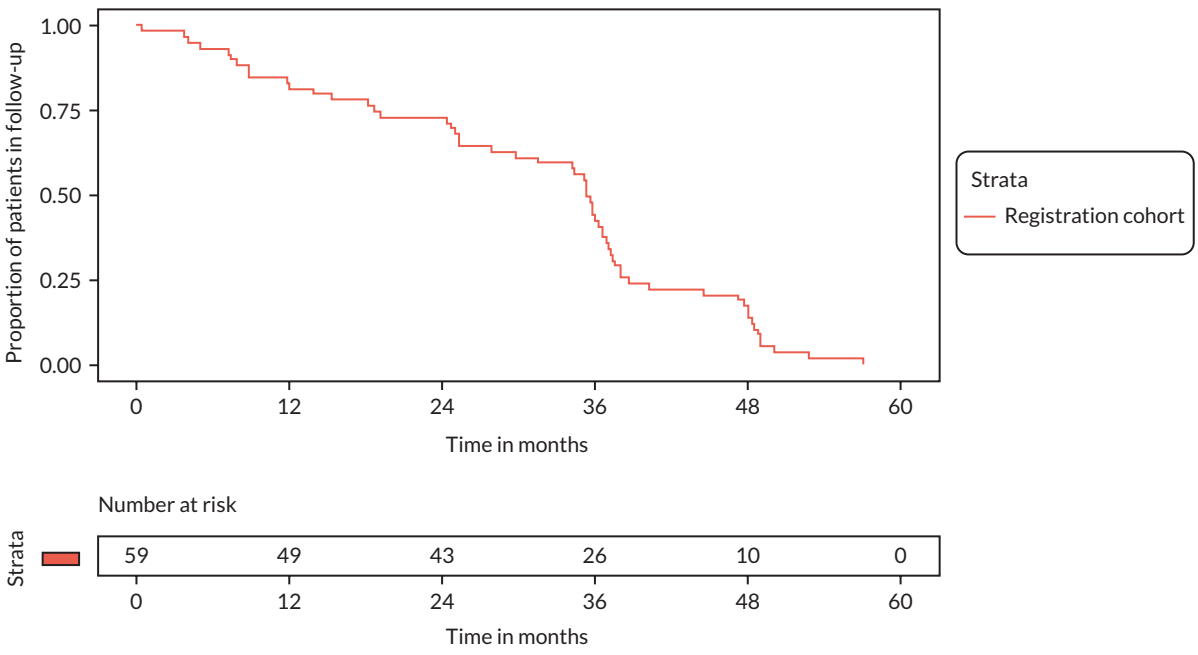

FIGURE 6 Length of patient follow-up (months) by treatment arm in Rational Review.

Chapter 9 Safety reporting

Reporting

Time frame for reporting adverse events: Adverse events are commonly encountered in patients receiving cancer treatment. All adverse events experienced by the patient were to be recorded in the patient notes. However, these were not to be collected by the Rational MCC Trial Office.

Reporting period for serious adverse events: Details of all serious adverse events (SAEs) (except those listed in the current version of the trials protocol) were to be documented and reported from commencement of the treatment of the primary until 28 days after the last protocol-defined treatment. Any SAEs that were thought to be possibly related to the protocol-defined treatment were still to be reported after this period.

Reporting group: All patients enrolled in the trial, regardless of whether they were enrolled in in Rational Compare or Rational Review.

All SAEs were graded according to the following scale:

1. mild
2. moderate
3. severe
4. life-threatening
5. fatal

Deaths

In total, there have been 20 reported deaths. One patient who was randomised to the trial (and allocated Prioritise Radiotherapy) died, and 19 patients who were registered to the observational cohort (Rational Review).

The following table (*Table 18*) shows aggregate data regarding cause of death.

TABLE 18 Summary of patient deaths by death cause

	N = 20
Cause of death [n (%)]	
Disease related	11 (55.00)
Treatment related – trial treatment (Rational Compare only)	0 (0.00)
Treatment related – non-trial treatment	0 (0.00)
Disease and trial treatment related (Rational Compare only)	0 (0.00)
Other cancer	1 (5.00)
Other non-cancer	4 (20.00)
Not known	4 (20.00)

Table 37 in *Appendix 3* shows a listing of all pertinent information regarding patients who have died while enrolled on the trial.

There were no COVID-19 attributable deaths; however, one patient had been infected COVID-19 in the months preceding their death.

Serious events

During the trial, there was one reported serious-related event, hospitalisation for grade 3 nausea and vomiting.

Chapter 10 Results for feasibility phase

Feasibility phase outcome measures

Site set-up and rate of registration

The disposition of patients in the Consolidated Standards of Reporting Trials (CONSORT) diagram is shown in Trial CONSORT diagram. The sites and their recruitment are set out in Trial recruitment, and data are provided in Trial populations relating to possible reasons patients were not recruited to Rational Compare. An overview of the feasibility site set-up and recruitment targets is set out in *Table 19*.

Time from randomisation to start of definitive treatment

Time from randomisation to the start of definitive treatment is defined as the number of whole days from the date of randomisation to the date of WLE or commencing of radiotherapy. These data are included in *Timing of interventions*.

Proportion of randomised patients undergoing the allocated treatment

The number of patients undergoing the allocated prioritised definitive treatment as a proportion of all randomised patients was only pertinent to (and thus presented for) those patients in Rational Compare. All five (100%, 95% CI 47.82% to 100%) underwent their allocated treatment. Sensitivity to CI method (Clopper–Pearson used above) is given in *Table 38* of *Appendix 4*. Surgical and pathological margin for WLE.

The surgical margin for all the patients who underwent surgery and who had a Definitive Surgery CRF submitted is presented in Data tables. Note that both patients randomised to surgery in Rational Compare had surgical margins narrower than planned in the protocol. One patient had a 14-mm MCC primary on the forehead, an initial incisional biopsy leaving residual disease, a 1-mm surgical margin citing ‘anatomical considerations’ as the reason, and closest pathological margin < 1 mm. This patient proceeded to postoperative radiotherapy. The other randomised patient had a 15-mm MCC primary on the upper limb, an initial excision biopsy with an involved margin, a surgical margin limited to 10 mm for unknown reasons and no residual disease identified on pathological examination.

Looking at the range of reported surgical margins in the non-randomised Rational Review population, the range went up to the planned maximum of 30 mm but includes a quarter of patients with margins 10 mm or less. The reasons cited for margins 10 mm or less were predominantly ‘anatomical considerations’. Note that one patient is described as having a ‘Palliative debulking – all positive margins followed by radical RT. Procedure was undertaken for palliative reasons not to achieve clear surgical margin’. We note that more than half of patients had no residual disease detected on pathological examination of the surgical specimen, and more than one-quarter had both peripheral and deep marginal clearance of residual MCC by at least 1 mm. However, this still leaves around one-fifth of patients with involved or uncertain pathological margins at definitive surgery according to the pathology reports.

TABLE 19 Site set-up and accrual targets

Time point	Metric	Achieved
12 months	5 eligible patients identified	Achieved
18 months	At least 10 centres active	13 sites recruiting
	At least 10 patients registered	34 patients registered
24 months	At least 20 patients randomised	4 patients randomised
30 months	At least 40 patients randomised	Time point not reached
	A monthly randomisation accrual rate of > 3/month	Time point not reached
	Definitive treatment routinely started within 4 weeks of randomisation in both arms	Time point not reached
	Suitable margin sizes routinely achieved in both arms	Time point not reached

Clinical treatment volume, planned treatment volume, dose and fractionation for definitive radiotherapy

The details for definitive radiotherapy for the primary MCC were provided on the Definitive Radiotherapy CRF and are presented in *Staging*. We note that the full dose and fraction number were delivered as planned for all patients.

Proportion undergoing adjuvant radiotherapy post wide local excision

Data on treatments undertaken are summarised in *Staging*.

Two patients were randomised to Prioritise Surgery for primary MCC. One patient (50.00%, 95% CI 1.26% to 98.74%) went on to undergo adjuvant radiotherapy. CIs calculated using the exact method (Clopper–Pearson) due to small sample size. The patient who proceeded to radiotherapy had a surgical margin < 10 mm and pathological margin < 1 mm. The other patient had had a prior excision biopsy, a surgical margin at the lowest end of that advised in the protocol, 10 mm, and no residual disease.

For patients recruited to Rational Review, for whom definitive treatment was determined by decision of the SSMDT and patient, 45 had surgery, of whom 18 (40%) additionally had postoperative radiotherapy for the primary MCC.

Time from randomisation to start of adjuvant treatment of the primary site post wide local excision

The time from randomisation is defined as the number of whole days from the date of randomisation to the date of commencing of radiotherapy for patients randomised to WLE. Only one patient was randomised to surgery and went on to undergo adjuvant radiotherapy, starting 81 days (2.6 months) after trial entry, and 67 days (2.2 months) after definitive WLE.

Proportion of patients at the point of randomisation with macroscopic disease (R2) or involved margins (R1) after initial biopsy

Data on margins after the initial biopsy of the primary MCC are presented in Regional node metastases. With respect to peripheral margins of patients randomised within Rational Compare, three (two randomised to radiotherapy and one to surgery) had apparently clear margins at least 1 mm prior to definitive treatment. The other two patients (one each randomised to radiotherapy or surgery) either had margin < 1 mm or the margin was clearly involved. However, all five randomised patients had a deep margin < 1 mm or involved or without data. Thus, no randomised patients had had a marginal excision through initial biopsy at the point of randomisation.

These data were expanded to include patients in Rational Review. A peripheral excision margin of at least 1 mm was reported for 42% and a deep margin at least 1 mm for 29% of patients. Combining the data showed that for only 24% of patients was there evidence of marginal excision prior to definitive intervention.

Data on the presence or otherwise of macroscopic disease at the site of primary MCC after biopsy and at the time of definitive intervention were assessed using data on the definitive treatment CRFs and validated by reference to the pathology reports and are presented in Macroscopic disease present at the primary site, after biopsy. Of the randomised patients, one of five (20.00%) had clear evidence of macroscopic disease at the time of definitive treatment: the patient was randomised to surgery and subsequently had adjuvant radiotherapy. Two randomised to radiotherapy were judged to have insufficient data to assess presence of macroscopic data.

These data were expanded to all patients. Of 54 patients with a primary MCC, 13 (24%) had clear evidence of macroscopic disease still present at the time of definitive treatment.

Chapter 11 Patient outcomes

Primary outcomes

The primary outcome measure is explained in *Objectives and outcome measures*.

During Rational Compare, 0 patients had loco-regional failure. One patient (allocated to Prioritise Surgery) had adjuvant radiotherapy to primary site following WLE and additionally to regional nodes (without proven nodal involvement); however, there was no evidence of macroscopic progression between the date of surgery and adjuvant radiotherapy.

Since no patient experienced loco-regional failure, the median loco-regional free survival time cannot be estimated, and loco-regional free survival estimates at 1 and 2 years post treatment for both the Prioritise Surgery and the Prioritise Radiotherapy arms are 100% (95% CI 100% to 100% for both times). *Figure 7* shows a Kaplan–Meier plot of loco-regional free survival time by treatment.

Due to the small sample size, Cox modelling to determine HRs (and thus the effect of treatment) has not been performed.

Secondary outcome measures

Proportion of patients alive and free of loco-regional disease

Alive and free of loco-regional disease means that at any point in time, the results of clinical evaluation and cross-sectional imaging (usually FDG CT-PET) demonstrate no evidence of persistent, recurrent or progressing macroscopic loco-regional disease, and that the patient is not currently undergoing loco-regional treatment. This measure was irrespective of whether loco-regional failure has been previously demonstrated, as long as prior failure has been treated with current disease remission. *Table 20* shows the proportion of patients alive and loco-regional-disease-free at 1, 2 and 3 years post randomisation.

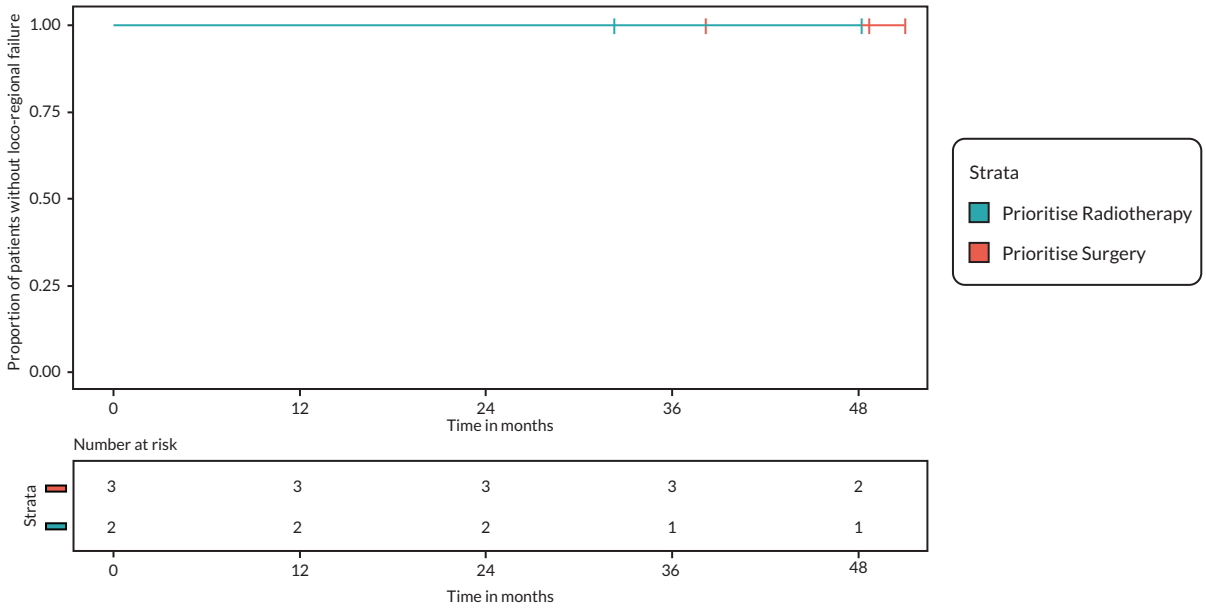

FIGURE 7 Loco-regional free survival time (months) by treatment arm in Rational Compare.

TABLE 20 Proportion of patients alive and free of loco-regional disease at 1, 2 and 3 years post randomisation

Allocated treatment	Event-free (alive and free of loco-regional disease)	Censored
At 1 year [n (%)]		
Prioritise Radiotherapy	3 (100.00)	
Prioritise Surgery	2 (100.00)	
At 2 years [n (%)]		
Prioritise Radiotherapy	3 (100.00)	
Prioritise Surgery	2 (100.00)	
At 3 years [n (%)]		
Prioritise Radiotherapy	3 (100.00)	0 (0.00)
Prioritise Surgery	1 (50.00)	1 (50.00)

Time to local failure (including in-field and in-transit metastases)

Time to local failure is here defined as the time from randomisation to macroscopic persistence, progression or recurrence between the primary site and regional nodal basin(s), during or after completion of treatment to the primary. The distance from the centre of the treated tumour to the nearest and furthest recurrence were to be recorded to permit evaluation whether recurrence is within the treated field or is an in-transit metastasis. Local progression should be confirmed by histological or cytological examination if possible. Microscopic evidence of MCC without macroscopic disease does not count as local progression.

During Rational Compare, no patients had persistent, progressive or recurrent disease between the primary and regional nodal basins. Since no patient experienced local failure, the median local failure-free survival time cannot be estimated, and local failure-free survival estimates at 1 and 2 years post treatment are 100% (95% CI 100% to 100% for both times). *Figure 8* shows a Kaplan–Meier plot of local failure-free survival time by treatment.

Due to the small sample size, Cox modelling to determine HRs (and thus the effect of treatment) has not been performed.

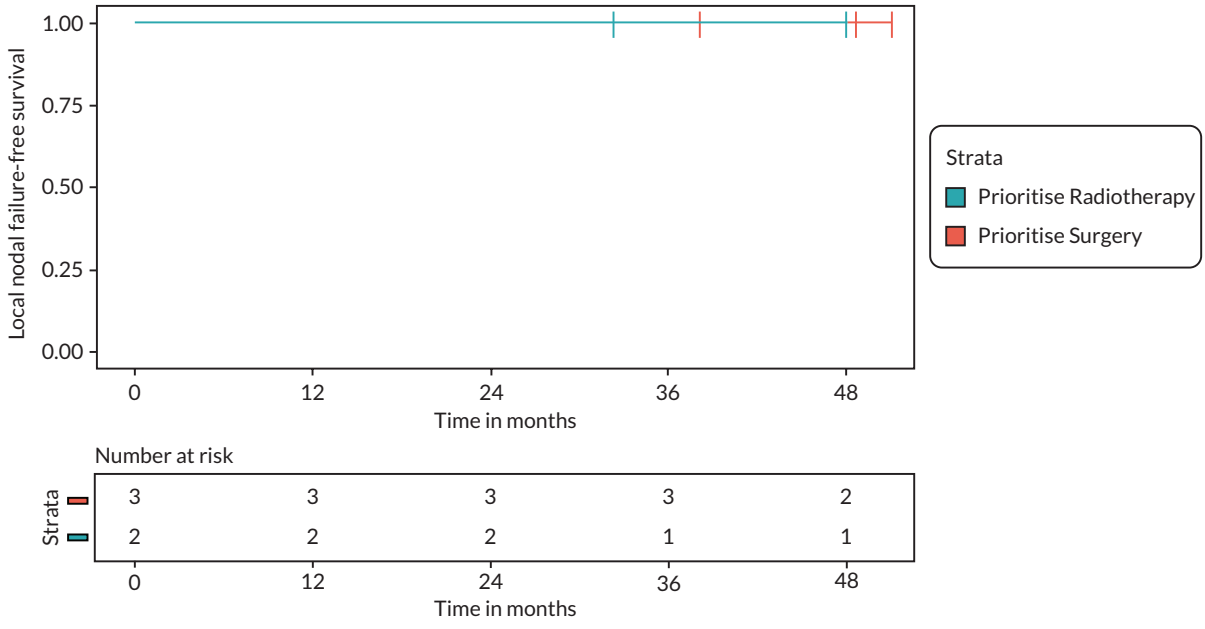

FIGURE 8 Local failure-free survival time (months) by treatment arm in Rational Compare.

Time to regional nodal failure

Time to regional nodal failure is here defined as the time from randomisation to macroscopic regional nodal persistence, progression or recurrence detected radiologically or by clinical evaluation. Regional nodal progression should be confirmed by histological or cytological examination if possible. Microscopic evidence of MCC without macroscopic disease did not count as local progression.

During Rational Compare, no patients had persistent, progressive or recurrent disease between the regional nodes. Since no patient experienced regional failure, the median regional failure-free survival time cannot be estimated, and regional failure-free survival estimates at 1 and 2 years post treatment are 100% (95% CI 100% to 100% for both times). *Figure 9* shows a Kaplan–Meier plot of regional failure-free survival time by treatment.

Due to the small sample size, Cox modelling to determine HRs (and thus the effect of treatment) has not been performed.

Time to distant progression

Time to distant progression is here defined as the time from randomisation to clinical or radiological evidence of MCC at a site distant to the regional nodal basin during or after loco-regional treatment.

One patient randomised to Rational Compare (Prioritise Radiotherapy) had a new MCC deposit (at a site distant to the primary MCC) 6.64 months after randomisation. Median progression-free survival time for those allocated Prioritise Radiotherapy could not be estimated (lower bound of 95% CI 6.64 months, upper bound cannot be estimated), while median overall survival for those allocated Prioritise Surgery cannot be estimated (due to a lack of events). Progression-free survival estimates at 1 and 2 years post treatment are 67% (95% CI 60% to 100% for both time points) for those allocated to Prioritise Radiotherapy, and 100% (95% CI 100% to 100% or both time points) for those allocated to Prioritise Surgery. *Figure 10* shows a Kaplan–Meier plot of distant progression-free survival time by treatment.

Due to the small sample size, Cox modelling to determine HRs (and thus the effect of treatment) has not been performed.

Progression-free survival

Progression-free survival is defined as the time to MCC progression or death or last known alive and free of progression up to 5 years from randomisation.

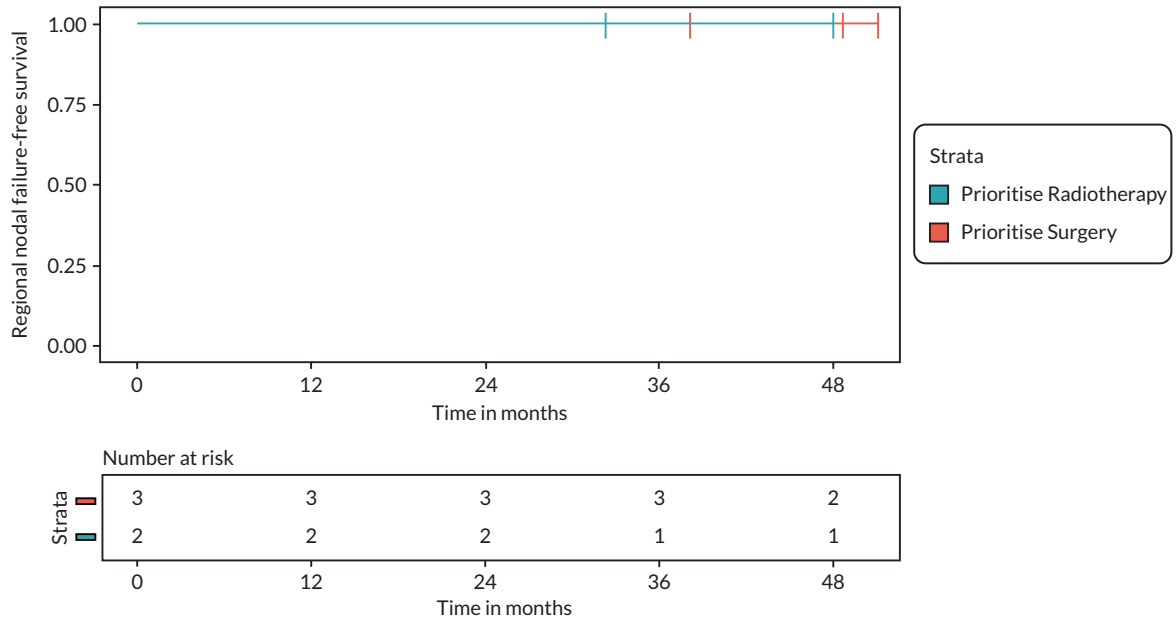

FIGURE 9 Regional failure-free survival time (months) by treatment arm in Rational Compare.

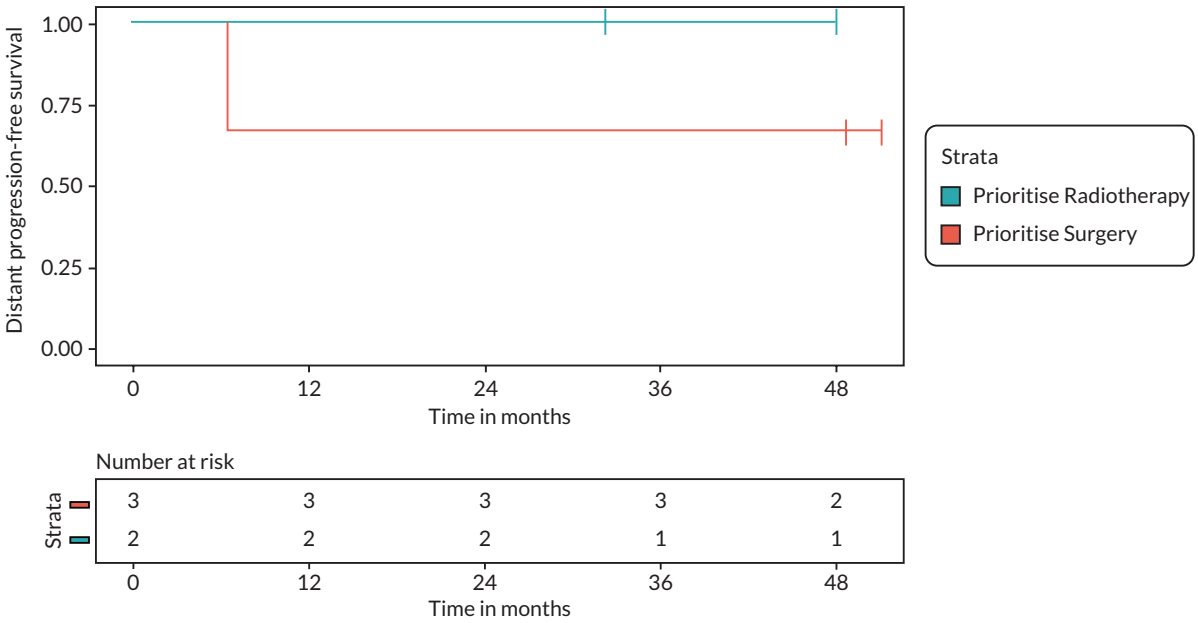

FIGURE 10 Distant progression-free survival time (months) by treatment arm in Rational Compare.

One patient randomised to Rational Compare (and allocated Prioritise Radiotherapy) progressed 1.05 years after randomisation. Such a progression was distant to the primary MCC. Median progression-free survival time for those allocated Prioritise Radiotherapy could not be estimated (lower bound of 95% CI 12.58 months, upper bound cannot be estimated), while median overall survival for those allocated Prioritise Surgery cannot be estimated (due to a lack of events). Progression-free survival estimates at 1 year post treatment are 100% (95% CI 100% to 100%) for both treatments. Progression-free survival estimates at 2 years post treatment are 67% (95% CI 30% to 100%) in the Prioritise Radiotherapy, and 100% (95% CI 100% to 100%) for the Prioritise Surgery arm. *Figure 11* shows a Kaplan–Meier plot of progression-free survival time by treatment.

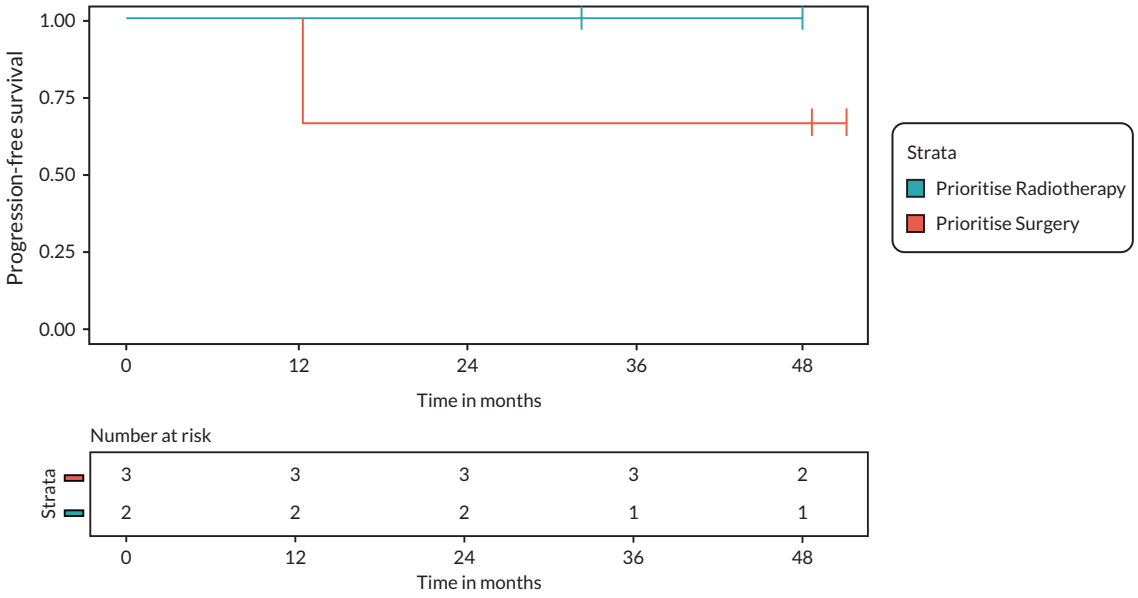

FIGURE 11 Progression-free survival time (months) by treatment arm in Rational Compare.

Due to the small sample size, Cox modelling to determine HRs (and thus the effect of treatment) has not been performed.

Overall survival

Overall survival is here defined as the time from randomisation to death, or last known alive, up to 5 years from randomisation.

One patient randomised to Rational Compare (and allocated Prioritise Radiotherapy) died 3.19 years after randomisation. Further details regarding this death can be found in Withdrawals (safety, deaths). Median overall survival time for those allocated Prioritise Radiotherapy was 38.23 months (3.19 years), while median overall survival for those allocated Prioritise Surgery cannot be estimated (due to a lack of events). Overall survival estimates at 1 and 2 years post treatment are 100% (95% CI 100% to 100% for both times) for both treatments. *Figure 12* shows a Kaplan–Meier plot of overall survival time by treatment.

Due to the small sample size, Cox modelling to determine HRs (and thus the effect of treatment) has not been performed.

Quality of life

The following QoL measures were to be completed at baseline, before treatment and at 3, 6, 9, 12 and 24 months after randomisation: EQ-5D-5L and EORTC-QLQ-C30.

No QoL data were returned for patients randomised to Rational Compare.

Exploratory outcome measures

Assessment of the additional value of routine cross-sectional imaging

Due to insufficient sample size in Rational Compare, exploratory analyses have not been performed.

Assessment of prognostic and predictive variables

Due to insufficient sample size in Rational Compare, exploratory analyses have not been performed.

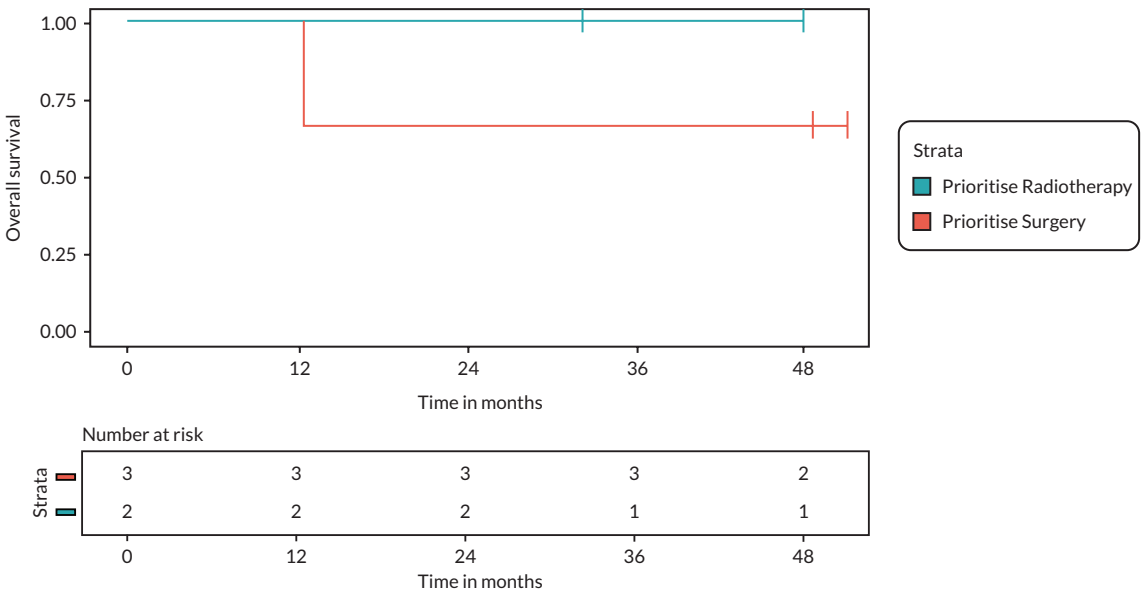

FIGURE 12 Overall survival time (months) by treatment arm in Rational Compare.

Subgroup analyses

Subgroup analyses were planned to be undertaken on the primary and some of the secondary outcome measures. The definition of subgroups was defined to be dependent on:

- history of immunosuppressive illness/treatment
- clinical, radiological and pathological stage (stage IA, IB, IIA, IIB, IIIA and IIIB/C)
- intent to undertake adjuvant regional radiotherapy for stage I or II disease
- primary status at randomisation (macroscopic disease, locally excised with or without marginal clearance)
- lymphocyte count
- intratumoural infiltration by CD3+ and CD8+ T lymphocytes
- primary treatment
- other factors deemed to have been of importance.

Chapter 12 Outcomes for all patients

No outcomes were planned for the registration cohort, Rational Review. Here, the same outcomes analysed for Rational Compare have been repeated for Rational Review, with the results presented according to the first treatment for the primary MCC. Due to the small number of patients recruited to Rational Compare, these patients have been amalgamated and included in these analyses. Definitions of outcomes are as set out in *Chapter 11*.

Time to loco-regional failure

During the Rational MCC trial, there were 26 loco-regional failure events: 2 in patients who had unknown primary MCC, 4 in patients who underwent radiotherapy, 13 in patients who underwent surgery only and 7 in patients who underwent surgery and radiotherapy.

Median loco-regional survival free time for each treatment stratum is given in *Table 21*. There are many instances where either the estimate or its associated CI cannot be ascertained. Such instances are indicated by non ascertainable (NA), instances where either the estimate or its associated CI cannot be ascertained.

Loco-regional survival estimates at landmark times is given in *Table 22*.

Figure 13 shows a Kaplan–Meier plot of loco-regional free survival time by treatment received.

Hazard ratios comparing all stratum to a common comparator cannot be accurately estimated and thus are not provided.

TABLE 21 Median loco-regional survival free time

Radiotherapy	Estimate not reached (95% CI 6.64 to NA)
Surgery	40.3 months (95% CI 5.90 to NA)
Surgery and radiotherapy	Estimate not reached (95% CI 12.77 to NA)
Unknown primary MCC	Estimate not reached (95% CI 8.16 to NA)
No data on MCC treatment	Not reached

NA, instances where either the estimate or its associated CI cannot be ascertained.

TABLE 22 Loco-regional survival estimates

Loco-regional survival estimates at 12 months are	
Radiotherapy	63.6% (95% CI 40.7%, 99.5%)
Surgery	59.7% (95% CI 43.9% to 81.3%)
Surgery and radiotherapy	71.6% (95% CI 53.2% to 96.3%)
Unknown primary MCC	60.0% (95% CI 29.3% to 100%)
No data on MCC treatment	No patient at risk
Loco-regional survival estimates at 24 months are	
Radiotherapy	63.6% (95% CI 40.7% to 99.5%)
Surgery	55.5% (95% CI 39.4% to 78.0%)
Surgery and radiotherapy	58.6% (95% CI 39.0% to 88.0%)
Unknown primary MCC	60.0% (95% CI 29.3% to 100%)
No data on MCC treatment	No patient at risk

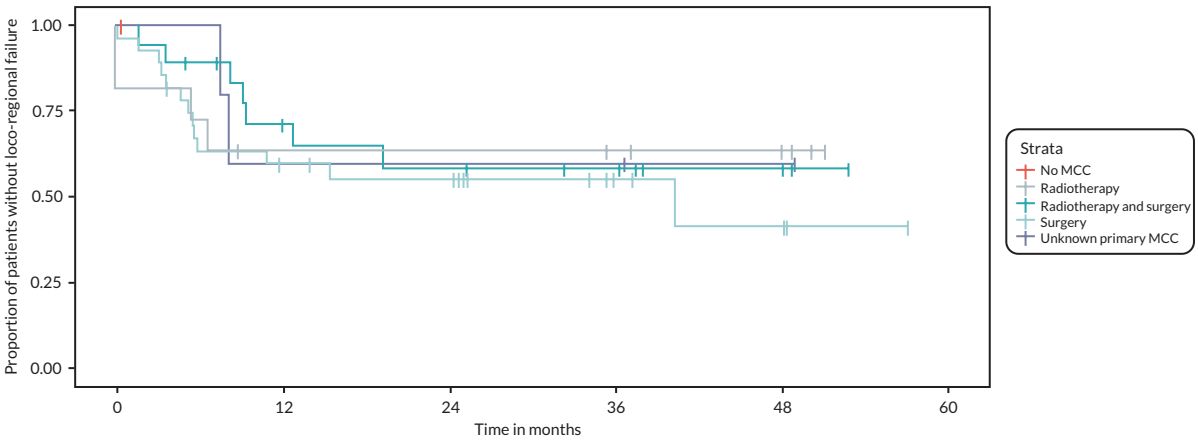

FIGURE 13 Loco-regional free survival time (months) by treatment received.

Proportion of patients alive and free of loco-regional disease

Table 23 shows the proportion of patients alive and loco-regional disease free at 1, 2 and 3 years post randomisation.

TABLE 23 Proportion of patients alive and free of loco-regional disease at 1, 2 and 3 years post randomisation

Received treatment	Event (either dead or loco-regional disease)	Event-free (alive and free of loco-regional disease)	Censored
At 1 year [n (%)]			
No data	0 (0.00)	0 (0.00)	1 (100.00)
Radiotherapy	0 (0.00)	8 (72.73)	3 (27.27)
Radiotherapy and surgery	0 (0.00)	17 (89.47)	2 (10.53)
Surgery	2 (7.14)	22 (78.57)	4 (14.29)
Unknown primary MCC	0 (0.00)	5 (100.00)	0 (0.00)
At 2 years [n (%)]			
No data	0 (0.00)	0 (0.00)	1 (100.00)
Radiotherapy	0 (0.00)	8 (72.73)	3 (27.27)
Radiotherapy and surgery	0 (0.00)	14 (73.68)	5 (26.32)
Surgery	3 (10.71)	19 (67.86)	6 (21.43)
Unknown primary MCC	0 (0.00)	4 (80.00)	1 (20.00)
At 3 years [n (%)]			
No data	0 (0.00)	0 (0.00)	1 (100.00)
Radiotherapy	0 (0.00)	7 (63.64)	4 (36.36)
Radiotherapy and surgery	0 (0.00)	10 (52.63)	9 (47.37)
Surgery	1 (3.57)	9 (32.14)	18 (64.29)
Unknown primary MCC	0 (0.00)	3 (60.00)	2 (40.00)

Time to local failure (including in-field and in-transit metastases)

Throughout Rational MCC, there were 10 local failures reported. Due to the low number of local events experienced, the median local failure-free survival time cannot be estimated for any stratum of treatment received. Instead, estimates at landmark times are given in *Table 24*.

TABLE 24 Local failure-free survival estimates at landmark times

12 months	
Radiotherapy	75.0% (95% CI 54.1% to 100%)
Surgery	86.1% (95% CI 74.4% to 99.8%)
Surgery and radiotherapy	100.0% (95% CI 100.0% to 100.0%)
Unknown primary MCC	100% (95% CI 100% to 100.0%)
No data on MCC treatment	No patient at risk
24 months	
Radiotherapy	75.0% (95% CI 54.1% to 100%)
Surgery	82.0% (95% CI 69.2% to 97.7%)
Surgery and radiotherapy	93.75% (95% CI 82.61% to 100.0%)
Unknown primary MCC	100% (95% CI 100% to 100.0%)
No data on MCC treatment	No patient at risk

Figure 14 shows a Kaplan–Meier plot of local failure-free survival time by treatment received.

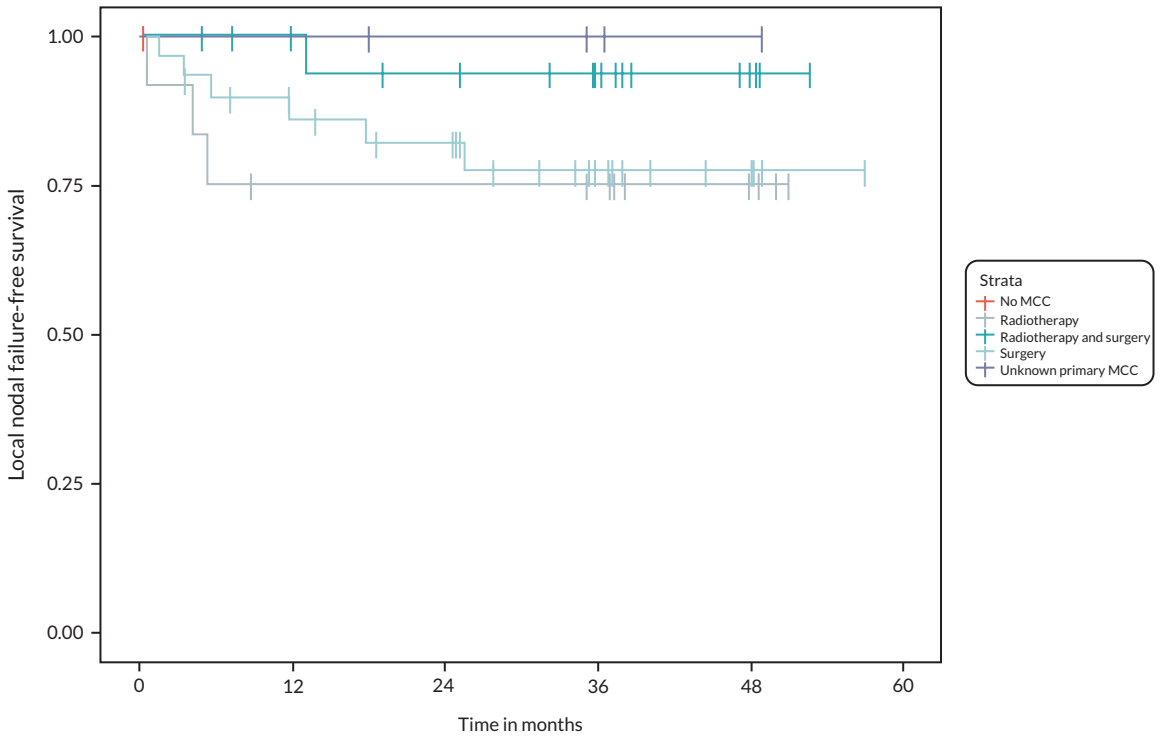

FIGURE 14 Local failure-free survival time (months) by treatment received.

As local failure events were only observed in the surgery only, and surgery and radiotherapy arms, HRs comparing all stratum to a common comparator cannot be accurately estimated and thus are not provided.

Time to regional nodal failure

Throughout Rational MCC, there were five regional failures reported in five patients.

The median time to regional failure could not be estimated for any of the treatment received stratum.

Regional failure-free survival estimates at 12 months are	
Radiotherapy	90.91% (95% CI 75.41% to 100%)
Surgery	88.0% (95% CI 76.0% to 100.0%)
Surgery and radiotherapy	100.0% (95% CI 100.0% to 100.0%)
Unknown primary MCC	100.0% (95% CI 100.0% to 100.0%)
No data on MCC treatment	No patient at risk
Local failure-free survival estimates at 24 months are	
Radiotherapy	90.91% (95% CI 75.41% to 100%)
Surgery	88.0% (95% CI 76.0% to 100.0%)
Surgery and radiotherapy	100.0% (95% CI 100.0% to 100.0%)
Unknown primary MCC	80.0% (95% CI 51.6% to 100.0%)
No data on MCC treatment	No patient at risk

Figure 15 shows a Kaplan–Meier plot of regional failure-free survival time by treatment.

Hazard ratios comparing all stratum to a common comparator cannot be accurately estimated and thus are not provided.

Time to distant progression

Throughout Rational MCC, there were 16 distant progression failures reported in 16 patients.

Median distant failure-free survival time for each treatment stratum is given in *Table 25*. There are many instances where either the estimate or its associated CI cannot be ascertained. Such instances are indicated by NA.

Distant failure-free survival estimates at landmark times are given in *Table 26*.

Figure 16 shows a Kaplan–Meier plot of distant failure-free survival time by treatment received.

Hazard ratios comparing all stratum to a common comparator cannot be accurately estimated and thus are not provided.

Progression-free survival

Progression-free survival is defined as the time to MCC progression or death or last known alive and free of progression up to 5 years from randomisation.

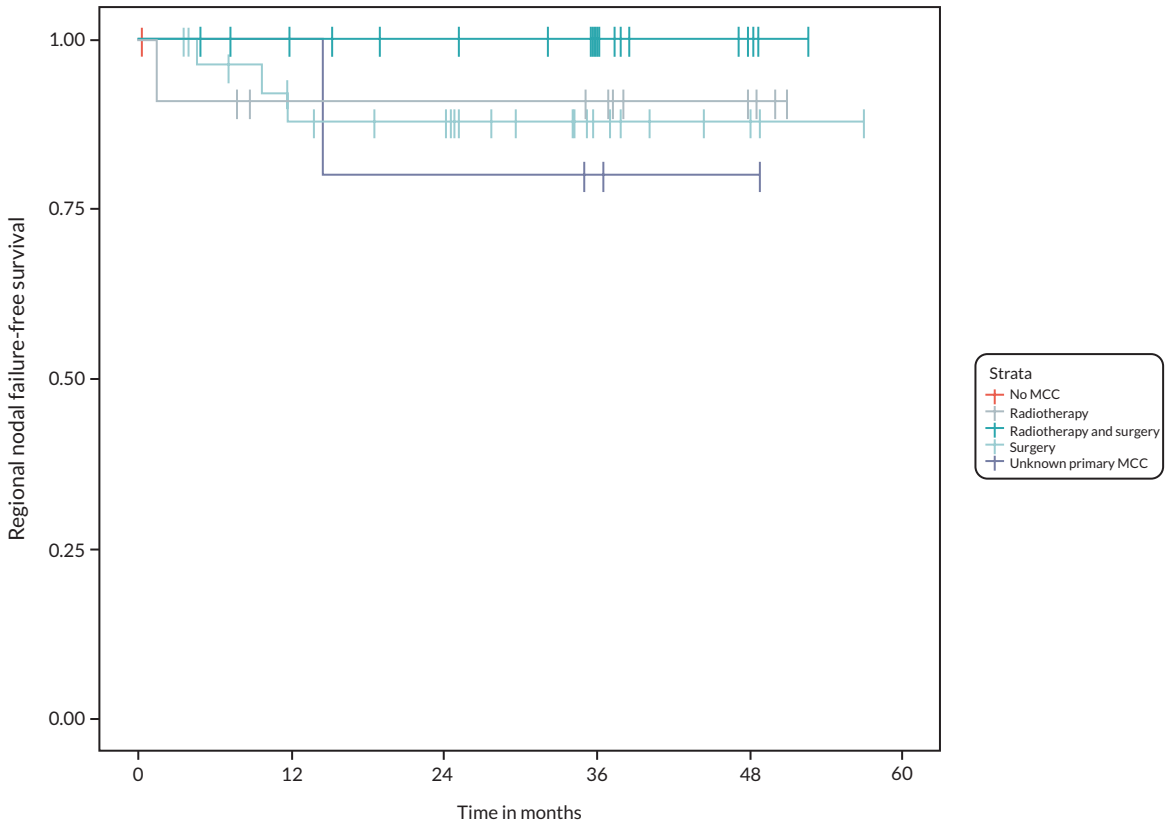

FIGURE 15 Regional failure-free survival time (months) by treatment received.

TABLE 25 Median distant failure-free survival time

Radiotherapy	Estimate not reached (95% CI 7.71 to NA)
Surgery	Not reached
Surgery and radiotherapy	Estimate not reached (95% CI 21.07 to NA)
Unknown primary MCC	Estimate not reached (95% CI 14.63 to NA)
No data on MCC treatment	Not reached

TABLE 26 Distance failure-free survival estimates at landmark times

12 months	
Radiotherapy	63.6% (95% CI 40.7% to 99.5%)
Surgery	92.6% (95% CI 83.2% to 100.0%)
Surgery and radiotherapy	94.7% (95% CI 85.2% to 100.0%)
Unknown primary MCC	80.0% (95% CI 51.6% to 100.0%)
No data on MCC treatment	No patient at risk
24 months	
Radiotherapy	63.6% (95% CI 40.7% to 99.5%)
Surgery	84.3% (95% CI 71.3% to 99.8%)
Surgery and radiotherapy	68.4% (95% CI 48.8% to 96.0%)
Unknown primary MCC	60.0% (95% CI 29.3% to 100.0%)
No data on MCC treatment:	No patient at risk

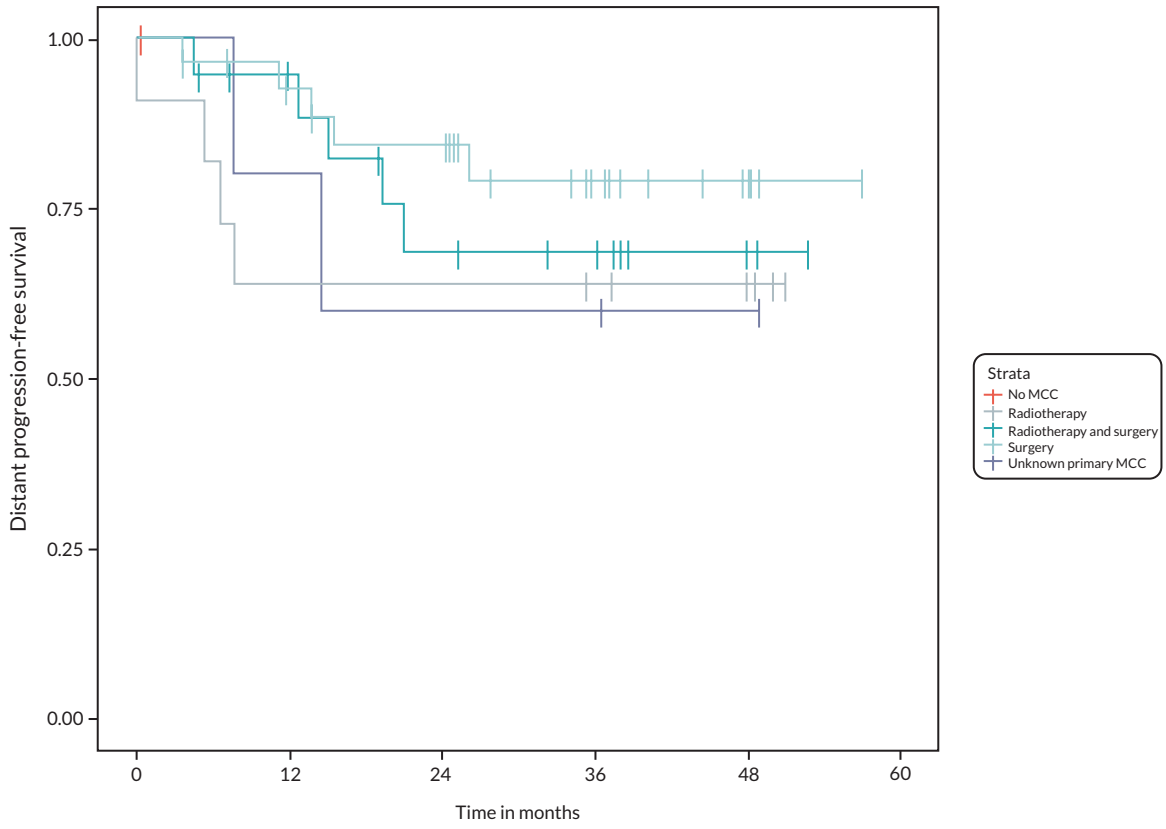

FIGURE 16 Distant progression-free survival time (months) by treatment received.

Throughout Rational MCC, there were 22 local failures reported in 20 patients.

The median progression-free survival time is given below.

Radiotherapy	38.2 months (95% CI 12.6 to NA)
Surgery	57.1 months (95% CI 37.3 to NA)
Surgery and radiotherapy	52.8 months (95% CI NA to NA)
Unknown primary MCC	Estimate not reached (95% CI 18.2 to NA)
No data on MCC treatment	Not reached
Progression-free survival estimates at 12 months are	
Radiotherapy	75.0% (95% CI 54.1.0% to 100.0%)
Surgery	89.3% (95% CI 78.5% to 100.0%)
Surgery and radiotherapy	94.4% (95% CI 84.4% to 100.0%)
Unknown primary MCC	100.0% (95% CI 100.0% to 100.0%)
No MCC	No patient at risk
Progression-free survival estimates at 24 months are	
Radiotherapy	66.7% (95% CI 44.7% to 99.5%)
Surgery	85.4% (95% CI 73.1% to 99.7%)
Surgery and radiotherapy	91.3% (95% CI 66.6% to 100.0%)
Unknown primary MCC	66.7% (95% CI 37.9% to 100.0%)
No MCC	No patient at risk

Figure 17 shows a Kaplan–Meier plot of progression-free survival time by treatment received.

Due to the low number of progression events, HRs comparing all stratum to a common comparator cannot be accurately estimated and thus are not provided.

Overall survival

During the trial, there were 20 reported deaths. Further details regarding this death can be found in *Deaths*.

Median overall survival time for each treatment stratum is given in *Table 27*. There are many instances where either the estimate or its associated CI cannot be ascertained. Such instances are indicated by NA.

Overall survival estimates at landmark times are given in *Table 28*.

Figure 18 shows a Kaplan–Meier plot of overall survival time by treatment.

Hazard ratios derived from a Cox model are given below to show the relative effect of treatment, each compared to the reference category of patients undergoing no definitive treatment. Due to low numbers of events, some HRs cannot accurately be ascertained, where this is the case they are not provided.

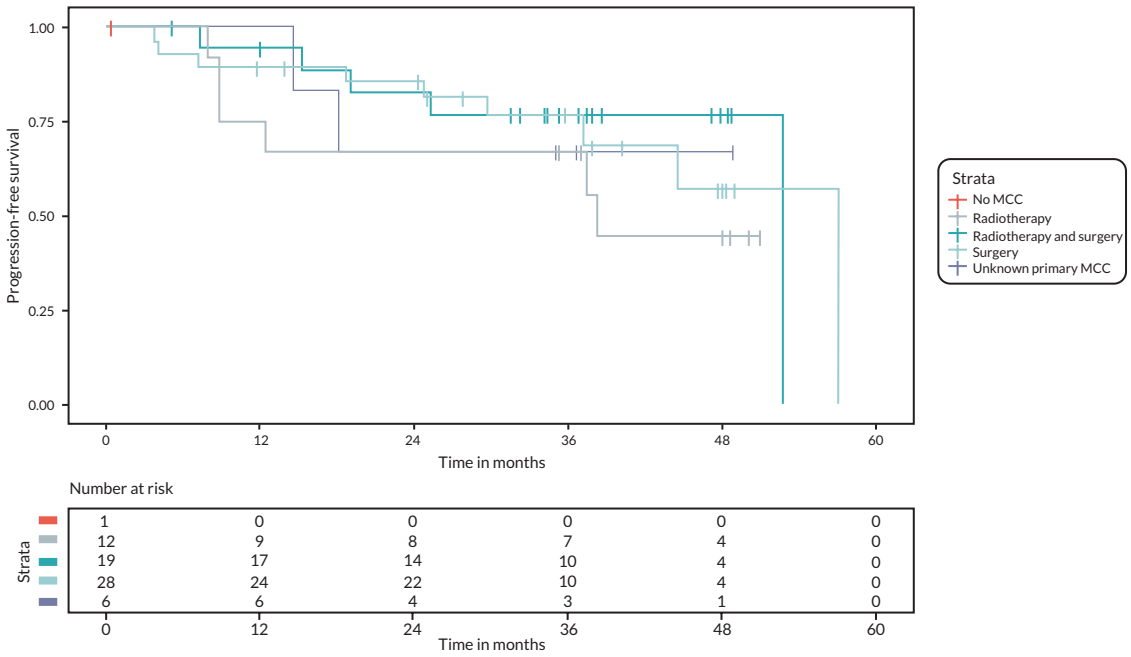

FIGURE 17 Progression-free survival time (months) by treatment received.

TABLE 27 Median overall survival time

Radiotherapy	38.2 months (95% CI 37.4 to NA)
Surgery	57.1 months (95% CI 37.3 to NA)
Surgery and radiotherapy	52.8 months (95% CI NA to NA)
Unknown primary MCC	Not reached
No primary MCC	Not reached

TABLE 28 Overall survival estimates at landmark times

12 months	
Radiotherapy	72.7% (95% CI 50.6% to 100.0%)
Surgery	89.3% (95% CI 78.5% to 100.0%)
Surgery and radiotherapy	94.4% (95% CI 84.4% to 100.0%)
Unknown primary MCC	100.0% (95% CI 100.0% to 100.0%)
No data on MCC treatment	No patient at risk
24 months	
Radiotherapy	72.7% (95% CI 50.6% to 100.0%)
Surgery	85.4% (95% CI 73.1% to 99.7%)
Surgery and radiotherapy	82.6% (95% CI 66.6% to 100.0%)
Unknown primary MCC	80.0% (95% CI 51.6% to 100.0%)
No data on MCC treatment	No patient at risk

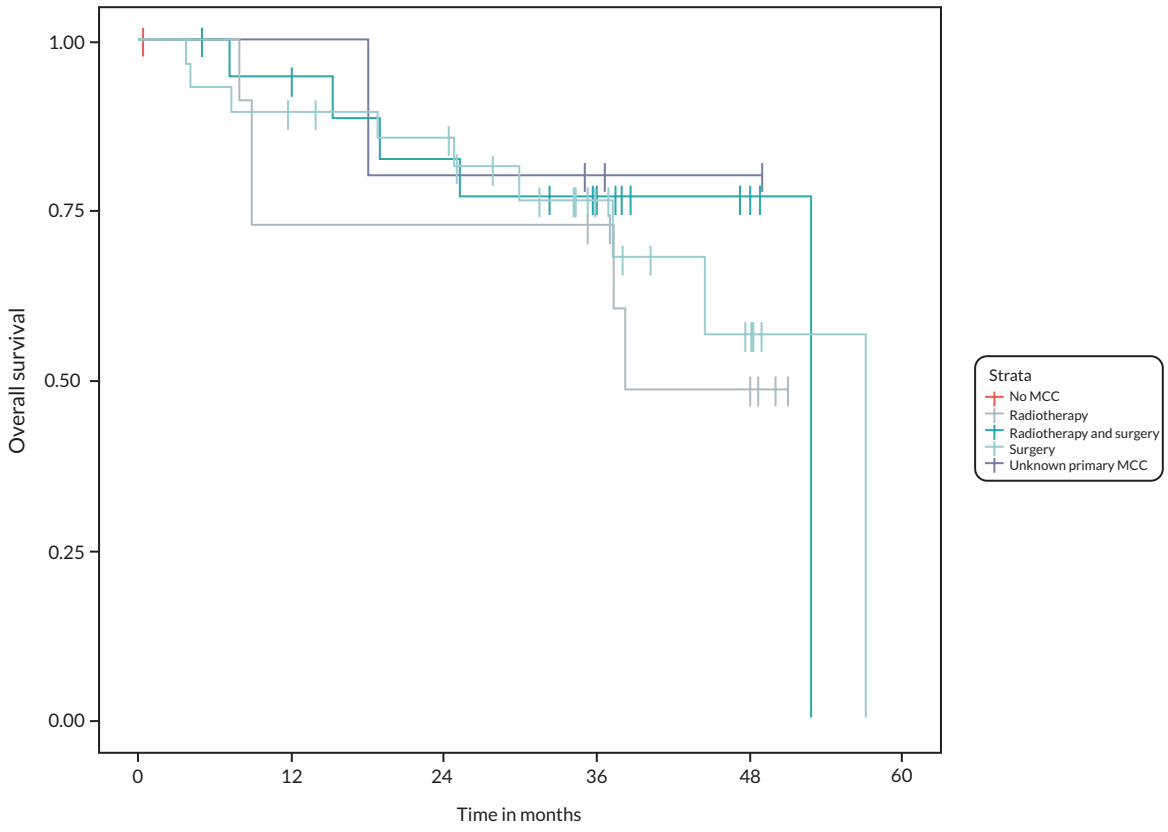

FIGURE 18 Overall survival time (months) by treatment received.

Radiotherapy	Reference category
Surgery	1.413 (95% CI 0.1756 to 11.37)
Surgery and radiotherapy	1.497 (95% CI 0.1383 to 10.36)
No definitive treatment	Cannot accurately be estimated
No primary MCC	Cannot accurately be estimated

Chapter 13 Biological samples

Analysis of immune profile

Blood samples were taken at baseline and 3 months and dispatched to the Human Biomaterials Resource Centre (HBRC), Institute of Biomedical Research Stores, University of Birmingham. Investigations were carried out in real time in the Department of Immunology, University Hospital Birmingham NHS Foundation Trust. Standardised flow cytometry of a fresh 4-ml ethylenediaminetetraacetic acid whole blood sample was used to provide true counts of circulating immune cells. Functional immune status will be assessed using a 7–10-ml lithium heparin blood sample, characterising the proliferation and cytokine release profile of immune cells in response to standardised stimuli. Results of investigations were not required prior to treatment.

At least one blood sample was received for 58 of 64 patients. The numbers per mm^3 of major circulating subpopulations were determined and results given in *Table 29*. Standard clinical laboratory lower limits of normal (LLN) are given. Only 22/58 (38%) patients scored above the LLN on each of the six markers of immune competence. Even using a more limited score of immune competence, 27/58 patients (47%) had scores above LLN on all three key markers of immune competence, the cell counts for CD45 + lymphocytes, CD4 + T helper cells and CD19 + B cells.

Additional data on proportions of lymphocytes according to their differentiation status are on file: B cells (naive, marginal, CD27-IgD-, switched memory, CD38lowCD21low, transitional and plasmoblasts), and CD4 + and CD8 + T cells (CDRA+, TCRαβ, CD$+CD8 +), EMRA (CD45RA + CD27-), naïve (CD45RA + CD27 +), effector memory (CD45RA-CD27-), central memory (CD45RA-CD27 +) as wells as counts of TCRγδ+ lymphocytes and NKT cells.

Tissue samples

Tissue from the MCC at the time of presentation, either from the primary or nodal biopsies or surgical specimen, is available in the HBRC for 61/64 patients, of whom 31 patients have contributed blocks and 55 slides.

TABLE 29 Counts per mm^3 of major circulating immune subtypes at registration or within 3 months of recruitment to the Rational MCC trial (*n* = 58)

	CD45 + lymphocytes	CD3 + T cells	CD8 + cytotoxic T cells	CD4 + helper T cells	NK natural killer cells	CD19 + B cells
Lower limit of normal (LLN)	< 1000	< 700	< 200	< 300	< 90	< 100
Mean	1602.03	1188.34	389.25	776.12	258.03	125.61
Median	1506.50	1116.00	338.00	655.50	247.50	93.40
IQR	1143.84	833.00	213.00	478.50	147.00	30.33
	1796.50	1345.00	525.25	937.50	346.37	184.98
Range	483.00	331.00	30.00	139.00	10.00	1.40
	5035.00	3179.00	1746.00	2419.00	747.00	1085.90
Below LLN *n*	46	47	44	55	53	28
%	79.31%	81.03%	75.86%	94.83%	91.38%	48.28%

Chapter 14 Deviations

The forthcoming sections contains deviation information on all patients recruited to the trial (regardless of whether they were enrolled in the randomised or registered components of the trial).

In total, during the Rational MCC trial, there were 125 deviations reported in 53 patients. *Table 30* shows aggregate information regarding the number of deviations according to the patient's entry type (registration or randomisation) and randomised treatment (where appropriate).

Table 31 displays the average number of deviations experienced by a patient according to trial entry method and randomised treatment.

Furthermore, *Table 32* shows summaries of all deviations categorised according to deviation type.

A line listing of deviations categorised as 'other' can be found in *Table 39* of *Appendix 5*.

TABLE 30 Summary of the total number of reported deviations stratified according to whether patients were randomised or registered to the trial as well as randomised treatment (where appropriate)

	Randomised treatment		
	Prioritise Radiotherapy [*n* (%)]	Prioritise Surgery [*n* (%)]	Total [*n* (%)]
Randomisation	10 (58.82)	7 (41.18)	17 (13.60)
Registration			108 (86.40)

TABLE 31 Summary of number of reported deviations per patient by trial entry modality and (where appropriate) randomised treatment

	Randomisation		
	Prioritise Radiotherapy	Prioritise Surgery	Registration
n	3	2	59
Mean (SD)	3.33 (0.58)	3.5 (2.12)	1.85 (1.64)
Median	3	3.5	1
IQR	(3–3.5)	(2.75–4.25)	(1–3)
Range	(3–4)	(2–5)	(0–7)

TABLE 32 Summary of deviations according to deviation type

Deviation type	*n* (%)
Patient found to be ineligible post recruitment	0 (0.00)
Delay to delivery of protocol-mandated treatment	5 (4.00)
Scheduled assessment not performed	78 (62.40)
Adjuvant regional or systemic therapy given for the primary (Rational Compare only)	0 (0.00)
Other deviation	42 (33.60)

Chapter 15 Discussion

Overview

Standard management of MCC is focused around the use of surgery and radiotherapy for primary and nodal metastases, with cytotoxic chemotherapy and the recently introduced immune checkpoint inhibitors offered for unresectable and metastatic disease.[41] Recent commercial investment results in published single-arm trials and randomised trials in progress to establish a place for immune checkpoint inhibitors as palliative and possibly adjuvant treatments. However, the evidence supporting first treatment for loco-regional MCC is based on retrospective experience but confounded by the lack of randomised trials and paucity of coherent prospective data.

The Rational MCC trial was designed to provide evidence supporting clinical decisions in the context of a rare cancer (the annual incidence of new MCC in the UK is 250–300), for which there was no proven standard of care or unity of practice. It was a pragmatic Phase III trial potentially recruiting any patient being offered radical treatment for primary MCC to a randomised comparison (Rational Compare) of either WLE or radiotherapy as the first definitive treatment for the primary, with a parallel observational study for patients for whom randomisation was inappropriate. This was designed to produce probabilities that one treatment was at least as good or better the other in terms of loco-regional control, so that results, even with a small sample size, could inform individual decisions. The study incorporated a parallel observational protocol (Rational Review) with definitive treatment allocated by regional SSMDT, including any patient with new stage I–III MCC not randomised into Compare, to maximise data collection on this rare cancer. Rational Compare and Review ran together through a feasibility phase, with a planned review to determine whether Compare could meet its objectives and to modify the design to support accrual, refine the question and reduce heterogeneity in the study population. The trial was closed after 64 patients were recruited predominantly to Rational Review.

Designing a trial for a rare cancer

The aim of this study was to provide evidence to enable clinicians and patients to make an individualised rational decision on how to treat primary MCC, from a randomised comparison between radical surgery, meaning a WLE aiming for margins between 10 and 30 mm and down to the first fascial layer, and radical radiotherapy aiming for equivalent margins. MCC is rare, and it was obviously not feasible to accrue a sample size sufficient to falsify a hypothesis. However, in this situation, comparing two treatments using existing resource, both of which are apparently in routine use (as opposed to the commissioning of a new service or funding for a drug), this level of precision is arguably unnecessary, whereas randomised data from a small sample would still be considerably more informative than pre-existing data from the cumulative thousands of non-randomised patients reported in retrospective case series and case reports. Sample size sets out the rationale, that, for example, for a sample size of 250 randomised patients, if the observed HR had been 0.8, there would have been at least an 80% chance the favoured treatment was at least as good as the alternative and < 10% chance of it being worse. These data would have been insufficient to determine a standard of care, but in each individual consultation, they would have informed the treatment decision alongside other patient and logistic factors.

Merkel cell carcinoma is a cancer of older people for whom clinical pathway standards have been established without randomised trials. We anticipated considerable variability between patients based on clinical circumstances and between treatment centres. To maximise accrual, we opted not to require narrow eligibility criteria: for example, permitting randomisation regardless of whether macroscopic disease was present or the presence of nodal involvement, providing the SSMDT was in equipoise. Patients could enter regardless of performance status, immune competence or presence of other cancers (all highly relevant to this population) as long as management was with radical intent. We limited staging procedures to cross-sectional imaging and diagnostic biopsy required for trial entry, omitting, for example, SLNB scans that are recommended as preferred staging tools in more recently published American and

European guidelines[42,43] because prior discussion with centre indicated a minority were routinely offering this procedure for MCC.

This study had a built-in feasibility phase. Although all recruiting centres had stated they were in equipoise between surgery versus radiotherapy as first treatment for the primary, the lack of national standard care pathways meant the potential for randomisation was genuinely uncertain, that is, this was an area of high risk to the project. Note that at the time this study opened, there was only one randomised trial for people with MCC published, which had failed to accrue.[24] Subsequently, trials have published, but these have been driven by the commercial development of novel systemic therapy as palliative treatment[44–47] and as a randomised Phase II trial in resectable MCC.[48] Given this uncertainty, firstly, we collected data on clinical practice for patient and treatment variables other than the randomised treatments. The plan was to use these to make operational changes to the trial design, potentially reducing the variation between patients, for example, by requiring SLNB or at least narrow margin excision of all macroscopic tumour prior to radiotherapy. We extended accrual to include a parallel observational study for all patients who were undergoing treatment for loco-regional MCC with radical intent even, if they were not randomised. This cohort potentially gave us an understanding of the reasons for non-randomisation that might feed into operational adaptations to the design, as well as expanding the data set of the presentation, management and outcome of MCC across multiple UK centres to support of future studies.

This design is novel, and irrespective of its outcomes, will inform the design of future trials for difficult-to-reach patients with rare cancers.

Feasibility outcomes from this trial

The aim of the feasibility phase was to demonstrate that a sufficient number of eligible patients could be identified and recruited over the course of the planned accrual period and to monitor and inform the design of the randomised trial.

Site set-up and rate of recruitment is summarised in Trial participants and Site set-up and rate of registration, and the disposition of the patients in the CONSORT diagram in Trial CONSORT diagram. The trial recruited 64 patients in total from 13 of the 14 active sites, but only 5 patients were randomised into Rational Compare. The trial met its earlier set-up and accrual targets but failed to meet the key randomisation target at 2 years. Accrual to Rational Compare was stopped immediately, and accrual to Rational Review continued to its intended close date 5 months later to maximise information from this rare cohort.

The trial achieved a high enrolment rate (64/144, 44%) of patients considered for eligibility, attesting to the high motivation of the recruiting teams. We looked at reasons why patients in Rational Review had not been randomised into Rational Compare in *Why did patients not enter Rational Compare?* The fact that two sites, including a high recruiting site, had services split over multiple NHS trusts and had not yet in place a shared care agreement, impacted negatively with seven patients recruited, apparently eligible for Compare, but unable to be randomised before Compare closed. We note that in nearly half of patients, registration postdated first definitive treatment, making them formally ineligible. However, detailed enquiries at sites showed that typically late registration was because randomisation had already been rejected by the SSMDT (including for anatomical reasons precluding radiotherapy) or by the patient, as well as for obvious reasons, such as five presenting with nodal disease without primary MCC.

We noted that the NHS had become a difficult environment for clinical trials because of limited resource and that Rational MCC had its own particular challenges: (1) staff shortages resulting in prolonged site set-up times and even a 6-month suspension of all trials at the lead site (Birmingham), (2) trial delivery across multiple departments with varied specialisation of the local principal investigators complicating site initiation, (3) multiple separate NHS trusts delivering different parts of multidisciplinary care without existing contractual agreements in place, notably radiotherapy and surgery, including the second highest recruiter still open only to Rational Review by the time the trial closed and (4) complex patient pathways, even though co-ordinated formally by the SSMDT, were variable between sites, for example, patients might be diagnosed in outlying hospitals and told a provisional treatment plan before SSMDT review and a decision about equipoise could be made. It became clear that the principal investigators and local coinvestigators

had to invest in the trial beyond what is normally expected of clinicians, to customise and improve referral and consultation pathways.

Overall, our review led us to conclude that even addressing shared care arrangements and complex referral pathways across sites to give greater opportunity for SSMDT and patients to be in equipoise, the randomisation rate would not be sufficient to continue the randomised trial.

We collected data relating to issues that might have informed operational changes to Rational Compare had it proceeded. Although Compare closed early, these are still relevant to future trials and possibly clinical practice. In the randomised trial, all five patients proceeded with the allocated treatment. MCC can progress rapidly, so we wanted to understand whether the times from randomisation to start of definitive treatment varied between the arms in a way that might disadvantage patients. None of the randomised patients progressed between randomisation and treatment and that 4/5 patients were treated in under 4 weeks from randomisation. We expanded this to look at the observational cohort, using the date of biopsy to date of first treatment (remembering registration postdated treatment for a proportion of patients). We note this averaged 9 weeks and could be up to 12 weeks.

A highly relevant question that potentially impacts on the decision whether to proceed directly from biopsy to radical radiotherapy (vs. delay and offer adjuvant radiotherapy after excision with wide surgical margins, aiming for clear pathological clearance and potentially with reconstruction) is whether excision biopsy might already have removed the primary. One of the five randomised patients had macroscopic disease post biopsy, and none had clear pathological margins from biopsy. Extending this to the observational cohort, we note in *Diagnostic and staging data for Merkel cell carcinoma* that 70% patients underwent excision as the initial diagnostic procedure. However, overall, only 24% had clear margins from initial biopsy, and conversely, 24% had macroscopic disease at the primary site post biopsy. Had the trial randomised more patients, an important area of exploration at the feasibility stage would have been whether proceeding to radiotherapy directly from biopsy without requiring marginal excision might have compromised early outcomes.

Postoperative radiotherapy was not a requirement for the surgical treatment pathway, lacking at the time a standard of care or high-quality evidence. We noted that one of the two patients randomised to surgery had adjuvant radiotherapy, and extending this to the observational cohort, 18/45 (40%) surgical patients had postoperative radiotherapy to the primary. Previously, excellent local disease control (96.4%) had been reported using surgery and adjuvant radiotherapy to primary MCC as a requirement to enter a trial addressing nodal treatment.[24] A systemic review of retrospective series reported 1- and 5-year local RFS of 90.5% and 87.9%, respectively, for 169 patients undergoing mixed surgical modalities plus adjuvant radiotherapy to the tumour bed,[16] with similarly high local control rates in more recent series.[19,25,49] This is reinforced by multivariate analysis of nearly 5000 patients presenting with stage I–III MCC in the US National Cancer Database (NCDB), demonstrating a 29% and 23% reduction in hazard of death with adjuvant radiotherapy for stage I and II MCC, respectively.[50] A recent retrospective analysis of 188 patients with localised MCC found that with, but not without, adjuvant radiotherapy, local control was excellent regardless of surgical margin size.[51]

Based on these data, including those from the observational cohort, had Rational Compare succeeded in randomising patients and continued to recruit, operational changes might have encouraged or required both postoperative radiotherapy for those randomised to WLE and narrow margin excision with direct closure for those randomised to radiotherapy. The two arms might have converged, and the critical difference between the arms might have been that the time interval from diagnosis to first radiotherapy would be potentially later with WLE and reconstruction compared to simple excision and direct closure. We note recent European consensus guidelines prioritise complete excision of the primary MCC with clinical safety margins of 1 cm followed by postoperative adjuvant radiotherapy on the tumour bed.[43]

Occult disease can be found in clinically negative nodes in 24% of MCC patients at presentation.[28] In a review of published retrospective series, positive sentinel nodes were detected in 30% of cases and false negative rate was 17%.[52] Both recent European[43] and American[42] consensus guidelines prioritise SLNB, at or before wide excision of the primary, as a staging procedure for patients with MCC without evidence of nodal metastases clinically or by imaging (stage I–II), taking into account factors such as age, performance status and the anatomic location of the primary. By contrast, in this study, only 15% patients underwent this staging procedure. This low take up and diversity of practice

had been anticipated and was why SLNB was not a requirement in the feasibility phase. Had the trial proceeded, the reasons for the low SLNB rate would have been investigated and the issue would have been addressed whether this should have become a requirement, possibly alongside at least narrow margin excision of the primary, as an operational adaptation.

Rational selection of radiotherapy or surgery

For completeness and in accordance with the statistical analysis plan, we presented the primary and secondary outcomes for the five randomised patients in Chapter 11. We note that for this tiny sample, loco-regional free survival estimates at 1 and 2 years post treatment were 100%, suggesting at most that there was no early signal that one arm was rapidly and consistently detrimental.

Extending this to the observational cohort, now including the five randomised patients, we can retrospectively categorise patients by the treatment actually received: surgery, surgery and postoperative radiotherapy and radiotherapy only. Importantly, this is not randomised, and inferences about treatment efficacy cannot be drawn. Although we saw no evidence of a difference between groups in time to loco-regional failure between these categories, although we note a lower proportion of patients who underwent surgery without radiotherapy alive and currently free of loco-regional disease at 3 years post enrolment and a higher proportion of patients who had surgery and radiotherapy free of local failure at 1 and 2 years, wide and overlapping CIs leave us unable to make any conclusions about future patients. There was no obvious difference in overall survival in relation to the initial treatment for the primary MCC.

We note that both the recent European[43] and American[42] consensus guidelines, postdating the start of this trial, Prioritise Surgery with a 1-cm or 1–2-cm margin, respectively. Both acknowledge the lack of randomised trial evidence supporting this. Had Rational Compare randomised sufficient patients and so continued to completion, it might have made a significant contribution clarifying this issue.

The study of patient, tumour and treatment variables in relation into outcomes

This trial also had as aims seeking evidence from a multicentre prospective study, including patient, tumour and treatment variables in relation to outcomes to improve the quality of clinical practice and support the development of future clinical trials.

Immune suppression or leukaemia/lymphoma are known to predict a more aggressive clinical course.[5,8,9] Two recent studies, interrogating large databases, asked whether there might be an interaction between radiotherapy efficacy for MCC and case note record of immune compromise conditions with conflicting results.[53,54] We note that 20% of patients in our study had a recognised condition, including B-cell malignancy, causing immune compromise. In addition, in our prospective design, we have results providing simple, and clinically available, counts of circulating immune populations. We note that only 38% patients had readings in the normal range for all six markers, and 47% if the readings are confined to just three key markers. Post hoc analysis, outside the scope of this initial report, is planned seeking association between these markers and MCC-specific events. Almost all patients have additional data on the differentiation and activation state of circulating immune cells, and either slides or tumour block available for digital pathology analysis. This will be used as planned to investigate CD8 infiltration in the tumour and offering potential for more detailed immune studies in relation to clinical data.

Strengths and limitations

This trial had a novel design specifically aimed at a rare cancer population, potentially hard to reach because they were elderly often dispersed away from regional specialist centres, in a setting of practice variation in which no components of the management pathway had been standardised based on high-quality evidence.

Firstly, although this was a Phase III trial to influence clinical practice, it was designed to generate a probability distribution comparing existing common treatment modalities that might influence individual decision-making without determining an overall standard of care. The guiding principle was, and remains, that randomised data from several hundred patients is a better guide to decision-making than retrospective data from many thousands. Similar designs might be used in other rare disease settings.

Second, the significant risks to successful randomisation were recognised in the trial design. For this reason, there were clear targets for feasibility. While the trial met the targets for site set-up and recruitment by 18 months, it failed to randomise 20 patients at 2 years resulting in closure, limiting the scale of investment in answering this question. This planned decision was informed by detailed internal audit of reasons for non-randomisation, including that SSMDT were not in equipoise for many patients, for example because of the anatomical location of the primary restricting treatment choice; that poor resourcing at trial sites was impacting on set-up times and accrual; that the different trial treatment options necessitated greater than normal multidisciplinary co-ordination in trial set-up and operation; that referral pathways extending over more than one hospital across considerable distance impacted on the informed consent process; and that establishing shared care arrangements was proving challenging at sites where the treatments were provided by separate NHS Trusts without contractual agreements.

Third, incorporating consenting but non-randomised patients in a prospective observational study meant that even though randomisation failed, detailed patient, tumour, treatment and outcome data, alongside measurements on circulating immune cells and tumour samples have been collected for most of a 64-patient cohort. This creates a framework to better understand UK clinical practice, inform the design of future trials for patients with this rare cancer and for further biological research.

The critical limitation of this study is that it has failed in its primary objective to influence clinical practice directly by failing to randomise patients between the arms: description of outcomes of non-randomised patients according to treatment given cannot be used to infer relative treatment benefit. Furthermore, feasibility objectives relating to operational modifications and exploratory objectives could not be addressed in such a small, randomised population. Some of these issues can to an extent be addressed using a post hoc analysis of all recruited patients, enabling some understanding of UK practice and influencing its development. The detailed data in the observational cohort have required considerable investment in data cleaning and clinical clarification than would be the case in a randomised trial, because in an observational study, detail is the primary value. This has delayed reporting of the trial data. Digital analysis of immunohistochemistry of tumour samples has proven more challenging than anticipated though offering greater opportunity for novel biological investigation as new techniques and software has become available.

Conclusions and recommendations for future research

Both WLE and radiotherapy are offered as first treatment for primary MCC in UK practice, but it remains uncertain whether one should be prioritised. We conclude from the feasibility phase of this trial that it would be impractical to attempt again to undertake a UK-based or international study to address whether radiotherapy or surgery represents the better first treatment for primary MCC.

On the face of it these are very different treatments. We observe that proceeding to radiotherapy directly from biopsy means many patients will have residual microscopic or macroscopic disease at the primary site, though it remains unclear if these matter given the radiosensitivity of MCC. Conversely, WLE results in excision with clear margins in a majority of patients. Only 40% of patients who underwent surgery proceeded to adjuvant radiotherapy. WLE necessitates reconstruction and healing for many patients, potentially delaying onset of adjuvant radiotherapy if this is used. However, we note the increasing consensus based on retrospective data that postoperative radiotherapy should be offered for primary MCC. Therefore, we anticipate that these treatment modalities for primary MCC might converge, with a standard emerging of narrow margin excision enabling earlier and more consistent use of adjuvant radiotherapy.

Recommendations for research are:

1. There is a need to develop UK practice guidelines that incorporate post hoc analysis of detailed results of Rational Review of practice across multiple NHS Trusts into UK practice, alongside systematic review of other published retrospective data on margin size and use of radiotherapy.
2. There needs to be continuing development of novel trial designs so that patients with rare diseases and hard to reach populations have treatments based on good-quality evidence. The design and outcomes of Rational MCC might inform the design of future studies for rare cancers. The guiding principle that randomised data from several hundred patients is a better guide to decision-making than retrospective data from many thousands means that similar designs might be used in other rare disease settings. Future high-risk trials in difficult to reach rare populations might incorporate a parallel observational cohort to reduce the risk of a trial closing with absolutely no return on investment.
3. Exploratory analysis of circulating immune cells and of the immune microenvironment in the MCC primary tumour samples will be explored in relation to the clinical data set and outcomes.

Equality, diversity and inclusion

By its nature, MCC predominantly affects people of historical North European ancestry with increased susceptibility to carcinogenic ultraviolet light, which overlaps with the population defined by the census as White. Ethnicity was not collected as part of the trial data set and therefore it is not possible to know whether the diversity of ethnicities was representative of the patient population. This population is mostly over the age of 70, and many are immunosuppressed. There were no exclusions to participation based upon these factors. The trial eligibility was purposely designed to maximise the opportunity for participation in research. Sites were encouraged to approach all patients meeting the general inclusion criteria to participate. Information about the trial was provided in paper format as a short summary and full patient information sheet (PIS) as well as on digital versatile disc and via electronic link to cater for differing preferences for receiving information about the trial. Additionally, the PIS was also made available in large font to make these more accessible.

Patient and public involvement

The trial was designed with the active participation of the lay/patient representative on the NCRI Melanoma CSG, including at the non-melanoma skin cancer subgroup strategic planning meeting in 27 November 2012, at which a radiotherapy versus surgery trial for MCC was prioritised, inclusion as a co-investigator, commentary on protocol development.

Patients with MCC and their carers contributed to meetings at the lead NHS trust at which the research concept and trial design was presented and discussed. They have reviewed the information and consent process, advocating the use of videos in addition to written information. They have reviewed the QoL instruments, selecting as meaningful for their experiences the use of the EORTC QLQC30 in addition to the EQ-5D-5L while rejecting the skin cancer index. Prior to Research Ethics Committee (REC) submission, feedback on the PISs was sought from local patients and was provided in the form of e-mails and phone calls. In response to our initial submission, the REC was still unclear on a few aspects of the PISs and also felt they were slightly too long. To overcome this issue, two patient representatives, with experience in reviewing PISs, provided feedback regarding how we may revise the documentation in light of the comments from the REC.

The decision to close the trial was taken in accordance with the trial feasibility design and was required by the funder. There was no contemporaneous patient and public involvement (PPI) in this decision. Subsequent activity has been focused on data cleaning and generation of a coherent data set, and this does not involve PPI. Furthermore, the advent of the COVID-19 pandemic inhibited normal trial activity, including PPI. Production of the extensive CSR with additional post hoc analysis of the observational data and preparation of manuscripts will require PPI, and patient focus groups will be sought.

Additional information

CRediT contribution statement

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Patient data statement

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that those are stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation

Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

Ethics statement

The trial first received a favourable ethical opinion from the West Midlands – Solihull Research Ethics Committee on the 29 January 2016 (REC Reference: 15/WM/0454). Subsequent amendments were approved for implementation on 7 March 2016 (non-substantial), 10 August 2016, 15 February 2017 (non-substantial), 15 December 2017 (non-substantial), 16 March 2017 (non-substantial), 30 November 2017 (substantial), 12 February 2018 (non-substantial) and 4 March 2019 (substantial). See *Table 33 Appendix 1* for more details of amendments. All participating sites obtained local Research and Development (R&D) department approval and were working to the latest version of the trial protocol.

The trial was performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, 1964, amended by the 48th World Medical Association (WMA) General Assembly, Somerset West, Republic of South Africa, 1996.

The was conducted in accordance with the Research Governance Framework for Health and Social Care (subsequently the UK Policy Framework for health and social care research 2017, Good Clinical Practice and the Data Protection Act 2018). Participants were identified using their unique trial number, initials and date of birth in the CRF and in correspondence between the Trial Office and participating site. Trial data were handled according to trial-specific guidelines. All essential trial documentation and source records will be securely retained for 10 years.

Information governance statement

The University of Birmingham is committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679.

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Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/EEWD6684.

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References

1. Lemos BD, Storer BE, Iyer JG, Phillips JL, Bichakjian CK, Fang LC, *et al*. Pathologic nodal evaluation improves prognostic accuracy in Merkel cell carcinoma: analysis of 5823 cases as the basis of the first consensus staging system. *J Am Acad Dermatol* 2010;**63**:751–61.
2. National Cancer Intelligence Network. *Rare Skin Cancer in England*; 2011. URL: www.ncin.org.uk/publications/data_briefings/rareskincancer (accessed 31 May 2023).
3. Ma JE, Brewer JD. Merkel cell carcinoma in immunosuppressed patients. *Cancers* 2014;**6**:1328–50.
4. Koljonen V, Kukko H, Pukkala E, Sankila R, Bohling T, Tukiainen E, *et al*. Chronic lymphocytic leukaemia patients have a high risk of Merkel-cell polyomavirus DNA-positive Merkel-cell carcinoma. *Br J Cancer* 2009;**101**:1444–7.
5. Penn I, First MR. Merkel's cell carcinoma in organ recipients: report of 41 cases. *Transplantation* 1999;**68**:1717–21.
6. Engels EA, Frisch M, Goedert JJ, Biggar RJ, Miller RW. Merkel cell carcinoma and HIV infection. *Lancet* 2002;**359**:497–8.
7. Hemminki K, Liu X, Ji J, Sundquist J, Sundquist K. Kaposi sarcoma and Merkel cell carcinoma after autoimmune disease. *Int J Cancer* 2012;**131**:E326–8.
8. Asgari MM, Sokil MM, Warton EM, Iyer J, Paulson KG, Nghiem P. Effect of host, tumor, diagnostic, and treatment variables on outcomes in a large cohort with Merkel cell carcinoma. *JAMA Dermatol* 2014;**150**:716–23.
9. Fields RC, Busam KJ, Chou JF, Panageas KS, Pulitzer MP, Allen PJ, *et al*. Recurrence after complete resection and selective use of adjuvant therapy for stage I through III Merkel cell carcinoma. *Cancer* 2012;**118**:3311–20.
10. Feng H, Shuda M, Chang Y, Moore PS. Clonal integration of a polyomavirus in human Merkel cell carcinoma. *Science* 2008;**319**:1096–100.
11. Chang Y, Moore PS. Merkel cell carcinoma: a virus-induced human cancer. *Annu Rev Pathol* 2012;**7**:123–44.
12. Allen PJ, Bowne WB, Jaques DP, Brennan MF, Busam K, Coit DG. Merkel cell carcinoma: prognosis and treatment of patients from a single institution. *J Clin Oncol* 2005;**23**:2300–9.
13. Samuel RJ, Matthews AG, Holme SA. Merkel cell carcinoma in Scotland 2000–2010. *Br J Dermatol* 2015;**173**:1073–5.
14. Jackson PC, Wallis K, Allgar V, Lind MJ, Stanley PR. Merkel cell carcinoma in East Yorkshire: a case series and literature review of current management. *J Plast Reconstr Aesth Surg* 2015;**68**:667–72.
15. Blythe JN, Macpherson D, Reuther WJ, Ethunandan M, Ilankovan V, Sharma S, *et al*. Management of early stage cutaneous Merkel cell carcinoma of the head and neck. *Br J Oral Maxill Surg* 2014;**52**:806–9.
16. Lewis KG, Weinstock MA, Weaver AL, Otley CC. Adjuvant local irradiation for Merkel cell carcinoma. *Arch Dermatol* 2006;**142**:693–700.
17. Ghadjar P, Kaanders JH, Poortmans P, Zaucha R, Krengli M, Lagrange JL, *et al*. The essential role of radiotherapy in the treatment of Merkel cell carcinoma: a study from the Rare Cancer Network. *Int J Radiat Oncol Biol Phys* 2011;**81**:e583–91.
18. Parvathaneni U, Iyer J, Nagase K, Parvathaneni K, Nghiem P. The safety and efficacy of primary radiation therapy without upfront surgery for Merkel cell carcinoma. *Int J Radiat Oncol Biol Phys* 2012;**84**:S168.
19. Pape E, Rezvoy N, Penel N, Salleron J, Martinot V, Guerreschi P, *et al*. Radiotherapy alone for Merkel cell carcinoma: a comparative and retrospective study of 25 patients. *J Am Acad Dermatol* 2011;**65**:983–90.

20. Sundaresan P, Hruby G, Hamilton A, Hong A, Boyer M, Chatfield M, Thompson JF. Definitive radiotherapy or chemoradiotherapy in the treatment of Merkel cell carcinoma. *Clin Oncol (R Coll Radiol)* 2012;**24**:e131–6.

21. Veness M, Foote M, Gebski V, Poulsen M. The role of radiotherapy alone in patients with merkel cell carcinoma: reporting the Australian experience of 43 patients. *Int J Radiat Oncol Biol Phys* 2010;**78**:703–9.

22. Veness M, Howle J. Radiotherapy alone in patients with Merkel cell carcinoma: the Westmead Hospital experience of 41 patients. *Australas J Dermatol* 2015;**56**:19–24.

23. Harrington C, Kwan W. Outcomes of Merkel cell carcinoma treated with radiotherapy without radical surgical excision. *Ann Surg Oncol* 2014;**21**:3401–5.

24. Jouary T, Leyral C, Dreno B, Doussau A, Sassolas B, Beylot-Barry M, *et al.*; Groupe de Cancérologie Cutanée of the Société Française de Dermatologie. Adjuvant prophylactic regional radiotherapy versus observation in stage I Merkel cell carcinoma: a multicentric prospective randomized study. *Ann Oncol* 2012;**23**:1074–80.

25. Senchenkov A, Barnes SA, Moran SL. Predictors of survival and recurrence in the surgical treatment of merkel cell carcinoma of the extremities. *J Surg Oncol* 2007;**95**:229–34.

26. Tsang G, O'Brien P, Robertson R, Hamilton C, Wratten C, Denham J. All delays before radiotherapy risk progression of Merkel cell carcinoma. *Australas Radiol* 2004;**48**:371–5.

27. National Comprehensive Cancer Network. *NCCN Clinical Practice Guidelines in Oncology: Merkel Cell Carcinoma v.1.2009*. Plymouth Meeting, PA: National Comprehensive Cancer Network; 2009.

28. Kachare SD, Wong JH, Vohra NA, Zervos EE, Fitzgerald TL. Sentinel lymph node biopsy is associated with improved survival in Merkel cell carcinoma. *Ann Surg Oncol* 2014;**21**(5):1624–30.

29. Fields RC, Busam KJ, Chou JF, Panageas KS, Pulitzer MP, Kraus DH, *et al*. Recurrence and survival in patients undergoing sentinel lymph node biopsy for merkel cell carcinoma: analysis of 153 patients from a single institution. *Ann Surg Oncol* 2011;**18**:2529–37.

30. Sadeghi R. Importance of sentinel node mapping in Merkel cell carcinoma: important new evidence by Tseng *et al*. *Am J Surg* 2015;**209**:1111.

31. Tseng J, Dhungel B, Mills JK, Diggs BS, Weerasinghe R, Fortino J, Vetto JT. Merkel cell carcinoma: what makes a difference? *Am J Surg* 2015;**209**:342–6.

32. Beylergil V, Carrasquillo JA. Molecular imaging and therapy of merkel cell carcinoma. *Cancers* 2014;**6**:1020–30.

33. Hawryluk EB, O'Regan KN, Sheehy N, Guo Y, Dorosario A, Sakellis CG, *et al*. Positron emission tomography/computed tomography imaging in Merkel cell carcinoma: a study of 270 scans in 97 patients at the Dana-Farber/Brigham and Women's Cancer Center. *J Am Acad Dermatol* 2013;**68**:592–9.

34. Slater D, Walsh M. *Standards and Datasets for Reporting Cancers: Dataset for the Histological Reporting of Primary Cutaneous Merkel Cell Carcinoma and Regional Lymph Nodes*. Royal College of Pathologists; 2014. URL: www.rcpath.org/static/cd3d3fab-eab2-43e4-8d9fec9c5d55fd7a/Dataset-for-the-histological-reporting-of-primary-cutaneous-Merkel-cell-carcinoma-and-regional-lymph-nodes.pdf (accessed 14 August 2025).

35. Durante M, Reppingen N, Held KD. Immunologically augmented cancer treatment using modern radiotherapy. *Trends Mol Med* 2013;**19**:565–82.

36. Angell H, Galon J. From the immune contexture to the immunoscore: the role of prognostic and predictive immune markers in cancer. *Curr Opin Immunol* 2013;**25**:261–7.

37. Paulson KG, Iyer JG, Tegeder AR, Thibodeau R, Schelter J, Koba S, *et al*. Transcriptome-wide studies of merkel cell carcinoma and validation of intratumoral CD8+ lymphocyte invasion as an independent predictor of survival. *J Clin Oncol* 2011;**29**:1539–46.

38. Paulson KG, Iyer JG, Simonson WT, Blom A, Thibodeau RM, Schmidt M, *et al*. CD8+ lymphocyte intratumoral infiltration as a stage-independent predictor of Merkel cell carcinoma survival: a population-based study. *Am J Clin Pathol* 2014;**142**:452–8.

39. Sihto H, Bohling T, Kavola H, Koljonen V, Salmi M, Jalkanen S, Joensuu H. Tumor infiltrating immune cells and outcome of Merkel cell carcinoma: a population-based study. *Clin Cancer Res* 2012;**18**:2872–81.

40. Pallan L, Hislop A, Birtwhistle J, Blackbourn D, Steven N. Differences in phenotype and function of the immune in Merkel Cell Cancer patients compared with control patient group. 2014 NCRI Cancer Conference, 6 November 2014, Liverpool, abstract no. B255.

41. Steven N, Lawton P, Poulsen M. Merkel cell carcinoma: current controversies and future directions. *Clin Oncol (R Coll Radiol)* 2019;**31**:789–96.

42. Bichakjian CK, Olencki T, Aasi SZ, Alam M, Andersen JS, Blitzblau R, *et al*. Merkel cell carcinoma, version 1.2018, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 2018;**16**:742–74.

43. Gauci ML, Aristei C, Becker JC, Blom A, Bataille V, Dreno B, *et al*.; European Dermatology Forum (EDF), the European Association of Dermato-Oncology (EADO) and the European Organization for Research and Treatment of Cancer (EORTC). Diagnosis and treatment of Merkel cell carcinoma: European consensus-based interdisciplinary guideline – update 2022. *Eur J Cancer* 2022;**171**:203–31.

44. D'Angelo SP, Lebbé C, Mortier L, Brohl AS, Fazio N, Grob JJ, *et al*. First-line avelumab in a cohort of 116 patients with metastatic Merkel cell carcinoma (JAVELIN Merkel 200): primary and biomarker analyses of a phase II study. *J ImmunoTher Cancer* 2021;**9**:e002646.

45. Nghiem P, Bhatia S, Lipson EJ, Sharfman WH, Kudchadkar RR, Brohl AS, *et al*. Three-year survival, correlates and salvage therapies in patients receiving first-line pembrolizumab for advanced Merkel cell carcinoma. *J ImmunoTher Cancer* 2021;**9**:e002478.

46. D'Angelo SP, Russell J, Lebbe C, Chmielowski B, Gambichler T, Grob JJ, *et al*. Efficacy and safety of first-line avelumab treatment in patients with stage IV metastatic Merkel cell carcinoma: a preplanned interim analysis of a clinical trial. *JAMA Oncol* 2018;**4**:e180077.

47. Nghiem P, Bhatia S, Lipson EJ, Sharfman WH, Kudchadkar RR, Brohl AS, *et al*. Durable tumor regression and overall survival in patients with advanced Merkel cell carcinoma receiving pembrolizumab as first-line therapy. *J Clin Oncol* 2019;**37**:693–702.

48. Topalian SL, Bhatia S, Amin A, Kudchadkar RR, Sharfman WH, Lebbé C, *et al*. Neoadjuvant nivolumab for patients with resectable Merkel cell carcinoma in the CheckMate 358 trial. *J Clin Oncol* 2020;**38**:2476–87.

49. Gunaratne DA, Howle JR, Veness MJ. Definitive radiotherapy for Merkel cell carcinoma confers clinically meaningful in-field locoregional control: a review and analysis of the literature. *J Am Acad Dermatol* 2017;**77**:142–8.e1.

50. Bhatia S, Storer BE, Iyer JG, Moshiri A, Parvathaneni U, Byrd D, *et al*. Adjuvant radiation therapy and chemotherapy in Merkel cell carcinoma: survival analyses of 6908 cases from the National Cancer Data Base. *J Natl Cancer Inst* 2016;**108**:djw042.

51. Tarabadkar ES, Fu T, Lachance K, Hippe DS, Pulliam T, Thomas H, *et al*. Narrow excision margins are appropriate for Merkel cell carcinoma when combined with adjuvant radiation: analysis of 188 cases of localized disease and proposed management algorithm. *J Am Acad Dermatol* 2021;**84**:340–7.

52. Gunaratne DA, Howle JR, Veness MJ. Sentinel lymph node biopsy in Merkel cell carcinoma: a 15-year institutional experience and statistical analysis of 721 reported cases. *Br J Dermatol* 2016;**174**:273–81.

53. Yusuf M, Gaskins J, May ME, Mandish S, Wall W, Fisher W, *et al*. Immune status and the efficacy of adjuvant radiotherapy for patients with localized Merkel cell carcinoma of the head and neck. *Clin Transl Oncol* 2020;**22**:2009–16.

54. Tseng YD, Nguyen MH, Baker K, Cook M, Redman M, Lachance K, *et al*. Effect of patient immune status on the efficacy of radiation therapy and recurrence-free survival among 805 patients with Merkel cell carcinoma. *Int J Radiat Oncol Biol Phys* 2018;**102**:330–9.

Appendix 1 Changes to the protocol

TABLE 33 Changes to the protocol

Version and date	Reason for amendment	Amendment number	Substantial or non-substantial	REC approval date
V1.0, 4 November 2015	Initial application	N/A	N/A	N/A
V2.0, 15 January 2016	Changes required following ethical review relating to provision of trial material to potential participants	N/A	N/A	29 January 2016
V2.0a, 3 March 2017	Non-substantial amendments: • Addition of/changes to trial personnel • Amended randomisation telephone number	N/A	Non-substantial	7 March 2016
V3.0, 11 October 2017	Additions: • Shared care model • Local follow-up process • Informed consent for Rational Review can be delegated to nurse or other delegated member of the research team • Additional dose regimen for radiotherapy • Screening/enrolment log instructions • Adition of/changes to trial personnel Clarifications: • Arm A and Arm B have now been made consistent through-out the protocol • Eligibility criteria • Inclusion/exclusion Criteria • Cross sectional imaging • Trial blood samples • Radiotherapy treatment – permitted modalities, radiother-apy quality assurance process • Surgical quality assurance process • Progression • Tissue sample collection • Expected SAE process • Archiving requirement • Appendix 4, Radiotherapy Protocol	1	Substantial	30 November 2017
V3.0a, 15 August 2018	Change in Data Protection Regulations	N/A	Non-substantial	12 February 2018
V4.0, 11 January 2019	Additions:	2	Substantial	4 March 2019

TABLE 33 Changes to the protocol (*continued*)

Version and date	Reason for amendment	Amendment number	Substantial or non-substantial	REC approval date
	• Closure of the Randomised Compare arm • Closure of the Registration, Review arm • Changes to trial personnel • Further requirements for data collection • Removal of requirement to perform CT-PET • Removal of requirement for central review of imaging Clarifications: • Duration of patient follow-up • Further information regarding analysis of the immune profile samples Further information regarding analysis of pathology samples			

Appendix 2 Definitive treatment for the primary Merkel cell carcinoma and loco-regional metastases

Details of Definitive Radiotherapy for the primary Merkel cell carcinoma

Tables 34 and *35*, respectively, present line listings of reasons for radiotherapy treatment interruptions and reasons why a larger radiological margin was not achieved.

TABLE 34 Information regarding interruptions to radiotherapy, one row per patient

Length of interruption (days)	Interruption	Method of compensation	Other methods
1	Yes	Weekend treatment	
1	Yes	Other	Treatment added to end
1	Yes	Weekend treatment	
1	Yes	Weekend treatment	

TABLE 35 Reasons larger radiotherapy margin was not achieved

Details
Lesion on bridge of nose, close to orbit, etc.
Superior margin < 20 mm of proximity to right eye
Nodal area – right axilla – no photography done, as this was done on the primary site – right elbow
Adjuvant radiotherapy to left wrist was done using electrons – information given above. Adjuvant radiotherapy to left axilla was done prophylactically – 50 Gy/25# CT planned with photons
Arena was not outlined. 8 cm × 5-cm electron cut-out used. 1-cm bolus used

Details of definitive surgery for the primary MCC

Table 36 gives reasons why a larger surgical margin was not achieved.

TABLE 36 Reasons larger WLE surgical margin was not achieved

Reason larger margin not achieved	Details
Anatomical consideration	A 1-cm WLE Merkel tumour left cheek IIB (direct closure)
Anatomical consideration	Anatomical consideration is ticked as maximum margin was achieved for this patient at the site of MCC
Anatomical consideration	Excision margins not recorded
Anatomical consideration	Location of lesion restricted size of margins
Anatomical consideration	Patient for follow-up radiotherapy
Anatomical consideration	Staged excision – scalp lesion. Further excision – no residual malignancy

TABLE 36 Reasons larger WLE surgical margin was not achieved (*continued*)

Reason larger margin not achieved	Details
Anatomical consideration	This is the margin required at site for MCC on the head/forehead if fully excised at biopsy
Anatomical consideration	
Anatomical consideration	
Anatomical consideration	
Anatomical consideration	
Anatomical consideration	
Anatomical consideration	
Anatomical consideration	
Anatomical consideration	
Anatomical consideration	
Anatomical consideration	
Anatomical consideration	
Anatomical consideration	
Anatomical consideration	
Anatomical consideration	
Anatomical consideration	
Anatomical consideration	
Other	Complete resection achieved at this margin
Other	Excision margin in line with local guidance, larger excision not met so closure suitable for radiotherapy – surgeon confirmation
Other	Had already had 10-mm excision previously
Other	Margins larger than 20 mm were not required clinically
Other	No involvement of underlying tissue, MCC only approximately 4 mm deep
Other	Procedure also involved neck dissection; therefore margin was sufficient
Other	Reason unknown
Other	SSMDT agreement for 20 mm
Other	Surgeon achieved margins he saw fit. Bigger margin not possible due to area tumour encompassed
Other	The surgeon has taken this margin and must have felt this was adequate. This is the WLE. The initial excision already had 5-mm peripheral clearance

Appendix 3 Safety reporting

Deaths

Table 37 gives a listing of pertinent death information.

TABLE 37 Listing of pertinent death information

Time to death (years)	Cause of death	Other reasons, specify
0.32	Other non-cancer	Sepsis
0.34	Disease related	
0.61	Disease related	
0.62	Disease related	
0.67	Disease related	
0.74	Disease related	
0.74	Not known	
1.28	Disease related	
1.52	Disease related	
1.56	Disease related	
1.59	Other non-cancer	Heart failure
2.06	Other cancer	Gastric cancer
2.11	Disease related	
2.48	Other non-cancer	Frailty of old age
3.11	Other non-cancer	Acute myocardial infarction
3.12	Not known	
3.19	Disease related	
3.72	Disease related	
4.4	Not known	
4.76	Not known	

Appendix 4 Results for feasibility phase

Feasibility phase outcome measures

Proportion of randomised patients undergoing the allocated treatment

As required in the analysis plan, CIs for this proportion are given in *Table 38*. Those calculated using the exact method (Clopper–Pearson) are here taken to be the principal estimates. However, to investigate whether the interpretation of the data is affected by the different estimation methods, other methods (including Wald, Wilson, Agresti–Coull and Jeffreys) are shown as sensitivity.

TABLE 38 Summary of 95% CIs for proportion of Rational Compare patients who underwent prioritised allocated treatment (5/5)

Clopper–Pearson	(47.82% to 100%)
Wald	(100% to 100%)
Wilson	(56.55% to 100%)
Agresti–Coull	(51.09% to 100%)
Jeffreys	(62.06% to 100%)

Appendix 5 Deviations

Table 39 shows a listing of deviations categorised as 'other'.

TABLE 39 Listing of deviations categorised as 'other'

Time to deviation (days)	Deviation reason
105	Patient had a recurrent MCC
98	Delayed in sending 3 months' blood sample
−1	Baseline bloods not taken
6	Photograph of scar not taken
377	12-month clinical assessment performed after a 12-month scan
642	Patient did not complete a QoL for month 21
−89	No photograph of primary lesion
4	Photograph not taken
4	Photograph not taken
8	Photograph not taken
105	Month 3 visit date out of window
346	As per data clarification form 518-imaging delayed
359	12-month scan performed after visit
−64	Medical photography not performed
845	Delayed month 24 visit
−19	No photography or tracing on definitive radiotherapy
383	12-month imaging delayed
419	Follow-up visit happened outside the ± 2-week window
264	Patient did not complete a quality of life for month 9, 15, 18
91	Clotted blood not taken
798	Delayed procedure
350	Delayed scan
350	12-month follow-up early
715	CT scan completed prior to clinical review
410	Delay in imaging scan
770	Imaging not performed
133	3-month blood sample collection – not done
1	Photo at surgery
384	Delayed month 12 form
62	3-month visit performed early
26	Photograph or tracing of radiotherapy not done
116	Absolute lymphocyte count not taken

TABLE 39 Listing of deviations categorised as 'other' (*continued*)

Time to deviation (days)	Deviation reason
97	3-month blood test not taken
27	Photograph/tracing not performed
104	Absolute lymphocyte count not taken
699	QoL not completed
−1	Photograph not taken
163	Follow-up visit early
126	Delayed 3-month f/u
777	24-month f/u delayed
12	Baseline bloods not taken
718	Imaging not done due to COVID-19

EME
HSDR
HTA
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