

Appendix A1: Summary of evidence from surveillance

2019 surveillance of Melanoma: assessment and management (2015) NICE guideline NG14

Summary of evidence from surveillance

Focused searches were undertaken to identify evidence related to specific parts of the guideline. Studies identified in searches are summarised from the information presented in their abstracts.

Feedback from topic experts who advised us on the approach to this surveillance review was considered alongside the evidence to reach a view on the need to update each section of the guideline.

1.1 [Communication and support](#)

Recommendations in this section of the guideline

- 1.1.1 To help people make decisions about their care, follow the recommendations on communication, information provision and support in NICE's guideline on [improving outcomes for people with skin tumours including melanoma](#), in particular the following 5 recommendations:
- 'Improved, preferably nationally standardised, written information should be made available to all patients. Information should be appropriate to the patients' needs at that point in their diagnosis and treatment, and should be repeated over time. The information given must be specific to the histopathological type of lesion, type of treatment, local services and any choice within them, and should cover both physical and psychosocial issues.'
 - 'Those who are directly involved in treating patients should receive specific training in communication and breaking bad news.'
 - 'Patients should be invited to bring a companion with them to consultations.'

- 'Each LSMDT [local hospital skin cancer multidisciplinary team] and SSMDT [specialist skin cancer multidisciplinary team] should have at least one skin cancer clinical nurse specialist (CNS) who will play a leading role in supporting patients and carers. There should be equity of access to information and support regardless of where the care is delivered.'
 - 'All LSMDTs and SSMDTs should have access to psychological support services for skin cancer patients.'
- 1.1.2 Follow the recommendations on follow-up in NICE's guideline on [improving outcomes for people with skin tumours including melanoma](#), in particular the following 2 recommendations:
- 'All patients should be given written instruction on how to obtain quick and easy access back to see a member of the LSMDT/SSMDT when necessary.'
 - 'All patients should be given both oral and written information about the different types of skin cancer and instruction about self-surveillance.'
- 1.1.3 Give people with melanoma and their families or carers advice about protecting against skin damage caused by exposure to the sun while avoiding vitamin D depletion.
- 1.1.4 Carry out a holistic needs assessment to identify the psychosocial needs of people with melanoma and their needs for support and education about the likelihood of recurrence, metastatic spread, new primary lesions and the risk of melanoma in their family members.
- 1.1.5 Follow the recommendations on communication and patient-centred care in NICE's guideline on [patient experience in adult NHS services](#).

Surveillance proposal

This section of the guideline should be retained.

Communication and support

2019 surveillance summary

Information needs

In a multicentre cross-sectional survey (1) (n=529) over half of people with melanoma reported having unmet information needs. The presence of unmet information needs was more likely in

patients currently receiving medical treatment, among those aged at least 55 years, and in those who generally had a high need for condition-specific information. Most unmet information needs were for information on treatment and were reported by patients with tumour progression. There was no difference in presence or scope of unmet information needs between metastatic and non-metastatic melanoma patients.

A survey (2) of 100 stage I-II melanoma patients in follow-up showed that only a minority could accurately describe all 4 of their tumour characteristics (Breslow tumour thickness, presence of ulceration, mitosis and American Joint Committee on Cancer [AJCC] stage). Verbally delivered information was clearest for patients to understand compared with information in a melanoma brochure. Most patients considered YouTube videos on self-inspection of skin and regional lymph nodes to be of value. Most patients preferred information to be delivered via multiple routes, with the highest proportion favouring verbal delivery of information from their physician.

A survey (3) of melanoma patients (n=31) showed that the majority used the internet as a source of information on melanoma, with melanoma treatment, screening and prevention the most commonly searched topics. Most participants considered the internet a useful source of melanoma information and that it increased their understanding of their diagnosis. Over half found melanoma websites at least somewhat difficult to understand. The majority reported that using the internet to find melanoma information had influenced their treatment decision and over half considered it had impacted on their specialist consultation.

Support needs

A systematic review (4) considered psychosocial outcomes in advanced (stage III/IV) melanoma patients (n=52 studies). Patients who were receiving chemotherapy or interferon-alpha experienced decreased emotional and social function, with increased distress, while patients on newer treatments were

found to have better emotional and social function. Descriptive studies showed decreased emotional and social function and increased distress in patients with advanced compared with localised disease. Patients with advanced disease were also found to have more supportive care needs, in amount, quality and the timing of information on melanoma, communication and emotional support from clinicians.

A cross-sectional study (5) (n=254) of melanoma patients from a single centre reported that patient self-evaluation could be useful in identifying patients requiring psycho-oncological support.

In a cross-sectional study (6) of patients with early stage melanoma (n=204) almost half experienced distress symptoms and a quarter reported anxiety symptoms. Depressive symptoms were reported less frequently. Patients were found to apply positive and active coping strategies.

An observational study (7) (n=136) in people with stage IA melanoma identified high fear of progression in a third of those surveyed. Factors significantly associated with a higher fear of progression included female sex, younger age, being in employment, and cancer diagnosis in related persons.

In a survey (8) of 116 inpatients with skin cancer the support needs among people with melanoma were found not to differ compared with those with squamous cell carcinoma or other types of skin cancer.

Patients newly diagnosed with clinical stage IB-II invasive melanoma (n=386) were surveyed (9). Almost half reported having at least one moderate-level or high-level unmet need. Highest needs were for help relating to fear of cancer spreading,

information on recurrence risk, and on outcomes when spread occurred. Patients who had undergone sentinel lymph node biopsy (SLNB) were significantly more likely to have moderate or high unmet needs for help with uncertainty about the future or lymphoedema. Emotional wellbeing was found to be worse in the sample compared with the general population. Supportive care needs at 2 year follow-up were also reported (10) (n=386). Stressful life events and anxiety were associated with supportive care needs at enrolment. The proportion of patients with supportive care needs decreased over the first 6 months and decreased further by 24 months in people remaining disease-free. However, people with recurrence or development of another primary tumour reported supportive care needs. Age, depression, anxiety and other stressful life events predicted persistent needs.

Preferences for frequency of follow-up were surveyed in an Australian study of people treated for localised melanoma (11). Of 230 people without a recurrent or new primary melanoma, a greater proportion of people preferred a standard compared with fewer scheduled clinic visit option. Factors identified as independently associated with a preference for fewer visits were higher disease stage, melanoma on a limb, living with others, no private health insurance and visiting a specialist for another chronic condition.

A health needs survey (12) (n=160) of melanoma patients treated at a single centre identified that the most prevalent symptom was anxiety. Most surveyed patients reported that their health provider did not address their symptoms and over

half requested education on melanoma-specific issues.

Interventions for information and support

In a longitudinal study (13) (n=242) self-efficacy for skin self-examination was found to significantly increase immediately after an educational intervention. This increase was maintained at 3 months and 12 months post-intervention. Higher patient-reported physician support was significantly related to higher self-efficacy.

Intelligence gathering

A topic expert highlighted new evidence on the psychological, physical and social impact of disease on patients (summarised above).

The NICE guideline [Patient experience in adult NHS services: improving the experience of care for people using adult NHS services](#) (CG138, published 2012) is relevant to the topics of communication and support in [melanoma: assessment and management](#).

Impact statement

A topic expert noted that evidence was available (summarised above) on the psychological, physical and social impact of disease on patients.

This evidence emphasises the presence of information and support needs in people with melanoma.

The included studies show that information needs may vary between melanoma patients. This guideline recommends that information should be appropriate to patient needs, which is supported by this evidence. The included studies also indicated that patients may value information provided via alternative

or multiple routes, including verbal delivery of information and the use of the internet.

NICE guideline [CG138](#) (patient experience in adult NHS services: improving the experience of care for people using adult NHS services) includes recommendations on the provision of information to patients. CG138 recommends that patients be provided with information and the support needed to make use of the information to promote active participation in care and self-management (recommendation 1.5.11). CG138 also states that patients should be given both oral and written information (recommendation 1.5.12) and information in an accessible format (recommendation 1.5.13). Information should be tailored to patients based on their preferences about level and type of information (CG138 recommendation 1.5.14).

A relatively large longitudinal study identified in surveillance shows that an educational intervention improved patient self-efficacy for self-examination. CG138 recommends that patients should also be given the opportunity to enter any available evidence-based patient-educational activities, including self-management programmes (recommendation 1.5.29).

The studies identified in this surveillance review are not considered to have potential impact on existing recommendations. Following consultation, it is proposed that recommendations under this section will be retained.

New evidence is unlikely to change guideline recommendations.

1.2 [Assessing melanoma](#)

Recommendations in this section of the guideline

Dermoscopy and other visualisation techniques

See [implementation: getting started](#) for information about putting recommendation 1.2.1 into practice.

- 1.2.1 Assess all pigmented skin lesions that are either referred for assessment or identified during follow-up in secondary or tertiary care, using dermoscopy carried out by healthcare professionals trained in this technique.
- 1.2.2 Do not routinely use confocal microscopy or computer-assisted diagnostic tools to assess pigmented skin lesions.

Photography

- 1.2.3 For a clinically atypical melanocytic lesion that does not need excision at first presentation in secondary or tertiary care:
 - use baseline photography (preferably dermoscopic) **and**

- review the clinical appearance of the lesion, and compare it with the baseline photographic images, 3 months after first presentation to identify early signs of melanoma.

Assessing and managing atypical spitzoid lesions

- 1.2.4 Discuss all suspected atypical spitzoid lesions at the specialist skin cancer multidisciplinary team meeting.
- 1.2.5 Make the diagnosis of a spitzoid lesion of uncertain malignant potential on the basis of the histology, clinical features and behaviour.
- 1.2.6 Manage a spitzoid lesion of uncertain malignant potential as melanoma.

Taking tumour samples for genetic testing

- 1.2.7 If targeted systemic therapy is a treatment option, offer genetic testing using:
 - a secondary melanoma tissue sample if there is adequate cellularity **or**
 - a primary melanoma tissue sample if a secondary sample is not available or is of inadequate cellularity.

Genetic testing in early-stage melanoma

- 1.2.8 Do not offer genetic testing of stage IA–IIB primary melanoma at presentation except as part of a clinical trial.
- 1.2.9 Consider genetic testing of stage IIC primary melanoma or the nodal deposits or in-transit metastases for people with stage III melanoma.
- 1.2.10 If insufficient tissue is available from nodal deposits or in-transit metastases, consider genetic testing of the primary tumour for people with stage III melanoma.

Surveillance proposal

This section of the guideline should be updated.

Dermoscopy and other visualisation techniques

2019 surveillance summary

A Cochrane systematic review (14) (n=51 study cohorts) assessed the diagnostic accuracy of visual inspection for detecting cutaneous invasive melanoma and atypical intraepidermal melanocytic variants (e.g. melanoma in situ, lentigo maligna) in adults

with limited previous testing and in people referred for further evaluation of a suspicious lesion. Studies were categorised based on whether the diagnosis was recorded by in-person or remote (image-based) assessment. Visual inspection was compared in test accuracy studies with a reference standard of histological confirmation or clinical follow-up. Accuracy was significantly higher using in-person diagnosis compared with image-

based evaluation. The review concluded that visual inspection may result in melanomas being missed if used on its own.

A Cochrane systematic review (15) considered dermoscopy (with and without visual inspection) for the diagnosis of cutaneous invasive melanoma and atypical intraepidermal melanocytic variants in adults (n=103 study cohorts). Studies were categorised based on whether the diagnosis was recorded by in-person or remote (image-based) assessment. The reference standard was either histological confirmation or clinical follow-up. For both in-person and image-based assessments, meta-analysis demonstrated dermoscopy to be significantly more accurate than visual inspection alone. Use of a named or published algorithm to aid dermoscopy interpretation was not found to significantly affect accuracy for in-person or image-based assessments.

A Cochrane systematic review (16) (n=18 publications, n=19 study cohorts) assessed the diagnostic accuracy of reflectance confocal microscopy (RCM) for detecting cutaneous invasive melanoma and atypical intraepidermal melanocytic variants in adults with any lesion suspicious for melanoma and lesions difficult to diagnose. The reference standard was either histological confirmation or clinical follow-up. Studies were considered at high or unclear risk of bias across most domains, with high or unclear concern on applicability of evidence. Meta-analysis demonstrated that RCM was more accurate than dermoscopy in people with any lesion suspicious for melanoma and in people with lesions more difficult to diagnose. Assuming fixed sensitivity of 90% for both tests, specificities were 82%

for RCM and 42% for dermoscopy for any lesion suspicious for melanoma (9 RCM datasets). Based on a hypothetical population of 1000 lesions (at median observed melanoma prevalence of 30%), this would result in a reduction in unnecessary excisions of 280 with RCM compared with dermoscopy (30 melanomas being missed by both tests). In studies in equivocal lesions, specificities of 86% for RCM and 49% for dermoscopy were reported (7 RCM datasets). Based on the median observed melanoma prevalence of 20%, this would result in a reduction of unnecessary excisions of 296 for RCM compared with dermoscopy (20 melanomas being missed by both tests). The review concluded that RCM may have a potential useful role in clinical practice, especially in evaluation of lesions difficult to diagnose using visual inspection and dermoscopy alone.

A Cochrane systematic review (17) (n=2 study cohorts) assessed the diagnostic accuracy of smartphone applications to rule out cutaneous invasive melanoma and atypical intraepidermal melanocytic variants in adults with suspicious skin lesions. Smartphone applications were for use by individuals in a community setting. The reference standard was histological confirmation or clinical follow-up and expert opinion. No meta-analysis was performed due to limited availability of data and poor quality of studies, including high risk of bias for selective participant recruitment and high rates of non-evaluable images. Concerns about applicability were also noted (due to included lesions being already selected for excision in a dermatology clinic and due to image capture by clinicians as opposed to smartphone app users). Of the 5 mobile

phone applications studied, 4 were based on artificial intelligence applications that classed lesion images using an algorithm. The remaining one application used store-and-forward dermatologist review of lesion images. Sensitivities ranged from 7% to 98% and specificities from 30% to 94%. The authors concluded that current evidence was limited and associated with low methodological quality.

Intelligence gathering

A topic expert commented that recommendations on assessment (in addition to recommendations on management, surgical and medical management) of melanoma are now outdated and not fit for purpose (no further detail provided).

Impact statement

Topic expert feedback highlighted that recommendations on assessment of melanoma were outdated and not fit for purpose.

Visual inspection

One Cochrane systematic review concluded that visual inspection may result in melanomas being missed if used in isolation. This finding does not impact on recommendations, since visual inspection used on its own is not recommended in the guideline.

Dermoscopy

Dermoscopy was found to be more accurate in diagnosis than visual inspection alone in a Cochrane systematic review. Since the use of dermoscopy for assessment of pigmented lesions is already recommended in the guideline, this finding

does not impact on current recommendations.

Reflectance confocal microscopy

A Cochrane systematic review reported that RCM may reduce the number of people undergoing unnecessary surgery compared with dermoscopy. However, variation and uncertainty in results and in study conduct were noted in the review as potentially reducing the reliability of findings. Studies included in the guideline suggested that RCM was more sensitive but less specific than dermoscopy in classification of lesions as melanoma. Routine use of RCM was not recommended in the guideline due to clinical time required, potential cost and the relatively high false positive rate. The guideline committee noted the NICE Diagnostics Assessment Programme guidance on VivaScope 1500 and 3000 systems for detection and monitoring skin lesions. This guidance ([DG19](#), published November 2015) stated there was currently insufficient evidence to recommend routine adoption in the NHS for deciding whether to biopsy and excise skin lesions in people with suspected melanoma. Seven of the 18 publications included in the Cochrane systematic review were published in 2014 or more recently. However, the review authors noted the paucity of data to compare RCM with dermoscopy and concluded that further research to compare RCM and dermoscopy in well described cohorts with difficult to diagnose skin lesions is needed. Recommendation 1.2.2 states that confocal microscopy should not be routinely used to assess pigmented skin lesions. Further well-conducted research may impact on this recommendation in the future.

Smartphone applications

A Cochrane systematic review identified a small number of studies evaluating the use of smartphone applications in ruling out melanoma. The reported sensitivities and specificities were very variable, and the review authors concluded that the current evidence was limited. Recommendation 1.2.2 states that computer-assisted diagnostic tools should not be used to

assess pigmented skin lesions. Since the currently available evidence on the use of smartphones in diagnosis of melanoma is limited, further well-conducted research is needed to impact on this recommendation in the future.

New evidence is unlikely to change guideline recommendations.

Taking tumour samples for genetic testing

2019 surveillance review

No new relevant studies were identified under this heading in this surveillance review.

Intelligence gathering

A topic expert highlighted the need to update this section, noting that genetic testing is stage dependent and requires revision based on the 8th edition of the AJCC system. It was also raised that an ongoing trial of adjuvant immunotherapy for stage II melanoma may result in the

need for upfront genetic testing of earlier stage melanoma in the future.

Impact statement

A topic expert commented that this section would require update. However, no evidence in this area fulfilling the criteria of the current surveillance review was found. Since the recommendations under this heading do not refer to specific stages of melanoma that have been redefined under the 8th edition of the AJCC system, it is not anticipated that the current recommendations would be impacted.

New evidence is unlikely to change guideline recommendations.

Genetic testing in early stage melanoma

2019 surveillance review

Focused searches were undertaken to identify studies comparing genetic testing

of stage 1a-IIIc melanoma tumours at diagnosis with no genetic testing at diagnosis on outcomes. No eligible studies were identified.

Intelligence gathering

Topic experts commented on the need for the role of cancer genomics and genetic testing in early melanoma to be evaluated. It was noted by a topic expert that it was important to update recommendations on genetic testing in view of the increased availability of effective adjuvant therapies and the introduction of the 8th edition of the American Joint Committee on Cancer (AJCC) staging system. A topic expert also highlighted ongoing research on adjuvant immunotherapy for high risk stage II patients who may require upfront genetic testing in the future.

Impact statement

Topic experts highlighted a need to reconsider recommendations in this

section in view of the considerably expanded range of pharmacotherapies for later stage melanoma available since the publication of the guideline. Although no eligible research studies were identified that compared genetic testing at diagnosis with no testing at diagnosis, the introduction of the revised AJCC 8th edition of staging has potential to impact on recommendations 1.2.8, 1.2.9 and 1.2.10 under this heading since these recommendations refer to specific stages of cancer (namely IA, IB and III) that have been redefined under the new edition.

New evidence identified that may change current recommendations.

1.3 Managing suboptimal vitamin D levels

Recommendations in this section of the guideline

See [implementation: getting started](#) for information about putting recommendations 1.3.1 and 1.3.2 into practice.

- 1.3.1 Measure vitamin D levels at diagnosis in secondary care in all people with melanoma.
- 1.3.2 Give people whose vitamin D levels are thought to be suboptimal advice on vitamin D supplementation and monitoring in line with local policies and NICE's guideline on [vitamin D](#).

Surveillance proposal

This section of the guideline should not be updated.

Managing suboptimal vitamin D levels

2019 surveillance summary

No relevant evidence was identified in this surveillance review.

Intelligence gathering

In considering whether any guideline recommendations should be updated in the guideline, a topic expert queried whether vitamin D testing was required in this guideline and whether this should be

offered by general practitioners (GPs) to all patients rather than just melanoma patients (no further details provided).

Impact statement

A topic expert queried whether vitamin D testing was required as part of this guideline. However, no research evidence was identified in this surveillance review that would change current recommendations.

New evidence is unlikely to change guideline recommendations.

1.4 Managing concurrent drug treatment

Recommendations in this section of the guideline

- 1.4.1 Do not withhold or change drug treatment for other conditions, except immunosuppressants, on the basis of a diagnosis of melanoma.
- 1.4.2 Consider minimising or avoiding immunosuppressants for people with melanoma.

Surveillance proposal

This section of the guideline should not be updated.

Managing concurrent drug treatment

2019 surveillance summary

No new relevant evidence was identified for this section in this surveillance review.

Intelligence gathering

A topic expert commented that the guideline should consider the avoidance of antibiotics for patients on

immunotherapies (noting that receipt of antibiotics during immunotherapy may render treatment ineffective).

Impact statement

A topic expert flagged that the guideline should consider the potential negative impact of antibiotic use on effectiveness of immunotherapy. However, no evidence in this area fulfilling the criteria of the current surveillance review was found.

New evidence is unlikely to change guideline recommendations.

1.5 Staging investigations

Recommendations in this section of the guideline

Sentinel lymph node biopsy

See [implementation: getting started](#) for information about putting recommendation 1.5.2 into practice.

- 1.5.1 Do not offer imaging or sentinel lymph node biopsy to people who have stage IA melanoma or those who have stage IB melanoma with a Breslow thickness of 1 mm or less.
- 1.5.2 Consider sentinel lymph node biopsy as a staging rather than a therapeutic procedure for people with stage IB–IIC melanoma with a Breslow thickness of more than 1 mm, and give them detailed verbal and written information about the possible advantages and disadvantages, using the table below.

Possible advantages of sentinel lymph node biopsy	Possible disadvantages of sentinel lymph node biopsy
The operation helps to find out whether the cancer has spread to the lymph nodes. It is better than ultrasound scans at finding very small cancers in the lymph nodes.	The purpose of the operation is not to cure the cancer. There is no good evidence that people who have the operation live longer than people who do not have it.
The operation can help predict what might happen in the future. For example, in people with a primary melanoma that is between 1 and 4 mm thick: <ul style="list-style-type: none">● around 1 out of 10 die within 10 years if the sentinel lymph node biopsy is negative● around 3 out of 10 die within 10 years if the sentinel lymph node biopsy is positive.	The result needs to be interpreted with caution. Of every 100 people who have a negative sentinel lymph node biopsy, around 3 will subsequently develop a recurrence in the same group of lymph nodes.

<p>People who have had the operation may be able to take part in clinical trials of new treatments for melanoma. These trials often cannot accept people who haven't had this operation.</p>	<p>A general anaesthetic is needed for the operation.</p>
	<p>The operation results in complications in between 4 and 10 out of every 100 people who have it.</p>

Imaging

- 1.5.3 Offer CT staging to people with stage IIC melanoma who have not had sentinel lymph node biopsy, and to people with stage III or suspected stage IV melanoma.
- 1.5.4 Include the brain as part of imaging for people with suspected stage IV melanoma.
- 1.5.5 Consider whole-body MRI for children and young people (from birth to 24 years) with stage III or suspected stage IV melanoma.

Surveillance proposal

This section of the guideline should be updated.

Sentinel lymph node biopsy

2019 surveillance summary

A Cochrane systematic review (18) addressed the review question of whether lymph node biopsy followed by lymph node dissection (compared with observation) improves survival for people with localised skin cancer. A single randomised controlled trial (RCT) (MSLT-I, 2001 participants) was included in the review that compared SLNB with observation in adults with melanoma (published as 8 different reports from 2005 to 2014). Participants were required to have i) Clark level III and Breslow thickness ≥ 1.00 mm or ii) Clark level IV or V with any Breslow thickness. The MSLT-I trial was already identified and included in the guideline.

Focused searches were undertaken as part of this surveillance review to identify studies in people with melanoma stages IA to IV comparing benefits and harms between imaging modalities.

One primary study (19) was a retrospective analysis of correlation between dermoscopy structures and SLNB positivity in consecutive melanomas > 0.75 mm Breslow thickness (stage not reported). Dermoscopy features correlated with SLNB positivity included presence of ulceration and blotch, absence of pigmented network, and histological ulceration. Dermoscopy SCORE was predictive of sentinel lymph node status. Addition of sex and Breslow thickness (SCOREBRESEX) maintained sensitivity and increased sensitivity.

Intelligence gathering

Several topic experts stated that the use of SLNB in melanoma needed to be evaluated, with cited issues including uncertainty on appropriate requirements for undergoing SLNB, approval of adjuvant treatments for stage III disease and the AJCC 8th edition staging changes. One topic expert also noted costs due to a large increase in the numbers of SLNBs being performed.

The publication of a [consensus statement](#) on the use of SLNB by the Melanoma Focus group was raised in topic expert feedback. It was recommended in this consensus document that the NG14 guideline be reviewed and revised urgently, in view of changes in the surgical and non-surgical management of melanoma.

Topic experts emphasised that staging for melanoma had changed with the introduction of the revised 8th edition of the AJCC system, with feedback from external correspondence highlighting that guidance on SLNB was considered to be out of date as a result.

Impact statement

A Cochrane systematic review was identified that included 1 RCT (MSLT-I) that compared SLNB with observation. This primary study was already included in the guideline. Therefore, it is unlikely that this review would impact on guideline recommendations.

An additional primary study showed that dermoscopy features may predict SLN status in melanoma patients. This evidence does not impact on current recommendations.

Several topic experts and feedback from external correspondence advised that guidance on SLNB needed to be updated (for example with regards to patient eligibility for SLNB). One of the key issues emphasised was the introduction of the 8th edition of the AJCC staging system.

This change in staging may have potential impact on recommendations 1.5.1 and 1.5.2, since these recommendations refer to specific stage definitions which have altered as a result of the 8th edition of the AJCC system.

New evidence identified that may change current recommendations.

Imaging

Focused searches were undertaken to identify studies in people with melanoma stages IA to IV comparing benefits and harms between imaging modalities.

Several studies were identified that compared the use of a variety of imaging methods in staging of melanoma. These are summarised in the table below.

Study and population	Test(s)	Methods	Key results
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CT			
Hafstrom, 2017 (20) Head and neck cutaneous melanoma (n=198, stage 1b to 4b)	CT staging before SLNB	Design: Retrospective review of patients with primary T1b-T4b head and neck melanoma clinically asymptomatic for metastatic disease referred for SLNB Outcome(s): Identification of metastasis and additional primary tumour(s), diagnostic accuracy	Initial CTs identified clinically occult melanoma metastases in 8.1% patients and advanced second primary tumours in 3.5% of patients. CT results false negative in 1% and false positive in 6% patients
Holtkamp, 2017 (21) Melanoma (n=143) SLN-positive patients (stage not reported) (computed tomography [CT] n=102, positron emission tomography-computed tomography [PET/CT] n=41)	CT (of various regions of body) compared with whole-body PET/CT in routine staging	Design: Retrospective study of imaging in routine staging in asymptomatic SLN-positive patients Outcome(s): Diagnostic performance	Metastases identified in 2/143 patients (1.4% true positive yield). CT: sensitivity 11%, specificity 73%, positive predictive value 4% PET/CT: sensitivity 17%, specificity 57%, positive predictive value 6% PET/CT and CT have low yield and low PPV and of limited value in routine staging
¹⁸ F-FDG PET			
Faut, 2018 (22) Metastatic melanoma (226 inguinal lymph node (LN) dissections in 223 patients)	¹⁸ F-FDG PET + contrast-enhanced CT scan compared with ¹⁸ F-FDG PET + low dose CT scan	Design: Retrospective analysis of patients receiving inguinal LN dissection with pelvic LN dissection for metastatic melanoma. Factors associated with pelvic node involvement determined using multivariable logistic regression analysis.	¹⁸ F-FDG PET + contrast-enhanced CT scan: negative predictive value 86% ¹⁸ F-FDG PET + low dose CT scan: negative predictive value 78% Tested imaging techniques are not able to accurately predict pelvic nodal involvement.

		Outcome(s): Pelvic nodal involvement, diagnostic accuracy	
Cha, 2018 (23) Cutaneous melanoma (n=103 patients, stage not reported)	¹⁸ F-FDG PET/CT for initial staging or evaluation of recurrence compared with LN metastasis determined by CT	Design: LNs confirmed pathologically or by follow-up imaging included. Outcome(s): detection of regional LN metastasis	In all LNs: PET/CT maximum standardised uptake value (SUVmax) >2.51: sensitivity 73.1%, specificity 88.9%, accuracy 80.0% CT: specificity 87.3%, accuracy 65.5% In non-enlarged regional LNs: SUVmax cut-off 1.4: highest NPV of 81.3% In enlarged LNs: SUVmax >2.4 sensitivity 90.7%, accuracy 88.9% for detection of metastatic LNs. High sensitivity and accuracy in patients with enlarged LNs
Bier, 2016 (24) Metastatic melanoma (n=50)	¹⁸ F-FDG PET/CT compared with CT Reference standard: PET/CT	Design: observational study Outcome(s): detection of bone and bone marrow infiltration	Contrast-enhanced CT lesion-based sensitivity 36.8%, specificity 87.9%, PPV 93.8%, NPV 21.8%, patient-based sensitivity 78.8% and specificity 82.4%. In 6 of 11 cases disseminated bone marrow involvement missed by CT
Bikhchandani, 2014 (25) Head and neck cutaneous melanoma (n=165, stage not reported, 106 node-negative, PET/CT n=47)	FDG PET initial staging compared with lymphatic sampling	Design: Retrospective review of clinically node-negative patients Outcome(s): Treatment course and outcomes	No cases of true distant metastasis identified on PET. PET failed to identify nodal metastasis in 2 patients with disease on lymphatic sampling.
Schaarschmidt, 2018 (26)	¹⁸ F-FDG PET/CT compared with ¹⁸ F-	Design: retrospective study comparing	PET/CT: LN true positive n=3, true

<p>Melanoma (n=52, stage not reported)</p>	<p>FDG PET/MR and ¹⁸F-FDG PET/MR including diffusion-weighted imaging (DWI) Reference standard: histopathology following SPECT/CT-guided SLNB</p>	<p>methods for staging. After hybrid imaging, lymphoscintigraphy including SPECT/CT identified SLNs before SLNB. Outcome(s): Diagnostic performance in detection of LN metastases</p>	<p>negative n=65, false positive n=3, false negative n=14, sensitivity 17.7%, specificity 95.6%, PPV 50.0%, NPV 82.3% PET/MR: LN true positive n=4, true negative n=63, false positive n=2, false negative n=13, sensitivity 23.5%, specificity 96.9%, PPV 66.7%, NPV 82.3% Additional use of DWI: 2 additional false positive results, true positives did not increase</p>
<p>Chandra, 2017 (28) Cutaneous melanoma (treatment-naïve, stage not reported, n=70)</p>	<p>PET/CT compared with conventional imaging (CI: CT and ultrasonography)</p>	<p>Design: prospective double-blinded study of PET/CT in preoperative staging Outcomes: Diagnostic performance</p>	<p>PET/CT: N staging sensitivity 86%, specificity 96%, negative predictive value 80%, positive predictive value 97% PET/CT: M staging sensitivity 87%, specificity 100%, negative predictive value 93%, positive predictive value 100% PET/CT greater diagnostic accuracy than CI for N staging and M staging (USG not reported) No significant difference between PET/CT and CI for N staging or M staging. 23% patients with clinically localised disease and 58% patients with clinically</p>

			palpable regional nodes upstaged by PET/CT
Multispectral optoacoustic imaging (MSOT)			
Stoffels, 2015 (27) Melanoma (stage not reported)	Multispectral optoacoustic imaging (MSOT)	Design: non-invasive detection of metastatic status of SLNs using multispectral optoacoustic imaging (MSOT) Outcome(s): identification and determination of SLN status	MSOT in combination with indocyanine green visualised SLNs in vivo in 20 patients with 100% concordance with (99m)Tc-marked SLN lymphoscintigraphy. MSOT 100% sensitivity and 48 to 62% specificity for detection of cancer-free SLNs (189 total LNs)
Ultrasound and fine needle aspiration			
Sijan, 2016 (29) Cutaneous melanoma (n=60, stage not reported)	Ultrasound-guided fine needle aspiration (US-FNAC) compared with SLNB Reference standard: histopathologic examination of SLNs from biopsy	Design: 60 patients divided into 3 groups: group I thin melanoma, group II intermediate thickness melanoma, group III thick melanoma. Outcome(s): presence of micro metastases in SLNs, detection rate	Group I detection rate: US-FNAC 0%, SLNB 10% Group II detection rate: US-FNAC 5%, SLNB 15% Group III detection rate: US-FNAC 30%, SLNB 45% US-FNAC 15% false negatives in melanoma ≥ 4 mm thickness US-FNAC sensitivity: group I 0%, group II 33.3%, group III 66.6%
Ternov, 2018 (30) Early stage melanoma (n=91: clinical stage I n=64, stage II n=27)	Targeted ultrasound and fine needle aspiration cytology (US-FNAC)	Design: prospective validation study. Patients examined by US-FNAC before SLNB. All patients received lymphoscintigraphy before US-FNAC Outcome(s): diagnostic accuracy	Overall US examination: sensitivity 30%, specificity 81%, positive predictive value 24%, negative predictive value 83%. FNAC specificity 76%.
Ultrasound and core needle biopsy			

<p>Bohelay, 2015 (31) Cutaneous melanoma (US-CNB n=71 confirmed, stage not reported)</p>	<p>Ultrasound-guided core needle biopsy (US-CNB) Two reference standards: histopathological examination of radical lymph node dissection or (when not available) clinical and radiological follow-up</p>	<p>Design: Retrospective review of patients undergoing US-CNB for suspicious of melanoma lymph node metastasis Outcome(s): Diagnostic and adverse events outcomes</p>	<p>US-CNB sensitivity 97.9%, specificity 100%, positive predictive value 100%. No adverse events reported after US-CNB. Study authors stated diagnostic value of US-CNB similar to fine needle aspiration cytology</p>
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Registry data on the impact of PET/CT on patient management across multiple tumour types, indications (including diagnosis, staging, suspected recurrence) and categories of management were collected in a prospective cohort at a single German centre (32). The frequency of change in clinical management (across indications) following PET/CT in melanoma was 46.0%.

An identified study described the development of the AJCC 8th edition of melanoma staging (33). Analysis of a large database led to changes to the Tumour, Node, Metastasis (TMN) classification and stage criteria. Key changes included: 1) tumour thickness to be measured to nearest 0.1 mm, 2) revised definitions of T1a and T1b stages, 3) revised pathological stage IA, 4) changes in N category descriptors to clinically occult and clinically apparent, 5) changes to stage III from 3 to 4 subgroups, 6) revised definitions of N subcategories, 7) descriptors added to M1 subcategories for lactate dehydrogenase level, 8) new M1d designation for central nervous system metastases. The authors described benefits including guiding patient management, improved prognostic

estimates and refined patient stratification into clinical trials.

Intelligence gathering

A topic expert noted that the role of radiology in early staging should be clarified (no further details provided).

A topic expert commented that the use of imaging as a staging tool needed to be evaluated, highlighting the use of PET/CT.

External correspondence received noted that accurate staging (including the brain) is important to allow initiation of appropriate treatment.

Impact statement

The guideline recommends (recommendation 1.5.3) that CT staging be offered to people with stage IIC melanoma who have not had SLNB, and to people with stage III or suspected stage IV melanoma. Two studies on the use of CT in staging were identified in this surveillance review. One study showed that preoperative CT before SLNB in melanoma may help identify metastases and could have a role in reducing the number of SLNB procedures. A second study reported that CT and PET/CT were of limited value in routine staging, but the

melanoma stage was not reported in the abstract. Therefore, it was considered that more evidence is needed before considering any change in this recommendation.

Recommendation 1.5.4 advises that the brain be included as part of imaging for people with suspected stage IV melanoma. External correspondence stated that confining imaging of the brain to stage IV disease only was no longer appropriate as accurate staging (including the brain) is needed to ensure initiation of appropriate treatments such as systemic therapy, which are available for stage IIIA and above. It is not explicitly stated in the identified studies whether the brain is imaged and so the potential impact of these studies on this recommendation is unclear.

Several primary studies were identified that evaluated the use of PET/CT in staging of melanoma. Topic experts commented that radiology in early staging and PET/CT in staging should be considered further. The guideline does not include recommendations on the use of PET/CT in staging. The availability of evidence since the publication of the review and topic expert feedback noting that PET/CT in staging should be considered has potential impact on recommendations under this section.

Multispectral optoacoustic imaging was demonstrated in a single primary study to have potential benefit in identifying and determining SLN status. However,

additional research is needed to confirm these results. The guideline does not include recommendations on the use of this imaging modality and further research would be required to impact on recommendations.

Primary evidence on the use of ultrasound-guided fine needle aspiration showed limited benefit in staging in patients with thin melanoma but the method may be of potential benefit in thicker melanoma staging. Therefore, while the current evidence is limited in number of studies, future research may confirm these results. Ultrasound-guided core needle biopsy (US-CNB) showed good diagnostic performance in detecting LN metastasis, but this was from a single primary study. One primary study indicated that high-frequency ultrasound may be of potential benefit in assessing thickness of melanoma. Additional research may support its use in staging in melanoma. The guideline does not include recommendations on the use of these techniques in staging and further research would be required to impact on recommendations.

The introduction of the 8th edition of the AJCC staging system has potential impact on this section that refer to specific stages of melanoma (recommendations 1.5.3, 1.5.4, and 1.5.5). Therefore, it is proposed that this section of the guideline be updated.

New evidence identified that may change current recommendations.

1.6 Managing stages 0–II melanoma

Recommendations in this section of the guideline

Excision

- 1.6.1 Consider a clinical margin of at least 0.5 cm when excising stage 0 melanoma.
- 1.6.2 If excision for stage 0 melanoma does not achieve an adequate histological margin, discuss further management with the multidisciplinary team.
- 1.6.3 Offer excision with a clinical margin of at least 1 cm to people with stage I melanoma.
- 1.6.4 Offer excision with a clinical margin of at least 2 cm to people with stage II melanoma.

Imiquimod for stage 0 melanoma

- 1.6.5 Consider topical imiquimod* to treat stage 0 melanoma in adults if surgery to remove the entire lesion with a 0.5 cm clinical margin would lead to unacceptable disfigurement or morbidity.
- 1.6.6 Consider a repeat skin biopsy for histopathological assessment after treatment with topical imiquimod for stage 0 melanoma, to check whether it has been effective.

* At the time of publication (July 2015) topical imiquimod did not have a UK marketing authorisation for this indication. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's [Prescribing guidance: prescribing unlicensed medicines](#) for further information.

Surveillance proposal

This section of the guideline should be updated.

Stage 0-II melanoma

2019 surveillance summary

A Cochrane systematic review (34) assessed the effects of all available (surgical and non-surgical) interventions to treat melanoma in situ (including lentigo maligna). One single centre RCT (90 participants) was included. Treatment with imiquimod 5% cream 5 days per week plus tazarotene 0.1% gel 2 days per week for 3 months (combination therapy) was compared with imiquimod 5% cream 5 days per week (monotherapy) for 3

months (before excision of the tumour footprint 2 months of cessation of topical treatment). The review authors noted that the study was open-label and analysis was not intention to treat. There was no significant difference in histological or clinical complete response at 5 months. Overall inflammation was significantly higher in the combination therapy group, with higher drop out in the combination therapy group due to adverse effects. The study concluded there was no clear evidence to support or refute addition of tazarotene to imiquimod therapy.

Intelligence gathering

A topic expert commented that managing stage I-II melanoma needed to be evaluated (no further details provided). An additional topic expert also noted stage 0-II melanoma needed to be considered (no further details provided).

A topic expert advised that treatment recommendations should be updated with regards to adjuvant and neoadjuvant treatment for melanoma, including stage II disease.

Topic expert feedback identified an ongoing study of systemic therapy in stage II disease (KEYNOTE-716) that could have potential future impact on management of stage II disease.

Topic experts also raised the introduction of an 8th edition of the AJCC staging system.

Impact statement

The identified Cochrane systematic review compared imiquimod combination therapy with imiquimod monotherapy for treatment of melanoma in situ and did not

show combination therapy was beneficial. As the current recommendation does not distinguish between imiquimod monotherapy and combination therapy, this systematic review does not have an impact.

A topic expert noted the need to consider adjuvant and neoadjuvant treatment for stage II disease. Recommendations do not currently cover systemic treatment for stage II melanoma. While no published evidence was identified, topic expert feedback highlighted an ongoing trial (KEYNOTE-716) of systemic therapy in stage II melanoma that may have potential future impact on recommendations under this section.

The introduction of the 8th edition of the AJCC staging system has the potential to impact on recommendation 1.6.3, since the definition of stage I disease has changed. Therefore, it is proposed that this section be updated.

New evidence identified that may change current recommendations.

1.7 Managing stage III melanoma

Recommendations in this section of the guideline

Completion lymphadenectomy

See [implementation: getting started](#) for information about putting recommendation 1.7.1 into practice.

- 1.7.1 Consider completion lymphadenectomy for people whose sentinel lymph node biopsy shows micro-metastases and give them detailed verbal and written information about the possible advantages and disadvantages, using the table below.

Possible advantages of completion lymphadenectomy	Possible disadvantages of completion lymphadenectomy
Removing the rest of the lymph nodes before cancer develops in them reduces the chance of the cancer returning in the same part of the body.	Lymphoedema (long-term swelling) may develop and is most likely if the operation is in the groin and least likely in the head and neck.
The operation is less complicated and safer than waiting until cancer develops in the remaining lymph nodes and then removing them.	In 4 out of 5 people, cancer will not develop in the remaining lymph nodes, so there is a chance that the operation will have been done unnecessarily.
People who have had the operation may be able to take part in clinical trials of new treatments to prevent future melanoma. These trials often cannot accept people who have not had this operation.	There is no evidence that people who have this operation live longer than people who do not have it.
	Having any operation can cause complications.

Lymph node dissection

1.7.2 Offer therapeutic lymph node dissection to people with palpable stage IIIB–IIIC melanoma or nodal disease detected by imaging.

Adjuvant radiotherapy

1.7.3 Do not offer adjuvant radiotherapy to people with stage IIIA melanoma.

1.7.4 Do not offer adjuvant radiotherapy to people with stage IIIB or IIIC melanoma unless a reduction in the risk of local recurrence is estimated to outweigh the risk of significant adverse effects.

Palliative treatment for in-transit metastases

1.7.5 Refer the care of all people with newly diagnosed or progressive in-transit metastases to the specialist skin cancer multidisciplinary team (SSMDT).

1.7.6 If palliative treatment for in-transit metastases is needed, offer palliative surgery as a first option if surgery is feasible.

1.7.7 If palliative surgery is not feasible for people with in-transit metastases, consider the following options:

- systemic therapy (for more information see [recommendations 1.8.5–1.8.9](#))
- isolated limb infusion
- isolated limb perfusion

- radiotherapy
- electrochemotherapy in line with NICE's interventional procedure guidance on [electrochemotherapy for metastases in the skin from tumours of non-skin origin and melanoma](#)
- CO₂ laser
- a topical agent such as imiquimod*.

Palliative treatment for superficial skin metastases

1.7.8 Consider topical imiquimod* to palliate superficial melanoma skin metastases.

*At the time of publication (July 2015) topical imiquimod did not have a UK marketing authorisation for this indication or for use in children and young people. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's [Prescribing guidance: prescribing unlicensed medicines](#) for further information.

Surveillance proposal

This section of the guideline should be updated.

Editorial amendment

[Section 1.7. Managing stage III melanoma](#) should be revised to allow cross-referencing to the [melanoma pathway](#) describing NICE technology appraisals of systemic treatments for stage III melanoma. We propose the following text be added: Following the development of this guideline, new technology appraisals are available that are relevant to this section. Please see the [melanoma pathway](#) for further information.

Managing stage III melanoma

2019 surveillance summary

Completion lymphadenectomy

A systematic review and meta-analysis (35) (n=4 RCTs) investigated survival in people with melanoma and lymph node metastasis who received immediate complete lymph node dissection (CLND) compared with observation only or delayed CLND. The 4 included RCTs demonstrated no significant difference in melanoma-specific survival. A sensitivity analysis showed that patients

with nodal metastasis had significantly better melanoma-specific survival if they underwent immediate CLND compared with delayed CLND.

The DeCOG-SLT multicentre phase III RCT (36) compared CLND (intention to treat n=240) with observation (intention to treat n=233) in patients with cutaneous melanoma following positive SLNB. The primary endpoint was distant metastasis-free survival, with a median follow-up of 35 months. The trial was stated by the study authors to be underpowered as it closed early (December 2014) due to

enrolment difficulties and a low event rate. Three-year distant metastasis-free survival was similar between people who had CLND compared with those in the observation group.

In the international MSLT-II RCT (37) people with melanoma with sentinel node metastases identified by standard pathological assessment or molecular assay received immediate CLND or nodal observation with ultrasonography. The primary endpoint of the study was melanoma-specific survival. A per-protocol analysis (n=1775) showed no significant difference in 3-year melanoma-specific survival between groups. Three-year disease-free survival was significantly better in the CLND group compared with observation (but authors noted these results should be considered with caution). More people who had CLND experienced lymphedema.

A retrospective observational study (38) (n=2172) compared CLND and observation in melanoma patients with intermediate thickness tumours and positive SLNB. Survival analysis and Cox regression analysis showed that CLND was not associated with improved survival.

An observational study (39) found that people with melanoma who received immediate completion lymphadenectomy after positive SLNB (n=502) had greater median disease-free survival and median progression-free survival compared with those who had delayed completion lymphadenectomy for regional recurrence after positive SLNB without immediate completion lymphadenectomy or after an earlier false negative SLNB (n=214).

An observational study (40) compared the survival of people with SLNB-positive

melanoma who received immediate CLND (n=375) and an observation group who did not have immediate CLND (n=96). The immediate CLND group was younger and had more sentinel lymph nodes removed. Compared with observation, people who had undergone CLND had significantly better 5-year nodal recurrence-free survival. Five-year and 10-year distant metastasis-free survival did not differ between groups. However, people who had CLND had better 5-year and 10-year melanoma-specific survival than those who did not have the procedure.

A retrospective database analysis (41) compared 5-year disease-specific survival between people with sentinel lymph node positive cutaneous melanoma of the head and neck who underwent CLND (n=210) and those who deferred the procedure (n=140). In the subgroup with the lowest risk of non-sentinel lymph node metastasis, younger people who received CLND had significantly better survival than people who received SLNB only. However, among those with a higher risk of non-sentinel lymph node metastasis, survival was similar between groups.

A single centre retrospective observational study (42) examined the effect of CLND compared with observation following SLNB in melanoma patients with multiple positive (n=78) and one positive (n=197) sentinel lymph nodes. Among those with multiple positive sentinel lymph nodes, CLND did not result in significantly better melanoma-specific survival or progression-free survival.

Intelligence gathering

A topic expert noted that the role of CLND is controversial and that more guidance is

needed on which patients (if any) should be offered the procedure. A topic expert also noted that there is a view in the clinical community since the guideline was published that CLND may have no proven value and that the recommendations in this area should be reconsidered.

Additional feedback also indicated that evidence should be reviewed of the benefit of CLND and whether ultrasound follow-up was acceptable.

A topic expert also commented that surgical management of melanoma, particularly decision-making in relation to SLNB-positive patients and patients with locoregional disease needed to be considered (no further details provided).

Topic experts advised that the 8th edition of the AJCC staging system had been introduced.

Impact statement

The guideline recommendation states that CLND should be considered for patients whose SLNB identifies micro metastases, supported by discussion of possible advantages and disadvantages to support patient choice.

The recommendations relating to the use of CLND in the guideline were based on a relatively small number of observational studies. The guideline committee noted that SLNB was the most sensitive staging method for melanoma and a

recommendation was needed on whether to proceed to CLND following SLNB.

Although the quality of included evidence in the guideline was of low quality, they considered that the patient should be made aware of the advantages and disadvantages of CLND and the decision on whether to undertake the procedure should be made by them.

A reasonable volume of new evidence has been published since the guideline was developed and identified in this surveillance review, including one systematic review and the MSLT-II and DeCOG-SLT RCTs. These studies indicated that CLND may be of only limited survival benefit. The findings from several observational studies also comparing CLND with observation were more variable. Therefore, this new evidence warrants review and has the potential to change current recommendations.

Topic experts also highlighted the need to update guidance on the use of CLND.

The introduction of the 8th edition of the AJCC staging system has potential to impact on recommendation 1.7.1 (since nomenclature has changed from microscopic nodal disease to clinically occult in the new staging edition).

New evidence identified that may change current recommendations.

2019 surveillance summary

Lymph node dissection

A retrospective observational study (43) (n=57) examined nodal recurrence and survival following neck dissections for regional metastases in cutaneous head and neck melanoma. At a median of 127 months follow-up there were no significant differences in nodal recurrence or 5-year survival between radical node dissection, modified radical node dissection and selective node dissection.

Intelligence gathering

A topic expert noted that the surgical management of melanoma, particularly decision-making in relation to SLNB-positive patients and patients with locoregional disease needed to be considered (no further details provided).

Topic experts also noted the introduction of the 8th edition of the AJCC staging system.

Impact statement

A topic expert commented on the need to re-evaluate surgical management of

melanoma, highlighting SLNB-positive patients and locoregional disease. The management of SLNB-positive by completion lymphadenectomy is discussed elsewhere in this surveillance review. Only one study was identified comparing methods for the management of regional metastases. The identified evidence does not impact on the current recommendation that therapeutic lymph node dissection be offered to people with palpable stage IIIB–IIIC melanoma or nodal disease detected by imaging (since the current recommendation does not recommend a specific method of therapeutic dissection).

There is potential impact of the 8th edition of the AJCC staging system on recommendation 1.7.2, as the definition of stage III disease has changed. Therefore, it is proposed that this section of the guideline be updated.

New evidence identified that may change current recommendations.

2019 surveillance review

Adjuvant radiotherapy

No new relevant evidence was identified in this surveillance review.

Intelligence gathering

No topic expert feedback was received specifically relating to radiotherapy. However, several topic experts noted the

introduction of the 8th edition of the AJCC staging system.

Impact statement

The 8th edition of the AJCC staging system has potential impact on recommendations 1.7.3 and 1.7.4 as the definition of stage III disease has changed.

New evidence identified that may change current recommendations.

2019 surveillance review

Systemic treatment for stage III disease

No new relevant evidence was identified under this section in this surveillance review.

Intelligence gathering

Topic experts highlighted numerous studies of the use of systemic therapies in people with stage III melanoma which are the subject of existing NICE technology appraisals, and are included in the managing melanoma section of the [NICE pathway for melanoma](#).

A topic expert noted that new evidence was available that indicated that adjuvant immunotherapy for stage III melanoma may be more effective if begun before tumour resection.

A topic expert noted that a heading for adjuvant treatment and systemics was not included in the guideline and that a patient decision aid would be helpful.

It was also noted by a topic expert that patients with resected in-transit metastases were eligible for adjuvant dabrafenib and trametinib.

Impact statement

The current guideline does not include recommendations for systemic treatment in people with stage III melanoma.

Topic experts highlighted the publication of numerous studies and NICE technology appraisals of systemic treatment for stage III disease.

A topic expert advised that adjuvant immunotherapy for stage III disease could be more effective if initiated before tumour resection. However, no studies were identified on this in the surveillance review.

A topic expert highlighted that patients with resected in-transit metastases were now eligible for dabrafenib and trametinib. While no studies were identified relating to this in the surveillance review, the section on palliative treatment for in-transit metastases should be revised to allow cross-referencing to the [melanoma pathway](#) describing NICE technology appraisals of systemic treatments.

A topic expert commented that there was no heading for adjuvant treatment and systemics in the guideline and considered that inclusion of a patient decision aid in the guideline would be useful.

[Section 1.7 Managing stage III melanoma](#) should be revised to allow cross-referencing to the [melanoma pathway](#) describing NICE technology appraisals of systemic treatments for stage III melanoma.

Evidence identified that may change current recommendations.

1.8 Managing stage IV melanoma

Recommendations in this section of the guideline

Management of oligometastatic stage IV melanoma

- 1.8.1 Refer the care of people who appear to have oligometastatic melanoma to the specialist skin cancer multidisciplinary team (SSMDT) for recommendations about staging and management.
- 1.8.2 Consider surgery or other ablative treatments (including stereotactic radiotherapy or radioembolisation) to prevent and control symptoms of oligometastatic stage IV melanoma in consultation with site-specific MDTs (such as an MDT for the brain or for bones).

Brain metastases

- 1.8.3 Discuss the care of people with melanoma and brain metastases with the SSMDT.
- 1.8.4 Refer people with melanoma and brain metastases that might be suitable for surgery or stereotactic radiotherapy to the brain and other central nervous system tumours MDT for a recommendation about treatment.

Systemic anticancer treatment

Targeted treatments

- 1.8.5 For adults, see NICE's technology appraisal guidance on [dabrafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma](#)*.
- 1.8.6 For adults, 'Vemurafenib is recommended as an option for treating BRAF V600 mutation-positive unresectable or metastatic melanoma only if the manufacturer provides vemurafenib with the discount agreed in the patient access scheme'^{**}. [This recommendation is from NICE's technology appraisal guidance on [vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma](#).]

Immunotherapy

- 1.8.7 For adults, see NICE's technology appraisal guidance on [ipilimumab for previously treated advanced \(unresectable or metastatic\) melanoma](#) and [ipilimumab for previously untreated advanced \(unresectable or metastatic\) melanoma](#)†.

Cytotoxic chemotherapy

- 1.8.8 Consider dacarbazine for people with stage IV metastatic melanoma if immunotherapy or targeted therapy are not suitable††.
- 1.8.9 Do not routinely offer further cytotoxic chemotherapy for stage IV metastatic melanoma to people previously treated with dacarbazine except in the context of a clinical trial.

*Dabrafenib has a marketing authorisation in the UK in monotherapy for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

**Vemurafenib has a UK marketing authorisation for 'the treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma'.

†Ipilimumab has a UK marketing authorisation for 'the treatment of advanced (unresectable or metastatic) melanoma in adults'.

††Although this use is common in UK clinical practice, at the time of publication (July 2015), dacarbazine did not have a UK marketing authorisation for this indication or for use in children and young people. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's [Prescribing guidance: prescribing unlicensed medicines](#) for further information.

Surveillance proposal

This section of the guideline should be updated.

Editorial amendment

[Section 1.8 Managing stage IV melanoma](#) should be revised to allow cross-referencing to the [melanoma pathway](#) describing NICE technology appraisals of systemic treatments for stage IV melanoma. We propose that recommendations 1.8.5, 1.8.6 (targeted treatments), and 1.8.7 (immunotherapy) be replaced with the following text: Following the development of this guideline, new technology appraisals are available that are relevant to this recommendation. Please see the [melanoma pathway](#) for further information.

Managing stage IV melanoma

2019 surveillance summary

A Cochrane systematic review (44) compared the effectiveness (survival) and harm (high-grade toxicity) of systemic treatments for people with unresectable lymph node metastasis and distant metastatic cutaneous melanoma with any other treatment. Network meta-analysis was used to indirectly compare, and rank treatments based on effectiveness and harm. This analysis included currently approved treatments (for which high to moderate quality evidence of efficacy was available). Chemotherapy was used as the common comparator. The systematic review included 122 RCTs (28,561 participants). 83 RCTs (21 difference comparisons) were included in meta-analyses.

Interventions were categorised as: conventional chemotherapy (including single agent and polychemotherapy), biochemotherapy (chemotherapy combined with cytokines e.g. interleukin-2 and interferon-alpha), immune checkpoint inhibitors (e.g. anti-CLTA4 and anti-PD1 monoclonal antibodies), small-molecule targeted drugs for melanomas with specific gene changes (e.g. BRAF inhibitors and MEK inhibitors), and other agents (e.g. anti-angiogenic drugs).

Results from the network meta-analysis are summarised below:

- Polychemotherapy compared with single agent chemotherapy: no significantly improved overall or progression-free survival, probable higher toxicity

- Biochemotherapy (chemotherapy combined with both interferon-alpha and interleukin-2) compared with chemotherapy: improved progression-free survival but no significantly improved overall survival, higher toxicity
- Immune checkpoint inhibitors - anti-CTLA4 monoclonal antibodies combined with chemotherapy compared with chemotherapy: probable improved progression-free survival but may not significantly improve overall survival. Likely higher toxicity for anti-CTLA4 monoclonal antibodies compared with chemotherapy alone
- Immune checkpoints inhibitors - anti-PD1 monoclonal antibodies compared with chemotherapy: improved overall survival, probable improved progression-free survival, possible reduced toxicity
- Immune checkpoint inhibitors - anti-PD1 monoclonal antibodies compared with anti-CTLA4 monoclonal antibodies: improved overall survival and progression-free survival, possible improved toxicity
- Immune checkpoint inhibitors - combination of anti-CTLA4 plus anti-PD1 monoclonal antibodies compared with anti-CTLA4 monoclonal antibodies alone: improved progression-free survival, possibly no significant difference in toxicity
- Small-molecule targeted drugs - BRAF inhibitors compared with chemotherapy: improved overall survival and progression-free survival, possibly no significant difference in toxicity
- Small-molecule targeted drugs - MEK inhibitors compared with chemotherapy: may not significantly improve overall survival, probable improved progression-free survival, probable higher toxicity
- Small-molecule targeted drugs - combination of BRAF plus MEK inhibitors compared with BRAF inhibitors: improved overall survival, probable improved progression-free survival, no likely significant difference in toxicity
- Other agents - anti-angiogenic drugs combined with chemotherapy compared with chemotherapy: probable improved overall survival and progression-free survival, may be no difference in toxicity
- Network meta-analysis ranking: combination of BRAF plus MEK inhibitors was most effective in progression-free survival and anti-PD1 monoclonal antibodies associated with lowest toxicity

The review authors concluded that (compared with chemotherapy) biochemotherapy (as chemotherapy combined with both interferon-alpha and interleukin-2) and BRAF inhibitors improved progression-free survival. BRAF inhibitors and anti-PD1 monoclonal antibodies improved overall survival.

Evidence suggested that combined treatments worked better than single treatments.

A retrospective study (45) evaluated the use of FDG PET compared with CT imaging in metastatic melanoma patients (n=104) treated with anti-PD1-based immunotherapy (67% anti-PD1 monotherapy, 31% combined with ipilimumab). At one year, proportions of patients with complete response (CT 28% vs. PET 75%) and partial response (CT 66% vs. PET 16%) were compared between PET and CT. The authors concluded that PET imaging may have benefit in the prediction of long-term treatment benefit and may inform treatment discontinuation.

An observational study (46) (n=60) examined the role of ¹⁸F-FDG PET/CT imaging in monitoring response to ipilimumab treatment in patients with metastatic melanoma. Tumour response on ¹⁸F-FDG PET/CT measured according to PET Response Criteria in Solid Tumours (PERCIST) was associated with overall survival.

Intelligence gathering

Several topic experts commented on the significant developments in the fields of targeted therapy and immunotherapy for stage IV melanoma since the publication of the guideline (including NICE technology appraisals).

A topic expert flagged aspects of stage IV disease that needed to be evaluated, including localised treatments for metastatic disease and brain metastases and the role of systematic anticancer therapy.

A topic expert commented that the effectiveness of systemic treatments impacts on the position of systemic therapy relative to other modalities, which should be reflected in the guidance. It was also noted that a section could be added on use of immunotherapy in patients with pre-existing auto-immune disease.

A topic expert also advised that the use of talimogene (as a local therapy now approved) (NICE TA410, published September 2016) should be considered.

Large changes (presumed increased) in costs were noted by a topic expert in relation to introduction of biological and immunotherapy for stage IV and stage III melanoma.

The introduction of the 8th edition of the AJCC staging system was commented on in topic expert feedback.

Impact statement

The range of treatment options available for stage IV melanoma has significantly expanded since the publication of the guideline, as evidenced by the topic expert comments and the numerous NICE technology appraisals on this topic. This section of the guideline requires revision to allow cross-referencing to the [melanoma pathway](#) which includes the current NICE technology appraisal guidance.

Identified studies indicate that imaging may have a useful role in monitoring treatment response. However, no recommendations relate to the use of imaging in monitoring response to treatment and therefore this evidence does not impact on current recommendations.

The introduction of the 8th edition of the AJCC staging system may have potential impact on recommendations 1.8.2 and 1.8.8 (as a new subcategory has been introduced under stage IV disease to denote central nervous system disease).

New evidence identified that may change current recommendations.

1.9 Follow-up after treatment for melanoma

Recommendations in this section of the guideline

Follow-up for all people who have had melanoma

- 1.9.1 Perform a full examination of the skin and regional lymph nodes at all follow-up appointments.
- 1.9.2 Consider personalised follow-up for people who are at increased risk of further primary melanomas (for example people with atypical mole syndrome, previous melanoma, or a history of melanoma in first-degree relatives or other relevant familial cancer syndromes).
- 1.9.3 Consider including the brain for people having imaging as part of follow-up after treatment for melanoma.
- 1.9.4 Consider imaging the brain if metastatic disease outside the central nervous system is suspected.
- 1.9.5 Consider CT rather than MRI of the brain for adults having imaging as part of follow-up or if metastatic disease is suspected.
- 1.9.6 Consider MRI rather than CT of the brain for children and young people (from birth to 24 years) having imaging as part of follow-up or if metastatic disease is suspected.
- 1.9.7 Provide psychosocial support for the person with melanoma and their family or carers at all follow-up appointments.
- 1.9.8 All local follow-up policies should include reinforcing advice about self-examination (in line with [recommendation 1.1.2](#)), and health promotion for people with melanoma and their families, including sun awareness, avoiding vitamin D depletion (in line with [recommendation 1.1.3](#)), and NICE guidance on [smoking cessation](#).
- 1.9.9 Continue to manage drug treatment for other conditions in line with recommendations [1.4.1](#) and [1.4.2](#) after treatment for melanoma.

Follow-up after stage 0 melanoma

- 1.9.10 Discharge people who have had stage 0 melanoma after completion of treatment and provide advice in line with recommendation 1.9.8.

Follow-up after stage IA melanoma

- 1.9.11 For people who have had stage IA melanoma, consider follow-up 2–4 times during the first year after completion of treatment and discharging them at the end of that year.
- 1.9.12 Do not routinely offer screening investigations (including imaging and blood tests) as part of follow-up to people who have had stage IA melanoma.

Follow-up after stages IB–IIB melanoma or stage IIC melanoma (fully staged using sentinel lymph node biopsy)

- 1.9.13 For people who have had stages IB–IIB melanoma or stage IIC melanoma with a negative sentinel lymph node biopsy, consider follow-up every 3 months for the first 3 years after completion of treatment, then every 6 months for the next 2 years, and discharging them at the end of 5 years.
- 1.9.14 Do not routinely offer screening investigations (including imaging and blood tests) as part of follow-up to people who have had stages IB–IIB melanoma or stage IIC melanoma with a negative sentinel lymph node biopsy.

Follow-up after stage IIC melanoma with no sentinel lymph node biopsy or stage III melanoma

- 1.9.15 For people who have had stage IIC melanoma with no sentinel lymph node biopsy, or stage III melanoma, consider follow-up every 3 months for the first 3 years after completion of treatment, then every 6 months for the next 2 years, and discharging them at the end of 5 years.
- 1.9.16 Consider surveillance imaging as part of follow-up for people who have had stage IIC melanoma with no sentinel lymph node biopsy or stage III melanoma and 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 multidisciplinary team agrees to a local policy and specific funding for imaging 6-monthly for 3 years is identified.

Take into account the possible advantages and disadvantages of surveillance imaging and discuss these with the person, using the table below.

Possible advantages of surveillance imaging (having regular scans)	Possible disadvantages of surveillance imaging (having regular scans)
If the melanoma comes back (recurrent melanoma), it is more likely to be detected sooner. It is possible that this could lead to a better outcome by allowing treatment with drugs (such as immunotherapy drugs) to start earlier.	Although early drug treatment of recurrent melanoma might improve survival, there is currently no evidence showing this.

Some people find it reassuring to have regular scans.	Some people find that having regular scans increases their anxiety.
	Scans expose the body to radiation, which can increase the risk of cancer in the future.
	Scans of the brain and neck increase the risk of developing cataracts.
	Scans of the chest cause a very small increase in the risk of thyroid cancer.
	Scans may show abnormalities that are later found to be harmless, causing unnecessary investigations and anxiety.

Follow-up after stage IV melanoma

1.9.17 Offer personalised follow-up to people who have had stage IV melanoma.

Surveillance proposal

This section of the guideline should be updated.

Follow-up after treatment for melanoma

2019 surveillance summary

Imaging

Focused searches were undertaken to identify studies in people with melanoma stages 1A to IV comparing benefits and harms between imaging modalities.

One systematic review (47) (n=7 studies) was identified that examined the diagnostic performance of PET for follow-up of cutaneous melanoma patients and detection of relapse. Mean sensitivity, specificity, PPV and NPV were 96%, 92%, 92% and 95% respectively, indicating good diagnostic performance in the follow-up of patients with melanoma.

Several primary studies were identified that compared imaging modalities in the follow-up of people with melanoma. These are summarised in the table below.

Study and population	Test(s)	Methods	Key results
Schule, 2016 (48) Melanoma (stage III/IV) (surveillance n=12)	¹⁸ F-FDG PET/CT compared with CT	Design: retrospective analysis Outcome(s): impact on treatment decisions	Significant overall survival benefit in patients in whom ¹⁸ F- FDG PET/CT excluded metastases or in whom metastases were completely removed vs. patients not eligible for surgery (41% vs. 10%).
Vensby, 2017 (49) Melanoma (n=238 patients, stage not reported)	FDG PET/CT compared with histology, MRI or fine needle aspiration	Design: retrospective analysis of follow-up after surgery. Patients had ≥ 1 PET/CT scan after initial surgery and staging. Outcome(s): Diagnostic performance in patients with and without clinical suspicion of relapse compared	Sensitivity 89%, specificity 92%, PPV 78%, NPV 97%. No significant difference in accuracy of PET/CT between patients with or without clinical suspicion of relapse.
Podlipnik, 2016 (50) Melanoma (stage IIB, IIC and III) (n=290 patients)	Intensive follow-up using imaging (CT of chest, abdomen and pelvis and brain MRI), periodic laboratory tests, regular physical examination and patient self-examination	Design: prospective cohort study examining intensive follow-up Outcome(s): performance of diagnostic methods for detection of melanoma metastasis	A total of 115 recurrences detected in 290 patients. Proportions detected using differing diagnostic methods were compared: CT 48.3%, brain MRI 7.6%, laboratory test 2.5%, physician 23.7%, patient 17.8%
Deike-Hofmann, 2018 (51) Melanoma (n=217 with melanoma brain metastases, MBM, metastases n=720)	Six MRI sequences (at time of initial diagnosis of first or new MBM): non-enhanced T1- weighted (T1w), contrast-enhanced T1w (ceT1w), T2-weighted (T2w), T2w-FLAIR, susceptibility-weighted (SWI) and diffusion- weighted (DWI) MRI	Design: review of records Outcome(s): sensitivity for early detection of MBM	Sensitivity: T1w 56.7%, ceT1w 99.7%, T2w 61.0%, T2w-FLAIR 77.0%, SWI 64.7%, DWI 48.4%. 7.3% (31/425) of lesions only identified on ceT1w but no other sequence.

Intelligence gathering

Topic expert feedback highlighted the increased availability of effective treatment options for melanoma and the importance of early detection of recurrence to allow access to these treatments.

Follow-up imaging techniques of interest to topic experts included:

- radiology (no further details provided)
- use of PET/CT in first line imaging with contrast-enhanced CT or MRI to identify brain deposits
- PET/CT in surveillance and ultrasound for monitoring of SLNB-positive patients who have not undergone CLND, alternated with CT scans

A topic expert flagged that there is wide variation in surveillance practice across the country which may result in inequity of treatment.

A topic expert highlighted that the results from the MSLT-II study may lead to costs associated with the increased use of surveillance CTs and ultrasound scans in stage III disease and above.

Topic experts advised that an 8th edition of the AJCC staging system had been introduced.

Impact statement

One systematic review was identified demonstrating good diagnostic performance of PET in surveillance and detection of recurrence in people with

melanoma. Current recommendations do not refer to the use of PET imaging in follow-up of melanoma. However, this review showed good diagnostic performance of PET, which may potentially impact on recommendations.

Current recommendations do not refer to PET/CT in surveillance. This technique was raised as being of interest in topic expert feedback. However, only a small number of comparative studies on PET/CT in surveillance were identified in the focused searches performed in this review. Further evidence would be required to have an impact on recommendations.

A report of an intensive surveillance schedule showed detection of recurrence by body CT and brain MRI. Recommendation 1.9.5 states to consider CT rather than MRI of the brain for adults having imaging in follow-up or if metastatic disease is suspected. While this study shows that recurrence was detected by brain MRI, this abstract did not provide evidence directly comparing CT and MRI in detection of recurrence in the brain and so does not impact on this recommendation.

In a primary study comparing modes of MRI contrast-enhanced T1-weighted MRI was found to be most sensitive in detecting melanoma brain metastases. As recommendations do not currently specify mode of MRI this study does not impact on current recommendations.

Topic experts advised that a new edition of the AJCC staging system had been developed. The introduction of this 8th edition of the AJCC staging system has the potential to impact on recommendations 1.9.11, 1.9.12, 1.9.13, 1.9.14, 1.9.15,

1.9.16 and 1.9.17 as these recommendations relate to specific stages affected by this revision. Therefore, it is proposed that this section be updated.

New evidence identified that may change current recommendations.

Research recommendations

In people with reported atypical spitzoid lesions, how effective are fluorescence in situ hybridisation (FISH), comparative genomic hybridisation (CGH) and tests to detect driver mutations compared with histopathological examination alone in predicting disease-specific survival?

Summary of findings

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

For people with lentigo maligna how effective is Mohs micrographic surgery compared with excision with a 0.5 cm clinical margin in preventing biopsy-proven local recurrence at 5 years?

Summary of findings

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

In people treated for high risk stage II and III melanoma does regular surveillance imaging improve melanoma-specific survival compared with routine clinical follow-up alone?

Summary of findings

Focused searches were performed in this area as part of this surveillance review. No eligible RCTs were identified.

In people with stage I-III melanoma does vitamin D supplementation improve overall survival?

Summary of findings

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

In people diagnosed with melanoma what is the effect of drug therapy to treat concurrent conditions on disease-specific survival?

Summary of findings

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

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Appendix A2: Summary of evidence from surveillance

2019 surveillance of Improving outcomes for people with skin tumours including melanoma (2006) NICE guideline CSG8

Summary of evidence from surveillance

A focused search was undertaken to identify evidence related to the guideline. Studies identified in the search are summarised from the information presented in their abstracts.

Feedback from topic experts who advised us on the approach to this surveillance review was considered alongside the evidence to reach a view on the need to update each section of the guideline.

Recommendations presented in the guideline have been summarised in this document.

Guideline History

The guideline has 2 documents which are reported in this summary of evidence:

- [Improving Outcomes for People with Skin Tumours including Melanoma: the manual \(2006\)](#)
- [Improving outcomes for people with skin tumours including melanoma \(update\): The management of low-risk basal cell carcinomas in the community \(2010\)](#)

Improving Outcomes for People with Skin Tumours including Melanoma: the manual (2006)

Patient-centred care

Recommendations in this section of the guideline

Putting patient and carer needs at the centre of service design

These recommendations cover commissioning to reflect the local population needs and local community consultation arrangements.

Communication, information provision and support

These recommendations cover staff training in communication with patients and carers, appropriate support and information for skin cancer patients.

Support for patients needing extensive treatment

These recommendations cover ensuring patients are offered information about support availability, including psychosocial, psychological and psychiatric interventions, palliative care and lymphoedema services for patients.

Quality assurance

These recommendations cover quality assurance informed by patient surveys and audits of care.

Surveillance proposal

This section of the guideline should be updated.

Patient-centred care

2019 surveillance summary

Communication, information provision and support

Information needs

In a multicentre cross-sectional survey (1) (n=529) over half of people with melanoma reported having unmet information needs. The presence of unmet information needs was more likely in patients currently receiving medical treatment, among those aged at least 55 years, and in those who generally had a high need for condition-specific information. Most unmet information needs were for information on treatment and were reported by patients with tumour progression. There was no difference in presence or scope of unmet

information needs between metastatic and non-metastatic melanoma patients.

A multicentre cross-sectional survey (2) of melanoma patients (67% clinical stage III or IV melanoma) found that the majority used medical consultations as their frequently used information resource. Over half wished for more advice on information resources from their physician, with only a minority of patients using self-help group services or cancer counselling centre services. Preferred media were the internet and booklets.

A survey (3) of 100 stage I-II melanoma patients in follow-up showed that only a minority could accurately describe all 4 of their tumour characteristics (Breslow tumour thickness, presence of ulceration, mitosis and American Joint Committee on Cancer [ALCC] stage). Orally delivered information was clearest for patients to understand compared with information in

a melanoma brochure. Most patients considered YouTube videos on self-inspection of skin and regional lymph nodes to be of value. Most patients preferred information to be delivered via multiple routes, with the highest proportion favouring oral delivery of information from their physician.

A survey (4) of melanoma patients (n=31) showed that the majority used the internet as a source of information on melanoma, with melanoma treatment, screening and prevention the most commonly searched topics. Most participants considered the internet a useful source of melanoma information and that it increased their understanding of their diagnosis. Over half found melanoma websites at least somewhat difficult to understand. The majority reported that this use had influenced their treatment decision and over half considered it had impacted on their specialist consultation.

Support needs

A systematic review (5) considered psychosocial outcomes in advanced (stage III/IV) melanoma patients (n=52 studies). Patients who were receiving chemotherapy or interferon-alpha experienced decreased emotional and social function, with increased distress, while patients on newer treatments were found to have better emotional and social function. Descriptive studies showed decreased emotional and social function and increased distress in patients with advanced compared with localised disease. Patients with advanced disease were also found to have more supportive care needs, in particular amount, quality and timing of information on melanoma, communication and emotional support from clinicians.

A cross-sectional study (6) (n=254) of melanoma patients from a single centre reported that patient self-evaluation could be useful in identifying patients requiring psycho-oncological support.

In a cross-sectional study (7) of patients with early stage melanoma (n=204) almost half experienced distress symptoms and a quarter reported anxiety symptoms. Depressive symptoms were reported less frequently. Patients were found to apply positive and active coping strategies.

An observational study (8) (n=136) in people with stage IA melanoma identified high fear of progression in a third of those surveyed. Factors significantly associated with a higher fear of progression included female sex, younger age, being in employment, and cancer diagnosis in related persons.

Patients newly diagnosed with clinical stage IB-II invasive melanoma (n=386) were surveyed (9). Almost half reported having at least one moderate-level or high-level unmet need. Highest needs were for help relating to fear of cancer spreading, information on recurrence risk, and on outcomes when spread occurred. Patients who had undergone sentinel lymph node biopsy (SLNB) were significantly more likely to have moderate or high unmet needs for help with uncertainty about the future or lymphoedema. Emotional wellbeing was found to be worse in the sample compared with the general population. Supportive care needs at 2 year follow-up were also reported (10) (n=386). Stressful life events and anxiety were associated with supportive care needs at enrolment. The proportion of patients with supportive care needs decreased over the first 6 months and

decreased further by 24 months in people remaining disease-free. However, people experiencing recurrence or development of another primary tumour experienced supportive care needs. Age, depression, anxiety and other stressful life events predicted persistent needs.

Preferences for frequency of follow-up (reflecting differing needs between patients) were surveyed in an Australian study of people treated for localised melanoma (11). Of 230 people without a recurrent or new primary melanoma, a greater proportion of people preferred the standard compared with fewer scheduled clinic visit option. Factors identified as independently associated with a preference for fewer visits were higher disease stage, melanoma on a limb, living with others, no private health insurance and visiting a specialist for another chronic condition.

A health needs survey (12) (n=160) of melanoma survivors treated at a single centre identified that the most prevalent symptom was anxiety. Most surveyed patients reported that their health provider did not address their symptoms and over half requested education on melanoma-specific issues.

Skin cancer inpatients and outpatients (n=250) were surveyed about their support needs (13). Patients who experienced distress mainly chose physicians and psychologists as potential contacts for support.

The need for support among 116 skin cancer inpatients did not differ significantly between patients with

melanoma, squamous cell carcinoma or other skin cancer types (14).

Interventions for information and support

In a longitudinal study (15) (n=242) self-efficacy for skin self-examination was found to significantly increase immediately after an educational intervention. This increase was maintained at 3 months and 12 months post-intervention. Higher patient-reported physician support was significantly related to higher self-efficacy.

Intelligence gathering

A topic expert noted (in surveillance for NICE guideline [NG14 \(Melanoma: assessment and management\)](#)) that increased evidence is available on the information and support requirements of melanoma patients, which is summarised in the NG14 2019 surveillance summary.

This section of the guideline refers to the role of cancer networks. Topic expert feedback indicated that cancer networks are now no longer operational.

Impact statement

The new evidence identified is essentially in line with current guideline recommendations that emphasise that information provided should be appropriate to patient needs.

This surveillance review and feedback from stakeholders indicates that this guidance, while outdated, has continuing value to service delivery. As such, it is proposed that this guidance be updated.

New evidence identified that may change current recommendations.

Organisation of skin cancer services

Recommendations in this section of the guideline

Cancer networks

These recommendations cover the requirement for 2 levels of multidisciplinary teams (MDT) for the management of patients with skin cancer and participation requirements:

- local hospital skin cancer multidisciplinary teams (LSMDTs)
- specialist skin cancer multidisciplinary teams (SSMDTs).

This section also covers the 2-week waiting time standard.

Network implementation

These recommendations cover audit/appraisal of the quality of current service provision to inform the networks.

Network-wide protocols

These recommendations cover agreed clinical protocols for referral and treatment.

Arrangements for skin cancer teams

These recommendations cover team working and engagement of services. They also cover arrangements for referral from LSMDTs to SSMDTs and combined working.

Coordination across teams

These recommendations cover coordination and communication between clinicians across teams and settings, a designated lead for communication and documentation of arrangements.

Patient information

These recommendations cover patient information, including support groups, healthcare contacts, relevant MDTs and information about the condition.

The local hospital skin cancer multidisciplinary team (LSMDT)

These recommendations cover the size and composition of the team and MDT review meeting processes (including patients who should be referred for MDT review).

The role of the LSMDT

These recommendations cover multiple roles for LSMDT including diagnosis, information provision/sharing, treatment, audit and referral.

Core membership of the LSMDT

These recommendations cover core membership of LSMDT, including nominated lead and deputies, skills, competencies and interests.

Members of the extended LSMDT

These recommendations cover maintaining close contact with all other professionals who are actively involved in treating and supporting patients, with example professions identified.

The specialist skin cancer multidisciplinary team (SSMDT)

These recommendations cover the remit and composition of the team. Recommendations also cover specific cases for referral to the SSMDT, management of those patients and collaboration between multiple SSMDTs.

The role of the SSMDT

These recommendations cover the timing of meetings and team activities, including specialist services, audit and training activities and professional management and contact arrangements.

Core membership of the SSMDT

These recommendations cover core membership of SSMDT, including nominated leads and deputies, skills, competencies and interests.

Members of the extended SSMDT

These recommendations cover composition based on example professions. Recommendations also cover commissioning arrangements that should be made by the cancer network for the funding of histopathology reviews and supra-network pathology referrals.

Organisation of LSMDT and SSMDT meetings

These recommendations cover arrangements for meetings, requirements and discussion points (including new cases and audit). These recommendations also set out managerial responsibility for meetings and the whole service.

Clinicians working in the community

These recommendations cover local arrangements for skin cancer services including training and skills.

Management of patients presenting in primary care

These recommendations cross-refer to NICE Referral guidelines for suspected cancer.

Structure and clinical governance

These recommendations cover the need for community clinicians to work to agreed protocols and accountability structures and audit processes.

Surveillance proposal

This section of the guidance should be updated.

Organisation of skin cancer services

2019 surveillance summary

Focused searches were undertaken as part of this surveillance review to identify studies comparing outcomes of MDTs with alternative compositions or MDT against no MDT. Identified studies are located within the various relevant sections of this evidence summary.

Cancer networks

This section recommends that all cancer networks should establish 2 levels of MDT (LSMDTs and SSMDTs) for the management of skin cancer. A retrospective chart review (16) of data from before and after the implementation of a head and neck squamous cell carcinoma MDT showed that timeliness of care significantly improved. While 2-year mortality was the same between groups, 5-year mortality was slightly (but not significantly) improved for patients diagnosed after the MDT was implemented.

Patient information

New evidence relating to patient information has been summarised in the above section entitled 'Communication,

information provision and support' and therefore is not duplicated here.

The role of the LSMDT

In an observational study (17), the role of centralised histopathological review in penile cancer was examined. Newly diagnosed squamous cell carcinomas of the penis (n=155) were referred to the regional supra-network MDT from 15 centres in North West England. Following review by the supra-network MDT, histological diagnosis was changed in 31% of instances, of which 60% were considered important changes that significantly altered patient management.

In an observational study (18) of 234 cases of invasive cutaneous melanoma in Sweden, interobserver variability between a general pathologist and pathologist experienced in melanoma was 68.8 to 84.8%. Over 15% of melanomas of 1 mm thickness or greater were re-classified following review as melanoma in situ or melanoma > 1 mm.

Core membership of the SSMDT

An observational study (19) reported on a 12 month review of dissections of regional lymph nodes for skin cancer from 5 plastic surgery units in South West England and Wales. Of a total of 163 dissections, 43% of patients experienced one or more

complications. During the 12-month period, a total of 8 axillary/groin dissections were performed per surgeon. A funnel plot showed that the prevalence of complications for individual surgeons were within the plot limit but that 10 procedures per consultant per year would allow improved assessment of the prevalence of complications.

A cross-sectional online survey (20) of 59 centres demonstrated that half of tumour board conference (TBC) meeting leaders were medical and/or surgical oncologists, with a third of meeting leaders being dermatologists. Ninety seven percent of participants reported that TBCs had moderate to significant impact on patient care.

Management of patients presenting in primary care

An observational study (21) undertaken in Dutch GPs showed that GPs treated actinic keratosis mostly with cryotherapy. Only a small proportion (13%) would take a biopsy for suspected malignancy. It was reported that a small proportion treated basal cell carcinoma, usually by excision, and that most face/neck regions excisions were not radical (66%). Referrals to a dermatologist (n=734) showed that referral diagnosis was correct in 44% of cases (n=323).

Scottish registry data (22) for people diagnosed with melanoma (n=9367) were analysed for the association between morbidity and mortality and the setting of primary melanoma excision (primary compared with secondary care). Data showed that patients receiving excision in primary care did not have poorer survival. Numbers of outpatient attendances and

hospital admissions were similar between primary and secondary care excisions.

Intelligence gathering

Topic expert feedback noted that cancer networks were no longer in operation and that the guideline was no longer fit for purpose for provision or commissioning services.

A topic expert also noted that content on melanoma was outdated and superseded by [melanoma: assessment and management](#) (NICE guideline NG14).

Topic expert feedback indicated that the structure and function of the MDT in skin cancer management, role of the extended MDT and the types of cases discussed should be reviewed (e.g. discussion of less cases of squamous cell carcinoma [SCC] and focusing more on complicated skin cancer and stage IV disease). Feedback also suggested that many cases of melanoma follow a specific pathway and do not need to be discussed. Topic expert feedback also highlighted that the composition of health care professionals involved in the MDT needed to be assessed, querying whether it was needed to involve the present number of healthcare workers (no further detail provided).

The SSMDT discussion of patients newly diagnosed with melanoma stage IIb or higher was raised by a topic expert as needing update (in relation to new staging (i.e. the introduction of the 8th edition of the AJCC staging) and access to SLNB).

A topic expert considered that the role of general practitioners with a special interest (GPwSI) in skin cancer management

needed to be updated (no further details provided).

A topic expert stated that the role of Mohs surgery and basal cell carcinoma (BCC) management should be considered (no further details provided).

Impact statement

The limited number of studies identified in the focused search for this surveillance review were not considered to have

potential impact on recommendations in this section.

This surveillance review and feedback from stakeholders indicates that this guidance, while outdated, has continuing value to service delivery. As such, it is proposed that this guidance be updated.

New evidence identified that may change current recommendations.

Initial investigation, diagnosis, staging and management

Recommendations in this section of the guideline

Investigation and diagnosis

These recommendations cover GP training, referral process and links with histopathology services. The recommendations also set out requirements for histopathology services.

Management of precancerous lesions

These recommendations cover referral options for the treatment of precancerous lesions.

Management of skin cancers

These recommendations cover the range of management of skin cancer options that should be available locally.

Surveillance proposal

This section of the guidance should be updated.

Initial investigation, diagnosis, staging and management

2011 Evidence Update

Investigation and diagnosis

A meta-analysis (Xing, 2011) (23) (n=74 studies) assessed the use of diagnostic imaging for melanoma. The review concluded that ultrasonography was superior in detection of regional lymph node metastasis and that positron emission tomography-computed tomography (PET/CT) was superior to CT in detection of distant metastases, both in staging and surveillance of melanoma.

Management of skin cancers

Surgical treatment

A systematic review and meta-analysis (Mocellin, 2010) (24) (n=5 RCTs) compared wide (3-5 cm) versus narrow (1-2 cm) excision margins in primary melanoma. The results were described in the evidence update as tentatively suggesting that narrow excision margins may be less safe, although limitations were reported, such as lack of reported data in some RCTs, non-homogeneity of study design between RCTs, and small number of included trials.

An RCT (Dessy, 2010) (25) (n=40 patients) compared 2 methods of ear reconstruction following wide tumour excision with BCC or SCC (stage T1 or T2) or melanoma (stage T1). Patients receiving revolving-door (RD) flap procedure had significantly better improved cosmetic outcome and colour and texture matching than those receiving full-thickness skin grafts.

The Multicentre Selective Lymphadenectomy Trial I (MSLT-I) RCT

(Faries, 2010) (26) (n=357 patients) compared immediate completion lymph node dissection ('early CLND' after SLNB) with therapeutic dissection ('delayed CLND' after clinical recurrence) in patients with cutaneous melanoma. No difference in morbidity was reported, but lymphoedema was significantly higher in the delayed CLND group.

Early and delayed CLND in cutaneous melanoma were compared (Pasquali, 2010) (27) in a retrospective non-randomised case series (n=190 patients) and a meta-analysis of 5 other non-randomised studies plus the case series performed in this work (n=2633 patients). No difference in 5-year survival was reported in the case series. The meta-analysis showed significantly higher risk of death following late CLND compared with early CLND.

Systemic therapy

A Cochrane systematic review (Lansbury, 2010) (28) (n=1 RCT) examined interventions for non-metastatic SCC of the skin. One RCT (n=65 patients) was included in the review, comparing adjuvant 13-cis-retinoic acid and interferon-alpha after surgery (with or without radiation treatment, with no adjuvant therapy after initial treatment). There was no difference in time to tumour recurrence between groups.

A systematic review and meta-analysis (Mocellin, 2010) (29) (n=14 RCTs, n=8122 patients) demonstrated significant improved disease-free survival and overall survival in patients with high risk melanoma treated with adjuvant interferon-alpha.

Two additional RCTs (Hansson, 2011, n=855 patients) (30), (Hauschild, 2011,

n=850 patients) (31) studied use of intermediate dose and low dose interferon-alpha respectively in patients with melanoma. Neither trial demonstrated significantly improved overall survival after adjuvant interferon-alpha treatment.

Two RCTs (32) (33) (Hodi, 2010, Robert 2011) of ipilimumab for metastatic melanoma were included. Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma was the subject of NICE technology appraisal [TA268](#) (published December 2012).

One RCT (Chapman, 2011) (34) of vemurafenib for treatment of BRAF V600-mutated metastatic melanoma was included. Vemurafenib for treatment of locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma was the subject of NICE technology appraisal [TA269](#) (published January 2015).

2019 surveillance summary

Investigation and diagnosis

Several studies (including several Cochrane systematic reviews) were identified that addressed the specific diagnostic accuracy of a range of methods in diagnosis of skin cancers. Some of this evidence was included in the surveillance review for [melanoma: assessment and management](#) (NICE guideline NG14).

Evidence was discussed in the surveillance review for this guidance (CSG8) if it was considered relevant to issues of service delivery (for example in-person versus remote modes of delivery, delivery by differing professional types etc).

Visual inspection

A Cochrane systematic review (35) (n=49 studies) assessed the diagnostic accuracy of visual inspection for detecting cutaneous invasive melanoma and atypical intraepidermal melanocytic variants in adults with limited previous testing and in people referred for further evaluation of a suspicious lesion. Studies were categorised based on whether the diagnosis was recorded by in-person or remote (image-based) assessment. Visual inspection was compared in test accuracy studies with a reference standard of histological confirmation or clinical follow-up. Accuracy was significantly higher using in-person diagnosis compared with image-based evaluation. The review concluded that visual inspection may result in melanomas being missed if used on its own.

Dermoscopy

A Cochrane systematic review (36) assessed visual inspection and dermoscopy (alone or used in combination) for diagnosis of BCC and cutaneous SCC (sSCC) in adults. Studies were grouped based on whether diagnosis was made in-person or using remote (image-based) evaluation. The reference standard was histological confirmation or clinical follow-up. Twenty four publications were included. Meta-analysis demonstrated that in-person dermoscopy evaluations were significantly more accurate than visual inspection alone for detecting BCC. The abstract stated that results for the image-based evaluations were very similar. There were not sufficient data available for conclusions to be made on the accuracy of the tests for the detection of sSCC.

In a Cochrane systematic review (37) dermoscopy (with and without visual inspection) for the diagnosis of cutaneous invasive melanoma and atypical intraepidermal melanocytic variants in adults was considered (n=104 studies). Studies were separated based on whether the diagnosis was recorded by in-person or remote (image-based) assessment. The reference standard was either histological confirmation or clinical follow-up. For both in-person and image-based assessments, meta-analysis demonstrated dermoscopy to be significantly more accurate than visual inspection alone. Use of a named or published algorithm to aid dermoscopy interpretation was not found to significantly affect accuracy for in-person or image-based assessments.

Teledermatology

A Cochrane systematic review (38) assessed the diagnostic accuracy of teledermatology in detection of any skin cancer (melanoma, BCC or sSCC) in adults in comparison with in-person diagnosis. The reference standard was histological confirmation or clinical follow-up and expert opinion. Twenty two studies were included. The review authors concluded that the evidence suggested teledermatology could correctly identify most malignant lesions but that the evidence base on accurate diagnosis of lesions and triaging from primary to secondary care was limited.

Imaging techniques

A Cochrane systematic review (39) assessed the diagnostic accuracy of smartphone applications to rule out cutaneous invasive melanoma and atypical intraepidermal melanocytic variants in adults with suspicious skin lesions.

Smartphone applications were for use by individuals in a community setting. The reference standard was histological confirmation or clinical follow-up and expert opinion. No meta-analysis was performed due to limited availability of data and poor quality of studies. Two studies were included. Of the 5 mobile phone applications, 4 were based on artificial intelligence applications that classed lesion images using an algorithm. The remaining one application used store-and-forward dermatologist review of lesion images. Sensitivities ranged from 7% to 98% and specificities from 30% to 84%. The authors concluded that current evidence was limited and associated with low methodological quality.

Management of precancerous lesions

A Cochrane systematic review (40) (n=9 RCTs, n=363 participants) investigated the effectiveness of therapeutic interventions for cutaneous Bowen's disease. The review showed that photodynamic therapy (PDT) was effective in lesion clearance and produced less scarring compared with cryotherapy or 5-fluorouracil. Cryotherapy was less effective than PDT and resulted in more scarring. 5-aminolevulinic acid with PDT (ALA-PDT) was reported to be significantly more effective in lesion clearance than 5-fluorouracil. Methyl aminolevulinate with PDT (MAL-PDT) resulted in no significant difference in clearance compared with 5-fluorouracil. One RCT demonstrated significantly better lesion clearance by imiquimod cream versus placebo. It was stated that it was not possible to draw definitive conclusions on comparative treatment effectiveness.

A Cochrane systematic review (41) (n=83 RCTs, n=10,036 participants) assessed the

effects of 24 topical, oral, mechanical and chemical interventions for actinic keratoses. It was reported that actinic keratoses were successfully treated using cryotherapy, diclofenac, 5-fluorouracil, imiquimod, ingenol mebutate, photodynamic therapy, resurfacing, and trichloroacetic acid peel, which were described as generally comparable in effectiveness. Skin irritation was noted for some treatments (e.g. diclofenac and 5-fluorouracil). Final cosmetic appearance was reported to vary between treatments. It was concluded that treatment choice would be dependent on number of lesions, desired treatment results of the individual, and treatment tolerance.

Management of skin cancers

Topical treatment

A Cochrane systematic review (42) assessed the effects of all available (surgical and non-surgical) interventions to treat melanoma in situ (including lentigo maligna). One single centre RCT (90 participants) was included. Treatment with imiquimod 5% cream 5 days per week plus tazarotene 0.1% gel 2 days per week for 3 months (combination therapy) was compared with imiquimod 5% cream 5 days per week (monotherapy) for 3 months (before excision of the tumour footprint 2 months of cessation of topical treatment). There was no significant difference in histological or clinical complete response at 5 months. Overall inflammation was significantly higher in the combination therapy group, with higher drop out in the combination therapy group due to adverse effects. The review concluded there was no clear evidence to support or refute addition of tazarotene to imiquimod therapy.

Sentinel lymph node biopsy (SLNB)

A Cochrane systematic review (43) assessed the effectiveness and safety of SLNB followed by CLND for the treatment of localised primary cutaneous melanoma. One RCT (MSLT-I, 2001 participants) was included that compared SLNB with observation (published as 8 reports from 2005 to 2014). Participants had removal of the primary tumour and were then randomised to receive SLNB or observation. SLNB-positive patients then underwent CLND. Participants in the observation group received lymph node removal only on disease recurrence. Data for overall survival were not reported. There was no significant difference in disease-specific survival between SLNB and observation at 10 years. Patients in the SLNB group had better disease-free survival at 10 years compared with observation. Benefit was reported for SLNB in local and regional recurrence. However, SLNB showed an unfavourable effect for rate of distant metastases as site of first recurrence. Short-term surgical morbidity was similar between SLNB and observation for wide excision of the tumour site but was less favourable to SLNB for regional nodal basin complications.

Surgical treatment

A Cochrane systematic review (44) aimed to compare the effectiveness, complications, acceptability and cost of Mohs micrographic surgery compared with surgical excision for periocular BCC. However, no eligible RCTs were identified.

The DeCOG-SLT multicentre phase III RCT (45) compared CLND (intention to treat n=240) with observation (intention to treat n=233) in patients with cutaneous

melanoma following positive SLNB. The primary endpoint was distant metastasis-free survival, with a median follow-up of 35 months. The trial was stated by the study authors to be underpowered as it closed early (December 2014) due to enrolment difficulties and a low event rate. Three-year distant metastasis-free survival was similar between people who had CLND compared with those in the observation group.

In the international MSLT-II RCT (46) people with melanoma with sentinel node metastases identified by standard pathological assessment or molecular assay received immediate CLND or nodal observation with ultrasonography. The primary endpoint of the study was melanoma-specific survival. A per-protocol analysis (n=1775) showed no significant difference in 3-year melanoma-specific survival between groups. Three-year disease-free survival was slightly better in the CLND group compared with observation (but authors noted these results should be considered with caution). More people who had CLND experienced lymphoedema.

Focused searches were undertaken as part of the surveillance review for [melanoma: assessment and management](#) (NICE guideline NG14) relating to the benefits and harms of lymph node dissection in patients with melanoma. These are not duplicated here.

Imaging

Registry data on the impact of PET/CT on patient management across multiple tumour types, indications (including diagnosis, staging, suspected recurrence) and categories of management were collected in a prospective cohort at a

single German centre (47). The frequency of change in clinical management (across indications) following PET/CT in melanoma was 46.0%.

A retrospective study (48) evaluated the use of FDG PET compared with CT imaging in metastatic melanoma patients (n=104) treated with anti-PD1-based immunotherapy (67% anti-PD1 monotherapy, 31% combined with ipilimumab). At 1 year, proportions of patients with complete response (CT 28% vs. PET 75%) and partial response (CT 66% vs. PET 16%) were compared between PET and CT. The authors concluded that PET imaging may have benefit in the prediction of long-term treatment benefit and may inform treatment discontinuation.

An observational study (49) (n=60) examined the role of ¹⁸F-FDG PET/CT imaging in monitoring response to ipilimumab treatment in patients with metastatic melanoma. Tumour response on ¹⁸F-FDG PET/CT measured according to PERCIST was associated with overall survival.

Focused searches were performed as part of the surveillance review for [melanoma: assessment and management](#) (NICE guideline NG14) to identify comparative studies on the use of imaging modalities in patients with melanoma. These findings are not duplicated here.

Systemic therapy

A Cochrane systematic review (50) assessed the survival effects of interferon-alpha as adjuvant treatment in people with high risk cutaneous melanoma i.e. those with regional lymph node metastasis [AJCC stage III] undergoing radical lymph node dissection, or those without nodal

disease but with primary tumour thickness greater than 1 mm (AJCC stage II). RCTs eligible for inclusion compared interferon-alpha to observation or any other treatment. Eighteen RCTs (10,499 participants) were included in this review. Seven RCTs (published from 1995 to 2011) were suitable for meta-analysis. Adjuvant interferon was associated with significantly better disease-free survival and overall survival. Grade 3 or 4 toxicity occurred in a minority of participants.

A Cochrane systematic review (51) compared the effectiveness (survival) and harm (high-grade toxicity) of systemic treatments for people with unresectable lymph node metastasis and distant metastatic cutaneous melanoma compared with any other treatment. Network meta-analysis was used to indirectly compare, and rank treatments based on effectiveness and harm. This analysis included currently approved treatments (for which high to moderate quality evidence of efficacy was available). Chemotherapy was used as the common comparator. The systematic review included 122 RCTs (28,561 participants). 83 RCTs (21 difference comparisons) were included in meta-analyses. Analysis included 19 RCTs (7632 participants) and generated 21 indirect comparisons.

Interventions were categorised as: conventional chemotherapy (including single agent and polychemotherapy), biochemotherapy (chemotherapy combined with cytokines e.g. interleukin-2 and interferon-alpha), immune checkpoint inhibitors (e.g. anti-CTLA4 and anti-PD1 monoclonal antibodies), small-molecule targeted drugs for melanomas with specific gene changes (e.g. BRAF inhibitors

and MEK inhibitors), and other agents (e.g. anti-angiogenic drugs).

Results from the network meta-analysis are summarised below:

- Polychemotherapy compared with single agent chemotherapy: no significantly improved overall or progression-free survival, probable higher toxicity
- Biochemotherapy (chemotherapy combined with both interferon-alpha and interleukin-2) compared with chemotherapy: improved progression-free survival but no significantly improved overall survival, higher toxicity
- Immune checkpoint inhibitors - anti-CTLA4 monoclonal antibodies combined with chemotherapy compared with chemotherapy: probable improved progression-free survival but may not significantly improve overall survival. Likely higher toxicity for anti-CTLA4 monoclonal antibodies compared with chemotherapy alone
- Immune checkpoints inhibitors - anti-PD1 monoclonal antibodies compared with chemotherapy: improved overall survival, probable improved progression-free survival, possible reduced toxicity
- Immune checkpoint inhibitors - anti-PD1 monoclonal antibodies compared with anti-CTLA4 monoclonal antibodies: improved overall survival and progression-free survival, possible improved toxicity

- Immune checkpoint inhibitors – combination of anti-CTLA4 plus anti-PD1 monoclonal antibodies compared with anti-CTLA4 monoclonal antibodies alone: improved progression-free survival, possibly no significant difference in toxicity
- Small-molecule targeted drugs – BRAF inhibitors compared with chemotherapy: improved overall survival and progression-free survival, possibly no significant difference in toxicity
- Small-molecule targeted drugs – MEK inhibitors compared with chemotherapy: may not significantly improve overall survival, probable improved progression-free survival, probable higher toxicity
- Small-molecule targeted drugs – combination of BRAF plus MEK inhibitors compared with BRAF inhibitors: improved overall survival, probable improved progression-free survival, no likely significant difference in toxicity
- Other agents – anti-angiogenic drugs combined with chemotherapy compared with chemotherapy: probable improved overall survival and progression-free survival, may be no difference in toxicity
- Network meta-analysis ranking: combination of BRAF plus MEK inhibitors was most effective in progression-free survival and anti-PD1 monoclonal antibodies associated with lowest toxicity

The review authors concluded that (compared with chemotherapy) biochemotherapy (as chemotherapy combined with both interferon-alpha and interleukin-2) and BRAF inhibitors improved progression-free survival. BRAF inhibitors and anti-PD1 monoclonal antibodies improved overall survival. Evidence suggested that combined treatments worked better than single treatments.

Intelligence gathering

Investigation and diagnosis

A topic expert commented that teledermatology and confocal microscopy needed to be reviewed (no further details provided).

A topic expert also advised in the surveillance review for CSG8 that genetic testing in melanoma needed to be considered.

Management of precancerous lesions

No topic expert feedback was provided.

Management of skin cancers

It was raised by topic experts that the changes in the AJCC staging system (with the introduction of the revised 8th edition) need to be addressed. The AJCC and UICC staging criteria were also commented as having implications for patient management for both melanoma and non-melanoma. The importance of accurate staging was emphasised in topic expert feedback, highlighting the new availability of adjuvant treatments and the need to ensure high risk patients are identified who are eligible for treatment. It was also noted that direct guidance on imaging would be helpful.

Topic expert feedback indicated that direct guidance was required on which patients may benefit from staging using SLNB (with reference to the new 8th edition of AJCC staging). It was highlighted that a lack of uniform staging guidance could lead to inequity as some patients may not have access to treatments if not fully staged.

Feedback from topic experts highlighted that the use of SLNB and lymph node dissection (completion lymphadenectomy, early versus delayed lymphadenectomy, number of dissections required for peer review) need to be reviewed (no further details provided). A topic expert stated it was important to provide national consensus on management of SLNB-positive patients and surgical management of locoregional disease (no further details provided).

Several topic experts commented on the considerable increase in available pharmacological treatments for skin cancer (including immunotherapy) that are not reflected in the guidance. Indeed, one topic expert noted that some treatment lists are now obsolete. A topic expert stated that treatment recommendations for non-melanoma skin cancer had changed, particularly for SCC and BCC. Treatment options for Merkel cell carcinoma have expanded (no further details provided). It was also noted that this section needed to consider new systemic treatments that alter the decision-making about whether to undertake surgery.

A topic expert also recommended that adjunctive radiotherapy be reviewed (no further details provided).

One topic expert advised that the use of adjuvant immunotherapy for stage III

disease before tumour resection should be evaluated. The impact of antibiotic use on immunotherapy was also flagged for evaluation.

The use of imaging in monitoring treatment response was noted by a topic expert as requiring update (no further details provided).

A topic expert stated that recommendations on assessment, surgical and medical management are outdated and not fit for purpose. It was stated that the guideline was no longer fit for purpose for provision or commissioning services.

Impact statement

Some studies identified in this surveillance review are also considered in the 2019 surveillance review for [melanoma: assessment and management](#) (NG14). Others identified in this surveillance review were not considered likely to have potential impact on recommendations in this section.

However, several issues were identified relating to this section in this surveillance review. These included changes in service delivery and provision of care since development of CSG8. For example, cancer networks are referred to repeatedly in CSG8 but are no longer in operation.

Topic expert feedback also highlighted several points that impact on this section. These include the changes in staging (e.g. AJCC and UICC staging) since the publication of the guideline that affect management of melanoma and non-melanoma skin cancers. Topic experts raised other developments in skin cancer management that impact this section, including surgical management of disease

and developments in systemic therapies since CSG8 publication.

This surveillance review and feedback from stakeholders has indicated that this guidance, while outdated, has continuing

value to service delivery. As such, it is proposed that this guidance be updated.

New evidence identified that may change current recommendations.

Follow-up

Recommendations in this section of the guideline

Background

These recommendations cover patient-tailored follow-up based on local protocols, including surveillance and care for people who may need lifelong surveillance.

Basal cell carcinoma and squamous cell carcinoma

These recommendations cover follow-up and surveillance for patients at low or high risk of recurrence.

Melanoma

These recommendations cover follow-up patterns for patients with melanoma.

Surveillance proposal

This section of the guidance should be updated.

Follow-up

2011 Evidence Update

Melanoma

A meta-analysis (Xing, 2011) (23) (n=74 studies) assessed the use of diagnostic imaging for melanoma. The review concluded that ultrasonography was superior in detection of regional lymph node metastasis and that PET/CT was

superior to CT in detection of distant metastases, both in staging and surveillance of melanoma.

An RCT (Murchie, 2010) (52) (n=142) showed that GP-led melanoma follow-up resulted in significantly better patient satisfaction compared with traditional hospital follow-up, at no expense to health status, anxiety or depression level of patients.

2019 surveillance summary

No new evidence was identified.

Intelligence gathering

This sub-section of the guidance refers to cancer networks. Topic expert feedback indicated that these are no longer in operation.

Topic expert feedback noted that the area of follow-up needed to be evaluated, for example relating to the follow-up of SCC patients and to the use of imaging in identification of brain deposits. It was noted in feedback that updated guidance on imaging was required in view of the availability of new therapies to improve survival (and that less intensive surveillance could limit access to treatment and lead to inequity of outcomes). Follow-up of non-melanoma patients was highlighted as requiring evaluation.

Impact statement

The 2 studies identified in surveillance both related to follow-up for melanoma.

Follow-up of non-melanoma patients was flagged by topic experts as needing further evaluation. However, no new evidence in

this area was included in this surveillance review.

The intelligence and topic expert feedback identified through this surveillance review indicated that the service delivery and provision of care for skin cancers have changed considerably since the guideline was developed. Cancer networks are referred to in this section, but these are no longer operational.

Topic expert feedback in this surveillance review indicated that staging systems for skin cancer have changed since the publication of this guideline (e.g. the AJCC and the UICC staging systems). Topic expert feedback noted that these changes in staging have implications for how melanoma and non-melanoma skin cancers are managed.

This surveillance review and feedback from stakeholders indicates that this guidance, while outdated, has continuing value to service delivery. As such, it is proposed that this guidance be updated.

New evidence identified that may change current recommendations.

Management of special groups

Recommendations in this section of the guideline

Generic recommendations for patients with uncommon risk factors or rare cancers

These recommendations cover tailored information, needs assessment and treatment protocol/pathways for special groups of patients. They also cover local liaison when dealing with this patient group.

Genetic predisposition

These recommendations cover referral and treatment options for patients with genetic predisposition.

Transplant patients

These recommendations cover treatment options for transplant patients who have precancerous skin lesions or who have developed a skin cancer.

Cutaneous lymphoma

These recommendations cover referral and treatment options for patients with lymphoma. They also cover local diagnostic and testing requirements.

Skin sarcomas

These recommendations cover local liaison between MDTs and the role of SSMDTs and specialist histopathology review for patients with sarcomas.

Children and young people

These recommendations cover children and young people diagnosed with skin cancer.

Surveillance proposal

This section of the guideline should be updated.

Management of special groups

2019 surveillance summary

Skin sarcomas

A Cochrane systematic review (53) (n=9 studies [n=6 RCTs, n=3 observational studies]) assessed treatment of severe or progressive Kaposi's sarcoma in adults infected with the human immunodeficiency virus (HIV). The review suggested that highly active antiretroviral therapy (HAART) in combination with chemotherapy may have more benefit in

reducing disease progression compared with HAART alone. In patients receiving HAART, there was reported to be no difference observed between liposomal doxorubicin, liposomal daunorubicin and paclitaxel.

Intelligence gathering

Topic expert feedback flagged that cancer networks are no longer in operation.

A topic expert commented that familial melanoma and management of genetic counselling and gene testing needed to be considered.

Impact statement

A topic expert raised the area of familial melanoma and genetic testing and counselling as requiring update in CSG8. Gene testing at diagnosis was considered in [melanoma: assessment and management](#) (NICE guideline NG14) and was the subject of an evidence search in the 2019 surveillance review for NG14.

The Cochrane systematic review identified in this surveillance review demonstrated that the use of combination therapy with HAART and chemotherapy was more effective than HAART alone. Since recommendations on specific pharmacological therapies are not

provided, this evidence does not impact on current recommendations in this section.

As described above, several key issues were identified in this surveillance review that impact on this guideline, including changes in service delivery and provision of care, staging, surgical and non-surgical management.

This surveillance review and feedback from stakeholders indicates that this guidance, while outdated, has continuing value to service delivery. As such, it is proposed that this guidance be updated.

New evidence identified that may change current recommendations.

Improving outcomes for people with skin tumours including melanoma (update) (2010)

The management of low-risk basal cell carcinomas in the community

Recommendations in this section of the guideline

Training, education and accreditation

These recommendations cover training and accreditation for healthcare professionals managing skin lesions in the community.

Commissioning

These recommendations cover commissioning based on local needs assessment of low-risk BCC and other groups, quality standards and referral plans.

Superficial BCCs

These recommendations cover doctors who manage patients with superficial BCCs (not usually classified as high risk) in the community.

Models of care

These recommendations specify the clinical criteria for triage that should be used to identify those BCCs that should be managed by one of 3 different groups of healthcare professionals in primary care:

- Low-risk BCCs for DES/LES – GPs performing skin surgery
- Model 1 practitioners - group 3 GPwSI in dermatology and skin surgery
- Model 2 practitioners - outreach community skin cancer services provided by acute trusts or LHBs linked to the LSMDT.

Quality assurance (histopathology)

These recommendations cover managing local skin lesion samples, data and managing results stemming from histopathology.

Quality assurance (data collection and audit)

These recommendations cover managing data, audit and registration for low-risk BCCs.

Clinical governance

These recommendations cover clinical governance arrangements and protocols for referral, treatment and follow-up.

Communication

These recommendations cover information, advice and support for patients and their families or carers.

Surveillance proposal

This section of the guideline should be updated.

The management of low-risk basal cell carcinomas in the community

2019 surveillance summary

An observational study (21) undertaken in Dutch general practitioners showed that

2019 surveillance of melanoma and improving outcomes for people with skin tumours including melanoma –
Evidence summaries

GPs treated actinic keratosis mostly with cryotherapy. Only a small proportion (13%) would take a biopsy for suspected malignancy. It was reported that a small proportion treated basal cell carcinoma, usually by excision, and that most face/neck regions excisions were not radical (66%). Referrals to a dermatologist

(n=734) showed that referral diagnosis was correct in 44% of cases (n=323).

Intelligence gathering

A topic expert considered that the role of GPwSI in skin cancer management needed to be reviewed (no further details provided).

Impact statement

A single observational study in Dutch GPs showed that a small proportion treated BCC (usually by excision) and face/neck excisions were typically not radical. The study showed that less than half of referral diagnoses were correct upon referral to a dermatologist. Recommendations in this section of the guideline cover management of specific types of BCC in the community according to specific types

of practitioner. This evidence supports the importance of dermatological expertise in management of skin cancer in the community but does not specifically describe the dermatological expertise of the GPs in the study and therefore does not impact on current recommendations.

This section of the guideline refers to service structures that are no longer operational (e.g. cancer networks, primary care trusts).

This surveillance review and feedback from stakeholders indicates that this guidance, while outdated, has continuing value to service delivery. As such, it is proposed that this guidance be updated.

New evidence identified that may change current recommendations.

Research recommendations

The guidance recommended that research be undertaken on teledermatology in the triage of patients with suspicious skin lesions (including clinical accuracy, cost-effectiveness, patient confidentiality and patient acceptability).

Summary of findings

A Cochrane systematic review (38) assessed the diagnostic accuracy of teledermatology in detection of any skin cancer (melanoma, BCC or sSCC) in adults in comparison with in-person diagnosis. The review authors concluded that the evidence base on accurate diagnosis of lesions and triaging from primary to secondary care was limited. Therefore, additional well-conducted primary research on clinical accuracy and cost-effectiveness, patient confidentiality and patient acceptability would be beneficial.

Three research priorities were proposed under the section of initial investigation, diagnosis, staging and management:

- Good quality research on efficacy of treatment modalities

- Studies with long-term follow-up comparing benefits of excisional surgery of non-melanoma skin cancer with other available treatments
- Further research on systemic photodynamic therapy

Summary of findings

New evidence has been published since the guidance on treatment efficacy, for example on lymph node dissection. The pharmacological treatment options for skin cancer have also significantly expanded, with efficacy evidence described in numerous NICE technology appraisals. Many treatment modalities for melanoma are also covered within [melanoma: assessment and management](#) (NICE guideline NG14).

The guidance recommended studies with long-term follow-up for the benefits of excisional surgery of non-melanoma skin cancer compared with other treatment options. No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

The guidance recommended further research on systemic photodynamic therapy. No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

The guidance identified as a research priority that well-designed ethics-committee-approved clinical trials of different follow-up methods be performed.

Summary of findings

New evidence has been published since the guidance on the use of imaging in follow-up. This topic was the subject of focused searches as part of the surveillance review for [melanoma: assessment and management](#) (NICE guideline NG14).

The guidance stated several research priorities on the management of special groups.

These included research on:

- Disease processes and patient management
- Chemotherapeutic agents and/or biological response modifiers
- Management of Gorlin's syndrome and familial melanoma
- Cutaneous lymphoma
- A programme of autologous and/or allogenic transplantation for cutaneous T-cell lymphoma in a research setting

- Anti-angiogenic agents for treatment of Kaposi's sarcoma
- Transplant-related skin malignancy including prevention, epidemiology, pathogenesis and treatment

Summary of findings

New evidence has been published since the guidance on the use of chemotherapeutic agents and/or biological response modifiers, many of which are covered by NICE technology appraisals.

What is the true nature of the epidemiology of basal cell carcinoma and the burden on NHS services?

Summary of findings

No new evidence was identified in this surveillance review addressing this research question.

For patients with low-risk basal cell carcinoma treated in the community, what are the factors that predict recurrence of treated low-risk basal cell carcinoma and what factors predict a good cosmetic result?

Summary of findings

No new evidence was identified in this surveillance review addressing this research question.

Is there a difference in outcome for patients whose low-risk basal cell carcinomas are resected by the different groups of healthcare professionals proposed in this guidance?

Summary of findings

No new evidence was identified in this surveillance review addressing this research question.

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