



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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Scientific summary

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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.

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