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

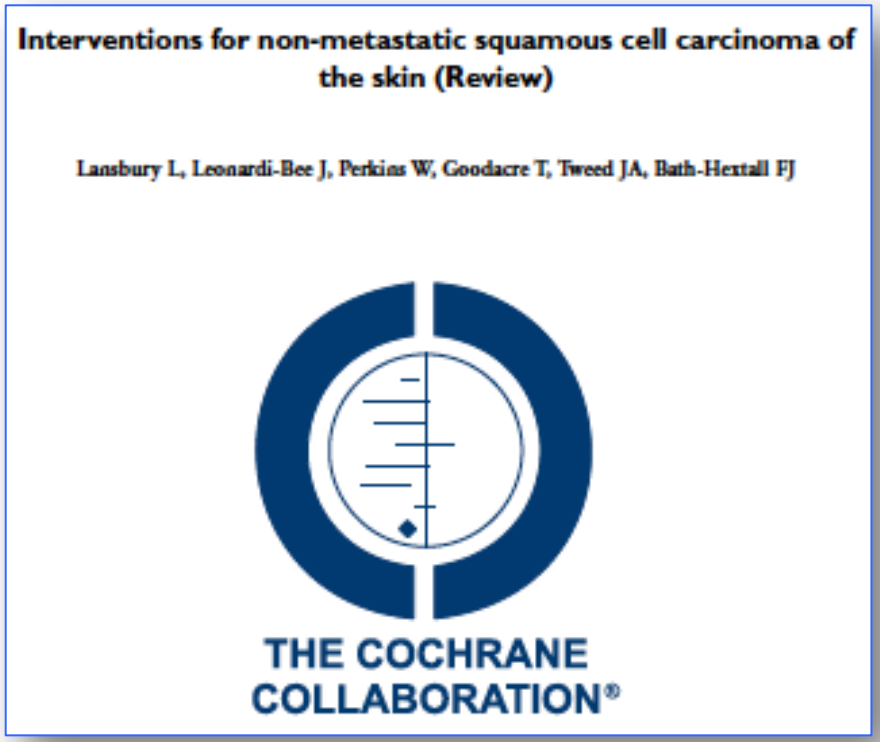
? Patient demographics

Louise Lansbury and Fiona Bath-Hextall
University of Nottingham, Centre for Evidence based Dermatology

- ***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***



Issue 4, 2010

Only one RCT

13-cis-retinoic acid and interferon as adjuvant treatment after surgery +/- radiotherapy for high risk primary SCC (Brewster, 2007)

BMJ

BMJ 2013;347:f6153 doi: 10.1136/bmj.f6153 (Published 4 November 2013)

RESEARCH

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

Louise Lansbury *research associate*[1], Fiona Bath-Hextall *reader in evidence based healthcare*[1 2], William Perkins *consultant dermatologist*[3], Wendy Stanton *librarian*[4], Jo Leonardi-Bee *associate professor in medical statistics*[5]

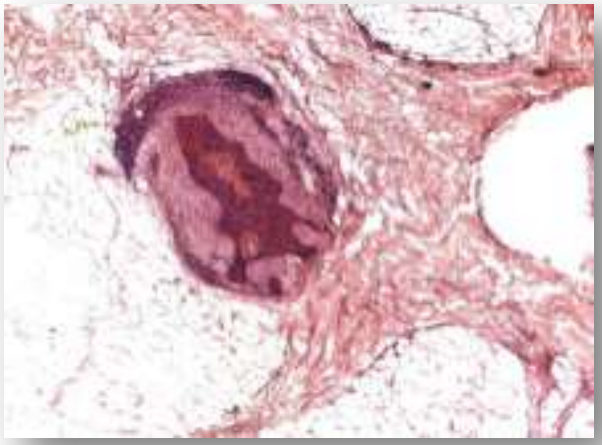
[1]Centre of Evidence Based Dermatology, University of Nottingham, Nottingham NG7 2NR, UK; [2]School of Health Sciences, University of Nottingham, Nottingham, UK; [3]Department of Dermatology, Nottingham University Hospitals NHS Trust, Queen's Medical Centre, Nottingham, UK; [4]Greenfield Medical Library, Nottingham Education Centre, University of Nottingham, UK; [5]Division of Epidemiology and Public Health, University of Nottingham, Nottingham City Hospital, Nottingham, UK

Surgery

118 publications

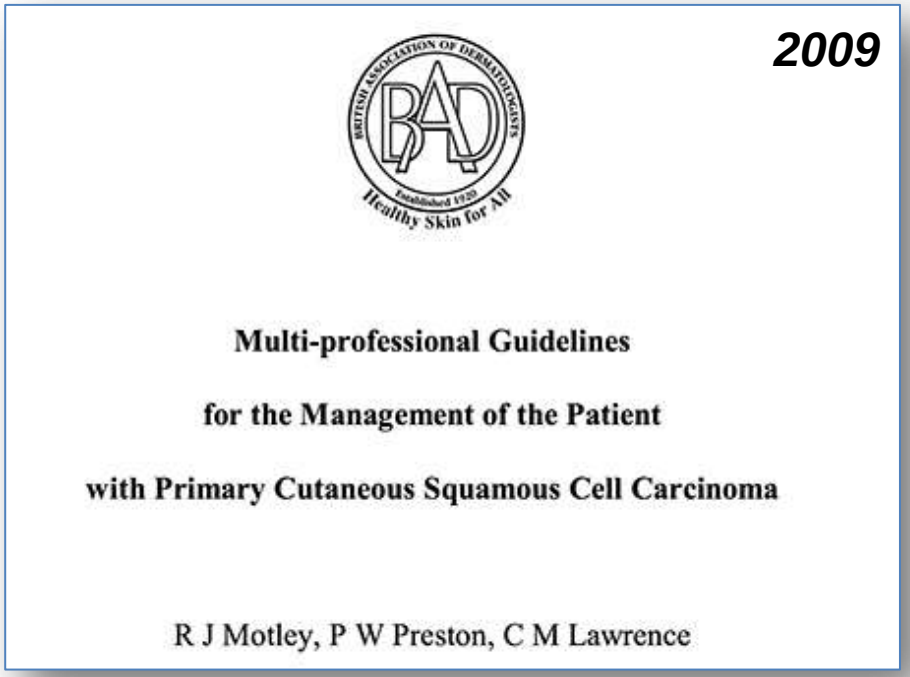
	No studies	No patients	Pooled estimate local recurrence	Regional recurrence
Mohs' micrographic surgery	16	1572	3.0%	4.2%
Standard excision	12	1144	5.4%	4.4%
Radiotherapy	13	1018	6.4%	2.6%

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**

NCRI Skin Cancer Clinical Studies Group

(NMSC Subgroup: dermatologists, oncologists, plastic surgeon/Mohs' surgeon, pathologist, consumer rep, statistician)

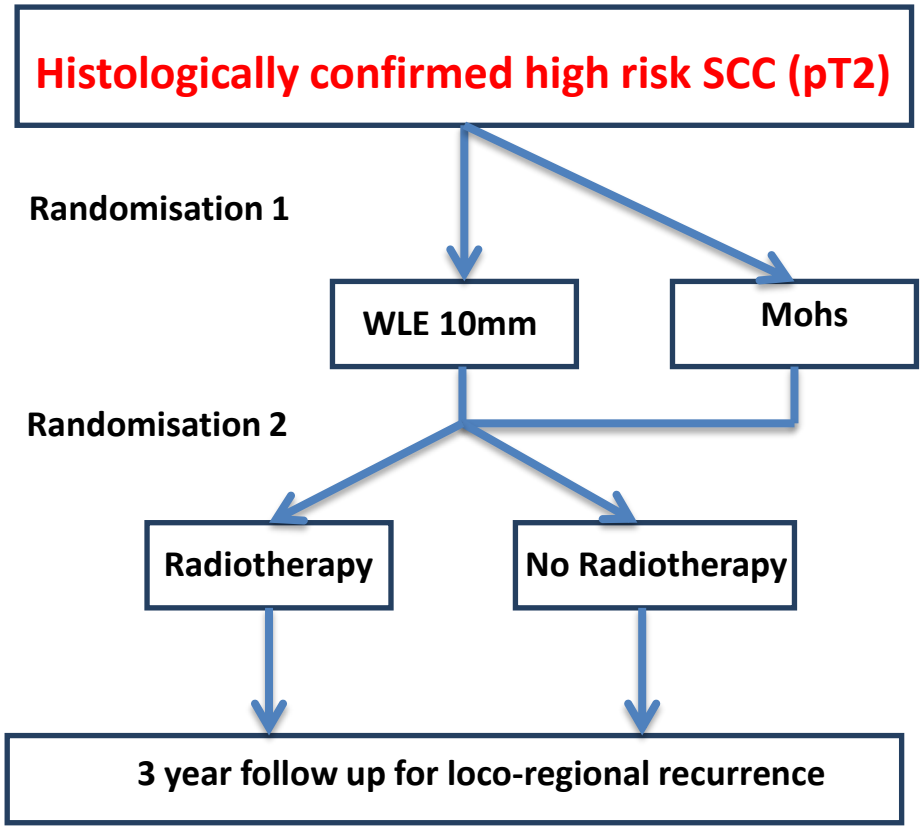
Proposal for a two-stage RCT for patients with high-risk primary SCC

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

COMMISSAR


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

The Royal College of Pathologists
Pathology: the science behind the cure

Standards and datasets for reporting cancers

Dataset for the histological reporting of primary cutaneous squamous cell carcinoma and regional lymph nodes (2nd edition)

October 2012, amended December 2012

Authors
Dr David Slater, Consultant Dermatopathologist, Sheffield Teaching Hospitals NHS Foundation Trust
Dr Maureen Walsh, Consultant Dermatopathologist, Royal Group of Hospitals, Belfast

Tis Carcinoma in situ
T1 <20mm diameter and <2 high risk features
T2 ≥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

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

STUDY

ONLINE FIRST

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

Arch Dermatol, 2013

Brigham & Women's Hospital T staging system

Built on 4 risk factors:

- **Tumour diameter ≥ 2cm**
- **Poorly differentiated**
- **Invasion beyond fat**
- **PNI in nerve calibre ≥0.1mm**

T1 = 0 risk factors

T2a = 1 risk factor

T2b = 2-3 risk factors

T3 = 4 risk factors or bone invasion

Evaluation of American Joint Committee on Cancer, International Union Against Cancer, and Brigham and Women's Hospital Tumor Staging for Cutaneous Squamous Cell Carcinoma. Karia et al, J Clin Oncol. 2013

Table 5. Comparison of Stage T2a and Stage T2b 5-Year Cumulative Incidences of Outcomes of Interest

	% (95% CI)			
Alternative T Stage	Local Recurrence	Nodal Metastasis	Disease-Specific Death	All-Cause Death
T2a	6 (2-14)	4 (2-12)	0 (No events)	24 (15-35)
T2b	18 (10-31)	37 (25-51)	20 (11-34)	47 (34-61)
χ^2 *P* value	.03	<.01	<.01	<.01

- **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 v BWH

Outcome	AJCC		BWH		
	T1	T2	T1	T2a	T2b
Local recurrence	2.9	9.2	3.2	7.9	16.1
Regional recurrence	0	4.9	1.3	4.5	9.7
Distant mets	0	0	0	0	0
SCC attributable death	0	1.5	0.7	4.7	0

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

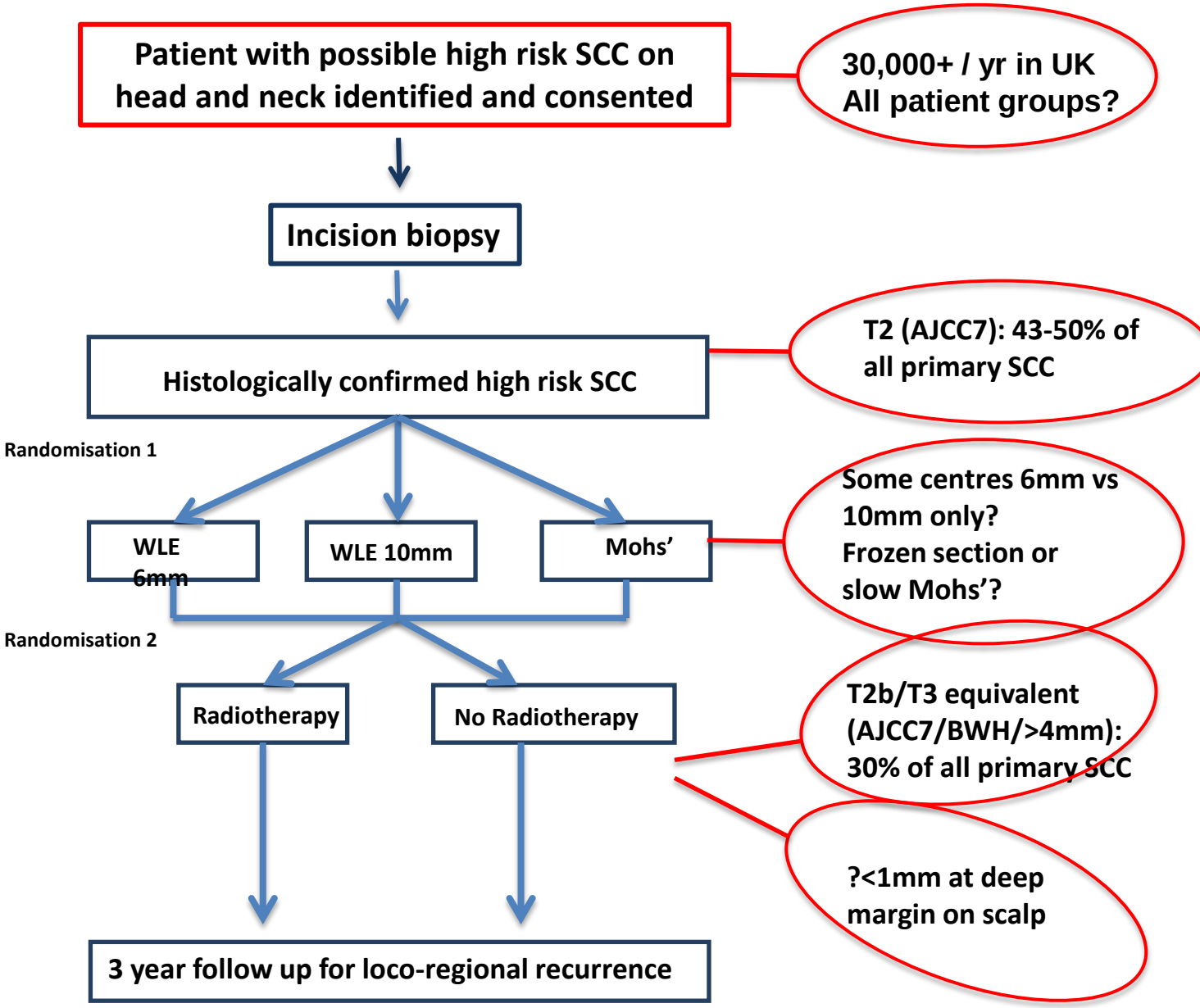
Postal questionnaire (n=24/29)
Focus group (n=7)

- **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

Input from the NFORC meeting *(January 2015)*

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
30,000+ / yr in UK
All patient groups?
Incision biopsy
Histologically confirmed high risk SCC
T2 (AJCC7): 43-50% of all primary SCC
Randomisation 1
WLE 6mm
WLE 10mm
Mohs'
Some centres 6mm vs 10mm only?
Frozen section or slow Mohs'?
Randomisation 2
Radiotherapy
No Radiotherapy
T2b/T3 equivalent (AJCC7/BWH/>4mm): 30% of all primary SCC
?<1mm at deep margin on scalp
3 year follow up for loco-regional recurrence

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

COMMISSAR

Feasible?
Recruitable?
Other concerns / comments?

Other trials we should be doing instead ?!!