RTN2 Trial
A Randomised Trial of Post-Operative Radiation Therapy Following Wide Excision of Neurotropic Melanoma of the Head and Neck

ANZMTG 01.09 TROG 08.09

Background and Rationale
Neurotropism, usually characterised by the presence of melanoma cells around nerve sheaths (perineural invasion) or within nerves (intraneural invasion), is an uncommon feature of the disease but it is this feature which predisposes towards a high local relapse rate. Uncontrolled studies suggest that radiation therapy may reduce the risk of local relapse in these patients although there are no randomised trials to confirm this hypothesis.

Study Objectives
To determine, in patients who have undergone surgery with curative intent for neurotropic melanoma of the head and neck, whether there is a difference in time to local relapse between patients treated with post-operative radiation therapy and those simply observed.

Study Hypothesis
Radiation therapy after surgery will improve local control of neurotropic melanoma.

Study Design
Multi-centre, open-label, stratified, 2-arm parallel Phase III trial.

Schema

Eligible Patients
Neurotropic melanoma of the head and neck (above clavicles) Definitive surgery with removal of all macroscopic (gross) disease*

Stratify
Institution Tumour Site

Randomise
Radiation Therapy Initial Observation
Dose 48 Gy in 20 fractions

* Resection of all palpable and visible disease without microscopic residual disease
Patient Accrual
The total patient accrual for this trial will be 100 patients accrued over five years.

Inclusion Criteria
Patients may be included in the trial only if they meet all of the following criteria:

- Tumour located above the clavicle and below the jaw or occiput (neck primary) or above the jaw/occiput (head primary)
- Complete macroscopic resection (minimum 1cm surgical excision margin) of all known invasive disease with 5mm microscopic margin
- Histologically confirmed neurotropic primary melanoma
  - Neurotropism is identified pathologically by the presence of melanoma cells around nerve sheaths (perineural invasion) or within nerves (intranerve invasion).
  - Occasionally, the tumour itself may form neuroid structures (termed ‘neural transformation’; this is also regarded as neurotropism)
  - “Normal”-looking nerves that appear to be “entrapped” within the tumour should not be regarded as neurotropism
- A 5mm histopathological margin on invasive disease is recommended (irrespective if whether the tumour is involving a nerve), unless constrained by an anatomical boundary.
- No previous surgery for melanoma (other than complete macroscopic resection as stated above) (i.e. Not recurrent disease)
- No evidence of in-transit, nodal or distant metastases as determined by clinical examination, sentinel node biopsy, elective nodal dissection, or any form of imaging.
- Aged 18 years or older
- Has provided written informed consent for participation in this trial
- ECOG performance status score of 2 or less
- Life expectancy greater than 6 months
- Patients capable of childbearing are using adequate contraception
- Available for follow up

Exclusion Criteria
Patients who fulfil any of the following criteria are not eligible for admission into the trial:

- Intercurrent illness that will interfere with the radiation therapy such as immunosuppression due to medication or medical condition.
- Clinical and/or MRI evidence of a named cranial or cervical nerve involvement by tumour
- Inability to localise surgical bed on any form of imaging and/or surgical margins (cm) not known
- Previous radical radiation therapy to the head and neck, excluding superficial radiation therapy to cutaneous SCC or basal cell carcinoma, which is not within or overlapping the tumour bed.
- High risk for poor compliance with therapy or follow-up as assessed by investigator
- Patients with in-transit, nodal or distant metastases
- Patients with prior cancers, except: those diagnosed ≥ 5 years ago with no evidence of disease relapse and clinical expectation of relapse of less than 5%; prior successfully treated Level 1 cutaneous melanomas ≥ 2 years ago; or non-melanoma skin cancer; or carcinoma in situ of the cervix.
- Albinism.
- Participation in other clinical trials with the same primary endpoint.
- Women who are pregnant or lactating.