Proposal for a 2-stage RCT in high risk primary SCC: COMMISSAR

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on behalf of
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Nottingham Centre for Evidence Based Medicine
NCRI Skin Cancer Clinical Studies Group
www.clinicaltrials.gov
7 interventional trials for cutaneous SCC
>1500 for melanoma

Lack of evidence for standard treatments

? Single entity of NMSC
? Misconceptions re prognosis
? Heterogeneity
? Patient demographics
Clinician survey as part of NIHR Programme Grant ‘Setting Priorities and Reducing Uncertainties for People with Skin Disease’.

Identification of areas of clinical importance for potential RCTs in management of SCC

**High risk SCC:**
- **Surgical margins**
- **Adjuvant radiotherapy**
Only **one** RCT
13-cis-retinoic acid and interferon as adjuvant treatment after surgery +/- radiotherapy for high risk primary SCC (Brewster, 2007)
RESEARCH

Interventions for non-metastatic squamous cell carcinoma of the skin: systematic review and pooled analysis of observational studies

Louise Lansbury research associate¹, Fiona Bath-Hextall reader in evidence based healthcare¹ ², William Perkins consultant dermatologist³, Wendy Stanton librarian⁴, Jo Leonardi-Bee associate professor in medical statistics⁵

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<table>
<thead>
<tr>
<th>Procedure</th>
<th>No studies</th>
<th>No patients</th>
<th>Pooled estimate local recurrence</th>
<th>Regional recurrence</th>
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<tbody>
<tr>
<td>Mohs’ micrographic surgery</td>
<td>16</td>
<td>1572</td>
<td>3.0%</td>
<td>4.2%</td>
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<tr>
<td>Standard excision</td>
<td>12</td>
<td>1144</td>
<td>5.4%</td>
<td>4.4%</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>13</td>
<td>1018</td>
<td>6.4%</td>
<td>2.6%</td>
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</table>
Adjuvant radiotherapy

Studies of adjuvant RT for PNI

n=5
Local recurrence 18.2%
Regional recurrence 8.3%
Metastasis 11.5%
Well differentiated < 2cm: 4mm margins

High risk (> 2 cm, moderately, poorly or undifferentiated, into subcutaneous tissue, ear, lip, scalp, eyelids or nose): at least 6 mm or Mohs’ micrographic surgery

No comment on role of adjuvant radiotherapy
Proposal for a two-stage RCT for patients with high-risk primary SCC
Stage 1: Wide local excision with 10mm margin vs Mohs’
Stage 2: Adjuvant radiotherapy vs no adjuvant radiotherapy

Conventional surgery versus Mohs’ Micrographic Surgery
for SCC and the role of Adjuvant Radiotherapy

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Histologically confirmed high risk SCC (pT2)

Randomisation 1

WLE 10mm

Mohs

Randomisation 2

Radiotherapy

No Radiotherapy

3 year follow up for loco-regional recurrence
Primary outcomes
- Time to loco-regional recurrence from initial randomisation up to 3 years after treatment.

Secondary outcomes
- Time to distant metastases within 3 years
- Time to tumour-related death within 3 years
- Overall disease-free survival
- Completeness of surgical excision
- Number of Mohs’ layers required to clearance of tumour
- Quality of Life measures
- Cosmetic appearance at baseline and 2 and 5 years post-treatment
- Within-trial cost analysis from an NHS perspective
Defining ‘high risk’: RCPath, AJCC7 and BWH classifications

**Tis**  Carcinoma in situ

- <20mm diameter and <2 high risk features

**T1**  <20mm diameter and <2 high risk features

- ≥20mm diameter or any size and ≥ 1 high risk features

**T3**  Invasion of maxilla, mandible, orbit or temporal bone

**T4**  Invasion of skeleton or perineural invasion of skull base

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**RCPath (2012)**

- Depth >4mm
- Clark ≥ V
- Perineural invasion
- Poor differentiation
- High-grade histological type
- Lymphovascular invasion

**AJCC (2010): 2 high risk features**

- Depth >2mm
- Clark >IV
- Ear/lip
- Perineural invasion
- Poor differentiation
Neither RCPath nor AJCC7 pT2 classifications give significant information about prognosis.

Evaluation of AJCC Tumor Staging for Cutaneous Squamous Cell Carcinoma and a Proposed Alternative Tumor Staging System

Anokhi Jambusaria-Pahlajani, MD, MSCE; Peter A. Kanetsky, PhD, MPH; Pritesh S. Karia, MPH; Wei-Ting Hwang, PhD; Joel M. Gelfand, MD, MSCE; Faith M. Whalen, MD; Rosalie Elenitsas, MD; Xiaowei Xu, MD, PhD; Chrysalyne D. Schmults, MD, MSCE
Brigham & Women’s Hospital T staging system

Built on 4 risk factors:

- Tumour diameter $\geq 2\text{cm}$
- Poorly differentiated
- Invasion beyond fat
- PNI in nerve calibre $\geq 0.1\text{mm}$

$T1 = 0$ risk factors

$T2a = 1$ risk factor

$T2b = 2-3$ risk factors

$T3 = 4$ risk factors or bone invasion
BWH classification not yet fully validated
AJCC7 for randomisation 1 and then stratified to include modified BWH for randomisation 2 (T2b/3 and >4mm depth as inclusion factors)?
Current RCPath dataset will identify these risk factors
Feasibility work: SCC case series

Louise Lansbury and Fiona Bath-Hextall

- Analysis of SCCs in Nottingham over 12 months 2006-7 (5y follow up)
- Population 1,070,000
- 357 SCC – 74% managed in dermatology
- 2010-11 also analysed

T1: 56.2%
T2: 43.4%
  ‘T2a’ (1 high risk feature): 32.2%
  ‘T2b’ (2+ high risk features): 11.2%
T3: 0.4%

Local recurrence: 6.2% (T1 3%; T2a 8%; T2b 16%)
Regional recurrence: 3.3% (T1 1.3%; T2a 4.5%; T2b 9.7%)
Distant mets: 0%
SCC attributable death: 1.5%
### AJCC vs BWH

<table>
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<tr>
<th>Outcome</th>
<th>AJCC</th>
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<th>BWH</th>
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<tr>
<td></td>
<td>T1</td>
<td>T2</td>
<td>T1</td>
<td>T2a</td>
<td>T2b</td>
<td></td>
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<tr>
<td>Local recurrence</td>
<td>2.9</td>
<td><strong>9.2</strong></td>
<td>3.2</td>
<td>7.9</td>
<td><strong>16.1</strong></td>
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<tr>
<td>Regional recurrence</td>
<td>0</td>
<td><strong>4.9</strong></td>
<td>1.3</td>
<td>4.5</td>
<td>9.7</td>
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<tr>
<td>Distant mets</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>SCC attributable death</td>
<td>0</td>
<td>1.5</td>
<td>0.7</td>
<td>4.7</td>
<td>0</td>
<td></td>
</tr>
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</table>
Feasibility study with patients

Louise Lansbury, Fiona Bath-Hextall

Evaluation of potential participants willingness to be randomised into the proposed trial and possible barriers to recruitment

Postal questionnaire (n=24/29)
Focus group (n=7)

- First stage surgical arm: 71% willing to be randomised
- Second stage adjuvant RT: 58% willing to be randomised

Confusion about the concepts of randomisation and clinical equipoise
Supportive
6mm versus MMS acceptable
Incision biopsy for diagnosis not punch
Concern about availability delays for MMS
Concern about scalp SCC – deep margins often <1mm
Frozen versus paraffin embedded margin control - ? ‘slow’ MMS
Patient with possible high risk SCC on head and neck identified and consented

Incision biopsy

Histologically confirmed high risk SCC

Randomisation 1

- WLE 6mm
- WLE 10mm
- Mohs'

Randomisation 2

- Radiotherapy
- No Radiotherapy

3 year follow up for loco-regional recurrence

30,000+ / yr in UK All patient groups?

T2 (AJCC7): 43-50% of all primary SCC

Some centres 6mm vs 10mm only? Frozen section or slow Mohs’?

T2b/T3 equivalent (AJCC7/BWH/>4mm): 30% of all primary SCC

?<1mm at deep margin on scalp
Next steps before final protocol and funding applications?

Feedback today…power calculations

Survey of clinicians willingness to participate – SSMTs
- availability and timing of access to MMS
- Experience in MMS for SCC
- comments on trial design

Further patient survey and focus groups

Radiotherapy and surgery working groups
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Feasible?
Recruitable?
Other concerns / comments?

Other trials we should be doing instead ?!!