FOLLOW UP OF CUTANEOUS MELANOMA IN THE UK

2022 update to the Melanoma Focus 2013 Position Paper

MELANOMA FOCUS

Follow-up of Cutaneous Melanoma in the UK

(2022 Update to the Melanoma Focus 2013 Position Paper)

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EXECUTIVE SUMMARY OF NEW RECOMMENDATIONS

(Please note: These are recommendations which should be tailored for individual patients as well as local radiology capacity and capability).

Stages	Risk level	Recommended follow-up
IA, IB, IIA	Low risk	Clinical review alone If SLNB considered but not done, do USS of draining lymph node basin/s (see additional notes on Pg 15)
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IIID or fully resected Stage IV	Very high risk	Clinical review + CT TAP (3 monthly year 1, 3-6 monthly years 2-3, annually years 4-5, then stop) + MRI head (6 monthly years 1-3, annually years 4-5, then stop, For brain mets treated with surgery/SRS, MRI head 3-6 monthly years 1-3, then consider longer follow-up intervals as clinically indicated. **If on adjuvant treatment see below***

* For patients on adjuvant systemic therapy, we recommend surveillance body scans every 3-4 months and head scans every 6 months whilst on treatment, and then as above after treatment, based on stage.

Introduction

There have been dramatic changes in the treatment options and clinical outcomes for patients with cutaneous melanoma in the past ten years. This position paper represents an update to the Melanoma Focus 2013 Position Paper, with new recommendations for the follow up of patients with resected Stage II, Stage III and Stage IV melanoma, based on the consensus views of a panel of melanoma experts in the UK. It is intended as a framework to inform clinical teams treating patients with melanoma.

This continues to be a very 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.

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Background

Since the 2013 Melanoma Focus Position Paper on follow-up for patients with cutaneous melanoma, there have been a number of significant developments in the management of cutaneous melanoma.

In January 2018 the American Joint Committee on Cancer (AJCC) published a new TNM staging system for cutaneous melanoma (Version 8). This revised the prognostic factors used to stage primary cutaneous melanoma and how they are combined to guide risk stratification, introduced new prognostic stage categories (Stage IIID and Stage IV M1d), and reported significantly improved survival statistics for patients with stage I-III melanoma (Gershenwald *et al*, 2017) compared to AJCC Version 7 (Balch *et al*, 2009).

Two large international clinical trials (DeCOG-SLT and MSLT-2) have provided practice changing evidence showing no survival benefit for Completion Lymph Node Dissection (CLND) in patients with a positive Sentinel Lymph Node Biopsy (SLNB) but no macroscopic (radiologically or clinically evident) lymph node disease (Leiter *et al*, 2016; Faries *et al*, 2017). Further detail on this can be found in the Melanoma Focus Sentinel Node Biopsy Guideline (Peach *et al*, 2020). As a result of this research, the practice of CLND for patients with positive SLNB but no macroscopic evidence of disease, has significantly reduced. This in turn has implications when considering follow-up guidelines for these patients.

Ongoing advances in both immunotherapy and targeted therapy have significantly increased the treatment options and survival outcomes for patients with unresectable Stage III or Stage IV disease. There is now clear evidence that patients treated with earlier stage and/or low volume disease are most likely to get prolonged benefit from these treatments (Robert *et al*, 2019; Larkin *et al*, 2019). This is particularly evident for immunotherapy treatment in patients with brain metastases, where steroid use to control symptoms due to bulky disease negatively impacts on outcome, whereas patients with asymptomatic/small volume metastases can have very good outcomes with surgery, stereotactic radiosurgery (SRS) and combination immunotherapy treatment (Long *et al*, 2018; Tawbi *et al*, 2017; Gaudy-Marqueste *et al*, 2017).

Adjuvant systemic therapy has now clearly demonstrated efficacy in improving both relapse free survival (RFS) and distant metastasis free survival (DMFS) for resected Stage III and

resected Stage IV melanoma (Ascierto *et al*, 2020; Dummer *et al*, 2020; Eggermont *et al*, 2021). Adjuvant pembrolizumab immunotherapy has also recently demonstrated improvement in RFS for patients with resected Stage IIB or IIC melanoma (Luke *et al*, 2021). In the UK the National Institute for Health and Care Excellence (NICE) approved pembrolizumab for the adjuvant treatment of resected Stage III melanoma in 2018 (based on the Keynote 054 study results) (Eggermont *et al*, 2018; Eggermont *et al*, 2021), nivolumab for the adjuvant treatment of resected Stage III and resected Stage IV melanoma in 2019 (based on the Checkmate 238 study) (Weber *et al*, 2017; Ascierto *et al*, 2020), and dabrafenib plus trametinib for the adjuvant treatment of BRAF mutant resected Stage III disease in 2018 (based on the COMBI-AD study) (Long *et al*, 2017; Dummer *et al*, 2020). Pembrolizumab for the adjuvant treatment of completely resected Stage IIB/C melanoma was approved by the US Food and Drug Administration (FDA) in December 2021 and is currently under review for this indication by the European Medicines Agency (EMA), with a decision expected early in 2022.

These adjuvant studies also provide robust data on patterns of melanoma recurrence, and demonstrate the frequency of distant metastases as first site of recurrence. For example, in the Keynote 054 study of patients with Stage III melanoma, distant metastasis as the first type of recurrence occurred in 23% of patients treated with adjuvant pembrolizumab and 33% of patients on placebo, with the brain as the first site of distant metastasis recurrence in 5% of patients treated with adjuvant pembrolizumab and 7% of patients on placebo (Eggermont *et al*, 2021). In the first interim analysis of Keynote 716 for patients with Stage IIB/C melanoma site of first recurrence was distant mets in 4.7% of patients in the pembro arm and 7.8% of patients in the placebo arm (Luke *et al*, 2021).

In addition to the improved treatment options and increased follow-up requirements due to improved survival, the incidence of melanoma continues to grow. It is now the fifth most common cancer in the UK and second commonest cancer in adults aged 25-49 (http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/skin-cancer/). These changes have occurred over a very short period of time, and have resulted in significantly increased resource utilisation and an impact on capacity in many centres.

Given the major changes to management and improvement in outcomes across all stages of melanoma, it is important to review how we follow-up these patients. In 2019 we conducted

a survey of colleagues across the UK who manage patients with melanoma. This showed that there was a lot of variation in practice, with much uncertainty and debate on this subject, as well as significant differences in ease of access to both MRI and PET-CT scanning. An update to the UK guidelines on surveillance follow-up for melanoma patients is therefore necessary. The aim of imaging surveillance follow-up remains the same as before, namely identifying and treating patients with low volume recurrent disease earlier, to maximise the benefits of treatment and improve survival, whilst balancing this against the risks of radiation exposure, patient anxiety and increased pressure on already stretched clinical resources.

Current published guidelines for melanoma surveillance

The European Society of Medical Oncology (ESMO) guidelines published in September 2019 (Michielin *et al*, 2019) commented that there is currently no consensus on how frequently patients should be followed up, including the use of surveillance imaging and blood tests. Recommendations vary from follow-up visits every 3 months, during the first 3 years and every 6-12 months thereafter, to no organised follow-up at all. The ESMO guidelines advise tailoring the intervals between clinical visits and imaging exams according to individual risk and personal needs of the patient. They recommend that sentinel node positive patients should be followed up with regular US examination, and note that sentinel node negative patients with T3b, T4a and T4b primary disease (ie: Stage IIB/C) have a high risk of relapse, with mortality at 10 years of about 20%.

The National Comprehensive Cancer Network (NCCN) guidelines published in March 2019 (Coit *et al*, 2019) recommend clinical review alone every 6-12 months for up to 5 years for Stage IA – IIA disease. For Stage IIB – IV resected disease with no evidence of disease (NED) the recommendations are clinical review every 3-6 months for years 1-2, every 3-12 months for years 3-5, then annually as clinically indicated. In addition, they recommend surveillance imaging every 3-12 months with CT thorax/abdomen/pelvis (CT TAP) with intravenous (IV) contrast, or whole-body FDG PET-CT. For neck imaging they recommend CT neck with IV contrast. Regarding brain scans, they advised MRI imaging periodically for up to 3 years in high risk patients (defined as Stage IIIC or higher). More frequent brain surveillance imaging is recommended for patients with prior brain metastases. Routine imaging after 3-5 years is not recommended.

In the UK, NICE has published two overarching melanoma guidelines: NICE guideline CSG8 (Improving outcomes for people with skin tumours including melanoma, published in 2006, last updated in 2010), and NICE guidance NG14 (Melanoma: assessment and management, published in 2015). An update to the NICE melanoma pathway was released in November 2020. Their recommendations on follow-up, based on AJCC version 7 staging system, are as follows:

- **Stage IA:** Clinical review 2-4 times during first year after completing treatment, then discharge.

- **Stage IB-IIC:** (with confirmed negative SLNB): Clinical review every 3 months for first 3 years, then every 6 months years 4 and 5, then discharge. No routine blood tests or scans.

- **Stage IIC (without SLNB) or Stage III:** Clinical review as per Stage IB-IIC. Consider surveillance imaging for those patients who would become eligible for systemic therapy as a result of early detection of metastatic disease if:
    - there is a clinical trial of the value of regular imaging, or
    - the specialist skin cancer MDT agrees to a local policy and specific funding for imaging 6-monthly for 3 years is identified.
    - the possible advantages and disadvantages of surveillance imaging are taken into account (Appendix B)
    - Previously the recommendations for this group were routine 6 monthly CT scans for first 3 years, then annually years 4 and 5, then stop. For routine brain imaging alongside body scans. Surveillance imaging not recommended for stage IIIA as 5 year survival >50% (based on AJCC v7 data).
- **Stage IV melanoma:** Offer a personalised follow-up to people who have had stage IV melanoma. Scan brain as part of fully staging disease.

With the introduction on the new AJCC version 8 staging system and significant developments in both treatment options and outcomes, the NICE guidelines are now quite out of date. NICE is in the process of updating both guidelines. A draft updated guideline was released for consultation in Jan 2022, with the final guidance planned for publication in July 2022.

Links to NICE documents:
https://www.nice.org.uk/guidance/csg8
https://www.nice.org.uk/guidance/ng14
https://www.nice.org.uk/guidance/indevelopment/gid-ng10155

In Australia guidelines last updated in 2018 by the Cancer Council Australia, in partnership with Melanoma Institute Australia, recommend no routine follow-up, blood tests or imaging for patients with AJCC version 8 Stage I – IIB melanoma. For Stage IIC and Stage III melanoma they recommend imaging every 3-12 months (CT or PET-CT scans) for the first 3 years of follow-up. MRI rather than CT scan is recommended for brain surveillance. They advise

annual clinical reviews up to 10 years post-surgery for Stage I melanoma, and more frequent reviews in the first 3 years, followed by annual reviews up to 8 years post-surgery for Stage II and Stage III melanoma.

[Cancer Council Australia Melanoma Guidelines Working Party. Clinical practice guidelines for the diagnosis and management of melanoma. Sydney: Cancer Council Australia. URL: https://wiki.cancer.org.au/australiawiki/index.php?oldid=213448. Available at: https://wiki.cancer.org.au/australia/Guidelines:Melanoma. Last accessed 10th December 2020]

For the previous 2013 Melanoma Focus Consensus Statement, patients with an expected five-year survival of ≤ 50% were considered high risk enough to warrant imaging surveillance follow-up. Based on the previous predicted five and ten survival figures with the AJCC TNM v7 staging system, this meant patients with Stage IIC, and Stage IIIB disease and above (Balch *et al*, 2009).

Patients with high risk disease are most likely to relapse in the first three years post-surgery, with at least 60% of all recurrences occurring within this period. The risk of recurrence reduces significantly thereafter. Based on this, for patients with "high risk" melanoma, the 2013 Consensus Statement recommended imaging surveillance with CT TAP or whole body PET-CT scan, plus MRI head, at baseline, every 6 months in years 1-3, and then annually in years 4-5 post-surgery.

With the version 8 AJCC staging criteria, the new predicted five and ten year melanoma specific survival figures are below (Gershenwald *et al*, 2017):

Stage (AJCC v8 staging)	**5 year survival rate**	**10 year survival rate**
IA	99%	98%
IB	97%	94%
IIA	94%	88%
IIB	87%	82%
IIC	82%	75%
IIIA	93%	88%
IIIB	83%	77%
IIIC	69%	60%
IIID	32%	24%

With these updated survival statistics, only patients with the new category of Stage IIID melanoma have a 5 year OS rate of <50% (the previous threshold for doing imaging surveillance during follow-up). However, the survey we conducted of melanoma experts across the UK in 2019 revealed a general consensus that imaging follow-up should still be done for patients with melanoma Stage IIC, IIIB and above, with some experts also advocating imaging surveillance for stage IIB and higher risk stage IIIA patients (essentially those who would meet the entry criteria for recent and ongoing trials of adjuvant systemic therapy). There are a number of reasons for this.

For patients with Stage II disease, whilst the individual risk of recurrence is low, these patients contribute to 30-50% of all melanoma deaths. Efforts are now being focused on trying to identify those patients who may relapse, and offer early treatment to those that do.

The outcomes for patients with inoperable Stage III and Stage IV disease have improved dramatically since the previous consensus statement was written. At that time, the expected median survival for Stage IV disease was 6-9 months and the expected survival for patients with asymptomatic brain metastases was 3-6 months. As a result of the recent advances in systemic treatment, the expected median survival for patients with Stage IV disease is now approximately 2 years but there is a wide range around this. For patients with symptomatic brain metastases, the expected median survival is approximately 12 months and long term survival is rare. (Vosoughi *et al*, 2018). For those patients with advanced melanoma who have good performance status and few adverse prognostic factors, and are fit for combination immunotherapy, the expected median survival is greater than 5 years and many patients will be cured by treatment (Wolchok *et al*, 2021). The routine use of systemic therapies that significantly improve outcomes, both after surgical resection of melanoma and for unresectable disease, justify the need to proactively identify patients with asymptomatic recurrent melanoma in order to ensure optimal access to life-extending and potentially life-saving interventions. Data from pivotal trials have helped identify the clinical factors that predict for long term survival. These include Performance Status, LDH and number of sites of metastases, all of which can potentially be influenced by speed of detection of recurrence.

Real world data support the benefits of regular imaging. In a retrospective review of 340 patients (seen at Memorial Sloan-Kettering Cancer Centre in New York between 1992 and

2004) symptomatic relapses were associated with shorter survival, compared with asymptomatic relapses detected by physician examination or surveillance scans (Romano *et al*, 2010). Following the publication of the Melanoma Focus 2013 Consensus Statement recommending routine imaging surveillance for "high risk" melanoma patients, a retrospective review of 173 patients managed at three UK tertiary centres (between July 2013 and June 2015) found that 66% of recurrences were asymptomatic and detected by surveillance scans (Lim *et al*, 2018). The most common sites of recurrence in this cohort were lymph nodes (60%) and lungs (37%). The median number of scans to the detection of relapse was 2 (range 1-5), as 65% of patients who relapsed did so within 1 year.

In the series by Lim *et al*, out of the 82 patients who relapsed, 6 patients (ie: 7.3%) had brain metastases at the time of recurrence, with 2 patients relapsing with brain-only disease. In the series by Romano *et al*, relapse with brain metastases occurred in 4% of patients with Stage IIIA disease, 7% with Stage IIIB disease and 13% with Stage IIIC disease (by AJCC v7 staging). Almost all relapses in the brain occurred within 3 years post-surgery (Romano *et al*, 2010).

Summary of background

The changes over the past 8 years mean that the stages of melanoma which are considered high risk enough to warrant imaging surveillance need to be re-defined. There is also a clear difference in survival across different Stage II and III groups, suggesting a binary definition of low risk and high risk disease is not sufficient to appropriately personalise surveillance follow-up.

Radiation risk review

It is now estimated that 1 in 2 people in the UK will be diagnosed with some form of cancer (not including non-melanoma skin cancer) during their lifetime. (https://www.cancerresearchuk.org/health-professional/cancer-statistics/risk/ lifetime-risk). Exposure to ionizing radiation from CT and PET-CT scans can increase this risk, and this needs to be weighed against the potential benefit of surveillance imaging. We have done an updated review of the radiation risk associated with regular imaging, to help inform discussions with patients. **Please see Appendix A for further details.**

2022 updated recommendations

1. CLASSIFICATION OF RISK

We recommend classifying all resected melanomas into one of 4 categories (low, moderate, high and very high risk), based on predicted risk of recurrence and Melanoma Specific Survival at 5 years. The definition of low / moderate / high / very high risk melanoma should be agreed at a local level by the Specialist Skin Multidisciplinary Team (SSMDT). Based on the AJCC v8 updated staging and Melanoma Specific Survival (MSS) curves (Gershenwald *et al*, 2017), we would recommend the following definitions:

1. Low risk (defined as MSS 5 year survival ≥ 90%)
   - ie: Stages I, IIA, IIIA (≤1mm deposit in SLNB).

2. Moderate risk (defined as MSS 5 year survival 80-90%)
   - ie: Stages IIB, IIC, IIIA (>1mm deposit in SLNB), 3B, and any patient whose primary melanoma has ≥11 mitoses per mm^2.

3. High risk (defined as MSS 5 year survival 60-80%)
   - ie: Stage IIIC.

4. Very high risk (defined as MSS 5 year survival <60%)
   - ie: Stages IIID and resected Stage IV.

2. REVISED SURVEILLANCE RECOMMENDATIONS:

(Please note: These are recommendations which should be tailored for individual patients as well as local radiology capacity and capability).

Stages	Risk level	Recommended follow-up
IA, IB, IIA	Low risk	Clinical review alone. If SLNB considered but not done, do USS of draining lymph node basin/s (see additional notes on Pg 15)
IIIA (≤1mm SLN deposit) Also earlier stages where SLNB considered appropriate but unable to complete.	Low risk Stage IIIA	Clinical review + USS of draining lymph node basin/s (6 monthly years 1-3, annually years 4-5, then stop) if not had CLND and not having cross-sectional imaging follow-up)
IIB, IIC IIIA (>1mm SLN deposit) IIIB Also earlier stages with high risk features (eg: primary with high mitotic rate).	Moderate risk	Clinical review + CT TAP/PET-CT & MRI head (6 monthly years 1-3, annually years 4-5, then stop) **If on adjuvant treatment see below***
IIIC	High risk	Clinical review + CT TAP/PET-CT & MRI head (6 monthly years 1-3, annually years 4-5, then stop) **If on adjuvant treatment see below***
IIID or fully resected Stage IV	Very high risk	Clinical review + CT TAP (3 monthly year 1, 3-6 monthly years 2-3, annually years 4-5, then stop) + MRI head (6 monthly years 1-3, annually years 4-5, then stop) For brain mets treated with surgery/SRS, MRI head 3-6 monthly years 1-3, then consider longer follow-up intervals as clinically indicated. **If on adjuvant treatment see below***

* For patients on adjuvant systemic therapy, we recommend surveillance body scans every 3-4 months and head scans every 6 months whilst on treatment, and then as above after treatment, based on stage.

3. Additional notes:

1. The patient must be informed of the risks and benefits of surveillance imaging (Appendix B).

2. The appropriateness of follow-up imaging and choice of modality should be determined by the treating clinician in discussion with the patient, taking into account patient factors (such as age, performance status, frailty and co-morbidities) and local factors such as radiology capacity and capability (appropriately trained ultra-sonographers, etc). However, the guidelines provided are considered a standard of care to be worked towards for patients whose life expectancy from other causes is expected to exceed their estimated melanoma specific survival.

3. The recommended CT and MRI imaging is with contrast, unless stated otherwise or there is a contra-indication to contrast.

4. For patients where SLNB is considered appropriate, as per the Melanoma Focus Sentinel Node Biopsy consensus statement (Peach *et al*, 2020) (ie: patients with pT2a - pT3a primary melanoma, and certain pT1b melanomas), but complete SLNB has not been possible for whatever reason (eg: there were too many draining lymph nodes, or the SLN was not identified or not accessible), and cross-sectional imaging follow-up is not indicated, we recommend USS follow up of all lymph node basins in which a SLN was identified (or the most likely draining LN basin for patients where a SLN was not identified). If Stage IB, consider USS 6 monthly in year 1, annually in years 2-3, then stop. If Stage IIA, consider 6 monthly in years 1-2, annually year 3, then stop.

5. For patients starting adjuvant treatment, we recommend baseline head and body scans within 6 weeks prior to commencing treatment, to exclude any recurrence.

6. If the primary melanoma was on the head or neck, imaging follow-up should include the neck, preferably MRI neck if possible (due to lower radiation risk to the thyroid with MRI vs CT).

7. Surveillance scans should include imaging of the brain, preferably MRI. Staging for patients with a new diagnosis of stage IV disease should also include brain imaging.

8. If MRI is contraindicated or not tolerated, CT head (+/- CT neck) is acceptable.

9. For younger patients (eg: age <30), we recommend considering a low radiation dose CT chest and MRI abdo/pelvis instead of a full dose CT TAP, because of the increased risk of radiation-induced cancer over time.

10. For pregnant patients the risks from CT and MRI will vary depending on the stage of pregnancy, and so appropriate imaging should be considered on a case by case basis, in discussion with a Radiologist, and if needed, a Medical Physics expert and/or Magnetic Resonance Safety Expert.

11. If the primary melanoma was truncal, then any locoregional recurrence is likely to be truncal and both CT and PET-CT should be equally sensitive at detecting such recurrence. If the primary was on a limb, then CT TAP would not pick up limb recurrence, whereas whole body PET-CT might. However, as most limb recurrences are palpable, either modality is acceptable for surveillance imaging, based on local preference and availability.

12. No blood tests are recommended for routine surveillance. Although this is common practice in many units, there are currently no randomised data to support doing routine blood tests as part of surveillance follow-up for melanoma. Retrospective reviews have not found any significant benefit from routine surveillance blood tests in picking up early recurrence.

Rationale for new recommendations

Below is a summary of the key discussion points that informed the development of this consensus statement, along with an indication of level of evidence and strength of recommendation, based on the 'Infectious Diseases Society of America – United States Public Health Service Grading System (Appendix C).

1. Classification of risk

Previously, melanoma was considered high risk if the expected five-year MSS was ≤50% (based on the AJCC v7 staging survival figures), and it was for these patients that imaging follow-up was recommended. With the publication of the new AJCC v8 staging criteria, the expected survival figures for all stages of melanoma have significantly improved. However, there is significance difference in survival for patients with Stage IIIC and IIID disease compared with earlier stages. It is also now evident that the risk of recurrence and death from melanoma in the first 12 months after surgery is significantly higher in patients with Stage IIID and resected Stage IV disease, compared with earlier Stage III disease. Thus, the new recommendations are to classify melanoma as low / moderate / high / very high risk, and to accordingly tailor a more individualised discussion of risk of recurrence, possible benefits of adjuvant treatment and follow-up surveillance imaging.

Moderate and high risk patients have similar published recurrence curves, and so we have recommended the same follow-up schedule for both groups. However their risk of melanoma related death is quite different. They are therefore presented separately in the recommendation table, as the discussion of risk vs benefit of both adjuvant treatment and surveillance imaging should be tailored accordingly.

Level of evidence: I

Strength of recommendation: A (strongly recommended)

2. Patients recommended to have surveillance follow-up imaging:

Previously surveillance imaging was only recommended for patients with a MSS ≤ 50%. However, there is now significant evidence to show that, if patients develop metastatic disease, the earlier this is detected, the better the chance of long-term response to systemic anti-cancer therapy (SACT) (Robert *et al*, 2019; Larkin *et al*, 2019). Therefore, the view of most melanoma experts surveyed was that imaging follow-up should now also be done for patients who have a five-year MSS >50%, and should include patients who would be potentially eligible for current ongoing trials of adjuvant therapy (ie: include patients with Stage IIB/IIC disease).

Level of evidence: II

Strength of recommendation: B (generally recommended)

3. Frequency of scans whilst on adjuvant systemic therapy:

For patients who receive adjuvant systemic therapy, we have recommended surveillance scans every 3-4 months whilst on treatment. This is in keeping with the frequency of scans done whilst on treatment in 3 landmark adjuvant studies (COMBI-AD, Checkmate 238 and Keynote 054), and reflects the current practice of most melanoma experts surveyed when preparing this revised statement. Although adjuvant treatment reduces the risk of recurrence, the rationale behind doing more frequent imaging whilst on treatment compared with surveillance follow-up alone is that this reduces the risk of continuing on with potentially harmful and costly systemic therapy when the disease has already recurred

Level of evidence: V

Strength of recommendation: B (generally recommended)

4. Imaging modality

Our recommendations on imaging modality are based on the following:

- CT scan of the thorax, abdomen and pelvis is a standard imaging technique for melanoma surveillance follow-up.
- MRI offers better sensitivity and specificity with no radiation dose for imaging of the brain compared with CT imaging.
- PET-CT provides a similar sensitivity and specificity to conventional CT imaging for detecting truncal metastases, but is better suited for evaluation of limbs for in-transit metastases.
- Modern PET-CT scans with a low dose CT component have a lower average radiation dose compared to CT Thorax, abdomen and pelvis (Appendix A) (Iball et al, 2017; Shrimpton et al, 2016).
- Capacity for MRI and PET scanning is variable across the UK.

Based on the above, we recommend the following:

- If the primary melanoma was truncal, then any recurrence is likely to be truncal and both CT and PET-CT should be equally sensitive at detecting such recurrence.
- If the primary was on a limb, then CT TAP would not pick up limb recurrence, whereas whole body PET-CT might. However, as most limb recurrences are palpable, either modality is acceptable for surveillance imaging, based on local preference and availability.
- If there is any evidence of truncal lymph node involvement (microscopic or macroscopic), the greatest risk of recurrence is visceral metastases, rather than limb recurrence, and so we recommend follow-up with CT TAP.

Level of evidence: V

Strength of recommendation: B (generally recommended)

5. Follow-up for patients with a positive SLNB

The optimum follow-up schedule for patients with a positive SLNB who do not undergo CLND is unclear. Also, the sensitivity of USS surveillance is operator dependent, and should only be used if the right skill set is available. In the MSLT2 study observation arm patients underwent USS of the draining lymph node basin every 4 months for the first 2 years of follow-up, then every 6 months during years 3 to 5. In the DeCOG-SLT study observation arm, the schedule was USS every 3 months and whole body imaging (CT/MRI/PET-CT or chest and abdominal US as a minimum) every 6 months for 3 years. The recurrence curve in the MSLT2 study showed the highest risk of recurrence in years 1-3 post SLNB (Faries *et al*, 2017). This, combined with a desire for USS surveillance frequency to match cross-sectional imaging follow-up for higher risk stages (for ease of reference) led to the following recommendation:

- For patients with low risk Stage IIIA melanoma, who do not undergo completion lymph node dissection, do not receive adjuvant therapy, and do not have cross-sectional imaging follow-up, we recommend USS surveillance of the draining lymph node basin/s every 6 months years 1-3, then annually years 4-5, then stop.

The same surveillance is recommended for patients where SLNB is considered appropriate, but has not been possible to do, as these patients have a worse nodal disease-free survival than patients with equivalent stage but confirmed negative SLN Moro *et al*, 2020).

Level of evidence: II

Strength of recommendation: B (generally recommended)

6. Surveillance brain imaging

The management of melanoma brain metastases remains a particular challenge, and the prognosis for many remains poor. The implications of a positive brain scan for patients are significant. For patients with a single or few brain metastases, a high rate of local control can be achieved with surgery and/or stereotactic radiosurgery. Also there is increasing evidence that both immunotherapy and targeted therapy can control brain metastases, particularly if the metastases are small and asymptomatic. We recommend that surveillance should include imaging of the brain, preferably MRI head, else CT head if MRI is contraindicated or unavailable. For patients with brain metastases treated with surgery/SRS, we recommend head scans every 3-6 months for up to 3 years, after which consider increasing follow-up intervals as clinically indicated. This is based on recommendation 7.2 of the ESMO consensus statement for the management of metastatic melanoma (published in Aug 2020), regarding clinical and imaging follow-up after stopping anti-PD1 therapy in patients with confirmed radiological control of disease (Keilholz *et al*, 2020).

Level of evidence: II
Strength of recommendation: A (strongly recommended)

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Appendix A:

Updated radiation risk assessment

Greater awareness of 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 increased incidence of a range of rare and common cancers (Sodickson et al, 2009; Pearce et al, 2012; Mathews et al, 2013).

We sought to quantify the radiation risk associated with regular imaging, in order that this can be discussed with patients. This appendix provides estimates of dose and risk for CT scans of: the thorax, abdomen and pelvis; CT scans of the head and neck; and PET-CT scans for tumour imaging. MRI scans do not involve ionising radiation and so do not pose a radiation risk.

The typical lifetime cancer risk from different scans is presented in the table below. The typical radiation dose per scan is presented later in this appendix.

Typical lifetime risk of cancer	
	Typical risk
Overall cancer risk from all causes	50%
CT Thorax, abdomen, pelvis scan	0.10 %
PET-CT scan	0.07 %
CT Head scan	0.01 %
CT Neck scan	0.02 %

The next table presents the estimated additional cancer risk in the lifetime of a 40-49 year old in normal health, if followed-up according to the whole body imaging guidelines recommended in this paper (i.e. between nine to fifteen CT TAP scans over five years).

Additional lifetime risk with recommended surveillance imaging schedule*
Surveillance imaging for Stage IIB – IIIC (without adjuvant treatment): **Max 9 x CT TAP over 5 years = 0.9% increased risk over lifetime**
Surveillance imaging for Stage IIB – IIIC (with adjuvant treatment): **Max 11 x CT TAP over 5 years = 1.1% increased risk over lifetime**
Surveillance imaging for Stage IIID – fully resected Stage IV (with or without adjuvant treatment): **Max 15 x CT TAP over 5 years = 1.5% increased risk over lifetime**

* Cancer risk for 40-49 year old in normal health

This estimated additional lifetime risk assumes an average life expectancy ≥10 years. Patients with a lower life expectancy are at significantly less risk of developing radiation-induced cancer from medical imaging (Lam et al, 2015). Risks are higher in younger patients because of the longer follow-up and the increased sensitivity of developing tissue to radiation. The risks are lower in older patients for the opposite reasons, as demonstrated later in this appendix.

If CT head is done instead of MRI head, the additional lifetime risk of cancer will be higher by 0.1-0.2%, as outlined below:

Additional lifetime risk* with recommended surveillance imaging schedule and CT head instead of MRI head
Surveillance imaging for Stage IIB – IIIC (without adjuvant treatment): **Max 9 x CT HTAP over 5 years = 1.0% increased risk over lifetime**
Surveillance imaging for Stage IIB – IIIC (with adjuvant treatment): **Max 11 x CT HTAP over 5 years = 1.2% increased risk over lifetime**
Surveillance imaging for Stage IIID – fully resected Stage IV (with or without adjuvant treatment): **Max 15 x CT HTAP over 5 years = 1.7% increased risk over lifetime**

* Cancer risk for 40-49 year old in normal health

If CT head & neck is done instead of MRI head & neck, the additional lifetime risk will be higher by 0.3-0.5%, as outlined below:

Additional lifetime risk* with recommended surveillance imaging schedule and CT head + neck instead of MRI head + neck
Surveillance imaging for Stage IIB – IIIC (without adjuvant treatment): **Max 9 x CT HNTAP over 5 years = 1.2% increased risk over lifetime**
Surveillance imaging for Stage IIB – IIIC (with adjuvant treatment): **Max 11 x CT HNTAP over 5 years = 1.4% increased risk over lifetime**
Surveillance imaging for Stage IIID – fully resected Stage IV (with or without adjuvant treatment): **Max 15 x CT HNTAP over 5 years = 2% increased risk over lifetime**

* Cancer risk for 40-49 year old in normal health

If PET-CT scans are used instead of CT TAP, the additional lifetime cancer risk will be slightly lower than with CT TAP follow-up (because of the low dose CT imaging used with most PET scans now, as explained below).

Typical radiation dose per scan

Doses are stated in the form of effective dose in mSv and have been taken from national surveys of computed tomography doses in the UK (Shrimpton et al, 2016; Iball et al, 2017; Holroyd et al, 2018) and the ARSAC Notes for Guidance. Risk calculations are based on age-, sex- and exam-specific risk coefficients published by PHE (HPA-CRCE-028 report) and are for individuals of normal health in each of those categories. They are tabulated for CT examinations. Risk coefficients for whole body uniform irradiation have been used for PET scans.

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.

The average doses for the scans range from 1.8 mSv for a CT head scan to 19 mSv for a CT Thorax, abdomen, and pelvis. This is equivalent to between approximately 8 months to 7 years exposure to natural background radiation in the UK. The average dose from the

radiopharmaceutical (FDG) used in a PET scan is 7.6 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 below gives the combined average dose lifetime risk for the radiopharmaceutical administration and CT scan with a dose of 6.9 mSv.

	Average dose (mSv)	% lifetime risk*
CT Thorax, abdomen, pelvis	19.0	0.10
PET-CT	14.5	0.07
CT Head	1.8	0.01
CT Neck	4.4	0.02
Annual UK background radiation	2.7	-

* Cancer risk for 40-49 year old in normal health

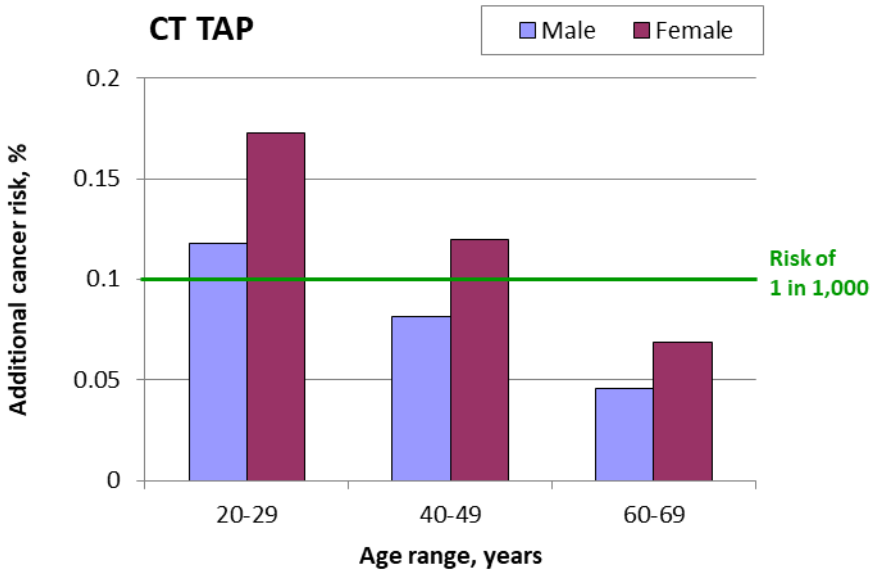
Risk categories for different scans by age:

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'. Body CT scans of younger patients fall into the 'moderate risk' category (risks between 1 in 100 and 1 in 1,000).

The following tables and graphs outline how the additional lifetime cancer risk per scan varies by age and sex.

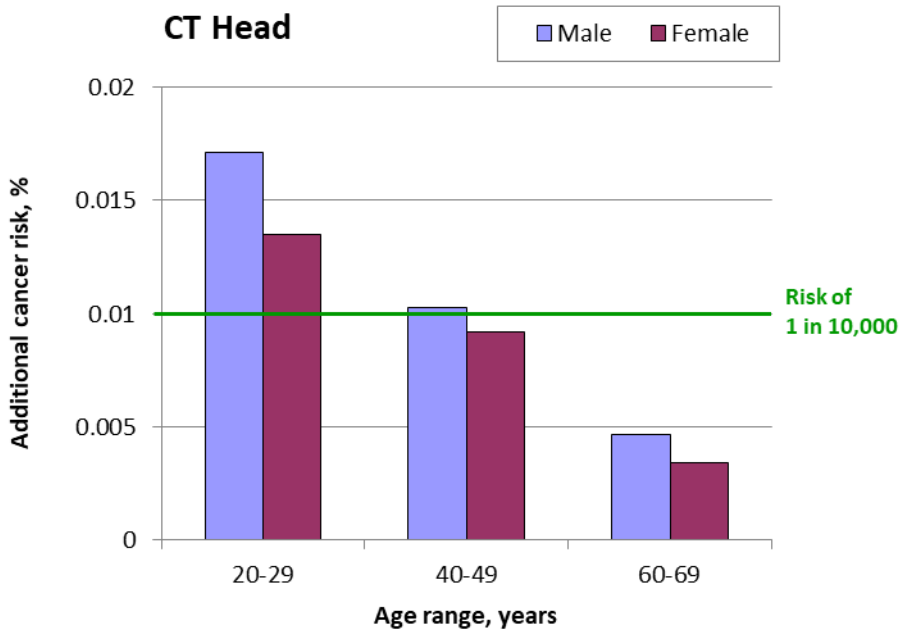
CT Thorax, Abdomen and Pelvis average dose: 19 mSv

Age (years)	Sex	Additional lifetime cancer risk	1 in X risk	Risk category
20-29	Male	0.12 %	800	Moderate
	Female	0.17 %	600	Moderate
40-49	Male	0.08 %	1200	Low
	Female	0.12 %	800	Moderate
60-69	Male	0.05 %	2200	Low
	Female	0.07 %	1500	Low



CT Head average dose: 1.8 mSv

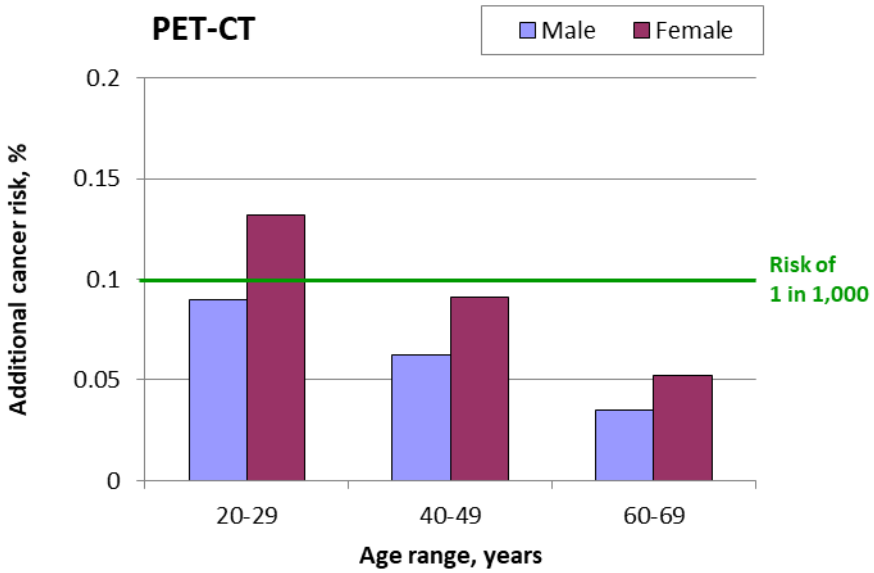
Age (years)	Sex	Additional lifetime cancer risk	1 in X risk	Risk category
20-29	Male	0.017 %	5800	Low
	Female	0.014 %	7400	Low
40-49	Male	0.010 %	9800	Low
	Female	0.009 %	10900	Very low
60-69	Male	0.005 %	21400	Very low
	Female	0.003 %	29200	Very low



PET-CT average dose: 14.5 mSv

As noted above the average dose from the radiopharmaceutical (FDG) used in a PET scan is 7.6 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 6.9 mSv.

Age (years)	Sex	Additional lifetime cancer risk	1 in X risk	Risk category
20-29	Male	0.09 %	1100	Low
	Female	0.13 %	800	Moderate
40-49	Male	0.06 %	1600	Low
	Female	0.09 %	1100	Low
60-69	Male	0.03 %	3000	Low
	Female	0.05 %	2100	Low



Links to documents

- HPA-CRCE-028 Radiation Risks from Medical X-ray Examinations as a Function of the Age and Sex of the Patient. Published 2011. http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317131197532

- ARSAC Notes for Guidance. Published 2020. **https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/912979/ARSAC_NfG_Sept_2020_FINAL_DRAFT_280820.pdf**

- https://www.cancerresearchuk.org/health-professional/cancer-statistics/risk#heading-Zero

Appendix B:

The possible advantages and disadvantages of surveillance imaging (adapted from the NICE melanoma pathway).

Possible advantages of surveillance imaging (having regular scans)	**Possible disadvantages of surveillance imaging**
Some people find it reassuring to have regular scans.	Some people find that having regular scans increases their anxiety.
Regular surveillance scans may pick up asymptomatic metastatic recurrence at an earlier stage, when surgical resection is still possible, or treatment with drugs can start earlier, which in turn is likely to lead to a better outcome.	Scans may show abnormalities that are later found to be harmless, causing unnecessary investigations and anxiety.
Surveillance scans of the brain can detect asymptomatic brain metastases, which respond better to treatment than symptomatic brain metastases. Also protective measures such as not driving can be taken earlier.	Scans expose the body to radiation, which can increase the risk of cancer in the future.
Surveillance scans during adjuvant therapy provide an opportunity to stop inappropriate and costly treatment early in the event of disease recurrence, and to adopt a more appropriate management plan sooner.	Regular imaging surveillance in resected Stage IIB/C and Stage III patients has significant resource implications.

Source: https://pathways.nice.org.uk/pathways/melanoma/melanoma-overview
[Accessed 10th December 2020]

Appendix C:

Levels of evidence:

I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity.
II	Small randomised trials or large randomised trials with a suspicious of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity.
III	Prospective cohort studies.
IV	Retrospective cohort studies or case-control studies.
V	Studies without control group, case reports, experts opinions.

Grades of recommendation:

A	Strong evidence for recommendation with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

Dykewicz CA. Summary of the guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. Clin Infect Dis 2001; 33: 139-144.

Appendix D:

Authors' full names (in alphabetical order) and institutions

Name	Institution
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Hook, Dr Jane	St James's University Hospital, Leeds
Larkin, Prof James	The Royal Marsden NHS Foundation Trust
Lorigan, Prof Paul	The Christie NHS Foundation Trust
Middleton, Prof Mark	Oxford University Hospitals NHS Foundation Trust
Mowatt, Mr David	The Christie NHS Foundation Trust
Nathan, Dr Paul	Mount Vernon Cancer Centre
Plummer, Prof Ruth	Newcastle Hospitals NHS Foundation Trust
Shaw, Dr Heather	Mount Vernon Cancer Centre
Waterston, Dr Ashita	The Beatson Institute for Cancer Research, Glasgow