2013 Position Paper:
Follow-Up of High Risk Cutaneous Melanoma in the UK

Authors *Larkin, Acland, Algurafi, Allan, Barlow, Board, Brown, Burrows, Chao, Clarke, Cook, Corrie, Dalgleish, Danson, Evans, Faust, Goodman, Gore, Harries, Harwood, Herbert, Highley, Hill, Kumar, MacKie, Marples, Marsden, Marshall, Middleton, Moncrieff, Mowatt, Mulatero, Nathan, S Nicholson, M Nicolson, Nobes, Ottensmeier, Patel, Plummer, Powell, Steven, Szlosarek, Talbot, Wagstaff, Waterston, Westwell, Yousaf, Lorigan*

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Contents

Introduction

There have been dramatic changes in the outcomes for patients with advanced melanoma in the past four years, with further improvements expected over the next few years. This position paper reports the consensus view of the majority of UK clinicians treating melanoma patients on how to follow up and investigate patients at a high risk of recurrence. It represents a significant departure from the BAD/MSG Guidelines published in 2010 and is intended as a framework to inform clinical teams treating patients with melanoma.

This is a dynamic field of medicine and we expect there to be debate over these recommendations. Comments are welcome and we will consider them when making future revisions. (Contacts: paul.lorigan@christie.nhs.uk or james.larkin@rmh.nhs.uk)

Surveillance of patients with resected cutaneous melanoma

Existing UK recommendations for melanoma surveillance were developed at a time when systemic therapy for advanced disease was largely ineffective. Over the past three years there have been significant advances in melanoma treatment. Two new agents, ipilimumab and vemurafenib, have been licensed and are available in the UK, both having shown significant survival benefits in pivotal Phase 3 trials (1, 2). Due to its mechanism of action, ipilimumab may work better in patients with low volume, asymptomatic disease. Dabrafenib and trametinib have been licensed by the FDA and EMA (3, 4). A number of other new drugs and combinations are showing significant activity, with an expectation that these will further improve survival for patients with advanced melanoma (5, 6, 7).

Historically, UK follow-up guidelines for patients at a high risk of recurrence have been conservative because there was no randomised evidence to support an intensive follow-up; neither were there any treatments that significantly improved survival for patients with advanced disease. The first assertion remains largely correct, though the poorer survival seen for UK patients compared with other European countries may reflect more advanced disease at presentation (8). We have considered in detail whether a trial comparing more intensive with less intensive follow up is warranted now. The conclusion of the majority was that the treatment landscape for patients is currently so unstable – with treatment algorithms changing very rapidly and new treatments having potential to dramatically improve survival – that it would impossible to identify a primary endpoint that would accurately reflect the reason for the study. It is anticipated that this will change in the next three to five years, and a study at that stage could become feasible.

A new surveillance policy (including imaging) is therefore necessary, aimed at identifying and treating patients with low volume recurrent disease earlier, including those with brain disease. This is particularly important to maximise the benefits of immunotherapy, where steroid use to control symptoms due to bulky disease negatively impacts on outcome (9). Evidence from the BRIM 2 study also

suggests that those patients most likely to get prolonged benefit from vemurafenib have earlier stage and less bulky disease (10). Waiting for patients to develop symptoms and bulky disease, with a consequent reduction of performance status and risk of a steroid requirement, is illogical as it is likely to render some of the newer therapies less effective.

Recent attention to the cancer risks of ionizing radiation has prompted debate about how to quantify the risks of diagnostic imaging, and how these risks need to be incorporated into the decision-making process when making recommendations for patient care. There is good evidence of a linear-no-threshold dose-response model, with an increase incidence of a range of rare and common cancers (11, 12, 13). Added to this is the risk of false-positive investigations, resulting in unnecessary further investigations with the associated implications for patients and the NHS. We have sought to quantify the radiation risk associated with regular imaging, so that this can be discussed with patients (Appendix B). Based on the imaging guidelines set out below (ie, nine scans in five years) the risk of a cancer in the lifetime of a 40-49 year old in normal health is an additional 0.6%, compared to the overall cancer risk from all causes of 40%. Risks are higher in younger patients and lower in older patients (14, 15, 16).

Typical lifetime risk		
CT Thorax, abdomen, pelvis	0.05%	per scan
CT Head	0.007%	per scan
PET-CT	0.06%	per scan
All follow-up imaging	0.6%	9 scans over 5 years
Overall cancer risk	40%	from all causes

There is no agreed definition of 'high risk' melanoma, but the AJCC staging system allows accurate prediction of five- and ten-year survival (17). Many clinicians would agree that patients with an expected five-year survival of ≤ 50% would be considered high risk and recent adjuvant therapy studies have included these patients. Patients with high risk disease have a very high risk of relapse for the first three years, with at least 60% of all recurrence occurring within this period. The risk of recurrence reduces significantly thereafter.

Recommendations

1. DEFINITION OF HIGH RISK (*new recommendation)*

The definition of 'high risk' melanoma should be agreed at a local level by the Specialist Skin Multidisciplinary Team (SSMDT).

Based on the entry criteria of a number of adjuvant studies, our recommendation is that the following should be considered high risk:

i. Any patient with satellite, in-transit or macroscopic nodal disease;
ii. Sentinel node positive patients deemed high risk (five year survival ≤50%) following SSMDT review of sentinel node pathology;
iii. Patients with T4b tumours.

2. SURVEILLANCE

Clinical review ***(unchanged from BAD/MSG Guidelines 2010)***

Recommendations for clinical review:

Years 1-3	3-monthly
Years 4-5	6-monthly
Years 6-10	annual

Blood tests ***(unchanged from BAD/MSG Guidelines 2010)***

No blood tests are recommended for routine surveillance.

There are currently no randomised data to support blood tests, although this is common practice in many units.

Imaging ***(new recommendation)***

CT scanning of the thorax, abdomen and pelvis is a standard imaging technique for melanoma. MRI offers better sensitivity and specificity with no radiation dose for imaging of the CNS compared with CT. PET CT affords higher sensitivity and specificity than conventional CT imaging and is particularly suited for lower limb

evaluation with comparable radiation dose to CT Thorax, abdomen and pelvis (18). Melanoma of the neck region should have MR surveillance in view of thyroid radiation dose considerations.

The implications of a positive brain scan for patients are significant. Whilst some patients may be treated successfully with surgery or stereotactic radiosurgery, for most the prognosis is very poor. Balancing the potential benefits of earlier treatment of asymptomatic disease (smaller volume, no requirement for steroids) against the impact on patients not being allowed to drive can only be done on an individual patient basis.

We recommend that surveillance should include imaging of the brain, but individual patient preference must be taken in to account.

Imaging surveillance recommendations

i. The patient must be aware and informed of the risk benefit of imaging protocols;

ii. The choice of modality will be determined by the local MDT.

iii. Imaging:

- CT chest, abdomen and pelvis ***or*** PET CT total body
  plus
- MRI head

iv. Imaging Frequency:

- Baseline
- Repeat 6 monthly to 3 years
- Then repeat annually to 5 years

3. MOLECULAR TESTING *(new recommendation)*

For patients with metastatic disease, molecular testing of the tumour to determine suitability for targeted therapy is now the standard of care. There is evidence that the type of mutation varies with age: eg, BRAF V600E mutations are more common in younger patients and BRAF V600K mutations are more common in older patients,

while the sensitivity and specificity of different molecular tests for determining these mutations varies (12). There are some reports of change in mutation status during disease progression, indicating that the most recent tissue available should be tested.

Molecular testing recommendations

i. All patients having follow up cross-sectional imaging should have tumour testing for BRAF mutations;

ii. The most recent tissue available should be tested;

iii. A clear Standard Operating Procedure (SOP) for managing samples must be in place, with particular reference to sample quality.

Appendix A: References

1 Hodi FS et al. ***Improved survival with ipilimumab in patients with metastatic melanoma.*** N Engl J Med. 2010;363(8):711-23.

2 Chapman PB et al. ***Improved survival with vemurafenib in melanoma with BRAF V600E mutation.*** N Engl J Med. 2011;364(26):2507-16.

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5 Flaherty K et al. ***Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations.*** N Engl J Med. 2012;367(18):1694-703.

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11 Pearce MS, et al. ***Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study.*** Lancet 2012;380:499-505.

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13 Sodickson A et al. ***Recurrent CT, Cumulative Radiation Exposure and Associated Radiation-induced Cancer Risks from CT of Adults.*** Radiology 2009; 251(1):175-84.

14 HPA-CRCE-012 ***Frequency and collective dose for medical and dental X-ray examinations in the UK,* 2008**
http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1287148001641

15 HPA-CRCE-028 ***Radiation Risks from Medical X-ray Examinations as a Function of the Age and Sex of the Patient***
http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317131197532

16 ARSAC ***Notes for Guidance***
http://www.arsac.org.uk/notes_for_guidance/documents/ARSACNFG2006Corrected2011.pdf

17 Balch C et al. ***Final version of 2009 AJCC melanoma staging and classification.*** J Clin Onc. 2009;27(36);6199-206.

18 Xing Y, et al. ***Contemporary diagnostic imaging modalities for the staging and surveillance of melanoma patients: a meta-analysis.*** J Natl Cancer Inst 2011;103:129–142.

Appendix B:
Doses for follow-up imaging for cutaneous melanoma

This appendix provides estimates of dose and risk for CT scans of: the thorax, abdomen and pelvis; CT scans of the brain; and PET-CT scans for tumour imaging.

Doses are stated in the form of effective dose in mSv and have been taken from Public Health England (Report HPA-CRCE-012) and the ARSAC Notes for Guidance. Risk calculations are based on age-, sex- and exam-specific risk coefficients published by PHE (Report HPA-CRCE-028) and are for individuals of normal health in each of those categories.

Effective doses are not intended for individual dose and risk assessment, but rather for the purposes of comparing radiation exposures to populations. However, they may be used as a guide in decision-making and communication with patients. Irrespective of the magnitude of the dose, all medical exposures should be justified as providing a net benefit to the patient.

Typical doses

The average doses for the scans range from 1.4 mSv to 11 mSv for a PET-CT with a low dose CT scan. This is equivalent to approximately 8 months to 5 years exposure to natural background radiation in the UK.

	Average dose (mSv)
CT Thorax, abdomen, pelvis	10.0
CT Head	1.4
PET-CT	11.0
Annual UK background radiation	2.2

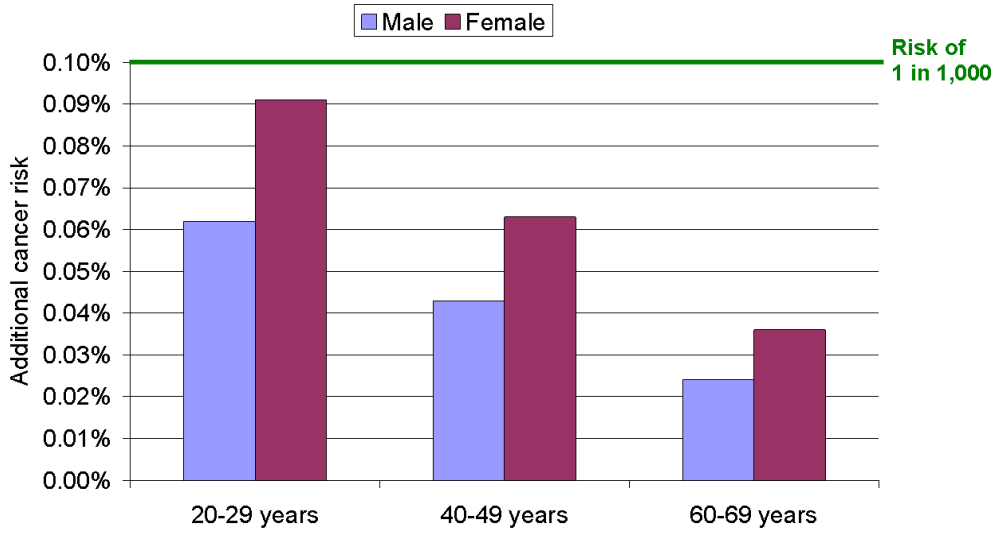
Typical risks

Most scans fall into the 'low risk' category (risks between 1 in 1,000 and 1 in 10,000), with the CT head scans of older patients being 'very low risk'. For patients that are followed-up with CT head and either CT thorax, abdomen and pelvis or PET-CT scans, the cumulative risk over 5 years would be 0.6% (approximately 1 in 200).

	Typical risk	Timescale
CT Thorax, abdomen, pelvis	0.05%	per scan
CT Head	0.007%	per scan
PET-CT	0.06%	per scan
All follow-up imaging	0.6%	over 5 years
Overall cancer risk from all causes	40%	over lifetime

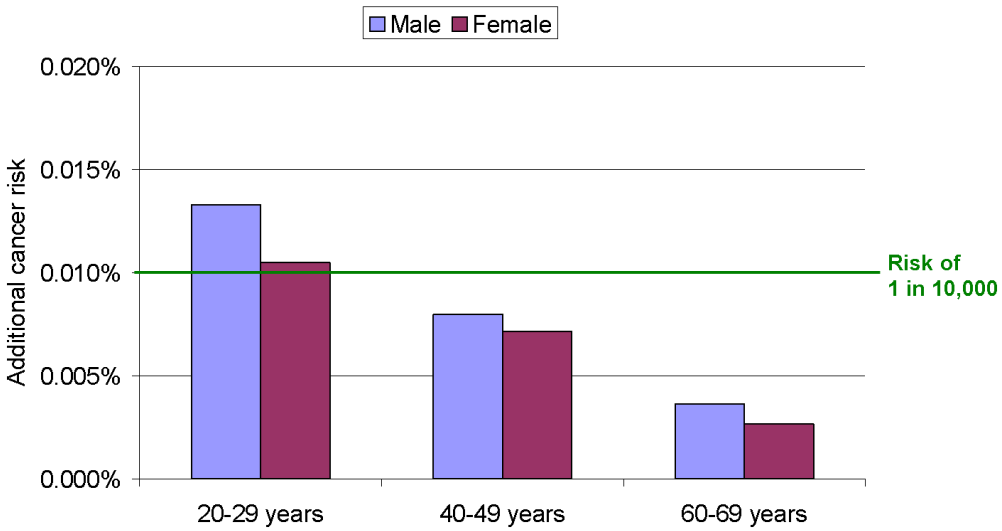
CT Thorax, Abdomen and Pelvis average dose: 10 mSv

Age (years)	Sex	Additional cancer risk	1 in X risk	Risk category
20-29	Male	0.06%	1600	Low
	Female	0.09%	1100	Low
40-49	Male	0.04%	2300	Low
	Female	0.06%	1600	Low
60-69	Male	0.02%	4200	Low
	Female	0.04%	2800	Low



CT Head average dose: 1.4 mSv.

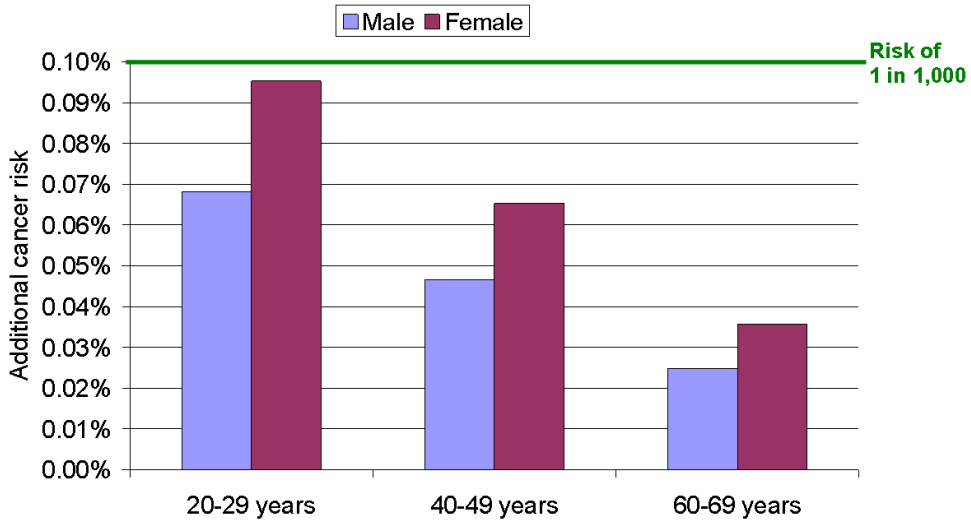
Age (years)	Sex	Additional cancer risk	1 in X risk	Risk category
20-29	Male	0.013%	7500	Low
	Female	0.011%	9500	Low
40-49	Male	0.008%	12500	Very low
	Female	0.007%	14000	Very low
60-69	Male	0.004%	27500	Very low
	Female	0.003%	37500	Very low



PET-CT average dose: 11 mSv

The average dose from the radiopharmaceutical (FDG) used in a PET scan is 8 mSv. A PET examination includes a CT scan. It is usually possible to use a lower dose scan for PET-CT than for CT on its own. The table and figures below give the combined risks for the radiopharmaceutical administration and CT scan with a dose of 3 mSv.

Age (years)	Sex	Additional cancer risk	1 in X risk	Risk category
20-29	Male	0.07%	1500	Low
	Female	0.10%	1000	Low
40-49	Male	0.05%	2200	Low
	Female	0.07%	1500	Low
60-69	Male	0.02%	4000	Low
	Female	0.04%	2800	Low



Links to documents

- HPA-CRCE-012 Frequency and collective dose for medical and dental X-ray examinations in the UK, 2008
  http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1287148001641

- HPA-CRCE-028 Radiation Risks from Medical X-ray Examinations as a Function of the Age and Sex of the Patient
  http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317131197532

- ARSAC Notes for Guidance
  http://www.arsac.org.uk/notes_for_guidance/documents/ARSACNFG2006Corrected2011.pdf

Appendix C: Authors' full names and institutions

	Name	Institution
1	Acland, Dr Katherine	Guy's and St Thomas' NHS Foundation Trust
2	Algurafi, Dr Hafiz	Southend University Hospital NHS Foundation Trust
3	Allan, Dr Rosemary	St George's Healthcare NHS Trust
4	Barlow, Dr Clare	Taunton and Somerset NHS Foundation Trust
5	Board, Dr Ruth	Lancashire Teaching Hospitals NHS Foundation Trust
6	Brown, Dr Ewan	Western General Hospital, Edinburgh
7	Burrows, Dr Lorna	Salisbury NHS Foundation Trust
8	Chao, Dr David	Royal Free Hospital, London
9	Clarke, Dr Amanda	Maidstone and Tunbridge Wells NHS Trust
10	Cook, Prof Martin	Royal Surrey County Hospital NHS Foundation Trust
11	Corrie, Dr Pippa	Cambridge University Hospitals NHS Foundation Trust
12	Dalgleish, Prof Angus	St George's, University of London
13	Danson, Dr Sarah	Weston Park Hospital, Sheffield
14	Evans, Prof Jeff	The Beatson Institute for Cancer Research, Glasgow
15	Faust, Dr Guy	Northampton General Hospital NHS Trust
16	Goodman, Dr Andrew	Royal Devon and Exeter NHS Foundation Trust
17	Gore, Prof Martin	Royal Marsden NHS Foundation Trust
18	Harries, Dr Mark	Guy's and St Thomas' NHS Foundation Trust
19	Harwood, Prof Catherine	Centre for Cutaneous Research Blizard Institute of Cell and Molecular Science Barts and the London School of Medicine and Dentistry, Queen Mary University of London
20	Herbert, Dr Chris	University Hospitals Bristol NHS Foundation Trust
21	Highley, Dr Martin	Plymouth Hospitals NHS Trust, Derriford Hospital,
22	Hill, Prof Jonathan	Lancashire Teaching Hospitals NHS Foundation Trust
23	Kumar, Dr Satish	Velindre Hospital, Cardiff
24	Larkin, Dr James	The Royal Marsden NHS Foundation Trust
25	Lorigan, Dr Paul	The Christie NHS Foundation Trust
26	MacKie, Prof Rona	University of Glasgow
27	Marples, Dr Maria	St James's University Hospital, Leeds
28	Marsden, Dr Jerry	University Hospitals Birmingham NHS Foundation Trust
29	Marshall, Dr Ernie	Clatterbridge Centre for Oncology NHS Foundation Trust
30	Middleton, Prof Mark	Oxford University Hospitals NHS Foundation Trust
31	Moncrieff, Mr Marc	Norfolk & Norwich University Hospital NHS Foundation Trust
32	Mowatt, Mr David	The Christie NHS Foundation Trust
33	Mulatero, Dr Clive	St James's Institute of Oncology, Leeds
34	Nathan, Dr Paul	East and North Hertfordshire NHS Trust
36	Nicholson, Dr Stephen	Imperial College Healthcare NHS Trust, London
35	Nicolson, Dr Marianne	Aberdeen NHS Grampian
37	Nobes, Dr Jenny	Norfolk & Norwich University Hospitals NHS Foundation Trust
38	Ottensmeier, Prof Christian	Southampton University Hospitals
39	Patel, Prof Poulam	Nottingham University Hospitals
40	Plummer, Prof Ruth	Newcastle Hospitals NHS Foundation Trust

41	Powell, Prof Barry	St George's, University of London
42	Steven, Dr Neil	University Hospital Birmingham NHS Foundation Trust
43	Sweetman, Dr Lorna	The Christie NHS Foundation Trust
44	Szlosarek, Dr Peter	Barts Health NHS Trust, London
45	Talbot, Dr Toby	Royal Cornwall Hospitals NHS Trust
46	Wagstaff, Prof John	Singleton Hospital, Swansea
47	Waterston, Dr Ashita	NHS Greater Glasgow and Clyde
48	Westwell, Dr Sarah	Brighton and Sussex University Hospitals NHS Trust
49	Yousaf, Dr Nadia	Imperial College Healthcare NHS Trust, London