DOI:
10.1002/14651858.CD012806.pub2

Document Version
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Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma.
Cochrane Database of Systematic Reviews 2019, Issue 7. Art. No.: CD012806.
DOI: 10.1002/14651858.CD012806.pub2.

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[Diagnostic Test Accuracy Review]

Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

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Editorial group: Cochrane Skin Group.
Publication status and date: New, published in Issue 7, 2019.

Citation: Dinnes J, Ferrante di Ruffano L, Takwoingi Y, Cheung ST, Nathan P, Matin RN, Chuchu N, Chan SA, Durack A, Bayliss SE, Gulati A, Patel L, Davenport C, Godfrey K, Subesinghe M, Traill Z, Deeks JJ, Williams HC, Cochrane Skin Cancer Diagnostic Test Accuracy Group. Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma. *Cochrane Database of Systematic Reviews* 2019, Issue 7. Art. No.: CD012806. DOI: 10.1002/14651858.CD012806.pub2.

ABSTRACT

Background

Melanoma is one of the most aggressive forms of skin cancer, with the potential to metastasise to other parts of the body via the lymphatic system and the bloodstream. Melanoma accounts for a small percentage of skin cancer cases but is responsible for the majority of skin cancer deaths. Various imaging tests can be used with the aim of detecting metastatic spread of disease following a primary diagnosis of melanoma (primary staging) or on clinical suspicion of disease recurrence (re-staging). Accurate staging is crucial to ensuring that patients are directed to the most appropriate and effective treatment at different points on the clinical pathway. Establishing the comparative accuracy of ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET)-CT imaging for detection of nodal or distant metastases, or both, is critical to understanding if, how, and where on the pathway these tests might be used.

Objectives

Primary objectives

We estimated accuracy separately according to the point in the clinical pathway at which imaging tests were used. Our objectives were:

• to determine the diagnostic accuracy of ultrasound or PET-CT for detection of **nodal metastases** before sentinel lymph node biopsy in adults with confirmed cutaneous invasive melanoma; and

• to determine the diagnostic accuracy of ultrasound, CT, MRI, or PET-CT for whole body imaging in adults with cutaneous invasive melanoma:

○ for detection of **any metastasis in adults with a primary diagnosis** of melanoma (i.e. primary staging at presentation); and

○ for detection of **any metastasis in adults undergoing staging of recurrence** of melanoma (i.e. re-staging prompted by findings on routine follow-up).

We undertook separate analyses according to whether accuracy data were reported per patient or per lesion.

Secondary objectives

We sought to determine the diagnostic accuracy of ultrasound, CT, MRI, or PET-CT for whole body imaging (detection of any metastasis) in mixed or not clearly described populations of adults with cutaneous invasive melanoma.

For study participants undergoing primary staging or re-staging (for possible recurrence), and for mixed or unclear populations, our objectives were:

• to determine the diagnostic accuracy of ultrasound, CT, MRI, or PET-CT for detection of nodal metastases;

• to determine the diagnostic accuracy of ultrasound, CT, MRI, or PET-CT for detection of distant metastases; and

• to determine the diagnostic accuracy of ultrasound, CT, MRI, or PET-CT for detection of distant metastases according to metastatic site.

Search methods

We undertook a comprehensive search of the following databases from inception up to August 2016: Cochrane Central Register of Controlled Trials; MEDLINE; Embase; CINAHL; CPCI; Zetoc; Science Citation Index; US National Institutes of Health Ongoing Trials Register; NIHR Clinical Research Network Portfolio Database; and the World Health Organization International Clinical Trials Registry Platform. We studied reference lists as well as published systematic review articles.

Selection criteria

We included studies of any design that evaluated ultrasound (with or without the use of fine needle aspiration cytology (FNAC)), CT, MRI, or PET-CT for staging of cutaneous melanoma in adults, compared with a reference standard of histological confirmation or imaging with clinical follow-up of at least three months' duration. We excluded studies reporting multiple applications of the same test in more than 10% of study participants.

Data collection and analysis

Two review authors independently extracted all data using a standardised data extraction and quality assessment form (based on the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2)). We estimated accuracy using the bivariate hierarchical method to produce summary sensitivities and specificities with 95% confidence and prediction regions. We undertook analysis of studies allowing direct and indirect comparison between tests. We examined heterogeneity between studies by visually inspecting the forest plots of sensitivity and specificity and summary receiver operating characteristic (ROC) plots. Numbers of identified studies were insufficient to allow formal investigation of potential sources of heterogeneity.

Main results

We included a total of 39 publications reporting on 5204 study participants; 34 studies reporting data per patient included 4980 study participants with 1265 cases of metastatic disease, and seven studies reporting data per lesion included 417 study participants with 1846 potentially metastatic lesions, 1061 of which were confirmed metastases. The risk of bias was low or unclear for all domains apart from participant flow. Concerns regarding applicability of the evidence were high or unclear for almost all domains. Participant selection from mixed or not clearly defined populations and poorly described application and interpretation of index tests were particularly problematic.

The accuracy of imaging for detection of regional nodal metastases before sentinel lymph node biopsy (SLNB) was evaluated in 18 studies. In 11 studies (2614 participants; 542 cases), the summary sensitivity of ultrasound alone was 35.4% (95% confidence interval (CI) 17.0% to 59.4%) and specificity was 93.9% (95% CI 86.1% to 97.5%). Combining pre-SLNB ultrasound with FNAC revealed summary sensitivity of 18.0% (95% CI 3.58% to 56.5%) and specificity of 99.8% (95% CI 99.1% to 99.9%) (1164 participants; 259 cases). Four studies demonstrated lower sensitivity (10.2%, 95% CI 4.31% to 22.3%) and specificity (96.5%,95% CI 87.1% to 99.1%) for PET-CT before SLNB (170 participants, 49 cases). When these data are translated to a hypothetical cohort of 1000 people eligible for SLNB, 237 of whom have nodal metastases (median prevalence), the combination of ultrasound with FNAC potentially

allows 43 people with nodal metastases to be triaged directly to adjuvant therapy rather than having SLNB first, at a cost of two people with false positive results (who are incorrectly managed). Those with a false negative ultrasound will be identified on subsequent SLNB.

Limited test accuracy data were available for whole body imaging via PET-CT for primary staging or re-staging for disease recurrence, and none evaluated MRI. Twenty-four studies evaluated whole body imaging. Six of these studies explored primary staging following a confirmed diagnosis of melanoma (492 participants), three evaluated re-staging of disease following some clinical indication of recurrence (589 participants), and 15 included mixed or not clearly described population groups comprising participants at a number of different points on the clinical pathway and at varying stages of disease (1265 participants). Results for whole body imaging could not be translated to a hypothetical cohort of people due to paucity of data.

Most of the studies (6/9) of primary disease or re-staging of disease considered PET-CT, two in comparison to CT alone, and three studies examined the use of ultrasound. No eligible evaluations of MRI in these groups were identified. All studies used histological reference standards combined with follow-up, and two included FNAC for some participants. Observed accuracy for detection of any metastases for PET-CT was higher for re-staging of disease (summary sensitivity from two studies: 92.6%, 95% CI 85.3% to 96.4%; specificity: 89.7%, 95% CI 78.8% to 95.3%; 153 participants; 95 cases) compared to primary staging (sensitivities from individual studies ranged from 30% to 47% and specificities from 73% to 88%), and was more sensitive than CT alone in both population groups, but participant numbers were very small.

No conclusions can be drawn regarding routine imaging of the brain via MRI or CT.

Authors' conclusions

Review authors found a disappointing lack of evidence on the accuracy of imaging in people with a diagnosis of melanoma at different points on the clinical pathway. Studies were small and often reported data according to the number of lesions rather than the number of study participants. Imaging with ultrasound combined with FNAC before SLNB may identify around one-fifth of those with nodal disease, but confidence intervals are wide and further work is needed to establish cost-effectiveness. Much of the evidence for whole body imaging for primary staging or re-staging of disease is focused on PET-CT, and comparative data with CT or MRI are lacking. Future studies should go beyond diagnostic accuracy and consider the effects of different imaging tests on disease management. The increasing availability of adjuvant therapies for people with melanoma at high risk of disease spread at presentation will have a considerable impact on imaging services, yet evidence for the relative diagnostic accuracy of available tests is limited.

PLAIN LANGUAGE SUMMARY

How good are ultrasound, CT, MRI, and PET-CT for identifying spread of disease in the body among people with melanoma?

What is the aim of the review?

We wanted to find out which imaging tests are better for identifying spread of disease among people with a first diagnosis of melanoma (primary staging) and among people with possible recurrence of melanoma (re-staging). We looked at the evidence for ultrasound, CT, MRI, and PET-CT and included 39 studies to answer these questions.

Why are imaging tests for melanoma important?

Melanoma is one of the most aggressive forms of skin cancer, with potential for metastases (cancer cells) to spread to the lymph nodes and other organs of the body. To make sure that people with melanoma receive the most appropriate and effective treatment, it is important to identify whether the disease has spread and to which parts of the body it has spread. This is called 'staging of disease'. Staging is done to find out if a melanoma has spread to regional lymph nodes or to lymph nodes close to the original melanoma, and to determine if the melanoma has spread to lymph nodes in other parts of the body or to organs of the body such as the liver or the brain (distant metastases). Imaging tests are tools that can be used to help find out how much the disease has spread. Several new treatments are now available for reducing the risk of spread of melanoma and for treating melanoma when it has spread.

What was studied in the review?

The review includes four imaging tests that create images of the body in different ways. Ultrasound uses high-frequency sound waves to create images, CT scans use ionising radiation in the form of X-rays (a very low dose of radiation), and MRI uses large magnets and non-ionising radiation in the form of radio waves (which are not harmful) to generate images of the body. PET-CT requires injection of a weakly radioactive substance (FDG). The PET part of the scan identifies areas of the body that take up a lot of FDG (indicating

possibly cancerous cells), and the CT part of the scan helps to improve image quality and to more accurately pinpoint areas using more FDG. Ultrasound can also be performed along with a fairly simple procedure called 'fine needle aspiration cytology' (FNAC), by which a very fine needle is used to take a small sample of cells from a lymph node that looks suspicious on ultrasound. A microscope is then used to identify whether or not the cells are malignant.

Imaging can be used at different time points after diagnosis of melanoma. Healthcare providers can use imaging to look at the regional lymph nodes closest to the melanoma before a type of surgery called sentinel lymph node biopsy is performed. Sentinel lymph node biopsy takes out the lymph nodes that are most likely to have metastases inside them so they can be tested in a laboratory. Imaging can also be used after sentinel lymph node biopsy or in people with higher-risk melanoma to look for any spread of disease. Imaging can be used in people who were treated for melanoma at an earlier point and who might be having a recurrence of their disease.

What are the main results of the review?

Ultrasound of regional lymph nodes before sentinel lymph node biopsy

We found 11 relevant studies including 2614 people. Three of these studies compared ultrasound on its own to ultrasound combined with FNAC. Results suggest that the combined procedure correctly identifies around one-fifth of people with metastases in the lymph nodes with very few false positive results (people with incorrect diagnosis of metastasis). These results can be illustrated by imagining a group of 1000 people with melanoma who are going to have sentinel lymph node biopsy, of whom 237 (24%) have metastases in the lymph nodes. The combination of ultrasound with FNAC potentially allows 43 people with lymph node metastases to be identified and avoid a sentinel lymph node biopsy, at a cost of two people with false positive results who might go on to have the wrong treatment. Those with metastases in the lymph nodes that are missed on ultrasound (false negatives) will be identified on subsequent SLNB.

Whole body imaging (detection of any metastases)

We found 24 studies, but only nine were clear about the point in the time course of disease that imaging was carried out. Six studies including 492 people looked at imaging for primary staging following a confirmed diagnosis of melanoma, and three studies in 589 people evaluated re-staging of disease in people with possible recurrence of disease.

Most of the studies (6/9) considered PET-CT, two in comparison to CT alone, and three studies examined the use of ultrasound. We did not find any suitable studies of MRI in these groups.

Overall results suggest that PET-CT is better for correctly identifying people with metastatic spread of disease who might be having a recurrence of disease (re-staging) than people who have a new diagnosis of melanoma (primary staging). PET-CT also seems to be better than CT for identifying spread of disease in both groups of people, but studies were very small and results might not be reliable.

How reliable are the results of the studies included in this review?

In most of our studies, a reliable diagnosis of spread of disease (or reference standard) was made by performing biopsy and by following up with people over time using clinical assessment and imaging. There was often a lack of detail on how patients were followed up and which tests were used. Lots of studies did not include people at clearly defined time points in the disease process, making it difficult to assess the relevance of their results. Reporting of application and interpretation of tests was poor.

To whom do the results of this review apply?

Thirty-three studies were done in Europe (85%), and the rest in North America (n = 4), Asia (n = 1), or Oceania (n = 1). The average age of people in the studies was between 50 and 67 years, and around half were men. Studies mostly included people with melanoma on any part of the body, but two included only people with melanoma on the head or neck. Studies often included people at different stages of disease, and we were not able to look at the accuracy of tests for people at any particular disease stage. Studies were small, and their results might not match what happens in real life.

What are the implications of this review?

Reviewers found some evidence to support the use of imaging with ultrasound combined with FNAC before sentinel lymph node biopsy, but further work is needed to establish cost-effectiveness. Limited evidence is available for whole body imaging for primary staging or re-staging of disease. Available evidence is focused on PET-CT; there are few comparisons with CT and no comparisons with MRI. Future research needs to look at more than test accuracy and must consider the effects of different imaging tests on treatment decisions for patients.

How up-to-date is this review?

The reviewers searched for and included studies published up to August 2016.*

*In these studies, biopsy and clinical or imaging follow-up were the reference standards (methods of establishing the final diagnosis).

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Question	**How accurate is ultrasound, CT, MRI, or PET-CT for staging or re-staging of cutaneous invasive melanoma in adults?**		
Population:	Adults with a confirmed diagnosis of melanoma undergoing imaging for staging purposes: • Before sentinel lymph node biopsy (SLNB) to identify nodal metastases • For full body staging following removal of the primary melanoma • For full body staging due to suspected recurrence of disease		
Index test(s):	Ultrasound with or without fine needle aspiration cytology (FNAC) Computed tomography (CT) Magnetic resonance imaging (MRI) Positron emission tomography-computed tomography (PET-CT)		
Comparator test:	All of the index tests may be used in comparison to each other		
Target condition:	For pre-SLNB imaging: detection of nodal metastases For all other imaging: detection of any metastases		
Reference standard:	Histology plus clinical or imaging follow-up		
Action:	If accurate, positive results of imaging before SLNB in some circumstances could allow patients with nodal metastases to proceed directly to commence adjuvant therapy and avoid an additional invasive procedure (SLNB). Accurate whole body imaging will allow appropriate locoregional and systemic therapies to be initiated in a timely manner		
Quantity of evidence (n = 39 studies)	**Number of studies**	**Number of participants**	**Number of cases**
Per patient data:	34	4980	1265
Per lesion data:	7	417 (1846 lesions)	1061 metastases
Limitations			

Risk of bias:	Some concerns due to poor reporting across almost all domains. Unclear risk for participant selection method (11/39) or exclusions not clearly described (3/39). High risk from exclusions on the basis of index test results (4/39). Low risk for the index test for pre-SLNB ultrasound (6/11), other ultrasound evaluation (3/5), CT (7/10), and MRI (4/4). For PET-CT, unclear risk from lack of description of blinded case note review to ascertain imaging results for retrospective studies (13/23) and high risk from data driven selection of test threshold (1/23). Unclear risk for reference standard from lack of detail on participant follow-up schedules (12/39). Lack of blinding of the histological diagnosis (2/39) or data collection on follow-up (3/39) to the index result. High risk from differential verification (20/39) and participant exclusions (13/39). Low risk for comparisons between tests (6/9)
Applicability of evidence to question:	High or unclear concern for applicability for almost all domains. High concern for participant selection from mixed populations (11/39) or data presented per lesion (5/39). Unclear concern from lack of clarity regarding study population. High concern for index tests from poor description of test thresholds (pre-SLNB ultrasound (1/11), other ultrasound (1/5), CT (5/10), MRI (3/4), PET-CT (4/23)) or consensus test interpretation (CT (6/10), MRI (2/4), PET-CT (11/23)). Unclear concern for application and interpretation of the index test (pre-SLNB US (10/11), CT (3/10), MRI (2/4), PET-CT (6/23)) or unclear observer expertise (pre-SLNB ultrasound (6/11), CT (3), MRI (2/4), PET-CT (6/23)). Unclear concern for applicability of the reference standard from lack of description of the target condition or no breakdown of cases according to nodal or distant metastases. Expertise of the histopathologist poorly described (6/39)

Findings

Thirty-nine studies reporting accuracy data for pre-SLNB imaging (n = 18) or for whole body imaging (n = 24) were included. The 24 studies of whole body imaging were of primary staging (n = 6) or staging for potential recurrence of disease (n = 3), or were conducted in mixed or not clearly described populations (n = 15). As we are unable to make clear statements regarding the expected accuracy of imaging at any particular point on the clinical pathway for the mixed population group, the findings presented are based on results for pre-SLNB imaging, and for primary staging and re-staging of melanoma only

Test: pre-SLNB imaging

Test	Studies: patients (cases)	Sensitivity (95% CI)	Specificity (95% CI)	Numbers in a cohort of 1000 lesions at a median prevalence of 23.7%[a]			
				TP (95% CI)	FN (95% CI)	FP (95% CI)	TN (95% CI)
US	11: 2614 (542)	35.4 (17.0 to 59.4)	93.9 (86.1 to 97.5)	84 (40 to 141)	153 (197 to 96)	47 (106 to 19)	716 (657 to 744)
US + FNAC	3: 1164 (259)	18.0 (3.58 to 56.5)	99.8 (99.1 to 99.9)	43 (8 to 134)	194 (229 to 103)	2 (7 to 1)	761 (756 to 762)

PET-CT	4: 170 (49)	10.2 (4.31 to 22.3)	96.5 (87.1 to 99.1)	24 (10 to 53)	213 (227 to 184)	27 (98 to 7)	736 (665 to 756)

Whole bodyimaging for primary staging of melanoma

Quantity of evidence (n = 6 studies)	Number of studies	Number of participants	Number of cases
Any metastases	3	81	51
Nodal metastases	3	373	68
Distant metastases	2	112	17

Findings

Four of the six studies evaluated PET-CT, one in comparison to CT

- In participants with primary melanomas > 4 mm thick (two studies), sensitivities for the detection of any metastases were 30% (95% CI 7% to 65%) to 47% (95% CI 29% to 65%), and specificities 73% (95% CI 45% to 92%) to 88% (95% CI 68% to 97%).
- One study of any participant referred for PET-CT demonstrated no false positive results for either CT or PET-CT for the detection of nodal metastases (specificity 100%, 95% CI 92% to 100%); however, sensitivity was higher for PET-CT (38%, 95% CI 14% to 68%) compared to CT (23%, 95% CI 5% to 54%). For the detection of distant metastases, two additional cases were detected with PET-CT (sensitivity 42%, 95% CI 15% to 72%) in comparison to CT (25%, 95% CI 5% to 57%) with no difference in specificity (93%, 95% CI 81% to 99%).
- One study of PET-CT suggested an SUVmax threshold $\geq$ 2.2 at baseline and predicted later recurrence with a sensitivity of 89% (95% CI 52% to 100%) and specificity 61% (95% CI 41% to 78%).

No data for MRI were identified. Results for ultrasound for the detection of nodal metastases (2 studies) were highly variable and likely subject to bias

Whole bodyimaging for re-staging of melanoma

Quantity of evidence (n = 3 studies)	Number of studies	Number of participants (lesions)	Number of cases (metastases)
Any metastases:	2 (1)	153 (139)	95 (87)
Nodal metastases:	1	460	37
Distant metastases:	0	N/A	N/A

Findings:

- Two studies of PET-CT for re-staging were pooled; summary sensitivity for the detection of any metastasis was 92.6% (95% CI 85.3% to 96.4%) and specificity 89.7% (95% CI 78.8% to 95.3%) (153 patients, 95 cases).
- In one of the two studies, PET-CT was more sensitive (89%, 95% CI 78% to 96%) than CT alone (increase of 21%). With similar specificity (88%, 95% CI 76% to 95%), PET-CT was more sensitive in the subgroup with stage IIIc to IV disease (100%, 95% CI 81% to 100%) than in those with less advanced disease (84%, 95% CI 69% to 94%). One study of ultrasound in clinically node negative patients undergoing follow-up demonstrated 100% sensitivity (95% CI 91% to 100%) for 'common signs of malignancy' or focal hypoechoic cortical thickening (considered test positive) with a specificity of 93% (95% CI 90% to 95%).

No data for MRI were identified.

[a]Median prevalence observed across 11 studies of pre-SLNB ultrasound (interquartile range: 25th percentile 20.5%, 75th percentile 25.4%).

CT: computed tomography; FN: false negative; FNAC: fine needle aspiration cytology; FP: false positive; MRI: magnetic resonance imaging; PET: positron emission tomography; SLNB: sentinel lymph node biopsy; TN: true negative; TP: true positive.

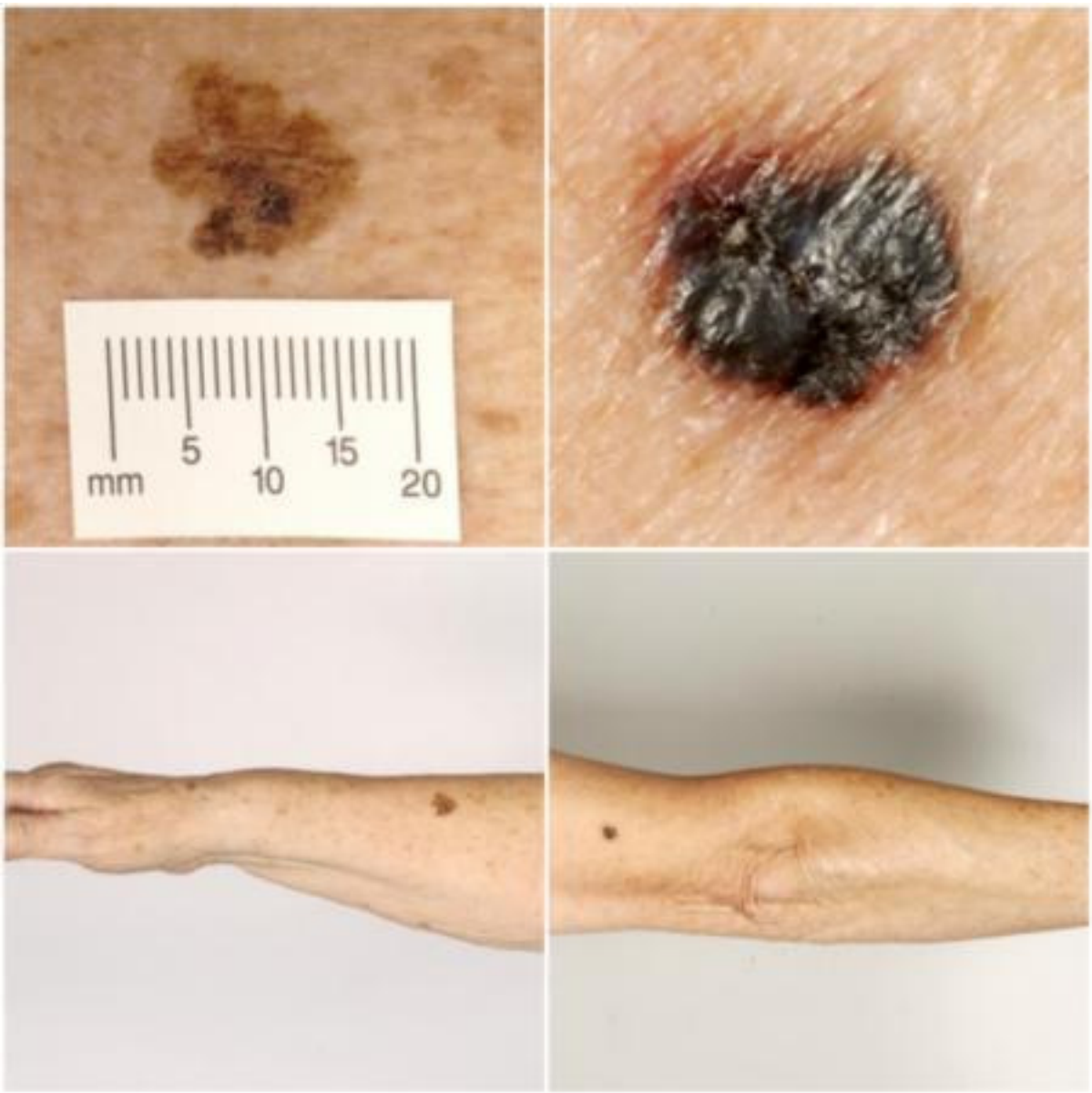
BACKGROUND

This review is one of a series of Cochrane Diagnostic Test Accuracy (DTA) reviews on the diagnosis and staging of melanoma and keratinocyte skin cancers conducted for the National Institute for Health Research (NIHR) Cochrane Systematic Reviews Programme. Appendix 1 shows the content and structure of the programme. Appendix 2 provides a glossary of terms used, and Appendix 3 presents a table of acronyms used.

Target condition being diagnosed

Melanoma is one of the most aggressive forms of skin cancer, with the potential to metastasise to other parts of the body via the lymphatic system and the bloodstream. Melanoma accounts for a small percentage of skin cancer cases but is responsible for up to 75% of skin cancer deaths (Boring 1994; Cancer Research UK 2017). Melanoma arises from uncontrolled proliferation of melanocytes - the epidermal cells that produce pigment or melanin. It most commonly arises in the skin but can occur in any organ that contains melanocytes, including mucosal surfaces, the back of the eye, and the lining around the spinal cord and brain. 'Cutaneous melanoma' refers to a skin lesion with malignant melanocytes present in the dermis, and includes superficial spreading and nodular, acral lentiginous, and lentigo maligna melanoma variants (Figure 1).

Figure 1. Sample photographs of superficial spreading melanoma (left) and nodular melanoma (right).



The incidence of melanoma rose to over 200,000 newly diagnosed cases worldwide in 2012 (Erdmann 2013; Ferlay 2015), with an estimated 55,000 deaths (Ferlay 2015). The highest incidence is observed in Australia, with 11,405 new cases of melanoma of the skin (ACIM 2014), and in New Zealand, with 2341 registered cases in 2010 (Cancer Society of New Zealand 2013). In the USA for 2014, the predicted incidence was 73,870 per annum, and the predicted number of deaths 9940 (Siegel 2015). The highest rates in Europe are seen in northwestern Europe and the Scandinavian countries, with highest incidence reported in Switzerland of 25.8 per 100,000 in 2012. Rates in the UK trebled from 4.6 and 6.0 per 100,000 in men and women, respectively, in England in 1990, to 18.6 and 19.6 per 100,000 in 2012 (EUCAN 2012). In the UK, melanoma has one of the fastest rising incidence rates of any cancer, and it shows the biggest projected increase in incidence between 2007 and 2030 (Mistry 2011). In the decade leading up to 2013, age standardised incidence increased by 46%, with 14,500 new cases in 2013 and 2459 deaths in 2014 (Cancer Research UK 2017a). Although overall incidence rates are higher in women than in men, the rate of incidence in men is increasing faster than in women (Arnold 2014).

The rising incidence of melanoma is thought to be primarily related to rising recreational sun exposure and tanning bed use, along with an increasingly ageing population with higher lifetime recreational ultraviolet (UV) exposure (Boniol 2012; Gandini 2005), in conjunction with possible earlier detection (Belbasis 2016; Linos 2009). Putative risk factors are reviewed in detail elsewhere (Belbasis 2016), but they can be broadly divided into host and environmental factors. Host factors include fair skin and light hair or eye colour; older age (Geller 2002); male sex (Geller 2002); previous skin cancer history (Tucker 1985); predisposing skin lesions (e.g. high melanocytic naevus counts) (Gandini 2005), clinically atypical naevi (Gandini 2005), and large congenital naevi (Swerdlow 1995)); genetically inherited skin disorders (e.g. xeroderma pigmentosum) (Lehmann 2011); and a family history of melanoma (Gandini 2005). Environmental factors include recreational and occupational exposure to sunlight (both cumulative and episodic burning) (Armstrong 1977; Gandini 2005); artificial tanning (Boniol 2012); and immunosuppression (e.g. in organ transplant recipients or human immunodeficiency virus (HIV)-positive individuals) (DePry 2011). Lower socioeconomic class may be associated with delayed presentation and thus more advanced disease at diagnosis (Reyes-Ortiz 2006).

The main prognostic indicators following diagnosis of cutaneous melanoma can be divided into histological and clinical factors. Histologically, Breslow thickness is the single most important predictor of survival, as it is a quantitative measure of tumour invasion or volume, and thus propensity to metastasise (Balch 2001). Other factors associated with poorer prognosis histologically include microscopic ulceration, mitotic rate, microscopic satellites, regression, lymphovascular invasion, and nodular (rapidly growing) or amelanotic (lacking in melanin pigment) subtypes (Moreau 2013; Shaikh 2012). Independent of tumour thickness, prognosis is worse in older people, males, and those with locally recurrent lesions, regional lymph node involvement, or primary lesion location on the scalp or neck (Zemelman 2014).

Following histological confirmation of diagnosis, the lesion is staged according to the American Joint Committee on Cancer (AJCC) Staging System to inform treatment strategy (the eighth version of the Staging System - AJCC 8 - is outlined in Gershenwald 2017). Stage 0 refers to melanoma in situ; stages I to II localised melanoma; stage III regional metastasis (spread to the lymph nodes, usually but not always those nearest to the primary tumour); and stage IV distant metastasis. A preliminary stage is assigned based on histological evaluation (thickness of primary lesion and presence of ulceration) and clinical (and sometimes radiological) assessment of regional lymph nodes. A pathological stage is then confirmed based on histology of the primary lesion and of the regional lymph nodes (if the patient has sentinel lymph node biopsy (SLNB) or completion lymphadenectomy (CLND) for those with clinically palpable lymph nodes) and imaging to confirm the presence or absence of disseminated disease, where indicated.

An American database of over 40,000 patients from 1998 onwards, which assisted the development of AJCC 8, indicated five-year survival of 99% for very early-stage melanoma, dropping to anything between 32% and 93% in stage III disease, depending on tumour thickness, the presence of ulceration, and the number of involved nodes (Gershenwald 2017). Before the advent of targeted therapy and immunotherapies, disseminated melanoma (to distant sites/visceral organs) was associated with median survival of six to nine months, one-year survival of 25%, and three-year survival of 15% (Balch 2009; Korn 2008).

Between 1975 and 2010, five-year relative survival for melanoma (i.e. not including death from other causes) in the United States increased from 80% to 94%, with survival for localised, regional, and distant disease estimated at 99%, 70%, and 18%, respectively, in 2010 (Cho 2014). However, mortality rates showed little change, at 2.1 per 100,000 deaths in 1975, and 2.7 per 100,000 in 2010 (Cho 2014). Increasing incidence of localised disease over the same period (from 5.7 to 21 per 100,000) suggests that much of the observed improvement in survival may be due to earlier detection and heightened vigilance (Cho 2014). New targeted therapies for advanced (stage IV) melanoma (e.g. *BRAF* inhibitors) have improved survival, and immunotherapies are evolving such that long-term survival is being documented (Rozeman 2018). No new data regarding survival prospects for patients with stage IV disease were analysed for the AJCC 8 staging guidelines because of lack of contemporary data (Gershenwald 2017).

Treatment of melanoma

Treatment of melanoma varies to some extent, according to the stage of disease upon diagnosis. For primary melanoma, the mainstay of treatment is complete lesion excision, with a safety margin some distance from the borders of the primary tumour to remove both the tumour and any malignant cells that might have spread into the surrounding skin (Garbe 2016; Marsden 2010; NICE 2015a; SIGN 2017; Sladden 2009). Recommended surgical margins vary according to tumour thickness - Garbe 2016 - and stage of disease at presentation - NICE 2015a. Evidence for further local or regional interventions such as wider surgical margins is limited (Sladden 2009; Wheatley 2016), although further trials in this area are planned.

Sentinel lymph node biopsy has been offered to those without clinically palpable lymph nodes as a means of providing prognostic information for several years, with the option of CLND in the event of a positive result (metastases identified on SLNB). Recent data (MLST II - Kyrgidis 2015 and Morton 2014 - and DeCOG - Leiter 2016 and Leiter 2018 - trials) show no survival benefit from CLND for this patient group, and the procedure is no longer a standard of care for most patients. Recent advances demonstrating longer recurrence-free survival for patients with stage III melanoma receiving *BRAF*-directed therapy or immunotherapies have resulted in use of SLNB as a test to identify patients who should be offered adjuvant treatment (Eggermont 2016; Eggermont 2018; Long 2017; Weber 2017). Currently available guidelines do not, as yet, reflect this recent change in practice (Garbe 2016; NICE 2015a). In the UK, the National Institute for Health and Care Excellence (NICE) has already approved dabrafenib and trametinib for adjuvant treatment of resected *BRAF* V600 mutation positive melanoma (NICE 2018a), with further appraisals of pembrolizumab for adjuvant treatment of melanoma with high risk of recurrence (NICE 2018b), as well as ongoing appraisals of nivolumab for adjuvant treatment of resected stage III and IV melanoma (NICE 2019a).

For stage IV melanoma, dacarbazine was the only drug approved worldwide for many years, with fotemustine used in some European countries (Avril 2004), and interleukin (IL)-2 given in the USA (Atkins 1999). Temozolomide has also been used, especially for people with brain metastases, because of its strong ability to pass the blood-brain barrier (Lukas 2014; Zhu 2014). This landscape has changed dramatically, with two distinct therapeutic approaches suggesting survival benefit in metastatic melanoma: (1) targeting mutations in tumour cells, and (2) providing immunomodulation (Chapman 2011; Chapman 2012; Dummer 2014; Hamid 2013; Hodi 2010; Larkin 2014; Robert 2015; Villanueva 2010). Several different therapies have now shown high response rates and, most important, have demonstrated for the first time in the treatment of melanoma the potential for a durable clinical response (Chapman 2011; Hamid 2013; Hodi 2010; Hodi 2016; Larkin 2015; Maio 2015; Sznol 2013). Several therapies are now recommended for use alone or in combination for particular subgroups of patients with metastatic melanoma, both in the UK - NICE 2018a - and beyond - Garbe 2016 - and have recently been the topic of a Cochrane Review (Pasquali 2018). An appraisal of encorafenib with binimetinib for advanced *BRAF* V600 mutation positive melanoma is under way (NICE 2019b), and several other treatments are currently suspended pending marketing authorisation applications from the companies concerned (NICE 2018c).

Psychosocial interventions to improve quality of life and general psychological distress after diagnosis for patients with cancer are also available. However, a Cochrane Review found considerable variation in the evidence to support such interventions (Galway 2012).

Index test(s)

Accurate staging of melanoma is more important than ever, in part to avoid unnecessary treatment and associated morbidity in those with early-stage disease, and in part to ensure that potentially effective therapies are initiated in a timely manner for those with nodal or distant metastatic disease.

Imaging techniques such as ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI) scans can be undertaken at several points along the clinical pathway, including on initial presentation of disease (primary staging), on development of recurrence (re-staging), and on follow-up after previous treatment for those who are asymptomatic for recurrence. The use of imaging during follow-up with no specific clinical indication for imaging (i.e. as a monitoring test for disease surveillance) is not the focus of our reviews. Historically, most staging in terms of imaging has been undertaken in people with clinical stage III and IV disease (see Clinical pathway). However, this landscape is changing as more adjuvant systemic therapies for melanoma are becoming available.

Imaging tests are typically undertaken and interpreted by radiologists, with decisions about patient management following imaging or SLNB made at multi-disciplinary team meetings that include oncologists, dermatologists, and surgeons (Clinical pathway).

Ultrasound

Ultrasound uses high-frequency sound waves to create images of the body. Ultrasound can be used to assist in detection of diseased lymph nodes with clinically node negative melanoma; in treatment of patients who have a positive imaging result, proceeding to fine needle aspiration cytology (FNAC) or core biopsy; and in treatment of patients who are negative on ultrasound alone or on ultrasound combined with FNAC proceeding to SLNB. A 2011 systematic review identified 21 studies of ultrasound for primary lymph node staging or surveillance; for primary staging, sensitivity was 60% for detection of diseased lymph nodes, with specificity of 97% (the number of studies that considered staging vs surveillance is unclear) (Xing 2011).

Computed tomography (CT) (non-contrast-enhanced or contrast-enhanced)

Computed tomography scans use ionising radiation in the form of X-rays to take cross-sectional images of the body (Bluemm 1983; van Waes 1983). This procedure involves varying amounts of radiation according to the area of the body to be scanned (Mahesh 2017), and it can be conducted with an intravenous contrast agent (contrast-enhanced) to increase the sensitivity of metastasis detection in solid organs.

Mohr 2009 describes contrast-enhanced CT as the best method of identifying intrathoracic metastases and as superior to X-ray for detection of mediastinal and hilar adenopathy associated with lymphatic spread and for assessment of lesions in the bone. Computed tomography can also be used for assessment of metastatic spread to the brain, but magnetic resonance imaging (MRI) is considered more sensitive (Goulart 2011). Overall specificity is reportedly high for detection of regional nodal and distant disease, but sensitivity varies from 23% to 85% for detection of lymph node metastases, and from 25% to 74% for assessment of distant spread (Xing 2011).

Magnetic resonance imaging (MRI) (non-contrast-enhanced or contrast-enhanced)

Magnetic resonance imaging scans use large magnets and non-ionising radiation in the form of radio waves to generate images of the body (Ai 2012). These scans are more expensive and take longer to carry out compared to CT scans (Whaley 2016b).

We did not identify any systematic reviews of MRI for melanoma staging through our scoping searches; however, several studies have considered whole body MRI (Jouvet 2014; Mosavi 2013), as well as MRI for detection of brain or hepatic metastases (Aukema 2010a; Sofue 2012). Because melanoma is one of the top three cancers responsible for brain metastases (Cagney 2017), the body of evidence for the incremental accuracy of MRI compared with other imaging tests must be considered.

PET-CT (positron emission tomography-computed tomography)

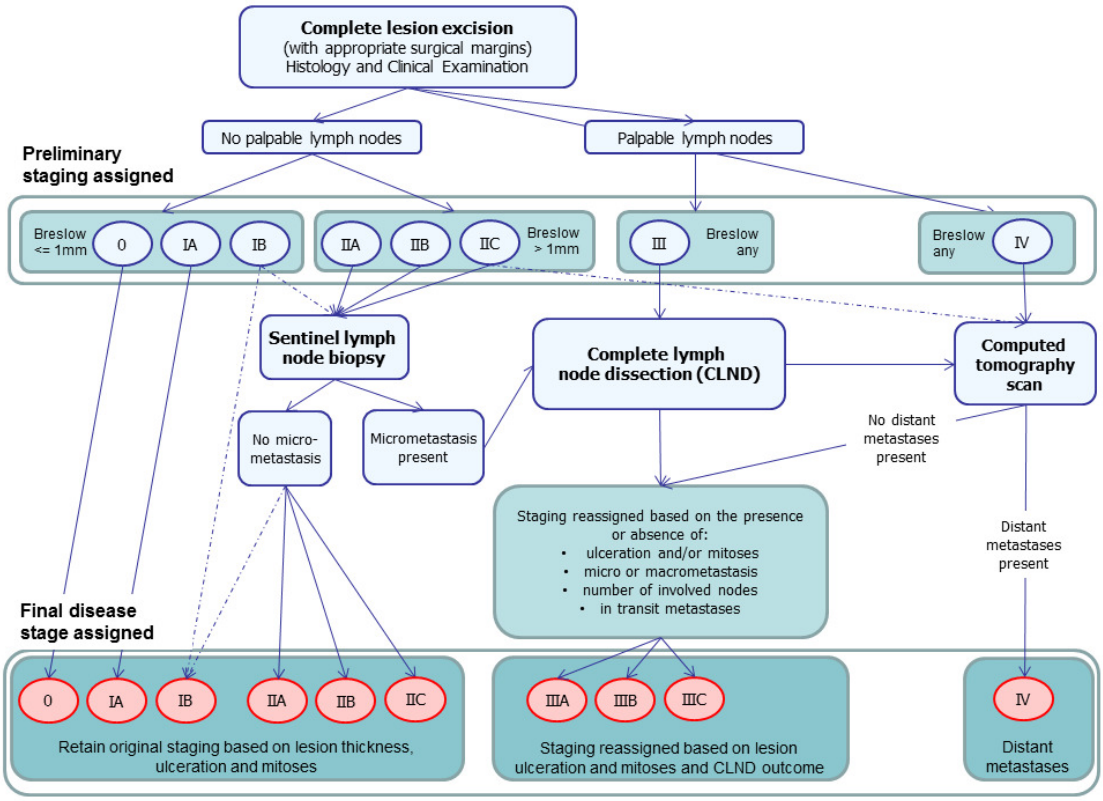
Positron emission tomography-computed tomography is a hybrid imaging technique that provides both functional and anatomical information. It involves injection of a weakly radioactive positron-emitting radiopharmaceutical, which is usually 2-deoxy-2-[^{18}F]fluoro-D-glucose (FDG), for the purposes of oncological imaging. The distribution of FDG throughout the body is represented on images, with malignant tissue usually demonstrating greater levels of FDG uptake than normal tissue (Lammertsma 2017). The low-dose CT component of the study generates attenuation factors that improve the quality of PET images and allows accurate anatomical localisation of areas of FDG uptake (IAEA 2016). Although initially, PET scanners were stand-alone devices, since 2004, all modern scanners have been integrated PET-CT scanners (Jones 2017). A systematic review of the added value of integrated PET-CT compared to PET alone across a range of cancers suggested a 10% increase in sensitivity of PET-CT compared to PET alone from a meta-analysis of 10 comparative studies (Gao 2013). For these reasons, PET alone has not been considered as an index test for this review.

In comparison to CT alone, PET-CT is generally considered to be a more sensitive test (Xing 2011); however, increases in sensitivity must be linked to any patient benefit in terms of changes in management and ultimately in patient outcomes (Schroer-Gunther 2012; Subesinghe 2013). It may be that PET-CT has the greatest added value for metastases in areas that are difficult to image with CT or other imaging modalities (Tan 2012), or for indeterminate metastases in areas such as the lung. Whether these assumptions are supported by current evidence has yet to be established. The evidence report for the NICE guideline in 2015 found no evidence "to suggest that earlier treatment of metastatic disease improves survival and therefore increased sensitivity was viewed currently as not an important issue" (NICE 2015d). With adjuvant therapy now an increasing option for melanoma, this conclusion seems likely to be revised in a future guideline update.

Clinical pathway

Staging of confirmed melanoma takes place in secondary and tertiary care settings only (NICE 2015a). Recommendations on the management of melanoma following diagnosis, published in the 2015 NICE Guideline (NICE 2015a), as well as in other UK guideline documents (Burkill 2014; Marsden 2010; Melanoma Taskforce 2011), are summarised in Figure 2 and are outlined below; however, practice varies across the UK. It is important to note that clinical practice is changing as more adjuvant therapies are licensed for the treatment of melanoma, and this is not adequately reflected by current guidelines. However, a consensus statement reflecting changes in decision thresholds for the use of SLNB for staging of melanoma has been published (Melanoma Focus 2018). Any key variations in practice recommended in European or US guidelines (ESMO 2019; Swetter 2019), or under consideration in a current Australian guideline update (Cancer Council Australia 2019; Gyorki 2018; Millward 2018; Morton 2018; Saw 2018), are also reflected below.

Figure 2. Summary of 2015 NICE guideline recommendations for the management of cutaneous melanoma following primary diagnosis (NICE 2015a); not necessarily reflective of current practice.



Following complete excision of the primary lesion, all patients should undergo preliminary staging. This involves a detailed clinical history to determine if there are any symptoms such as weight loss suggesting metastatic spread of disease, followed by a thorough clinical examination, including whole body skin examination, palpation of the lymph nodes, and full abdominal and chest examination (Figure 2). A preliminary stage is assigned on the basis of histopathology results for the primary lesion(s). Those with palpable lymph nodes are automatically assigned to clinical stage III or IV, and those with no palpable lymph nodes are assigned a stage between 0 and IIC, according to the thickness of the tumour (Breslow) and the presence of ulceration (Gershenwald 2017).

The results of all investigations carried out during the process of diagnosis are discussed at a multi-disciplinary team meeting (Melanoma Taskforce 2011), where decisions regarding further staging procedures are made. This could be a local skin multi-disciplinary team or, for those with stage IIB disease and above, a specialist skin multi-disciplinary team (Marsden 2010). Teams should include dermatologists, surgeons (including plastic surgeons), medical and clinical oncologists, radiologists, histopathologists, skin cancer nurse specialists, physiotherapists, psychologists, lymphoedema service providers, occupational therapists, and cosmetic camouflage advisors (Melanoma Taskforce 2011).

On current UK guidance (based on AJCC version 7 (Balch 2009)), no further staging investigations beyond a full clinical examination are recommended for people with thin melanomas (≤ 1 mm) without ulceration or mitoses, and SLNB is reserved for those with stage IB or stage II disease (NICE 2015a). Current practice is now based on staging according to AJCC version 8, for example, with 'thin' melanomas now defined as < 0.8 mm in thickness without evidence of ulceration (Gershenwald 2017). Furthermore, with the advent of new adjuvant therapies, SLNB is now considered essential in determining eligibility for systemic adjuvant therapy (Gyorki 2018; Melanoma Focus 2018; Swetter 2019), and imaging is used in sentinel node positive patients to confirm absence of further disease spread (ESMO 2019; Swetter 2019). SLNB is recommended for those with primary melanoma greater than 1.0 mm and should be considered for some patients with thinner melanomas (i.e. melanomas < 0.8 mm with ulceration, and

melanomas 0.8 to 1.0 mm with or without ulceration), especially in the presence of lymphovascular invasion or a mitotic rate of at least 2 per mm² (Melanoma Focus 2018). Those with clinically palpable lymph nodes or with significant nodal disease identified on imaging are likely to undergo CLND, with the option of adjuvant therapy for those with no evidence of distant metastases.

Available recommendations on the optimal choice of imaging tests vary to some extent, even within the UK (Burkill 2014; Melanoma Focus 2014; NICE 2015a). Computed tomography is generally the imaging test of choice; however, some centres additionally offer high-resolution ultrasound, MRI, or PET-CT scans. The National Institute for Health and Care Excellence recommends CT staging to identify those who may benefit from systemic therapy among those with stage IIC, stage III, or suspected stage IV disease (NICE 2015a), as well as imaging of the brain (with CT for adults and MRI for children and young adults) only if metastatic disease outside the central nervous system is suspected (NICE 2015a). However, the Melanoma Focus position paper recommends that all 'high-risk' patients should undergo CT of the chest, abdomen, and pelvis (or whole body PET-CT), plus MRI of the head, as standard treatment (Melanoma Focus 2014). In current clinical practice, eligibility for imaging is likely to diverge from both of these target groups; however, the emergence of new treatment options is not likely to impact the choice of imaging tests performed nor body sites imaged.

European guidelines recommend pre-SLNB baseline lymph node (LN) ultrasound for stage IB to IIA disease, and CT or PET for stage IIB and upwards (ESMO 2019). Australian guidelines in Morton 2018 and US guidelines in Swetter 2019 recommend against baseline imaging for all asymptomatic and clinically node negative patients. In the United States, CT or PET-CT may be considered for sentinel lymph node (SLN) positive disease but otherwise should be reserved for investigation of specific signs or symptoms or nodal or distant metastases (Swetter 2019). In Australia, US and FNAC are recommended to identify the extent of regional LN involvement in clinically node positive melanoma (Saw 2018), as well as whole body PET-CT with CT or MRI of the brain for clinical stage III or IV disease (Saw 2018; Millward 2018).

The Royal College of Radiologists guideline recommends that scans should be tailored according to the site of the primary lesion and most likely the regional lymph node basin. In general, CT imaging of the head, chest, abdomen, and pelvis should be employed for lower limb and lower body wall lesions, with CT of the neck added for upper limb, scalp, neck, and upper torso primary tumours (Burkill 2014). Magnetic resonance imaging may be more appropriate for imaging the central nervous system (Burkill 2014). Although PET-CT has been suggested to have a role in imaging the lower limbs, further evidence is required (Burkill 2014).

Genotyping is also now offered to identify *BRAF* mutations to allow further planning of systemic treatment (Melanoma Taskforce 2011; NICE 2018a; NICE 2019b).

Prior test(s)

Consideration of the degree of prior testing that study participants have undergone is key to interpretation of resulting test accuracy indices, which are known to vary according to the spectrum or case mix of included participants (Lachs 1992; Leeflang 2013; Moons 1997; Usher-Smith 2016). Prior testing can be considered in two ways. First, the results of any tests undertaken around the time of application of the index test may contribute to the decision to undertake the index test in any particular study participant. For example, PET-CT may be undertaken because of the presence of high-risk primary melanoma characteristics or because of abnormal findings on abdominal ultrasound or chest X-ray; the likelihood of abnormal findings on PET-CT, and therefore sensitivity or specificity, may be influenced by the results of any tests previously undergone.

Second, prior testing can be considered in terms of the place on the clinical pathway or the time course of disease that patients have reached. People undergoing imaging for staging following a primary diagnosis of melanoma are less likely to have metastatic spread of disease compared to those for whom imaging is prompted by signs of recurrence, and the nature of any disease spread is likely to vary between a primary staging population and patients undergoing follow-up, who may have already undergone previous treatment such as complete lymphadenectomy. Reinhardt 2006 evaluated the accuracy of CT, PET, and PET-CT in 250 participants with melanoma "at different time points in the course of disease", including primary staging after sentinel node biopsy (n = 75); therapy control after chemotherapy for metastatic disease (n = 42); staging of clinically suspected recurrent disease (n = 65); and assessment during follow-up within five years of primary treatment (n = 68). For both nodal and distant staging, the overall sensitivity and specificity of each test masked likely variations in accuracy between subgroups. For example, the overall sensitivity and specificity of CT for detection of nodal metastases were 85% and 87%, but when estimated for each subgroup of participants, the sensitivity of CT ranged from 67% for those undergoing follow-up to 93% for those having imaging for treatment evaluation, and specificities ranged from 73% for the treatment evaluation group to 93% for those having primary staging (Reinhardt 2006). The overall pooled analysis suggested statistically significant differences in sensitivities (CT 73% vs PET-CT 99%; $P < 0.0001$) and in specificities (CT 88% vs PET-CT 98%; $P < 0.0001$) for detection of distant metastases, but for the primary staging subgroup, no difference in sensitivities was observed (93.8% for both tests) and the difference in specificities was non-significant (CT 94.9% vs PET-CT 98.3%) (Reinhardt 2006). For the re-staging subgroup, differences in both sensitivities (CT 85% vs PET-CT 100%) and specificities (CT 79% vs PET-CT 96%) between tests were observed (Reinhardt 2006). Although subgroup numbers were relatively small, these findings lend support to the hypothesis that the clinical pathway does affect test accuracy in this context, although as for other tests and diseases, the mechanisms of action can be

complex and difficult to identify (Leeflang 2013).

Role of index test(s)

Ultrasound with FNAC as a triage test before SLNB was originally promoted as having a role in fast-tracking those with positive cytology results (micro-metastases identified) to CLND, while those with negative cytology may proceed to SLNB, as required (Voit 2014). With the changing clinical pathway and lack of evidence for survival benefit from CLND (Leiter 2018; Morton 2014), the only potential role for ultrasound and FNAC in the UK is considered to be seen at centres where SLNB is not immediately available (with a positive cytology result indicating that adjuvant therapy should be initiated); however this approach is still recommended for use following primary melanoma diagnosis in Europe (ESMO 2019), as well as for clinically node positive melanoma in Australia (Saw 2018).

No role has been recommended for imaging tests in early-stage disease. The need to rule out distant metastases among those who are otherwise eligible for adjuvant therapy suggests that imaging might now be used in a much more broadly defined patient group than previously. To date, CT has been recommended as the imaging approach of choice for detection of nodal and distant spread for those with stage III or IV disease (and for those with stage IIC if no SLNB has been performed) (NICE 2015a). Positron emission tomography-computed tomography is increasingly used; however, practice varies across the country, primarily according to availability. The advantages of disease management derived from PET-CT are not yet known. The most appropriate role for MRI in staging melanoma in adults, other than for central nervous system disease, remains unclear.

Alternative test(s)

Several other tests may be used to inform disease management following a diagnosis of melanoma.

Sentinel lymph node biopsy, which allows detection of metastatic spread to the regional lymph node basins, is the topic of another review in this series of reviews (Ferrante di Ruffano 2019).

Core needle biopsy of the lymph nodes, as in Whaley 2016a, or FNAC, as in Hall 2013, to confirm the presence of macro-metastases can be guided by simple palpation or, for more deep-seated lesions, via image-based guidance to identify micro-metastases (requiring use of a microscope for visualisation) (Bohelay 2015). Although the accuracy of core needle biopsy compared to fine needle aspiration has been identified as a key clinical question for investigation, this topic is beyond the scope of these reviews, which focus primarily on detection of non-palpable metastatic disease.

Genetic testing of primary melanoma specimens, for *BRAF* mutations for example, is used increasingly (NICE 2015a), particularly with the emergence of systemic treatments for *BRAF* V600 mutation positive melanoma (Chapman 2011; Chapman 2012; Larkin 2014; Larkin 2015). However, its purpose is to inform systemic treatment decisions rather than to serve as an integral part of the staging procedure itself. Biomarkers, such as S100, are used in countries such as Germany as a marker of prognosis (Gray 2014), or of early disease relapse (Peric 2011), rather than for staging purposes per se (Egberts 2010; Pirpiris 2010), and lactate dehydrogenase (LDH) is part of AJCC staging for stage IV (Pirpiris 2010); however, these approaches are beyond the scope of our reviews.

Rationale

Appropriate staging of melanoma is crucial for ensuring that patients are directed to the most appropriate and effective treatment. Several tests are available to assist in the staging of melanoma; however, their comparative accuracy for detection of nodal or distant metastases, or both, according to histological stage at presentation is unclear.

The NICE guideline recommendations for staging (see Clinical pathway) were based on available systematic reviews of both SLNB and imaging tests (Hall 2013; Jimenez-Requena 2010; Krug 2008; Rodriguez 2014; Valsecchi 2011; Xing 2011), with some supplementary data derived from primary studies (NICE 2015d). Most reviews are limited in terms of currency (de Rosa 2011; Jimenez-Requena 2010; Krug 2008; Valsecchi 2011; Warycha 2009; Xing 2011), with literature searches in most cases extending only as recently as 2009 (Jimenez-Requena 2010; Krug 2008; Valsecchi 2011; Xing 2011). Furthermore, the only review that compared accuracy across imaging tests did not consider histological stage (Xing 2011). Two reviews provide a more recent evaluation of PET and PET-CT (search dates up to 2012 and 2011, respectively) (Rodriguez 2014; Schroer-Gunther 2012); however, the Schroer-Gunther 2012 review also relied on previously published reviews (Jimenez-Requena 2010; Krug 2008), with supplementary searching for more recently published studies, and the Rodriguez 2014 review included only stage III melanoma. The Schroer-Gunther 2012 review relied on quality assessment that was carried out for the original systematic reviews, and only a small number of studies were eventually included; the review authors themselves recommend that future reviews should include a broader range of study designs (Schroer-Gunther 2012).

The comparative accuracy of imaging tests according to stage of disease therefore remains to be determined. Furthermore, any evidence for or against the routine use of brain scanning in stage III melanoma with either CT or MRI remains to be identified. Positron emission tomography-computed tomography is increasingly used, but any additional role of this test compared with CT or MRI needs to be examined according to particular patient groups.

This review follows a generic Cochrane DTA protocol for staging of melanoma (Dinnes 2017). The Background and Methods sections of this review therefore include some text that was originally published in the protocol (Dinnes 2017), along with text that overlaps some of our other reviews for the diagnosis or staging of melanoma (e.g. Dinnes 2018; Ferrante di Ruffano 2019).

OBJECTIVES

Primary objectives

We estimated accuracy separately according to the point in the clinical pathway at which imaging tests were used. Our objectives were:

- to determine the diagnostic accuracy of ultrasound or PET-CT for detection of nodal metastases before sentinel lymph node biopsy in adults with confirmed cutaneous invasive melanoma; and
- to determine the diagnostic accuracy of ultrasound, CT, MRI, or PET-CT for whole body imaging in adults with cutaneous invasive melanoma:
  - for detection of any metastasis in adults with a primary diagnosis of melanoma (i.e. primary staging at presentation); and
  - for detection of any metastasis in adults undergoing staging of recurrence of melanoma (i.e. re-staging prompted by findings on routine follow-up).

We undertook separate analyses according to whether accuracy data were reported per patient or per lesion.

Secondary objectives

We sought to determine the diagnostic accuracy of ultrasound, CT, MRI, or PET-CT for whole body imaging (detection of any metastasis) in mixed or not clearly described populations of adults with cutaneous invasive melanoma.

For study participants undergoing primary staging or re-staging (for possible recurrence), and for mixed or unclear populations, our objectives were:

- to determine the diagnostic accuracy of ultrasound, CT, MRI, or PET-CT for detection of nodal metastases;
- to determine the diagnostic accuracy of ultrasound, CT, MRI, or PET-CT for detection of distant metastases; and
- to determine the diagnostic accuracy of ultrasound, CT, MRI, or PET-CT for detection of distant metastases according to metastatic site.

Investigation of sources of heterogeneity

We aimed to consider a range of potential sources of heterogeneity for investigation, as outlined in our generic protocol and described in Appendix 4, but insufficient data were identified to allow any heterogeneity investigations to be undertaken.

METHODS

Criteria for considering studies for this review

Types of studies

We included test accuracy studies that allow comparison of results of the index test versus a reference standard, including:

- prospective and retrospective studies;
- studies where all participants receive a single index test and a reference standard;
- studies where all participants receive more than one index test(s) (concurrently) and a reference standard;
- studies where participants are allocated (by any method) to receive different index tests or combinations of index tests and all receive a reference standard (between-person comparative studies);
- studies that recruit a series of participants unselected by true disease status; and
- diagnostic case-control studies that separately recruit diseased and non-diseased groups (Rutjes 2005).

We excluded follow-up and surveillance studies using repeated imaging tests to detect disease recurrence, as defining the most appropriate follow-up schedule for melanoma patients is not the primary objective of these reviews.

We excluded studies if it was not possible to derive the numbers of true positives, false positives, false negatives, and true negatives from data provided in the paper, and we excluded small studies with fewer than five disease positive or fewer than five disease negative participants or lesions identified on imaging. Although the size threshold of five is arbitrary, such small studies are likely to yield unreliable estimates of sensitivity or specificity, and are unlikely to add precision to estimates of accuracy.

We included studies reporting either lesion-based or participant-based analyses; however, we accorded more weight to those reporting data on a per participant basis as detection of multiple metastatic sites in an individual patient may have a disproportionate effect on estimates of test accuracy based on per lesion data. Furthermore, treatment following staging is generally directed to the patient rather than to the individual metastatic lesion, making the patient the more appropriate unit of analysis.

We excluded studies available only as conference abstracts.

Participants

We included studies in adults with cutaneous melanoma at any primary site who were undergoing staging, either following primary presentation of disease or following recurrence of disease. We included for completeness studies that included mixed populations of patients, or where the clinical pathway could not be determined, but we undertook no statistical pooling. We included studies if up to 10% of participants had other forms of melanoma such as ocular or mucosal melanoma. We included studies with greater proportions of participants with non-cutaneous melanoma

and studies including participants with other forms of cancer only if test results for participants with cutaneous melanoma could be differentiated.

Index tests

Studies reporting accuracy data for a *single application* of one or more of the following tests were eligible for inclusion.

- Ultrasound (with or without subsequent FNAC or core biopsy).
- CT (non-contrast-enhanced or contrast-enhanced).
- PET-CT (^{18} FDG only).
- MRI (non-contrast-enhanced or contrast-enhanced).

We included any threshold for deciding test positivity, either qualitative or quantitative.

We excluded studies reporting *multiple applications of the same test* in more than 10% of study participants because of anticipated effects on test accuracy (multiple tests increasing the chance of detection of metastases, thereby increasing test sensitivity and reducing specificity). The threshold of 10% is arbitrary but allows for inclusion of studies primarily focused on evaluating the accuracy of a single test application for staging of disease. We excluded studies of surveillance imaging following initial definitive treatment.

Target conditions

Primary target conditions were defined as detection of:

- nodal metastases in participants scheduled for SLNB (to identify those who should proceed directly to CLND); and
- any metastases for all other staging.

Two additional definitions of the target condition were considered in secondary analyses, namely, detection of:

- any nodal metastases; and
- any distant metastases (combined or by metastatic site).

Reference standards

Acceptable reference standards include:

- histology of lymph node or distant specimens, with samples obtained by core biopsy, SLNB, or lymph node dissection;
- cytology of lymph node specimens, with samples obtained by core biopsy or fine needle aspiration;
- clinical or radiological follow-up to identify nodal or distant recurrence of at least three months; and
- any combination of the above.

We excluded studies using cross-sectional imaging-based reference standards (i.e. direct comparison of the index test vs an alternative reference standard imaging test).

Search methods for identification of studies

Electronic searches

The Information Specialist (SB) carried out a comprehensive search for published and unpublished studies. A single large literature search was conducted to cover all topics in the programme grant (see Appendix 1 for a summary of reviews included in the programme grant). This allowed screening of search results for potentially relevant papers for all reviews at the same time. A search combining disease-related terms with terms related to test names, using both text words and subject headings, was formulated. The search strategy was designed to capture studies evaluating tests for the diagnosis or staging of skin cancer. As a majority of records were related to searches for tests for staging of disease, a filter using terms related to cancer staging and to accuracy indices was applied to the staging test search to try to eliminate irrelevant studies, for example, those using imaging tests to assess treatment effectiveness. A sample of 300 records that would be missed by applying this filter was screened and the filter adjusted to include potentially relevant studies. When piloted on MEDLINE, inclusion of the filter for staging tests reduced the overall numbers by around 6000. The final search strategy, incorporating the filter, was subsequently applied to all bibliographic databases as listed below (Appendix 5). The final search result was cross-checked against the list of studies included in five systematic reviews; our search identified all but one of these studies, and this study was not indexed on MEDLINE. The Information Specialist devised the search strategy, with input from the Information Specialist from Cochrane Skin. No additional limits were used.

We searched the following bibliographic databases to 29 August 2016 for relevant published studies.

- MEDLINE via OVID (from 1946).
- MEDLINE In-Process & Other Non-Indexed Citations via OVID.
- Embase via OVID (from 1980).

We searched the following bibliographic databases to 30 August 2016 for relevant published studies.

- Cochrane Central Register of Controlled Trials (CENTRAL; 2016, Issue 7), in the Cochrane Library.
- Cochrane Database of Systematic Reviews (CDSR; 2016, Issue 8), in the Cochrane Library.
- Cochrane Database of Abstracts of Reviews of Effects (DARE; 2015, Issue 2).
- CRD HTA (Health Technology Assessment) database (2016, Issue 3).
- Cumulative Index to Nursing and Allied Health Literature (CINAHL) via EBSCO from 1960.

We searched the following databases for relevant unpublished studies using a strategy based on the MEDLINE search.

- Conference Proceedings Citation Index (CPCI), via Web of Science™ (from 1990; searched 28 August 2016).
- Science Citation Index (SCI) Expanded™ via Web of Science™ (from 1900, using the 'Proceedings and Meetings Abstracts' Limit function; searched 29 August 2016).

We searched the following trials registers using the search terms 'melanoma', 'squamous cell', 'basal cell', and 'skin cancer' combined with 'diagnosis'.

- Zetoc (from 1993; searched 28 August 2016).
- US National Institutes of Health Ongoing Trials Register (www.clinicaltrials.gov; searched 29 August 2016).
- NIHR Clinical Research Network Portfolio Database (www.nihr.ac.uk/research-and-impact/nihr-clinical-research-network-portfolio/; searched 29 August 2016).
- World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch/; searched 29 August 2016).

We aimed to identify all relevant studies regardless of language or publication status (published, unpublished, in press, or in progress), but because of time constraints, we were unable to follow up on potentially relevant studies identified from conference abstracts. We applied no date limits.

Searching other resources

We screened relevant systematic reviews identified by the searches for their included primary studies, and we included any missed by our searches. We checked the reference lists of all included papers, and subject experts within the author team reviewed the final list of included studies. We conducted no electronic citation searching.

Data collection and analysis

Selection of studies

At least one review author (JDi or NC) screened titles and abstracts and discussed and resolved any queries by consensus. A pilot screen of 539 MEDLINE references showed good agreement (89% with a kappa of 0.77) between screeners. Primary test accuracy studies and test accuracy reviews (for scanning of reference lists) of any test used to investigate suspected melanoma, basal cell carcinoma (BCC), or cutaneous squamous cell carcinoma (cSCC) were included at initial screening. Inclusion criteria were applied independently by both a clinical review author (from one of a team of 12 clinician reviewers) and a methodologist review author (JDi, NC, or LFR) to all full-text articles, and disagreements were resolved by consensus or by a third party (JDe, CD, HW, RM) (Appendix 6). No study authors were contacted in regard to study eligibility because of the volume of data retrieved. Authors of eligible studies were contacted when insufficient data were presented to allow for construction of 2×2 contingency tables.
The study selection process is described in a PRISMA-DTA flowchart (McInnes 2018).

Data extraction and management

One clinical (SAC, AD, AG, LP) and at least one methodologist review author (LFR, JDi) extracted data concerning details of study design, participants, index test(s) or test combinations, criteria for index test positivity, reference standards, and data required to populate a 2×2 diagnostic contingency table for each index test using a piloted data extraction form. Disagreements were resolved through discussion or by a third party (JDe, CD, HW, RM).

Dealing with multiple publications and companion papers

In the event of multiple reports of a primary study, the most complete and up-to-date data source available was used to contribute 2×2 contingency table data to eliminate double-counting of datasets. When possible, yield of information regarding study methods and participants was maximised by extracting relevant data from multiple publications.

Assessment of methodological quality

We assessed risk of bias and applicability of included studies using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) checklist (Whiting 2011), which had been tailored to the review topic (Appendix 7). We piloted the modified QUADAS-2 tool on a small number of included full-text articles. One clinical (as detailed above) and at least one methodologist review author (LFR, JDi, BH, or SB) independently assessed quality for the remaining studies; any disagreement was resolved by consensus or by a third party when necessary (JDe, CD, HW, RM).

Statistical analysis and data synthesis

We conducted separate analyses first according to whether study participants were recruited on primary presentation of melanoma or with a disease recurrence, and second according to our primary and secondary objectives (i.e. detection of any metastasis (which must include both nodal and distant recurrence) and detection of nodal metastasis alone or detection of any distant metastasis, as defined under Target condition being diagnosed).
Studies may report test accuracy per lesion or per patient. Our unit of analysis for primary analyses was the patient, as study participants may have multiple metastatic sites at any one time, such that a per lesion analysis may overestimate test accuracy.
We initially explored the data by plotting estimates of sensitivity and specificity on coupled forest plots and in receiver operating characteristic (ROC) space for each index test. We performed

meta-analyses using the bivariate method to produce summary operating points (summary sensitivities and specificities) with 95% confidence and prediction regions (Chu 2006; Macaskill 2010; Reitsma 2005). When few studies were available for a meta-analysis, we simplified the bivariate model to univariate fixed-effect or random-effects logistical regression models depending on whether or not heterogeneity was observed on forest plots and in ROC space (Takwoingi 2015). If there were only two or three studies and we observed heterogeneity on the plots, we did not pool the data, as a fixed-effect approach would be inappropriate and the number of studies too small to reliably estimate random effects.

To compare the accuracy of the index tests, we performed both direct and indirect test comparisons, as comparative studies are scarce (Takwoingi 2013). To formally compare index tests, we added a co-variate for test type to a bivariate model (i.e. bivariate meta-regression). We used likelihood ratio tests to assess the statistical significance of differences in sensitivity and specificity by comparing models without the co-variate terms versus models containing the co-variate terms. Using parameter estimates from bivariate meta-regression models, we calculated absolute differences in sensitivity and specificity. We obtained 95% confidence intervals and P values for these differences using the delta method and the Wald test, respectively. When the number of studies in a direct comparison was insufficient for meta-regression, we examined individual study results and computed absolute differences in sensitivity and specificity for each comparative study. We calculated 95% confidence intervals (CIs) for these differences using the Newcombe-Wilson method without continuity correction (Newcombe 1998).

We conducted analyses using Review Manager 5 (Review Manager 2014), along with the *meqrlogit* command in the statistical software STATA version 15 (STATA 2017).

Investigations of heterogeneity

We initially examined heterogeneity between studies by visually inspecting forest plots of sensitivity and specificity and summary ROC plots. We identified insufficient numbers of studies to allow meta-regression to formally investigate potential sources of heterogeneity.

Sensitivity analyses

We performed no sensitivity analyses because limited data were available.

Assessment of reporting bias

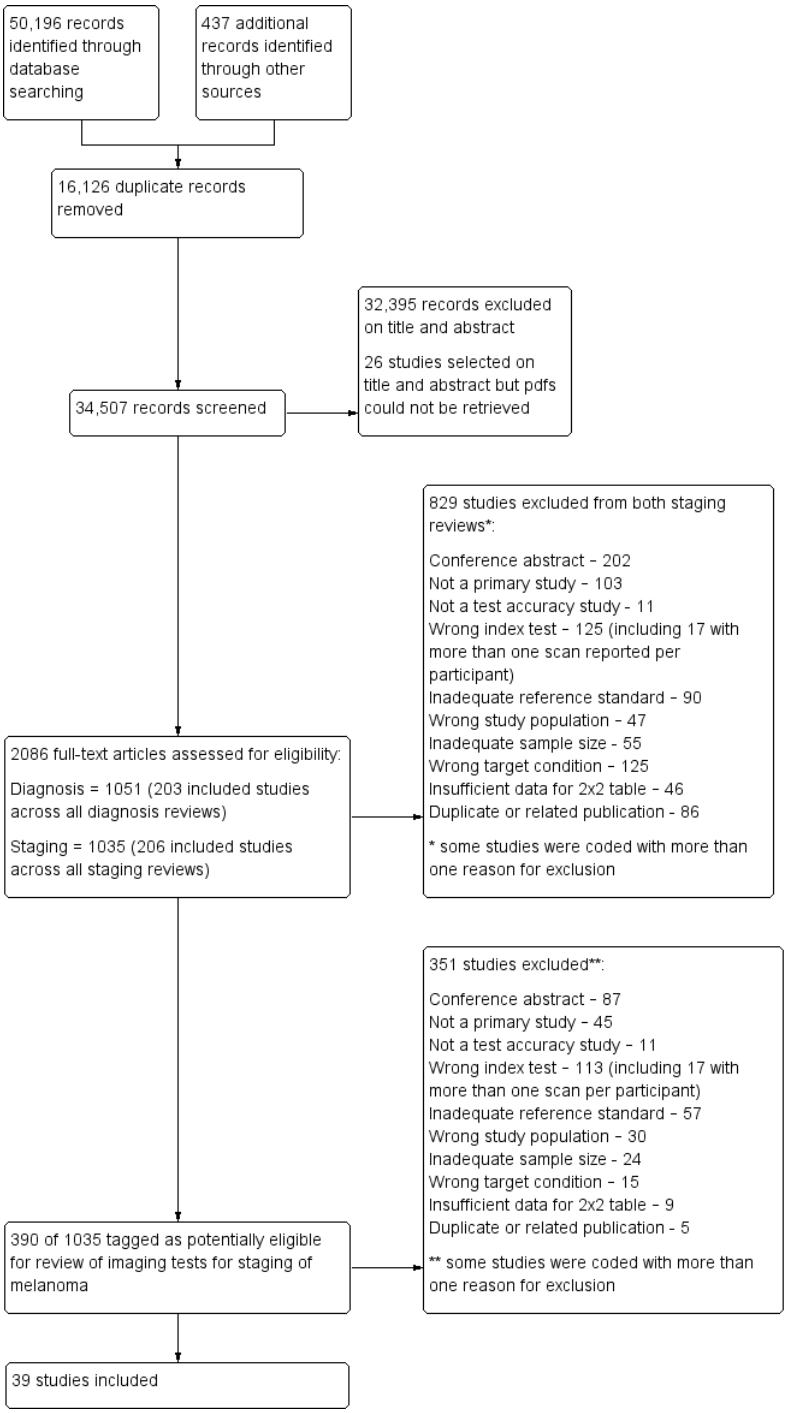
Because of uncertainty about the determinants of publication bias for diagnostic accuracy studies and the inadequacy of tests for detecting funnel plot asymmetry (Deeks 2005), we did not assess publication bias.

RESULTS

Results of the search

We identified and screened for inclusion a total of 34,507 unique references. Of these, we reviewed 1035 full-text papers for eligibility for any one of the reviews of tests for staging of melanoma or cSCC. Of the 1035 full-text papers assessed, we excluded 829 from all reviews in our series (see Figure 3 PRISMA flow diagram of search and eligibility results).

Figure 3. PRISMA flow diagram.



Of the 390 studies tagged as potentially eligible for this review of imaging tests for staging of melanoma, we included 39 publications. Exclusions were due to publication as a conference abstract (n = 202), not a primary study (n = 103), not a test accuracy study (no index test and or reference standard reported) (n = 11), wrong index test (n = 125; including 17 studies with more than one scan reported per participant), inadequate reference standard (n = 90), wrong study population (n = 47), inadequate sample size (n = 55), wrong target condition (n = 125), missing data to complete 2×2 contingency table (n = 46), and duplicate or related publication (n = 86). We have provided a list of the 351 publications excluded from this review with reasons for exclusion in Characteristics of excluded studies. We contacted the authors of four included studies for further details of study methods (Chai 2012; Reinhardt 2006; Stoffels 2012; Voit 2014). We received a response in regard to one study (Reinhardt 2006), but study authors did not provide the additional data requested.

The 39 included study publications provide 195 contingency table datasets for a total of 5204 study participants. Thirty-four studies reported data on a per patient basis, including two that also reported data per lesion identified on imaging (Cachin 2014; Iagaru 2007), and five reported data only on a per lesion basis (Dellestable 2011; Hausmann 2011; Jouvet 2014; Pfannenberg 2007; Pfluger 2011). The 34 studies that reported data per patient included 4980 study participants, 1265 of whom had confirmed metastatic disease. The seven studies that reported data per lesion included 417 study participants with 1846 potentially metastatic lesions identified on imaging, 1061 of which were confirmed metastases. Table 1 cross-tabulates the index tests evaluated and the population groups and target conditions considered in the 39 included studies. Eighteen studies considered the use of imaging for nodal metastases before SLNB; 11 of these studies considered the use of ultrasound, and eight evaluated PET-CT. Twenty-four studies evaluated the use of imaging as a staging tool in study participants undergoing primary staging on diagnosis of melanoma (n = 6) or re-staging for recurrence of disease (n = 3), or inclusion of mixed (n = 11) or not clearly described populations (n = 4). The imaging tests evaluated included ultrasound (n = 5), CT (n = 10), MRI (n = 4), and PET-CT (n = 15) for detection of any metastases (n = 14), nodal metastases (n = 14), or distant metastases (n = 9). Five studies also reported data separately by metastatic site.

Methodological quality of included studies

The overall methodological quality of all included study cohorts is summarised in Figure 4 and Figure 5. Studies were generally at low or unclear risk of bias and of high or unclear concern regarding applicability of the evidence.

Figure 4. Risk of bias and applicability concerns graph: review authors' judgements about each domain presented as percentages across included studies.

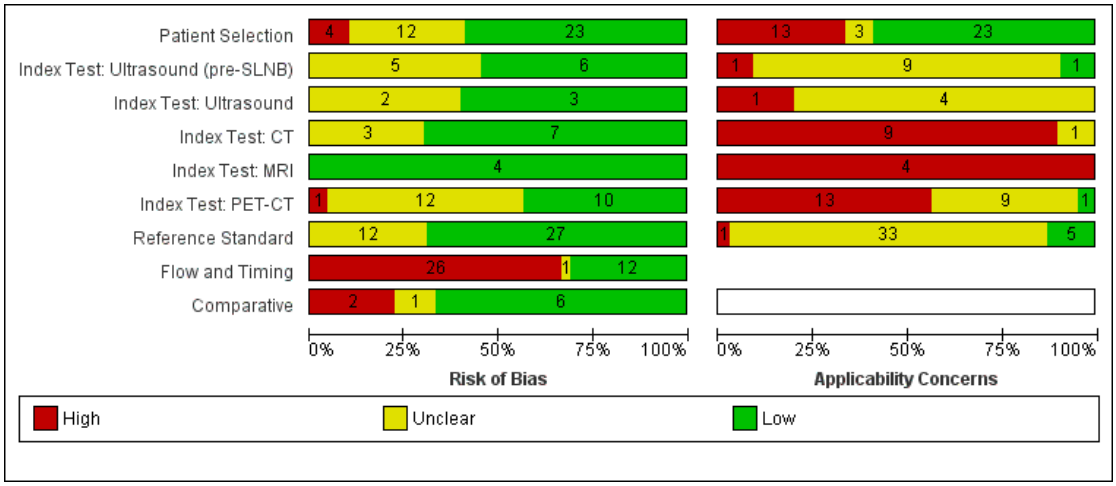
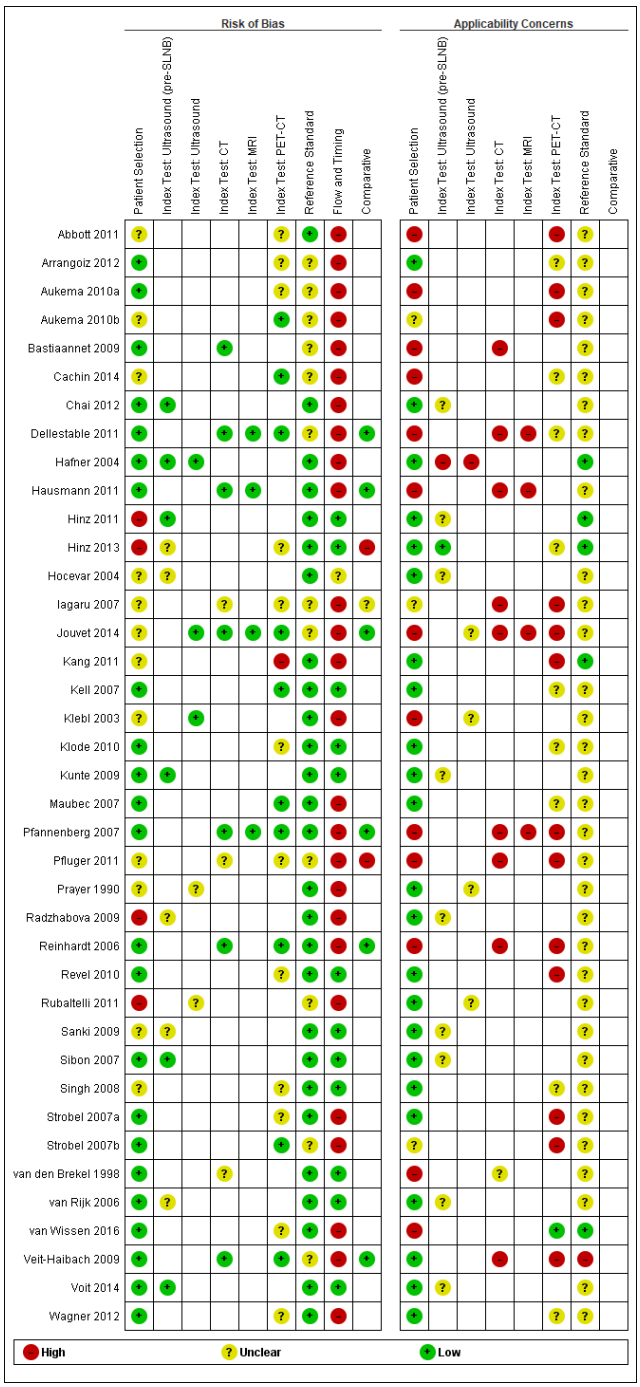


Figure 5. Risk of bias and applicability concerns summary: review authors' judgements about each domain for each included study.



Over half of studies (23; 59%) were at low risk of bias for participant selection. High risk of bias was observed in four studies (10%) because of inappropriate participant exclusions; all excluded study participants on the basis of findings on the index test (ultrasound in all cases) (Hinz 2011; Hinz 2013; Radzhabova 2009; Rubaltelli 2011). Those at unclear risk of bias (n = 12) did not clearly describe participant recruitment as random or consecutive (n = 11) (all except Iagaru 2007) (Abbott 2011; Aukema 2010b; Cachin 2014; Hocevar 2004; Iagaru 2007; Jouvet 2014; Kang 2011; Klebl 2003; Pfluger 2011; Prayer 1990; Sanki 2009; Singh 2008), or did not clearly report participant exclusions (n = 3) (Iagaru 2007; Kang 2011; Pfluger 2011).

Over half of evaluations were considered at low risk of bias for the index test (55% (6/11) for pre-SLNB ultrasound; 60% (3/5) for other uses of ultrasound; 70% (7/10) for CT; 100% (4/4) for MRI; and 43% (10/23) for PET-CT). Across the 11 evaluations of pre-SLNB ultrasound, five (45%) studies were retrospective or unclear in the nature of their design and did not describe blinded case note review to ascertain imaging test results (Hinz 2013; Hocevar 2004; Radzhabova 2009; Sanki 2009; van Rijk 2006). The same rationale for unclear risk of bias was made for two of the five (40%) other evaluations of ultrasound (Prayer 1990; Rubaltelli 2011), three evaluations of CT (30%) (Iagaru 2007; Pfluger 2011; van den Brekel 1998), and 13 (57%) evaluations of PET-CT (Abbott 2011; Arrangoiz 2012; Aukema 2010a; Hinz 2013; Iagaru 2007; Kang 2011; Klode 2010; Pfluger 2011; Revel 2010; Singh 2008; Strobel 2007a; van Wissen 2016; Wagner 2012). One evaluation of pre-SLNB ultrasound - Radzhabova 2009 - and one of PET-CT - Iagaru 2007 - did not clearly prespecify the index test threshold. One study of PET-CT - Kang 2011 - retrospectively selected the maximum standardised uptake value (SUVmax) threshold for PET-CT using ROC analysis and therefore scored high risk of bias for this domain.

Most studies (27/39) were judged at low risk of bias for the reference standard; the 12 studies at unclear risk of bias provided no information on the follow-up schedule used to determine final disease status (Arrangoiz 2012; Aukema 2010a; Aukema 2010b; Bastiaannet 2009; Cachin 2014; Dellestable 2011; Iagaru 2007; Jouvet 2014; Pfluger 2011; Rubaltelli 2011; Strobel 2007b; Veit-Haibach 2009). Although blinding of the reference standard diagnosis did not contribute to overall risk of bias, two studies clearly reported blinding of the histological diagnosis (Pfannenberg 2007; Sibon 2007), and three reported blinding of data collection on follow-up (Hausmann 2011; Pfannenberg 2007; Reinhardt 2006). Two studies reported no blinding of histological diagnosis (Cachin 2014; Singh 2008), and three reported no blinding to the original imaging result during follow-up (Abbott 2011; Cachin 2014; Jouvet 2014).

Two-thirds of studies were at high risk of bias for participant flow and timing (26/39), and one was judged as having unclear risk. High risk of bias was considered in one study because of performance of the imaging test (PET-CT) up to four months after the reference standard (SLNB) (Maubec 2007); in 19 studies (49%) because of differential verification (Abbott 2011; Arrangoiz 2012; Aukema 2010a; Aukema 2010b; Bastiaannet 2009; Cachin 2014; Dellestable 2011; Hausmann 2011; Iagaru 2007; Jouvet 2014; Kang 2011; Klebl 2003; Pfannenberg 2007; Pfluger 2011; Prayer 1990; Reinhardt 2006; Strobel 2007a; Strobel 2007b; Veit-Haibach 2009); and in 13 studies (33%) because of exclusion of participants from the analysis (Bastiaannet 2009; Cachin 2014; Chai 2012; Dellestable 2011; Hafner 2004; Hausmann 2011; Klebl 2003; Pfannenberg 2007; Pfluger 2011; Radzhabova 2009; Rubaltelli 2011; van Wissen 2016; Wagner 2012).

Among the nine studies providing direct comparisons of index tests, six were judged at low risk of bias for the comparative domain. Pfluger 2011 was considered at high risk of bias, as PET-CT and CT images were interpreted side by side, and in Hinz 2013, only a subgroup of those with US also underwent PET-CT. In two studies, blinding between tests was not clearly described (Hinz 2013; Iagaru 2007).

In terms of applicability of evidence to the review question, 40% (n = 16) of studies were of high or unclear concern due to participant selection (Figure 4). High concern was primarily due to inclusion of participants from mixed population groups (including primary staging, re-staging, or patient follow-up) (Abbott 2011; Aukema 2010a; Bastiaannet 2009; Cachin 2014; Dellestable 2011; Klebl 2003; Pfannenberg 2007; Pfluger 2011; Reinhardt 2006; van den Brekel 1998; van Wissen 2016), or it was due to the presentation of only per lesion rather than per patient data (Dellestable 2011; Hausmann 2011; Jouvet 2014; Pfannenberg 2007; Pfluger 2011). Three studies were of unclear concern due to lack of clear description of the indication for imaging (Aukema 2010b; Iagaru 2007; Strobel 2007b).

Almost all test evaluations were considered at high or unclear concern around applicability of the index test. For pre-SLNB ultrasound, there was high concern from lack of detail regarding the threshold used (n = 1) (Hafner 2004), and unclear concern resulted from lack of information on application and interpretation of the index test (n = 9) (Chai 2012; Hafner 2004; Hinz 2011; Hocevar 2004; Kunte 2009; Radzhabova 2009; Sibon 2007; van Rijk 2006; Voit 2014), or regarding the expertise of the observer performing the ultrasound examination (n = 6) (Chai 2012; Hinz 2011; Kunte 2009; Radzhabova 2009; Sanki 2009; van Rijk 2006).

For CT, six evaluations were of high concern due to use of consensus test interpretation (Iagaru 2007; Jouvet 2014; Pfannenberg 2007; Pfluger 2011; Reinhardt 2006; Veit-Haibach 2009), two for MRI (Jouvet 2014; Pfannenberg 2007), and 11 for PET-CT (Aukema 2010a; Aukema 2010b; Iagaru 2007; Jouvet 2014; Kang 2011; Pfannenberg 2007; Pfluger 2011; Reinhardt 2006; Revel

2010; Strobel 2007a; Strobel 2007b). Only five CT evaluations described the provision of usual clinical information to test interpreters (Jouvet 2014; Pfannenberg 2007; Pfluger 2011; Reinhardt 2006; Veit-Haibach 2009), one evaluation of MRI (Pfannenberg 2007), and four for PET-CT (Pfannenberg 2007; Pfluger 2011; Reinhardt 2006; Revel 2010). Three CT evaluations were unclear on the information provided to assist test interpretation (Bastiaannet 2009; Dellestable 2011; van den Brekel 1998), two for MRI (Dellestable 2011; Hausmann 2011), and six for PET-CT (Dellestable 2011; Kell 2007; Klode 2010; Maubec 2007; Singh 2008; Veit-Haibach 2009).

Inadequate details of test threshold were provided in five evaluations of CT (Bastiaannet 2009; Dellestable 2011; Iagaru 2007; Jouvet 2014; Reinhardt 2006), three for MRI (Dellestable 2011; Hausmann 2011; Jouvet 2014), and four for PET-CT (Abbott 2011; Hinz 2013; Jouvet 2014; Reinhardt 2006). Threshold details were unclear for one study for both CT and MRI (Pfannenberg 2007), as were six for PET-CT (Aukema 2010a; Aukema 2010b; Dellestable 2011; Klode 2010; Maubec 2007; Wagner 2012). Two CT evaluations were unclear with regard to observer expertise (Dellestable 2011; van den Brekel 1998), one for MRI (Dellestable 2011), and seven for PET-CT (Arrangoiz 2012; Dellestable 2011; Hinz 2013; Kell 2007; Klode 2010; Maubec 2007; Revel 2010).

For applicability of the reference standard, five studies were considered of low concern (Hafner 2004; Hinz 2011; Hinz 2013; Kang 2011; van Wissen 2016), and one was rated of high concern because it did not present data for the primary target condition of any metastasis (nodal plus distant metastases) (Veit-Haibach 2009). The remaining 33 studies were considered at unclear concern for applicability because they did not clearly define the target condition or provide a breakdown according to nodal or distant metastases. Only five studies described the expertise of the histopathologist (Hafner 2004; Hinz 2011; Hinz 2013; Kang 2011; van Wissen 2016); the remaining studies were rated of unclear concern.

Findings

1. Imaging for detection of nodal metastases before SLNB

Imaging before SLNB can be used to identify patients with nodal metastatic disease that is not detectable clinically such that they can bypass the SLNB procedure and undergo complete lymph node dissection. Eighteen studies were included, 10 of which considered the use of pre-SLNB ultrasound (Chai 2012; Hafner 2004; Hinz 2011; Hocevar 2004; Kunte 2009; Radzhabova 2009; Sanki 2009; Sibon 2007; van Rijk 2006; Voit 2014); seven evaluated PET-CT (Arrangoiz 2012; Kell 2007; Klode 2010; Maubec 2007; Revel 2010; Singh 2008; Wagner 2012), and one evaluated both tests (Hinz 2013). Three studies of ultrasound also presented accuracy data for ultrasound combined with FNAC (i.e. complete lymph node dissection recommended only if both ultrasound and FNAC were positive for metastases) (Hocevar 2004; van Rijk 2006; Voit 2014).

Forest plots of study data are provided in Figure 6. Summary estimates for indirect and direct comparisons of tests are presented in Table 2 and Figure 7. Summary details of all studies in this section are presented alphabetically in Appendix 8.

Figure 6. Forest plot of all data for pre-SLNB ultrasound, ultrasound plus FNAC, or PET-CT for the detection of nodal metastasis.
(HN MM - head and neck only malignant melanoma.)

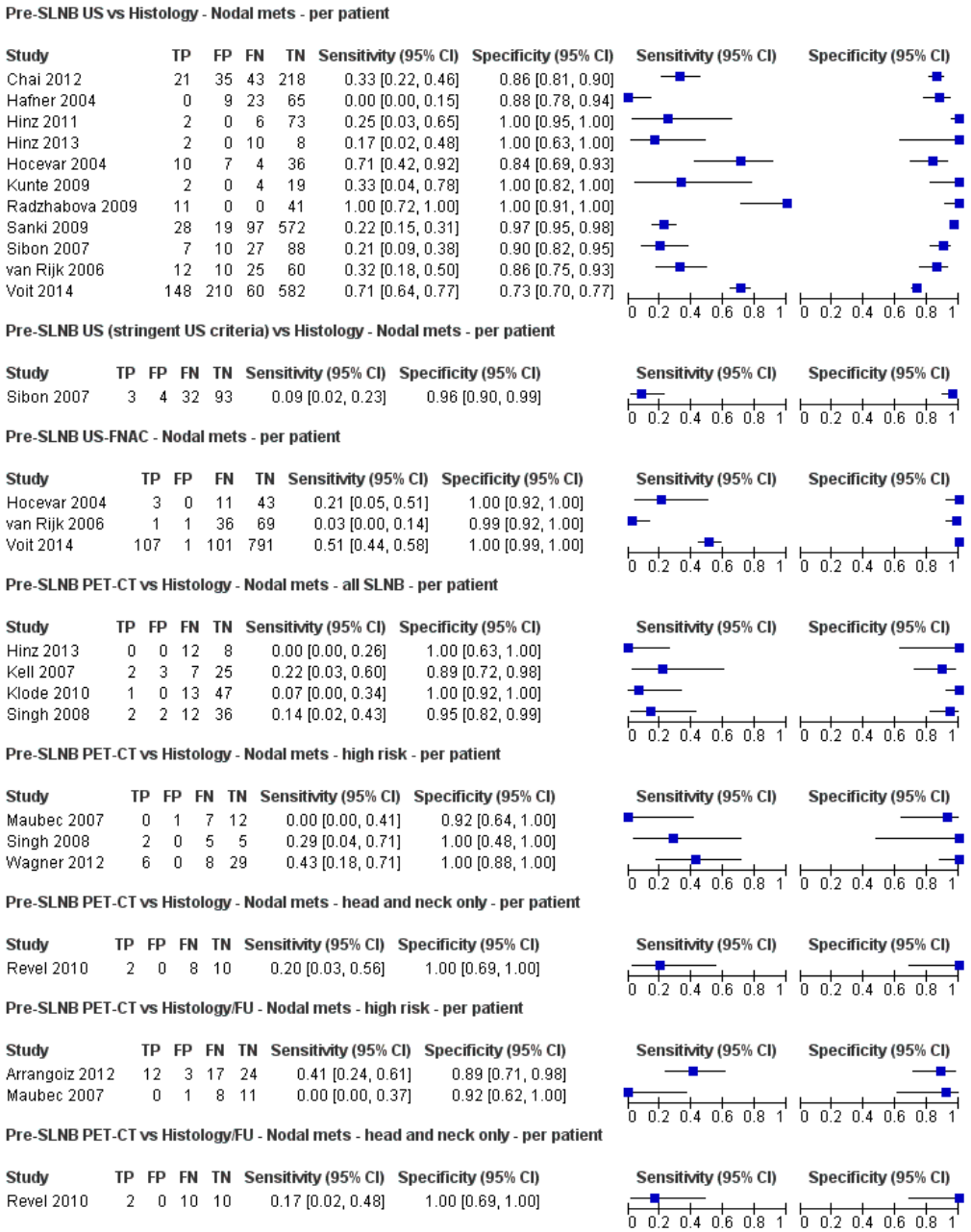
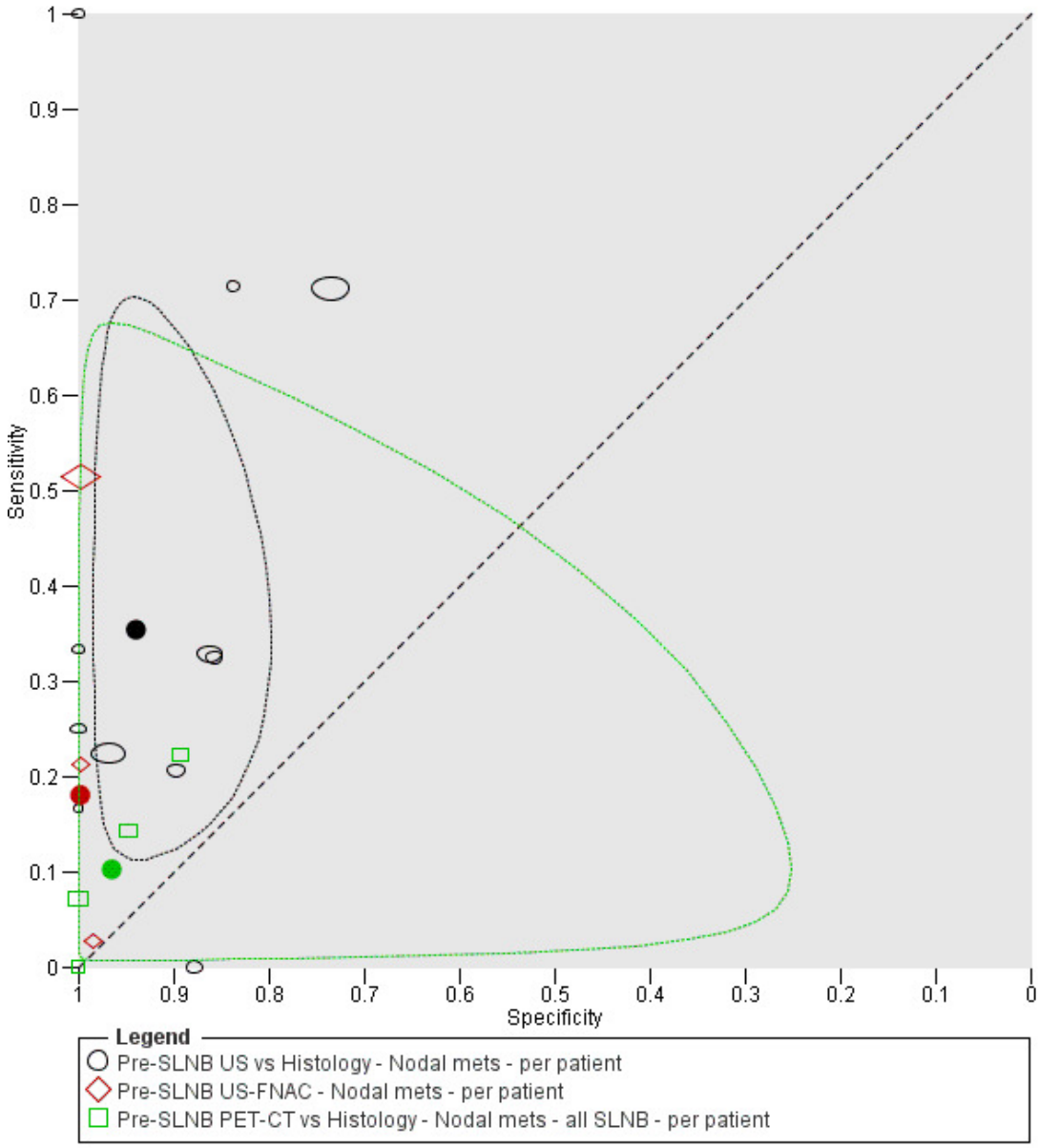


Figure 7. Summary ROC plot comparing pre-SLNB ultrasound vs ultrasound plus FNAC vs PET-CT.



Description of studies

Study design and setting. Four of the 18 studies (22%) were prospective case series (Hafner 2004; Hinz 2011; Kunte 2009; Maubec 2007), nine (50%) were retrospective (Arrangoiz 2012; Chai 2012;

Hinz 2013; Kell 2007; Klode 2010; Revel 2010; Sibon 2007; van Rijk 2006; Wagner 2012), and five (28%) did not clearly report the design (Hocevar 2004; Radzhabova 2009; Sanki 2009; Singh 2008; Voit 2014). Studies were conducted in Europe (n = 14), Australia (n = 1; Sanki 2009), and the USA (n = 3; Arrangoiz 2012; Chai 2012; Kell 2007).

Participants. Thirteen of the 18 studies (72%) were considered to have been conducted in 'standard' SLNB populations, either reporting the inclusion of participants with primary melanomas with Breslow thickness of at least 0.76 mm or 1 mm unless other adverse prognostic factors were present such as Clark level of at least IV, ulceration, or regression (Chai 2012; Hafner 2004; Hinz 2011; Kell 2007; Klode 2010; Kunte 2009; Sanki 2009; Sibon 2007; Singh 2008; van Rijk 2006; Voit 2014), or reporting including 'candidates for SLNB' with no further detail (Hocevar 2004; Radzhabova 2009). One study restricted inclusion to participants with head and neck melanoma only (Revel 2010), and the remaining four studies included only higher-risk participants, with Breslow thickness of at least 2 mm (Hinz 2013), or 4 mm (Arrangoiz 2012; Maubec 2007; Wagner 2012).

A total of 2894 participants were included, with 640 nodal metastases identified (prevalence 22%, ranging from 10% in Hinz 2011 to 60% in Hinz 2013). Sample sizes ranged from 20 participants in Hinz 2013 and Maubec 2007 to 1000 in Voit 2014. When reported (n = 11), the ages of included participants ranged from one year in Hocevar 2004 to 94 years in Voit 2014. The mean age of included participants was reported in 11 studies (the median of reported means was 57.5 years, range 50 to 67 years), and the median age was reported in five studies (the median of reported means was 58 years, range 55 to 62 years); five studies reported neither the mean nor median age of included study participants (Hinz 2013; Hocevar 2004; Radzhabova 2009; Sanki 2009; Wagner 2012). When reported (n = 15), 48% of included participants were male. Of 11 studies reporting the site of the primary melanoma lesion (excluding Revel 2010, which included head and neck melanomas only), the percentage of participants with head and neck melanoma ranged from 0% in Hinz 2013 to 36% in Maubec 2007 (median 14%), and melanoma of the extremities, including the hands or feet where documented, from 32% in Maubec 2007 to 56% in Kunte 2009 (median 50%).

Ultrasound. The 11 studies of pre-SLNB ultrasound were all conducted in standard SLNB populations, although Hinz 2013 restricted inclusion to participants with melanomas at least 2 mm thick or with risk factors such as ulceration or regression. The two studies by Hinz and colleagues excluded participants with classic sonographic signs of lymphatic metastasis (Hinz 2011; Hinz 2013), whereas Radzhabova 2009 included only those who were positive on US or in whom metastases could not be excluded.

Studies employed mainly B-mode ultrasound, with two studies also employing Doppler ultrasound in all participants (Hinz 2011; Voit 2014). B-mode ultrasound frequencies were variable, mainly ranging from 5 or 6 MHz to 10 or 12 MHz in each study, apart from Voit 2014, which used three transducers ranging from 1 to 18 MHz in frequency. Ultrasound was performed before lymphoscintigraphy in five studies (Chai 2012; Hafner 2004; Hinz 2011; Hinz 2013; Sibon 2007), after lymphoscintigraphy in two studies (Sanki 2009; Voit 2014), and both before and after lymphoscintigraphy in four studies (Hocevar 2004; Kunte 2009; Radzhabova 2009; van Rijk 2006). Lymph node basins were imaged according to the site of the primary melanoma (Chai 2012; Hafner 2004; Hinz 2011; Hinz 2013; Sibon 2007; Voit 2014), according to the site marked following lymphoscintigraphy (Sanki 2009; Voit 2014), or this information was not reported (Hocevar 2004; Kunte 2009; Radzhabova 2009; van Rijk 2006). Criteria for detection of nodal metastases were clearly described in all studies apart from Hafner 2004 (Appendix 8). Ultrasound was reported to be performed by dermatologists (Kunte 2009), sonographers (Voit 2014), radiologists (Hafner 2004; Hocevar 2004; Sibon 2007), or nuclear medicine physicians (Sanki 2009), or this was not reported.

PET-CT. Of the eight studies of PET-CT before SLNB, four were conducted in any participant eligible for SLNB (Hinz 2013; Kell 2007; Klode 2010; Singh 2008); one in those with head and neck melanoma (Revel 2010); and three in higher-risk melanoma populations (Arrangoiz 2012; Maubec 2007; Wagner 2012). Singh 2008 also reported data for the subgroup of participants with higher-risk melanoma (Breslow thickness > 4 mm). When reported (n = 3), studies employed two-dimensional (2D) PET (Wagner 2012), three-dimensional (3D) PET (Maubec 2007), or either 2D or 3D PET (Arrangoiz 2012). PET was combined with unenhanced - in Arrangoiz 2012, Kell 2007, and Maubec 2007 - or contrast-enhanced - in Hinz 2013, Klode 2010, and Singh 2008 - CT scans (use of contrast not reported in Revel 2010 and Wagner 2012). When reported, CT was used for attenuation correction (Arrangoiz 2012; Hinz 2013; Revel 2010; Singh 2008; Wagner 2012), as well as for anatomical localisation (Revel 2010; Wagner 2012).

Criteria for the detection of nodal metastases were not reported in Hinz 2013, were based on a qualitative assessment of increased ^{18}FDG uptake in six studies (Kell 2007; Klode 2010; Maubec 2007; Revel 2010; Singh 2008; Wagner 2012), and were based on a quantitative assessment of focal uptake in Arrangoiz 2012 (SUV $\geq$ 2.5) (see Appendix 8). Performance and interpretation of PET-CT were not clearly described. For example, Wagner 2012 reported interpretation by a nuclear medicine specialist, while two others mentioned an in-house medical physicist - Singh 2008 - and a team of radiologists and nuclear physicians - Arrangoiz 2012. Only Revel 2010 and Wagner 2012 reported the provision of clinical or other radiological findings to assist PET-CT interpretation.

Reference standard. Ten studies (56%) evaluated the accuracy of imaging in comparison to histology from SLNB alone (Hinz 2011; Hinz 2013; Kell 2007; Klode 2010; Kunte 2009; Radzhabova 2009; Revel 2010; Sanki 2009; Sibon 2007; Singh 2008), seven studies (39%) included histology results from participants pro-

ceeding directly to CLND as well as SLNB results as a reference standard (Chai 2012; Hafner 2004; Hocevar 2004; Maubec 2007; van Rijk 2006; Voit 2014; Wagner 2012), and one study reported only data for histology based on CLND or SLNB combined with follow-up to determine any false negative results on PET-CT as the reference standard (Arrangoiz 2012).

Participant exclusions. Five studies reported the exclusion of between two and eight participants primarily due to technical failure of SLNB (sentinel node not identified or SLNB not performed) (Chai 2012; Hafner 2004; Maubec 2007; Revel 2010; Wagner 2012), and in one study (Radzhabova 2009), 100 participants did not undergo SLNB on the basis of a negative ultrasound finding.

Results: ultrasound for detection of nodal metastases

Across the 11 ultrasound evaluations, sensitivity for detection of nodal metastasis in comparison to a histological reference standard (SLNB or LCND) ranged from 0% in Hafner 2004 to 33% in Chai 2012 and Kunte 2009 in eight studies, and from 71% in Hocevar 2004 and Voit 2014 to 100% in Radzhabova 2009 in three. Specificity ranged from 73% in Voit 2014 to 100% in Kunte 2009, Hinz 2011, Hinz 2013, and Radzhabova 2009) (Figure 6). Radzhabova 2009 included a highly selected group of study participants, which likely explains the perfect sensitivity and specificity observed. The particularly low sensitivity in Hafner 2004 (0%) may be related to the use of only a 5-MHz ultrasound transducer, but this study was poorly reported and other explanations may be possible. The relatively high sensitivities (both 71%) in Hocevar 2004 and Voit 2014 are also difficult to explain based on the information reported. In terms of specificity, Kunte 2009, Hinz 2011, and Hinz 2013 all applied ultrasound before and after the use of lymphoscintigraphy, which is likely to have contributed to the 100% specificity observed.

The summary sensitivity of ultrasound across the 11 studies was 35.4% (95% CI 17.0% to 59.4%) and summary specificity was 93.9% (86.1% to 97.5%) for 2614 participants and 542 confirmed cases of nodal metastasis (Table 2; Figure 7).

The three studies that reported the accuracy of ultrasound combined with FNAC reported decreased sensitivity but increased specificity in comparison to ultrasound alone. Sensitivities ranged from 3% (95% CI 0% to 14%) in van Rijk 2006 to 51% (95% CI 44% to 58%) in Voit 2014, and specificities ranged from 99% (95% CI 92% to 100%) in van Rijk 2006 to 100% (95% CI 99% to 100%) in Voit 2014 (Figure 6). The summary sensitivity was 18.0% (95% CI 3.58% to 56.5%), and summary specificity was 99.8% (95% CI 99.1% to 99.9%), based on 1164 participants and 259 cases (Table 2; Figure 7).

Results: PET-CT for detection of nodal metastases

The four studies comparing PET-CT to histology based on SLNB in standard SLNB populations reported sensitivities ranging from 0% (95% CI 0% to 26%) in Hinz 2013 to 22% (95% CI 3% to 60%) in Kell 2007, and specificities from 89% (95% CI 72% to 98%) in Kell 2007 to 100% (95% CI 63% to 100%) in Hinz 2013 and 100% (95% CI 92% to 100%) in Klode 2010 (Figure 6). The summary sensitivity was 10.2% (95% CI 4.31% to 22.3%) and summary specificity was 96.5% (95% CI 87.1% to 99.1%) for 170 participants and 49 confirmed cases of nodal metastasis (Table 2; Figure 7).

Data from the three studies in higher-risk melanoma populations (75 participants with 28 cases) that compared PET-CT to histology based on SLNB alone could not be pooled because of substantial heterogeneity likely resulting from small sample sizes (Maubec 2007; Singh 2008; Wagner 2012). Sensitivities ranged from 0% (95% CI 0% to 41%) in Maubec 2007 to 43% (95% CI 18% to 71%) in Wagner 2012, and specificities from 92% (95% CI 64% to 100%) in Maubec 2007 to 100% (95% CI 48% to 100%) in Singh 2008 and 100% (95% CI 88% to 100%) in Wagner 2012 (Figure 6).

One of these studies - Maubec 2007 - and Arrangoiz 2012 reported data for PET-CT compared to histology based on SLNB plus follow-up to identify false negatives. Maubec 2007 identified one additional false negative result on follow-up, but sensitivity (0%) and specificity (92%) remained the same with marginal changes to CIs (95% CI 0% to 37% for sensitivity and 62% to 100% for specificity). Arrangoiz 2012 reported sensitivity of PET-CT as 41% (95% CI 24% to 61%) and specificity as 89% (95% CI 71% to 98%) (Figure 6).

Revel 2010 reported the sensitivity of PET-CT as 20% (95% CI 3% to 56%) and 100% (95% CI 69% to 100%) for 20 participants with head and neck melanoma when compared to SLNB alone as a reference standard. Adding data for a follow-up reference standard identified two additional nodal metastases missed on PET-CT for sensitivity of 17% (95% CI 2% to 48%) and specificity of 100% (95% CI 69% to 100%) (Figure 6).

Results: comparison between tests

Upon comparison of ultrasound alone, ultrasound plus FNAC, and PET-CT, summary sensitivities were not statistically significantly different (P = 0.07), and summary specificities were significantly higher for ultrasound plus FNAC compared to the other two modalities (P < 0.001) (Table 2; Figure 7).

The direct comparison of ultrasound alone versus ultrasound plus FNAC suggested higher sensitivity (58.7%, 95% CI 36.5% to 77.9%) but lower specificity (79.4%, 95% CI 70.0% to 86.4%) (3 studies; 1164 participants; 259 cases of nodal metastases) for ultrasound alone compared to the overall pooled result. Requiring both ultrasound and FNAC to be positive for nodal metastases (as an indicator for CLND instead of SLNB) reduced sensitivity by 40.7% (95% CI 6.50% to 75.0%; P = 0.02) but increased specificity by 20.4% (95% CI 12.2% to 28.6%; P < 0.001) (Table 2).

2. Whole body imaging for detection of any metastases, nodal metastases, and distant metastases

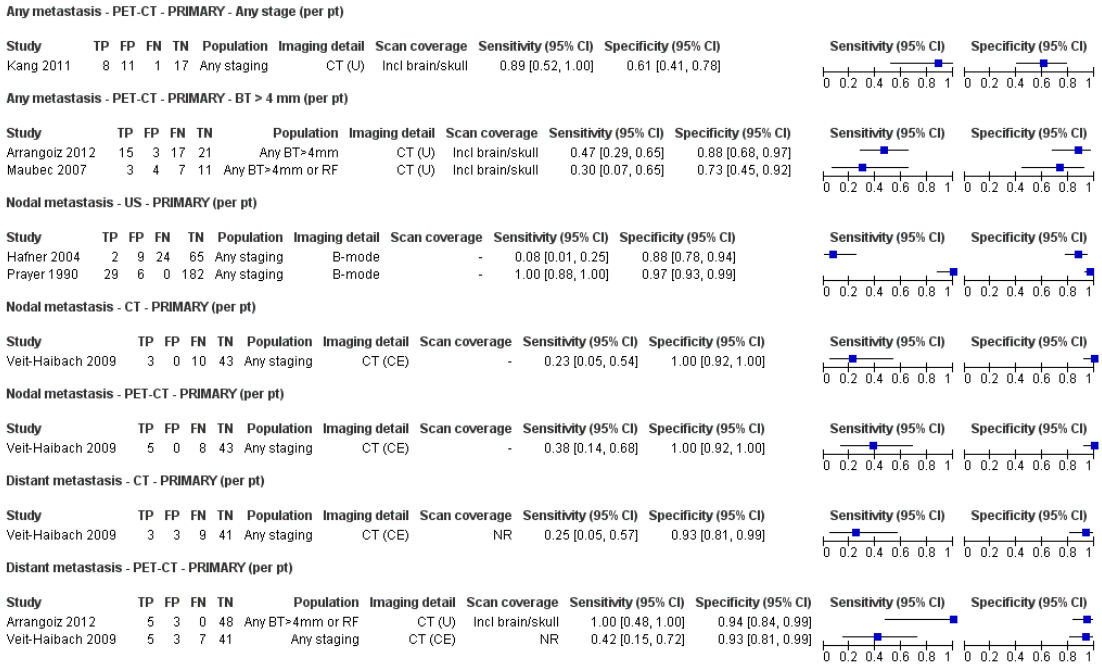
Twenty-four studies evaluated whole body imaging. Summary characteristics of all studies are tabulated alphabetically in Appendix 9, and a narrative description is provided in Appendix 10. Results are presented below according to the population group studied, the target condition and imaging test, and the presentation of data per patient and per lesion.

Primary staging

Six studies recruited participants undergoing primary staging following a confirmed diagnosis of melanoma (Arrangoiz 2012; Hafner 2004; Kang 2011; Maubec 2007; Prayer 1990; Veit-Haibach 2009). Two studies included any participant following diagnosis of melanoma (Kang 2011; Veit-Haibach 2009); two excluded those with distant metastases on diagnosis (Hafner 2004; Maubec 2007). Maubec 2007 restricted data to those with melanomas at least 4 mm in thickness; one study included clinically node positive participants but did not report exclusion of those with distant metastases (Prayer 1990), and one included only clinically node negative participants with melanomas of at least 4 mm Breslow thickness (Arrangoiz 2012). Three studies also reported data for pre-SLNB imaging (Arrangoiz 2012; Hafner 2004; Maubec 2007), two of which reported subgroup data for clinically node negative participants who underwent SLNB (Hafner 2004; Maubec 2007). All six studies reported accuracy data on a per patient basis; no per lesion data were identified.

Forest plots of all available study data are presented in Figure 8. Summary details of all studies in this section are presented alphabetically in Appendix 9. Sensitivities and specificities from studies evaluating more than one target condition (any metastasis, nodal metastasis, or distant metastasis) are tabulated in Appendix 11.

Figure 8. Forest plot of imaging for primary staging, for the detection of any metastases, nodal metastases, and distant metastases (per patient and per lesion data).



Results: detection of any metastases

Three studies presented data for detection of any metastasis in 118 study participants with 51 cases of metastatic disease (Figure 8) (Arrangoiz 2012; Kang 2011; Maubec 2007); the prevalence of metastases ranged from 24% in Kang 2011 to 57% in Arrangoiz

2012.

CT. No data on CT were identified for participants undergoing primary staging of melanoma.

MRI. No data on MRI were identified for participants undergoing primary staging of melanoma.

PET-CT. Three studies presented per patient data for PET-CT for detection of any metastasis; no per lesion data were identified.

Two studies evaluated PET-CT in participants with melanomas ≥ 4 mm in thickness: one reported sensitivity and specificity for detection of any metastases of 47% (95% CI 29% to 65%) and 88% (95% CI 68% to 97%) (56 participants; 32 cases of metastatic disease) (Arrangoiz 2012); and in the other (Maubec 2007), sensitivity was 30% (95% CI 7% to 65%) and specificity 73% (95% CI 45% to 92%) (25 participants; 10 cases of metastatic disease) (Figure 8). Arrangoiz 2012 identified four patients with distant metastases whose disease would have been missed without PET-CT imaging (prevalence of distant metastases 4/56; 7%). In the other study (Maubec 2007), no distant metastases were identified, but all three false positive results suggested possible distant metastases.

The third study evaluated PET-CT for the prediction of subsequent recurrence in any participant following diagnosis of melanoma (Kang 2011). Stage of disease on presentation was reported as stage 0 (n = 7), stage I or II (n = 23), stage III (n = 6), and stage IV (n = 1); all patients underwent curative surgery for primary and metastatic lesions. The sensitivity of PET-CT for the prediction of later recurrence at an SUVmax ≥ 2.2 at baseline was 89% (95% CI 52% to 100%) and specificity 61% (95% CI 41% to 78%) (37 participants; nine cases of metastatic disease) (Figure 8). The accuracy of PET-CT for initial staging was not reported. Three of the nine patients who developed recurrence during follow-up were stage III or greater at presentation.

Results: detection of nodal metastases

Three studies presented data for the detection of nodal metastases in 373 participants with 68 cases of nodal metastases (Hafner 2004; Prayer 1990; Veit-Haibach 2009) (Figure 8); the prevalence of nodal metastases ranged from 13% in Prayer 1990 to 26% in Hafner 2004.

Ultrasound. Two studies evaluated the use of ultrasound in any participant following the diagnosis of melanoma, including those who were clinically node positive (Hafner 2004; Prayer 1990). Hafner 2004 restricted inclusion to those with melanomas ≥ 1 mm in thickness, and all underwent SLNB including three with clinically detectable nodal metastases (data for clinically node negative are reported in the pre-SLNB imaging section above). The sensitivity of ultrasound was 8% (95% CI 1% to 25%) and specificity 88% (95% CI 78% to 94%) (100 participants, 26 with nodal metastases) (Figure 8); the only true positive results were both detected on physical examination. In Prayer 1990, the sensitivity of ultrasound was 100% (95% CI 88% to 100%) and specificity 97% (95% CI 93% to 99%) (217 participants, 29 with nodal metastases) (Figure 8). These results are likely to be influenced by incorporation bias and inadequate follow-up to identify false negatives on ultrasound. Of 217 included participants, 15% (35/217) had suspicious findings on palpation; however, among these, only those who were also found to have suspicious nodes on ultrasound had histological verification (n = 15). This left 17 who were positive on palpation but negative on ultrasound, along with 165 who were negative on both palpation and ultrasound, with a six-month follow-up reference standard.

Other imaging tests. One study presented data comparing CT with PET-CT for the detection of nodal metastases in all participants referred for PET-CT after primary melanoma resection (Veit-Haibach 2009). No false positive results were obtained with either test (specificity 100%, 95% CI 92% to 100%), but sensitivity was higher for PET-CT (38%, 95% CI 14% to 68%) compared to CT (23%, 95% CI 5% to 54%) (56 participants, 13 with nodal metastases) (Figure 8). Initial staging procedures including histology of the primary lesion, SLNB, and all imaging procedures apart from PET-CT identified four of the 13 participants with nodal metastases, two of whom were identified only on SLNB and were missed by all imaging tests (Veit-Haibach 2009). Both CT and PET-CT correctly identified additional participants with nodal metastases (one and three, respectively) that were not picked up by other staging procedures at the time of melanoma diagnosis. No data on MRI to detect nodal disease were identified for participants undergoing primary staging of melanoma.

Results: detection of distant metastases

Two studies presented data for the detection of distant metastases in 112 participants with 17 cases of distant metastases (Arrangoiz 2012; Veit-Haibach 2009) (Figure 8); the prevalence of distant metastases was 9% in Arrangoiz 2012 and 21% in Veit-Haibach 2009.

CT. One study presented data for CT: sensitivity for the detection of 12 distant metastases was 25% (95% CI 5% to 57%) and specificity 93% (95% CI 81% to 99%) (56 participants) (Veit-Haibach 2009).

MRI. No per patient data on MRI were identified for participants undergoing primary staging of melanoma.

PET-CT. Veit-Haibach 2009 provided a direct comparison of CT with PET-CT; two additional cases of distant metastases were detected in comparison to CT (sensitivity 42%, 95% CI 15% to 72%), with no difference in specificity (93%, 95% CI 81% to 99%) (Figure 8).

Arrangoiz 2012 evaluated the use of PET-CT in clinically node negative participants with primary melanoma greater than 4 mm in thickness and no indications for distant metastases; all five distant metastases were detected by PET-CT (sensitivity 100%, 95% CI 48% to 100%), with three false positive results (specificity 94%, 95% CI 84% to 99%) (56 participants).

Results: detection of distant metastases by metastatic site

No data were identified for the detection of metastatic disease according to metastatic site in participants undergoing imaging for primary staging of melanoma.

In three of six studies, scan coverage was reported to include the skull (Arrangoiz 2012; Kang 2011; Maubec 2007), but the detection of brain metastases was not separately documented.

Re-staging

Three studies recruited participants undergoing imaging for re-staging of disease following a clinical indication of recurrence (Iagaru 2007; Rubaltelli 2011; Strobel 2007a). One study included any participant having imaging for re-staging purposes (Iagaru 2007), and two included clinically node negative participants either undergoing ultrasound of the regional lymph nodes as part of a follow-up program (Rubaltelli 2011), or with raised serum S100 (> 0.2 μg/L) during follow-up (Strobel 2007a).

Forest plots of all available study data are presented in Figure 9. Summary estimates of sensitivity and specificity are presented in Table 2. Summary details of all studies in this section are presented alphabetically in Appendix 9.

Figure 9. Forest plot of imaging for re-staging of melanoma, for the detection of any metastases or nodal metastases (per patient and per lesion data).

Results: detection of any metastases

Two studies provided per patient data for the detection of any metastasis in 153 participants with 95 cases of metastatic disease (Figure 9); the prevalence of any metastasis was 53% in Iagaru 2007 and 83% in Strobel 2007a.

CT. In one study, the sensitivity of CT for detection of any metastasis on a per patient basis was 68% (95% CI 54% to 80%) and specificity 94% (95% CI 83% to 99%) (106 participants; 56 cases of metastatic disease) (Iagaru 2007).

MRI. No data on MRI were identified for participants undergoing re-staging of melanoma.

PET-CT. Two studies evaluated PET-CT on a per-patient basis in 153 participants, 95 of whom had confirmed metastases (Iagaru 2007; Strobel 2007a); summary sensitivity was 92.6% (95% CI 85.3% to 96.4%) and specificity 89.7% (95% CI 78.8% to 95.3%) (Table 2).

Comparison of PET-CT with CT in Iagaru 2007 demonstrated PET-CT to be more sensitive (89%, 95% CI 78% to 96%) than CT alone (increase of 21%), with similar specificity (88%, 95%

CI 76% to 95%). Similar results were observed on a per lesion basis (Figure 9). Although numbers were small, PET-CT was more sensitive in the subgroup with stage IIIc to IV disease who underwent PET-CT for re-staging after therapy (100%, 95% CI 81% to 100%) (n = 32; 18 with metastatic disease) than in those with less advanced disease (84%, 95% CI 69% to 94%).

Results: detection of nodal metastases

One study presented per patient data for the detection of nodal recurrence after primary treatment in 460 participants with 37 cases of nodal metastases (prevalence 8%) (Rubaltelli 2011) (Figure 9).
Ultrasound. Considering participants with 'common signs of malignancy' or with focal hypoechoic cortical thickening as positive for metastases detected all participants with nodal metastases (sensitivity 100%, 95% CI 91% to 100%) with a specificity of 93% (95% CI 90% to 95%) (460 participants, 37 with nodal metastases) (Rubaltelli 2011). The combination of contrast-enhanced ultrasound with B-mode ultrasound for participants with focal cortical thickening (presence of perfusion defects corresponding to the cortical focal thickening required for a positive test result) increased specificity to 100% (95% CI 98% to 100%).
Other imaging tests. No data on CT, MRI, or PET-CT for the detection of nodal metastases were identified for participants undergoing re-staging for recurrence of melanoma.

Results: detection of distant metastases

No data were identified for the detection of distant metastases in participants undergoing re-staging for disease recurrence.

Results: detection of distant metastases by metastatic site

Two of three studies conducted in participants undergoing imaging for re-staging of melanoma included imaging of the brain and documented some results for the detection of brain metastases.
In Iagaru 2007, one of the nine lesions classified as a false negative on PET-CT was a brain lesion that was identified by MRI during follow-up; the total number of brain metastases identified in the study was not reported.
In Strobel 2007a, two brain metastases were identified on PET-CT, both of which were confirmed to be malignant on the reference standard.

3. Staging in mixed or not clearly described populations

Studies in mixed and not clearly described populations have been considered together on the basis that we would be unable to make clear statements regarding the expected accuracy of imaging at any particular point on the clinical pathway for either subset of studies. Table 3 describes variability in the clinical pathway and indications for imaging, inclusion criteria, and stage of disease of participants included in these studies.
Fifteen studies were conducted in mixed population groups (n = 11), including participants undergoing primary staging, re-staging, and follow-up imaging (i.e. at more than one point in the clinical pathway) (Abbott 2011; Aukema 2010a; Bastiaannet 2009; Cachin 2014; Dellestable 2011; Klebl 2003; Pfannenberg 2007; Pfluger 2011; Reinhardt 2006; van den Brekel 1998; van Wissen 2016), or did not clearly describe the clinical pathway in included participants (n = 4) (Aukema 2010b; Hausmann 2011; Jouvet 2014; Strobel 2007b).
Stage of disease on recruitment was not reported in four studies (Aukema 2010a; Cachin 2014; Klebl 2003; Strobel 2007b), two studies included any stage of disease (with 56% (Reinhardt 2006) and 73% (Dellestable 2011) at stage III or stage IV), six included only stage III melanoma (Abbott 2011; Aukema 2010b; Bastiaannet 2009; Pfluger 2011; van den Brekel 1998; van Wissen 2016), one included stage IV only (Jouvet 2014), and two included either stage III or IV melanoma (both with just under 40% with stage III disease) (Hausmann 2011; Pfannenberg 2007).
Nine of the fifteen studies reported accuracy data only on a per patient basis (Abbott 2011; Aukema 2010a; Aukema 2010b; Bastiaannet 2009; Klebl 2003; Reinhardt 2006; Strobel 2007b; van den Brekel 1998; van Wissen 2016), five reported data per lesion (Dellestable 2011; Hausmann 2011; Jouvet 2014; Pfannenberg 2007; Pfluger 2011), and one reported both per patient and per lesion data (Cachin 2014). Of those reporting per lesion data, two studies reported accuracy data only for those imaging abnormalities identified by each test (Dellestable 2011; Jouvet 2014), such that comparative studies reported different numbers of lesions and confirmed metastases per index test evaluated (Dellestable 2011; Jouvet 2014). Three studies included all lesions detected by any index test so that the number of lesions included in each 2×2 contingency table was the same for every test (Hausmann 2011; Pfannenberg 2007; Pfluger 2011); two included all lesions considered suspicious by any one index test (Hausmann 2011; Pfannenberg 2007); and one reported including only lesions considered positive for melanoma on at least one index test (Pfluger 2011). Variation in lesion inclusion has the potential to reduce sensitivity in studies that included all lesions detected by any index test, as any metastases missed by any one test would count as false negative results in the contingency table; any missed benign lesions would be considered true negative results, but a large number of lesions would need to be missed to have any detectable effect on specificity.
The considerable clinical heterogeneity between studies in terms of population groups, stages of disease, lesion selection, differences between tests, and definitions of target conditions (either including or excluding imaging of the brain) means that no conclusions can be drawn from studies in mixed and not clearly described populations (Table 3; Appendix 9). Study results are therefore described narratively in Appendix 12.

DISCUSSION

Summary of main results

There is a considerable volume of literature evaluating the accuracy of imaging tests for staging of melanoma, but other than the specific use of imaging to identify nodal metastases before sentinel lymph node biopsy (SLNB), only a small number of identified studies were eligible for our review and were conducted in well-defined populations of participants undergoing primary staging or re-staging for disease recurrence. In terms of methodological quality, studies were generally at low or unclear risk of bias, with methods of participant selection and blinded case note review particularly poorly reported. Studies were of high or unclear concern regarding the applicability of evidence due to participant selection from mixed or not clearly defined populations, poorly described application and interpretation of the index test or observer expertise, and lack of definition of the target condition (e.g. including or excluding the detection of metastases of the brain, no breakdown of cases according to nodal or distant metastases). Because few studies compared eligible tests and because available data for magnetic resonance imaging (MRI) were limited and information regarding the stage of disease at diagnosis was lacking, we could not fully answer the review question.

Four main findings can be drawn from our review.

1. Pre-SLNB ultrasound combined with fine needle aspiration cytology (FNAC) allows around a fifth of patients with nodal metastases to be identified with few false positive results.

Half of all included studies (18/39) considered the use of imaging before SLNB to identify people with nodal metastases, particularly the use of ultrasound with or without FNAC (n = 11). Study populations were well defined and included people likely to be considered eligible for SLNB in routine practice. Studies primarily used B-mode ultrasound, although two also used Doppler ultrasound in all participants, and the use of ultrasound before or after lymphoscintigraphy to identify sentinel nodes varied.

Summary of findings presents key results and translates summary estimates to a hypothetical cohort of 1000 lesions. Given that completion lymphadenectomy (CLND) is no longer a standard of care for patients who are eligible for SLNB, the previously postulated benefit from ultrasound and FNAC of triaging those with nodal metastases on cytology directly to CLND is no longer relevant. We have therefore framed the potential benefit from ultrasound and FNAC in terms of access to adjuvant therapy, but any benefit would be incurred only if a result from imaging and cytology could be obtained significantly more quickly than an SLNB result, or, if SLNB was not available or was contraindicated.

All imaging tests had poor sensitivity, detecting at best a third of people with nodal metastases that were not clinically detectable (sensitivity of 35.4% for ultrasound alone); however, all summary specificities were higher than 90%.

With use of the median prevalence of nodal metastases observed across the 11 studies of ultrasound, a test sensitivity of 35.4% would correctly identify 84 of 237 people with nodal metastases but with 47 false positive results, or people who would be incorrectly considered for adjuvant therapy. Combining ultrasound with FNAC, such that only those positive on both ultrasound and subsequent FNAC would be considered to have nodal disease (i.e. a more narrowly defined threshold for test positivity), reduces by 41 the number of people with nodal metastases who are correctly identified (from 84 to 43) but also reduces to two the number with false positive results. In other words, for every 1000 people eligible for SLNB, ultrasound with FNAC has the potential to allow around a fifth of those with nodal metastases to be considered for adjuvant therapy without the need for a more invasive procedure (SLNB), at a cost of two people being inappropriately managed (false negatives).

However, considerable between-study differences were observed, such that the number of people with false positive results could range between one and seven, and the number of people with false negative results could range between 8 and 134. Results were also dominated by a single large study of 1000 participants from an expert group (Voit 2014), and it is difficult to determine whether these results could be replicated.

2. Limited test accuracy data were available for whole body imaging via positron emission tomography-computed tomography (PET-CT) for primary staging or re-staging for disease recurrence and none evaluated MRI.

Of 24 studies meeting the inclusion criteria for this review, only six clearly recruited participants who were undergoing primary staging following a confirmed diagnosis of melanoma and three recruited participants undergoing imaging for re-staging of disease following some clinical indication of recurrence. Most of the studies (6/9) considered PET-CT, two in comparison to CT alone, and three studies examined the use of ultrasound. None of the studies included in these groups evaluated MRI. Observed sensitivities and specificities for the detection of any metastases for PET-CT appeared to be higher for those having re-staging of disease (summary sensitivity from two studies was 92.6% and specificity 89.7%) compared to primary staging (sensitivities ranged from 30% to 47% and specificities from 73% to 88%) and were more sensitive than CT alone in both population groups, but participant numbers were very small.

3. No conclusions can be drawn regarding routine imaging of the brain with either MRI or CT.

We excluded from this review a number of studies that reported data for 'conventional imaging' including CT or MRI because they did not have clearly defined imaging protocols whereby all included participants underwent both tests (Finkelstein 2004; Fuster 2004; Gulec 2003; Oehr 1999; Paquet 2000; Rinne 1998). Furthermore we identified no eligible studies reporting data for MRI in primary or re-staging populations.

Of the studies conducted in mixed populations, scan coverage variably included the brain such that the definition of the target condition of any metastasis could either include or specifically exclude

the detection of brain metastases. Generally speaking, studies were too small to include significant numbers of brain lesions. Only two studies in mixed population groups identified a sufficient number of brain metastases to allow sensitivities to be estimated. Jouvet 2014 showed CT with intravenous (IV) contrast and MRI with ultrafast gradient echo sequences to have sensitivities of 95% (CT) or more (100% for MRI) compared to 65% sensitivity for MRI without ultrafast gradient echo sequences. In Cachin 2014, PET-CT detected one of seven confirmed metastases of the brain (sensitivity 14%, 95% CI 0% to 58%).

4. There are high concerns regarding the applicability of the evidence, although risk of bias is generally low.

Study quality was moderate in terms of risk of bias, and there are real concerns regarding the applicability of the evidence to the review question. Much of this concern is due to the inclusion of mixed and not clearly defined participant groups. There was a tendency to include participants based on the availability of results for a particular test, but more careful consideration of the indication for imaging is needed before the comparative accuracy of tests at different points on the clinical pathway can be established. Although there is an understandable temptation to translate results from mixed populations to a primary staging or re-staging setting, there is at least some evidence that accuracy varies by pathway and in different ways for different tests (Reinhardt 2006), and this is supported by work in other fields (Leeflang 2013).

Further concerns around applicability relate to reporting of data per lesion as opposed to per patient, not only potentially impacting estimates of test sensitivity and specificity but making it more difficult to consider the implications of testing for patient management unless further information is provided in the papers. Although one might expect sensitivity to be inflated by per lesion data, effects on accuracy are not always clear cut. Cachin 2014 was one of the few studies reporting data both per patient and per lesion; both the sensitivity and specificity of PET-CT were higher for data reported per patient (87% and 71%) compared to those reported per lesion (80% and 54%). The detection of additional metastatic lesions by any one test is of limited benefit if there is no resulting change in stage of disease classification or in patient management options. For example, in Pfluger 2011, the five lesions found to be false negative on unenhanced PET-CT were all identified in patients with multiple metastases, such that there would have been no impact on TNM stage; on the other hand, all six false positive lesions were identified in otherwise metastasis-free patients who were falsely upstaged from M0 to M1.

We also noted variations in the scan coverage between studies, which will impact the definition of the target condition, and limited information was provided on the thresholds used to identify the presence of metastases.

Strengths and weaknesses of the review

The strengths of this review include an in-depth and comprehensive electronic literature search, systematic review methods including double extraction of papers by both clinicians and methodologists, and attempts to contact study authors to clarify data. A detailed and replicable analysis of methodological quality was undertaken and a clear analysis structure was adopted.

In comparison to other available systematic reviews of imaging tests (e.g. Catalano 2011; Danielsen 2014; El-Maraghi 2008; Rodriguez 2014; Sadigh 2014; Schroer-Gunther 2012; Xing 2011), our review covers a more recent search period and a broader review question, including both primary staging and re-staging of melanoma, as opposed to one or the other (Danielsen 2014; Schroer-Gunther 2012), and this review considers the comparative accuracy of different tests as opposed to reviewing a single test (as in all other reviews apart from Xing 2011). We have also separately considered data according to reporting of study data per patient as opposed to per lesion - an approach not taken by any of the other identified systematic reviews.

Our stringent application of review inclusion criteria means that we excluded a considerable proportion of studies included in previous reviews. For example, across a selection of four reviews considering PET, we included only 3 of 12 (El-Maraghi 2008), 7 of 12 (Xing 2011), 3 of 9 (Rodriguez 2014), and 1 of 7 studies included in those reviews (Danielsen 2014). We excluded studies on the basis of having evaluated PET alone rather than PET-CT (Acland 2000; Acland 2001; Belhocine 2002; Fink 2004; Havenga 2003; Koskivuo 2007; Longo 2003; Nguyen 1999; Steinert 1998; Tyler 2000; Vereecken 2005; Wagner 1999; Wagner 2005), a combination of PET and PET-CT, which could not be differentiated from each other (Horn 2006; Wagner 2011), use of PET for treatment response (Beasley 2012; Raymond 2011), use of an inadequate reference standard (e.g. minimum follow-up period was not reported) (Peric 2011), inadequate sample size (Libberecht 2005), or inability to estimate the 2×2 data (Mottaghy 2007). We included all five PET-CT studies included by Schroer-Gunther and colleagues for primary staging of melanoma (Schroer-Gunther 2012), but we considered two of the five to have been conducted in mixed rather than primary staging populations (Aukema 2010b; Strobel 2007b).

A similar picture was observed for other tests. We included only 7 of 22 studies of ultrasound and 4 of 13 studies of CT alone that were included by Xing 2011, 6 of 24 studies of ultrasound from Catalano 2011, and 2 of 8 studies of CT in Sadigh 2014. The most common reason for exclusion of studies of ultrasound from this review was the reporting of more than one ultrasound scan per patient (e.g. Binder 1997; Brountzos 2003; Schmid-Wendtner 2003; Tregnaghi 1997; Voit 2001). For CT, it was the reporting of accuracy data for CT combined with other imaging tests such as MRI in Finkelstein 2004 and Fuster 2004 or reporting of more than one CT scan per patient in Sawyer 2009 and Swetter 2002, inadequate reference standards (Buzaid 1993; Buzaid 1995; Chomyn 1992; Holder 1998), or the inclusion of more than 10%

of participants with non-cutaneous melanoma (Brady 2006; Sofue 2012).

The main concerns for this review result from the poor reporting of primary studies, in particular, limiting assessment of studies according to clinical pathway, by stage of disease on diagnosis, and by varying definitions of the target condition. This review is also somewhat limited by the date of the last search (2016); however, imaging of melanoma has not been a particularly fast-moving field (with only 7 of 39 included studies published in the five years before the search); furthermore, we are not aware of publication of any landmark studies in the interim period.

Applicability of findings to the review question

Varying definitions of eligible study populations and lack of clarity regarding the patient pathway and any prior testing restrict the extent to which our findings can be applied in the clinical setting.

AUTHORS' CONCLUSIONS

Implications for practice

We identified a disappointing lack of evidence for imaging in populations of participants that were clearly defined according to the clinical pathway. Studies were generally small and reported data according to the number of lesions identified as opposed to the number of study participants included. We identified some evidence to suggest that imaging with ultrasound combined with fine needle aspiration cytology (FNAC) before sentinel lymph node biopsy (SLNB) may have a limited role, but further work is needed to identify whether the suggested benefit in terms of avoiding SLNB is cost-effective. Much of the evidence for whole body imaging for primary staging or re-staging of disease is focused on positron emission tomography-computed tomography (PET-CT), and comparative data with CT or magnetic resonance imaging (MRI) are lacking. Increasing availability of adjuvant therapies for melanoma is bound to have a considerable impact on imaging services, but the evidence base to support any increase in imaging for primary staging of disease is limited.

Implications for research

Although there are challenges in designing studies that will remain relevant at the point of publication of findings in such a rapidly changing landscape, and despite potential limitations in service provision in terms of access to different imaging modalities, key questions remain around the most appropriate use of imaging tests for melanoma. In particular, studies need to go beyond diagnostic accuracy and must consider the effects of different imaging tests on patient management.

First, the role of ultrasound of the regional lymph nodes following a primary diagnosis of melanoma is unclear. When combined with FNAC, ultrasound has the potential to avoid SLNB in around a quarter of people with lymph node metastases, allowing them to proceed directly to adjuvant therapy; however, whether this approach would actually be implemented in clinical practice, and for which patients or at which centres of care, needs to be determined. An economic model using currently available data, potentially incorporating downstream consequences as more adjuvant therapies become available, would determine the circumstances under which this pathway saves resources and is worthwhile.

For whole body staging, comparative accuracy studies that incorporate changes to patient management as a result of imaging are needed both for those undergoing primary staging following a confirmed diagnosis of melanoma and for those undergoing re-staging of disease on clinical suspicion of recurrence. For primary staging in particular, more clarity is needed regarding who should undergo whole body staging in terms of whether this should be restricted to those with confirmed stage III or IV disease (identified clinically or following SLNB), or whether there is a role for more widespread imaging in high-risk groups, for example. A survey of current practice in the UK would be useful, to identify which imaging tests are being used in which patient groups across the country and why.

Studies should carry out blinded comparisons of routine imaging using contrast-enhanced CT of the neck, chest, abdomen, and pelvis and contrast-enhanced CT of the head, with full body ^{18}FDG PET-CT, and with post-contrast whole body MRI, or MRI of the head alone, in all participants. The final diagnosis should be established by histology and with the implementation of a clearly defined imaging follow-up schedule in all study participants. Study results in terms of accuracy should be reported per lesion and per patient and should be reported by metastatic site to allow an assessment of the success and failure of contrast-enhanced CT and ^{18}FDG PET-CT in different areas of the body. Imaging of the brain with contrast-enhanced CT versus MRI could also be performed.

It is essential that future research studies be clear about the diagnostic pathway followed by study participants, and they should conform to the updated Standards for Reporting of Diagnostic Accuracy (STARD) guideline (Bossuyt 2015).

ACKNOWLEDGEMENTS

Members of the Cochrane Skin Cancer Diagnostic Test Accuracy Group include the following.

- The full project team (Susan Bayliss, Naomi Chuchu, Clare Davenport, Jonathan Deeks, Jacqueline Dinnes, Lavinia Ferrante

di Ruffano, Kathie Godfrey, Rubeta Matin, Colette O'Sullivan, Yemisi Takwoingi, Hywel Williams).

- Our 12 clinical reviewers (Rachel Abbott, Ben Aldridge, Oliver Bassett, Sue Ann Chan, Alana Durack, Monica Fawzy, Abha Gulati, Jacqui Moreau, Lopa Patel, Daniel Saleh, David Thompson, Kai Yuen Wong) and two methodologists (Lavinia Ferrante di Ruffano and Louise Johnston), who assisted with full-text screening, data extraction, and quality assessment across the entire suite of reviews of diagnosis and staging and skin cancer.
- Our expert advisor and co-author Manil Subesinghe.
- All members of our Advisory Group (Jonathan Bowling, Seau Tak Cheung, Colin Fleming, Matthew Gardiner, Abhilash Jain, Susan O'Connell, Pat Lawton, John Lear, Mariska Leeflang, Richard Motley, Paul Nathan, Julia Newton-Bishop, Miranda Payne, Rachael Robinson, Simon Rodwell, Julia Schofield, Neil Shroff, Hamid Tehrani, Zoe Traill, Fiona Walter, Angela Webster).

We wish to thank Dr. Olga Sphadaruk for her assistance in assessing the eligibility of a Russian paper and members of the University of Birmingham Test Evaluation Research Group for assistance with data extraction and quality assessment for this review (Sophie Beese, Rita Champaneria, Bella Harris, John O'Rourke, Claire Smith).

The Cochrane Skin editorial base wishes to thank Robert Dellavalle, who was the Dermatology Editor for this review; the clinical referees Clare Barlow and Fergus Macbeth; the Cochrane Diagnostic Test Accuracy Editorial Team; and Dolores Matthews, who copy-edited the review.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Abbott 2011

Study characteristics	
Patient sampling	**Design:** non-comparative; retrospective (Prosp. database: yes) **Country:** UK **Data collection:** NR; up to May 08 **Inclusion criteria:** stage III: micro-metastases on SLNB or clinically detectable nodal metastases on diagnosis or FU
Patient characteristics and setting	**Presentation:** mixed (either undergoing FU after prior SLNB/LND for micro-metastases or presenting with clinically detectable nodal disease at or subsequent to initial diagnosis (primary/FU)) **Number patients:** 34 (microscopic group 20; macroscopic group 14) **Number primary lesions:** 34 **Number LNBs/metastases**: NR **Stage of disease:** IIIA 18, 53%; IIIB 10, 29%; IIIC 6, 18% **Median age:** microscopic group 50 y - macroscopic group 63 y **Range:** microscopic group 19 74 y; macroscopic group 48 79 y **Male:** microscopic group 14, 70%; macroscopic group 6, 43% **Primary lesion site:** HN 1, 3%; upper extremity 3, 9%; trunk 20, 59%; lower extremity 10, 29% **Breslow/Clark:** microscopic group mean BT 2.27 mm (1.2 to 9.7 mm) **Macroscopic group:** mean BT 2.01 mm (1.0 to 13 mm) **Ulceration:** NR **Other:** NR
Index tests	**PET-CT:** 2D; CT (NR) **Machine:** General Electric ST, Wisconsin, USA **Scan coverage:** skull base to upper thigh **Contrast:** NR **CT parameters:** NR **FDG:** 400 MBq **Breath hold:** NR **CT used for:** attenuation correction and lesion localisation **Reconstruction:** iterative technique using an ordered subset expectation-maximisation algorithm **Threshold:** clearly indicative/highly suspicious for malignancy considered positive **Number observers:** NR **Qualification (experience):** nuclear medicine consultants (experienced) **Diagnosis (single, consensus, etc.):** NR **Info provided during test interpretation:** clinical NR; other tests NR
Target condition and reference standard(s)	**Histology/Imaging FU** **Histological detail (n, %):** NR, mixture of excisions and LND (5, 15%). **Histopathologist:** NR **FNAC (n, %):** N/A (0) **Follow-up (n, %):** clinical and/or radiological FU (incl PET-CT) (34, 100%) **FU schedule:** every 3 months for clinical examination; annual PET (second annual PET reported for 15/34 (44%) and third annual for 4/34 (12%)). All FU clinically ≥ 6 months following each

	surveillance PET-CT **FU duration:** microscopic mean 38 months (21 to 54 months); macroscopic mean 34 months (15 to 52 months) **Reference blinding:** aware of prior PET-CT results during FU # **Target condition** **Data:** per pt **Definition:** any (excl brain; including local, ITM) **Prevalence:** 7/34 = 21%; 4 local or ITM, 2 nodal, 1 distant metastasis
Flow and timing	**Index to histology interval:** NR **Index to FU interval:** 3 months **Exclusions:** n = 0
Comparative	
Notes	**Other results:** 3 recurrences occurred in microscopic group (1 ITM and 1 pulmonary detected by PET-CT plus 1 local recurrence missed on first annual PET-CT); 4 clinically undetected recurrences occurred in macroscopic group (2 LN, 1 local detected by PET-CT, and 1 ITM missed by staging PET-CT)

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Does the study report results for participants at the same point in the clinical pathway and who would be eligible for imaging in normal practice?	No		
Did the study report data on a per patient rather than per lesion basis?	Yes		
		Unclear	**High**
DOMAIN 2: Index Test PET-CT			

Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
Was the imaging test applied and interpreted in a clinically applicable manner?	Unclear		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No		
Was the test interpreted by an experienced examiner?	Yes		
		Unclear	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Were the reference standard results based on patient follow-up interpreted without knowledge of the original imaging test result?	No		
Does the study use the same definition of disease positive as the primary review question (i.e. any mets) OR is it possible to disaggregate or regroup data such that data matching the review question can be extracted?	Yes		
Was histology or cytology interpretation carried out by an experienced histopathologist or	Unclear		

Abbott 2011 (*Continued*)

by a dermatopathologist?			
		Low	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	No		
Were all patients included in the analysis?	Yes		
		High	

Arrangoiz 2012

Study characteristics	
Patient sampling	**Design:** non-comparative; retrospective (medical record review) **Country:** USA **Data collection:** Jan 03 to Jan 09 **Inclusion criteria:** node negative; BT > 4 mm
Patient characteristics and setting	**Presentation:** primary **Number patients:** 56 **Number primary lesions:** 56 **Number LNBs/metastases:** NR **Stage of disease:** all T4, clinically node negative, and negative for distant metastases **Mean age:** 67 years; **Median age:** NR; **Range:** 26 to 89 years **Male:** 32 (57%) **Primary lesion site:** trunk 16, 29%; extremities 28, 50%; head and neck 12, 21% **Breslow/Clark:** BT median 6 mm; mean 9 mm; range 4.1 to 40 mm **Ulceration:** 34, 61% **Other:** satellitosis: 25, 45%
Index tests	**PET-CT:** 2D or 3D; CT (U, helical, low dose) **Machine:** GE Discovery LS PET/CT Scanner (from 2003 to 10/2010) or a Siemens Biograph 16 PET/CT Scanner (from 10/2010 onwards) SUV values reportedly comparable with cross-calibration by manufacturer-trained field engineers and in-house medical physicist **Scan coverage:** WB; vertex of the head down to feet for all patients **Contrast:** U **CT parameters:** Discovery LS - 140 kVp, 90 mA; Siemens Biograph - 130 kVp, 100 mA; 5 mm **FDG:** 15 mCi (IV)

	Breath hold: normal breathing **CT used for:** attenuation correction; co-registered images **Reconstruction:** Discovery LS - ordered subsets expectation maximisation (OSEM) algorithm with 28 subsets and 2 iterations. Siemens Biograph - rueX algorithm with 21 subsets and 2 iterations **Threshold:** SUV 2.5 **Number observers:** NR; 'in-house medical physicist' mentioned **Qualification (experience):** NR; 'in-house medical physicist' mentioned (NR) **Diagnosis (single, consensus, etc.):** unclear **Info provided during test interpretation:** clinical NR; other tests NR
Target condition and reference standard(s)	Histology (SLNB, CLND, biopsy); FU **Histological detail (n, %):** NR (54, 96% (48 SNB and 6 LND)). **Histopathologist:** NR **FNAC (n, %):** NR (NR) **Follow-up (n, %):** NR; 2/56 had no SLNB or LND reported so must have had some follow-up to confirm absence of disease. Also the number D+ reported by authors in Table 4 does not add up to combined SLNB/CLND numbers D+; presume that 4 of SLNB negative must have recurred with regional disease at some point (NR) **FU schedule:** NR **FU duration:** NR **Reference blinding:** NR **Target condition** **Data:** per pt **Definition:** any mets (NR; scan incl head); **Prevalence:** 32/56 = 57% **Definition:** nodal mets; **Prevalence:** 29/56 = 52% **Definition:** distant mets (not documented; scan incl head); **Prevalence:** 5/56 = 9%
Flow and timing	**Index to histology interval:** NR; states that 6 "proceeded directly to therapeutic lymph node dissection" after PET **Index to FU interval:** NR **Exclusions:** n = 0; N/A
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		

Does the study report results for participants at the same point in the clinical pathway and who would be eligible for imaging in normal practice?	Yes		
Did the study report data on a per patient rather than per lesion basis?	Yes		
		Low	**Low**
DOMAIN 2: Index Test PET-CT			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
Was the imaging test applied and interpreted in a clinically applicable manner?	Unclear		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes		
Was the test interpreted by an experienced examiner?	Unclear		
		Unclear	**Unclear**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Were the reference standard results based on patient follow-up interpreted without knowledge	Unclear		

of the original imaging test result?			
Does the study use the same definition of disease positive as the primary review question (i.e. any mets) OR is it possible to disaggregate or regroup data such that data matching the review question can be extracted?	Yes		
Was histology or cytology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Unclear	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	No		
Were all patients included in the analysis?	Yes		
		High	

Aukema 2010a

Study characteristics	
Patient sampling	**Design:** non-comparative; retrospective (Prosp. database: NR) **Country:** Netherlands **Data collection:** Aug 2006 to Mar 2009 **Inclusion criteria:** raised S100 during FU after resection of nodal or distant metastases or with high-risk primary tumour
Patient characteristics and setting	**Presentation:** mixed (15 treated for locoregional recurrence and 5 for distant mets; remaining 26 followed up after primary melanoma treatment) **Number patients:** 46 **Number primary lesions:** NR **Number LNBs/metastases:** NR **Stage of disease:** NR; unfavorable primary tumour (n = 6); primary melanoma with simultaneous nodal metastases (n = 18); unknown primary melanoma with nodal metastasis (n = 2); locoregional

	recurrence (n = 15); distant recurrence (n = 5) **Mean age:** 59 years; **Range:** 25 to 93 years **Male:** NR **Primary lesion site:** NR **Breslow/Clark:** NR **Ulceration:** NR **Other:** NR
Index tests	**PET-CT:** NR; CT (U) **Machine:** Gemini II, Philips, Eindhoven, The Netherlands **Scan coverage:** whole body; not described **Contrast:** U **CT parameters:** kV NR; 40 mAs; 5 mm **FDG:** 180 to 240 MBq (4.9 to 6.5 mCi) **Breath hold:** no breath hold instructions reported **CT used for:** attenuation correction; PET fused to low-dose CT **Reconstruction:** NR **Threshold:** NR; "hypermetabolic lesions" # **MRI:** patients underwent MRI of the brain; insufficient data to include separate 2×2 **Machine:** Achieva, Philips, Eindhoven, The Netherlands **Scan coverage:** brain **Contrast:** yes, not documented **MRI parameters:** transversal T2-weighted; axial fluid attenuated inversion recovery (FLAIR) imaging, diffusion-weighted imaging and pre- and post-contrast coronal T1-weighted 3D-FFE imaging **Tesla:** 3.0 **Number observers:** 3 **Qualification (experience):** nuclear medicine physicians (experienced') **Diagnosis (single, consensus,etc.):** consensus of 3 **Info provided during test interpretation:** clinical NR; other tests NR; MRI brain also conducted
Target condition and reference standard(s)	**FNAC/histology/imaging FU** **Histological detail (n, %):** NR (13, 28.3%). **Histopathologist:** NR **FNAC (n, %):** N/A (0) **Follow-up (n, %):** clinical exam; CT (33, 71.7%) **FU schedule:** NR **FU duration:** for disease negative only (n = 19): median 12 months (4 to 32 months); NR for full sample **Reference blinding:** NR **Target condition** **Data:** per pt **Definition:** any (not documented; brain NR) **Prevalence:** 23/46 = 50%
Flow and timing	**Index to histology interval:** NR **Index to FU interval:** **Exclusions:** n = NR
Comparative	

Notes	**Other result:** "MRI revealed 2 brain metastases of 2 and 4 mm in 1 patient (2%). This patient also had other distant metastases that were detected by PET-CT"		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Does the study report results for participants at the same point in the clinical pathway and who would be eligible for imaging in normal practice?	No		
Did the study report data on a per patient rather than per lesion basis?	Yes		
		Low	**High**
DOMAIN 2: Index Test PET-CT			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
Was the imaging test applied and interpreted in a clinically applicable manner?	No		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Unclear		

Was the test interpreted by an experienced examiner?	Yes		
		Unclear	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Were the reference standard results based on patient follow-up interpreted without knowledge of the original imaging test result?	Unclear		
Does the study use the same definition of disease positive as the primary review question (i.e. any mets) OR is it possible to disaggregate or regroup data such that data matching the review question can be extracted?	Unclear		
Was histology or cytology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Unclear	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	No		
Were all patients included in the analysis?	Yes		

Aukema 2010a (*Continued*)

		High	

Aukema 2010b

Study characteristics	
Patient sampling	**Design:** non-comparative; prospective **Country:** Netherlands **Data collection:** Oct 06 to Mar 09 **Inclusion criteria:** clinically node positive with no sign of distant metastases; primary/re-staging NR
Patient characteristics and setting	**Presentation:** unclear (NR; all have palpable and proven LN metastases) **Number patients:** 70 **Number primary lesions:** 70 **Number LNBs/metastases:** 73 **Stage of disease:** ≥ stage IIIb (all with clinically palpable nodes) **Mean age:** 58 y; **Median age:** NR; **Range:** NR **Male:** 37 (54%) **Primary lesion site:** upper extremity 4, 6%; lower extremity 37, 53%; trunk 19, 27%; head/neck 9, 13%; unknown primary 1, 1% **Breslow/Clark:** Breslow: median 3 mm **Ulceration:** NR **Other:** NR
Index tests	**PET-CT:** 2D; CT (U) **Machine:** Gemini II, Philips, Eindhoven, The Netherlands **Scan coverage:** WB according to primary lesion site (i.e. with regard to inclusion of cranium or lower extremities) **Contrast:** U **CT parameters:** kV NR; 40 mAs; 5 mm **FDG:** 180 to 240 MBq **Breath hold:** no breath hold instructions reported **CT used for:** attenuation correction; PET fused to low-dose CT **Reconstruction:** PET was fused with low-dose CT after correction for attenuation **Threshold:** NR; "metabolically active" # **MRI:** patients underwent MRI of the brain; insufficient data to include separate 2×2 **Machine:** Achieva, Philips, Eindhoven, The Netherlands **Scan coverage:** brain **Contrast:** yes, not documented **MRI parameters:** transversal T2-weighted; axial fluid attenuated inversion recovery (FLAIR) imaging, diffusion-weighted imaging and pre- and post-contrast coronal T1-weighted 3D-FFE imaging **Tesla:** 3.0 # **Number observers:** 3 **Qualification (experience):** nuclear medicine physicians (NR) **Diagnosis (single, consensus,etc.):** consensus of 3

Aukema 2010b (*Continued*)

	Info provided during test interpretation: clinical NR; other tests NR; MRI brain also conducted
Target condition and reference standard(s)	**FNAC/histology/imaging FU** **Histological detail (n, %):** NR (NR; 11 with histology or cytology). **Histopathologist:** NR **FNAC (n, %):** NR (NR; 11 with histology or cytology) **Follow-up (n, %):** CT, ultrasound, or clinical follow-up for TP cases (59; 84%) **FU schedule:** NR **FU duration:** ≥ 6 months **Reference blinding:** NR # **Target condition** **Data:** per pt **Definition:** any mets (incl in transit mets and skull according to primary lesion site); **Prevalence:** 30/70 = 43% **Metastases:** PET-CT detected additional involved LNBs (3) and 'distant' metastases (20); false negative results included ITM (2), liver metastases (1), extensive metastases 3 months post PET-CT (1)
Flow and timing	**Index to histology interval:** N/A **Index to FU interval:** NR **Exclusions:** n = 0; N/A
Comparative	
Notes	**Other result:** MRI: detected brain mets in 5 pts, 4 with multiple other metastases detected by PET-CT and 1 with solitary brain metastases. Outcome: 2 received dexamethasone and radiotherapy of the brain, 1 was treated with temozolomide, and 1 received supportive care; solitary brain metastasis removed surgically and underwent adjuvant whole brain radiotherapy; no signs of recurrent disease at 15 months

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Does the study report results for participants at the same point in the clinical pathway and who would be eligible for imaging in	Unclear		

normal practice?			
Did the study report data on a per patient rather than per lesion basis?	Yes		
		Unclear	**Unclear**
DOMAIN 2: Index Test PET-CT			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Was the imaging test applied and interpreted in a clinically applicable manner?	No		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Unclear		
Was the test interpreted by an experienced examiner?	Yes		
		Low	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Were the reference standard results based on patient follow-up interpreted without knowledge of the original imaging test result?	Unclear		

Aukema 2010b (*Continued*)

Does the study use the same definition of disease positive as the primary review question (i. e. any mets) OR is it possible to disaggregate or regroup data such that data matching the review question can be extracted?	Yes		
Was histology or cytology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Unclear	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	No		
Were all patients included in the analysis?	Yes		
		High	

Bastiaannet 2009

Study characteristics	
Patient sampling	**Design:** within-person comparison; prospective **Country:** Netherlands **Data collection:** Jul 2003 to Dec 2007 **Inclusion criteria:** node positive (clinical or histology/cytology proven) candidates for CLND
Patient characteristics and setting	**Presentation:** mixed (primary (LN mets diagnosed at time of primary diagnosis) 39, 15.5%; recurrence (LN mets identified ≤ 3 years since primary dx) 145, 57.8%; recurrence (> 3 years since primary dx) 67, 26.7%) **Number patients:** 251 **Number primary lesions:** 251 **Number LNBs/metastases:** NR **Stage of disease:** III (100%) **Mean age:** reported in Bastiannet 2012 as 56.9 years (n = 253); **Range:** 19 to 93 years - 76 (30.3%) < 50 years; 99 (39.4%) 50 to 65 years; 76 (30.3%) > 65 years **Male:** 152 (61%)

	Primary lesion site: HN 29, 11.6%; upper extremities 26, 10.4%; trunk 93, 37.0%; lower extremities 88, 35.0%; unknown primary 15, 6.0% **Breslow/Clark:** Breslow: ≤ 1 mm 32, 12.8%; 1.0 to 2.0 mm 73, 29.1%; ≥ 2.0 129, 51.4%; unknown primary 15, 5.9%; missing 2, 0.8% **Clark level:** I/II/III (n = 84; 33.5%), IV/V (n = 144; 57.4%), unknown primary (n = 15; 5.9%), missing (n = 8; 3.2%) **Ulceration:** yes 53, 21.1%; unknown 15, 6% **Other:** localisation of SLN: neck 43, 17.1%; axilla 94, 37.5%; inguinal 114, 45.4%
Index tests	**CT:** CE, spiral, multi-slice **Machine:** NR **Scan coverage:** chest, abdomen plus neck for those with LN in the neck **Contrast:** oral and IV **CT parameters:** NR; 'multi-slice' **Breath hold:** no breath hold instructions reported **Threshold:** NR (presence/absence of mets) **Number observers:** NR **Qualification (experience):** attending staff nuclear medicine physicians (NR) **Diagnosis (single, consensus, etc.):** NR **Info provided during test interpretation:** clinical NR; other tests blinded to PET
Target condition and reference standard(s)	**Histology/FU** **Histological detail (n, %):** cytopathology, histopathology (NR). **Histopathologist:** NR **FNAC (n, %):** NR (NR) **Follow-up (n, %):** bone scan, MRI, 'follow-up' (251, 100%) **FU schedule:** NR **FU duration:** median 13.7 months; minimum 6 months stated for index test positive, NR for index test negative **Reference blinding:** NR **Target condition** **Data:** per pt **Definition:** distant mets (including lymph nodes beyond regional LNs) **Prevalence:** 78/251 = 31% **Metastases:** 120 TP metastatic sites identified by CT included liver (20), lung (41), abdomen (13) , bone (10), subcutaneous (5), other (11); 16 patients FN on CT had metastases in the bone (5), lung (5), multiple sites (2), liver (2), sternal (1), leg (1) Presenting LN metastases were correctly identified by CT in 231/151 patients and by PET alone in 229/251
Flow and timing	**Index to histology interval:** NR **Index to FU interval:** NR **Exclusions:** n = 8; excluded due to follicular structure (n = 1), > 13 years between primary and lymph nodes (n = 3), incidence abroad (n = 1), mucosal melanoma (n = 2), primary melanoma treated as benign lesion (n = 1)
Comparative	
Notes	**Other result:** (1) accuracy of PET alone, (2) change in treatment resulting from PET and/or CT

Bastiaannet 2009 (*Continued*)

Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Does the study report results for participants at the same point in the clinical pathway and who would be eligible for imaging in normal practice?	No		
Did the study report data on a per patient rather than per lesion basis?	Yes		
		Low	**High**
DOMAIN 2: Index Test CT			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Was the imaging test applied and interpreted in a clinically applicable manner?	Unclear		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No		
Was the test interpreted by an experienced examiner?	Yes		

Bastiaannet 2009 (*Continued*)

		Low	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Were the reference standard results based on patient follow-up interpreted without knowledge of the original imaging test result?	Unclear		
Does the study use the same definition of disease positive as the primary review question (i.e. any mets) OR is it possible to disaggregate or regroup data such that data matching the review question can be extracted?	Yes		
Was histology or cytology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Unclear	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	No		
Were all patients included in the analysis?	No		
		High	

Cachin 2014

Study characteristics	
Patient sampling	**Design:** non-comparative; prospective **Country:** France **Data collection:** Aug 2008 to Sep 2010 **Inclusion criteria:** prior history of cutaneous or ocular MM undergoing staging or re-staging including (a) newly diagnosed at any TNM stage, (b) known visceral or cutaneous MM metastases with unknown primary tumour, or (c) MM without metastases (included to assess test specificity)
Patient characteristics and setting	**Presentation:** mixed (melanoma status at inclusion was one of the following: "newly diagnosed cutaneous or ocular melanoma at any TNM stage, presence of known visceral melanoma metastases, or cutaneous melanoma metastases with unknown primary tumour. Patients with melanoma without metastases were also included, principally to assess the specificity of the imaging. Also states imaging was for staging or for re-staging") **Number patients:** 87 **Number primary lesions:** NR **Number LNBs/metastases:** 85 **Stage of disease:** NR; 45 (51% were diagnosed with melanoma mets on study Inclusion) **Mean age:** NR; **Median age:** NR; **Range:** NR **Male:** 42 (48.3%) **Primary lesion site:** NR **Breslow/Clark:** Breslow thickness (mm): < 1.0: 12, 13.8%; 1.0 to 2.0: 34, 39.1%; ≥ 2.0, 41, 47.1% **Clark level:** I 3, 3.4%; II 2, 2.3%; III 20, 23.0%; IV 46, 52.9%; V 3, 3.4%; not known 13, 14.9% **Ulceration:** NR **Other:** cutaneous melanoma pigmentation: pigmented 51, 58.6%; achromic 7, 8.0%; not known 29, 33.3%
Index tests	**PET-CT:** NR; SPECT used in 4 of 8 centres **Machine:** Discovery ST2, GE; Biograph 6, Siemens; Biograph HIREZ True Point, Siemens; Discovery ST4, GE; Gemini Dual, Philips; Gemini, Philips **Scan coverage:** WB (not further described) **Contrast:** NR **CT parameters:** SPECT; N/A **FDG:** 3 to 5 MBq/kg **Breath hold:** NR **CT used for:** PET 'correlated' with CT abnormalities **Reconstruction:** iterative in 6 of 8 centres; filtered back-projection in 2 of 8 centres **Threshold:** PET positive if there was focal uptake greater than mediastinal or liver uptake that could not clearly be related to physiological processes; negative when a normal distribution of tracer was observed, even if the CT scan showed abnormalities. Bone accumulations were considered positive when the uptake was higher than in normal bone marrow. Any instance of equivocal PET uptake was considered positive **Number observers:** NR **Qualification (experience):** nuclear physician (experienced) **Diagnosis (single, consensus, etc.):** single **Info provided during test interpretation:** clinical NR; other tests NR; PET interpretation independent of CT and then correlated with CT

Target condition and reference standard(s)	**Histology/Imaging FU/FU** **Histological detail (n, %):** NR; "a total of 25 biopsies (1 per patient) were performed." (25; 28. 7%). **Histopathologist:** NR **FNAC (n, %):** N/A (N/A) **Follow-up (n, %):** could include CT scan, biopsy, pathology, clinical follow-up (87, 100%) **FU schedule:** NR **FU duration:** ≥ 6 months **Reference blinding:** NR **Target condition** **Data:** per pt **Definition:** any (incl brain, subcutaneous mets); **Prevalence:** 39/67 = 58% **Data:** per lesion **Definition:** any (incl brain, subcutaneous); **Prevalence:** 85/176 = 48% **Definition:** nodal; **Prevalence:** 20/39 = 51% **Definition:** distant (incl brain and skin); **Prevalence:** 65/137 = 47% **Definition:** bone; **Prevalence:** 14/34 = 41% **Definition:** lung; **Prevalence:** 10/27 = 37% **Definition:** soft tissue; **Prevalence:** 16/25 = 64% **Definition:** skin; **Prevalence:** 7/9 = 78% **Definition:** brain; **Prevalence:** 7/9 = 78%
Flow and timing	**Index to histology interval:** NR **Index to FU interval:** NR **Exclusions:** n = 20; 12 did not undergo FDG PET due to imaging cancellation; 8 are unaccounted for (text describes 75 having PET but reports results for only 67)
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Does the study report results for participants at the same point in the clinical pathway and who would be eligible for imaging in	No		

normal practice?			
Did the study report data on a per patient rather than per lesion basis?	Yes		
		Unclear	**High**
DOMAIN 2: Index Test PET-CT			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Was the imaging test applied and interpreted in a clinically applicable manner?	Unclear		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes		
Was the test interpreted by an experienced examiner?	Yes		
		Low	**Unclear**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Were the reference standard results based on patient follow-up interpreted without knowledge of the original imaging test result?	No		

Cachin 2014 (*Continued*)

Does the study use the same definition of disease positive as the primary review question (i. e. any mets) OR is it possible to disaggregate or regroup data such that data matching the review question can be extracted?	Yes		
Was histology or cytology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Unclear	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	No		
Were all patients included in the analysis?	No		
		High	

Chai 2012

Study characteristics	
Patient sampling	**Design:** non-comparative; retrospective (Prosp. database: yes) **Country:** USA **Data collection:** Jun 2005 to Sep 2009 **Inclusion criteria:** node negative, BT > 0.76 mm or < 0.76 mm with high-risk features such as ulceration, high mitotic rate, or positive deep margin
Patient characteristics and setting	**Presentation:** primary (pre-SLNB) **Number patients:** 325 **Number primary lesions:** 325 **Number LNBs/metastases:** 347 LNBs **Stage of disease:** NR **Mean age:** NR; **Median age:** 58 years; **Range:** 18 to 86 years **Male:** 189 (58%) **Primary lesion site:** head and neck 34 (10.5%), trunk 129 (39.7%), upper extremity 101 (31.1%) , lower extremity 61 (18.8%)

	Breslow/Clark: BT median (range) 1.78 (0.42 to 14.4); BT ≤ 1.00 56 (17.2%), 1.01 to 2.00 136 (41.8%), 2.01 to 4.00 88 (27.1%), 4.00 44 (13.5%), unknown 1 (0.3%) **Clark level:** III 24 (7.4%), IV 275 (84.6%), V 20 (6.2%), unknown 6 (1.8%) **Ulceration:** 97, 29.8%; unknown 16, 4.9% **Other:** regression present 26 (8.0%), unknown 15 (4.6%). **Growth phase:** radial 20 (6.2%), vertical 283 (87.1%), unknown 22 (6.7%) **Angiolymphatic invasion:** present 15 (4.6%), unknown 20 (6.2%) **Mitotic rate:** 0 9 (2.8%), C1 303 (93.2%), unknown 23 (7.1%)
Index tests	**US:** B mode; linear array **Machine: NR** **Scan coverage:** acc to primary MM site and discretion of attending surgeon (extremity melanomas - ipsilateral groin or axilla, MM of hand or forearm also had epitrochlear US and of lower leg had popliteal US; HN MM - ipsilateral neck, parotid, and supraclavicular US; MM on trunk according to Sappey's line - at or above the beltline included axillary ultrasound, at or below included groin ultrasound, lesions close to the midline had bilateral US) **Contrast:** N/A **FNAC:** If US performed the day before SLNB, US-guided FNAC was offered; FNAC +ve proceeded to CLND, FNAC- to SLNB as planned **Threshold:** US - classed as "abnormal," "suspicious," or "indeterminate - recommending a short-term follow-up" were considered positive (criteria described in detail) **Number observers:** NR **Qualification (experience):** NR (NR) **Diagnosis (single, consensus, etc.):** NR **Info provided during test interpretation:** clinical NR; other tests NR
Target condition and reference standard(s)	**Histology (CLND/SLNB)** **Histological detail (n, %):** H&E (serial section); IHC (NR) (325, 100%). **Histopathologist:** NR **FNAC (n, %):** NR; all positive on CLND (6, 1.8%) **Follow-up (n, %):** NR (NR; presume 100%) **FU schedule:** NR **FU duration:** NR; FU for SLNB negatives mentioned but no description given **Reference blinding:** NR **Target condition** **Data:** per pt **Definition:** nodal mets; **Prevalence:** 64/317 = 20%
Flow and timing	**Index to histology interval:** US performed either immediately or several days before LS **Index to FU interval:** NR **Exclusions:** n = 8; 1 patient had ultrasound of a non-draining nodal basin, while the actual draining basin identified by lymphoscintigraphy was not examined with ultrasound; this patient was not included in further analysis for comparison between ultrasound and SLNB. Plus 7 SLN positive who did not get US
Comparative	
Notes	
Methodological quality	

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Does the study report results for participants at the same point in the clinical pathway and who would be eligible for imaging in normal practice?	Yes		
Did the study report data on a per patient rather than per lesion basis?	Yes		
		Low	**Low**
DOMAIN 2: Index Test Ultrasound (pre-SLNB)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Was the imaging test applied and interpreted in a clinically applicable manner?	Unclear		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes		
Was the test interpreted by an experienced examiner?	Unclear		
		Low	**Unclear**
DOMAIN 3: Reference Standard			

Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Were the reference standard results based on patient follow-up interpreted without knowledge of the original imaging test result?			
Does the study use the same definition of disease positive as the primary review question (i.e. any mets) OR is it possible to disaggregate or regroup data such that data matching the review question can be extracted?	Yes		
Was histology or cytology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Low	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
		High	

Dellestable 2011

Study characteristics	
Patient sampling	**Design:** within-person comparison; prospective **Country:** France **Data collection:** Aug 2006 to May 2007 **Inclusion criteria:** PET-CT for primary staging or follow-up of MM, regardless of AJCC stage or indication for examination **Excluded if** contraindications to MRI or iodine injection
Patient characteristics and setting	**Presentation:** mixed (both primary staging and FU; breakdown reported but not legible on scanned pdf) **Number patients:** 40 **Number primary lesions:** 40 **Number LNBs/metastases:** NR; 72 lesions **Stage of disease:** AJCC I to II 11, 27.5%; AJCC III to IV 29, 72.5% **Mean age:** 57 years; **Range:** 27 to 85 years **Male:** 20 (50%) **Primary lesion site:** NR **Breslow/Clark:** BT mean 3.2 mm, median 2.7 mm, range 0.6 to 11 mm **Ulceration:** NR **Other:** NR
Index tests	**CT** **Machine:** VCT (General Electric Healthcare, Wisconsin, USA) **Scan coverage:** skull, neck, thorax, abdomen, pelvis **Contrast:** iodised injection was administered by the same venous route as for previous examinations **CT parameters:** NR **Breath hold:** no breath hold instructions reported **Threshold:** NR **MRI:** WB, DW, T2STIR, CE 3D gradient echo **Machine:** Signa Excite HD MRI (General Electric Healthcare, Milwaukee, United States) **Scan coverage:** WB; head to lower limbs **MRI parameters:** T2STIR, T1, diffusion, 3D gradient echo T1 after gadolinium injection **Magnet:** 1.5 T **Threshold:** NR # **PET-CT:** NR; CT (CE) **Machine:** Biograph "coupled to an X-ray scanner for attenuation correction and anatomical registration" **Scan coverage:** WB; top of the skull to the feet **Contrast:** unclear; contrast is reported for CT; however CT component of PET-CT is not clear **CT parameters:** NR **FDG:** 5.5 MBq/kg **Breath hold:** no breath hold instructions reported **CT used for:** attenuation correction and anatomical registration **Reconstruction:** NR **Threshold:** focal uptake; unusual location or visual or quantitative intensity (SUV measurement) **Number observers:** 3 **Qualification (experience):** NR (NR)

Dellestable 2011 (*Continued*)

	Diagnosis (single, consensus, etc.): single with consensus if results of any modality disagree **Info provided during test interpretation:** clinical NR; other tests - each of the 3 exams was interpreted by a different reader, who had no knowledge of results of the other 2
Target condition and reference standard(s)	**Histology/Imaging or clin FU** **Histological detail (n, %):** NR (36 lesions, 28% of 128). **Histopathologist:** NR **FNAC (n, %):** N/A (0) **Follow-up (n, %):** clinical or radiological (72, 56%) **FU schedule:** NR **FU duration:** > 4 months **Reference blinding:** N/A **Target condition** **Data:** per lesion **Definition:** any (incl brain); **Prevalence:** CT 72/119 = 61%; MRI 70/117 = 60%; PET-CT 72/119 = 61% **Definition:** nodal; **Prevalence:** CT 31/39 = 79%; MRI 31/40 = 78%; PET-CT 31/38 = 82% **Definition:** site specific (bone); **Prevalence:** CT 14/17 = 82%; MRI 14/16 = 88%; PET-CT 14/17 = 82% **Definition:** site specific (liver); **Prevalence:** CT 4/21 = 19%; MRI 4/26 = 15%; PET-CT 4/25 = 16% **Definition:** site specific (lung); **Prevalence:** CT 13/16 = 81%; MRI 13/14 = 93%; PET-CT 13/15 = 87%
Flow and timing	**Index to histology interval:** NR **Index to FU interval:** NR **Exclusions:** CT n = 20 lesions; 4 lesions with indeterminate reference and 16 not picked up by CT; MRI n = 9 lesions; 4 lesions with indeterminate reference and 7 not picked up by MRI; PET-CT n = 9 lesions; 4 lesions with indeterminate reference and 5 not picked up by PET
Comparative	(1) Each of the three exams was interpreted by a different reader, who had no knowledge of results of the other 2 (2) Tests were consecutively applied, same day (3) Prospective study included all patients scheduled for PET-CT
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		

Did the study avoid inappropriate exclusions?	Yes		
Does the study report results for participants at the same point in the clinical pathway and who would be eligible for imaging in normal practice?	No		
Did the study report data on a per patient rather than per lesion basis?	No		
		Low	**High**
DOMAIN 2: Index Test CT			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Was the imaging test applied and interpreted in a clinically applicable manner?	Unclear		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No		
Was the test interpreted by an experienced examiner?	Unclear		
		Low	**High**
DOMAIN 2: Index Test MRI			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		

Dellestable 2011 (*Continued*)

Was the imaging test applied and interpreted in a clinically applicable manner?	Unclear		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No		
Was the test interpreted by an experienced examiner?	Unclear		
		Low	**High**
DOMAIN 2: Index Test PET-CT			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Was the imaging test applied and interpreted in a clinically applicable manner?	Unclear		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Unclear		
Was the test interpreted by an experienced examiner?	Unclear		
		Low	**Unclear**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		

Were the reference standard results based on patient follow-up interpreted without knowledge of the original imaging test result?	Unclear		
Does the study use the same definition of disease positive as the primary review question (i.e. any mets) OR is it possible to disaggregate or regroup data such that data matching the review question can be extracted?	Yes		
Was histology or cytology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Unclear	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	No		
Were all patients included in the analysis?	No		
		High	
DOMAIN 5: Comparative			
1) was each index test result interpreted without knowledge of the results of other index tests or testing strategies?	Yes		
2) Was the interval between application of index tests	Yes		
3) Was it predetermined that all index tests should be given to all study participants?	Yes		

Dellestable 2011 (*Continued*)

		Low	

Hafner 2004

Study characteristics	
Patient sampling	**Design:** within-person comparison; prospective **Country:** Switzerland **Data collection:** Aug 1999 to Mar 2002 **Inclusion criteria:** any cutaneous MM with BT ≥ 1 mm without evidence of detectable distant metastasis (includes clinically palpable)
Patient characteristics and setting	**Presentation:** primary (pre-SLNB/any primary) **Number patients:** 101 **Number primary lesions:** 101 **Number LNBs/metastases:** 105 LNBs; 136 SLNs **Stage of disease:** NR; stage IV (evidence of distant mets) excluded **Median age:** 55 years; **Range:** 18 to 79 years **Male:** 55 (55%) **Primary lesion site:** limbs 49, 49%; trunk 35, 35%; H&N 16, 16% **Breslow/Clark:** Breslow: 1.01 to 2 mm 38; 2.01 to 4 mm 43; > 4.0 mm 19 **Ulceration:** NR **Other:** NR
Index tests	**US:** B-mode **Machine:** Acuson Sequoia 512 or General Electric Logiq 700 Experty, with dedicated 5-MHz curved array probes **Scan coverage:** regional lymph nodes of the groins, axillae, and neck (abdominal US also performed) **Contrast:** N/A **FNAC:** clinically or radiologically suspect LN mets underwent FNAC; FNAC+ underwent SLNB and CLND in same procedure **Threshold:** NR; 'radiologically suspect' **Number observers:** 1 **Qualification (experience):** radiologist (NR) **Diagnosis (single, consensus, etc.):** single **Info provided during test interpretation:** clinical unclear; clinical exam by dermatologist and US by radiologist; other tests NR
Target condition and reference standard(s)	**Histology (CLND/SLNB)** **Histological detail (n, %):** SLN id - hot or blue node; SLN positive based on EORTC and UICC recommendations (100; 100%). **Histopathologist:** all specimens were examined by an experienced pathologist **FNAC (n, %):** appears that some had FNAC before SLNB but not clearly reported: "In the presence of a clinically or radiologically suspect lymph node metastasis, fine-needle aspiration was performed. If the lymph node proved to be cytologically positive for melanoma metastasis, SN biopsy was performed" (n NR; abstract reports 3 LN mets identified on physical exam, 2 of which were detected by US) **Follow-up (n, %):** NR; implies CT but could include any of study tests (chest X-ray, US, PET,

	CT) (NR) **FU schedule:** NR **FU duration:** 20 months (8 to 39) **Reference blinding:** NR # **Target condition** **Data:** per pt **Definition:** nodal mets **Prevalence:** 23/97 = 24%, including 3 clinically node positive 26/100 = 26%
Flow and timing	**Index to histology interval:** 2 weeks **Index to FU interval:** 6 months **Exclusions:** n = 4; 1 sentinel node was not found intraoperatively; 3 clinically node positive were excluded by Bham team for pre-SLNB analysis
Comparative	
Notes	**Other result:** no confirmed distant mets detected at time of imaging; 9 patients with suspicious findings on imaging were negative for progression/recurrence at 12 months; PET (2), abdominal US (3), chest X-ray (4) 5/26 SLNB positive and 4/74 SLNB negative patients had recurrence OR progression (no breakdown by US result was given). Recurrences in the SLN positive group were 1 nodal and 4 distant, and in the SLN negative group were 4 nodal plus 1 ITM and 1 distant mets in 2 patients with nodal recurrences

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Does the study report results for participants at the same point in the clinical pathway and who would be eligible for imaging in normal practice?	Yes		
Did the study report data on a per patient rather than per lesion basis?	Yes		

Hafner 2004 (*Continued*)

		Low	**Low**
DOMAIN 2: Index Test Ultrasound (pre-SLNB)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Was the imaging test applied and interpreted in a clinically applicable manner?	Unclear		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No		
Was the test interpreted by an experienced examiner?	Yes		
		Low	**High**
DOMAIN 2: Index Test Ultrasound			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Was the imaging test applied and interpreted in a clinically applicable manner?	Unclear		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No		
Was the test interpreted by an experienced examiner?	Yes		
		Low	**High**

Hafner 2004 (*Continued*)

DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Were the reference standard results based on patient follow-up interpreted without knowledge of the original imaging test result?			
Does the study use the same definition of disease positive as the primary review question (i.e. any mets) OR is it possible to disaggregate or regroup data such that data matching the review question can be extracted?	Yes		
Was histology or cytology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
		High	

Hausmann 2011

Study characteristics	
Patient sampling	**Design:** within-person comparison; prospective **Country:** Germany **Data collection:** NR; 18-month period **Inclusion criteria:** AJCC stage III or IV MM; clinical indication for imaging was positive sentinel node biopsy or suspicious lesions on ultrasound or X-ray studies **Excluded if** second tumours
Patient characteristics and setting	**Presentation:** unclear (pts described as having undergone previous assessment of tumour spread based on ADO (German) guidelines but staging/re-staging not described; indication for imaging was SLN+ or suspicious lesions were identified on ultrasound or X-ray) **Number patients:** 50 eligible; 33 included **Number primary lesions:** 50 **Number LNBs/metastases:** NR **Stage of disease:** full sample only: stage III (19); stage IV (31) **Mean age:** full sample only: 59.6 years; **Range:** full sample only: 26 to 86 years **Male:** full sample only: 32 (64%) **Primary lesion site:** NR **Breslow/Clark:** NR **Ulceration:** NR **Other:** NR
Index tests	**CT:** U + CE, multi-detector **Machine:** multi-detector CT (Somatom Volume Zoom, Siemens Healthcare Sector, Erlangen) **Scan coverage:** skull base to pelvis; CT and MR compared for "neck to the pelvis" only; sites imaged included lungs, liver, spleen, kidneys, adrenal glands, subcutaneous tissue, lymph nodes, muscle, bone marrow, and "other" **Contrast:** U + CE **CT parameters:** NR **Breath hold:** no breath hold instructions reported **Threshold:** NR (presence/absence of mets) # **MRI:** U + CE; 'standard sequences' **Machine:** Magnetom Avanto, Siemens Healthcare Sector, Erlangen **Scan coverage:** WB; NR. CT and MR compared for "neck to the pelvis" only; sites imaged included lungs, liver, spleen, kidneys, adrenal glands, subcutaneous tissue, lymph nodes, muscle, bone marrow, and "other" **MRI parameters:** standard sequences with parallel imaging techniques **Magnet:** 1.5 T **Threshold:** NR (presence/absence of mets) # **Number observers:** 4 (results for 2 included) **Qualification (experience):** radiologist (high) **Diagnosis (single, consensus, etc.):** single **Info provided during test interpretation:** clinical diagnosis/age/sex; other tests blinded to MRI/CT

Target condition and reference standard(s)	**Histology or Imaging FU** **Histological detail (n, %):** NR (NR). **Histopathologist:** **FNAC (n, %):** (0) **Follow-up (n, %):** physical examination, blood tests, ultrasound studies, X-rays, CT scans of the body from the neck to the pelvis (WB-CT) as well as MRI of the head (MRI-CR) (33, 100%) **FU schedule:** 3 to 12 months **FU duration:** ≥ 3 months **Reference blinding:** FU by an independent radiologist **Target condition** **Data:** per lesion **Definition:** any mets (excl brain); **Prevalence:** 455/824 = 55% **Definition:** nodal: 192/379 = 51% **Definition:** site specific (liver): 33/67 = 49% **Definition:** site specific (lung): 145/197 = 74%a **Definition:** site specific (subcutaneous): 33/46 = 72% **Definition:** site specific (other): 51/118 = 43% (estimated by adding individual 2×2s for originally reported 'Other' category plus adrenal, kidney, muscle, and spleen sites)
Flow and timing	**Index to histology interval:** N/A **Index to FU interval:** minimum 3 months **Exclusions:** n = 17; no WB-CT follow-up undertaken
Comparative	(1) Test interpretation blinded (2) Within 14 days (3) Prospective study; indication for testing was positive SLNB or findings on US or X-ray
Notes	**Other result:** results presented by region and for less experienced observers, 3 and 4; also presented number of mets detected by cranial MR but no 2×2 extractable

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Does the study report results for participants at the same point in the clinical pathway and who would be eligible for imaging in normal practice?	Unclear		

Did the study report data on a per patient rather than per lesion basis?	No		
		Low	**High**
DOMAIN 2: Index Test CT			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Was the imaging test applied and interpreted in a clinically applicable manner?	Unclear		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No		
Was the test interpreted by an experienced examiner?	Yes		
		Low	**High**
DOMAIN 2: Index Test MRI			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Was the imaging test applied and interpreted in a clinically applicable manner?	Unclear		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No		

Was the test interpreted by an experienced examiner?	Yes		
		Low	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Were the reference standard results based on patient follow-up interpreted without knowledge of the original imaging test result?	Yes		
Does the study use the same definition of disease positive as the primary review question (i.e. any mets) OR is it possible to disaggregate or regroup data such that data matching the review question can be extracted?	Yes		
Was histology or cytology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Low	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	No		
Were all patients included in the analysis?	No		

Hausmann 2011 (*Continued*)

		High	
DOMAIN 5: Comparative			
1) was each index test result interpreted without knowledge of the results of other index tests or testing strategies?	Yes		
2) Was the interval between application of index tests	Yes		
3) Was it predetermined that all index tests should be given to all study participants?	Yes		
		Low	

Hinz 2011

Study characteristics	
Patient sampling	**Design:** non-comparative; prospective **Country:** Germany **Data collection:** Oct 2007 to Feb 2009 **Inclusion criteria:** clinically node negative, BT ≥ 1 mm or < 1 mm with risk factors such as ulceration or regression **Excluded if** sono-morphological criteria for lymph node metastases
Patient characteristics and setting	**Presentation:** primary (pre-SLNB but includes a secondary nodular SSM) **Number patients:** 81 **Number primary lesions:** 81 **Number LNBs/metastases:** NR; 170 SLNs **Stage of disease:** NR **Mean age:** 52.8 years; **Median age:** NR; **Range:** SD 15.4 years; range reported for node positive only (36 to 62 years) **Male:** 48 (59%) **Primary lesion site:** head 2, 2.5%; trunk 36, 44.4%; upper ext 14, 17.2%; lower ext 23, 28.4%; acral 6, 7.4% **Breslow/Clark:** median BT 1.68 mm (0.76 to 6.00 mm); 0.75 to 1.00 mm 20, 25%; 1.01 to 1.50 mm 24, 30%; 1.51 to 2.00 mm 12, 15%; 2.01 to 4.00 mm 18, 22%; > 4 mm 7, 9% **Clark levels:** II 1, 1%; III 26, 32%; IV 47, 58%; V 7, 9% **Ulceration:** 14, 17.3% **Other:** NR
Index tests	**US:** B-mode (linear array); Doppler **Machine:** Nemio SSA-550A; Toshiba Diagnostic Ultrasound System, Neuss, Germany **Scan coverage:** LN areas predicted by sites of melanoma

	Contrast: N/A **FNAC:** N/A **Threshold:** positive radiological findings according to published criteria plus PD signs of accessory peripheral vessels or displacement of intranodal vessels or asymmetrical avascular areas or aberrant course of central vessels **Number observers:** 1 of 4 clinicians trained in USS imaging **Qualification (experience):** NR; broad experience in dermato-oncology and special ultrasound skills (NR) **Diagnosis (single, consensus, etc.):** unclear; appears as though single observer **Info provided during test interpretation:** clinical NR; likely full info available; other tests NR
Target condition and reference standard(s)	**Histology (SLNB)** **Histological detail (n, %):** H&E (serial section); IHC (S-100, HMB 45, and Melan A); mets categorised as macro or micro mets or as cluster of cells (10 to 30 grouped cells) in the subcapsular space or interfollicular zone, or isolated melanoma cells (1 to ≤ 20 individual cells) (ref Starz 2001) (1). **Histopathologist:** 2 experienced dermatopathologists **FNAC (n, %):** NR (NR) **Follow-up (n, %):** not stated (N/A) **FU schedule:** NR **FU duration:** not stated **Reference blinding:** NR **Target condition** **Data:** per pt **Definition:** nodal mets; **Prevalence:** 8/81 = 10%
Flow and timing	**Index to histology interval:** NR **Index to FU interval:** NR **Exclusions:** n = 0
Comparative	
Notes	**Other result:** of 7 FN LNBs, 3 were classified as reactive on US and 4 were not visualised; the 2 TPs were both correctly classified pre-LS and post-LS. Of 8 SLN positive, all described in text as micro-mets, but Table 2 describes 5 as > 2 mm and 3 as ≤ 2 mm; both TPs were > 2 mm

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	No		

Does the study report results for participants at the same point in the clinical pathway and who would be eligible for imaging in normal practice?	Yes		
Did the study report data on a per patient rather than per lesion basis?	Yes		
		High	**Low**
DOMAIN 2: Index Test Ultrasound (pre-SLNB)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Was the imaging test applied and interpreted in a clinically applicable manner?	Unclear		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes		
Was the test interpreted by an experienced examiner?	Unclear		
		Low	**Unclear**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Were the reference standard results based on patient follow-up interpreted without knowledge			

Hinz 2011 (*Continued*)

of the original imaging test result?			
Does the study use the same definition of disease positive as the primary review question (i.e. any mets) OR is it possible to disaggregate or regroup data such that data matching the review question can be extracted?	Yes		
Was histology or cytology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Hinz 2013

Study characteristics	
Patient sampling	**Design:** within-person comparison; retrospective (retrospective computer-aided search of preoperatively performed staging procedures) **Country:** Germany **Data collection:** Jan 2009 to Jan 2011 **Inclusion criteria:** high risk cutaneous MM; implies BT $\geq$ 2.0 mm or RF such as ulceration or regression **Excluded if** classic sonographic signs of lymphatic metastasis
Patient characteristics and setting	**Presentation:** primary (pre-SLNB) **Number patients:** 20 **Number primary lesions:** 20 **Number LNBs/metastases:** 59 SLN **Stage of disease:** NR

	Mean age: full sample 55.2 years; **Median age:** NR; **Range:** full sample SD 13.3 years **Male:** 9 (45%) **Primary lesion site:** trunk n = 10 (50%); upper extremity n = 3 (15%); lower extremity n = 4 (20%); acral n = 3 (15%) **Breslow/Clark:** BT 1.01 to 2 mm n = 3 (15%), 2.10 to 4 mm n = 9 (45%), > 4 mm n = 8 (40%) **Clark level:** III n = 1 (5%); IV n = 16 (80%); V n = 3 (15%) **Ulceration:** 7, 35% **Other:**
Index tests	**US:** B-mode **Machine:** Nemio SSA-550A; Toshiba Diagnostic Ultrasound System, Neuss, Germany **Scan coverage:** all relevant regional LN basins depending on localisation of the primary melanoma **Contrast:** N/A **FNAC:** N/A **Threshold:** morphology criteria of Solbiati 1988, Vassalo 1992, and Voit 2010; suspicious LNs were re-examined with US after LS **PET-CT:** 2D/3D NR; CE-CT, helical. Reinhardt 2006 states helical, dual detector **Machine:** Biograph; Siemens Medical Solutions Inc., Erlangen, Germany **Scan coverage:** WB; Reinhardt 2006: "base of the skull to the apex of the lungs, ... from the shoulders to upper thighs, ... from the proximal femura to the tip of the toes" **Contrast:** Reinhardt 2006: iodinated oral contrast agent (Peritrast-oral-GI; Köhler Chemie GmbH, Alsbach, Germany) **CT parameters:** 130 kV, 40 mAs (Reinhardt 2006); 5 mm (Reinhardt 2006) **FDG:** 371 ± 41 MBq (Reinhardt 2006) **Breath hold:** limited breath hold technique for CT and shallow breathing for PET **CT used for:** Reinhardt 2006: attenuation correction based on re-scaling of the CT image **Reconstruction:** iterative reconstruction with attenuation correction based on re-scaling of the CT image as described elsewhere (Kinahan 2003) **Threshold:** NR **Number observers:** unclear **Qualification (experience):** US by physicians with broad experience in dermato-oncology (NR); NR for PET-CT **Diagnosis (single, consensus, etc.):** unclear; appears as though single observer for US, NR for PET-CT **Info provided during test interpretation:** clinical: clinical exam/US performed by same clinician; other tests: before PET-CT
Target condition and reference standard(s)	**Histology (SLNB)** **Histological detail (n, %):** H&E (Serial); IHC (S-100, HMB 45, and Melan A). Mets were classified according to Carlson et al (2003) - macro-metastasis (> 2 mm), micro-metastasis (≤ 2 mm), cluster of cells (10 to 30 grouped cells) in the subcapsular space or interfollicular zone, or isolated melanoma cells (1 to ≤ 20 individual cells) in subcapsular sinuses. **Histopathologist:** 2 experienced **FNAC (n, %):** - (0) **Follow-up (n, %):** - (0) **FU schedule:** N/A **FU duration:** N/A **Reference blinding:** NR **Target condition** **Data:** per pt

Hinz 2013 (*Continued*)

	Definition: nodal mets; **Prevalence:** 12/20 = 60% (17/59 SLN = 29%)		
Flow and timing	**Index to histology interval:** before lymphoscintigraphy **Index to FU interval:** N/A **Exclusions:** n = 0		
Comparative	(1) Blinding unclear; US undertaken before CT (2) Tests undertaken consecutively (3) Only subgroup of those with US had PET-CT; reason NR		
Notes	**Other result:** no FU for FNs reported; all 17 disease positive were micro-metastases		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	No		
Does the study report results for participants at the same point in the clinical pathway and who would be eligible for imaging in normal practice?	Yes		
Did the study report data on a per patient rather than per lesion basis?	Yes		
		High	**Low**
DOMAIN 2: Index Test Ultrasound (pre-SLNB)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		

Was the imaging test applied and interpreted in a clinically applicable manner?	Yes		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes		
Was the test interpreted by an experienced examiner?	Yes		
		Unclear	**Low**
DOMAIN 2: Index Test PET-CT			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
Was the imaging test applied and interpreted in a clinically applicable manner?	Yes		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No		
Was the test interpreted by an experienced examiner?	Unclear		
		Unclear	**Unclear**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		

Were the reference standard results based on patient follow-up interpreted without knowledge of the original imaging test result?			
Does the study use the same definition of disease positive as the primary review question (i.e. any mets) OR is it possible to disaggregate or regroup data such that data matching the review question can be extracted?	Yes		
Was histology or cytology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	
DOMAIN 5: Comparative			
1) was each index test result interpreted without knowledge of the results of other index tests or testing strategies?	Unclear		
2) Was the interval between application of index tests	Yes		
3) Was it predetermined that all index tests should be given to all study participants?	No		

Hinz 2013 (*Continued*)

		High	

Hocevar 2004

Study characteristics	
Patient sampling	**Design:** within-person comparison; unclear design **Data collection:** Jun 2002 to Aug 2003 **Inclusion criteria:** MM candidates for SLNB (SLNB eligibility NR)
Patient characteristics and setting	**Presentation:** primary (pre-SLNB) **Number patients:** 57 **Number primary lesions:** 57 **Number LNBs/metastases:** 61 **Stage of disease:** NR **Mean age:** NR; **Median age:** NR; **Range:** 1 to 93 years **Male:** 21 (37%) **Primary lesion site:** 14, 25% head; 19, 38% trunk; 24, 42% extremity **Breslow/Clark:** BT < 1 mm 2, 4%; BT 1 to 2 mm 23, 40%; BT 2.01 to 4 mm 20, 35%; BT > 4 mm 12, 21% **Clark level:** unknown 2, 4%; III 23, 42%; IV 26, 44%; V 6, 10% **Ulceration:** 21, 37%; unknown 3, 5%
Index tests	**US:** B-mode; linear array transducer with small parts probe **Machine:** Power Vision 800, Toshiba Corporation, Ottawa, Japan **Scan coverage:** NR **Contrast:** N/A **FNAC:** US + ve; Giemsma stained according to Papanicolaou method, and if necessary, immunocytochemical reaction with monoclonal antibody HMB45 and S100 on an automatic immunostainer **Threshold:** rounded appearance of the LN, Ioss of the hilar echogenic reflex, and deformed radial nodal vascularity **Number observers:** 1 **Qualification (experience):** oncological radiologist (NR) **Diagnosis (single, consensus, etc.):** single **Info provided during test interpretation:** clinical NR; other tests NR
Target condition and reference standard(s)	**Histology (CLND or SLNB)** **Histological detail (n, %):** H&E (step sectioned); IHC (S100). If negative, additional sections stained with S100 and HMB45 (CLND; SLNB). **Histopathologist:** NR **FNAC (n, %):** melanoma cells in lymph node sample from FNA (14/17 US + ve underwent FNAC) **Follow-up (n, %):** NR (NR) **FU schedule:** NR **FU duration:** NR **Reference blinding:** NR **Target condition** **Data:** per pt **Definition:** nodal mets; **Prevalence:** 14/57 = 25%

Flow and timing	**Index to histology interval:** NR **Index to FU interval:** NR **Exclusions:** n = 0		
Comparative			
Notes	**Other result:** no FU to identify FNs; 10/14 disease positive were macro-metastases; US alone correctly picked up 2/4 micro-metastases		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Does the study report results for participants at the same point in the clinical pathway and who would be eligible for imaging in normal practice?	Yes		
Did the study report data on a per patient rather than per lesion basis?	Yes		
		Unclear	**Low**
DOMAIN 2: Index Test Ultrasound (pre-SLNB)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
Was the imaging test applied and interpreted in a clinically applicable manner?	Unclear		

Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes		
Was the test interpreted by an experienced examiner?	Yes		
		Unclear	**Unclear**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Were the reference standard results based on patient follow-up interpreted without knowledge of the original imaging test result?			
Does the study use the same definition of disease positive as the primary review question (i.e. any mets) OR is it possible to disaggregate or regroup data such that data matching the review question can be extracted?	Yes		
Was histology or cytology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Low	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		

Were all patients included in the analysis?	Yes		
		Unclear	

Iagaru 2007

Study characteristics	
Patient sampling	**Design:** within-person comparison; retrospective (Prosp. database: NR) **Country:** USA **Data collection:** Jan 2003 to Jun 2005 **Inclusion criteria:** PET-CT for MM re-staging
Patient characteristics and setting	**Presentation:** re-staging (all patients had the study requested for disease re-staging) **Number patients:** 106 **Number primary lesions:** NR **Number LNBs/metastases:** 139 metastatic lesions **Stage of disease:** 76 stage I to IIIc; 30 stage IIIb to IV **Mean age:** 56.8 years ± 15.9 years; **Median age:** NR; **Range:** 20 to 87 years **Male:** 68 (64.1%) **Primary lesion site:** NR **Breslow/Clark:** BT at initial diagnosis (n = 76): mean 3.56 mm, 0.4 to 25 mm; < 1 mm in 6 (8%) , 1 to 4.0 mm in 58 (76%), > 4 mm in 12 (16%) **Clark level (n = 70):** 3 (4%), level II; 13 (19%), level III; 43 (61%), level IV; 11 (16%), level V **Ulceration:** NR **Other:** NR
Index tests	**CT:** U, multi-slice helical **Machine:** Discovery LS PET/CT unit (GE Medical Systems, Milwaukee, WI) **Scan coverage:** WB; top of the head to the ankles **Contrast:** N/A **CT parameters:** 140 kV, 40 mA; 5 mm **Breath hold:** no breath hold instructions reported **Threshold:** NR # **PET-CT:** 2D; CT (U, multi-slice helical) **Machine:** Discovery LS PET/CT unit (GE Medical Systems, Milwaukee, WI) **Scan coverage:** WB; top of the head to the ankles **Contrast:** U **CT parameters:** 140 kV, 40 mA; 5 mm **FDG:** 15 mCi **Breath hold:** no breath hold instructions reported **CT used for:** attenuation correction and anatomical localisation **Reconstruction:** standard iterative algorithm (OSEM, 2 iterative steps, 28 subsets) using GE software release 5.0 **Threshold:** SUVmax ≥ 2.5 #

	Number observers: NR **Qualification (experience):** nuclear medicine physicians and radiologists (board certified) **Diagnosis (single, consensus, etc.):** consensus **Info provided during test interpretation:** clinical - NR for original interpretation or for re-interpretation; other tests - NR for original interpretation or for re-interpretation
Target condition and reference standard(s)	**Histology/FU** **Histological detail (n, %):** NR (97, 91.5%). **Histopathologist:** NR **FNAC (n, %):** N/A **Follow-up (n, %):** NR (9, 8.5%) **FU schedule:** NR **FU duration:** NR **Reference blinding:** PET-CT and pathology reported were 'reviewed'; no blinding described **Target condition** **Data:** per pt **Definition:** any mets (incl skin and brain) **Prevalence per patient:** 56/106 = 53% (stage I to IIIc 38/76 = 50%; stage IIIb to IV 18/30 = 60%) **Prevalence per lesion:** 87/139 = 63% **Metastases:** of the 50 patients TP on PET-CT: 7 were residual MM, 34 'metastases', and 9 'widespread metastases'. FN on PET-CT documented only per lesion: 6 recurrences at the resection site, 2 sub-centimetre soft tissue nodules, and 1 brain lesion (identified by MRI presumably during follow-up)
Flow and timing	**Index to histology interval:** NR **Index to FU interval:** NR **Exclusions:** n = 0; N/A
Comparative	(1) Blinding between tests unclear (2) Test interval consecutive; same scanner (3) Retrospective; all had PET-CT with separate interpretation of CT alone
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		

Does the study report results for participants at the same point in the clinical pathway and who would be eligible for imaging in normal practice?	Unclear		
Did the study report data on a per patient rather than per lesion basis?	Yes		
		Unclear	**Unclear**
DOMAIN 2: Index Test CT			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
Was the imaging test applied and interpreted in a clinically applicable manner?	No		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No		
Was the test interpreted by an experienced examiner?	Yes		
		Unclear	**High**
DOMAIN 2: Index Test PET-CT			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Unclear		
Was the imaging test applied and interpreted in a clinically applicable manner?	No		

Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes		
Was the test interpreted by an experienced examiner?	Yes		
		Unclear	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Were the reference standard results based on patient follow-up interpreted without knowledge of the original imaging test result?	Unclear		
Does the study use the same definition of disease positive as the primary review question (i.e. any mets) OR is it possible to disaggregate or regroup data such that data matching the review question can be extracted?	Unclear		
Was histology or cytology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Unclear	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	No		

Iagaru 2007 (*Continued*)

Were all patients included in the analysis?	No		
		High	
DOMAIN 5: Comparative			
1) was each index test result interpreted without knowledge of the results of other index tests or testing strategies?	Unclear		
2) Was the interval between application of index tests	Yes		
3) Was it predetermined that all index tests should be given to all study participants?	Yes		
		Unclear	

Jouvet 2014

Study characteristics	
Patient sampling	**Design:** within-person comparison; prospective **Country:** France **Data collection:** Mar 2009 to Jan 2012 **Inclusion criteria:** AJCC stage IV cutaneous MM referred for simultaneous staging by PET-CT, CT, superficial lymph node US, and MRI
Patient characteristics and setting	**Presentation:** unclear (no details; referred for simultaneous staging) **Number patients:** 37 **Number primary lesions:** NR **Number LNBs/metastases:** 209 lesions (n varies per test) **Stage of disease:** stage IV: 37 (100%) **Mean age:** NR; **Median age:** NR; **Range:** NR **Male:** NR (0%) **Primary lesion site:** NR **Breslow/Clark:** NR **Ulceration:** NR **Other:** NR
Index tests	**US:** B-mode **Machine:** NR; 12.5-MHz surface probe **Scan coverage:** putative lymphatic drainage area of the primary melanoma **Contrast:** N/A **FNAC:** N/A

	Threshold: circular/ovoid hypoechoic lymph node and no hyperechoic hilum # **CT:** CE; helical; 16 row **Machine:** CT Philips Scanner (Philips Medical System, Eindhoven, The Netherlands) **Scan coverage:** neck/chest/abdomen/pelvis; "cervico-thoraco-abdomino-pelvic helicoidal acquisition"; then skull **Contrast:** iodinated IV injection **CT parameters:** 120 kV, 250 mAs (neck to pelvis); 140 kV, 120 mAs (skull); 1.25 mm (neck to pelvis); 2.5 mm (skull) **Breath hold:** no breath hold instructions reported **Threshold:** NR (presence/absence of mets) # **MRI (DW)** and **MRI (DW + VIBE):** DW, VIBE - 3D echo gradient CE, T1 - skull **Machine:** AVANTO (33 mT, 120 mT/m, Siemns, Erlangen, Germany) **Scan coverage:** WB; top of skull to feet **MRI parameters:** echo-planar DW; axial with coronal reconstruction; VIBE (3D gradient echo w CE); T1 axial on skull **Magnet:** 1.5 T **Threshold:** NR (presence/absence of mets) # **PET-CT:** 3D GSO; CT (CE, helical; 2 row) **Machine:** Gemini PET-CT (Philips Medical System, Eindhoven, The Netherlands) **Scan coverage:** skull base to the feet (lower limb MM); skull to thighs (MM head, upper limbs, and trunk) **Contrast:** CE **CT parameters:** 120 to 140 kV, 100 mAs; 6.5 mm **FDG:** 5.2 MBq/kg 1 hour before scanning **Breath hold:** no breath hold instructions reported **CT used for:** unclear; PET was attenuation corrected but does not state using CT, PET images superimposed with CT data **Reconstruction:** attenuation corrected PET data were iteratively reconstructed and superimposed with CT data **Threshold:** NR (presence/absence of mets) **#** **US, CT, MRI:** **Number observers:** 1 **Qualification (experience):** radiologist (experienced). **Diagnosis (single, consensus, etc.):** consensus of 2 (all images interpreted independently by 2 examiners; discordant results resolved by consensus) Presume ultrasound also undertaken by radiologist **Info provided during test interpretation:** clinical - NR; other tests - blinded **PET-CT:** **Number observers:** 2 **Qualification (experience):** nuclear medicine specialist (experienced) **Diagnosis (single, consensus, etc.):** consensus of 2 (all images interpreted independently by 2 examiners; discordant results resolved by consensus) **Info provided during test interpretation:** clinical - NR; other tests - blinded

Target condition and reference standard(s)	**FNAC, FU:** **Histological detail (n, %):** N/A (0). **Histopathologist:** NR **FNAC (n, %):** no details; FNAC was performed in 5 cases, and all other positive cases have been diagnosed on the basis of progression of the target (5, 13.5%) **Follow-up (n, %):** 'sequential imaging'; not further described (32; 86.5%) **FU schedule:** NR **FU duration:** > 9 months **Reference blinding:** N/A **Target condition** **Data:** per lesion **Definition:** any mets (incl brain, subcut); **Prevalence:** CT 115/209 = 55%; MRI 125/218 = 57% **Definition:** any (excl brain mets); **Prevalence:** CT 95/186 = 51%; MRI 105/195 = 54%; PET-CT 104/191 = 54% **Definition:** nodal; **Prevalence:** all tests 23/53 = 43% **Definition:** nodal (superficial); **Prevalence:** all tests 13/33 = 39% (per LNB) **Definition:** site specific (bone); **Prevalence:** CT 15/33 = 45%; MRI 16/35 = 46%; PET-CT 16/35 = 46% **Definition:** site specific (liver); **Prevalence:** all tests 12/27 = 44% **Definition:** site specific (lung); **Prevalence:** all tests 31/45 = 69% **Definition:** site specific (local); **Prevalence:** MRI, PET-CT only 10/22 = 45%
Flow and timing	**Index to histology interval:** NR **Index to FU interval:** NR **Exclusions:** n = 0; N/A
Comparative	(1) "All the examiners were unaware to the results of the other imaging techniques" (2) "All examinations were performed within a mean interval of 7 days" (3) Prospective; "referred for simultaneous staging"
Notes	**Other result:** provides K values for inter- and intra-observer agreements, but not the 2×2 tables for each observer

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		

Does the study report results for participants at the same point in the clinical pathway and who would be eligible for imaging in normal practice?	Unclear		
Did the study report data on a per patient rather than per lesion basis?	No		
		Unclear	**High**
DOMAIN 2: Index Test Ultrasound			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Was the imaging test applied and interpreted in a clinically applicable manner?	Yes		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes		
Was the test interpreted by an experienced examiner?	Unclear		
		Low	**Unclear**
DOMAIN 2: Index Test CT			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Was the imaging test applied and interpreted in a clinically applicable manner?	No		

Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No		
Was the test interpreted by an experienced examiner?	Yes		
		Low	**High**
DOMAIN 2: Index Test MRI			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Was the imaging test applied and interpreted in a clinically applicable manner?	No		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No		
Was the test interpreted by an experienced examiner?	Yes		
		Low	**High**
DOMAIN 2: Index Test PET-CT			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Was the imaging test applied and interpreted in a clinically applicable manner?	No		
Were thresholds or criteria for diagnosis reported in sufficient	No		

Jouvet 2014 (*Continued*)

detail to allow replication?			
Was the test interpreted by an experienced examiner?	Yes		
		Low	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Were the reference standard results based on patient follow-up interpreted without knowledge of the original imaging test result?	No		
Does the study use the same definition of disease positive as the primary review question (i.e. any mets) OR is it possible to disaggregate or regroup data such that data matching the review question can be extracted?	Yes		
Was histology or cytology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Unclear	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	No		

Jouvet 2014 (*Continued*)

Were all patients included in the analysis?	Yes		
		High	
DOMAIN 5: Comparative			
1) was each index test result interpreted without knowledge of the results of other index tests or testing strategies?	Yes		
2) Was the interval between application of index tests	Yes		
3) Was it predetermined that all index tests should be given to all study participants?	Yes		
		Low	

Kang 2011

Study characteristics	
Patient sampling	**Design:** non-comparative; retrospective (medical record review) **Country:** S Korea **Data collection:** Mar 2005 to Sep 2009 **Inclusion criteria:** newly diagnosed cutaneous MM undergoing staging work-up with PET-CT (any stage, including clinically node positive)
Patient characteristics and setting	**Presentation:** primary (any) **Number patients:** 37 **Number primary lesions:** 37 **Number LNBs/metastases:** NR **Stage of disease:** stage 0: 7 (18.9%); stage I: 6 (16.2%); stage II: 17 (45.9%); stage III: 6 (16.2%); stage IV: 1 (2.7%) **Mean age:** 61.7y ± 13.6 years; **Median age:** NR; **Range:** 48.1 to 75.3 years **Male:** 17 (45.9%) **Primary lesion site:** hand/foot 23 (62.1%), trunk 6 (16.2), head/neck 4 (10.8%), extremity 4 (10.8%) **Breslow/Clark:** BT < 1.0 mm 8, 22%; ≥ 1 mm 15, 41%; NR 14, 38% **Ulceration:** present 7, 19%; absent 30, 81% **Other:** mean SUVmax 2.8 ± 2.3
Index tests	**PET-CT:** CT (U, 6 slice or 16 slice) **Machine:** Reveal RT-HiRez CTIMI (Knoxville, TN, USA), a 6-slice CT; or Discovery ST (GE Health Systems, Milwaukee, Wl, USA), a 16-slice CT

	Scan coverage: vertex of skull to knees; plus lower limbs if with lower leg MM **Contrast:** U **CT parameters:** Reveal RT-HiRez 130 kV, 95 mA; Discovery ST 140 kV, 160 mA; Reveal RT-HiRez 2.5 mm; Discovery ST 3.75 mm **FDG:** 350 to 400 MBq **Breath hold:** NR; 'standard protocol' **CT used for:** unclear; combined PET-CT unit; mentions identification of anatomical location on fused PET-CT image **Reconstruction:** ordered subset expectation-maximisation **Threshold:** SUVmax ≥ 2.2 (set using ROC analysis) # **Number observers:** 2 **Qualification (experience):** nuclear physicians (experienced) **Diagnosis (single, consensus, etc.):** consensus of 2 **Info provided during test interpretation:** clinical - NR; other tests - N/A
Target condition and reference standard(s)	**Histology/Imaging FU** **Histological detail (n, %):** reported for only 6 of disease positive group (6 (16.2%)). **Histopathologist:** experienced dermatopathologist and pathologist **FNAC (n, %):** N/A (0) **Follow-up (n, %):** clinical, CT, PET-CT (37 (100%)) **FU schedule:** physical examination every 3 months for 1 to 2 years, then every 6 months; imaging every 6 to 12 months and/or when clinically indicated **FU duration:** median followup 24.3 ± 11.7 months (range 8 to 55 months) **Reference blinding:** NR # **Target condition** **Data:** per pt **Definition:** any mets (incl brain, local/skin); **Prevalence:** 9/37 = 24%
Flow and timing	**Index to histology interval:** NR **Index to FU interval:** 3 months **Exclusions:** n = 0
Comparative	
Notes	**Other result:** sites of recurrence were LN (3); distant (5; lung or liver); 'local' (2); skin (1); 3 patients died related to CMM

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		

Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Does the study report results for participants at the same point in the clinical pathway and who would be eligible for imaging in normal practice?	Yes		
Did the study report data on a per patient rather than per lesion basis?	Yes		
		Unclear	**Low**
DOMAIN 2: Index Test PET-CT			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	No		
Was the imaging test applied and interpreted in a clinically applicable manner?	No		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes		
Was the test interpreted by an experienced examiner?	Yes		
		High	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		

Kang 2011 (*Continued*)

Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Were the reference standard results based on patient follow-up interpreted without knowledge of the original imaging test result?	Unclear		
Does the study use the same definition of disease positive as the primary review question (i.e. any mets) OR is it possible to disaggregate or regroup data such that data matching the review question can be extracted?	Yes		
Was histology or cytology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Yes		
		Low	**Low**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	No		
Were all patients included in the analysis?	Yes		
		High	

Kell 2007

Study characteristics	
Patient sampling	**Design:** non-comparative; retrospective (prospective database) **Country:** USA **Data collection:** NR; 12-month period **Inclusion criteria:** MM, BT $\geq$ 0.76 mm, candidates for SLNB who underwent PET-CT (46/83

	with SLNB)
Patient characteristics and setting	**Presentation:** primary (pre-SLNB) **Number patients:** 37 **Number primary lesions:** NR **Number LNBs/metastases:** NR **Stage of disease:** NR **Mean age:** 61.4 years; **Median age:** NR; **Range:** NR **Male:** NR (0%) **Primary lesion site:** NR **Breslow/Clark:** mean BT 2.4 mm **Ulceration:** NR **Other:** NR
Index tests	**PET-CT:** CT (U) **Machine:** NR **Scan coverage:** base of skull to feet **Contrast:** U **CT parameters:** NR **FDG:** NR **Breath hold:** NR; standard protocols **CT used for:** NR **Reconstruction:** NR; combined PET-CT images **Threshold:** quantitative for areas of abnormally increased 18-FDG uptake relative to surrounding normal tissues and areas of increased physiological uptake # **Number observers:** NR **Qualification (experience):** NR (NR) **Diagnosis (single, consensus, etc.):** NR **Info provided during test interpretation:** clinical - NR; other tests - NR
Target condition and reference standard(s)	**Histology (SLNB)** **Histological detail (n, %):** NR (37, 100%). **Histopathologist:** NR **FNAC (n, %):** N/A (0) **Follow-up (n, %):** NR (NR) **FU schedule:** NR **FU duration:** NR **Reference blinding:** NR # **Target condition** **Data:** per pt **Definition:** nodal mets; **Prevalence:** 9/37 = 24%
Flow and timing	**Index to histology interval:** NR **Index to FU interval:** N/A **Exclusions:** n = 0; 46 with SLNB but no PET-CT could not be included
Comparative	

Notes	**Other result:** PET-CT revealed no unheralded metastatic disease but did identify a second occult malignancy in 4 (10.8%) patients undergoing therapy for melanoma		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Does the study report results for participants at the same point in the clinical pathway and who would be eligible for imaging in normal practice?	Yes		
Did the study report data on a per patient rather than per lesion basis?	Yes		
		Low	**Low**
DOMAIN 2: Index Test PET-CT			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Was the imaging test applied and interpreted in a clinically applicable manner?	Unclear		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes		

Was the test interpreted by an experienced examiner?	Unclear		
		Low	**Unclear**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Were the reference standard results based on patient follow-up interpreted without knowledge of the original imaging test result?			
Does the study use the same definition of disease positive as the primary review question (i.e. any mets) OR is it possible to disaggregate or regroup data such that data matching the review question can be extracted?	Yes		
Was histology or cytology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Low	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		

		Low	

Klebl 2003

Study characteristics	
Patient sampling	**Design:** within-person comparison (US vs palpation) **Country:** Germany **Data collection:** Aug 1997 to Dec 1998 **Inclusion criteria:** MM Clark level IV or V undergoing FU after primary surgery
Patient characteristics and setting	**Presentation:** mixed (primary (n = 8), follow-up (n = 75)) **Number patients:** 83 **Number primary lesions:** 83 **Number LNBs/metastases:** NR; 653 LNs examined **Stage of disease:** NR **Mean age:** NR; **Median age:** NR; **Range:** NR **Male:** 46 (55%) **Primary lesion site:** NR **Breslow/Clark:** Clark level IV 68, 82%; level V 15, 18% **Ulceration:** NR
Index tests	**US:** B-mode US; high-resolution linear array **Machine:** HDI Ultramark 9 using a high-resolution 5- to 10-MHz linear sonicator **Scan coverage:** cervical, axillary, and inguinal LNBs **Contrast:** N/A **FNAC:** no **Threshold:** suspicious/indeterminate/benign based on diameter, shape, echogenicity, and vascularisation pattern # **Number observers:** NR **Qualification (experience):** NR (NR) **Diagnosis (single, consensus, etc.):** NR **Info provided during test interpretation:** clinical - unclear; could be same examiner as for LN palpation; other tests - NR
Target condition and reference standard(s)	**Histology (NR), FU** **Histological detail (n, %):** NR (17, 20%). **Histopathologist:** NR **FNAC (n, %):** N/A (0) **Follow-up (n, %):** NR (62, 75%) **FU schedule:** suspicious, but not clearly malignant findings were reviewed at intervals of 6 to 8 weeks. For unremarkable findings, a check was carried out after 6 to 12 months as part of the tumour follow-up **FU duration:** minimum 1 year; mean time since primary surgery 2.6 ± 2.3 years **Reference blinding:** NR # **Target condition** **Data:** per pt

	Definition: nodal mets; **Prevalence:** 17/79 = 22%		
Flow and timing	**Index to histology interval:** NR **Index to FU interval:** 6 to 8 weeks for control visit, 6 to 12 months for FU visit **Exclusions:** n = 4; 4 were indeterminate on follow-up so that a final diagnosis could not be made		
Comparative			
Notes			
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Does the study report results for participants at the same point in the clinical pathway and who would be eligible for imaging in normal practice?	No		
Did the study report data on a per patient rather than per lesion basis?	Yes		
		Unclear	**High**
DOMAIN 2: Index Test Ultrasound			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Was the imaging test applied and interpreted in a clinically	Unclear		

applicable manner?			
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes		
Was the test interpreted by an experienced examiner?	Unclear		
		Low	**Unclear**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Were the reference standard results based on patient follow-up interpreted without knowledge of the original imaging test result?	Unclear		
Does the study use the same definition of disease positive as the primary review question (i.e. any mets) OR is it possible to disaggregate or regroup data such that data matching the review question can be extracted?	Yes		
Was histology or cytology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Low	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		

Did all patients receive the same reference standard?	No		
Were all patients included in the analysis?	No		
		High	

Klode 2010

Study characteristics	
Patient sampling	**Design:** non-comparative; retrospective (prospective database NR) **Country:** Germany **Data collection:** Jan 2004 to Dec 2006 **Inclusion criteria:** primary MM AJCC stage I or II (BT > 1 mm)
Patient characteristics and setting	**Presentation:** primary (pre-SLNB) **Number patients:** 61 **Number primary lesions:** NR **Number LNBs/metastases:** 174 SLNs **Stage of disease:** NR (I or II) **Mean age:** 58.8; **Median age:** 61; **Range:** 31 to 82 **Male:** 36 (0.5901%) **Primary lesion site:** trunk and lower limbs 26, 42.6%; upper extremities 9, 14.8%; NR for remaining 27 lesions **Breslow/Clark:** BT mean 2.62 mm, median 2.0 mm, range 1 to 8 mm **Ulceration:** 15, 24.6% **Other:** NR
Index tests	**PET-CT:** 2D/3D NR; CE-CT **Machine:** Siemens Biograph Duo PET-CT scanner (Siemens, Erlangen) **Scan coverage:** cranial base to mid-femur; additional views according to melanoma localisation **Contrast:** iodine-containing contrast agent **CT parameters:** NR **FDG:** 349 mBq **Breath hold:** breath hold instructions NR **CT used for:** NR **Reconstruction:** NR **Threshold:** NR; hypermetabolic tumour focus # **Number observers:** NR **Qualification (experience):** NR (NR) **Diagnosis (single, consensus, etc.):** NR **Info provided during test interpretation:** clinical - NR; other tests - NR

Klode 2010 (*Continued*)

Target condition and reference standard(s)	**Histology (SLNB)** **Histological detail (n, %):** H&E (serial); IHC (S100, MElanA, HMB45). Tumour focus < 2.0 mm defined as micro-metastasis; ≥ 2.0 mm macro-metastasis (61, 100%) **Histopathologist:** NR **FNAC (n, %):** N/A (N/A) **Follow-up (n, %):** NR (61, 100%) **FU schedule:** NR **FU duration:** median 38 months, 13 to 55 months **Reference blinding:** NR # **Target condition** **Data:** per pt **Definition:** nodal mets; **Prevalence:** 14/61 = 23% (17/174 SLNs = 10%)
Flow and timing	**Index to histology interval:** median 14 days PET to SLNB **Index to FU interval:** NR **Exclusions:** n = 0; 60 patients with SLNB did not agree to preop PET
Comparative	
Notes	**Other result:** 174 SLNs removed from 68 lymphatic drainage areas. The TP result was a macro-mets > 10 mm; of the 16 FNs on PET-CT, 2 were macro-mets (5.5 mm and 10 mm) and 14 were micro-mets. On FU, disease progression observed in 6 patients (3 of whom died), 3 of whom were SLN positive (PET-CT result NR)

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Does the study report results for participants at the same point in the clinical pathway and who would be eligible for imaging in normal practice?	Yes		
Did the study report data on a per patient rather than per lesion basis?	Yes		

Klode 2010 (*Continued*)

		Low	**Low**
DOMAIN 2: Index Test PET-CT			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
Was the imaging test applied and interpreted in a clinically applicable manner?	Unclear		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Unclear		
Was the test interpreted by an experienced examiner?	Unclear		
		Unclear	**Unclear**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Were the reference standard results based on patient follow-up interpreted without knowledge of the original imaging test result?			
Does the study use the same definition of disease positive as the primary review question (i.e. any mets) OR is it possible to disaggregate or regroup data such that data matching the review question can be extracted?	Yes		

Klode 2010 (*Continued*)

Was histology or cytology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Low	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Kunte 2009

Study characteristics	
Patient sampling	**Design:** non-comparative; prospective **Data collection:** Dec 2002 to Mar 2003 **Inclusion criteria:** cutaneous MM SLNB candidates; reported as 'mainly' ≥ 1.0 mm BT or risk factors (ulceration or regression or Clark level IV and V)
Patient characteristics and setting	**Presentation:** primary (pre-SLNB) **Number patients:** 25 **Number primary lesions:** 25 **Number LNBs/metastases:** 68 LNBs; 35 SLNs **Stage of disease:** NR **Mean age:** 54 years; **Median age:** NR; **Range:** NR **Male:** 15 (60%) **Primary lesion site:** limbs 14, 56%; head and neck 2, 8%; trunk 9, 36% **Breslow/Clark:** Breslow ≤ 1 mm 8, 32%; 1.01 to 2 mm 11, 44%; 2.01 to 4 mm 5, 20%; > 4.0 mm 1, 4% **Ulceration:** 6, 24% **Other:** regression 0, 0%
Index tests	**US:** B-mode; linear transducer **Machine:** SSA-340 A; Toshiba Medical Systems, Neuss, Germany **Scan coverage:** regional lymphatic basins **Contrast:** N/A **FNAC:** no

	Threshold: qualitative presence of morphological features (described) # **Number observers:** 2 **Qualification (experience):** dermatologists (experienced) **Diagnosis (single, consensus, etc.):** unclear **Info provided during test interpretation:** clinical - unclear; may be same dermatologists as for clinical exam; other tests - pre and post lymphoscintigraphy ultrasound
Target condition and reference standard(s)	**Histology (SLNB)** **Histological detail (n, %):** H&E (serial section); IHC (S-100, HMB 45, NKiC3, Melan A). LNs with histologically proven tumour deposits were considered metastatic except when fewer than 4 isolated tumour cells were present. The metastatic deposit was documented for each SLN concerning location within the LN and size (micro-metastasis and macro-metastasis) (25, 100%). **Histopathologist:** NR **FNAC (n, %):** - (0) **Follow-up (n, %):** - (0) **FU schedule:** N/A **FU duration:** N/A **Reference blinding:** NR # **Target condition** **Data:** per pt **Definition:** nodal mets; **Prevalence:** 6/25 = 24% (6/35 SLN; 17%)
Flow and timing	**Index to histology interval:** < 24 hours **Index to FU interval:** N/A **Exclusions:** n = NR; NR
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Does the study report results for participants at the same point	Yes		

in the clinical pathway and who would be eligible for imaging in normal practice?			
Did the study report data on a per patient rather than per lesion basis?	Yes		
		Low	**Low**
DOMAIN 2: Index Test Ultrasound (pre-SLNB)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Was the imaging test applied and interpreted in a clinically applicable manner?	Unclear		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes		
Was the test interpreted by an experienced examiner?	Unclear		
		Low	**Unclear**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Were the reference standard results based on patient follow-up interpreted without knowledge of the original imaging test result?			

Does the study use the same definition of disease positive as the primary review question (i. e. any mets) OR is it possible to disaggregate or regroup data such that data matching the review question can be extracted?	Yes		
Was histology or cytology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Low	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Maubec 2007

Study characteristics	
Patient sampling	**Design:** non-comparative; prospective **Country:** France **Data collection:** Jan 2004 to Jun 2005 **Inclusion criteria:** any MM BT > 4 mm; SLNB planned if clinically node negative **Excluded if** presence of distant mets (those with clinically palpable nodes were included but no SLNB was given and no 2×2 can be estimated)
Patient characteristics and setting	**Presentation:** primary (pre-SLNB) and primary (any) **Number patients:** 25 **Number primary lesions:** 26 **Number LNBs/metastases:** 20 from 19 pts **Stage of disease:** all T4; 3 clinically node positive; post surgery: AJCC stage IIB 10, 40%; IIC 4, 16%; IIIA 4, 16%; IIIB 6, 24%; IIIC in 1, 4% **Mean age:** 60 years; **Range:** 14 to 87 years **Male:** 15 (0.6%)

	Primary lesion site: trunk 8, 32%; limbs 8; 32%; head and neck 9, 36% **Breslow/Clark:** mean BT 6.6 mm, range 4.8 to 12.5 mm **Ulceration:** 9, 36%
Index tests	**PET-CT:** 3D; CT (U) **Machine:** Biograph, LSO System, Siemens Medical Systems, Germany; full-ring tomograph (ECAT ACCEL, CPS Innovation, Knoxville, Tennesee), single-slice spiral CT (Somatom Emotion, Siemens Medical Solutions) **Scan coverage:** WB; "top of the head to the mid-thigh and included if necessary, the lower limbs" **Contrast:** U **CT parameters:** 110 kV; 80 mA; 5 mm **FDG:** 5 MBq/kg **Breath hold:** normal breathing; "no breath hold instructions" **CT used for:** NR; integrated system **Reconstruction:** iterative algorithm (FORE and AWOSEM) with 2 iterations, 8 subsets, and a 5-mm full-width half maximum (FWHM) Gaussian post filter **Threshold:** uptake site suspicious for malignancy or not clearly explained by a benign aetiology (SUV estimated but does not appear to formally contribute to diagnosis) # **Number observers:** NR **Qualification (experience):** NR (NR) **Diagnosis (single, consensus, etc.):** NR **Info provided during test interpretation:** clinical - NR; other tests - NR
Target condition and reference standard(s)	**Histology (SLNB, CLND)** **Histological detail (n, %):** H&E (serial); IHC (S100, HMB45, Melan A). Processed according to EORTC melanoma group (22, 88%; 3 node positive underwent CLND; 19 had SLNB; 3 no surgery). **Histopathologist:** NR **FNAC (n, %):** N/A (N/A) **Follow-up (n, %):** NR (25, 100%) **FU schedule:** mean 11 months (2 to 19 months) **Reference blinding:** NR # **Target condition** **Data:** per pt (data per LNB but counted as per patient as 20 LNBs examined in 19 patients) **Definition:** nodal mets (pre-SLNB population); **Prevalence:** 7/20 = 35%; 1 FN identified on FU **Definition:** any mets (full population); **Prevalence:** 7/25 = 28% (no distant metastases identified)
Flow and timing	**Index to histology interval:** NR; some PET performed up to 4 months after SLNB **Index to FU interval:** NR **Exclusions:** n = 6; 3 clinically node positive underwent CLND (all PET+ and N+); 3 did not undergo any surgery
Comparative	
Notes	**Other result:** 3 PET +ve for distant mets; all found to to be FP
Methodological quality	

Maubec 2007 (*Continued*)

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Does the study report results for participants at the same point in the clinical pathway and who would be eligible for imaging in normal practice?	Yes		
Did the study report data on a per patient rather than per lesion basis?	Yes		
		Low	**Low**
DOMAIN 2: Index Test PET-CT			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Was the imaging test applied and interpreted in a clinically applicable manner?	Unclear		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Unclear		
Was the test interpreted by an experienced examiner?	Unclear		
		Low	**Unclear**
DOMAIN 3: Reference Standard			

Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Were the reference standard results based on patient follow-up interpreted without knowledge of the original imaging test result?			
Does the study use the same definition of disease positive as the primary review question (i.e. any mets) OR is it possible to disaggregate or regroup data such that data matching the review question can be extracted?	Yes		
Was histology or cytology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Low	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	No		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		High	

Pfannenberg 2007

Study characteristics	
Patient sampling	**Design:** within-person comparison; prospective **Country:** Germany **Data collection:** Sep 2004 to Sep 2005 **Inclusion criteria:** stage III or IV cutaneous MM undergoing imaging for exclusion of widespread disease; confirmation of local disease before surgical resection; further characterisation of abnormal radiological, clinical, and laboratory (S100 protein, lactic dehydrogenase) findings; routine melanoma surveillance of high-risk MM
Patient characteristics and setting	**Presentation:** mixed (included exclusion of widespread disease and confirmation of local disease before surgical resection (n = 9); characterisation of abnormal radiological, clinical, and laboratory findings (n = 48); routine melanoma surveillance in high-risk patients (n = 7)) **Number patients:** 64 **Number primary lesions: NR** **Number LNBs/metastases:** 420 **Stage of disease:** stage III (25, 39%); stage IV (39, 61%) **Mean age:** 57.8 years; **Range:** 23.3 to 79.1 years **Male:** 41 (64%) **Primary lesion site:** NR **Breslow/Clark:** mean BT 2.69 mm (0.6, 12 mm) **Ulceration:** NR **Other:** NaR
Index tests	**CT:** CT (CE, 16 row multi-slice) **Machine:** Hi-Rez Biograph 16 (Siemens Medical Solutions, Knoxville, TN) **Scan coverage:** base of the skull to the lower legs **Contrast:** Ultravist 370, Schering GmbH, Berlin, Germany, plus 1000 ml Mannitol 2% as a negative oral contrast agent before CT **CT parameters:** 120 kV, 120 to 160 mAs; 5 mm (axial, with an increment of 5 mm) and 3 mm (coronal with an increment of 2 mm) **Breath hold:** CT: patients were asked to stop breathing in normal expiration during contrast-enhanced CT scans for optimal co-registration **Threshold:** based on morphological characteristics and enhancement pattern; region-specific nodal size criteria based on measurement of the small axis diameter # **MRI:** CE; multiple phased-array; axial and coronal **Machine:** Avanto, Siemens AG, Erlangen, Germany **Scan coverage:** head to toe **MRI parameters:** N/A **Magnet:** N/A **Threshold:** based on morphological characteristics and enhancement pattern; detected lymph nodes smaller than 10 mm but with brighter signal on T1 sequences due to the paramagnetic effect of melanin; also were rated as suspicious # **PET-CT:** 3D; CT (CE, 16 row multi-slice) **Machine:** Hi-Rez Biograph 16 (Siemens Medical Solutions, Knoxville, TN) **Scan coverage:** base of the skull to the lower legs **Contrast:** Ultravist 370, Schering GmbH, Berlin, Germany, plus 1000 mL Mannitol 2% as a

	negative oral contrast agent before CT **CT parameters:** 120 kV, 120 to 160 mAs; 5 mm (axial, with an increment of 5 mm) and 3 mm (coronal with an increment of 2 mm) **FDG:** 370 MBq F-FDG IV 55 to 65 minutes before scanning **Breath hold:** CT: patients were asked to stop breathing in normal expiration during contrast-enhanced CT scans for optimal co-registration **CT used for:** attenuation corrected and co-registered **Reconstruction:** iteratively reconstructed using commercial software (eSoft; Siemens, Erlangen, Germany) **Threshold:** for PET: any focal tracer uptake exceeding normal regional tracer accumulation was assessed as a malignant lesion. Lesions rated malignant or probably malignant were considered to be malignant # **Number observers:** 6 **Qualification (experience):** 2 dermato-oncologists; 2 radiologists (2 specialists in nuclear medicine, 2 CT radiologists, and 2 MRI radiologists) **Diagnosis (single, consensus, etc.):** consensus of 2 or 4 **Info provided during test interpretation:** clinical - aware of clinical status; other tests - blinded to results of other imaging studies and previous tests
Target condition and reference standard(s)	**Histology/Imaging/FU** **Histological detail (n, %):** NR; confirmed by histology after resection; 65 (15%). **Histopathologist:** NR **FNAC (n, %):** N/A (N/A) **Follow-up (n, %):** PET-CT, CT, dedicated MRI, ultrasound, bone scan or radiography, tumour markers (S100, lactic dehydrogenase), other laboratory and clinical tests (267 (64%) lesions by imaging follow-up, 88 (21%) lesions by clinical follow-up) **FU schedule:** regular 3-month interval follow-up schedule **FU duration:** mean 252.5 days (range 99 to 474 days) **Reference blinding:** N/A # **Target condition** **Data:** per lesion **Definition:** any metastases (excl brain); **Prevalence:** 297/420 = 71% **Definition:** nodal; **Prevalence:** 102/158 = 65% **Definition:** distant (excl local); **Prevalence:** 136/182 = 75% **Definition:** site specific (bone); **Prevalence:** 35/50 = 70% **Definition:** site specific (lung); **Prevalence:** 53/70 = 76% **Definition:** site specific (local); **Prevalence:** 59/80 = 74% **Definition:** site specific (other); **Prevalence:** 13/25 = 52%
Flow and timing	**Index to histology interval:** NR **Index to FU interval:** every 3 months **Exclusions:** n = 36; no wbMRI (n = 25; due to metallic implants or claustrophobia (5 patients) ; refusal of a second whole body examination on the same day (17 patients) or abortion of the examination (3 patients); no evidence of tumour spread (3 patients); lack of follow-up data for lesion characterisation (8 patients))

Pfannenberg 2007 (*Continued*)

Comparative	(1) Blinded to the results of other imaging studies and previous tests (2) 24-hour to 72-hour interval (3) prospective; consecutively referred for staging
Notes	**Other result:** when changes in the treatment schedule were analysed for the influence of different imaging procedures, PET/ CT performed best; 90.2% of the changes could be motivated by PET-CT alone, 87.8% by wbMRI alone (cerebral metastases excluded), 75.6% by PET alone, and 73. 2% by CT alone # Text states that MRI sensitivity increased from 79.8% to 86.9% on retrospective review of images not blinded to the other imaging tests (i.e. FNs reduced from 60 to 39)

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Does the study report results for participants at the same point in the clinical pathway and who would be eligible for imaging in normal practice?	No		
Did the study report data on a per patient rather than per lesion basis?	No		
		Low	**High**
DOMAIN 2: Index Test CT			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		

Was the imaging test applied and interpreted in a clinically applicable manner?	No		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Unclear		
Was the test interpreted by an experienced examiner?	Yes		
		Low	**High**
DOMAIN 2: Index Test MRI			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Was the imaging test applied and interpreted in a clinically applicable manner?	No		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Unclear		
Was the test interpreted by an experienced examiner?	Yes		
		Low	**High**
DOMAIN 2: Index Test PET-CT			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Was the imaging test applied and interpreted in a clinically	No		

applicable manner?			
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes		
Was the test interpreted by an experienced examiner?	Yes		
		Low	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Were the reference standard results based on patient follow-up interpreted without knowledge of the original imaging test result?	Yes		
Does the study use the same definition of disease positive as the primary review question (i. e. any mets) OR is it possible to disaggregate or regroup data such that data matching the review question can be extracted?	Yes		
Was histology or cytology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Low	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		

Pfannenberg 2007 (*Continued*)

Did all patients receive the same reference standard?	No		
Were all patients included in the analysis?	No		
		High	
DOMAIN 5: Comparative			
1) was each index test result interpreted without knowledge of the results of other index tests or testing strategies?	Yes		
2) Was the interval between application of index tests	Yes		
3) Was it predetermined that all index tests should be given to all study participants?	Yes		
		Low	

Pfluger 2011

Study characteristics	
Patient sampling	**Design:** within-person comparison; retrospective (Prosp. database NR) **Country:** Germany **Data collection:** NR; 3.5-year period **Inclusion criteria:** MM with regional LN metastases (NR if clinically detectable or micro-metastases) undergoing PET-CT for primary staging or during follow-up. Included only lesions considered malignant by at least 1 of the 3 modalities
Patient characteristics and setting	**Presentation:** mixed (PET-CT was done for primary staging and for follow-up) **Number patients:** 50 **Number primary lesions:** NR **Number LNBs/metastases:** 232 lesions **Stage of disease:** NR **Mean age:** 57 years; **Range:** 29 to 85 years **Male:** 36 (72%) **Primary lesion site:** NR **Breslow/Clark:** NR **Ulceration:** NR **Other:** NR

Index tests	**CT:** U & CE, dual-slice, helical **Machine:** Philips Gemini PET/CT System (Philips, Hamburg, Germany), consisting of a dedicated GSO full-ring PET scanner and a dual-slice helical CT scanner **Scan coverage:** WB; from the skull including the legs **Contrast:** reports for unenhanced and CE using 120 mL (2.5 mL/s) of iodine-containing contrast medium **CT parameters:** U - 140 kV, 20 mAs, 5 mm; CE - 120 kV, 145 mAs, 2.5 mm **Breath hold:** CT expiration protocols for shallow free breathing during the emission scan for CE only **Threshold:** unenhanced - abnormal soft tissue masses and/or enlarged LNs (diameter > 1.0 cm); contrast enhanced - same plus degree of contrast enhancement # **PET-CT:** 3D; CT (U and CE, dual-slice, helical) **Machine:** Philips Gemini PET/CT System (Philips, Hamburg, Germany), consisting of a dedicated GSO full-ring PET scanner and a dual-slice helical CT scanner **Scan coverage:** WB; from the skull including the legs **Contrast:** 120 mL (2.5 mL/s) of iodine-containing contrast medium **CT parameters:** 120 kV, 145 mAs, 2.5 mm **FDG:** 200 MBq **Breath hold:** CT expiration protocols for shallow free breathing during the emission scan **CT used for:** unclear; reports side-by-side PET-CT display with spatially synchronised images **Reconstruction:** NR **Threshold:** non-physiologically increased uptake of FDG with SUVmax > 2.5. CT (U and CE) and PET alone first analysed separately, followed by combined PET-CT analysis using a side-by-side display with spatially synchronised images to ensure the same lesion was assessed on both modalities. For lesions with discrepant results on CT and PET, the finding of the modality with the higher diagnostic confidence score was accepted. If results from both modalities were discrepant and had the same diagnostic confidence score value, the lesion was judged positive.Confidence scores were assigned as follows: (1) both observers uncertain about positive or negative findings, (2) one observer uncertain and one observer certain and (3) both observers certain. If there were no signs of an active tumour lesion or physiological changes in one modality, the diagnostic confidence score "3" was assigned to this "lesion" that was suspicious for melanoma involvement in another modality # **Number observers:** 2 **Qualification (experience):** NR (experienced); consensus **Info provided during test interpretation:** clinical - knowledge of clinical data but blinded to any imaging. Other tests - PET-CT viewed side by side
Target condition and reference standard(s)	**Histology/FU** **Histological detail (n, %):** NR (41, 17.7%). **Histopathologist:** NR **FNAC (n, %):** N/A (0) **Follow-up (n, %):** used an imaging method 'appropriate to the respective lesion (38 PET-CT scans, 8 CT scans, 4 ultrasound examinations)' (191, 82.3%) **FU schedule:** NR **FU duration:** ≥ 6 months; no further detail **Reference blinding:** NR # **Target condition** **Data:** per pt

Pfluger 2011 (*Continued*)

	Definition: any (incl subcutaneous, brain); **Prevalence:** 151/232 = 65% **Metastases:** only FP and FN results were documented by anatomical site. FNs on CE CT included subcutaneous (6), bone or bone marrow (5), muscular (4), LN (4), liver (3). FNs on unenhanced PET-CT included 3 liver, 1 LN, 1 spleen (no FNs on CE, PET-CT)
Flow and timing	**Index to histology interval:** NR **Index to FU interval:** NR **Exclusions:** n = NR; in cases of new tumour lesions during the follow-up period, these lesions were not included in the study. The reason for not including these lesions was the fact that non-detectable lesions in CT or 18F-FDG PET cannot be distinguished from non-existent lesions in the case of a newly detected tumour lesion during follow-up
Comparative	(1) Combined PET-CT analysis using a side-by-side display with spatially synchronised images to ensure the same lesion was assessed on both modalities (2) Same scanner (3) Retrospective; all with PET-CT
Notes	**Other result:** all 6 FPs on PET-CT would have affected TNM classification as they would have been single metastatic lesions in otherwise metastasis-free patients. The 5 FNs on unenhanced PET-CT did not affect TNM classification as all were identified in patients with multiple metastases (stage M1c)

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Unclear		
Does the study report results for participants at the same point in the clinical pathway and who would be eligible for imaging in normal practice?	No		
Did the study report data on a per patient rather than per lesion basis?	No		
		Unclear	**High**

Pfluger 2011 (*Continued*)

DOMAIN 2: Index Test CT			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
Was the imaging test applied and interpreted in a clinically applicable manner?	No		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes		
Was the test interpreted by an experienced examiner?	Yes		
		Unclear	**High**
DOMAIN 2: Index Test PET-CT			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
Was the imaging test applied and interpreted in a clinically applicable manner?	No		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes		
Was the test interpreted by an experienced examiner?	Yes		
		Unclear	**High**
DOMAIN 3: Reference Standard			

Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Were the reference standard results based on patient follow-up interpreted without knowledge of the original imaging test result?	Unclear		
Does the study use the same definition of disease positive as the primary review question (i.e. any mets) OR is it possible to disaggregate or regroup data such that data matching the review question can be extracted?	Unclear		
Was histology or cytology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Unclear	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	No		
Were all patients included in the analysis?	No		
		High	
DOMAIN 5: Comparative			
1) was each index test result interpreted without knowledge of the results of other index tests	No		

Pfluger 2011 (*Continued*)

or testing strategies?			
2) Was the interval between application of index tests	Yes		
3) Was it predetermined that all index tests should be given to all study participants?	Yes		
		High	

Prayer 1990

Study characteristics	
Patient sampling	**Design:** within-person comparison (US vs palpation); unclear **Country:** Austria **Data collection:** NR; 18-month period **Inclusion criteria:** primary MM investigated before or after removal of the primary melanoma in postoperative follow-up
Patient characteristics and setting	**Presentation:** primary (LNs investigated before or after removal of the primary melanoma in postoperative follow-up) **Number patients:** 217 **Number primary lesions:** NR **Number LNBs/metastases:** NR **Stage of disease:** NR **Mean age:** 56 years; **Median age:** NR; **Range:** 25 to 82 years **Male:** 104 (48%) **Primary lesion site:** HN 42, 19%; arm 61, 28%; shoulder 23, 11%; leg 91, 42% **Breslow/Clark:** BT < 0.75 mm 25, 12%; 0.75 to 1.5 mm 96, 44%; 1.5 to 3.00 mm 79, 36%; > 3 mm 17, 8% **Clark level:** II 93; III 89; IV 33 **Ulceration:** NR **Other:** NR
Index tests	**US:** B-mode **Machine:** ATL 'Ultramark 8' with an anular array and detachable elastomere **Scan coverage:** primary LNs depending on tumour localisation. Cervical (42); axillary (84); inguinal (91) **Contrast:** N/A **FNAC:** N/A **Threshold:** suspicious - circular and oval masses with poor echo; longitudinally configurated LNs with echogenic eccentric hilum regarded as "enlarged reactively" # **Number observers:** 1 **Qualification (experience):** radiologist (NR) **Diagnosis (single, consensus, etc.):** single

Prayer 1990 (*Continued*)

	Info provided during test interpretation: clinical - unclear; different clinicians for palpation (dermatologist) and for US (radiologist); other tests - NR
Target condition and reference standard(s)	**Histology (presume LND), FU for US negative** **Histological detail (n, %):** NR (29, 13%). **Histopathologist:** NR **FNAC (n, %):** N/A (0) **Follow-up (n, %):** NR (188, 87%) **FU schedule:** every 2 months **FU duration:** 6 months **Reference blinding:** NR # **Target condition** **Data:** per pt **Definition:** nodal mets; **Prevalence:** 29/217 = 13%
Flow and timing	**Index to histology interval:** NR **Index to FU interval:** 2 months **Exclusions:** n = 0
Comparative	
Notes	**Other result:** there were no false-negative US results (i.e. melanoma metastases did not occur within the following 6 months in any of the patients classified as having no suspect regional lymph nodes) . The smallest metastasis detected by ultrasound was 11 mm in diameter

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Does the study report results for participants at the same point in the clinical pathway and who would be eligible for imaging in normal practice?	Yes		
Did the study report data on a per patient rather than per lesion basis?	Yes		

Prayer 1990 (*Continued*)

		Unclear	**Low**
DOMAIN 2: Index Test Ultrasound			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
Was the imaging test applied and interpreted in a clinically applicable manner?	Unclear		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes		
Was the test interpreted by an experienced examiner?	Unclear		
		Unclear	**Unclear**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Were the reference standard results based on patient follow-up interpreted without knowledge of the original imaging test result?	Unclear		
Does the study use the same definition of disease positive as the primary review question (i.e. any mets) OR is it possible to disaggregate or regroup data such that data matching the review question can be extracted?	Yes		

Prayer 1990 (*Continued*)

Was histology or cytology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Low	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	No		
Were all patients included in the analysis?	Yes		
		High	

Radzhabova 2009

Study characteristics	
Patient sampling	**Design:** non-comparative; unclear **Country:** Russia **Data collection:** NR **Inclusion criteria:** clinically node negative MM and SLNB (based on US result)
Patient characteristics and setting	**Presentation:** primary (pre-SLNB) **Number patients:** 152 **Number primary lesions:** NR **Number LNBs/metastases:** NR **Stage of disease:** NR **Mean age:** NR; **Median age:** NR; **Range:** NR **Male:** NR (0%) **Primary lesion site:** NR **Breslow/Clark:** NR **Ulceration:** NR **Other:** NR
Index tests	**US:** B-mode; sectoral and linear **Machine:** NR **Scan coverage:** NR **Contrast:** N/A **FNAC:** N/A **Threshold:** test positive considered as high PSV, EDV, S/D, and PI < 1000. Mets could not be

	excluded if PSV and PI were high but EDV = 0, S/D was undetectable (PI - pulse index, PSV - peak systolic volume, EDV - end-diastolic volume, Stuart index) # **Number observers:** NR **Qualification (experience):** NR (NR) **Diagnosis (single, consensus, etc.):** NR **Info provided during test interpretation:** clinical - NR; other tests - NR
Target condition and reference standard(s)	**Histo (SLNB); FU** **Histological detail (n, %):** NR (52, 100%). **Histopathologist:** NR **FNAC (n, %):** N/A (0) **Follow-up (n, %):** NR (0) **FU schedule:** NR **FU duration:** NR **Reference blinding:** NR # **Target condition** **Data:** per pt **Definition:** nodal mets; **Prevalence:** 11/52 = 21%
Flow and timing	**Index to histology interval:** NR **Index to FU interval:** NR **Exclusions:** n = 100; benign on US did not get SLNB
Comparative	
Notes	2 FN on SLNB identified during FU; all 100 with no SLNB reportedly disease free on FU

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	No		
Does the study report results for participants at the same point in the clinical pathway and who would be eligible for imaging in normal practice?	Yes		

Did the study report data on a per patient rather than per lesion basis?	Yes		
		High	**Low**
DOMAIN 2: Index Test Ultrasound (pre-SLNB)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Unclear		
Was the imaging test applied and interpreted in a clinically applicable manner?	Unclear		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes		
Was the test interpreted by an experienced examiner?	Unclear		
		Unclear	**Unclear**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Were the reference standard results based on patient follow-up interpreted without knowledge of the original imaging test result?			
Does the study use the same definition of disease positive as the primary review question (i.	Yes		

Radzhabova 2009 (*Continued*)

e. any mets) OR is it possible to disaggregate or regroup data such that data matching the review question can be extracted?			
Was histology or cytology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Low	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
		High	

Reinhardt 2006

Study characteristics	
Patient sampling	**Design:** within-person comparison; retrospective (Prosp. database NR) **Country:** Germany **Data collection:** Nov 2002 to Jun 2004 **Inclusion criteria:** cutaneous MM referred for PET-CT for primary staging after sentinel node biopsy, for therapy control after chemotherapy of metastatic disease, for staging of clinically suspected recurrent disease, and during follow-up within 5 years of primary treatment **Excluded if** inadequate reference standard (no histology or FU < 1 year)
Patient characteristics and setting	**Presentation:** mixed (primary staging after sentinel node biopsy (n = 75); therapy control after chemotherapy of metastatic disease (n = 42), staging of clinically suspected recurrent disease (n = 65), during follow-up within 5 years of primary treatment (n = 68)) **Number patients:** 250 **Number primary lesions:** 250 **Number LNBs/metastases:** NR; 670 lesions identified **Stage of disease:** initial pathology: stage I 22, 9%; stage II 88, 35%; stage III 108, 43%; stage IV 32, 13% **Mean age:** 58 years ± 16 years **Male:** 145 (58%)

	Primary lesion site: NR **Breslow/Clark:** tumour depth ≤ 1.0 mm 29, 12%; 1.01 to 2.0 mm 68, 27%; 2.01 to 4.0 mm 66, 26%; > 4.0 mm 64, 26% **Ulceration:** NR **Other:** NR
Index tests	**CT:** CE, helical, dual detector **Machine:** Biograph; Siemens Medical Solutions Inc., Hoffman Estates, Illinois, USA **Scan coverage:** WB; base of skull to tip of toes in 3 parts **Contrast:** Peritrast-oral-GI; Kohler Chemie GmbH, Alsbach, Germany **CT parameters:** 130 kV, 40 mAs, 5 mm **Breath hold:** limited breath hold for CT and shallow breathing for PET **Threshold:** NR; states only that accuracy was assessed according to current AJCC staging classification # **PET-CT:** CT (CE), helical, dual detector **Machine:** Biograph; Siemens Medical Solutions Inc., Hoffman Estates, Illinois, USA **Scan coverage:** WB; base of skull to tip of toes in 3 parts **Contrast:** Peritrast-oral-GI; Kohler Chemie GmbH, Alsbach, Germany **CT parameters:** 130 kV, 40 mAs, 5 mm **FDG:** 371 ± 40 MBq FDG through an anterior cubital vein **Breath hold:** limited breath hold for CT and shallow breathing for PET **CT used for:** attenuation correction based on re-scaling of the CT image **Reconstruction:** iteratively reconstructed with attenuation correction on the basis of re-scaling of the CT image as described elsewhere (Kinahan 2003) # **Threshold:** NR; states only that accuracy was assessed according to current AJCC staging classification **Number observers:** NR **Qualification (experience):** NR; consensus by each of 2 experienced investigators **Diagnosis (single, consensus, etc.):** consensus (of 2) **Info provided during test interpretation:** clinical - routine clinical fashion - same clinical clinical information about each patient; other tests - blinded to competitive imaging procedure
Target condition and reference standard(s)	**Histology (SLNB or other biopsy), FU** **Histological detail (n, %):** no details; 100, 40% for N-staging (including 15 with SLNB); 20, 8% for M-staging. **Histopathologist:** NR **FNAC (n, %):** N/A (N/A) **Follow-up (n, %):** all available clinical information, laboratory tests, radiologic and nuclear medicine imaging studies such as MRI, contrast-enhanced CT, ultrasound, and bone scans (250, 100%) **FU schedule:** every 3 months **FU duration:** ≥ 1 year **Reference blinding:** blinded to standard of reference; data collection for the reference standard was done by a physician unaware of the results of PET-CT imaging # **Target condition** **Data:** per pt **Definition:** any (excl brain); **Prevalence:** 116/250 = 46%

	Definition: nodal; **Prevalence:** 78/250 = 31% **Definition:** distant; **Prevalence:** 84/250 = 34% **Metastases:** distant metastases included distant LN, lungs, and other organs (numbers per group NR and not further differentiated by anatomical site)
Flow and timing	**Index to histology interval:** NR **Index to FU interval:** 3 months **Exclusions:** n = 0
Comparative	(1) Blinded to competitive imaging procedure (2) Same scanner; CT performed 1 minute before PET (3) All undergoing PET-CT
Notes	**Other result:** data reported by clinical setting, for differentiation by metastatic sites (M1A to M1C) , and for detection of visceral and non-visceral metastases, but number diseased per group is not given such that 2×2 cannot be estimated

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Does the study report results for participants at the same point in the clinical pathway and who would be eligible for imaging in normal practice?	No		
Did the study report data on a per patient rather than per lesion basis?	Yes		
		Low	**High**
DOMAIN 2: Index Test CT			
Were the index test results interpreted without knowledge of the results of the reference stan-	Yes		

dard?			
If a threshold was used, was it pre-specified?	Yes		
Was the imaging test applied and interpreted in a clinically applicable manner?	No		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No		
Was the test interpreted by an experienced examiner?	Yes		
		Low	**High**
DOMAIN 2: Index Test PET-CT			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Was the imaging test applied and interpreted in a clinically applicable manner?	No		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No		
Was the test interpreted by an experienced examiner?	Yes		
		Low	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		

Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Were the reference standard results based on patient follow-up interpreted without knowledge of the original imaging test result?	Yes		
Does the study use the same definition of disease positive as the primary review question (i.e. any mets) OR is it possible to disaggregate or regroup data such that data matching the review question can be extracted?	Yes		
Was histology or cytology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Low	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	No		
Were all patients included in the analysis?	Yes		
		High	
DOMAIN 5: Comparative			
1) was each index test result interpreted without knowledge of the results of other index tests or testing strategies?	Yes		

2) Was the interval between application of index tests	Yes		
3) Was it predetermined that all index tests should be given to all study participants?	Yes		
		Low	

Revel 2010

Study characteristics	
Patient sampling	**Design:** non-comparative; retrospective (Prosp. database NR) **Country:** France **Data collection:** Jan 2005 to Sep 2008 **Inclusion criteria:** clinically node negative HN MM qithpre-SLNB PET-CT **Excluded if** or > 1 month between PET-CT and SLNB
Patient characteristics and setting	**Presentation:** primary (pre-SLNB) **Number patients:** 22 **Number primary lesions:** 22 **Number LNBs/metastases:** 21 **Stage of disease:** stage I or II **Mean age:** 60 years; **Range:** 18 to 88 years **Male:** 16 (73%) **Primary lesion site:** scalp 5, 23%; cheek 3, 14%; cervical or neck 3, 14%; atrial region (ear, mastoid, temples) 6, 27%; palpebral or periorbital 4, 18%; frontal 1, 5% **Breslow/Clark:** 4.5 mm (0.26 to 10 mm) **Ulceration:** unknown
Index tests	**PET-CT:** **Machine:** Biograph 2 (Siemens1 Germany) (2003 to 2007); Biograph 6 True V imager (Siemens1) (2007 onwards) **Scan coverage:** WB; vertex to the toes **Contrast:** NR **CT parameters:** Biograph 2: 130 kV, 80 mAs; Biograph 6: 130 kV, 4D Care Dose; Biograph 2: 5 mm Biograph 6: 4 mm **FDG:** 5.5 MBq/kg for Biograph 2; 4 MBq/kg for Biograph 6 True V; Flucis1, Schering, Cisbio International **Breath hold:** no breath hold instructions reported **CT used for:** appears to be used for attenuation correction; also describes anatomical localisation on fused images **Reconstruction:** iterative reconstruction algorithms using Osem 3D, with correction of scatter and attenuation **Threshold:** any hypermetabolic focus more intense than the surrounding background, including equivocal foci, was systematically compared with the corresponding anatomical structure on the coupled CT, after accuracy of registration on merged PET-CT images was verified. An FN was

	considered present if a patient was SLN positive and PET-CT for the same basin was negative, regardless of whether PET was positive for a different LNB # **Number observers:** 2 **Qualification (experience):** NR (NR) **Diagnosis (single, consensus, etc.):** consensus of 2 **Info provided during test interpretation:** clinical - localisation of the initial tumor and standard clinical and radiological assessment were known during image interpretation; other tests - standard radiological assessment - known but blinded to review of PET alone
Target condition and reference standard(s)	**Histology (SLNB); FU** **Histological detail (n, %):** H&E; IHC (S100, HMB45, melanA antibodies) (22, 100%). **Histopathologist: NR** **FNAC (n, %):** N/A (N/A) **Follow-up (n, %):** NR (22/22, 100%) **FU schedule:** NR **FU duration:** mean 17 months (range 1 to 44) **Reference blinding:** NR # **Target condition** **Data:** per pt **Definition:** nodal mets; **Prevalence:** 10/20 = 50% (excluding 2 SLNB failures (histo only reference standard)); 12/22 = 55% (including 2 SLNB failures (histo + FU reference standard))
Flow and timing	**Index to histology interval:** 12 days; PET undergone in month before surgery **Index to FU interval:** NR **Exclusions:** n = 2; 2 test fails (no SN detected; however data can be extracted excluding these)
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		

Does the study report results for participants at the same point in the clinical pathway and who would be eligible for imaging in normal practice?	Yes		
Did the study report data on a per patient rather than per lesion basis?	Yes		
		Low	**Low**
DOMAIN 2: Index Test PET-CT			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
Was the imaging test applied and interpreted in a clinically applicable manner?	No		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	No		
Was the test interpreted by an experienced examiner?	Yes		
		Unclear	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Were the reference standard results based on patient follow-up interpreted without knowledge			

of the original imaging test result?			
Does the study use the same definition of disease positive as the primary review question (i.e. any mets) OR is it possible to disaggregate or regroup data such that data matching the review question can be extracted?	Yes		
Was histology or cytology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Low	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Rubaltelli 2011

Study characteristics	
Patient sampling	**Design:** NC; unclear **Country:** Italy **Data collection:** Jun 2008 to Dec 2009 **Inclusion criteria:** cutaneous MM with US of regional LNs as part of follow-up **Excluded if** or malignant on B-mode US as assessed by usual US features
Patient characteristics and setting	**Presentation:** re-staging (all undergoing postoperative follow-up designed to ensure early identification of lymph node metastases) **Number patients:** 436 **Number primary lesions:** NR **Number LNBs/metastases:** NR **Stage of disease:** NR **Mean age:** 54 years; **Median age:** 58 years; **Range:** 27 to 81 years

	Male: full sample: 240 (52%) **Primary lesion site:** NR **Breslow/Clark:** NR **Ulceration:** NR **Other:** NR
Index tests	**US:** B-mode plus contrast-enhanced US for subgroup; linear array transducers **Machine:** Sonoline Elegra Scanner (Siemens Healthcare) **Scan coverage:** variable: axillary lymph nodes for MM of the upper limbs, inguinal lymph nodes for MM of the lower limbs, both axillary and inguinal lymph nodes for MM of the trunk, and cervical and supraclavicular lymph nodes for MM of the head and neck (72 neck, 248 axillary, and 354 inguinal LNBs were examined). LNBs identified on B-mode US were examined with CE US **Contrast:** sulfur hexafluoride microbubbles (SonoVue, Bracco) **FNAC:** yes as ref standard **Threshold:** B-mode - focal hypoechoic cortical thickening - focal area of cortex at least twice as thick as the cortex in the remainder of the same lymph node. CE - perfusion defects corresponding to cortical focal thickening; homogeneous intense enhancement of the cortex considered benign # **Number observers:** 1 of 3 **Qualification (experience):** sonologist (high) **Diagnosis (single, consensus, etc.):** single **Info provided during test interpretation:** clinical - NR; other tests - NR
Target condition and reference standard(s)	**FNAC; histo in FNAC+, FU in some FNAC-** **FNAC (n, %):** no details (436, 100%) **Histological detail (n, %):** no details (13, 3%). **Histopathologist:** NR **Follow-up (n, %):** US, clinical exam (31/44 negative on CE-US, 70%) **FU schedule:** NR **FU duration:** 6 to 16 months (median, 10 months) **Reference blinding:** NR **Target condition** **Data:** per pt **Definition:** nodal mets; **Prevalence:** 13/436 = 3%
Flow and timing	**Index to histology interval:** US and FNAC consecutive **Index to FU interval:** NR **Exclusions:** n = 24; definite signs of malignancy on B-mode US
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			

Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	No		
Does the study report results for participants at the same point in the clinical pathway and who would be eligible for imaging in normal practice?	Yes		
Did the study report data on a per patient rather than per lesion basis?	Yes		
		High	**Low**
DOMAIN 2: Index Test Ultrasound			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
Was the imaging test applied and interpreted in a clinically applicable manner?	Unclear		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes		
Was the test interpreted by an experienced examiner?	Yes		
		Unclear	**Unclear**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		

Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Were the reference standard results based on patient follow-up interpreted without knowledge of the original imaging test result?	Unclear		
Does the study use the same definition of disease positive as the primary review question (i.e. any mets) OR is it possible to disaggregate or regroup data such that data matching the review question can be extracted?	Yes		
Was histology or cytology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Unclear	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
		High	

Sanki 2009

Study characteristics	
Patient sampling	**Design:** non-comparative; unclear (cites ethics approval for MSLT-I and MSLT-II trials, so likely prospective database at a minimum; text states that US findings were extracted from original reports, however, which implies retrospective) **Country:** Australia

	Data collection: Jan 2001 to Aug 2005 **Inclusion criteria:** SLNB; BT > 1 mm or < 1 mm with adverse histological features, such as Clark level IV to V invasion, ulceration, or high mitotic rate
Patient characteristics and setting	**Presentation:** primary (pre-SLNB) **Number patients:** 716 **Number primary lesions:** NR **Number LNBs/metastases:** 871 LNBs **Stage of disease:** NR **Mean age:** NR; **Median age:** NR; **Range:** NR **Male:** NR (0%) **Primary lesion site:** NR **Breslow/Clark:** NR **Ulceration:** NR **Other:** NR
Index tests	**US:** B-mode US; linear array transducer with high-resolution small-parts probe **Machine:** ATL Ultramark-9 HDI with a linear array L10-5 transducer (Advanced Technology Laboratories Australia Pty Ltd, New South Wales, Australia); Toshiba Aplio US System (Toshiba, Otawara-Shi, Japan) with PLT-1204AT probe (Toshiba) **Scan coverage:** sites marked by nuclear medicine physician during LS **Contrast:** N/A **FNAC:** N/A **Threshold:** reclassification of original report as suspicious, or highly probable (e.g. increased vascular signature, rounding of the normal ovoid shape of the nodes, loss of normal hilar echoes, presence of focal low-level subcapsular space echoes) # **Number observers:** NR **Qualification (experience):** nuclear medicine physician (NR) **Diagnosis (single, consensus, etc.):** single **Info provided during test interpretation:** clinical - NR; other tests - result of lymphoscintigraphy known
Target condition and reference standard(s)	**Histology (SLNB)** **Histological detail (n, %):** H&E (serial section); IHC (S100, HMB45); (716, 100%). **Histopathologist:** NR **FNAC (n, %):** N/A (0) **Follow-up (n, %):** NR (100% (not ref standard for US) **FU schedule:** NR FU duration: 13.5 months (mean, 18.4 months) **Reference blinding:** NR # **Target condition** **Data:** per pt **Definition:** nodal mets; **Prevalence:** 125/716 = 17% (144/871 LNBs = 17%)
Flow and timing	**Index to histology interval:** SLN performed within 24 hours of LS and US **Index to FU interval:** NR **Exclusions:** n = 0

Sanki 2009 (*Continued*)

Comparative			
Notes	**Other result:** 24 FNs on SLNB were reported; not broken down by US result		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Does the study report results for participants at the same point in the clinical pathway and who would be eligible for imaging in normal practice?	Yes		
Did the study report data on a per patient rather than per lesion basis?	Yes		
		Unclear	**Low**
DOMAIN 2: Index Test Ultrasound (pre-SLNB)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
Was the imaging test applied and interpreted in a clinically applicable manner?	Yes		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes		

Was the test interpreted by an experienced examiner?	Unclear		
		Unclear	**Unclear**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Were the reference standard results based on patient follow-up interpreted without knowledge of the original imaging test result?			
Does the study use the same definition of disease positive as the primary review question (i.e. any mets) OR is it possible to disaggregate or regroup data such that data matching the review question can be extracted?	Yes		
Was histology or cytology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Low	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		

Sanki 2009 (*Continued*)

		Low	

Sibon 2007

Study characteristics	
Patient sampling	**Design:** non-comparative; retrospective (prospective database with prospective re-interpretation of US images) **Country:** France **Data collection:** Jan 1999 to May 2005 **Inclusion criteria:** SLNB; BT > 1 mm or < 1 mm with adverse histological features, such as Clark level IV to V invasion, ulceration, or high mitotic rate
Patient characteristics and setting	**Presentation:** primary (pre-SLNB) **Number patients:** 131 **Number primary lesions:** 132 **Number LNBs/metastases:** NR; 189 SLNs **Stage of disease:** NR **Mean age:** 56 years; **Range:** 17 to 92 years **Male:** 70 (53%) **Primary lesion site:** arms 18, 13.6%; legs 43, 33%; trunk 48, 32%; hands/feet 10, 8%; HN 18, 14% **Breslow/Clark:** mean BT 2.60 ± 2.91 mm; ≤ 1 mm 12, 9%; 1.01 to 2.00 mm 67, 51%; 2.01 to 4.00 mm 16, 27%; unknown 1, 1% **Clark level:** II 8, 6%; III 30, 23%; IV 88, 66%, V 7, 5%; unknown 1, 1% **Ulceration:** 37, 28% **Other:** regression 13, 10%
Index tests	**US:** B-mode; linear transducer **Machine:** Power Vision 6000 (Toshiba Medical France SA, Puteaux, France) **Scan coverage:** site of the excised primary melanoma scar and followed paths of the lymphatic vessels to lymph node area(s) **Contrast:** N/A **FNAC:** N/A **Threshold:** stringent criteria: circular/oval hypoechoic lymph node with Solbiati index < 1.5 and no hyperechoic hilum; non-stringent criteria included presence of 1 or 2 of stringent criteria and/or 1 or 2 minor criteria (nodular hypoechoic focus within a lymph node with an irregular lymph node margin) # **Number observers:** unclear how many undertook the original examination but 1 radiologist reviewed all images **Qualification (experience):** radiologist (high) **Diagnosis (single, consensus, etc.):** single **Info provided during test interpretation:** clinical - NR for original interpretation or for re-interpretation; other tests - radiologist reviewed original radiology reports and images

Sibon 2007 (*Continued*)

Target condition and reference standard(s)	**Histology (SLNB)** **Histological detail (n, %):** H&E (serial section); IHC (S-100 and HMB45) for H&E negative only. Any size of tumour deposit was considered metastatic unless < 5 isolated tumour cells present (131, 100%). **Histopathologist:** NR **FNAC (n, %):** N/A (-) **Follow-up (n, %):** NR (NR) **FU schedule:** NR **FU duration:** NR **Reference blinding:** re-interpretaion blinded to patient outcomes # **Target condition** **Data:** per pt **Definition:** nodal mets; **Prevalence:** 35/133 = 26%
Flow and timing	**Index to histology interval:** US 24 hours before LS **Index to FU interval:** NR **Exclusions:** n = 0
Comparative	
Notes	**Other result:** US detected 1/24 micro-metastases < 2 mm and 2/11 macro-metastases ≥ 2 mm (both > 5 mm) identified on SLNB

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Does the study report results for participants at the same point in the clinical pathway and who would be eligible for imaging in normal practice?	Yes		
Did the study report data on a per patient rather than per lesion basis?	Yes		
		Low	**Low**

Sibon 2007 (*Continued*)

DOMAIN 2: Index Test Ultrasound (pre-SLNB)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Was the imaging test applied and interpreted in a clinically applicable manner?	Unclear		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes		
Was the test interpreted by an experienced examiner?	Yes		
		Low	**Unclear**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
Were the reference standard results based on patient follow-up interpreted without knowledge of the original imaging test result?			
Does the study use the same definition of disease positive as the primary review question (i.e. any mets) OR is it possible to disaggregate or regroup data such that data matching the review question can be extracted?	Yes		

Sibon 2007 (*Continued*)

Was histology or cytology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Low	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Singh 2008

Study characteristics	
Patient sampling	**Design:** non-comparative; unclear **Country:** Germany **Data collection:** NR **Inclusion criteria:** primary MM undergoing SLNB (all > 1 mm)
Patient characteristics and setting	**Presentation:** primary (pre-SLNB) **Number patients:** 52 **Number primary lesions:** NR **Number LNBs/metastases:** 67 LNBs; 111 SLNs **Stage of disease:** all stage I or II **Mean age:** 55 years; **Median age:** 61 years; **Range:** 17 to 76 years **Male:** 36 (69%) **Primary lesion site:** extremities 23, 44%; trunk 16, 31%; HN 13, 25% **Breslow/Clark:** mean 3.46 mm, range 1.0 to 12.0 mm **Ulceration:** NR **Other:** NR
Index tests	**PET-CT:** helical, CT (CE, dual detector) **Machine:** Biograph; Siemens Medical Solutions Inc., Hoffman Estates, Illinois, USA **Scan coverage:** WB; base of skull to tip of toes in 3 parts **Contrast:** Peritrast-oral-GI; Kohler Chemie GmbH, Alsbach, Germany **CT parameters:** 130 kV, 40 mAs, 5 mm **FDG:** 370 ± 40 MBq FDG through an anterior cubital vein

	Breath hold: limited breath hold for CT and shallow breathing for PET **CT used for:** attenuation correction based on re-scaling of CT image; image fusion **Reconstruction:** iterative (not further detailed) **Threshold:** any focal uptake more than background unless it was found to be a false positive focus (physiological accumulation or brown fat tissue) in fusion imaging # **Number observers:** 2 **Qualification (experience):** 2 experienced observers assessed FDG PET-CT fusion imaging independently; also refers to team of radiologists and nuclear physicians (experienced) **Diagnosis (single, consensus, etc.):** consensus **Info provided during test interpretation:** clinical - NR; other tests - PET before LS
Target condition and reference standard(s)	**Histology (SLNB)** **Histological detail (n, %):** "the surgeons knew the FDG-PET findings"; H&E with IHC only in H&E negative (52, 100%). **Histopathologist:** NR **FNAC (n, %):** N/A **Follow-up (n, %):** N/A **FU schedule:** N/A **FU duration:** N/A **Reference blinding:** NR # **Target condition** **Data:** per pt **Definition:** nodal mets; **Prevalence:** 14/52 = 27% (BT > 4 mm 7/12 = 58%; BT ≤ 4 mm 7/40 = 17%)
Flow and timing	**Index to histology interval:** PET before LS before SLNB **Index to FU interval:** NR **Exclusions:** n = 0
Comparative	
Notes	**Other result:** 2 TPs; both BT ≥ 4 mm; FPs < 4 mm

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		

Does the study report results for participants at the same point in the clinical pathway and who would be eligible for imaging in normal practice?	Yes		
Did the study report data on a per patient rather than per lesion basis?	Yes		
		Unclear	**Low**
DOMAIN 2: Index Test PET-CT			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
Was the imaging test applied and interpreted in a clinically applicable manner?	Unclear		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes		
Was the test interpreted by an experienced examiner?	Yes		
		Unclear	**Unclear**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	No		
Were the reference standard results based on patient follow-up interpreted without knowledge			

Singh 2008 (*Continued*)

of the original imaging test result?			
Does the study use the same definition of disease positive as the primary review question (i.e. any mets) OR is it possible to disaggregate or regroup data such that data matching the review question can be extracted?	Yes		
Was histology or cytology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Low	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Strobel 2007a

Study characteristics	
Patient sampling	**Design:** non-comparative; retrospective (Prosp. database NR) **Country:** Switzerland **Data collection:** Jan 2005 to Jan 2006 **Inclusion criteria:** high-risk melanoma (BT > 4 mm, or Clark level III or IV, or known resected metastases) and raised S-100 (> 0.2 μg/L) undergoing follow-up after primary treatment **Excluded if** FDG PET/ CT and S-100B measurement > 2 weeks apart; treatment initiated between PET-CT and tumour marker measurement; or systemic therapy before PET-CT investigation
Patient characteristics and setting	**Presentation:** re-staging (all patients followed up according to updated Swiss melanoma guidelines) **Number patients:** 47 **Number primary lesions:** 47 **Number LNBs/metastases:** NR **Stage of disease:** NR

	Mean age: 58.4 years; **Range:** 20 to 83 years **Male:** 20 (43%) **Primary lesion site:** NR **Breslow/Clark:** BT 1.02 to 15 mm; unknown in 9 **Ulceration:** NR **Other:** NR
Index tests	**PET-CT:** 2D PET, CT (CE, multi-slice, helical) **Machine:** Discovery LS or Discovery ST (GE Health Systems, Milwaukee, WI); integrated PET scanner (GE Advance Nxi, GE Health Systems, Milwaukee, WI) with a multi-slice helical CT (LightSpeed Plus or Lightspeed 16; GE Health Systems, Milwaukee, WI) **Scan coverage:** head to knees with scanning of lower legs for patients with primary tumours of the lower extremities **Contrast:** oral CT contrast agent given 15 minutes before injection of 18F-FDG **CT parameters:** 140 kV, 40 mAs, 4.25 mm **FDG:** 370 to 400 MBq **Breath hold:** CT: breath holding in the normal expiratory position **CT used for:** attenuation correction, fused **Reconstruction:** standard iterative algorithm (OSEM) **Threshold:** FDG uptake clearly greater than background and established morphological CT criteria; if a focal FDG-active lesion was detected, the exact anatomical localisation was determined on fused PET-CT images. Lesions with 18F-FDG uptake in physiological sites or benign variants (e. g. muscles, brown fatty tissue, pulmonary infiltrations) were determined as benign # **Number observers:** 2 **Qualification (experience):** nuclear radiology physicians (experienced) **Diagnosis (single, consensus, etc.):** consensus of 2 **Info provided during test interpretation:** clinical - blinded to serum S-100B; other tests - blinded
Target condition and reference standard(s)	**Histology/cytology/imaging/FU** **Histological detail (n, %):** no details (29, 62%; 20 distant mets and 9 LN mets). **Histopathologist:** NR **FNAC (n, %):** no details (4, 8.5%) **Follow-up (n, %):** MRI, PET-CT follow-up, clinical follow-up (47, 100%) **FU schedule:** follow-up PET-CT examinations 3 or 6 months later; no clinical suspicion of metastases arose > 6 months after the scan **FU duration:** minimum 6 months (range 6 to 18 months in all patients) **Reference blinding:** NR **Target condition** **Data:** per pt **Definition:** any (incl brain, subcut); **Prevalence:** 39/47 = 83%; included 9 regional LN metastases and 30 distant metastases, including 12 with lung metastases and 2 with brain metastases (not further documented)
Flow and timing	**Index to histology interval:** NR **Index to FU interval:** 3 months **Exclusions:** n = 0
Comparative	

Notes	**Other result:** reports characteristics of those with elevated S-100 but no mets detected on imaging Two brain metastases detected on PET-CT - elevated FDG uptake compared with normal brain tissue or additional bleeding. Both confirmed on reference standard; method not documented; however both showed perifocal vasogenic oedema on CT		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Does the study report results for participants at the same point in the clinical pathway and who would be eligible for imaging in normal practice?	Yes		
Did the study report data on a per patient rather than per lesion basis?	Yes		
		Low	**Low**
DOMAIN 2: Index Test PET-CT			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
Was the imaging test applied and interpreted in a clinically applicable manner?	No		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes		

Was the test interpreted by an experienced examiner?	Yes		
		Unclear	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Were the reference standard results based on patient follow-up interpreted without knowledge of the original imaging test result?	Unclear		
Does the study use the same definition of disease positive as the primary review question (i.e. any mets) OR is it possible to disaggregate or regroup data such that data matching the review question can be extracted?	Yes		
Was histology or cytology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Low	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	No		
Were all patients included in the analysis?	Yes		

Strobel 2007a (*Continued*)

		High	

Strobel 2007b

Study characteristics	
Patient sampling	**Design:** non-comparative; prospective **Country:** Switzerland **Data collection:** Aug 2004 to Apr 2005 **Inclusion criteria:** high-risk melanoma (BT > 4 mm, or Clark level III or IV, or known resected metastases) and raised S-100 (> 0.2 μg/L) undergoing follow-up after primary treatment **Excluded if** systemic therapy before PET-CT investigation
Patient characteristics and setting	**Presentation:** unclear (NR; PET-CT for depiction or exclusion of metastases) **Number patients:** 124 **Number primary lesions:** NR **Number LNBs/metastases:** NR **Stage of disease:** NR **Mean age:** 54.4 years; **Range:** 15 to 82 years **Male:** 59 (48%) **Primary lesion site:** NR **Breslow/Clark:** NR **Ulceration:** NR **Other:** NR
Index tests	**PET-CT:** CT (CE, multi-slice, helical) **Machine:** Discovery LS or Discovery ST (GE Health Systems, Milwaukee, WI) **Scan coverage:** head to knees with scanning of lower legs for patients with primary tumours of lower extremities **Contrast:** oral CT contrast agent given 15 minutes before injection of 18F-FDG **CT parameters:** 140 kV, 40 mAs, 4.25 mm **FDG:** 350 to 400 MBq **Breath hold:** CT: breath holding in normal expiratory position **CT used for:** attenuation correction, fused **Reconstruction:** standard iterative algorithm (OSEM) **Threshold:** results presented based on co-registered PET-CT alone and on PET-CT with separate interpretation of CT component. Mets present if detected by 1 or both readers. FDG uptake clearly greater than background (plus established morphological CT criteria for separate CT interpretation) ; if a focal FDG-active lesion was detected, the exact anatomical localisation was determined on fused PET-CT images. Lesions with 18F-FDG uptake in physiological sites or benign variants (e.g. muscles, brown fatty tissue, pulmonary infiltrations) were determined as benign. Semi-quantitative analysis of FDG uptake in terms of SUVmax also conducted # **Number observers:** 2 **Qualification (experience):** nuclear radiology physicians (experienced (13 years and 7 years)) **Diagnosis (single, consensus, etc.):** consensus of 2 **Info provided during test interpretation:** clinical - blinded to serum S-100B; other tests - blinded

Strobel 2007b (*Continued*)

Target condition and reference standard(s)	**Histology/cytology/imaging/FU** **Histological detail (n, %):** no details (20, 16.1%). **Histopathologist:** NR **FNAC (n, %):** no details (21, 16.9%) **Follow-up (n, %):** MRI, PET-CT follow-up, clinical follow-up (124, 100%, 18 D+ and 61 D- had status confirmed by PET-CT or clinical FU; 4 D- had MRI to confirm absence of mets and 10/53 D+) **FU schedule:** NR **FU duration:** minimum 6 months (range 6 to 18 months in all patients) **Reference blinding:** N/A # **Target condition** **Data:** per pt **Definition:** any (incl brain, subcut); **Prevalence:** 53/124 = 43% **Metastases**: documented only for FNs; 7 patients with metastases were missed by PET-CT without a dedicated CT readout, including in the lungs (4), iliac LNs (1), or gluteal subcutaneous tissue (1) and the psoas muscle (1)
Flow and timing	**Index to histology interval:** NR **Index to FU interval:** NR **Exclusions:** n = 3; chemotherapy before PET-CT
Comparative	
Notes	**Other result:** text describes detection of brain metastases on initial PET-CT; lesion confirmed by MRI 3 days later

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Does the study report results for participants at the same point in the clinical pathway and who would be eligible for imaging in normal practice?	Unclear		

Did the study report data on a per patient rather than per lesion basis?	Yes		
		Low	**Unclear**
DOMAIN 2: Index Test PET-CT			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Was the imaging test applied and interpreted in a clinically applicable manner?	No		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes		
Was the test interpreted by an experienced examiner?	Yes		
		Low	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Were the reference standard results based on patient follow-up interpreted without knowledge of the original imaging test result?	Unclear		
Does the study use the same definition of disease positive as the primary review question (i.	Unclear		

Strobel 2007b (*Continued*)

e. any mets) OR is it possible to disaggregate or regroup data such that data matching the review question can be extracted?			
Was histology or cytology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Unclear	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	No		
Were all patients included in the analysis?	Yes		
		High	

van den Brekel 1998

Study characteristics	
Patient sampling	**Design:** non-comparative; retrospective (prospective database NR) **Country:** Netherlands **Data collection:** Jan 1989 to May 1995 **Inclusion criteria:** HN MM with CT before neck dissection, including therapeutic and elective (i.e. negative on palpation). Also included primary and recurrent
Patient characteristics and setting	**Presentation:** mixed (interval between treatment of primary and neck dissection ranged from 0 to 8.8 years (mean 21 months)) **Number patients:** 26 **Number primary lesions:** 26 **Number LNBs/metastases:** NR **Stage of disease:** stage III (palpable LN) 18, 69%; stageI I and II 8, 31% **Mean age:** 54.5 years; **Range:** 55 to 83 years **Male:** 18 (69%) **Primary lesion site:** scalp 6, 23%; temporal 3, 12%; ear 4, 15%; anterior face 4, 15%; neck 1, 4%; shoulder 1, 4%; upper limb 1, 4%; nasal mucosa 1, 4%; unknown primary 5, 19% **Breslow/Clark:** BT 0.8 to 22 mm **Ulceration:** NR

van den Brekel 1998 (*Continued*)

	Other: NR		
Index tests	**CT:** CE **Machine:** NR **Scan coverage:** neck **Contrast:** IV bolus plus drip infusion of iodine contrast **CT parameters:** NR; 5 mm for 24 pts; 2 mm for 2 pts (both FN) **Breath hold:** NR **Threshold:** presence of necrosis or axial diameter > 10 or > 11 mm # **Number observers:** 2 **Qualification (experience):** NR; co-authors (NR) **Diagnosis (single, consensus, etc.):** unclear **Info provided during test interpretation:** clinical - NR; other tests - NR		
Target condition and reference standard(s)	**Histology (LND)** **Histological detail (n, %):** no details (26, 100%). **Histopathologist:** NR **FNAC (n, %):** N/A (0) **Follow-up (n, %):** N/A (0) **FU schedule:** N/A **Reference blinding:** CT scored blinded to histopathological outcome; NR for record review # **Target condition** **Data:** per pt **Definition:** nodal (neck); **Prevalence:** 21/26 = 81%		
Flow and timing	**Index to histology interval:** 4 weeks **Index to FU interval:** N/A **Exclusions:** n = 0		
Comparative			
Notes	**Other result:** both FNs on CT were with 8-mm CT slice thickness		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		

Does the study report results for participants at the same point in the clinical pathway and who would be eligible for imaging in normal practice?	No		
Did the study report data on a per patient rather than per lesion basis?	Yes		
		Low	**High**
DOMAIN 2: Index Test CT			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
Was the imaging test applied and interpreted in a clinically applicable manner?	Unclear		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes		
Was the test interpreted by an experienced examiner?	Unclear		
		Unclear	**Unclear**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Were the reference standard results based on patient follow-up interpreted without knowledge			

van den Brekel 1998 (*Continued*)

of the original imaging test result?			
Does the study use the same definition of disease positive as the primary review question (i.e. any mets) OR is it possible to disaggregate or regroup data such that data matching the review question can be extracted?	Yes		
Was histology or cytology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Low	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

van Rijk 2006

Study characteristics	
Patient sampling	**Design:** within-person comparison; retrospective (prospective database NR) **Country:** Netherlands **Data collection:** Nov 2000 to Dec 2004 **Inclusion criteria:** SLNB candidates; cutaneous MM BT > 1 mm or Clark ≥ level IV
Patient characteristics and setting	**Presentation:** primary (pre-SLNB) **Number patients:** 107 **Number primary lesions:** 107 **Number LNBs/metastases:** NR; 37 with metastases in 42 LNBs **Stage of disease:** NR **Mean age:** 50 years; **Median age:** NR; **Range:** 15 to 52 years **Male:** 57 (53%) **Primary lesion site:** HN 6, 6%; trunk 43, 40%; arm 24, 22%; leg 34, 32%

	Breslow/Clark: median BT 2.0 mm (0.6 to 12.5 mm) **Clark level:** II 1, 1%; III 37, 35%; IV 55, 51%; V 9, 8%; undeterminable 5, 5% **Ulceration:** 32, 30%
Index tests	**US and US plus FNAC:** B-mode linear array **Machine:** Siemens Elegra (Erlangen, Germany) or a Kretz Voluson 730 Expert (GE Medical Systems, Zipf, Austria) **Scan coverage:** NR **Contrast:** N/A **FNAC:** US positive (suspicious) underwent FNAC 21- or 22-gauge needle (Figure 1), aspirated material air dried, methanol fixated and stained (May-Grunwald-Giemsa). FNAC+ underwent CLND **Threshold:** US alone suspicious - length-depth ratio < 2, conversion of a fatty hilum to a hypoechoic hilum, substantial cortical asymmetry or focal area of low-level echoes in the subcapsular sinus of the node, and diameter > 5 mm for LN of the neck. US + FNAC - US positive and metastases on FNAC # **Number observers:** NR **Qualification (experience):** NR (NR) **Diagnosis (single, consensus, etc.):** NR **Info provided during test interpretation:** clinical - NR; other tests - NR
Target condition and reference standard(s)	**Histology (SLNB; CLND)** **Histological detail (n, %):** CLND not described; SLNB H&E (minimum 6 levels); IHC (S100, HMB45). Metastases were classified as > 2 mm in diameter or < 2 mm, as 2 mm is the current spatial resolution of ultrasonography according to Rossi et al (107, 100%). **Histopathologist:** NR **FNAC (n, %):** N/A (22 but not as part of reference standard) **Follow-up (n, %):** NR (2/107; 2% (reported only for 2 positive on FNAC)) **FU schedule:** NR **FU duration:** NR **Reference blinding:** NR # **Target condition** **Data:** per pt **Definition:** nodal mets; **Prevalence:** 37/107 = 35%
Flow and timing	**Index to histology interval:** 1 to several days **Index to FU interval:** N/A **Exclusions:** n = 0
Comparative	
Notes	**Other result:** FU of 2 FNAC positive participants is reported but no further reference to any recurrences. A breakdown of micro- vs macro-metastases is also reported for those positive on histology. Of the 12 TPs on ultrasound, 7 (58%) were macro-metastases and 5 (42%) were micro-metastases; of the 25 FNs on US, 8 (32%) were macro-metastases and 17 (68%) micro-metastases The single patient who was TP on US & FNAC had macro-metastasis; of the 36 who were FN on US & FNAC, 14 (39%) were macro-metastases and 22 (61%) were micro-metastases

van Rijk 2006 (*Continued*)

Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Does the study report results for participants at the same point in the clinical pathway and who would be eligible for imaging in normal practice?	Yes		
Did the study report data on a per patient rather than per lesion basis?	Yes		
		Low	**Low**
DOMAIN 2: Index Test Ultrasound (pre-SLNB)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
Was the imaging test applied and interpreted in a clinically applicable manner?	Unclear		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes		
Was the test interpreted by an experienced examiner?	Unclear		
		Unclear	**Unclear**

van Rijk 2006 (*Continued*)

DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Were the reference standard results based on patient follow-up interpreted without knowledge of the original imaging test result?			
Does the study use the same definition of disease positive as the primary review question (i.e. any mets) OR is it possible to disaggregate or regroup data such that data matching the review question can be extracted?	Yes		
Was histology or cytology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Low	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

van Wissen 2016

Study characteristics	
Patient sampling	**Design:** non-comparative; retrospective **Country:** Netherlands **Data collection:** 2003 to 2013 **Inclusion criteria:** stage IIIB or IIIC MM with palpable groin metastases; selected for therapeutic combined groin dissection (CGD)
Patient characteristics and setting	**Presentation:** mixed (discussion states: "large proportion of our patients were initially treated for their primary tumour at other hospitals, and sometimes years prior to the current groin dissection") **Number patients:** 70 **Number primary lesions:** 70 **Number LNBs/metastases:** NR **Stage of disease:** only stage III B & C **Mean age:** NR; **Median age:** 58 years; **Range:** 24 to 83 years **Male:** 35 (50%) **Primary lesion site:** leg 58, 83%; trunk 6, 9%; arm 0, 0%; unknown 6, 9% **Breslow/Clark:** BT, mm: ≤ 1.00 6 (9%); ≤ 2.00 15 (21%); 2.01 to 4.00 15 (21%); > 4.00 12 (17%); missing/unknown 22 (31%) **Ulceration:** yes 11 (16%); missing/unknown 40 (57%) **Other:** extracapsular invasion 14 (19%)
Index tests	**PET-CT:** CT (U) **Machine:** Gemini II; Philips, Eindhoven, The Netherlands **Scan coverage:** WB; not further described **Contrast:** none **CT parameters:** Kv NR, 40 mAs, 2 to 5 MM **FDG:** 180 to 240 MBq **Breath hold:** standard acquisition protocols **CT used for:** attenuation correction; fused images **Reconstruction:** NR **Threshold:** FDG uptake (qualitative assessment); indeterminate on PET-CT considered negative by study authors but have been extracted as both test positive and test negative for this review # **Number observers:** 1 **Qualification (experience):** nuclear medicine (NR) **Diagnosis (single, consensus, etc.):** single **Info provided during test interpretation:** clinical - NR; other tests - NR
Target condition and reference standard(s)	**Histology (CGD)** **Histological detail (n, %):** no details (70, 100%). **Histopathologist:** originally different pathologists; reports reviewed by single expert pathologist for study purposes **FNAC (n, %):** N/A **Follow-up (n, %):** NR (not for ref purposes) **FU schedule:** NR **FU duration:** median 16 months (0 to 71 months) **Reference blinding:** NR # **Target condition**

	Data: per pt **Definition:** nodal (superficial groin mets only); **Prevalence:** 59/69 = 86% **Definition:** nodal (deep groin mets only); **Prevalence:** 24/67 = 36%
Flow and timing	**Index to histology interval:** NR **Index to FU interval:** NR **Exclusions:** n = 4; missing pathology - 1 excluded from superficial LN analysis and 3 from deep node analysis
Comparative	
Notes	**Other result:** 7/10 disease negative had diagnostic resection of a lymph node before lymph node dissection. PET-CT is likely to have shown inflammation after this resection rather than residual disease in the groin Also reports 30-day complications and DFS and OS according to pathology positive/negative iliac nodal status

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Does the study report results for participants at the same point in the clinical pathway and who would be eligible for imaging in normal practice?	No		
Did the study report data on a per patient rather than per lesion basis?	Yes		
		Low	**High**
DOMAIN 2: Index Test PET-CT			
Were the index test results interpreted without knowledge of the results of the reference stan-	Unclear		

dard?			
If a threshold was used, was it pre-specified?	Yes		
Was the imaging test applied and interpreted in a clinically applicable manner?	Yes		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes		
Was the test interpreted by an experienced examiner?	Yes		
		Unclear	**Low**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Were the reference standard results based on patient follow-up interpreted without knowledge of the original imaging test result?			
Does the study use the same definition of disease positive as the primary review question (i.e. any mets) OR is it possible to disaggregate or regroup data such that data matching the review question can be extracted?	Yes		
Was histology or cytology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Yes		
		Low	**Low**

van Wissen 2016 (*Continued*)

DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
		High	

Veit-Haibach 2009

Study characteristics	
Patient sampling	**Design:** within-person comparison; prospective **Country:** Germany **Data collection:** NR **Inclusion criteria:** any primary MM referred for PET-CT **Excluded if** insufficient FU
Patient characteristics and setting	**Presentation:** primary (any); any primary MM referred for PET-CT **Number patients:** 56 **Number primary lesions:** 56 **Number LNBs/metastases:** NR **Stage of disease:** presentation stage I or II 44, 79%; stage III or IV 12, 21% **Mean age:** 62 years; **Median age:** NR; **Range:** 23 to 86 years **Male:** 27 (48.2%) **Primary lesion site:** trunk 26, 46%; upper extremities 10, 18%; lower extremity 18, 32%; HN 2, 4% **Breslow/Clark:** NR **Ulceration:** NR **Other:** NR
Index tests	**CT:** CE; 2-slice **Machine:** Biograph Duo PET/CT System (Siemens Molecular Imaging, Hoffman Estates, IL); integrates a dual-slice CT scanner (Somatom Emotion, Siemens Medical Solutions, Forchheim, Germany) and a full-ring, BGO-based PET Tomograph (Siemens Molecular Imaging) **Scan coverage:** WB; no further detail, just states caudocranial direction **Contrast:** dual-phase injection of 140 mL of 300 mmol/mL iodinated contrast agent (90 mL at a rate of 3 mL/s, and 50 mL at a rate of 1.5 mL/s; dual-phase used to ensure fully diagnostic (portal venous phase) CT data in the abdomen) **CT parameters:** NR **Breath hold:** NR **Threshold:** nodal mets - lesion size and central necrosis for malignancy; fatty hilum and calcifications

	for benign. For size: short-axis diameter threshold of 1.5 cm for jugulodigastric and pre-carinal LNs and threshold of 1 cm for all other LNs of the neck, thorax, and abdomen. Distant mets - detection of soft tissue masses (or focal cutaneous thickening) with contrast enhancement # **PET-CT:** full-ring CT (CE; 2-slice) **Machine:** Biograph Duo PET/CT System (Siemens Molecular Imaging, Hoffman Estates, IL); integrates a dual-slice CT scanner (Somatom Emotion, Siemens Medical Solutions, Forchheim, Germany) and a full-ring, BGO-based PET tomograph (Siemens Molecular Imaging) **Scan coverage:** WB; no further detail, just states caudocranial direction **Contrast:** 140 mL of 300 mmol/mL iodinated contrast agent **CT parameters:** NR **FDG:** 330 to 350 MBq **Breath hold:** NR **CT used for:** attenuation correction **Reconstruction:** reconstructed iteratively (FORE-OSEM, 2 iterations, 8 subsets, 128×128 matrix with 5-mm gaussian smoothing) **Threshold:** nodal mets - increased glucose metabolism and independent of size. Diatant mets - qualitative + SUV; detection of soft tissue masses (or focal cutaneous thickening) with contrast enhancement in different body compartments and in conjunction with focally increased glucose metabolism above the surrounding tissue level on FDG PET/ CT; supported by SUVmax $\geq$ 1.5 for cutaneous lesions, $\geq$ 2.5 for other extrahepatic lesions, and $\geq$ 3.5 for intrahepatic lesions # **Number observers:** 2 **Qualification (experience):** radiologists and and nuclear medicine specialist for PET-CT (NR) **Diagnosis (single, consensus, etc.):** consensus of 2 **Info provided during test interpretation:** clinical - provided patient-specific clinical background (first diagnosis of melanoma, postsurgical resection status, location of resection site) but blinded to clinical exam and histopathology of primary tumour; other tests - blinded to other imaging procedures
Target condition and reference standard(s)	**Histology/FU** **Histological detail (n, %):** all patients with suspected metastases on imaging, histopathological evaluation of at least 1 metastatic site served as the standard of reference for both N-stage and M-stage during the clinical course. Total of 14 patients had SLNB within 4 weeks of the initial PET-CT procedure (unclear; 14 with SLNB, 25%). **Histopathologist:** NR **FNAC (n, %):** N/A (0) **Follow-up (n, %):** imaging, tumour markers, physical examination (56, 100%) **FU schedule:** NR **FU duration:** mean 780 days (range 102 to 1390 days); roughly equivalent to 25.6 months (3.3 to 45.7 months) **Reference blinding:** N/A # **Target condition** **Data:** per pt **Definition:** nodal; **Prevalence:** 13/56 = 23% **Definition:** distant; **Prevalence:** 12/56 = 21% (no breakdown by anatomical site) **Metastases:** 12 patients with nodal and/or distant mets reported as detected on initial staging; 4 patients with nodal mets (stage III) and 8 with distant (stage IV). PET-CT correctly classified 6/12 and CT correctly classified 3/12. A further 6 patients had metastases detected on follow-up for

	a total of 18 patients with any metastases Of the 8 FNs on PET-CT and 10 FNs on CT alone, 2 were micro-metastases identified by SLNB		
Flow and timing	**Index to histology interval:** 4 weeks for SLNB **Index to FU interval:** NR **Exclusions:** n = 0		
Comparative	(1) Blinded to other imaging procedures (2) Same scanner (3) All referred for PET-CT		
Notes			
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Does the study report results for participants at the same point in the clinical pathway and who would be eligible for imaging in normal practice?	Yes		
Did the study report data on a per patient rather than per lesion basis?	Yes		
		Low	**Low**
DOMAIN 2: Index Test CT			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		

Was the imaging test applied and interpreted in a clinically applicable manner?	No		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes		
Was the test interpreted by an experienced examiner?	Yes		
		Low	**High**
DOMAIN 2: Index Test PET-CT			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Was the imaging test applied and interpreted in a clinically applicable manner?	No		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes		
Was the test interpreted by an experienced examiner?	Yes		
		Low	**High**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		

Were the reference standard results based on patient follow-up interpreted without knowledge of the original imaging test result?	Unclear		
Does the study use the same definition of disease positive as the primary review question (i.e. any mets) OR is it possible to disaggregate or regroup data such that data matching the review question can be extracted?	No		
Was histology or cytology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Unclear	**High**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Unclear		
Did all patients receive the same reference standard?	No		
Were all patients included in the analysis?	Yes		
		High	
DOMAIN 5: Comparative			
1) was each index test result interpreted without knowledge of the results of other index tests or testing strategies?	Yes		
2) Was the interval between application of index tests	Yes		
3) Was it predetermined that all index tests should be given to all study participants?	Yes		

Veit-Haibach 2009 (*Continued*)

		Low	

Voit 2014

Study characteristics	
Patient sampling	**Design:** within-person comparison (US vs US + FNAC); unclear ('prospective database') **Country:** Germany **Data collection:** July 2001 to Nov 2010 **Inclusion criteria:** SLNB candidates; BT > 1 mm thickness or Clark IV/V, ulcerated, and/or regressed
Patient characteristics and setting	**Presentation:** primary (pre-SLNB) **Number patients:** 1000 **Number primary lesions:** 1000 **Number LNBs/metastases:** NR **Stage of disease:** NR **Mean age:** 59 years; **Median age:** 62 years; **Range:** 15 to 94 years **Male:** 567 (57%) **Primary lesion site:** NR **Breslow/Clark:** mean BT 2.58 mm; median BT 1.57 mm. BT < 1 mm 288 29%; 1 to 2 mm 308 31%; 2 to 4mm 231 23%; > 4 mm 173 17% **Clark level:** II 32, 3%; III 341, 34%; IV 554, 56%; V 54, 6%, unknown 13, 1% **Ulceration:** 242, 24% **Other:** regression absent 633, 63%; present 300, 30%, unknown 67, 7%
Index tests	**US and US + FNAC**. B mode & Doppler **Machine:** NR **Scan coverage:** LNBs; patients first underwent a lymphoscintigraphy, which assists the ultrasonographist to better focus their examination **Contrast:** N/A **FNAC:** US positive underwent FNAC with 26 gauge needle; smears considered adequate if around 100 cells present. Cyto results reported to the surgeon, who decided whether to proceed with SLNB or direct to LND **Threshold:** malignant on US if total loss of central echoes (LCE) or LN enlarged and balloon shaped (BS); suspicious if peripheral perfusion present or central echo wandering towards the rim. NR for FNAC # **Number observers:** 3 **Qualification (experience):** ultrasonographist (mixed; 1 expert and 2 trained but less expert) **Diagnosis (single, consensus, etc.):** unclear; likely single **Info provided during test interpretation:** clinical - NR; other tests - LS result available
Target condition and reference standard(s)	**Histology (SLNB or CLND)** **Histological detail (n, %):** H&E (serial); IHC (S100, HMB45); microanatomical location of metastases and SN tumour burden were assessed according to Dewar and Rotterdam criteria, respectively (1). **Histopathologist:** NR **FNAC (n, %):** not as reference

	Follow-up (n, %): no details (1000; 100%) **FU schedule:** NR **FU duration:** mean 56 m; median 53 m; range 1 to 132 m **Reference blinding:** NR # **Target condition** **Data:** per pt **Definition:** nodal mets; **Prevalence:** 208/1000 = 21%
Flow and timing	**Index to histology interval:** preoperative **Index to FU interval:** NR **Exclusions:** n = 0
Comparative	
Notes	**Other result:** 332 patients underwent FNAC; however authors report as 342 (including 10 US malignant as FNAC positive even though no FNAC was undertaken) There were 198 patients (20%) with recurrences and 81 melanoma-related deaths (8%) during this follow-up (not broken down by index test)

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Does the study report results for participants at the same point in the clinical pathway and who would be eligible for imaging in normal practice?	Yes		
Did the study report data on a per patient rather than per lesion basis?	Yes		
		Low	**Low**
DOMAIN 2: Index Test Ultrasound (pre-SLNB)			

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Was the imaging test applied and interpreted in a clinically applicable manner?	Unclear		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes		
Was the test interpreted by an experienced examiner?	Yes		
		Low	**Unclear**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Were the reference standard results based on patient follow-up interpreted without knowledge of the original imaging test result?			
Does the study use the same definition of disease positive as the primary review question (i.e. any mets) OR is it possible to disaggregate or regroup data such that data matching the review question can be extracted?	Yes		
Was histology or cytology interpretation carried out by an experienced histopathologist or	Unclear		

Voit 2014 (*Continued*)

by a dermatopathologist?			
		Low	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
		Low	

Wagner 2012

Study characteristics	
Patient sampling	**Design:** non-comparative; retrospective (Prospective database NR) **Country:** France **Data collection:** Sep 2003 - Sep 2006 **Inclusion criteria:** SLNB candidates; BT ≥ 4 mm or BT > 1 mm with ulceration
Patient characteristics and setting	**Presentation:** primary (pre-SLNB) **Number patients:** 48 **Number primary lesions:** 48 **Number LNBs/Metastases:** NR **Stage of disease:** stage IIA 8, 16.7%; stage IIB 19, 39.6%; stage IIC 19, 39.6%; stage NR 2, 4.2% (both BT > 4 mm) **Mean age:** NR; **Median age:** NR; **Range:** NR **Male:** 25 (52%) **Primary lesion site:** NR **Breslow/Clark:** mean BT 7.6 mm (±4.5) (range 1.1 to 18 mm) **Ulceration:** 19, 39.6%; NR 2, 4.1% **Other:** NR
Index tests	**PET-CT**. 2D; CT (NR) **Machine:** Discovery ST; General Electric Healthcare, Waukesha, WI, USA) **Scan coverage:** WB; not further described **Contrast:** NR **CT parameters:** 140 kV, 200 mA, 7.5 mm **FDG:** 370 MBq (Glucotep Cyclopharma, St Beauzire, France) **Breath hold:** normal breathing; "remain rested, to refrain from speaking, and to minimize swallowing" **CT used for:** attenuation correction and anatomical correlation

	Reconstruction: iterative OSEM (Ordered Subset Expectation Maximisation) algorithm (3 iterations; 10 subsets) **Threshold:** abnormally increased FDG uptake in a lymph node in the drainage territory of the melanoma # **Number observers:** NR **Qualification (experience):** nuclear medicine specialist (high) **Diagnosis (single, consensus, etc.):** unclear; 'at least one' **Info provided during test interpretation:** clinical - aware of all clinical findings; other tests - NR
Target condition and reference standard(s)	**Histology (SLNB, CLND)** **Histological detail (n, %):** NR; describes tumoural deposit < 200 Um (n = 4), > 200 Um (n = 5), and perinodal tumoural deposit (n = 1) (43, 89.6%; 2 CLND only, 1 SLNB + CLND, 40 SLNB only). **Histopathologist:** NR **FNAC (n, %):** N/A **Follow-up (n, %):** FU reported but only for possible distant mets and not nodal **FU schedule:** NR **FU duration:** minimum 12 months **Reference blinding:** NR # **Target condition** **Data:** per pt **Definition:** nodal mets; **Prevalence:** 14/43 = 33%
Flow and timing	**Index to histology interval:** before SLNB **Index to FU interval:** NR **Exclusions:** n = 5; SLNB not performed for technical reasons
Comparative	
Notes	**Other result:** result presented for detection of distant mets but only 1 D+ so does not meet sample size restrictions (2×2 0, 6, 1, 41)

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		

Does the study report results for participants at the same point in the clinical pathway and who would be eligible for imaging in normal practice?	Yes		
Did the study report data on a per patient rather than per lesion basis?	Yes		
		Low	**Low**
DOMAIN 2: Index Test PET-CT			
Were the index test results interpreted without knowledge of the results of the reference standard?	Unclear		
If a threshold was used, was it pre-specified?	Yes		
Was the imaging test applied and interpreted in a clinically applicable manner?	Yes		
Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Unclear		
Was the test interpreted by an experienced examiner?	Yes		
		Unclear	**Unclear**
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
Were the reference standard results based on patient follow-up interpreted without knowledge			

of the original imaging test result?			
Does the study use the same definition of disease positive as the primary review question (i.e. any mets) OR is it possible to disaggregate or regroup data such that data matching the review question can be extracted?	Yes		
Was histology or cytology interpretation carried out by an experienced histopathologist or by a dermatopathologist?	Unclear		
		Low	**Unclear**
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	No		
		High	

2D: two-dimensional; 3D: three-dimensional; AJCC: American Joint Committee on Cancer; AWOSEM: attenuation weighted ordered subsets expectation maximization: BT: Breslow thickness; CE: contrast enhanced; CLND: completion lymphadenectomy; CMM: cutaneous malignant melanoma; CT: computed tomography; DFS: disease-free survival; DW: diffusion weighted; EDV: end-diastolic volume; EORTC: European Organisation for Research and Treatment of Cancer; FDG: fluorodeoxyglucose; FFE: fast field echo; FLAIR: fluid attenuated inversion recovery; FN: false negative; FNAC: fine needle aspiration cytology; FORE: Fourier rebinned; FP: false positive; FU: follow-up; FWHM: full-width half maximum; H&N: head and neck; HD: high definition; HN: head and neck; IHC: immunohistochemistry; ITM: in-transit metastases; LN: lymph node; LNB: lymph node biopsy; LND: lymphadenectomy; MM: malignant melanoma; MRI: magnetic resonance imaging; N/A: not applicable; NR: not reported; OS: overall survival; OSEM: ordered subsets expectation-maximization; PD: Power Doppler; PET-CT: positron emission tomography-computed tomography; PI: pulse index; PSV: peak systolic volume; RF: risk factors; SLNB: sentinel lymph node biopsy; SPECT: single-photon emission computed tomography; SSM: superficial spreading melanoma; SUVmax: maximum standardised uptake volume; T2STIR: T2-weighted short tau inversion recovery; TNM: tumour node metastasis; TP: true positive; UICC: Union for International Cancer Control; US: ultrasound; WB: whole body.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abbott 2009	Conference abstract
Abdi 1988	Inadequate reference standard
Abella-Columna 2002	Not a primary study
Acland 2000	Wrong index test
Acland 2001	Wrong index test
Agarwal 2008	Not a primary study
Ahmed 2015	Conference abstract
Akcali 2007	Inadequate reference standard
Aldridge 2010	Conference abstract
Aloia 2006	Inadequate sample size; wrong index test; inadequate reference standard
Alvarado 2007	Not a primary study
Angeles 2014	Conference abstract
Ardizzoni 1987	Inadequate sample size; wrong index test
Arrangoiz 2011	Conference abstract
Ashour 2016	Conference abstract
Bafounta 2004	Systematic review
Baker 2011	Conference abstract
Baker 2012	Conference abstract
Baker 2014	Multiple scans reported per participant
Balagula 2012	Wrong index test
Ban 2013	Conference abstract
Barsky 2014	Inadequate reference standard
Bastiaannet 2006	Not test accuracy

(*Continued*)

Bastiaannet 2008	Conference abstract
Bastiaannet 2008a	Conference abstract
Bastiaannet 2008b	Conference abstract
Bastiaannet 2009a	Conference abstract
Bastiaannet 2010	Conference abstract
Bastiaannet 2012	Duplicate or related publication
Beasley 2010	Conference abstract
Beasley 2012	Wrong study population
Beitollahi 2013	Conference abstract
Belhocine 2002	Inadequate sample size; wrong index test
Ben Lakhdar 2011	Conference abstract
Bernabo 2015	Conference abstract; wrong index test
Beyeler 2006	Wrong study population
Bhatia 2012	Wrong study population
Bier 2016	Inadequate reference standard
Biersack 1987	Wrong target condition; wrong index test
Bikhchandani 2014	Wrong index test
Binder 1997	Multiple scans reported per participant
Binns 2012	Conference abstract
Blend 1992	Wrong index test
Blessing 1995	Wrong index test
Blum 2000	Multiple scans reported per participant; exclusion on 2×2
Blum 2006	Wrong study population; wrong target condition
Bode 2011	Conference abstract; wrong index test

(*Continued*)

Bohelay 2014	Conference abstract
Bohuslavizki 2000	Wrong index test; inadequate reference standard
Boni 1995	Wrong index test; inadequate reference standard
Boni 1996	Not a primary study
Boni 1996a	Inadequate sample size
Borrego 2006	Wrong index test
Boy 2011	Conference abstract; wrong index test
Brady 2006	Wrong study population
Breitenbauch 2015	Inadequate sample size; inadequate reference standard
Brenner 1999	Wrong index test
Bronstein 2012	Wrong study population
Brountzos 2003	Multiple scans reported per participant
Buckle 2016	Wrong target condition; wrong index test
Bude 2004	Not a primary study
Buerke 2011	Wrong target population; inadequate reference standard
Buzaid 1993	Inadequate reference standard
Buzaid 1995	Inadequate reference standard; exclusion on 2×2
Bydder 1981	Inadequate reference standard
Cachin 2012	Conference abstract
Catalano 2010	Not a primary study
Catalano 2010a	Not a primary study
Catalano 2010b	Not a primary study
Catalano 2011	Systematic review
Catalano 2015	Wrong index test

(*Continued*)

Chai 2010	Conference abstract
Cho 2005	Inadequate reference standard
Chomyn 1992	Inadequate reference standard
Clark 2006	Wrong index test
Clement 1998	Wrong target condition
Clement 2001	Wrong target condition
Clemente-Ruiz 2012	Wrong target condition; wrong index test
Cobben 2003	Wrong index test
Connell 2003	Not a primary study
Constantinidou 2008	Wrong index test
Cordova 2006	Wrong index test
Cousen 2014	Inadequate reference standard
Crippa 2000	Wrong index test
Curtis 1982	Inadequate sample size; inadequate reference standard
Dalle 2006	Not test accuracy; wrong study population
Damian 1996	Wrong index test
Danielsen 2013	Systematic review
Davidson 2011	Conference abstract
Davis 1991	Inadequate sample size
De Giorgi 2010	Wrong index test
De Rosa 2010	Not test accuracy; inadequate reference standard
DeRose 2010	Conference abstract
Dietlein 1999	Wrong target condition; wrong index test
Diodato 2015	Conference abstract

(*Continued*)

Doiron 1981	Wrong index test; inadequate reference standard
Dresel 2003	Wrong study population
Drzezga 2012	Inadequate sample size
Eigtved 2000	Wrong index test
El-Maraghi 2008	Not a primary study; systematic review
Emmett 2012	Not a primary study
Facius 2002	Wrong index test
Fakhry 2009	Inadequate sample size; wrong index test
Falk 2007	Multiple scans reported per participant
Faries 2010	Wrong index test
Ferrandiz 2016	Not test accuracy; inadequate reference standard
Fink 2004	Wrong index test
Finkelstein 2004	Wrong index test
Fletcher 2008	Not a primary study; systematic review
Fogarty 2006	Inadequate reference standard
Fohne 2015	Conference abstract
Friedman 2004	Not a primary study; systematic review
Fuster 2003	Conference abstract
Fuster 2004	Wrong study population
Garbe 2003	Not test accuracy
Gellen 2015	Multiple scans reported per participant
Ghanem 2005	Inadequate reference standard
Giles 2014	Conference abstract; wrong index test
Ginaldi 1981	Inadequate reference standard

(*Continued*)

Giovagnorio 2003	Wrong target condition
Gold 2007	Wrong target condition; wrong index test
Grigolato 2011	Conference abstract
Gritters 1993	Wrong index test
Gulec 2003	Inadequate reference standard
Gupta 2012	Conference abstract; inadequate sample size
Haddad 2013	Conference abstract
Haddad 2013a	Inadequate sample size
Hall 2013	Not a primary study; systematic review
Harlan 2010	Inadequate sample size
Harris 2005	Wrong index test
Havenga 2003	Wrong index test
Heaston 1983	Inadequate reference standard
Herceg 2012	Conference abstract
Herceg 2013	Conference abstract
Herceg 2014	Conference abstract
Herceg 2015	Conference abstract
Heusner 2011	Inadequate sample size
Hinz 2010	Inadequate sample size
Ho Shon 2008	Not a primary study
Hofmann 2002	Multiple scans reported per participant; inadequate reference standard
Hofmann 2011	Wrong index test
Hoh 1993	Wrong target condition

(*Continued*)

Holder 1998	Wrong index test; inadequate reference standard
Holtas 1981	Inadequate reference standard
Horn 2006	Inadequate sample size; wrong index test; inadequate reference standard
Horn 2010	Wrong index test
Hu 2009	Inadequate reference standard
Hughes 2013	Not test accuracy
Hunyadi 2002	Wrong index test; inadequate reference standard
Iscoe 1987	Inadequate sample size
Ismaheel 2016	Inadequate reference standard
Jackson 2014	Not test accuracy
Jadvar 2000	Wrong index test; inadequate reference standard
Jenicke 2001	Wrong index test; inadequate reference standard
Jennings 2009	Not a primary study
Jimenez-Requena 2010	Not a primary study; systematic review
Johnson 1997	Inadequate reference standard; exclusion on 2×2
Jones 2014	Conference abstract
Kader 2016	Wrong study population; wrong index test
Kelly 2013	Not a primary study
Knappe 2000	Wrong study population
Koskivuo 2007	Wrong index test
Krug 2000	Wrong index test; inadequate reference standard
Krug 2008	Systematic review
Krug 2009	Conference abstract; not a primary study

(*Continued*)

Krug 2010	Not a primary study
Kuvshinoff 1997	Inadequate reference standard
Lanka 2005	Wrong study population
Laurent 2010	Duplicate or related publication (see Dellestable 2011)
Leon-Ferre 2015	Conference abstract
Lewin 2015	Conference abstract
Liszkay 2010	Conference abstract
Loffler 2003	Inadequate reference standard
Longo 2003	Wrong index test; exclusion on 2×2
Loose 1990	Multiple scans reported per participant
Macfarlane 1998	Wrong index test
Machet 2005	Multiple scans reported per participant
Majchrzak 2013	Inadequate sample size
Mayerhoefer 2012	Wrong study population
McIvor 2014	Wrong index test
McNamara 2005	Conference abstract; wrong index test
Medina-Quiroz 2010	Conference abstract
Mendenhall 2012	Not a primary study
Mercier 2001	Wrong index test
Meyers 2009	Inadequate reference standard
Meyers 2009a	Wrong index test
Mijnhout 2001	Systematic review
Mijnhout 2002	Wrong index test
Miner 2011	Conference abstract

(*Continued*)

Minn 2011	Not a primary study
Miranda 2004	Inadequate sample size
Miranda 2006	Not a primary study
Mocellin 2007	Not a primary study; systematic review
Moehrle 1999	Wrong study population
Morton 2007	Not a primary study
Mosavi 2013	Inadequate reference standard
Mottaghy 2007	Exclusion on 2×2 data
Mozzillo 2013	Wrong study population; wrong index test
Mruck 1999	Wrong index test
Muller 2006	Not a primary study
Muller-Horvat 2006	Wrong study population
Nazarian 1996	Inadequate reference standard
Nazarian 1998	Wrong study population
Niebling 2013a	Conference abstract
Niebling 2013b	Wrong index test; duplicate or related publication
Niederkohr 2007	Inadequate reference standard
Novikov 2012	Wrong index test
Oehr 1999	Wrong index test
Ogata 2014	Inadequate sample size
Omlor 1996	Multiple scans reported per participant
Orfaniotis 2012	Multiple scans reported per participant; inadequate reference standard
Ortega-Candil 2016	Not test accuracy; exclusion on 2×2

(*Continued*)

Padovano 2013	Conference abstract
Panagiotou 2001	Wrong index test
Pandalai 2011	Inadequate reference standard
Paquet 2000	Wrong index test
Pecegueiro 2005	Wrong index test; inadequate reference standard
Pellacani 2006	Not test accuracy
Peric 2011	Inadequate reference standard
Petersen 2016	Systematic review
Pleiss 2007	Wrong index test; inadequate reference standard
Poduje 2012	Inadequate sample size
Poyraz 2012	Inadequate reference standard
Prakoso 2007	Wrong index test
Prakoso 2011	Inadequate reference standard
Prichard 2002	Systematic review
Punjabi 2006	Not a primary study
Querellou 2010	Multiple scans reported per participant
Querellou 2011	Not a primary study
Ramirez 2015	Conference abstract
Renna 2015	Conference abstract
Rep 2011	Conference abstract; wrong index test
Rinne 1998	Wrong index test
Roarke 2008	Inadequate sample size
Roh 2008	Wrong study population; wrong index test
Rossi 1997	Wrong target condition; inadequate sample size

(*Continued*)

Rossi 1999	Conference abstract
Rossi 2000	Duplicate or related publication
Rossi 2003	Exclusion on 2×2 data
Rossi 2008	Not a primary study
Rudolph 2010	Conference abstract
Sadigh 2014	Systematic review
Saiag 2005	Multiple scans reported per participant
Saiag 2010	Conference abstract
Samimi 2010	Wrong study population; wrong target condition
Samples 2012	Conference abstract
Sanli 2010	Conference abstract
Santha 2011	Conference abstract
Sarandi 2008	Not a primary study
Sawyer 2009	Multiple scans reported per participant
Schafer-Hesterberg 2007	Not a primary study
Schafer-Hesterberg 2008	Not a primary study
Schauwecker 2003	Wrong index test
Scheier 2015	Conference abstract
Scheier 2016	Inadequate reference standard
Schmid-Wendtner 2002	Inadequate reference standard
Schmid-Wendtner 2003	Multiple scans reported per participant
Schmid-Wendtner 2004	Inadequate reference standard
Schule 2016	Inadequate reference standard
Schwimmer 2000	Systematic review

(*Continued*)

Sergieva 2012	Conference abstract
Serra-Arbeloa 2015	Conference abstract; systematic review
Seshadri 2006	Inadequate sample size; wrong index test
Shah 2015	Conference abstract
Shintani 2008	Inadequate sample size
Sigmund 1985	Wrong study population
Sijan 2010	Wrong study population
Singnurkar 2016	Inadequate reference standard
Smith 2011	Conference abstract
Sofue 2012	Wrong study population
Soler 1997	Wrong index test
Solivetti 2006	Wrong target condition; inadequate reference standard
Solivetti 2012	Not test accuracy
Solivetti 2014	Wrong study population; wrong target condition
Solomon 2004	Wrong study population; wrong target condition; wrong index test
Son 2016	Inadequate sample size
Srivastava 2012	Wrong index test
Starritt 2005	Inadequate sample size
Stas 2002	Wrong index test
Stecco 2016	Wrong study population
Steinert 1998	Wrong index test; inadequate reference standard
Stoffels 2012	Exclusion on 2×2 data
Stoffels 2014	Wrong index test; inadequate reference standard
Stoffels 2016	Conference abstract; wrong target condition

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Stretch 2005	Wrong index test
Stucker 2002	Wrong study population; wrong index test
Subesinghe 2012	Conference abstract
Subesinghe 2013	Wrong study population; multiple scans reported per participant
Supriya 2014	Wrong study population
Swetter 2002	Multiple scans reported per participant
Tejera-Vaquerizo 2007	Wrong index test
Testori 2005	Exclusion on 2×2 data
Thompson 2002	Not a primary study
Thompson 2011	Conference abstract
Tomaszewski 2014	Wrong study population
Tregnaghi 1997	Multiple scans reported per participant
Tyler 2000	Wrong index test
Ulrich 2015	Conference abstract
Uren 1999	Inadequate reference standard
Valdes 2011	Wrong index test
Valk 1996	Not a primary study
Van Akkooi 2012	Conference abstract
Van Akkooi 2013	Conference abstract
Van Akkooi 2014	Conference abstract
Van Akkooi 2015	Conference abstract
Van den Broucke 2010	Conference abstract
Van der Ploeg 2007	Wrong index test
Van der Ploeg 2009a	Wrong index test

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Van der Ploeg 2009b	Wrong index test
Van der Ploeg 2011	Wrong study population
Vereecken 2005	Wrong index test
Vidal-Sicart 2010	Conference abstract
Voit 1999	Wrong index test; multiple scans reported per participant
Voit 2000	Wrong index test
Voit 2001	Wrong index test
Voit 2005	Conference abstract
Voit 2006	Conference abstract; duplicate or related publication
Voit 2009a	Conference abstract; duplicate or related publication
Voit 2009b	Conference abstract (overlaps Voit 2014)
Voit 2009c	Conference abstract
Voit 2010a	Not a primary study
Voit 2010b	Not a primary study
Voit 2010c	Duplicate or related publication
Voit 2010d	Conference abstract; duplicate or related publication
Voit 2011a	Conference abstract
Voit 2011b	Wrong index test
Voit 2011c	Conference abstract
Voit 2013	Conference abstract
Voit 2016	Wrong index test; duplicate or related publication (overlaps Voit 2014)
Von Schulthess 1998	Wrong index test
Wagner 1997	Wrong index test
Wagner 1999	Wrong index test

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Wagner 2001	Wrong index test
Wagner 2005	Wrong index test
Wagner 2009a	Conference abstract
Wagner 2009b	Conference abstract
Wagner 2011	Wrong index test
Wasif 2013	Conference abstract
Webb 2012	Conference abstract
Weisinger 1998	Conference abstract
Weiss 1995	Wrong index test; not test accuracy
Windorbska 2007	Inadequate reference standard
Winkler 2013	Wrong study population
Wong 2011	Conference abstract
Xing 2010	Conference abstract
Xing 2011	Systematic review
Yancovitz 2007	Inadequate reference standard
Yang 2003	Inadequate reference standard
Zender 2014	Wrong index test
Zimmermann 2000	Wrong index test
Zukauskaite 2013	Inadequate reference standard

DATA

Presented below are all the data for all of the tests entered into the review.

Tests. Data tables by test

Test	No. of studies	No. of participants
1 Pre-SLNB US vs Histology - Nodal mets - per patient	11	2604
2 Pre-SLNB US (stringent US criteria) vs Histology - Nodal mets - per patient	1	132
3 Pre-SLNB US-FNAC - Nodal mets - per patient	3	1164
4 Pre-SLNB PET-CT vs Histology - Nodal mets - all SLNB - per patient	4	170
5 Pre-SLNB PET-CT vs Histology - Nodal mets - high risk - per patient	3	75
6 Pre-SLNB PET-CT vs Histology - Nodal mets - head and neck only - per patient	1	20
7 Pre-SLNB PET-CT vs Histology/FU - Nodal mets - high risk - per patient	2	76
8 Pre-SLNB PET-CT vs Histology/FU - Nodal mets - head and neck only - per patient	1	22
9 Any metastasis - PET-CT - PRIMARY - Any stage (per pt)	1	37
10 Any metastasis - PET-CT - PRIMARY - BT > 4 mm (per pt)	2	81
11 Any metastasis - CT - RE-STAGING - Any stage (per pt)	1	106
12 Any metastasis - PET-CT - RE-STAGING - Any stage (per pt)	2	153
13 Any metastasis - PET-CT - RE-STAGING - Stage IIIb or less (per pt)	1	76
14 Any metastasis - PET-CT - RE-STAGING - Stage IIIc to IV (per pt)	1	30

15 Any metastasis - CT- MIXED - All data (per pt)	1	250
16 Any metastasis - PET-CT - MIXED - All data (per pt)	6	591
17 Any metastasis - PET-CT (plus CT) - Mixed - Any stage (per pt)	1	124
18 Any metastasis - PET-CT - RE-STAGING - Any stage (per lesion)	1	139
19 Any metastasis - CT- MIXED - All data (per lesion)	5	1770
20 Any metastasis (incl brain) - CT (U) - MIXED (per lesion)	1	232
21 Any metastasis (incl brain) - CT (CE) - MIXED (per lesion)	1	209
22 Any metastasis - MRI - MIXED - All data (per lesion)	4	1556
23 Any metastasis (excl brain) - MRI (DW + VIBE) - MIXED (per lesion)	1	195
24 Any metastasis (incl brain) - MRI (DW) - MIXED (per lesion)	1	218
25 Any metastasis (incl brain) - MRI (DW + VIBE) - MIXED (per lesion)	1	218
26 Any metastasis (incl brain) - MRI plus CT - MIXED (per lesion)	1	116
27 Any metastasis - PET-CT - MIXED - All data (per lesion)	5	1138
28 Any metastasis (incl brain) - PET-CT (U) - MIXED (per lesion)	1	232
29 Any metastasis (direct test comparisons) - CT - Mixed - Stage III/IV (per lesion)	3	1430
30 Any metastasis (direct test comparisons) - MRI - Mixed - Stage III/IV (per lesion)	3	1439
31 Any metastasis (direct test comparisons) - PET-CT - Mixed - Stage III/IV (per lesion)	2	611
32 Nodal metastasis - US - PRIMARY (per pt)	2	317
33 Nodal metastasis - CT - PRIMARY (per pt)	1	56
34 Nodal metastasis - PET-CT - PRIMARY (per pt)	1	56

35 Nodal metastasis - US - RE-STAGING (per pt)	1	460
36 Nodal metastasis - US plus US (CE) - RE-STAGING (per pt)	1	460
37 Nodal metastasis - US - MIXED (per pt)	1	79
38 Nodal metastasis - CT - MIXED (per pt)	2	276
39 Nodal metastasis (superficial groin) - PET-CT (indeterminate test positive) - MIXED (per pt)	1	69
40 Nodal metastasis (superficial groin) - PET-CT (indeterminate test negative) - MIXED (per pt)	1	69
41 Nodal metastasis (deep groin) - PET-CT (indeterminate test positive) - MIXED (per pt)	1	67
42 Nodal metastasis (deep groin) - PET-CT (indeterminate test negative) - MIXED (per pt)	1	67
43 Nodal metastasis - PET-CT - MIXED (per pt)	1	250
44 Nodal metastasis - CT - MIXED - All data (per lesion)	4	629
45 Nodal metastasis - MRI - MIXED - All data (per lesion)	4	630
46 Nodal metastasis - MRI (DW + VIBE) - MIXED (per lesion)	1	53
47 Nodal metastasis - PET-CT - MIXED - All data (per lesion)	4	288
48 Superficial nodal metastasis - US - Mixed - stage IV (per LNB)	1	33
49 Superficial nodal metastasis - CT - Mixed - stage IV (per LNB)	1	33
50 Superficial nodal metastasis - MRI - Mixed - stage IV (per LNB)	1	33
51 Superficial nodal metastasis - MRI (DW + VIBE) - Mixed - Stage IV (per lesion)	1	33
52 Superficial nodal metastasis - PET-CT - Mixed - stage IV (per LNB)	1	33
53 Distant metastasis - CT - PRIMARY (per pt)	1	56
54 Distant metastasis - PET-CT - PRIMARY (per pt)	2	112

55 Distant metastasis - CT - MIXED - All data (per pt)	2	501
56 Distant metastasis - PET-CT - MIXED - All data (per pt)	1	250
57 Distant metastasis - CT - Mixed - All data (per lesion)	4	920
58 Distant metastasis - MRI - Mixed - All data (per lesion)	4	926
59 Distant metastasis - PET-CT - Mixed - All data (per lesion)	4	618
60 Distant metastasis (excl brain) - MRI (DW + VIBE) - Mixed - stage III/IV (per lesion)	1	142
61 Distant metastasis (incl brain) - MRI (DW) - Mixed - stage III/IV (per lesion)	1	165
62 Distant metastasis (incl brain) - MRI (DW + VIBE) - Mixed - stage III/IV (per lesion)	1	165
63 Bone metastasis - CT- MIXED - All data (per lesion)	3	97
64 Bone metastasis - MRI - MIXED - All data (per lesion)	3	99
65 Bone metastasis - MRI (DW + VIBE) - MIXED - All data (per lesion)	1	35
66 Bone metastasis - PET-CT - MIXED - All data (per lesion)	4	133
67 Liver metastasis - CT- MIXED - All data (per lesion)	4	150
68 Liver metastasis - MRI - MIXED - All data (per lesion)	4	155
69 Liver metastasis - MRI (DW + VIBE) - Mixed - stage III/IV (per lesion)	1	27
70 Liver metastasis - PET-CT - MIXED - All data (per lesion)	4	94
71 Lung metastasis - CT - MIXED - All data (per lesion)	4	325
72 Lung metastasis - MRI - MIXED - All data (per lesion)	4	325
73 Lung metastasis - MRI (DW + VIBE) - Mixed - stage III/IV (per lesion)	1	45
74 Lung metastasis - PET-CT - MIXED - All data (per lesion)	4	155
75 Soft tissue metastasis - PET-CT - MIXED (per lesion)	1	25
76 Local/subcutaneous metastasis - CT - MIXED (per lesion)	3	139

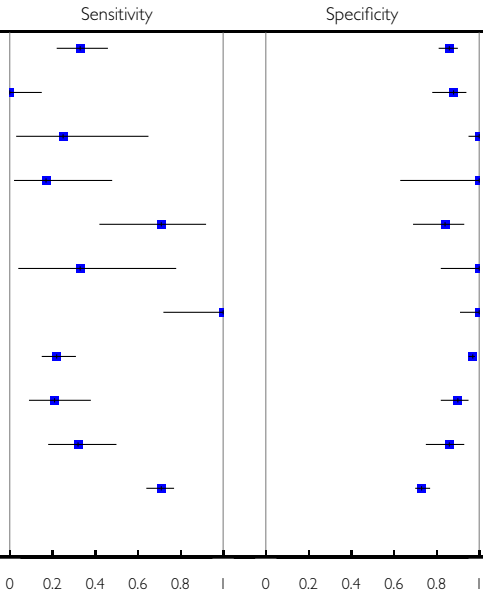
77 Local/subcutaneous metastasis - MRI - MIXED (per lesion)	3	148
78 Local/subcutaneous metastasis - MRI (DW + VIBE) - MIXED (per lesion)	1	22
79 Local/subcutaneous metastasis - PET-CT - MIXED (per lesion)	3	102
80 Brain metastasis - CT- MIXED - All data (per lesion)	1	20
81 Brain metastasis - MRI (DW) - MIXED - All data (per lesion)	1	20
82 Brain metastasis - MRI (DW + VIBE) - MIXED - All data (per lesion)	1	20
83 Brain metastasis - PET-CT - MIXED - All data (per lesion)	1	9
93 'Other' metastasis - CT - Mixed - Any stage (per lesion)	1	26
94 'Other' metastasis - MRI - Mixed - Any stage (per lesion)	1	21
95 'Other' metastasis - PET-CT - Mixed - Any stage (per lesion)	1	26
96 'Other' metastasis - CT - Mixed - stage III/IV (per lesion)	2	160
97 'Other' metastasis - MRI - Mixed - stage III/IV (per lesion)	2	160
98 'Other' metastasis - PET-CT - Mixed - stage III/IV (per lesion)	1	25

Test 1. Pre-SLNB US vs Histology - Nodal mets - per patient.

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 1 Pre-SLNB US vs Histology - Nodal mets - per patient

Study	TP	FP	FN	TN	Sensitivity	Specificity
Chai 2012	21	35	43	218	0.33 [0.22, 0.46]	0.86 [0.81, 0.90]
Hafner 2004	0	9	23	65	0.0 [0.0, 0.15]	0.88 [0.78, 0.94]
Hinz 2011	2	0	6	73	0.25 [0.03, 0.65]	1.00 [0.95, 1.00]
Hinz 2013	2	0	10	8	0.17 [0.02, 0.48]	1.00 [0.63, 1.00]
Hocevar 2004	10	7	4	36	0.71 [0.42, 0.92]	0.84 [0.69, 0.93]
Kunte 2009	2	0	4	19	0.33 [0.04, 0.78]	1.00 [0.82, 1.00]
Radzhabova 2009	11	0	0	41	1.00 [0.72, 1.00]	1.00 [0.91, 1.00]
Sanki 2009	28	19	97	572	0.22 [0.15, 0.31]	0.97 [0.95, 0.98]
Sibon 2007	7	10	27	88	0.21 [0.09, 0.38]	0.90 [0.82, 0.95]
van Rijk 2006	12	10	25	60	0.32 [0.18, 0.50]	0.86 [0.75, 0.93]
Voit 2014	148	210	60	582	0.71 [0.64, 0.77]	0.73 [0.70, 0.77]

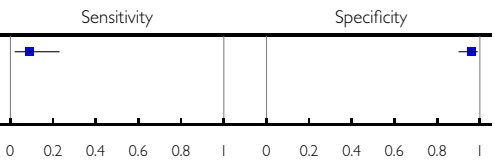


Test 2. Pre-SLNB US (stringent US criteria) vs Histology - Nodal mets - per patient.

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 2 Pre-SLNB US (stringent US criteria) vs Histology - Nodal mets - per patient

Study	TP	FP	FN	TN	Sensitivity	Specificity
Sibon 2007	3	4	32	93	0.09 [0.02, 0.23]	0.96 [0.90, 0.99]

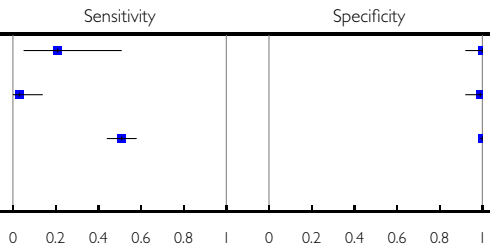


Test 3. Pre-SLNB US-FNAC - Nodal mets - per patient.

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 3 Pre-SLNB US-FNAC - Nodal mets - per patient

Study	TP	FP	FN	TN	Sensitivity	Specificity
Hocevar 2004	3	0	11	43	0.21 [0.05, 0.51]	1.00 [0.92, 1.00]
van Rijk 2006	1	1	36	69	0.03 [0.00, 0.14]	0.99 [0.92, 1.00]
Voit 2014	107	1	101	791	0.51 [0.44, 0.58]	1.00 [0.99, 1.00]

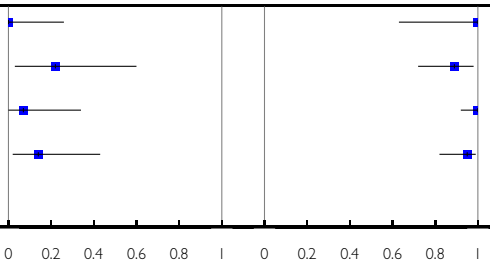


Test 4. Pre-SLNB PET-CT vs Histology - Nodal mets - all SLNB - per patient.

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 4 Pre-SLNB PET-CT vs Histology - Nodal mets - all SLNB - per patient

Study	TP	FP	FN	TN	Sensitivity	Specificity
Hinz 2013	0	0	12	8	0.0 [0.0, 0.26]	1.00 [0.63, 1.00]
Kell 2007	2	3	7	25	0.22 [0.03, 0.60]	0.89 [0.72, 0.98]
Klode 2010	1	0	13	47	0.07 [0.00, 0.34]	1.00 [0.92, 1.00]
Singh 2008	2	2	12	36	0.14 [0.02, 0.43]	0.95 [0.82, 0.99]

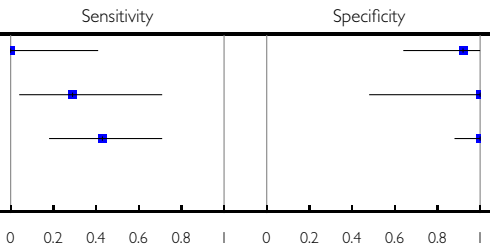


Test 5. Pre-SLNB PET-CT vs Histology - Nodal mets - high risk - per patient.

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 5 Pre-SLNB PET-CT vs Histology - Nodal mets - high risk - per patient

Study	TP	FP	FN	TN	Sensitivity	Specificity
Maubec 2007	0	1	7	12	0.0 [0.0, 0.41]	0.92 [0.64, 1.00]
Singh 2008	2	0	5	5	0.29 [0.04, 0.71]	1.00 [0.48, 1.00]
Wagner 2012	6	0	8	29	0.43 [0.18, 0.71]	1.00 [0.88, 1.00]

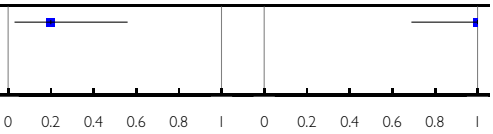


Test 6. Pre-SLNB PET-CT vs Histology - Nodal mets - head and neck only - per patient.

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 6 Pre-SLNB PET-CT vs Histology - Nodal mets - head and neck only - per patient

Study	TP	FP	FN	TN	Sensitivity	Specificity
Revel 2010	2	0	8	10	0.20 [0.03, 0.56]	1.00 [0.69, 1.00]

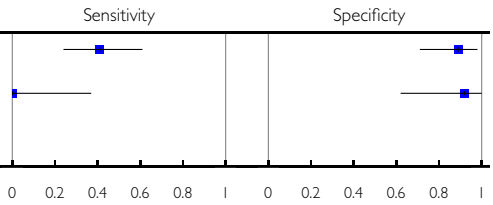


Test 7. Pre-SLNB PET-CT vs Histology/FU - Nodal mets - high risk - per patient.

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 7 Pre-SLNB PET-CT vs Histology/FU - Nodal mets - high risk - per patient

Study	TP	FP	FN	TN	Sensitivity	Specificity
Arrangoiz 2012	12	3	17	24	0.41 [0.24, 0.61]	0.89 [0.71, 0.98]
Maubec 2007	0	1	8	11	0.0 [0.0, 0.37]	0.92 [0.62, 1.00]

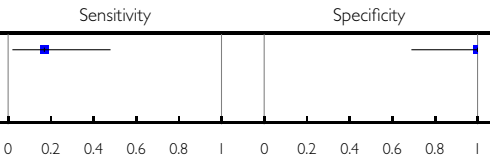


Test 8. Pre-SLNB PET-CT vs Histology/FU - Nodal mets - head and neck only - per patient.

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 8 Pre-SLNB PET-CT vs Histology/FU - Nodal mets - head and neck only - per patient

Study	TP	FP	FN	TN	Sensitivity	Specificity
Revel 2010	2	0	10	10	0.17 [0.02, 0.48]	1.00 [0.69, 1.00]

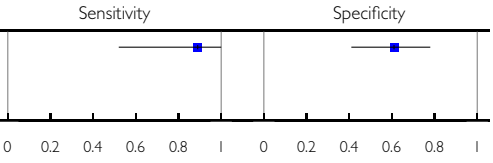


Test 9. Any metastasis - PET-CT - PRIMARY - Any stage (per pt).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 9 Any metastasis - PET-CT - PRIMARY - Any stage (per pt)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Kang 2011	8	11	1	17	0.89 [0.52, 1.00]	0.61 [0.41, 0.78]

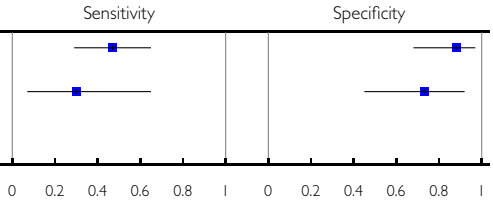


Test 10. Any metastasis - PET-CT - PRIMARY - BT > 4 mm (per pt).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 10 Any metastasis - PET-CT - PRIMARY - BT > 4 mm (per pt)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Arrangoiz 2012	15	3	17	21	0.47 [0.29, 0.65]	0.88 [0.68, 0.97]
Maubec 2007	3	4	7	11	0.30 [0.07, 0.65]	0.73 [0.45, 0.92]

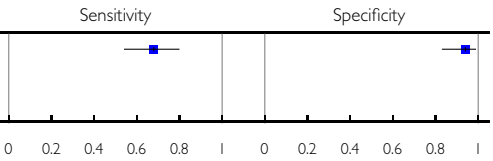


Test 11. Any metastasis - CT - RE-STAGING - Any stage (per pt).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 11 Any metastasis - CT - RE-STAGING - Any stage (per pt)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Iagaru 2007	38	3	18	47	0.68 [0.54, 0.80]	0.94 [0.83, 0.99]

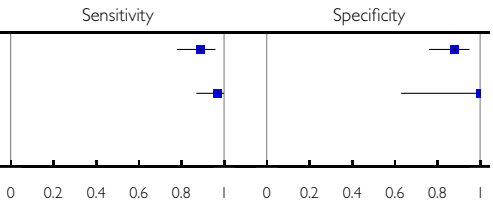


Test 12. Any metastasis - PET-CT - RE-STAGING - Any stage (per pt).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 12 Any metastasis - PET-CT - RE-STAGING - Any stage (per pt)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Iagaru 2007	50	6	6	44	0.89 [0.78, 0.96]	0.88 [0.76, 0.95]
Strobel 2007a	38	0	1	8	0.97 [0.87, 1.00]	1.00 [0.63, 1.00]

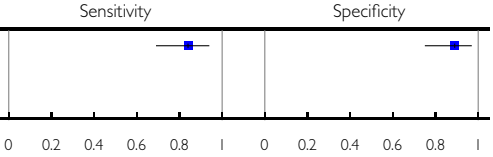


Test 13. Any metastasis - PET-CT - RE-STAGING - Stage IIIb or less (per pt).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 13 Any metastasis - PET-CT - RE-STAGING - Stage IIIb or less (per pt)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Iagaru 2007	32	4	6	34	0.84 [0.69, 0.94]	0.89 [0.75, 0.97]

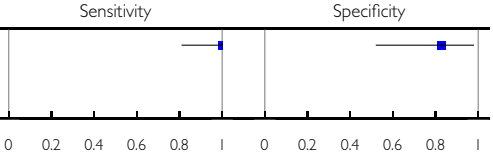


Test 14. Any metastasis - PET-CT - RE-STAGING - Stage IIIc to IV (per pt).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 14 Any metastasis - PET-CT - RE-STAGING - Stage IIIc to IV (per pt)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Iagaru 2007	18	2	0	10	1.00 [0.81, 1.00]	0.83 [0.52, 0.98]

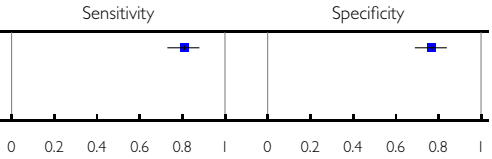


Test 15. Any metastasis - CT- MIXED - All data (per pt).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 15 Any metastasis - CT- MIXED - All data (per pt)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Reinhardt 2006	94	31	22	103	0.81 [0.73, 0.88]	0.77 [0.69, 0.84]

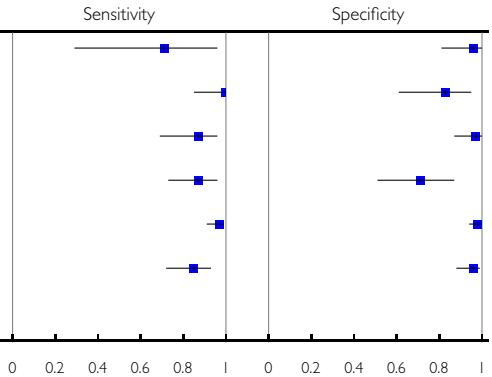


Test 16. Any metastasis - PET-CT - MIXED - All data (per pt).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 16 Any metastasis - PET-CT - MIXED - All data (per pt)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Abbott 2011	5	1	2	26	0.71 [0.29, 0.96]	0.96 [0.81, 1.00]
Aukema 2010a	23	4	0	19	1.00 [0.85, 1.00]	0.83 [0.61, 0.95]
Aukema 2010b	26	1	4	39	0.87 [0.69, 0.96]	0.98 [0.87, 1.00]
Cachin 2014	34	8	5	20	0.87 [0.73, 0.96]	0.71 [0.51, 0.87]
Reinhardt 2006	112	3	4	131	0.97 [0.91, 0.99]	0.98 [0.94, 1.00]
Strobel 2007b	45	3	8	68	0.85 [0.72, 0.93]	0.96 [0.88, 0.99]

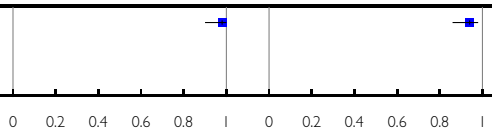


Test 17. Any metastasis - PET-CT (plus CT) - Mixed - Any stage (per pt).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 17 Any metastasis - PET-CT (plus CT) - Mixed - Any stage (per pt)

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Strobel 2007b	52	4	1	67	0.98 [0.90, 1.00]	0.94 [0.86, 0.98]		

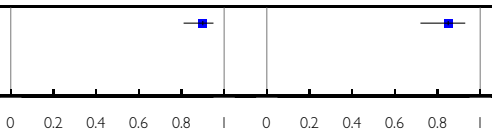


Test 18. Any metastasis - PET-CT - RE-STAGING - Any stage (per lesion).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 18 Any metastasis - PET-CT - RE-STAGING - Any stage (per lesion)

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Iagaru 2007	78	8	9	44	0.90 [0.81, 0.95]	0.85 [0.72, 0.93]		

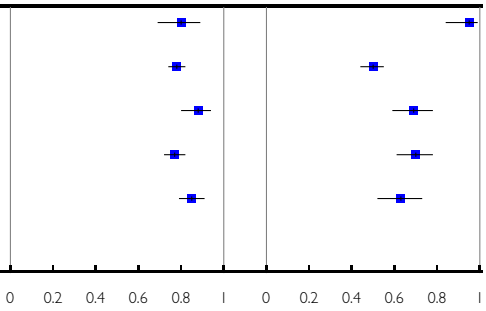


Test 19. Any metastasis - CT- MIXED - All data (per lesion).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 19 Any metastasis - CT- MIXED - All data (per lesion)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Dellestable 2011	53	2	13	40	0.80 [0.69, 0.89]	0.95 [0.84, 0.99]
Hausmann 2011	356	186	99	183	0.78 [0.74, 0.82]	0.50 [0.44, 0.55]
Jouvet 2014	84	28	11	63	0.88 [0.80, 0.94]	0.69 [0.59, 0.78]
Pfannenberg 2007	229	37	68	86	0.77 [0.72, 0.82]	0.70 [0.61, 0.78]
Pfluger 2011	129	30	22	51	0.85 [0.79, 0.91]	0.63 [0.52, 0.73]

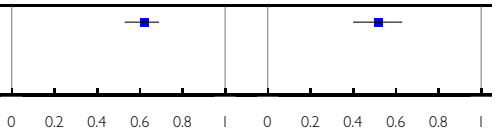


Test 20. Any metastasis (incl brain) - CT (U) - MIXED (per lesion).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 20 Any metastasis (incl brain) - CT (U) - MIXED (per lesion)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Pfluger 2011	93	39	58	42	0.62 [0.53, 0.69]	0.52 [0.40, 0.63]

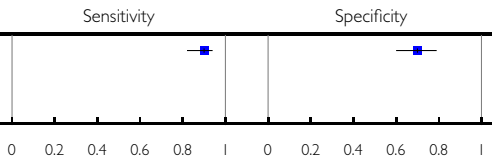


Test 21. Any metastasis (incl brain) - CT (CE) - MIXED (per lesion).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 21 Any metastasis (incl brain) - CT (CE) - MIXED (per lesion)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Jouvet 2014	103	28	12	66	0.90 [0.82, 0.94]	0.70 [0.60, 0.79]

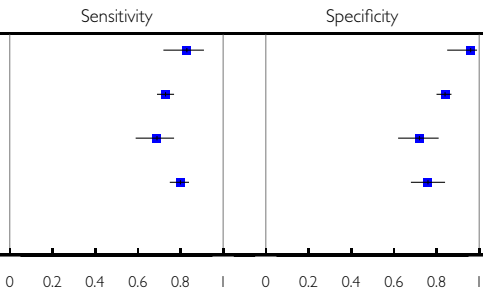


Test 22. Any metastasis - MRI - MIXED - All data (per lesion).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 22 Any metastasis - MRI - MIXED - All data (per lesion)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Dellestable 2011	58	2	12	45	0.83 [0.72, 0.91]	0.96 [0.85, 0.99]
Hausmann 2011	334	60	121	309	0.73 [0.69, 0.77]	0.84 [0.80, 0.87]
Jouvet 2014	72	25	33	65	0.69 [0.59, 0.77]	0.72 [0.62, 0.81]
Pfannenberg 2007	237	29	60	94	0.80 [0.75, 0.84]	0.76 [0.68, 0.84]



Test 23. Any metastasis (excl brain) - MRI (DW + VIBE) - MIXED (per lesion).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 23 Any metastasis (excl brain) - MRI (DW + VIBE) - MIXED (per lesion)

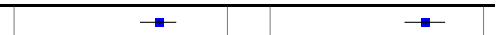
Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Jouvet 2014	85	12	20	78	0.81 [0.72, 0.88]	0.87 [0.78, 0.93]		

Test 24. Any metastasis (incl brain) - MRI (DW) - MIXED (per lesion).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 24 Any metastasis (incl brain) - MRI (DW) - MIXED (per lesion)

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Jouvet 2014	85	25	40	68	0.68 [0.59, 0.76]	0.73 [0.63, 0.82]		



Test 25. Any metastasis (incl brain) - MRI (DW + VIBE) - MIXED (per lesion).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 25 Any metastasis (incl brain) - MRI (DW + VIBE) - MIXED (per lesion)

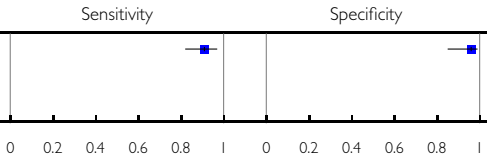
Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Jouvet 2014	105	12	20	81	0.84 [0.76, 0.90]	0.87 [0.79, 0.93]		

Test 26. Any metastasis (incl brain) - MRI plus CT - MIXED (per lesion).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 26 Any metastasis (incl brain) - MRI plus CT - MIXED (per lesion)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Dellestable 2011	64	2	6	44	0.91 [0.82, 0.97]	0.96 [0.85, 0.99]

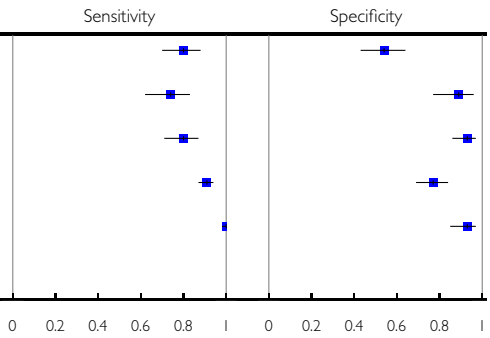


Test 27. Any metastasis - PET-CT - MIXED - All data (per lesion).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 27 Any metastasis - PET-CT - MIXED - All data (per lesion)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Cachin 2014	68	42	17	49	0.80 [0.70, 0.88]	0.54 [0.43, 0.64]
Dellestable 2011	53	5	19	42	0.74 [0.62, 0.83]	0.89 [0.77, 0.96]
Jouvet 2014	83	6	21	81	0.80 [0.71, 0.87]	0.93 [0.86, 0.97]
Pfannenberg 2007	269	28	28	95	0.91 [0.87, 0.94]	0.77 [0.69, 0.84]
Pfluger 2011	151	6	0	75	1.00 [0.98, 1.00]	0.93 [0.85, 0.97]

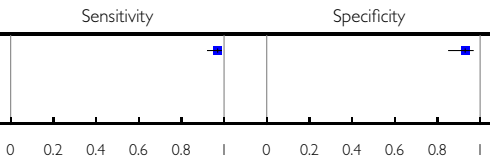


Test 28. Any metastasis (incl brain) - PET-CT (U) - MIXED (per lesion).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 28 Any metastasis (incl brain) - PET-CT (U) - MIXED (per lesion)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Pfluger 2011	146	6	5	75	0.97 [0.92, 0.99]	0.93 [0.85, 0.97]

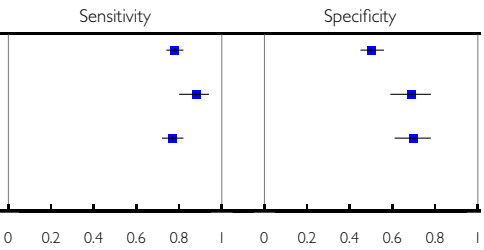


Test 29. Any metastasis (direct test comparisons) - CT - Mixed - Stage III/IV (per lesion).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 29 Any metastasis (direct test comparisons) - CT - Mixed - Stage III/IV (per lesion)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Hausmann 2011	356	183	99	186	0.78 [0.74, 0.82]	0.50 [0.45, 0.56]
Jouvet 2014	84	28	11	63	0.88 [0.80, 0.94]	0.69 [0.59, 0.78]
Pfannenberg 2007	229	37	68	86	0.77 [0.72, 0.82]	0.70 [0.61, 0.78]

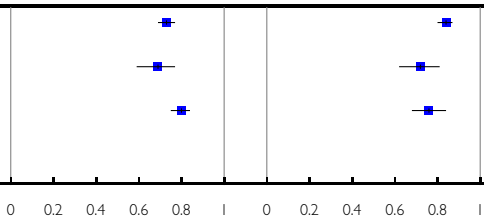


Test 30. Any metastasis (direct test comparisons) - MRI - Mixed - Stage III/IV (per lesion).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 30 Any metastasis (direct test comparisons) - MRI - Mixed - Stage III/IV (per lesion)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Hausmann 2011	334	60	121	309	0.73 [0.69, 0.77]	0.84 [0.80, 0.87]
Jouvet 2014	72	25	33	65	0.69 [0.59, 0.77]	0.72 [0.62, 0.81]
Pfannenberg 2007	237	29	60	94	0.80 [0.75, 0.84]	0.76 [0.68, 0.84]

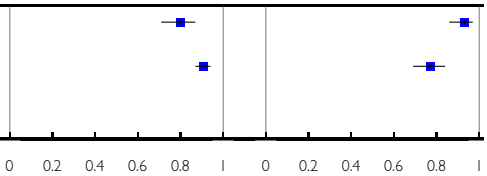


Test 31. Any metastasis (direct test comparisons) - PET-CT - Mixed - Stage III/IV (per lesion).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 31 Any metastasis (direct test comparisons) - PET-CT - Mixed - Stage III/IV (per lesion)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Jouvet 2014	83	6	21	81	0.80 [0.71, 0.87]	0.93 [0.86, 0.97]
Pfannenberg 2007	269	28	28	95	0.91 [0.87, 0.94]	0.77 [0.69, 0.84]

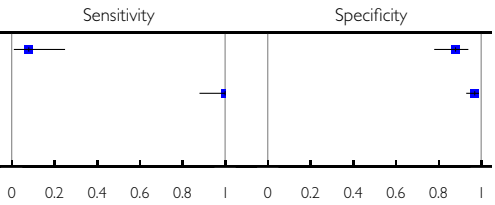


Test 32. Nodal metastasis - US - PRIMARY (per pt).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 32 Nodal metastasis - US - PRIMARY (per pt)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Hafner 2004	2	9	24	65	0.08 [0.01, 0.25]	0.88 [0.78, 0.94]
Prayer 1990	29	6	0	182	1.00 [0.88, 1.00]	0.97 [0.93, 0.99]

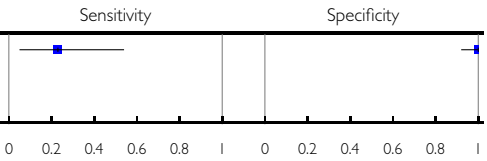


Test 33. Nodal metastasis - CT - PRIMARY (per pt).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 33 Nodal metastasis - CT - PRIMARY (per pt)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Veit-Haibach 2009	3	0	10	43	0.23 [0.05, 0.54]	1.00 [0.92, 1.00]

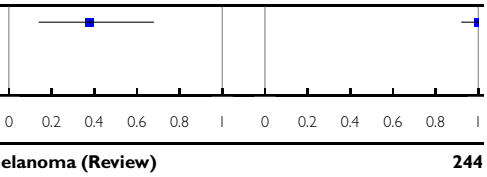


Test 34. Nodal metastasis - PET-CT - PRIMARY (per pt).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 34 Nodal metastasis - PET-CT - PRIMARY (per pt)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Veit-Haibach 2009	5	0	8	43	0.38 [0.14, 0.68]	1.00 [0.92, 1.00]

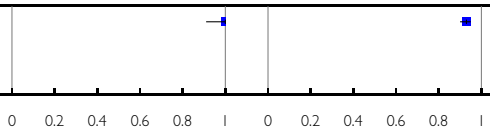


Test 35. Nodal metastasis - US - RE-STAGING (per pt).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 35 Nodal metastasis - US - RE-STAGING (per pt)

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Rubaltelli 2011	37	31	0	392	1.00 [0.91, 1.00]	0.93 [0.90, 0.95]		

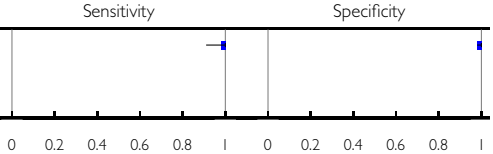


Test 36. Nodal metastasis - US plus US (CE) - RE-STAGING (per pt).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 36 Nodal metastasis - US plus US (CE) - RE-STAGING (per pt)

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Rubaltelli 2011	37	2	0	421	1.00 [0.91, 1.00]	1.00 [0.98, 1.00]		

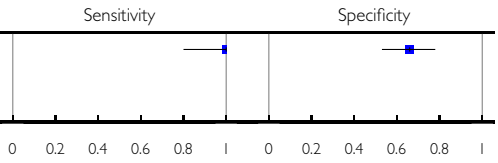


Test 37. Nodal metastasis - US - MIXED (per pt).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 37 Nodal metastasis - US - MIXED (per pt)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Klebl 2003	17	21	0	41	1.00 [0.80, 1.00]	0.66 [0.53, 0.78]

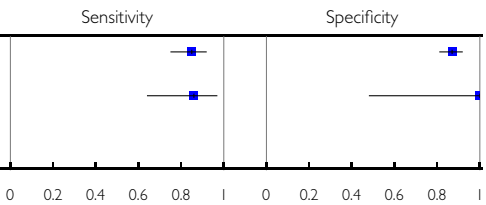


Test 38. Nodal metastasis - CT - MIXED (per pt).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 38 Nodal metastasis - CT - MIXED (per pt)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Reinhardt 2006	66	22	12	150	0.85 [0.75, 0.92]	0.87 [0.81, 0.92]
van den Brekel 1998	18	0	3	5	0.86 [0.64, 0.97]	1.00 [0.48, 1.00]

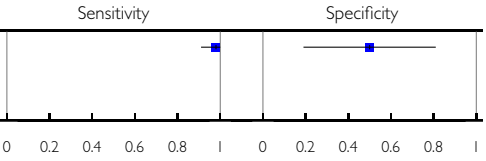


Test 39. Nodal metastasis (superficial groin) - PET-CT (indeterminate test positive) - MIXED (per pt).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 39 Nodal metastasis (superficial groin) - PET-CT (indeterminate test positive) - MIXED (per pt)

Study	TP	FP	FN	TN	Sensitivity	Specificity
van Wissen 2016	58	5	1	5	0.98 [0.91, 1.00]	0.50 [0.19, 0.81]

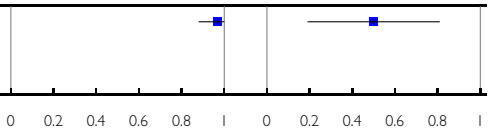


Test 40. Nodal metastasis (superficial groin) - PET-CT (indeterminate test negative) - MIXED (per pt).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 40 Nodal metastasis (superficial groin) - PET-CT (indeterminate test negative) - MIXED (per pt)

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
van Wissen 2016	57	5	2	5	0.97 [0.88, 1.00]	0.50 [0.19, 0.81]		

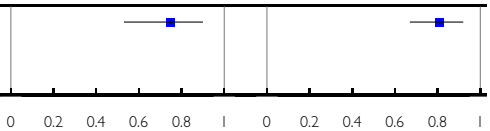


Test 41. Nodal metastasis (deep groin) - PET-CT (indeterminate test positive) - MIXED (per pt).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 41 Nodal metastasis (deep groin) - PET-CT (indeterminate test positive) - MIXED (per pt)

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
van Wissen 2016	18	8	6	35	0.75 [0.53, 0.90]	0.81 [0.67, 0.92]		

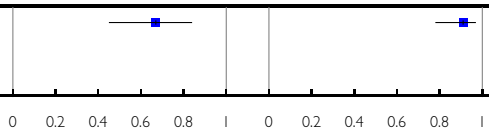


Test 42. Nodal metastasis (deep groin) - PET-CT (indeterminate test negative) - MIXED (per pt).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 42 Nodal metastasis (deep groin) - PET-CT (indeterminate test negative) - MIXED (per pt)

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
van Wissen 2016	16	4	8	39	0.67 [0.45, 0.84]	0.91 [0.78, 0.97]		

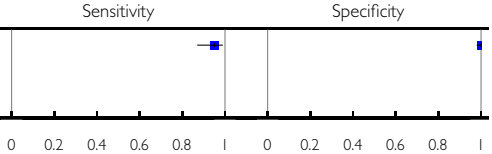


Test 43. Nodal metastasis - PET-CT - MIXED (per pt).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 43 Nodal metastasis - PET-CT - MIXED (per pt)

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Reinhardt 2006	74	0	4	172	0.95 [0.87, 0.99]	1.00 [0.98, 1.00]		

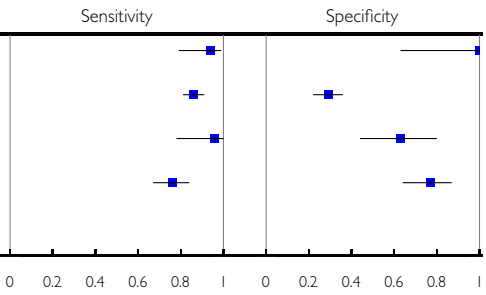


Test 44. Nodal metastasis - CT - MIXED - All data (per lesion).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 44 Nodal metastasis - CT - MIXED - All data (per lesion)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Dellestable 2011	29	0	2	8	0.94 [0.79, 0.99]	1.00 [0.63, 1.00]
Hausmann 2011	166	133	26	54	0.86 [0.81, 0.91]	0.29 [0.22, 0.36]
Jouvet 2014	22	11	1	19	0.96 [0.78, 1.00]	0.63 [0.44, 0.80]
Pfannenberg 2007	78	13	24	43	0.76 [0.67, 0.84]	0.77 [0.64, 0.87]

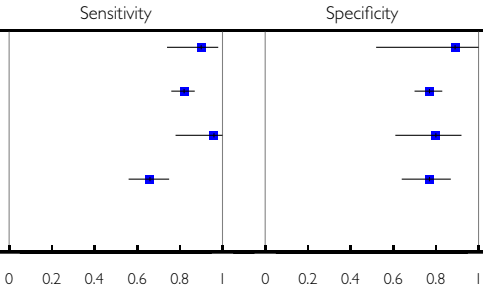


Test 45. Nodal metastasis - MRI - MIXED - All data (per lesion).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 45 Nodal metastasis - MRI - MIXED - All data (per lesion)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Dellestable 2011	28	1	3	8	0.90 [0.74, 0.98]	0.89 [0.52, 1.00]
Hausmann 2011	157	43	35	144	0.82 [0.76, 0.87]	0.77 [0.70, 0.83]
Jouvet 2014	22	6	1	24	0.96 [0.78, 1.00]	0.80 [0.61, 0.92]
Pfannenberg 2007	67	13	35	43	0.66 [0.56, 0.75]	0.77 [0.64, 0.87]

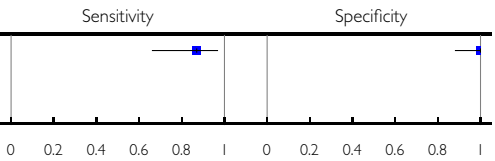


Test 46. Nodal metastasis - MRI (DW + VIBE) - MIXED (per lesion).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 46 Nodal metastasis - MRI (DW + VIBE) - MIXED (per lesion)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Jouvet 2014	20	0	3	30	0.87 [0.66, 0.97]	1.00 [0.88, 1.00]

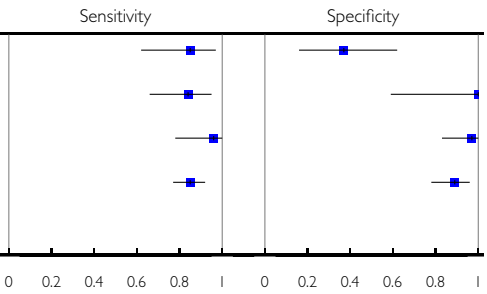


Test 47. Nodal metastasis - PET-CT - MIXED - All data (per lesion).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 47 Nodal metastasis - PET-CT - MIXED - All data (per lesion)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Cachin 2014	17	12	3	7	0.85 [0.62, 0.97]	0.37 [0.16, 0.62]
Dellestable 2011	26	0	5	7	0.84 [0.66, 0.95]	1.00 [0.59, 1.00]
Jouvet 2014	22	1	1	29	0.96 [0.78, 1.00]	0.97 [0.83, 1.00]
Pfannenberg 2007	87	6	15	50	0.85 [0.77, 0.92]	0.89 [0.78, 0.96]

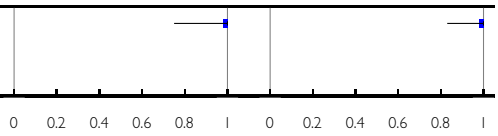


Test 48. Superficial nodal metastasis - US - Mixed - stage IV (per LNB).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 48 Superficial nodal metastasis - US - Mixed - stage IV (per LNB)

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Jouvet 2014	13	0	0	20	1.00 [0.75, 1.00]	1.00 [0.83, 1.00]		

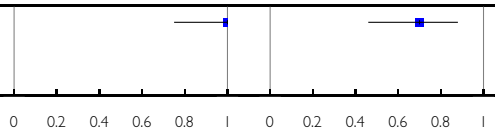


Test 49. Superficial nodal metastasis - CT - Mixed - stage IV (per LNB).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 49 Superficial nodal metastasis - CT - Mixed - stage IV (per LNB)

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Jouvet 2014	13	6	0	14	1.00 [0.75, 1.00]	0.70 [0.46, 0.88]		

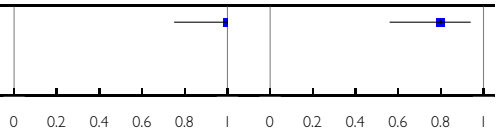


Test 50. Superficial nodal metastasis - MRI - Mixed - stage IV (per LNB).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 50 Superficial nodal metastasis - MRI - Mixed - stage IV (per LNB)

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Jouvet 2014	13	4	0	16	1.00 [0.75, 1.00]	0.80 [0.56, 0.94]		



Test 51. Superficial nodal metastasis - MRI (DW + VIBE) - Mixed - Stage IV (per lesion).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 51 Superficial nodal metastasis - MRI (DW + VIBE) - Mixed - Stage IV (per lesion)

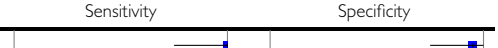
Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Jouvet 2014	13	1	0	19	1.00 [0.75, 1.00]	0.95 [0.75, 1.00]		

Test 52. Superficial nodal metastasis - PET-CT - Mixed - stage IV (per LNB).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 52 Superficial nodal metastasis - PET-CT - Mixed - stage IV (per LNB)

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Jouvet 2014	13	1	0	19	1.00 [0.75, 1.00]	0.95 [0.75, 1.00]		

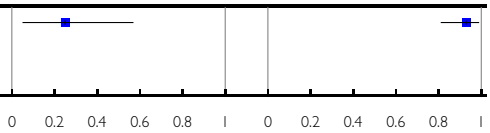


Test 53. Distant metastasis - CT - PRIMARY (per pt).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 53 Distant metastasis - CT - PRIMARY (per pt)

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Veit-Haibach 2009	3	3	9	41	0.25 [0.05, 0.57]	0.93 [0.81, 0.99]		

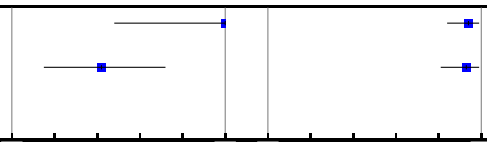


Test 54. Distant metastasis - PET-CT - PRIMARY (per pt).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 54 Distant metastasis - PET-CT - PRIMARY (per pt)

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Arrangoiz 2012	5	3	0	48	1.00 [0.48, 1.00]	0.94 [0.84, 0.99]		
Veit-Haibach 2009	5	3	7	41	0.42 [0.15, 0.72]	0.93 [0.81, 0.99]		



Test 55. Distant metastasis - CT - MIXED - All data (per pt).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 55 Distant metastasis - CT - MIXED - All data (per pt)

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Bastiaannet 2009	61	11	17	162	0.78 [0.67, 0.87]	0.94 [0.89, 0.97]		
Reinhardt 2006	62	20	22	146	0.74 [0.63, 0.83]	0.88 [0.82, 0.92]		

Test 56. Distant metastasis - PET-CT - MIXED - All data (per pt).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 56 Distant metastasis - PET-CT - MIXED - All data (per pt)

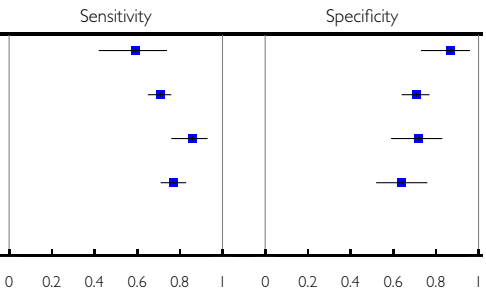
Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Reinhardt 2006	83	4	1	162	0.99 [0.94, 1.00]	0.98 [0.94, 0.99]		

Test 57. Distant metastasis - CT - Mixed - All data (per lesion).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 57 Distant metastasis - CT - Mixed - All data (per lesion)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Dellestable 2011	24	5	17	34	0.59 [0.42, 0.74]	0.87 [0.73, 0.96]
Hausmann 2011	186	53	77	129	0.71 [0.65, 0.76]	0.71 [0.64, 0.77]
Jouvet 2014	62	17	10	44	0.86 [0.76, 0.93]	0.72 [0.59, 0.83]
Pfannenberg 2007	151	24	44	43	0.77 [0.71, 0.83]	0.64 [0.52, 0.76]

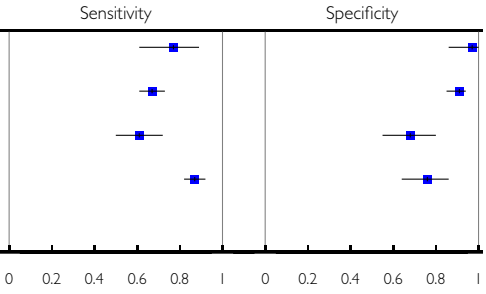


Test 58. Distant metastasis - MRI - Mixed - All data (per lesion).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 58 Distant metastasis - MRI - Mixed - All data (per lesion)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Dellestable 2011	30	1	9	37	0.77 [0.61, 0.89]	0.97 [0.86, 1.00]
Hausmann 2011	177	17	86	165	0.67 [0.61, 0.73]	0.91 [0.85, 0.94]
Jouvet 2014	50	19	32	41	0.61 [0.50, 0.72]	0.68 [0.55, 0.80]
Pfannenberg 2007	170	16	25	51	0.87 [0.82, 0.92]	0.76 [0.64, 0.86]

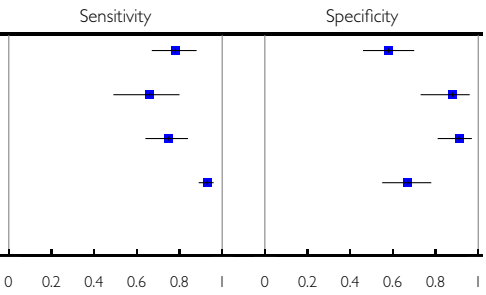


Test 59. Distant metastasis - PET-CT - Mixed - All data (per lesion).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 59 Distant metastasis - PET-CT - Mixed - All data (per lesion)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Cachin 2014	51	30	14	42	0.78 [0.67, 0.88]	0.58 [0.46, 0.70]
Dellestable 2011	27	5	14	35	0.66 [0.49, 0.80]	0.88 [0.73, 0.96]
Jouvet 2014	61	5	20	52	0.75 [0.64, 0.84]	0.91 [0.81, 0.97]
Pfannenberg 2007	182	22	13	45	0.93 [0.89, 0.96]	0.67 [0.55, 0.78]

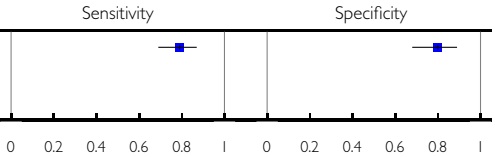


Test 60. Distant metastasis (excl brain) - MRI (DW + VIBE) - Mixed - stage III/IV (per lesion).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 60 Distant metastasis (excl brain) - MRI (DW + VIBE) - Mixed - stage III/IV (per lesion)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Jouvet 2014	65	12	17	48	0.79 [0.69, 0.87]	0.80 [0.68, 0.89]

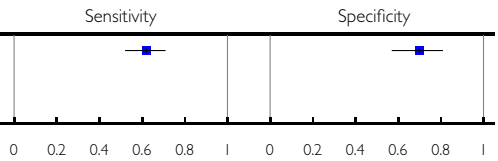


Test 61. Distant metastasis (incl brain) - MRI (DW) - Mixed - stage III/IV (per lesion).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 61 Distant metastasis (incl brain) - MRI (DW) - Mixed - stage III/IV (per lesion)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Jouvet 2014	63	19	39	44	0.62 [0.52, 0.71]	0.70 [0.57, 0.81]

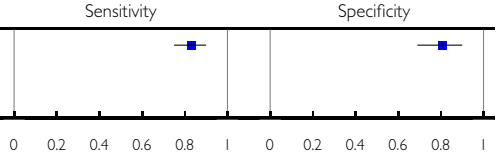


Test 62. Distant metastasis (incl brain) - MRI (DW + VIBE) - Mixed - stage III/IV (per lesion).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 62 Distant metastasis (incl brain) - MRI (DW + VIBE) - Mixed - stage III/IV (per lesion)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Jouvet 2014	85	12	17	51	0.83 [0.75, 0.90]	0.81 [0.69, 0.90]

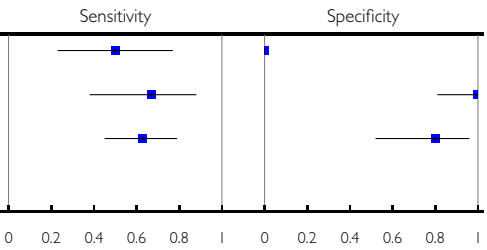


Test 63. Bone metastasis - CT- MIXED - All data (per lesion).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 63 Bone metastasis - CT- MIXED - All data (per lesion)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Dellestable 2011	7	0	7	0	0.50 [0.23, 0.77]	0.0 [0.0, 0.0]
Jouvet 2014	10	0	5	18	0.67 [0.38, 0.88]	1.00 [0.81, 1.00]
Pfannenberg 2007	22	3	13	12	0.63 [0.45, 0.79]	0.80 [0.52, 0.96]

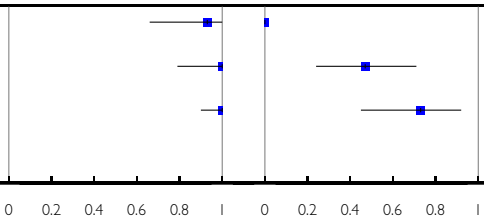


Test 64. Bone metastasis - MRI - MIXED - All data (per lesion).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 64 Bone metastasis - MRI - MIXED - All data (per lesion)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Dellestable 2011	13	0	1	0	0.93 [0.66, 1.00]	0.0 [0.0, 0.0]
Jouvet 2014	16	10	0	9	1.00 [0.79, 1.00]	0.47 [0.24, 0.71]
Pfannenberg 2007	35	4	0	11	1.00 [0.90, 1.00]	0.73 [0.45, 0.92]

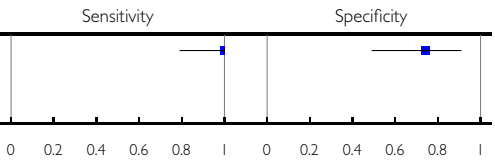


Test 65. Bone metastasis - MRI (DW + VIBE) - MIXED - All data (per lesion).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 65 Bone metastasis - MRI (DW + VIBE) - MIXED - All data (per lesion)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Jouvet 2014	16	5	0	14	1.00 [0.79, 1.00]	0.74 [0.49, 0.91]

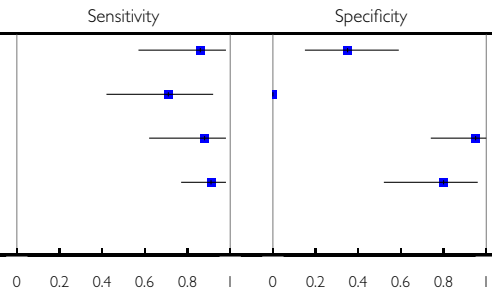


Test 66. Bone metastasis - PET-CT - MIXED - All data (per lesion).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 66 Bone metastasis - PET-CT - MIXED - All data (per lesion)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Cachin 2014	12	13	2	7	0.86 [0.57, 0.98]	0.35 [0.15, 0.59]
Dellestable 2011	10	0	4	0	0.71 [0.42, 0.92]	0.0 [0.0, 0.0]
Jouvet 2014	14	1	2	18	0.88 [0.62, 0.98]	0.95 [0.74, 1.00]
Pfannenberg 2007	32	3	3	12	0.91 [0.77, 0.98]	0.80 [0.52, 0.96]

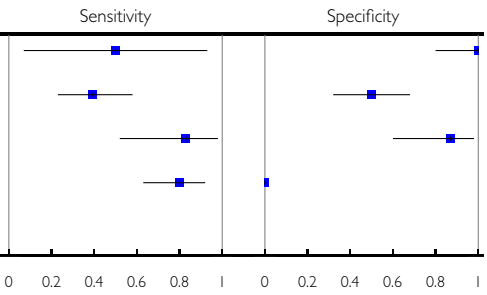


Test 67. Liver metastasis - CT- MIXED - All data (per lesion).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 67 Liver metastasis - CT- MIXED - All data (per lesion)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Dellestable 2011	2	0	2	17	0.50 [0.07, 0.93]	1.00 [0.80, 1.00]
Hausmann 2011	13	17	20	17	0.39 [0.23, 0.58]	0.50 [0.32, 0.68]
Jouvet 2014	10	2	2	13	0.83 [0.52, 0.98]	0.87 [0.60, 0.98]
Pfannenberg 2007	28	0	7	0	0.80 [0.63, 0.92]	0.0 [0.0, 0.0]

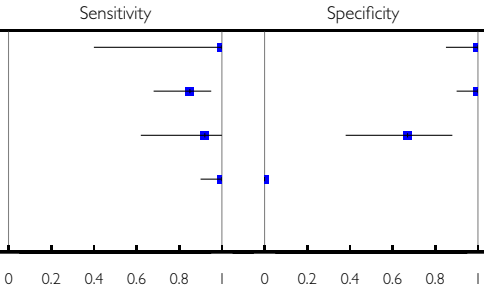


Test 68. Liver metastasis - MRI - MIXED - All data (per lesion).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 68 Liver metastasis - MRI - MIXED - All data (per lesion)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Dellestable 2011	4	0	0	22	1.00 [0.40, 1.00]	1.00 [0.85, 1.00]
Hausmann 2011	28	0	5	34	0.85 [0.68, 0.95]	1.00 [0.90, 1.00]
Jouvet 2014	11	5	1	10	0.92 [0.62, 1.00]	0.67 [0.38, 0.88]
Pfannenberg 2007	35	0	0	0	1.00 [0.90, 1.00]	0.0 [0.0, 0.0]

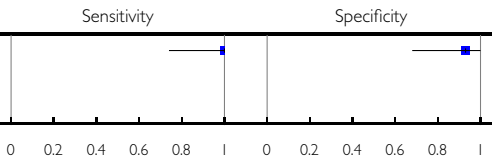


Test 69. Liver metastasis - MRI (DW + VIBE) - Mixed - stage III/IV (per lesion).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 69 Liver metastasis - MRI (DW + VIBE) - Mixed - stage III/IV (per lesion)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Jouvet 2014	12	1	0	14	1.00 [0.74, 1.00]	0.93 [0.68, 1.00]

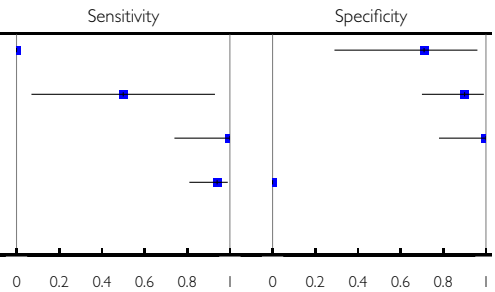


Test 70. Liver metastasis - PET-CT - MIXED - All data (per lesion).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 70 Liver metastasis - PET-CT - MIXED - All data (per lesion)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Cachin 2014	0	2	0	5	0.0 [0.0, 0.0]	0.71 [0.29, 0.96]
Dellestable 2011	2	2	2	19	0.50 [0.07, 0.93]	0.90 [0.70, 0.99]
Jouvet 2014	12	0	0	15	1.00 [0.74, 1.00]	1.00 [0.78, 1.00]
Pfannenberg 2007	33	0	2	0	0.94 [0.81, 0.99]	0.0 [0.0, 0.0]

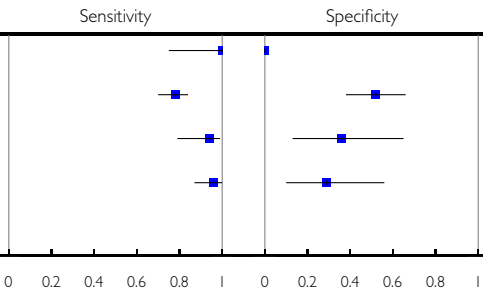


Test 71. Lung metastasis - CT - MIXED - All data (per lesion).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 71 Lung metastasis - CT - MIXED - All data (per lesion)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Dellestable 2011	13	0	0	0	1.00 [0.75, 1.00]	0.0 [0.0, 0.0]
Hausmann 2011	113	25	32	27	0.78 [0.70, 0.84]	0.52 [0.38, 0.66]
Jouvet 2014	29	9	2	5	0.94 [0.79, 0.99]	0.36 [0.13, 0.65]
Pfannenberg 2007	51	12	2	5	0.96 [0.87, 1.00]	0.29 [0.10, 0.56]

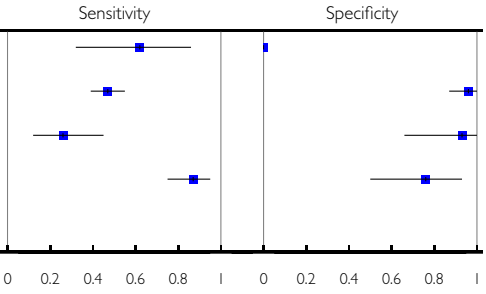


Test 72. Lung metastasis - MRI - MIXED - All data (per lesion).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 72 Lung metastasis - MRI - MIXED - All data (per lesion)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Dellestable 2011	8	0	5	0	0.62 [0.32, 0.86]	0.0 [0.0, 0.0]
Hausmann 2011	68	2	77	50	0.47 [0.39, 0.55]	0.96 [0.87, 1.00]
Jouvet 2014	8	1	23	13	0.26 [0.12, 0.45]	0.93 [0.66, 1.00]
Pfannenberg 2007	46	4	7	13	0.87 [0.75, 0.95]	0.76 [0.50, 0.93]

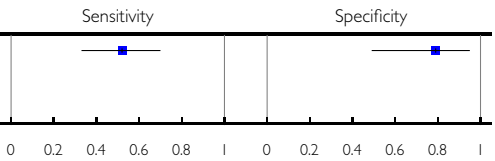


Test 73. Lung metastasis - MRI (DW + VIBE) - Mixed - stage III/IV (per lesion).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 73 Lung metastasis - MRI (DW + VIBE) - Mixed - stage III/IV (per lesion)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Jouvet 2014	16	3	15	11	0.52 [0.33, 0.70]	0.79 [0.49, 0.95]

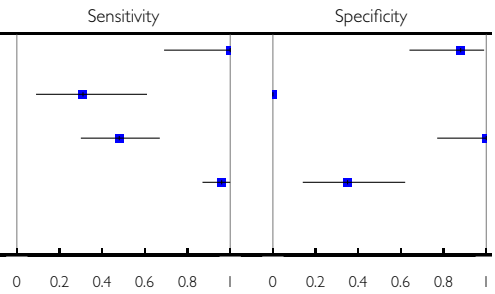


Test 74. Lung metastasis - PET-CT - MIXED - All data (per lesion).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 74 Lung metastasis - PET-CT - MIXED - All data (per lesion)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Cachin 2014	10	2	0	15	1.00 [0.69, 1.00]	0.88 [0.64, 0.99]
Dellestable 2011	4	0	9	0	0.31 [0.09, 0.61]	0.0 [0.0, 0.0]
Jouvet 2014	15	0	16	14	0.48 [0.30, 0.67]	1.00 [0.77, 1.00]
Pfannenberg 2007	51	11	2	6	0.96 [0.87, 1.00]	0.35 [0.14, 0.62]

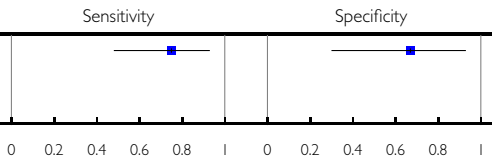


Test 75. Soft tissue metastasis - PET-CT - MIXED (per lesion).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 75 Soft tissue metastasis - PET-CT - MIXED (per lesion)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Cachin 2014	12	3	4	6	0.75 [0.48, 0.93]	0.67 [0.30, 0.93]

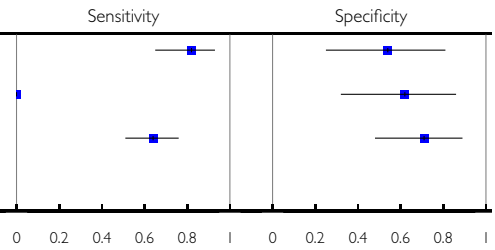


Test 76. Local/subcutaneous metastasis - CT - MIXED (per lesion).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 76 Local/subcutaneous metastasis - CT - MIXED (per lesion)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Hausmann 2011	27	6	6	7	0.82 [0.65, 0.93]	0.54 [0.25, 0.81]
Jouvet 2014	0	5	0	8	0.0 [0.0, 0.0]	0.62 [0.32, 0.86]
Pfannenberg 2007	38	6	21	15	0.64 [0.51, 0.76]	0.71 [0.48, 0.89]

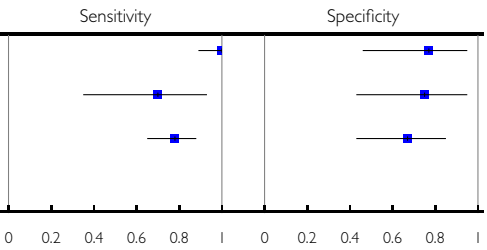


Test 77. Local/subcutaneous metastasis - MRI - MIXED (per lesion).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 77 Local/subcutaneous metastasis - MRI - MIXED (per lesion)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Hausmann 2011	33	3	0	10	1.00 [0.89, 1.00]	0.77 [0.46, 0.95]
Jouvet 2014	7	3	3	9	0.70 [0.35, 0.93]	0.75 [0.43, 0.95]
Pfannenberg 2007	46	7	13	14	0.78 [0.65, 0.88]	0.67 [0.43, 0.85]

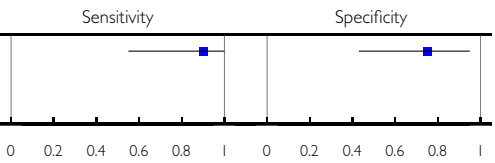


Test 78. Local/subcutaneous metastasis - MRI (DW + VIBE) - MIXED (per lesion).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 78 Local/subcutaneous metastasis - MRI (DW + VIBE) - MIXED (per lesion)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Jouvet 2014	9	3	1	9	0.90 [0.55, 1.00]	0.75 [0.43, 0.95]

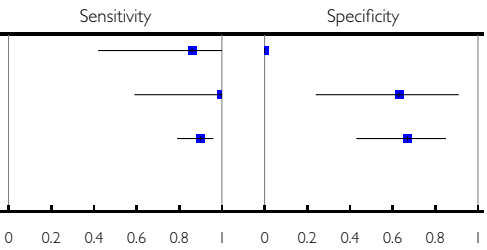


Test 79. Local/subcutaneous metastasis - PET-CT - MIXED (per lesion).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 79 Local/subcutaneous metastasis - PET-CT - MIXED (per lesion)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Cachin 2014	6	0	1	0	0.86 [0.42, 1.00]	0.0 [0.0, 0.0]
Jouvet 2014	7	3	0	5	1.00 [0.59, 1.00]	0.63 [0.24, 0.91]
Pfannenberg 2007	53	7	6	14	0.90 [0.79, 0.96]	0.67 [0.43, 0.85]

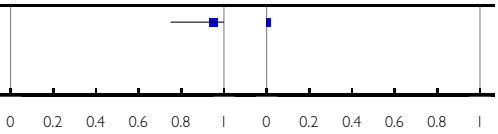


Test 80. Brain metastasis - CT- MIXED - All data (per lesion).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 80 Brain metastasis - CT- MIXED - All data (per lesion)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Jouvet 2014	19	0	1	0	0.95 [0.75, 1.00]	0.0 [0.0, 0.0]

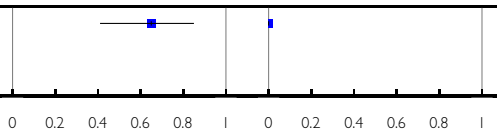


Test 81. Brain metastasis - MRI (DW) - MIXED - All data (per lesion).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 81 Brain metastasis - MRI (DW) - MIXED - All data (per lesion)

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Jouvet 2014	13	0	7	0	0.65 [0.41, 0.85]	0.0 [0.0, 0.0]		

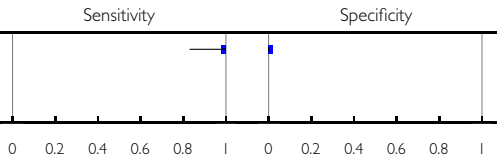


Test 82. Brain metastasis - MRI (DW + VIBE) - MIXED - All data (per lesion).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 82 Brain metastasis - MRI (DW + VIBE) - MIXED - All data (per lesion)

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Jouvet 2014	20	0	0	0	1.00 [0.83, 1.00]	0.0 [0.0, 0.0]		

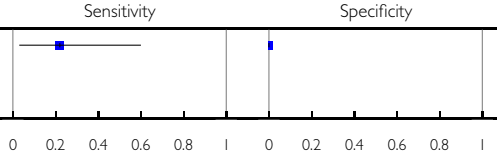


Test 83. Brain metastasis - PET-CT - MIXED - All data (per lesion).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 83 Brain metastasis - PET-CT - MIXED - All data (per lesion)

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Cachin 2014	2	0	7	0	0.22 [0.03, 0.60]	0.0 [0.0, 0.0]		



Test 93. 'Other' metastasis - CT - Mixed - Any stage (per lesion).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 93 'Other' metastasis - CT - Mixed - Any stage (per lesion)

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Dellestable 2011	2	4	8	12	0.20 [0.03, 0.56]	0.75 [0.48, 0.93]		

Test 94. 'Other' metastasis - MRI - Mixed - Any stage (per lesion).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 94 'Other' metastasis - MRI - Mixed - Any stage (per lesion)

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Dellestable 2011	5	1	3	12	0.63 [0.24, 0.91]	0.92 [0.64, 1.00]		

Test 95. 'Other' metastasis - PET-CT - Mixed - Any stage (per lesion).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 95 'Other' metastasis - PET-CT - Mixed - Any stage (per lesion)

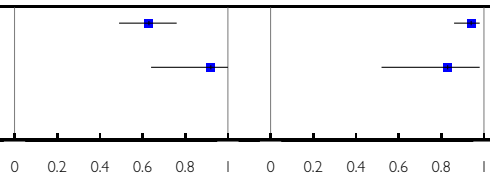
Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Dellestable 2011	11	3	1	11	0.92 [0.62, 1.00]	0.79 [0.49, 0.95]		

Test 96. 'Other' metastasis - CT - Mixed - stage III/IV (per lesion).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 96 'Other' metastasis - CT - Mixed - stage III/IV (per lesion)

Study	TP	FP	FN	TN	Sensitivity	Specificity	Sensitivity	Specificity
Hausmann 2011	33	5	19	78	0.63 [0.49, 0.76]	0.94 [0.86, 0.98]		
Pfannenberg 2007	12	2	1	10	0.92 [0.64, 1.00]	0.83 [0.52, 0.98]		

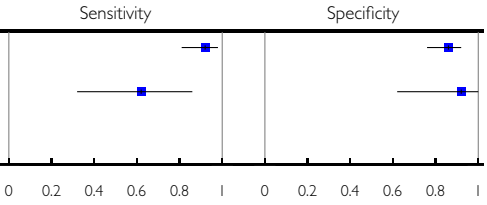


Test 97. 'Other' metastasis - MRI - Mixed - stage III/IV (per lesion).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 97 'Other' metastasis - MRI - Mixed - stage III/IV (per lesion)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Hausmann 2011	48	12	4	71	0.92 [0.81, 0.98]	0.86 [0.76, 0.92]
Pfannenberg 2007	8	1	5	11	0.62 [0.32, 0.86]	0.92 [0.62, 1.00]

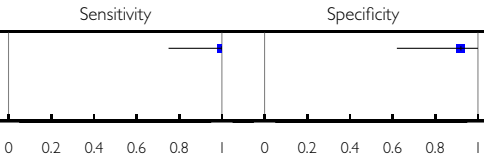


Test 98. 'Other' metastasis - PET-CT - Mixed - stage III/IV (per lesion).

Review: Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma

Test: 98 'Other' metastasis - PET-CT - Mixed - stage III/IV (per lesion)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Pfannenberg 2007	13	1	0	11	1.00 [0.75, 1.00]	0.92 [0.62, 1.00]



ADDITIONAL TABLES

Table 1. Cross-tabulation of studies by index test, population group, and target condition

Study	US	US-FNAC	CT	MRI	PET-CT	Population group	Population detail	Reference standard	Any metastases	Distant metastases	Nodal metastases	Other sites
PRIMARY STAGING												
Arrangoiz 2012	-	-	-	-	X	Primary (any); primary	BT > 4 mm	SLNB/ CLND/	Per patient	Per patient	Per patient/	-

Table 1. Cross-tabulation of studies by index test, population group, and target condition (*Continued*)

						(pre-SLNB)		FU			Pre-SLNB	
Chai 2012	X	-	-	-	-	Primary (pre-SLNB)	Standard SLNB	SLNB/ CLND ± FU	-	-	Pre-SLNB	-
Hafner 2004	X	-	-	-	(X)	Primary (pre-SLNB); primary	Standard SLNB Any (incl N+)	SLNB/ CLND	-	-	Per patient/ Pre-SLNB	-
Hinz 2011	X	-	-	-	-	Primary (pre-SLNB)	Standard SLNB	SLNB	-	-	Pre-SLNB	-
Hinz 2013	X	-	-	-	X	Primary (pre-SLNB)	High risk (BT ≥ 2.0 mm or other RF)	SLNB	-	-	Pre-SLNB	-
Hocevar 2004	X	X	-	-	-	Primary (pre-SLNB)	Standard SLNB	SLNB/ CLND	-	-	Pre-SLNB	-
Kang 2011	-	-	-	-	X	Primary (any)	All staging (incl N+)	Histology/FU	per patient	-	-	-
Kell 2007					X	Primary (pre-SLNB)	Standard SLNB	SLNB	-	-	Pre-SLNB	-
Klode 2010	-	-	-	-	X	Primary (pre-SLNB)	Standard SLNB	SLNB	-	-	Pre-SLNB	-
Kunte 2009	X	-	-	-	-	Primary (pre-SLNB)	Standard SLNB	SLNB	-	-	Pre-SLNB	-
Maubec 2007	-	-	-	-	X	Primary (any); primary (pre-	BT > 4 mm	SLNB/ CLND ± FU	Per patient	-	Pre-SLNB	-

Table 1. Cross-tabulation of studies by index test, population group, and target condition (*Continued*)

						SLNB)						
Prayer 1990	X	-	-	-	-	Primary (any)	All staging (incl N+)	CLND/ FU	-	-	Per patient	-
Radzhabc 2009	X	-	-	-	-	Primary (pre-SLNB)	Standard SLNB; any (incl N+)	SLNB ± FU	-	-	Pre-SLNB	-
Revel 2010	-	-	-	-	X	Primary (pre-SLNB)	HN MM	SLNB	-	-	Pre-SLNB	-
Sanki 2009	X	-	-	-	-	Primary (pre-SLNB)	Standard SLNB	SLNB			Pre-SLNB	
Sibon 2007	X	-	-	-	-	Primary (pre-SLNB)	Standard SLNB	SLNB	-	-	Pre-SLNB	-
Singh 2008	-	-	-	-	X	Primary (pre-SLNB)	Standard SLNB/ BT > 4 mm	SLNB	-	-	Pre-SLNB	-
van Rijk 2006	X	X	-	-	-	Primary (pre-SLNB)	Standard SLNB	SLNB/ CLND	-	-	pre-SLNB	-
Veit-Haibach 2009	-	-	X	-	X	Primary (any)	All staging (incl N+)	Histology/FU	-	Per patient	Per patient	-
Voit 2014	X	X	-	-	-	Primary (pre-SLNB)	Standard SLNB	SLNB/ CLND	-	-	Pre-SLNB	-
Wagner 2012	-	-	-	-	X	Primary (pre-SLNB)	High risk (BT ≥ 4 mm or > 1 mm and ulcerated)	SLNB/ CLND	-	-	Pre-SLNB	-

Table 1. Cross-tabulation of studies by index test, population group, and target condition (*Continued*)

RE-STAGING												
Iagaru 2007	-	-	X	-	X	Re-staging	Any re-staging	Histology/FU	Per patient /Per lesion	-	-	-
Rubaltelli 2011	X	-	-	-	-	Re-staging	Any FU and suspicious on B-mode US	FNAC/ Histology/FU	-	-	Per patient	-
Strobel 2007a	-	-	-	-	X	Re-staging	High risk (BT > 4 mm, etc.), elevated S100	Histology/Cytology/ FU	Per patient	-	-	-
MIXED OR UNCLEARLY REPORTED												
Abbott 2011	-	-	-	-	X	Mixed	Stage III	Histology/FU	Per patient	-	-	-
Aukema 2010a	-	-	-	(X - Brain)	X	Mixed	S100 positive	FNAC/ Histology/ Imaging FU	Per patient	-	-	-
Aukema 2010b	-	-	-	(X - Brain)	X	Unclear	Node positive	FNAC/ Histology/FU	Per patient	-	-	-
Bastiaannet 2009	-	-	X	-	(X)	Mixed	All node positive	Histology/FU	-	Per patient	-	-
Cachin 2014	-	-	-	-	X	Mixed	Stage III	Histology/ Imaging/FU	Per patient/Per lesion	Per lesion	Per lesion	Per lesion
Dellestab 2011	-	-	X	X	X	Mixed	All staging	Histology/FU	Per lesion	Per lesion	Per lesion	Per lesion

Table 1. Cross-tabulation of studies by index test, population group, and target condition (*Continued*)

Hausmann 2011	-	-	X	X	-	Unclear	Stage III/IV	Histology/FU	Per lesion	Per lesion	Per lesion	Per lesion
Jouvet 2014	X	-	X	X	X	Unclear	Stage IV	FNAC/FU	Per lesion	Per lesion	Per lesion	Per lesion
Klebl 2003	X	-	-	-	-	Mixed	Clark IV/V in FU	Histology/FU	-	-	per patient	-
Pfannenberg 2007	-	-	X	X	X	Mixed	Stage III/IV	Histology/Imaging/FU	Per lesion	Per patient	Per lesion	Per lesion
Pfluger 2011	-	-	X	-	X	Mixed	All stage III	Histology/FU	Per patient	-	-	-
Reinhardt 2006	-	-	X	-	X	Mixed	All staging (incl N+)	Histology/FU	Per patient	Per patient	Per patient	-
Strobel 2007b	-	-	-	-	X	Unclear	High risk (BT > 4 mm, etc.)	Histology/Cytology/FU	Per patient	-	-	-
van den Brekel 1998			X	-	-	Mixed	HN MM and N+	Histology	-	-	Per patient	-
van Wissen 2016	-	-	-	-	X	Mixed	Stage IIIB/IIIC palpable groin mets	Histology (combined groin dissection)	-	-	Per patient	-

BT: Breslow thickness; CLND: complete lymph node dissection; CT: computed tomography; FNAC: fine needle aspiration cytology; FU: follow-up; HN: head and neck; MM: malignant melanoma; MRI: magnetic resonance imaging; mm: millimetre; N+: node positive; PET: positron emission tomography; RF: risk factor; SLNB: sentinel lymph node biopsy; US: ultrasound.

Table 2. Summary results from studies of imaging for primary staging or re-staging

Test	Studies	Participants (cases)	Sensitivity (95% CI), %	Specificity (95% CI), %
Comparison of imaging tests before SLNB				
Indirect comparison of imaging tests for detection of nodal metastasis (per patient data)				
US	11	2614 (542)	35.4 (17.0 to 59.4)	93.9 (86.1 to 97.5)
US-FNAC	3	1164 (259)	18.0 (3.58 to 56.5)	99.8 (99.1 to 99.9)
PET-CT	4	170 (49)	10.2 (4.31 to 22.3)	96.5 (87.1 to 99.1)
Difference			P = 0.07	P < 0.001
Direct comparison of imaging tests for detection of nodal metastasis (per patient data)				
US	3	1164 (259)	58.7 (36.5 to 77.9)	79.4 (70.0 to 86.4)
US-FNAC	3	1164 (259)	18.0 (3.58 to 56.5)	99.8 (99.1 to 99.9)
Difference			-40.7 (-75.0 to -6.50), P = 0.02	+20.4 (+12.2 to +28.6), P < 0.001
Whole body imaging				
Imaging for re-staging for the detection of any metastasis (per patient data)				
PET-CT	2[a]	153 (95)	92.6 (85.3 to 96.4)	89.7 (78.8 to 95.3)

CI: confidence interval; CT: computed tomography; FNAC: fine needle aspiration cytology; PET: positron emission tomography; SLNB: sentinel lymph node biopsy; US: ultrasound.

[a] Where there were only two studies, estimates of summary sensitivity and summary specificity were obtained by using univariate fixed-effect logistic regression models to pool sensitivities and specificities separately.

Table 3. Characteristics of studies conducted in mixed or unclear population groups

Study Population group	Participant inclusion criteria and reported indications for imaging	Stage of disease on presentation	Imaging tests	Patients/cases (prevalence) [lesions/metastases (prevalence)]	Average no. metastases per patient
PER PATIENT DATA					
Abbott 2011 **Mixed** - primary or follow-up	Undergoing FU after prior SLNB/ CLND for micrometastases or presenting with	Stage: IIIA 18, 53% IIIB 10, 29% IIIC 6, 18%	PET-CT (NR)	34/7 (21%)	N/A

Table 3. Characteristics of studies conducted in mixed or unclear population groups (*Continued*)

	clinically detectable nodal disease at or subsequent to initial diagnosis				
Aukema 2010a **Mixed** - primary or re-staging	Asymptomatic S100 positive. Previously treated for locoregional recurrence (n = 15) or distant metastases (n = 5); or with unfavourable primary tumour (n = 6), primary melanoma with simultaneous nodal metastases (n = 20)	Any (stage NR)	PET-CT (U)	46/23 (50%)	N/A
Aukema 2010b **Unclear**	Palpable and pathology proven lymph node metastases and no signs of distant metastases. Imaging to identify further 'undetected' disease	Stage III: 100%	PET-CT (U)	70/30 (43%)	N/A
Bastiaannet 2009 **Mixed** - primary or re-staging	Node positive (clinical or histology/cytology proven) candidates for CLND; imaging to identify further disease. Includes those with LN mets diagnosed at time of primary diagnosis 39, 15.5%; LN metastases identified ≤ 3 years since primary diagnosis 145, 57.8%; recurrence > 3 years since primary diagnosis 67, 26.7%	Stage III (100%)	CT (CE)	251/78 (31%) distant metastases	N/A
Cachin 2014 **Mixed** - staging or re-staging	Any primary MM, visceral metastases, or cutaneous metas-	Any; 51% with metastases	PET-CT (NR)	67/39 (58%) [176/85 (48%)]	N/A

Table 3. Characteristics of studies conducted in mixed or unclear population groups (*Continued*)

	tases from unknown primary				
Klebl 2003 **Mixed**	Clark level IV or V undergoing FU after primary surgery. Reports primary (n = 8) and imaging during follow-up (n = 75)	Any (NR)	US	79/17 (22%) nodal	N/A
Reinhardt 2006 **Mixed** - primary, re-staging, FU, disease response	All with PET-CT for primary staging after sentinel node biopsy (n = 75); therapy control after chemotherapy of metastatic disease (n = 42); staging of clinically suspected recurrent disease (n = 65); during follow-up within 5 years of primary treatment (n = 68)	Stage I 22, 9% Stage II 88, 35% Stage III 108, 43% Stage IV 32, 13%	CT (CE) PET-CT (CE)	250/116 (46%)	N/A
Strobel 2007b **Unclear**	High risk melanoma (BT > 4 mm, or Clark level III or IV, or known resected metastases) with PET-CT for depiction or exclusion of metastases	Any (NR)	PET-CT (CE)	124/53 (43%)	N/A
van den Brekel 1998 **Mixed** - primary and recurrence	Head and neck MM with CT before neck dissection, including therapeutic and elective (negative on palpation). "Interval between the treatment of the primary and the neck dissection ranged from 0 to 8. 8 years (mean: 21 months)"	Stage I to II 8, 31% Stage III 18, 69%	CT (CE)	26/21 (81%) nodal	N/A

Table 3. Characteristics of studies conducted in mixed or unclear population groups (*Continued*)

van Wissen 2016 **Mixed** - primary and recurrence	Stage IIIB or IIIC MM with palpable groin metastases; selected for therapeutic combined groin dissection. Discussion states: "large proportion of our patients were initially treated for their primary tumour at other hospitals, and sometimes years prior to the current groin dissection"	All stage IIIB and C	PET-CT (U)	69/59 (superficial nodes 86%) 67/24 (deep nodes 36%)	N/A
PER LESION DATA					
Cachin 2014 **Mixed** - staging or re-staging	Any primary MM, visceral metastases, or cutaneous metastases from unknown primary. Lesions with equivocal focal uptake considered test positive *Only 1 eligible index test*	Any: 51% with metastases	CT (NR)	67/39 (58%) [176/85 (48%)]	1 (85/67)
Dellestable 2011 **Mixed** - primary or follow-up	All with PET-CT regardless of AJCC stage or indication for examination *Number of lesions included varies per test*	Stage I to II: 27.5% Stage III to IV: 72.5%	CT (CE) MRI (DW) PET-CT	40 [108/66 (61%)] [117/70 (60%)] [119/72 (61%)]	2 (72/40)
Hausmann 2011 **Unclear**	AJCC stage III or IV with positive SLNB or suspicious lesions on ultrasound or X-ray studies *Number of lesions included same per test*	Stage III 38% Stage IV 62%	CT (CE) MRI (NR)	33 All tests [824/455 (55%)]	14 (455/33)
Jouvet 2014 **Unclear**	AJCC stage IV. *Number of lesions included varies per test*	Stage IV: 100%	CT (CE) MRI (DW) MRI (DW + ultrafast GE)	37 (218 lesions) [209/115 (55%)] [218/125 (57%)] [191/104 excl brain	3 (125/37)

Table 3. Characteristics of studies conducted in mixed or unclear population groups (*Continued*)

			PET-CT	(54%)]	
Pfannenberg 2007 **Mixed** - incl primary, FU, and NR	Stage III or IV imaged before surgery due to abnormal radiological, clinical, and laboratory findings, or routine surveillance in high risk *Number of lesions included same per test*	Stage III: 39% Stage IV: 61%	CT (CE) MRI (DW + ultrafast GE) PET-CT	64 All tests [420/297 (71%)]	5 (297/64)
Pfluger 2011 **Mixed** - primary or follow-up	Melanoma with regional lymph node metastases; excluded any lesions newly arising during follow-up *Number of lesions included same per test*	Stage III: 100%	CT (CE); CT (U) PET-CT (CE); (U)	50 All tests [232/151 (65%)]	3 (151/50)

AJCC: American Joint Cancer Committee; BT: Breslow thickness; CE: contrast enhanced; CLND: complete lymph node dissection; CT: computed tomography; DW: diffusion weighted; FNAC: fine needle aspiration cytology; FU: follow-up; GE: gradient echo; HN: head and neck; LN: lymph node; MM: malignant melanoma; MRI: magnetic resonance imaging; mm: millimetre; N+: node positive; N/A: not applicable; NR: not reported; PET: positron emission tomography; SLNB: sentinel lymph node biopsy; U: unenhanced; US: ultrasound; VIBE: MRI sequence.

APPENDICES

Appendix 1. Current content and structure of the Programme Grant

	LIST OF REVIEWS	Number of studies
	Diagnosis of melanoma	
1	Visual inspection	49
2	Dermoscopy ± visual inspection	104
3	Teledermatology	22

(*Continued*)

4	Smartphone applications	2
5a	Computer-aided diagnosis - dermoscopy-based techniques	42
5b	Computer-aided diagnosis - spectroscopy-based techniques	Review amalgamated into 5a
6	Reflectance confocal microscopy	18
7	High frequency ultrasound	5
	Diagnosis of keratinocyte skin cancer (BCC and cSCC)	
8	Visual inspection ± Dermoscopy	24
5c	Computer-aided diagnosis - dermoscopy-based techniques	Review amalgamated into 5a
5d	Computer-aided diagnosis - spectroscopy-based techniques	Review amalgamated into 5a
9	Optical coherence tomography	5
10	Reflectance confocal microscopy	10
11	Exfoliative cytology	9
	Staging of melanoma	
12	Imaging tests (ultrasound, CT, MRI, PET-CT)	39
13	Sentinel lymph node biopsy	155
	Staging of cSCC	
14	Imaging tests review	Review dropped; only 1 study identified
15	Sentinel lymph node biopsy	Review amalgamated into 13 above (n = 15 studies)

Appendix 2. Glossary of terms

Term	Definition
Adjuvant therapy or treatment	A treatment given after the main treatment for cancer to reduce the risk of recurrence
Adverse event	Detrimental change in health occurring in a person receiving the treatment whether or not it has been caused by the treatment
Axillary	In the armpit.
Biopsy	Removal of a sample of tissue from the body to assist in diagnosis or inform the choice of treatment of a disease
BRAF V600 mutation	*BRAF* is a human gene that makes a protein called B-Raf, which is involved in the control of cell growth. *BRAF* mutations (damaged DNA) occur in around 40% of melanomas, which can then be treated with particular drugs
BRAF inhibitors	Therapeutic agents that inhibit the serine-threonine protein kinase *BRAF* mutated metastatic melanoma.
Breslow thickness	A scale for measuring the thickness of melanomas by the pathologist using a microscope, measured in mm from the top layer of skin to the bottom of the tumour
Cervical (lymph nodes)	Lymph nodes found in the neck area of the body.
Computed tomography (CT)	Imaging technique in which the person lies on a table within an X-ray gantry. The images are acquired using a spiral (helical) path and banks of detectors, allowing presentation of the internal organs and blood vessels in different projections including 3D views
Coronal	Frontal plane dividing the body into front and back.
False negative	An individual who is truly positive for a disease, but whom a diagnostic test classifies as disease-free
False positive	An individual who is truly disease-free, but whom a diagnostic test classifies as having the disease
Histopathology	The study of tissue, usually obtained by biopsy or excision, for example under a microscope
Incidence	The number of new cases of a disease in a given time period.
Inguinal	Lymph nodes in or just above or just below the groin.
Isolated limb perfusion	A medical procedure that directly delivers a drug through the bloodstream in a limb to the site affected by melanoma
Local recurrence	Re-growth of a tumour in the area from which it was originally removed

(*Continued*)

Locoregional recurrence	Re-growth of a tumour in the area from which it was originally removed or in the regional lymph nodes (usually nearest to the original tumour site)
Lymph node	Lymph nodes filter the lymphatic fluid (clear fluid containing white blood cells) that travels around the body to help fight disease; they are located throughout the body often in clusters (nodal basins)
Lymph node dissection	Surgical removal or 1 or more lymph nodes in the absence of proven involvement with melanoma
Lymphadenectomy	Lymphadenectomy or lymph node dissection is a surgical operation to remove 1 or more groups of lymph nodes
Lymphoscintigraphy	An imaging technique used to identify the lymph drainage basin, determine the number of sentinel nodes, differentiate sentinel nodes from subsequent nodes, locate the sentinel node in an unexpected location, and mark the sentinel node over the skin for biopsy. It requires the injection of a radioisotope into the skin around the biopsy scar and a scan some hours later to determine to which lymph nodes the tracer has travelled
Lymphovascular invasion	Tumour cells that have spread to involve the blood vessels and lymphatic vessels within the skin
Magnetic resonance imaging (MRI)	A type of scan that uses a magnetic field and radio waves to produce images of sections of the body
Mediastinal and hilar adenopathy	Enlargement of the pulmonary lymph nodes.
MEK inhibitors	Drugs that inhibit the mitogen-activated protein kinase enzymes, which are often up-regulated in melanoma
Meta-analysis	A form of statistical analysis used to synthesise results from a collection of individual studies
Metastases/metastatic disease	Spread of cancer away from the primary site to somewhere else through the bloodstream or the lymphatic system
Micro-metastases	Micro-metastases are metastases so small that they can be seen only under a microscope
Mitotic rate	Microscopic evaluation of the number of cells actively dividing in a tumour
Morbidity	Detrimental effects on health.
Mortality	Either (1) the condition of being subject to death; or (2) the death rate, which reflects the number of deaths per unit of population in relation to any specific region, age group, disease, treatment, or other classification, usually expressed as deaths per 100, 1000, 10, 000, or 100,000 people

(*Continued*)

Multi-disciplinary team	A team with members from different healthcare professions and specialties (e.g. urology, oncology, pathology, radiology, nursing). Cancer care in the National Health Service (NHS) uses this system to ensure that all relevant health professionals are engaged to discuss the best possible care for a patient
Nodal basin	Cluster of lymph nodes that filter lymphatic fluid as it travels around the body; clusters are located under the arm (axilla) and in the groin, neck, chest, and abdomen
Oncology	The study of cancers. This term also refers to the medical specialty of cancer care, with particular reference to the use of radiotherapy or drugs to treat cancer. The medical specialty is often split into clinical oncology (doctors who use radiotherapy and drug treatment) and medical oncology (doctors who use drug treatment)
Palpation	Feeling with the fingers or hands as part of a clinical examination of the body
Positron emission tomography (PET)	A nuclear medicine imaging technique whereby a radioactive glucose (usually ^{18}FDG) is administered intravenously before a scan is conducted to create an image using colours to show where the FDG (or other radioactive tracer) has been taken up in the body
Prevalence	The proportion of a population found to have a condition.
Prognostic factors/indicators	Specific characteristics of a cancer or the person who has it that might affect the patient's prognosis
Radiotherapy	The use of radiation, usually high-energy X-rays, to control the growth of cancer cells
RAS-RAF-MEK-ERK signalling pathway	A chain of proteins that allow signals from a receptor on the surface of a cell to be sent to the DNA in the cell nucleus; a mutation in one of the proteins in the pathway is associated with the development of many cancers
Recurrence	Recurrence occurs when new cancer cells are detected following treatment. This can occur either at the site of the original tumour or at other sites in the body
Relapse	Where cancer starts to grow again after treatment.
Sagittal	Median plane dividing the body into left and right.
Sensitivity	In this context, the term is used to mean the proportion of individuals with a disease who have that disease correctly identified by the study test
Sentinel lymph node biopsy (SLNB)	A radioactive tracer and blue dye are injected into the skin surrounding the primary lesion and the 'sentinel' lymph nodes to which the tracer drains are located by imaging (usually lymphoscintigraphy) and then are removed and examined for nodal metastatic spread that cannot be detected clinically or on imaging
Signal transduction	Occurs when extracellular signalling molecules activate a specific receptor, which then triggers cellular pathways

(*Continued*)

Staging	Clinical description of the size and spread of a patient's tumour, fitting into internationally agreed categories
Stereotactic radiotherapy	A technique for delivering high-dose radiotherapy very accurately to small areas inside the body, which reduces damage done by radiotherapy to adjacent healthy tissues
Subclinical (disease)	Disease that usually is asymptomatic and is not easily observable (e.g. by clinical or physical examination)
Systemic treatment	Treatment, usually given by mouth or by injection, that reaches and affects cancer cells throughout the body rather than targeting one specific area
Ultrasound	A type of scan in which high-frequency sound waves are used to outline a part of the body

Appendix 3. Table of acronyms

Acronym	Definition
μm	micrometre
AK	actinic keratosis
ANN	artificial neural network
BCC	basal cell carcinoma
BD	Bowen's disease
BPC	between-person comparison (of tests)
CAD	computer-assisted diagnosis
CCS	case-control study
CS	case series
cSCC	cutaneous squamous cell carcinoma
D-	disease negative
D+	disease positive
Derm-CAD	digital dermoscopy-based computer-assisted diagnosis

(*Continued*)

DF	dermatofibroma
DRS	diffuse reflectance spectroscopy
DRSi	diffuse reflectance spectroscopy imaging
Dx	diagnosis
EIS	electrical impedance spectroscopy
FN	false negative
FP	false positive
FU	follow- up
GP	general practitioner
H&E	haematoxylin and eosin stain
HFUS	high-frequency ultrasound
Hz	hertz
KHz	kilohertz
K-NN	k nearest neighbour
MHz	megahertz
MiS	melanoma in situ (or lentigo maligna)
MM	malignant melanoma
mm	millimetre
MSI	multi-spectral imaging
N/A	not applicable
NC	non-comparative
nm	nanometre
NPV	negative predictive value
NR	not reported

(*Continued*)

P	prospective
PPV	positive predictive value
PSL	pigmented skin lesion
R	retrospective
RCM	reflectance confocal microscopy
RCT	randomised controlled trial
SCC	squamous cell carcinoma
SD	standard deviation
se	sensitivity
sp	specificity
spectro-CAD	spectroscopy-based computer-assisted diagnosis
SK	seborrhoeic keratosis
SSM	superficial spreading melanoma
SVM	support vector machine
TN	true negative
TS	telespectrophotometry system
VI	visual inspection
UNREF	unreferred population
WPC	within-person comparison (of tests)
WPC-algs	within-person comparison (of algorithms)

Appendix 4. Proposed sources of heterogeneity

These may vary between reviews but may include the following.

i. Population characteristics

- AJCC stage of disease
- Sentinel lymph node status (for imaging studies only)
- Clinical nodal status (for imaging studies only)
- Primary tumour site (head and neck, trunk, limb, and other)

ii. Index test characteristics

- Differences in test positivity thresholds (e.g. for SLNB, the tracer threshold for a 'hot' vs 'cold' node)
- Other relevant test characteristics as appropriate to the test under consideration

iii. Reference standard characteristics

- Reference standard used (histology, clinical, or imaging-based follow-up; concurrent imaging-based reference standard)

iv. Study quality

- Consecutive or random sample of participants recruited
- Index test interpreted, blinded to the reference standard result
- Index test interpreted, blinded to the result of any other index test
- Presence of partial or differential verification bias (whereby only a sample of those subject to the index test are verified by the reference test or by the same reference test, with selection dependent on the index test result)
- Use of an adequate reference standard
- Overall risk of bias

Appendix 5. Final search strategies

Melanoma search strategies to August 2016
Database: Ovid MEDLINE(R) 1946 to August Week 3 2016
Search strategy:
1 exp melanoma/
2 exp skin cancer/
3 exp basal cell carcinoma/
4 basalioma$1.ti,ab.
5 ((basal cell or skin) adj2 (cancer$1 or carcinoma$1 or mass or masses or tumour$1 or tumor$1 or neoplasm$1 or adenoma$1 or epithelioma$1 or lesion$1 or malignan$ or nodule$1)).ti,ab.
6 (pigmented adj2 (lesion$1 or mole$ or nevus or nevi or naevus or naevi or skin)).ti,ab.
7 (melanom$1 or nonmelanoma$1 or non-melanoma$1 or melanocyt$ or non-melanocyt$ or nonmelanocyt$ or keratinocyt$).ti,ab.
8 nmsc.ti,ab.
9 (squamous cell adj2 (cancer$1 or carcinoma$1 or mass or masses or tumor$1 or tumour$1 or neoplasm$1 or adenoma$1 or epithelioma$1 or epithelial or lesion$1 or malignan$ or nodule$1) adj2 (skin or epiderm$ or cutaneous)).ti,ab.
10 (BCC or CSCC or NMSC).ti,ab.
11 keratinocy$.ti,ab.
12 Keratinocytes/
13 or/1-12
14 dermoscop$.ti,ab.
15 dermatoscop$.ti,ab.
16 photomicrograph$.ti,ab.

17 exp epiluminescence microscopy/
18 (epiluminescence adj2 microscop$).ti,ab.
19 (confocal adj2 microscop$).ti,ab.
20 (incident light adj2 microscop$).ti,ab.
21 (surface adj2 microscop$).ti,ab.
22 (visual adj (inspect$ or examin$)).ti,ab.
23 ((clinical or physical) adj examin$).ti,ab.
24 3 point.ti,ab.
25 three point.ti,ab.
26 pattern analys$.ti,ab.
27 ABCD$.ti,ab.
28 menzies.ti,ab.
29 7 point.ti,ab.
30 seven point.ti,ab.
31 (digital adj2 (dermoscop$ or dermatoscop$)).ti,ab.
32 artificial intelligence.ti,ab.
33 AI.ti,ab.
34 computer assisted.ti,ab.
35 computer aided.ti,ab.
36 neural network$.ti,ab.
37 exp diagnosis, computer-assisted/
38 MoleMax.ti,ab.
39 image process$.ti,ab.
40 automatic classif$.ti,ab.
41 image analysis.ti,ab.
42 SIAscop$.ti,ab.
43 Aura.ti,ab.
44 (optical adj2 scan$).ti,ab.
45 MelaFind.ti,ab.
46 SIMSYS.ti,ab.
47 MoleMate.ti,ab.
48 SolarScan.ti,ab.
49 VivaScope.ti,ab.
50 (high adj3 ultraso$).ti,ab.
51 (canine adj2 detect$).ti,ab.
52 ((mobile or cell or cellular or smart) adj ((phone$1 adj2 app$1) or application$1)).ti,ab.
53 smartphone$.ti,ab.
54 (DermoScan or SkinVision or DermLink or SpotCheck).ti,ab.
55 Mole Detective.ti,ab.
56 Spot Check.ti,ab.
57 (mole$1 adj2 map$).ti,ab.
58 (total adj2 body).ti,ab.
59 exfoliative cytolog$.ti,ab.
60 digital analys$.ti,ab.
61 (image$1 adj3 software).ti,ab.
62 (teledermatolog$ or tele-dermatolog$ or telederm or tele-derm or teledermoscop$ or tele-dermoscop$ or teledermatoscop$ or tele-dermatoscop$).ti,ab.
63 (optical coherence adj (technolog$ or tomog$)).ti,ab.
64 (computer adj2 diagnos$).ti,ab.
65 exp sentinel lymph node biopsy/
66 (sentinel adj2 node).ti,ab.
67 nevisense.mp. or HFUS.ti,ab.
68 electrical impedance spectroscopy.ti,ab.

69 history taking.ti,ab.
70 patient history.ti,ab.
71 (naked eye adj (exam$ or assess$)).ti,ab.
72 (skin adj exam$).ti,ab.
73 physical examination/
74 ugly duckling.mp. or UD.ti,ab.
75 ((physician$ or clinical or physical) adj (exam$ or triage or recog$)).ti,ab.
76 ABCDE.mp. or VOC.ti,ab.
77 clinical accuracy.ti,ab.
78 Family Practice/ or Physicians, Family/ or clinical competence/
79 (confocal adj2 microscop$).ti,ab.
80 diagnostic algorithm$1.ti,ab.
81 checklist$.ti,ab.
82 virtual imag$1.ti,ab.
83 volatile organic compound$1.ti,ab.
84 dog$1.ti,ab.
85 gene expression analy$.ti,ab.
86 reflex transmission imag$.ti,ab.
87 thermal imaging.ti,ab.
88 elastography.ti,ab.
89 or/14-88
90 (CT or PET).ti,ab.
91 PET-CT.ti,ab.
92 (FDG or F18 or Fluorodeoxyglucose or radiopharmaceutical$).ti,ab.
93 exp Deoxyglucose/
94 deoxy-glucose.ti,ab.
95 deoxyglucose.ti,ab.
96 CATSCAN.ti,ab.
97 exp Tomography, Emission-Computed/
98 exp Tomography, X-ray computed/
99 positron emission tomograph$.ti,ab.
100 exp magnetic resonance imaging/
101 (MRI or fMRI or NMRI or scintigraph$).ti,ab.
102 exp echography/
103 Doppler echography.ti,ab.
104 sonograph$.ti,ab.
105 ultraso$.ti,ab.
106 doppler.ti,ab.
107 magnetic resonance imag$.ti,ab.
108 or/90-107
109 (stage$ or staging or metasta$ or recurrence or sensitivity or specificity or false negative$ or thickness$).ti,ab.
110 "Sensitivity and Specificity"/
111 exp cancer staging/
112 or/109-111
113 108 and 112
114 89 or 113
115 13 and 114

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations August 29, 2016

Search strategy:

1 basalioma$1.ti,ab.
2 ((basal cell or skin) adj2 (cancer$1 or carcinoma$1 or mass or masses or tumour$1 or tumor$1 or neoplasm$1 or adenoma$1 or epithelioma$1 or lesion$1 or malignan$ or nodule$1)).ti,ab.
3 (pigmented adj2 (lesion$1 or mole$ or nevus or nevi or naevus or naevi or skin)).ti,ab.

4 (melanom$1 or nonmelanoma$1 or non-melanoma$1 or melanocyt$ or non-melanocyt$ or nonmelanocyt$ or keratinocyt$).ti,ab.
5 nmsc.ti,ab.
6 (squamous cell adj2 (cancer$1 or carcinoma$1 or mass or masses or tumor$1 or tumour$1 or neoplasm$1 or adenoma$1 or epithelioma$1 or epithelial or lesion$1 or malignan$ or nodule$1) adj2 (skin or epiderm$ or cutaneous)).ti,ab.
7 (BCC or CSCC or NMSC).ti,ab.
8 keratinocy$.ti,ab.
9 or/1-8
10 dermoscop$.ti,ab.
11 dermatoscop$.ti,ab.
12 photomicrograph$.ti,ab.
13 (epiluminescence adj2 microscop$).ti,ab.
14 (confocal adj2 microscop$).ti,ab.
15 (incident light adj2 microscop$).ti,ab.
16 (surface adj2 microscop$).ti,ab.
17 (visual adj (inspect$ or examin$)).ti,ab.
18 ((clinical or physical) adj examin$).ti,ab.
19 3 point.ti,ab.
20 three point.ti,ab.
21 pattern analys$.ti,ab.
22 ABCD$.ti,ab.
23 menzies.ti,ab.
24 7 point.ti,ab.
25 seven point.ti,ab.
26 (digital adj2 (dermoscop$ or dermatoscop$)).ti,ab.
27 artificial intelligence.ti,ab.
28 AI.ti,ab.
29 computer assisted.ti,ab.
30 computer aided.ti,ab.
31 neural network$.ti,ab.
32 MoleMax.ti,ab.
33 image process$.ti,ab.
34 automatic classif$.ti,ab.
35 image analysis.ti,ab.
36 SIAscop$.ti,ab.
37 Aura.ti,ab.
38 (optical adj2 scan$).ti,ab.
39 MelaFind.ti,ab.
40 SIMSYS.ti,ab.
41 MoleMate.ti,ab.
42 SolarScan.ti,ab.
43 VivaScope.ti,ab.
44 (high adj3 ultraso$).ti,ab.
45 (canine adj2 detect$).ti,ab.
46 ((mobile or cell or cellular or smart) adj ((phone$1 adj2 app$1) or application$1)).ti,ab.
47 smartphone$.ti,ab.
48 (DermoScan or SkinVision or DermLink or SpotCheck).ti,ab.
49 Mole Detective.ti,ab.
50 Spot Check.ti,ab.
51 (mole$1 adj2 map$).ti,ab.
52 (total adj2 body).ti,ab.
53 exfoliative cytolog$.ti,ab.
54 digital analys$.ti,ab.
55 (image$1 adj3 software).ti,ab.

56 (teledermatolog$ or tele-dermatolog$ or telederm or tele-derm or teledermoscop$ or tele-dermoscop$ or teledermatoscop$ or tele-dermatoscop$).ti,ab.
57 (optical coherence adj (technolog$ or tomog$)).ti,ab.
58 (computer adj2 diagnos$).ti,ab.
59 (sentinel adj2 node).ti,ab.
60 nevisense.mp. or HFUS.ti,ab.
61 electrical impedance spectroscopy.ti,ab.
62 history taking.ti,ab.
63 patient history.ti,ab.
64 (naked eye adj (exam$ or assess$)).ti,ab.
65 (skin adj exam$).ti,ab.
66 ugly duckling.mp. or UD.ti,ab.
67 ((physician$ or clinical or physical) adj (exam$ or triage or recog$)).ti,ab.
68 ABCDE.mp. or VOC.ti,ab.
69 clinical accuracy.ti,ab.
70 (Family adj (Practice or Physicians)).ti,ab.
71 (confocal adj2 microscop$).ti,ab.
72 clinical competence.ti,ab.
73 diagnostic algorithm$1.ti,ab.
74 checklist$.ti,ab.
75 virtual imag$1.ti,ab.
76 volatile organic compound$1.ti,ab.
77 dog$1.ti,ab.
78 gene expression analy$.ti,ab.
79 reflex transmission imag$.ti,ab.
80 thermal imaging.ti,ab.
81 elastography.ti,ab.
82 or/10-81
83 (CT or PET).ti,ab.
84 PET-CT.ti,ab.
85 (FDG or F18 or Fluorodeoxyglucose or radiopharmaceutical$).ti,ab.
86 deoxy-glucose.ti,ab.
87 deoxyglucose.ti,ab.
88 CATSCAN.ti,ab.
89 positron emission tomograph$.ti,ab.
90 (MRI or fMRI or NMRI or scintigraph$).ti,ab.
91 Doppler echography.ti,ab.
92 sonograph$.ti,ab.
93 ultraso$.ti,ab.
94 doppler.ti,ab.
95 magnetic resonance imag$.ti,ab.
96 or/83-95
97 (stage$ or staging or metasta$ or recurrence or sensitivity or specificity or false negative$ or thickness$).ti,ab.
98 96 and 97
99 82 or 98
100 9 and 99

Database: Embase 1974 to 2016 August 29

Search strategy:
1 *melanoma/
2 *skin cancer/
3 *basal cell carcinoma/
4 basalioma$.ti,ab.

5 ((basal cell or skin) adj2 (cancer$1 or carcinoma$1 or mass or masses or tumour$1 or tumor$1 or neoplasm$ or adenoma$ or epithelioma$ or lesion$ or malignan$ or nodule$)).ti,ab.
6 (pigmented adj2 (lesion$1 or mole$ or nevus or nevi or naevus or naevi or skin)).ti,ab.
7 (melanom$1 or nonmelanoma$1 or non-melanoma$1 or melanocyt$ or non-melanocyt$ or nonmelanocyt$ or keratinocyt$).ti,ab.
8 nmsc.ti,ab.
9 (squamous cell adj2 (cancer$1 or carcinoma$1 or mass or tumor$1 or tumour$1 or neoplasm$1 or adenoma$1 or epithelioma$1 or epithelial or lesion$1 or malignan$ or nodule$1) adj2 (skin or epiderm$ or cutaneous)).ti,ab.
10 (BCC or cscc).mp. or NMSC.ti,ab.
11 keratinocyte.ti,ab.
12 keratinocy$.ti,ab.
13 or/1-12
14 dermoscop$.ti,ab.
15 dermatoscop$.ti,ab.
16 photomicrograph$.ti,ab.
17 *epiluminescence microscopy/
18 (epiluminescence adj2 microscop$).ti,ab.
19 (confocal adj2 microscop$).ti,ab.
20 (incident light adj2 microscop$).ti,ab.
21 (surface adj2 microscop$).ti,ab.
22 (visual adj (inspect$ or examin$)).ti,ab.
23 ((clinical or physical) adj examin$).ti,ab.
24 3 point.ti,ab.
25 three point.ti,ab.
26 pattern analys$.ti,ab.
27 ABCD$.ti,ab.
28 menzies.ti,ab.
29 7 point.ti,ab.
30 seven point.ti,ab.
31 (digital adj2 (dermoscop$ or dermatoscop$)).ti,ab.
32 artificial intelligence.ti,ab.
33 AI.ti,ab.
34 computer assisted.ti,ab.
35 computer aided.ti,ab.
36 neural network$.ti,ab.
37 MoleMax.ti,ab.
38 exp diagnosis, computer-assisted/
39 image process$.ti,ab.
40 automatic classif$.ti,ab.
41 image analysis.ti,ab.
42 SIAscop$.ti,ab.
43 (optical adj2 scan$).ti,ab.
44 Aura.ti,ab.
45 MelaFind.ti,ab.
46 SIMSYS.ti,ab.
47 MoleMate.ti,ab.
48 SolarScan.ti,ab.
49 VivaScope.ti,ab.
50 confocal microscop$.ti,ab.
51 (high adj3 ultraso$).ti,ab.
52 (canine adj2 detect$).ti,ab.
53 ((mobile or cell$ or cellular or smart) adj ((phone$1 adj2 app$1) or application$1)).ti,ab.
54 smartphone$.ti,ab.
55 (DermoScan or SkinVision or DermLink or SpotCheck).ti,ab.

56 Spot Check.ti,ab.
57 Mole Detective.ti,ab.
58 (mole$1 adj2 map$).ti,ab.
59 (total adj2 body).ti,ab.
60 exfoliative cytolog$.ti,ab.
61 digital analys$.ti,ab.
62 (image$1 adj3 software).ti,ab.
63 (optical coherence adj (technolog$ or tomog$)).ti,ab.
64 (teledermatolog$ or tele-dermatolog$ or telederm or tele-derm or teledermoscop$ or tele-dermoscop$ or teledermatoscop$).mp. or tele-dermatoscop$.ti,ab.
65 (computer adj2 diagnos$).ti,ab.
66 *sentinel lymph node biopsy/
67 (sentinel adj2 node).ti,ab.
68 nevisense.ti,ab.
69 HFUS.ti,ab.
70 electrical impedance spectroscopy.ti,ab.
71 history taking.ti,ab.
72 patient history.ti,ab.
73 (naked eye adj (exam$ or assess$)).ti,ab.
74 (skin adj exam$).ti,ab.
75 *physical examination/
76 ugly duckling.ti,ab.
77 UD sign$.ti,ab.
78 ((physician$ or clinical or physical) adj (exam$ or recog$ or triage)).ti,ab.
79 ABCDE.ti,ab.
80 clinical accuracy.ti,ab.
81 *general practice/
82 (confocal adj2 microscop$).ti,ab.
83 clinical competence/
84 diagnostic algorithm$.ti,ab.
85 checklist$1.ti,ab.
86 virtual image$1.ti,ab.
87 volatile organic compound$1.ti,ab.
88 VOC.ti,ab.
89 dog$1.ti,ab.
90 gene expression analys$.ti,ab.
91 reflex transmission imaging.ti,ab.
92 thermal imaging.ti,ab.
93 elastography.ti,ab.
94 dog$1.ti,ab.
95 gene expression analys$.ti,ab.
96 reflex transmission imaging.ti,ab.
97 thermal imaging.ti,ab.
98 elastography.ti,ab.
99 or/14-93
100 PET-CT.ti,ab.
101 (CT or PET).ti,ab.
102 (FDG or F18 or Fluorodeoxyglucose or radiopharmaceutical$).ti,ab.
103 exp Deoxyglucose/
104 CATSCAN.ti,ab.
105 deoxyglucose.ti,ab.
106 deoxy-glucose.ti,ab.
107 *positron emission tomography/

108 *computer assisted tomography/
109 positron emission tomograph$.ti,ab.
110 *nuclear magnetic resonance imaging/
111 (MRI or fMRI or NMRI or scintigraph$).ti,ab.
112 *echography/
113 Doppler.ti,ab.
114 sonograph$.ti,ab.
115 ultraso$.ti,ab.
116 magnetic resonance imag$.ti,ab.
117 or/100-116
118 (stage$ or staging or metasta$ or recurrence or sensitivity or specificity or false negative$ or thickness$).ti,ab.
119 "Sensitivity and Specificity"/
120 *cancer staging/
121 or/118-120
122 117 and 121
123 99 or 122
124 13 and 123

Database: Cochrane Library (Wiley) 2016 searched 30 August 2016 CDSR issue 8 of 12 2016 CENTRAL Issue 7 of 12 2016 HTA Issue 3 of 4 July 2016 DARE Issue 3 of 4 2015

Search strategy:
#1 melanoma* or nonmelanoma* or non-melanoma* or melanocyt* or non-melanocyt* or nonmelanocyt* or keratinocyte*
#2 MeSH descriptor: [Melanoma] explode all trees
#3 "skin cancer*"
#4 MeSH descriptor: [Skin Neoplasms] explode all trees
#5 skin near/2 (cancer* or carcinoma* or mass or masses or tumour* or tumor* or neoplasm* or adenoma* or epithelioma* or lesion* or malignan* or nodule*)
#6 nmsc
#7 "squamous cell" near/2 (cancer* or carcinoma* or mass or masses or tumour* or tumor* or neoplasm* or adenoma* or epithelioma* or lesion* or malignan* or nodule*) near/2 (skin or epiderm* or cutaneous)
#8 "basal cell" near/2 (cancer* or carcinoma* or mass or masses or tumour* or tumor* or neoplasm* or adenoma* or epithelioma* or lesion* or malignan* or nodule*)
#9 pigmented near/2 (lesion* or nevus or mole* or naevi or naevus or nevi or skin)
#10 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9
#11 dermoscop*
#12 dermatoscop*
#13 Photomicrograph*
#14 MeSH descriptor: [Dermoscopy] explode all trees
#15 confocal near/2 microscop*
#16 epiluminescence near/2 microscop*
#17 incident next light near/2 microscop*
#18 surface near/2 microscop*
#19 "visual inspect*"
#20 "visual exam*"
#21 (clinical or physical) next (exam*)
#22 "3 point"
#23 "three point"
#24 "pattern analys*"
#25 ABDC
#26 menzies
#27 "7 point"
#28 "seven point"
#29 digital near/2 (dermoscop* or dermatoscop*)
#30 "artificial intelligence"

#31 “AI”
#32 “computer assisted”
#33 “computer aided”
#34 AI
#35 “neural network*”
#36 MoleMax
#37 “computer diagnosis”
#38 “image process*”
#39 “automatic classif*”
#40 SIAscope
#41 “image analysis”
#42 “optical near/2 scan*”
#43 Aura
#44 MelaFind
#45 SIMSYS
#46 MoleMate
#47 SolarScan
#48 Vivascope
#49 “confocal microscopy”
#50 high near/3 ultraso*
#51 canine near/2 detect*
#52 Mole* near/2 map*
#53 total near/2 body
#54 mobile* or smart near/2 phone*
#55 cell next phone*
#56 smartphone*
#57 “mitotic index”
#58 DermoScan or SkinVision or DermLink or SpotCheck
#59 “Mole Detective”
#60 “Spot Check”
#61 mole* near/2 map*
#62 total near/2 body
#63 “exfoliative cytolog*”
#64 “digital analys*”
#65 image near/3 software
#66 teledermatolog* or tele-dermatolog* or telederm or tele-derm or teledermoscop* or tele-dermoscop* or teledermatoscop* or tele-dermatolog*
#67 “optical coherence” next (technolog* or tomog*)
#68 computer near/2 diagnos*
#69 sentinel near/2 node*
#70 #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67 or #68 or #69
#71 ultraso*
#72 sonograph*
#73 MeSH descriptor: [Ultrasonography] explode all trees
#74 Doppler
#75 CT or PET or PET-CT
#76 “CAT SCAN” or “CATSCAN”
#77 MeSH descriptor: [Positron-Emission Tomography] explode all trees
#78 MeSH descriptor: [Tomography, X-Ray Computed] explode all trees
#79 MRI

#80 MeSH descriptor: [Magnetic Resonance Imaging] explode all trees
#81 MRI or fMRI or NMRI or scintigraph*
#82 "magnetic resonance imag*"
#83 MeSH descriptor: [Deoxyglucose] explode all trees
#84 deoxyglucose or deoxy-glucose
#85 "positron emission tomograph*"
#86 #71 or #72 or #73 or #74 or #75 or #76 or #77 or #78 or #79 or #80 or #81 or #82 or #83 or #84 or #85
#87 stage* or staging or metasta* or recurrence or sensitivity or specificity or "false negative*" or thickness*
#88 MeSH descriptor: [Neoplasm Staging] explode all trees
#89 #87 or #88
#90 #89 and #86
#91 #70 or #90
#92 #10 and #91
#93 BCC or CSCC or NMCS
#94 keratinocy*
#95 #93 or #94
#96 #10 or #95
#97 nevisense
#98 HFUS
#99 "electrical impedance spectroscopy"
#100 "history taking"
#101 "patient history"
#102 naked next eye near/1 (exam* or assess*)
#103 skin next exam*
#104 "ugly duckling" or (UD sign*)
#105 MeSH descriptor: [Physical Examination] explode all trees
#106 (physician* or clinical or physical) near/1 (exam* or recog* or triage*)
#107 ABCDE
#108 "clinical accuracy"
#109 MeSH descriptor: [General Practice] explode all trees
#110 confocal near microscop*
#111 "diagnostic algorithm*"
#112 MeSH descriptor: [Clinical Competence] explode all trees
#113 checklist*
#114 "virtual image*"
#115 "volatile organic compound*"
#116 dog or dogs
#117 VOC
#118 "gene expression analys*"
#119 "reflex transmission imaging"
#120 "thermal imaging"
#121 elastography
#122 #97 or #98 or #99 or #100 or #101 or #102 or #103 or #104 or #105 or #106 or #107 or #108 or #109 or #110 or #111 or #112 or #113 or #114 or #115 or #116 or #117 or #118 or #119 or #120 or #121
#123 #70 or #122
#124 #96 and #123
#125 #96 and #90
#126 #125 or #124
#127 #10 and #126

Database: CINAHL Plus (EBSCO) 1937 to 30 August 2016

Search strategy:
S1 (MH "Melanoma") OR (MH "Nevi and Melanomas+")
S2 (MH "Skin Neoplasms+")

S3 (MH "Carcinoma, Basal Cell+")
S4 basalioma*
S5 (basal cell) N2 (cancer* or carcinoma* or mass or masses or tumor* or tumour* or neoplasm* or adenoma* or epithelioma* or lesion* or malignan* or nodule*)
S6 (pigmented) N2 (lesion* or mole* or nevus or nevi or naevus or naevi or skin)
S7 melanom* or nonmelanoma* or non-melanoma* or melanocyt* or non-melanocyt* or nonmelanocyt*
S8 nmsc
S9 TX BCC or cscc or NMSC
S10 (MH "Keratinocytes")
S11 keratinocyt*
S12 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11
S13 dermoscop* or dermatoscop* or photomicrograph* or (3 point) or (three point) or ABCD* or menzies or (7 point) or (seven point) or AI or Molemax or SIASCOP* or Aura or MelaFind or SIMSYS or MoleMate or SolarScan or smartphone* or DermoScan or SkinVision or DermLink or SpotCheck
S14 (epiluminescence or confocal or incident or surface) N2 (microscop*)
S15 visual N1 (inspect* or examin*)
S16 (clinical or physical) N1 (examin*)
S17 pattern analys*
S18 (digital) N2 (dermoscop* or dermatoscop*)
S19 (artificial intelligence)
S20 (computer) N2 (assisted or aided)
S21 (neural network*)
S22 (MH "Diagnosis, Computer Assisted+")
S23 (image process*)
S24 (automatic classif*)
S25 (image analysis)
S26 SIAScop*
S27 (optical) N2 (scan*)
S28 (high) N3 (ultraso*)
S29 elastography
S30 (mobile or cell or cellular or smart) N2 (phone*) N2 (app or application*)
S31 (mole*) N2 (map*)
S32 total N2 body
S33 exfoliative cytolog*
S34 digital analys*
S35 image N3 software
S36 teledermatolog* or tele-dermatolog* or telederm or tele-derm or teledermoscop* or tele-dermoscop* or teledermatoscop* or tele-dermatoscop* teledermatolog* or tele-dermatolog* or telederm or tele-derm or teledermoscop*
S37 (optical coherence) N1 (technolog* or tomog*)
S38 computer N2 diagnos*
S39 sentinel N2 node
S40 (MH "Sentinel Lymph Node Biopsy")
S41 nevisense or HFUS or checklist* or VOC or dog*
S42 electrical impedance spectroscopy
S43 history taking
S44 "Patient history"
S45 naked eye
S46 skin exam*
S47 physical exam*
S48 ugly duckling
S49 UD sign*
S50 (physician* or clinical or physical) N1 (exam*)
S51 clinical accuracy

S52 general practice
S53 (physician* or clinical or physical) N1 (recog* or triage)
S54 confocal microscop*
S55 clinical competence
S56 diagnostic algorithm*
S57 checklist*
S58 virtual image*
S59 volatile organic compound*
S60 gene expression analys*
S61 reflex transmission imag*
S62 thermal imaging
S63 S13 or S14 or S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59 OR S60 OR S61 OR S62
S64 CT or PET
S65 PET-CT
S66 FDG or F18 or Fluorodeoxyglucose or radiopharmaceutical*
S67 (MH "Deoxyglucose+")
S68 deoxy-glucose or deoxyglucose
S69 CATSCAN
S70 CAT-SCAN
S71 (MH "Deoxyglucose+")
S72 (MH "Tomography, Emission-Computed+")
S73 (MH "Tomography, X-Ray Computed")
S74 positron emission tomograph*
S75 (MH "Magnetic Resonance Imaging+")
S76 MRI or fMRI or NMRI or scintigraph*
S77 echography
S78 doppler
S79 sonograph*
S80 ultraso*
S81 magnetic resonance imag*
S82 S64 OR S65 OR S66 OR S67 OR S68 OR S69 OR S70 OR S71 OR S72 OR S73 OR S74 OR S75 OR S76 OR S77 OR S78 OR S79 OR S80 OR S81
S83 stage* or staging or metasta* or recurrence or sensitivity or specificity or (false negative*) or thickness
S84 (MH "Neoplasm Staging")
S85 S83 OR S84
S86 S82 AND S85
S87 S63 OR S86
S88 S12 AND S87

Database: Science Citation Index SCI Expanded (Web of Science) 1900 to 30 August 2016
Conference Proceedings Citation Index (Web of Science) 1900 to 1 September 2016

Search strategy:
#1 (melanom* or nonmelanom* or non-melanoma* or melanocyt* or non-melanocyt* or nonmelanocyt* or keratinocyt*)
#2 (basalioma*)
#3 ((skin) near/2 (cancer* or carcinoma or mass or masses or tumour* or tumor* or neoplasm* or adenoma* or epithelioma* or lesion* or malignan* or nodule*))
#4 ((basal) near/2 (cancer* or carcinoma* or mass or masses or tumour* or tumor* or neoplasm* or adenoma* or epithelioma* or lesion* or malignan* or nodule*))
#5 ((pigmented) near/2 (lesion* or mole* or nevus or nevi or naevus or naevi or skin))
#6 (nmsc or BCC or NMSC or keratinocy*)

#7 ((squamous cell (cancer* or carcinoma* or mass or masses or tumour* or tumor* or neoplasm* or adenoma* or epithelioma* or lesion* or malignan* or nodule*))
#8 (skin or epiderm* or cutaneous)
#9 #8 AND #7
#10 #9 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
#11 ((dermoscop* or dermatoscop* or photomicrograph* or epiluminescence or confocal or "incident light" or "surface microscop*" or "visual inspect*" or "physical exam*" or 3 point or three point or pattern analy* or ABCDE or menzies or 7 point or seven point or dermoscop* or dermatoscop* or AI or artificial or computer aided or computer assisted or neural network* or Molemax or image process* or automatic classif* or image analysis or siascope or optical scan* or Aura or melafind or simsys or molemate or solarscan or vivascope or confocal microscop* or high ultraso* or canine detect* or cellphone* or mobile* or phone* or smartphone or dermoscan or skinvision or dermlink or spotcheck or spot check or mole detective or mole map* or total body or exfoliative psychology or digital or image software or optical coherence or teledermatology or telederm* or teledermoscop* or teledermatoscop* or computer diagnos* or sentinel))
#12 ((nevisense or HFUS or impedance spectroscopy or history taking or patient history or naked eye or skin exam* or physical exam* or ugly duckling or UD sign* or physician* exam* or physical exam* or ABCDE or clinical accuracy or general practice or confocal microscop* or clinical competence or diagnostic algorithm* or checklist* or virtual image* or volatile organic or VOC or dog* or gene expression or reflex transmission or thermal imag* or elastography))
#13 #11 or #12
#14 ((PET or CT or FDG or deoxyglucose or deoxy-glucose or fluorodeoxy* or radiopharma* or CATSCAN or positron emission or computer assisted or nuclear magnetic or MRI or FMRI or NMRI or scintigraph* or echograph* or Doppler or sonograph* or ultraso* or magnetic reson*))
#15 ((stage* or staging or metast* or recurrence or sensitivity or specificity or false negative* or thickness*))
#16 #14 AND #15
#17 #16 OR #13
#18 #10 AND #17
Refined by: DOCUMENT TYPES: (MEETING ABSTRACT OR PROCEEDINGS PAPER)

Appendix 6. Full text inclusion criteria

Criterion	Inclusion	Exclusion
Study design	**For diagnostic and staging reviews** • Any study for which a 2×2 contingency table can be extracted, e.g. ○ diagnostic case-control studies ○ 'cross-sectional' test accuracy studies with retrospective or prospective data collection ○ studies where estimation of test accuracy was not the primary objective but test results for both index and reference standard were available ○ RCTs of tests or testing strategies where participants were randomised between index tests and all undergo a reference standard (i.e. accuracy RCTs)	• < 5 melanoma cases (diagnosis reviews) • < 10 participants (staging reviews) • Studies developing new criteria for diagnosis unless a separate 'test set' of images were used to evaluate the criteria (mainly digital dermoscopy) • Studies using 'normal' skin as controls • Letters, editorials, comment papers, narrative reviews • Insufficient data to construct a 2×2 table
Target condition	• Melanoma • Keratinocyte skin cancer (or non-melanoma skin cancer) ○ BCC or epithelioma	• Studies exclusively conducted in children • Studies of non-cutaneous melanoma or SCC

(*Continued*)

	○ cSCC	
Population	**For diagnostic reviews** • Adults with a skin lesion suspicious for melanoma, BCC, or cSCC (other terms include pigmented skin lesion/nevi, melanocytic, keratinocyte, etc.) • Adults at high risk of developing melanoma skin cancer, BCC, or cSCC **For staging reviews** • Adults with a diagnosis of melanoma or cSCC undergoing tests for staging of lymph nodes or distant metastases or both	• People suspected of other forms of skin cancer • Studies conducted exclusively in children
Index tests	**For diagnosis** • Visual inspection/clinical examination • Dermoscopy/dermatoscopy • Teledermoscpoy • Smartphone/mobile phone applications • Digital dermoscopy/artificial intelligence • Confocal microscopy • Ocular coherence tomography • Exfoliative cytology • High-frequency ultrasound • Canine odour detection • DNA expression analysis/gene chip analysis • Other **For staging** • CT • PET • PET-CT • MRI • Ultrasound +/fine needle aspiration cytology (FNAC) • SLNB +/high-frequency ultrasound • Other Any test combination and in any order Any test positivity threshold Any variation in testing procedure (e.g. radioisotope used)	• Sentinel lymph biopsy for therapeutic rather than staging purposes • Tests to determine melanoma thickness • Tests to determine surgical margins/lesion borders • Tests to improve histopathology diagnose • LND
Reference standard	**For diagnostic studies** • Histopathology of the excised lesion • Clinical follow-up of non-excised/benign appearing lesions with later histopathology if suspicious • Expert diagnosis (studies should not be included if expert diagnosis is the sole reference standard) **For studies of imaging tests for staging:**	**For diagnostic studies** • Exclude if any disease positive participants have diagnosis unconfirmed by histology • Exclude if > 50% of disease negative participants have diagnosis confirmed by expert opinion with no histology or follow-up • Exclude studies of referral accuracy, i.e. comparing referral decision with expert diagnosis,

(*Continued*)

	Histopathology (via LND or SLMB) Clinical/radiological follow-up A combination of the above **For studies of SLNB accuracy for staging**: LND of both SLN+ and SLn participants to identify all diseased nodes LND of SLN+ participants and follow-up of SLN participants to identify a subsequent nodal recurrence in a *previously investigated* nodal basin	unless evaluations of teledermatology or mobile phone applications

BCC: basal cell carcinoma; cSCC: cutaneous squamous cell carcinoma; CT: computed tomography; FNAC: fine needle aspiration cytology; LND: lymph node dissection; MRI: magnetic resonance imaging; PET: positron emission tomography; PET-CT: positron emission tomography-computed tomography; RCT: randomised controlled trial; SCC: squamous cell carcinoma; SLN+: positive sentinel lymph node; SLn: negative sentinel lymph node; SLNB: sentinel lymph node biopsy

Appendix 7. QUADAS interpretation

Item	Response (delete as required)
PARTICIPANT SELECTION (1) - RISK OF BIAS	
1) Was a consecutive or random sample of participants or images enrolled?	**Yes** - if paper states consecutive or random **No** - if paper describes other method of sampling **Unclear** - if participant sampling not described
2) Was a case-control design avoided?	**Yes** - if consecutive or random or case-control design clearly not used **No** - if study described as case-control or describes sampling specific numbers of participants with particular diagnoses **Unclear** - if not described
3) Did the study avoid inappropriate exclusions both for melanoma and for cutaneous squamous cell carcinoma (cSCC) staging?	**Yes** - if inappropriate exclusions were avoided **No** - if lesions were excluded that might affect test accuracy, e.g. indeterminate results or where disagreement between evaluators was observed **Unclear** - if not clearly reported
4) For between-person comparative (BPC) studies only (i.e. allocating different tests to different study participants such as randomised controlled trials (RCTs)):	
• a) were the same participant selection criteria used for those allocated to each test?	**Yes** - if same selection criteria were used for each index test **No** - if different selection criteria were used for each index test **Unclear** - if selection criteria per test were not described **N/A** - if only 1 index test was evaluated or all participants received all tests

(*Continued*)

• b) was the potential for biased allocation between tests avoided through adequate generation of a randomised sequence?	**Yes** - if adequate randomisation procedures are described **No** - if inadequate randomisation procedures are described **Unclear** - if the method of allocation to groups is not described (a description of 'random' or 'randomised' is insufficient) **N/A** - if only 1 index test was evaluated or all participants received all tests
• c) was the potential for biased allocation between tests avoided through concealment of allocation before assignment?	**Yes** - if appropriate methods of allocation concealment are described **No** - if appropriate methods of allocation concealment are not described **Unclear** - if the method of allocation concealment is not described (sufficient detail to allow a definite judgement is required) **N/A** - if only 1 index test was evaluated
Could the selection of participants have introduced bias?	
v FOR NON-COMPARATIVE (NC) STUDIES	
If answers to all of questions 1) and 2) and 3) was 'Yes':	***Risk is Low***
If answers to any one of questions 1) or 2) or 3) was 'No':	***Risk is High***
If answers to any one of questions 1) or 2) or 3) was 'Unclear':	***Risk Unclear***
v FOR BETWEEN-PERSON COMPARATIVE STUDIES	
If answers to all of questions 1) and 2) and 3) and 4) was 'Yes':	***Risk is Low***
If answers to any one of questions 1) or 2) or 3) or 4) was 'No':	***Risk is High***
If answers to any one of questions 1) or 2) or 3) or 4) was 'Unclear':	***Risk Unclear***
PARTICIPANT SELECTION (1) - CONCERNS REGARDING APPLICABILITY	
For sentinel lymph node biopsy and imaging tests:	
1) Does the study report results for participants unselected by stage of disease or site of primary lesion, i.e. the study does not focus solely on those with a particular stage of disease such as American Joint Committee on Cancer (AJCC) stage I or melanoma $\leq$ 1 mm in thickness?	**Yes** - if an unrestricted group of participants have been included **No** - if a selected group of study participants have been included, e.g. those with clinical stage I disease or only those with thin melanoma **Unclear** - if insufficient details are provided to determine the spectrum of included participants
2) Did the study report data on a per patient rather than per lesion basis?	**Yes** - if a per patient analysis was reported **No** - if a per lesion analysis only was reported **Unclear** - if it is not possible to assess whether data are presented on a per patient or per lesion basis

(*Continued*)

For imaging tests only:	
3) Does the study focus primarily on participants undergoing primary staging or those undergoing staging for disease recurrence?	**Yes** - if at least 80% of study participants are undergoing primary staging following diagnosis of a primary cutaneous melanoma or staging of recurrence **No** - if less than 80% of study participants are undergoing primary staging following diagnosis of a cutaneous melanoma or staging of recurrence **Unclear -** if insufficient details are provided to determine the proportion of patients undergoing primary staging vs those undergoing staging of recurrence
Is there concern that the included participants do not match the review question?	
If the answer to question 1) or 2) (and 3)) was 'Yes':	***Concern is Low***
If the answer to question 1) or 2) (and 3)) was 'No':	***Concern is High***
If the answer to question 1) or 2) (and 3)) was 'Unclear':	***Concern is Unclear***
INDEX TEST (2) - RISK OF BIAS (to be completed per test evaluated)	
1) Was the index test or testing strategy result interpreted without knowledge of the results of the reference standard?	**Yes** - if index test described as interpreted without knowledge of reference standard result, or for prospective studies, if index test is always conducted and interpreted before the reference standard **No** - if index test described as interpreted in knowledge of reference standard result **Unclear** - if index test blinding is not described
2) Was the diagnostic threshold at which the test was considered positive prespecified?	**Yes** - if threshold was prespecified (i.e. before analysing study results) **No** - if threshold was not prespecified **Unclear** - if not possible to tell whether or not diagnostic threshold was prespecified
For imaging tests only:	
3) For studies reporting the accuracy of multiple diagnostic thresholds (tumour characteristic or parameter) for the same index test, was each threshold interpreted without knowledge of the results of the others?	**Yes** - if thresholds were selected prospectively and each was interpreted by a different reader, or if study implements a retrospective (or no) cutoff **No** - if study uses prospective threshold and report states reported by same reader **Unclear** - if no mention of number of readers for each threshold or if prespecification of threshold not reported **N/A** - multiple diagnostic thresholds not reported for the same index test

(*Continued*)

4) For within-person comparison (WPC) of index tests or testing strategies (i.e. > 1 index test applied per participant), was each index test result interpreted without knowledge of the results of other index tests or testing strategies?	**Yes** - if all index tests were described as interpreted without knowledge of the results of the others **No** - if the index tests were described as interpreted in the knowledge of the results of the others **Unclear** - if it is not possible to tell whether knowledge of other index tests could have influenced test interpretation **N/A** - if only 1 index test was evaluated
Could the conduct or interpretation of the index test have introduced bias?	
v FOR NC and BPC STUDIES item 3) / 4) to be added	
If answers to questions 1) and 2) was 'Yes':	***Risk is Low***
If answers to either questions 1) or 2) was 'No':	***Risk is High***
If answers to either questions 1) or 2) was 'Unclear':	***Risk is Unclear***
v FOR WPC STUDIES	
If answers to all questions 1), 2) for any index test and 3) was 'Yes':	***Risk is Low***
If answers to any one of questions 1) or 2) for any index test or 3) was 'No':	***Risk is High***
If answers to any one of questions 1) or 2) for any index test or 3) was 'Unclear':	***Risk is Unclear***
INDEX TEST (2) - CONCERN ABOUT APPLICABILITY	
1) Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication? This item applies equally to studies using objective and more subjective approaches to test interpretation. For sentinel lymph node biopsy (SLNB) studies, this requires description of the tracer threshold for identification of the SLN and the histological assessment	**Yes** - if the criteria for diagnosis of the target disorder were reported in sufficient detail to allow replication **No** - if the criteria for diagnosis of the target disorder were not reported in sufficient detail to allow replication **Unclear** - if some but not sufficient information on criteria for diagnosis to allow replication were provided
2) Was the test interpretation carried out by an experienced examiner?	**Yes** - if the test was interpreted by an experienced examiner as defined in the review protocol **No** - if the test was not interpreted by an experienced examiner (see above) **Unclear** - if the experience of the examiner(s) was not reported in sufficient detail to judge or if examiners described as 'Expert' with no further detail given
Is there concern that the index test, its conduct, or interpretation differ from the review question?	

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If answers to questions 1) and 2) was 'Yes':	***Concern is Low***
If answers to questions 1) or 2) was 'No':	***Concern is High***
If answers to questions 1) or 2) was 'Unclear':	***Concern is Unclear***
REFERENCE STANDARD (3) - RISK OF BIAS	
1) Is the reference standard likely to correctly classify the target condition?	
a) DISEASE POSITIVE - 1 or more of: - Histological confirmation of metastases following lymph node dissection (or SLNB or core biopsy for imaging studies) - Clinical/radiological follow-up to identify clinically detectable disease in a mapped nodal basin (SLNB studies) - Clinical/radiological follow-up to identify any metastases (imaging studies) subsequently confirmed on histology	**Yes** - if all disease positive participants underwent 1 of the listed reference standards **No** - if a final diagnosis for any disease positive participant was reached without histopathology **Unclear** - if the method of final diagnosis was not reported for any disease positive participant
b) DISEASE NEGATIVE - 1 or more of: - Histological confirmation of absence of disease in a mapped nodal basin following lymph node dissection (or following SLNB for imaging studies) - Clinical/radiological follow-up of test negative participants	**Yes** - if at least 90% of disease negative participants underwent 1 of the listed reference standards **No** - if more than 10% of benign diagnoses were reached by concurrent imaging test **Unclear** - if the method of final diagnosis was not reported for any participant with benign or disease negative diagnosis
2) Were the histology-based reference standard results interpreted without knowledge of the results of the index test?	**Yes** - if the histopathologist was described as blinded to the index test result **No** - if the histopathologist was described as having knowledge of the index test result **Unclear** - if blinded histology interpretation was not clearly reported
3) Were the reference standard results based on patient follow-up interpreted without knowledge of the results of the index test?	**Yes** - if the clinician or radiologist was described as blinded to the index test result **No** - if the clinician or radiologist was described as having knowledge of the index test result **Unclear** - if blinded interpretation was not clearly reported
Could the reference standard, its conduct, or its interpretation have introduced bias?	
If answers to questions 1) and 2) and 3) was 'Yes':	***Risk is Low***
If answers to questions 1) or 2) or 3) was 'No':	***Risk is High***
If answers to questions 1) or 2) or 3) was 'Unclear':	***Risk is Unclear***

(*Continued*)

REFERENCE STANDARD (3) - CONCERN ABOUT APPLICABILITY	
1) Does the study use the same definition of disease positive as the primary review question, or is it possible to fully disaggregate data such that data matching the review question can be extracted?	**Yes** - same definition of disease positive used, or patients can be disaggregated and re-grouped according to review definition **No** - some patients cannot be disaggregated For SLNB review - disease positive includes participants with any nodal recurrence (not restricted to clinical recurrence in same nodal basin) For imaging reviews - participants with nodal vs distant recurrences cannot be disaggregated **Unclear** - definition of disease positive not clearly reported
For studies of imaging tests:	
2) The result of another imaging test (without patient follow-up to determine later emergence of disease) was not used as a reference standard	**Yes** - if imaging-based diagnosis was not used as a reference standard for any participant **No** - if imaging-based diagnosis was used as a reference standard for any participant **Unclear** - if not clearly reported
3) Item on observer experience could be included? Is there concern that the target condition as defined by the reference standard does not match the review question?	
If answers to all questions 1), 2) and 3) was 'Yes':	***Concern is Low***
If answers to any one of questions 1) or 2) or 3) was 'No':	***Concern is High***
If answers to any one of questions 1) or 2) or 3) was 'Unclear':	***Concern is Unclear***
***For teledermatology studies only:**	
If answers to questions 1) and 3) was 'Yes':	***Concern is Low***
If answers to questions 1) or 3) was 'No':	***Concern is High***
If answers to questions 1) or 3) was 'Unclear':	***Concern is Unclear***
FLOW AND TIMING (4): RISK OF BIAS	
1) Was there an appropriate interval between index test and reference standard?	
• a) For index test positive participants, was the interval between index test and histological reference standard ≤ 1 month?	**Yes** - if study reports ≤ 1 month between index and histological reference standard **No** - if study reports > 1 month between index and histological reference standard **Unclear** - if study does not report interval between index and

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	histological reference standard
• b) If reference standard is clinical or imaging-based follow up of index test negative participants, was there less than 6 months between application of index test(s) and first follow-up visit?	**Yes** - if study reports a follow-up visit within 6 months of application of the index test **No** - if study reports the first follow-up visit beyond 6 months of the index test **Unclear** - if study does not report timing of follow-up visits
2) Did all participants receive the same reference standard?	**Yes** - if all participants underwent the same reference standard **No** - if more than 1 reference standard was used **Unclear** - if not clearly reported
3) Were all participants included in the analysis?	**Yes** - if all participants were included in the analysis **No** - if some participants were excluded from the analysis **Unclear** - if not clearly reported
4) For WITHIN-PERSON COMPARISON (WPC) of index tests: Was the interval between application of index tests ≤ 1 month? Could the participant flow have introduced bias?	**Yes** - if study reports ≤ 1 month between index tests **No** - if study reports > 1 month between index tests **Unclear** - if study does not report interval between index tests
v FOR NON-COMPARATIVE and BPC STUDIES	
If answers to questions 1) and 2) and 3) was 'Yes':	***Risk is Low***
If answers to any one of questions 1) or 2) or 3) was 'No':	***Risk is High***
If answers to any one of questions 1) or 2) or 3) was 'Unclear':	***Risk is Unclear***
v FOR WITHIN-PERSON COMPARATIVE STUDIES (WPCs)	
If answers to all questions 1), 2), 3), and 4) was 'Yes':	***Risk is Low***
If answers to any one of questions 1), 2), 3), or 4) was 'No':	***Risk is High***
If answers to any one of questions 1), 2), 3), or 4) was 'Unclear':	***Risk is Unclear***

Appendix 8. Summary characteristics of studies for pre-SLNB imaging

Study Country Pt/lesion number	Study design Outcome: prevalence	Presentation Inclusion criteria Imaging eligibility	Age, gender, site, BT, Clark	Index test	Threshold Observers	Reference Exclusions
Arrangoiz 2012 USA **Patients:** 56 **Primary lesions:** 56 **LNBs/ Metastases:** NR	**NC** **Retrospective** (medical record review not described) **Data:** per pt **Nodal mets:** 29/56 = 52%	**Primary (pre-SLNB)** **Stage of disease:** all T4 and clinically node negative and negative for distant metastases **Inclusion:** node negative; BT > 4 mm	**Mean age:** 67; **Median age:** NR; **Range:** 26 to 89 years **Male:** 32 (57%) **Site:** trunk 16, 29%; extremities 28, 50%; HN 12, 21% **BT** median 6 mm; mean 9 mm; range 4.1 to 40 mm	**PET-CT.** 2D or 3D; CT (U, helical, low dose) **Scan coverage:** WB; vertex of the head down to feet for all patients **Contrast:** U **CT parameters:** Discovery LS - 140 kVp, 90mA; Siemens Biograph - 130 kVp, 100 mA; 5 mm **^{18}FDG:** 15 mCi (IV) **Breath hold:** normal breathing **CT used for:** attenuation correction; co-registered images **Reconstruction:** Discovery LS - OSEM algorithm; Siemens Biograph - TrueX (iterative reconstruction) algorithm	SUV of 2.5 **Info provided:** NR **No. observers:** NR; 'in-house medical physicist' mentioned **Diagnosis:** unclear	**Histology** (54, 96% (48 SLNB and 6 LND)) **FNAC** (n NR) **FU** (n NR): no details **Histology interval:** NR; states that 6 "proceeded directly to therapeutic lymph node dissection" after PET **FU interval:** NR **Exclusions:** n = 0; N/A
Chai 2012 USA **Patients:** 325 **Primary lesions:** 325 **LNBs/ Metastases:** 347	**NC** **Retrospective** (prospective database reported) **Data:** per pt **Nodal mets:** 64/317 = 20%	**Primary (pre-SLNB)** **Stage of disease:** NR **Inclusion:** node negative, **BT** > 0.76 mm or < 0.76 mm with high-risk features such as	**Mean age:** NR; **Median age:** 58; **Range:** 18 to 86 **Male:** 189 (58%) **Site:** HN 34 (10.5%) Trunk 129 (39.7%) Upper extremity	**US.** B-mode; linear array (9 or 12 MHz); US before LS **Scan coverage:** according to primary MM site and discretion of attending surgeon	US - classed as "abnormal," "suspicious," or "indeterminate recommending a short-term follow-up" were considered positive (criteria de-	**Histology** (325, 100%) **FNAC** (6, 1.8%) **FU** (NR; presume 100%) : NR; FU for SLNB negatives is reported but no description is given

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		ulceration, high mitotic rate, or a positive deep margin	101 (31.1%) Lower extremity 61 (18.8%) **BT** median (range) 1.78 (0.42 to 14.4) **Clark's level** III 24 (7.4%), IV 275 (84.6%), V 20 (6.2%), unknown 6 (1.8%)	**Contrast:** N/A	scribed in detail) **Info provided:** NR **No. observers:** NR (NR) **Diagnosis:** NR	**Histology interval:** US performed either immediately or several days before LS **FU interval:** NR **Exclusions:** n = 8; 1 draining basin identified by LS was not examined with US; plus 7 SLN positive who did not get **US**
Hafner 2004 Switzerland **Patients:** 101 **Primary lesions:** 101 **LNBs/Metastases:** 105 LNBs; 136 SLNs	**WPC Prospective Data:** per pt **Nodal mets:** 23/97 = 24%	**Primary (pre-SLNB) Stage of disease:** NR; stage IV (evidence of distant mets) excluded **Inclusion:** any cutaneous MM with **BT** ≥ 1 mm without evidence of detectable distant metastasis (includes clinically palpable) **Excluded if** < 1 mm	**Median age:** 55; **Range:** 18 to 79 **Male:** 55 (55%) **Site:** limbs 49, 49%, trunk 35, 35%, HN 16, 16% **BT:** 1.01 to 2 mm 38; 2.01 to 4 mm 43; > 4.0 mm 19	**US.** B-mode (5 Mhz); US before LS **Scan coverage:** regional lymph nodes of the groins, axillae, and neck (abdominal US also performed) **Contrast:** N/A	NR; 'radiologically suspect' **Info provided:** unclear; clinical exam by dermatologist and US by radiologist **No. observers:** 1; radiologist (NR) **Diagnosis:** single	**Histology** (100; 100%) **FNAC** (NR (abstract reports 3 LN mets identified on physical exam, 2 of which were detected by US)): **FU** (n NR): 20 months (8 to 39) **Histology interval:** 2 weeks **FU interval:** 6 months **Exclusions:** n = 4; 1 sentinel node was not found intraoperatively; 3 clinically node positive excluded by Bham team
Hinz 2013 Germany **Patients:** 20 **Primary lesions:** 20 **LNBs/Metastases:** 59 SLN removed	**WPC Retrospective** (retrospective computer-aided search of preoperatively performed staging procedures)	**Primary (pre-SLNB) Stage of disease:** NR **Inclusion:** high risk cutaneous MM; implies BT ≥ 2.0 mm or RF such	**Mean age:** full sample: 55.2; **Median age:** NR; **Range:** Full sample: SD 13.3 years **Male:** 9 (45%) . **Site:** trunk n = 10 (50%); up-	**PET-CT.** 2D/3D NR; CE-CT, helical. Reinhardt 2006 states helical, dual detector (N/A) **Scan coverage:** WB; Reinhardt 2006:	**PET-CT:** NR **Info provided:** NR **No. observers:** unclear; no details **Diagnosis:** unclear **US:** morphology	**Histology** (20 (100%)) **FNAC** (0): **histology interval:** NR **FU interval:** N/A **Exclusions:** n = 0

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	Data: per pt **Nodal mets:** 12/20 = 60%	as ulceration or regression **Excluded if** 'further risk factors' or classic sonographic signs of lymphatic metastasis	per extremity n = 3(15%); lower extremity n = 4 (20%); acral n = 3(15%) **BT**: 1.01 to 2 mm n = 3 (15%), 2.10 to 4 mm n = 9 (45%), > 4 mm n = 8 (40%); **Clark's level** III n = 1(5%); IV n = 16(80%); V n = 3 (15%)	"base of the skull to the apex of the lungs, ... from the shoulders to upper thighs, ... from the proximal femur to the tip of the toes" **Contrast:** Reinhardt 2006: iodinated oral contrast agent (Peritrast-oral-GI; Köhler Chemie GmbH, Alsbach, Germany) **CT parameters:** 130 kV, 40 mAs (Reinhardt 2006); 5 mm (Reinhardt 2006) **^{18}FDG:** 371 ± 41 MBq (Reinhardt 2006) **Breath hold:** limited breath hold technique for CT and shallow breathing for PET **CT used for:** Reinhardt 2006: attenuation correction based on re-scaling of the CT image **Reconstruction:** iterative as described elsewhere (Kinahan 2003) **US.** B-mode (6.0- to 11.0-MHz linear trans-	criteria (Solbiati 1988; Vassalo 1992; Voit 2010d); suspicious LNs were re-examined with US after LS **Info provided:** clinical exam/US performed by same clinician **No. observers:** unclear; physicians with broad experience in dermato-oncology (NR) **Diagnosis:** unclear; appears as though single observer	

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				ducer); US pre- and post-LS **Scan coverage:** all relevant regional LN basins depending on localisation of the primary melanoma **Contrast:** N/A		
Hinz 2011 Germany **Patients:** 81 **Primary lesions:** 81 **LNBs/ Metastases:** NR; 170 SLNs	**NC** **Prospective** **Data:** per pt **Nodal mets:** 8/81 = 10%	**Primary (pre-SLNB)** (? 1 secondary nodular SSM) **Stage of disease:** NR **Inclusion:** clinically node negative, **BT** ≥ 1 mm or < 1 mm with risk factors such as ulceration or regression	**Mean age:** 52.8; **Median age:** NR; **Range:** SD 15.4; node positive given (36 to 62) **Male:** 48 (0.5925%). **Site:** HN 2,2.5%; Trunk 36, 44.4%; Upper extremity 14, 17.2%; Lower extremity 23, 28.4%; Acral 6, 7.4% **Median BT** 1.68 mm (0.76 to 6.00 mm) **Clark's level**: 1 1, 1.4%; 2 26, 35.6%; 3 39, 53.4%; 4 7, 9.6%	**US.** B-mode (linear array); Doppler (6.0 to 11.0 MHz linear transducer); US pre- and post-LS **Scan coverage:** LN areas predicted by sites of melanoma **Contrast:** N/A	Positive radiological findings according to published criteria **Info provided:** NR; likely full info available **No. observers:** 1 of 4 clinicians trained in USS imaging; NR; broad experience in dermato-oncology and special ultrasound skills (NR) **Diagnosis:** unclear; appears as though single observer	**Histology** (1) **FNAC** (n NR) **FU** (N/A): not stated **Histology interval:** NR **FU interval:** NR **Exclusions:** n = 0
Hocevar 2004 Slovenia **Patients:** 57 **Primary lesions:** 57 **LNBs/ Metastases:** 61	**WPC** Design unclear **Data:** per pt **Nodal mets:** 14/57 = 25%	**Primary (pre-SLNB)** **Stage of disease:** NR **Inclusion:** MM candidates for SLNB	**Mean age:** NR; **Median age:** NR; **Range:** 1 to 93 **Male:** 21 (0.37%). **Site:** 14, 25% head, 19, 38% trunk, 24, 42% extremity **BT** < 1 mm 2, 4%, **BT** 1 to 2 mm 23, 40%, **BT** 2.01 to 4 mm 20, 35%, **BT** > 4	**US.** B-mode; linear array transducer with small parts probe (12 and 15 MHz); US before LS **Scan coverage:** NR **Contrast:** N/A **Breath hold:** regional lymph nodes US + FNAC for	Rounded appearance of the LN, Ioss of the hilar echogenic reflex, and deformed radial nodal vascularity **Info provided:** NR **No. observers:** 1; oncological radiologist (NR) **Diagnosis:** sin-	**Histology** (CLND; SLNB) **FNAC** (14/17 US positive underwent **FNAC**) **FU** (n NR): no details **Histology interval:** NR **FU interval:** NR **Exclusions:** n = 0

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			mm 12, 21% **Clark's level** unknown - 2, 4%, 3 23; 42%, 4 26; 44%, 5 6, 10%	those positive on US	gle	
Kell 2007 USA **Patients:** 37 **Primary lesions:** NR **LNBs/ Metastases:** NR	**NC** **Retrospective** (prospective database reported) **Data:** per pt **Nodal mets:** 9/37 = 24%	**Primary (pre-SLNB)** **Stage of disease:** NR **Inclusion:** MM, BT > 0.75 mm, candidates for SLNB	**Mean age:** 61.4 years; **Median age:** NR; **Range:** NR **Male:** NR (0%). **Site:** NR **Mean BT:** 2.4 mm	**PET-CT.** 2D/3D NR; CT (U) **Scan coverage:** base of skull to feet **Contrast:** U **CT parameters:** NR **^{18}FDG:** NR **Breath hold:** NR **CT used for:** NR **Reconstruction:** NR	Quantitative for areas of abnormally increased ^{18}FDG uptake **Info provided:** NR **No. observers:** NR; no details. **Diagnosis:** NR	**Histology** (37, 100%) **FNAC** (0): **FU** (n NR): no details **Histology interval:** NR **FU interval:** NR **Exclusions:** n = 0; 46 with SLNB but no PET-CT could not be included
Klode 2010 Germany **Patients:** 61 **Primary lesions:** NR **LNBs/ Metastases:** NR	**NC** **Retrospective** **Data:** per pt **Nodal mets:** 14/61 = 23%	**Primary (pre-SLNB)** **Stage of disease:** NR (I or II) **Inclusion:** primary MM AJCC stage I or II (BT > 1 mm)	**Mean age:** 58.8; **Median age:** 61; **Range:** 31 to 82 **Male:** 36 (0.5901%). **Site:** trunk and lower limbs 26, 42.6%; upper extremities 9, 14.8%; NR for remaining 27 lesions **BT:** mean 2.62 mm, median 2.0 mm, range 1 to 8 mm	**PET-CT.** 2D/3D NR; CE-CT **Scan coverage:** cranial base to mid femur; additional views according to melanoma localisation **Contrast:** iodine-containing contrast agent **CT parameters:** NR **^{18}FDG:** 349 mBq **Breath hold:** breath hold instructions NR **CT used for:** NR **Reconstruction:** NR	NR; hypermetabolic tumour focus **Info provided:** NR **No. observers:** NR; no details **Diagnosis:** NR	**Histology** (61, 100%) **FNAC** (N/A) **FU** (61, 100%): median 38 months, 13 to 55 months **Histology interval:** median 14 days PET to SLNB **FU interval:** NR **Exclusions:** n = 0; 60 patients with SLNB did not agree to pre-op PET
Kunte 2009 Germany **Patients:** 25 **Primary**	**NC** **Prospective** (Prosp database: N/A)	**Primary (pre-SLNB)** (NR). **Stage of disease:** NR	**Mean age:** 54; **Median age:** NR; **Range:** NR **Male:** 15 (60%)	**US.** B-mode; linear transducer (7.5 to 10MHz)	Qualitative presence of morphological features	**Histology** (51% n = 35) **FNAC** (0):

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lesions: 25 **LNBs/Metastases:** 68 LNBs; 35 SLNs	**Data:** per pt **Nodal mets:** 6/35 = 17% **Data:** per SLN **Nodal mets:** 6/35 = 17%	**Inclusion:** cutaneous MM SLNB candidates; 'mainly' ≥ 1.0 mm **BT** or RF (ulceration or regression or Clark level IV and V)	. **Site:** Limbs 14, 56%; HN 2, 8%; trunk 9 36% **BT:** ≤ 1 mm 8, 32%; 1.01 to 2 mm 11, 44%; 2.01 to 4 mm 5 20%; > 4.0 mm 1, 4%	; US pre- and post-LS **Scan coverage:** regional lymphatic basins **Contrast:** N/A **Breath hold:** regional LN basins	(described) **Info provided:** unclear; may be same dermatologists as for clinical exam **No. observers:** 2; dermatologists (experienced). **Diagnosis:** unclear	**FU** (0): - **Histology interval:** < 24 hours **FU interval:** N/A **Exclusions:** n = NR
Maubec 2007 France **Patients:** 25 **Primary lesions:** 26 **LNBs/Metastases:** 20 from 19 pts	**NC** **Prospective** (Prosp database: N/A) **Data:** per pt **Nodal mets:** 7/20 = 35%; 1 FN identified on FU	**Primary (pre-SLNB)** **Stage of disease:** all T4; post surgery AJCC stage IIB 10, 40%; IIC 4, 16%; IIIA 4, 16%; IIIB 6, 24%; IIIC in 1, 4% **Inclusion:** any MM **BT** > 4 mm; SLNB planned if clinically node negative	**Mean age:** 60; **Range:** 14 to 87 **Male:** 15 (0.6%) . **Site:** trunk 8, 32%; limbs 8; 32%; head and neck 9, 36% M**ean BT** 6.6 mm, range 4.8 to 12.5 mm	**PET-CT.** 3D; CT (U) **Scan coverage:** WB; "top of the head to the mid-thigh and included if necessary, the lower limbs" **Contrast:** U **CT parameters:** 110 kV; 80 mA; 5 mm ^{18}**FDG:** 5 MBq/kg **Breath hold:** normal breathing; "no breath hold instructions" **CT used for:** NR; integrated system **Reconstruction:** iterative algorithm (FORE and AWOSEM)	Uptake site suspicious for malignancy or not clearly explained by a benign etiology (SUV estimated but does not appear to formally contribute to diagnosis) **Info provided:** NR **No. observers:** NR; no details. **Diagnosis:** NR	**Histology** (22, 88%; 3 node positive underwent CLND; 19 had SLNB; 3 no surgery) **FNAC** (N/A) **FU** (25, 100%): mean 11 months (2 to 19 months) **Histology interval:** NR **FU interval:** NR **Exclusions:** n = 6; 3 clinically N+ underwent CLND (all PET+ and N+); 3 did not undergo any surgery
Radzhabova 2009 Russia **Patients:** 152 **Primary lesions:** NR **LNBs/Metastases:** NR	**NC** **Design unclear** **Data:** per pt **Nodal mets:** 11/52 = 21%; 2 FNS identified on FU	**Primary (pre-SLNB)** **Stage of disease:** NR **Inclusion:** clinically node negative MM and SLNB (based on	**Mean age:** NR; **Median age:** NR; **Range:** NR **Male:** NR (0%). **Site:** NR NR	**US.** B-mode; sectoral and linear (7 to 10 MHz); pre-LS **Scan coverage:** NR **Contrast:** N/A	High PSV, EDV, Stuart index, and PI < 1000. Mets could not be excluded if PSV and PI were high but EDV = 0, Stuart index	**Histology** (52, 100%) **FNAC** (0): **FU** (NR): **Histology interval:** NR **FU interval:** NR **Exclusions:** n =

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		US result)		**Breath hold:** N/A	was undetectable (PI = pulse index, PSV = peak systolic volume, EDV = end-diastolic volume, Stuart index) **Info provided:** NR **No. observers:** NR; no details. **Diagnosis:** NR	100; benign on US did not get SLNB
Revel 2010 France **Patients:** 22 **Primary lesions:** 22 **LNBs/ Metastases:** 21	**WPC** **Retrospective** **Data:** per pt **Nodal mets:** 10/20 = 50%; 2 FN identified on FU	**Primary (pre-SLNB)** **Stage of disease:** stage I or II **Inclusion:** clinically node negative HN MM with pre-SLNB PET-CT **Excluded if** > 1 month between PET-CT and SLNB	**Mean age:** 60. **Range:** 18 to 88 **Male:** 16 (73%). **Site:** scalp 5, 23%; cheek 3, 14%; cervical or neck 3, 14%; atrial region (ear, mastoid, temples) 6, 27%; palpebral or periorbital 4, 18%; frontal 1, 5% BT: 4.5 mm (0.26 to 10 mm)	**PET-CT.** 2D/3D NR **Scan coverage:** WB; vertex to the toes **Contrast:** NR **CT parameters:** Biograph 2: 130 kV, 80 mAs Biograph 6: 130 kV, 4D Care Dose; Biograph 2: 5 mm Biograph 6: 4 mm **^{18}FDG:** 5.5 MBq/kg for Biograph 2; 4 MBq/kg for Biograph 6 True V; Flucis1, Schering, Cisbio International **Breath hold:** no breath hold instructions reported **CT used for:** appears to be used for attenuation correction; also describes anatomical localisation	Any hypermetabolic focus more intense than the surrounding background, including equivocal foci, compared with the corresponding anatomical structure on coupled CT **Info provided:** localisation of the initial tumour and the standard clinical and radiological assessment were known **No. observers:** 2; no details. **Diagnosis:** consensus of 2	**Histology** (22, 100%) **FNAC** (N/A) **FU** (22/22, 100%): mean 17 months (range 1 to 44)^ **Histology interval**: 12 days **FU interval**: NR **Exclusions:** n = 2; 2 test fails (no SN detected)

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				on fused images **Reconstruction:** OSEM 3D		
Sanki 2009 Australia **Patients:** 716 **Primary lesions:** NR **LNBs/ Metastases:** 871	**NC** **Design unclear** **Data:** per pt **Nodal mets:** 125/716 = 17%	**Primary (pre-SLNB)** **Stage of disease:** NR **Inclusion:** SLNB; **BT** > 1 mm or < 1 mm with adverse histological features, such as Clark's level IV to V invasion, ulceration, or high mitotic rate	**Mean age:** NR; **Median age:** NR; **Range:** NR **Male:** NR (0%). **Site:** NR NR	**US.** B-mode US; linear array transducer with high-resolution small-parts probe 5 to 10 MHz (linear transducer); 10 to 14 MHz (small parts probe); LS before US **Scan coverage:** sites marked by nuclear medicine physician during LS **Contrast:** N/A **Breath hold:** N/A	Re-classification of original report as suspicious, or highly probable, e.g. increased vascular signature, rounding of the normal ovoid shape of the nodes, loss of normal hilar echoes, presence of focal low-level subcapsular space echoes **Info provided:** NR **No. observers:** NR; nuclear medicine physician (NR) **Diagnosis:** single	**Histology** (716, 100%) **FNAC** (0) **FU** (100% (SLNB; not ref standard for US)): 13.5 months (mean, 18.4 months) **Histology interval:** SLN performed within 24 hours of LS and US **FU interval:** NR **Exclusions:** n = 0
Sibon 2007 France **Patients:** 131 **Primary lesions:** 132 **LNBs/ Metastases:** NR; 189 SLNs	NC **Retrospective** (prospective database reported; plus prospective re-interpretation of US images) **Data:** per pt **Nodal mets:** 35/133 = 26%	**Primary (pre-SLNB)** **Stage of disease:** NR **Inclusion:** SLNB; **BT** > 1 mm or < 1 mm with adverse histological features, such as Clark's level IV to V invasion, ulceration, or high mitotic rate	**Mean age:** 56; **Range:** 17 to 92 years **Male:** 70 (53.4%). **Site:** arms 18, 13.6%, legs 43, 33%; trunk 48, 32%; hands/feet 10, 8%; HN 18, 14% **Mean BT** 2.60 ± 2.91 mm **Clark's level** II 8, 6%; III 30, 23%; IV 88, 66%, V 7, 5%; unknown 1, 1%	**US.** B-mode; linear transducer (6 to 12 MHz); US before LS **Scan coverage:** site of the excised primary melanoma scar and followed the paths of the lymphatic vessels to the lymph node area(s) **Contrast:** N/A **Breath hold:** N/A	Stringent criteria: circular/oval hypoechoic lymph node with a Solbiati index < 1.5 and no hyperechoic hilum; Non-stringent criteria included the presence of 1 or 2 stringent criteria **Info provided:** NR for original interpretation or for re-interpretation **No. observers:** NR; 1 radiolo-	**Histology** (131, 100%) **FNAC** (-): **FU** (n NR): no details **Histology interval:** NR **FU interval:** NR **Exclusions:** n = 0; using stringent criteria, US detected 1/24 micro-metastases < 2 mm (as measured by US) and 2/11 macro-metastases ≥ 2 mm

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					gist reviewed all images; radiologist (high) **Diagnosis:** single	(both > 5 mm)
Singh 2008 Germany **Patients:** 52 **Primary lesions:** NR **LNBs/Metastases:** 67 LNBs; 111 SLNs	**NC** Unclear **Data:** per pt **Nodal mets:** 14/52 = 27% > 4 mm BT: 7/12 = 58% ≤ 4 mm BT: 7/40 = 18%	**Primary (pre-SLNB)** **Stage of disease:** all I or II **Inclusion:** primary MM undergoing SLNB (all > 1 mm)	**Mean age:** 55; **Median age:** 61; **Range:** 17 to 76 **Male:** 36 (69 %). **Site:** extremities 23, 44%; trunk 16, 31%; HN 13, 25% **Mean BT** 3.46 mm, range 1.0 mm to 12.0 mm	**PET-CT.** Helical, CT (CE, dual detector) **Scan coverage:** WB; base of skull to tip of toes in 3 parts **Contrast:** Peritrast-oral-GI; Kohler Chemie GmbH, Alsbach, Germany **CT parameters:** 130 kV, 40 mAs; 5 mm **^{18}FDG:** 370 ± 40 MBq ^{18}FDG through an anterior cubital vein **Breath hold:** limited breath hold for CT and shallow breathing for PET **CT used for:** attenuation correction based on re-scaling of CT image; image fusion **Reconstruction:** iterative (not further detailed)	Any focal uptake more than background unless it was found to be a false positive focus (physiological accumulation or brown fat tissue) in fusion imaging **Info provided:** NR **No. observers:** 2; two experienced observers assessed ^{18}FDG PET-CT fusion imaging independently; also refers to team of radiologists and nuclear physicians (experienced) **Diagnosis:** consensus	**Histology** (52, 100%) **FNAC** (N/A) **FU** (n NR): no details **Histology interval:** PET before LS before SLNB **FU interval:** NR **Exclusions:** n = 0; 2 TP both **BT** ≥ 4 mm and FPs < 4 mm
van Rijk 2006 Netherlands **Patients:** 107 **Primary lesions:** 107	**WPC** **Retrospective** **Data:** per pt **Nodal mets:** 37/107 = 35%	**Primary (pre-SLNB)** **Stage of disease:** NR **In-**	**Mean age:** 50; **Range:** 15 to 52 **Male:** 57 (53%). **Site:** HN 6, 6%; trunk 43, 40%;	**US.** B-mode linear array (7.5 MHz; 6 to 12 MHz); US before LS	Suspicious - length-depth ratio < 2, conversion of a fatty hilum to a hy-	**Histology** (107, 100%) **FNAC** (22; not part of ref standard)

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LNBs/ Metastases: NR; 37 D+ in 42 LNBs		**clusion:** SLNB candidates; cutaneous MM **BT** > 1 mm or Clark ≥ level IV	arm 24, 22%; leg 34, 32% **median BT** 2.0 mm (0.6 to 12.5 mm) **Clark's level** II 1, 1%; III 37, 35%; IV 55, 51%; V 9, 8%; undeterminable 5, 5%	**Scan coverage:** NR **Contrast:** N/A **Breath hold:** N/A US + FNAC for US positive	poechoic hilum, substantial cortical asymmetry or a focal area of low-level echoes in the subcapsular sinus of the node and diameter > 5 mm for LN of the neck **Info provided:** NR **No. observers:** NR; no details **Diagnosis:** NR	**FU** (2/107; 2% (reported only for 2 positive on **FNAC**)): NR **Histology interval:** NR **FU interval:** NR **Exclusions:** n = 0; FU of 2 FNAC positive participants is reported but no further reference is made to any recurrences
Voit 2014 Germany **Patients:** 1000 **Primary lesions:** 1000 **LNBs/ Metastases:** NR	**WPC** Design unclear **Data:** per pt **Nodal mets:** 208/1000 = 21%	**Primary (pre-SLNB)** **Stage of disease:** NR **Inclusion:** SLNB candidates; **BT** > 1 mm thickness, or Clark IV/V, ulcerated and/or regressed	**Mean age:** 59; **Median age:** 62; **Range:** 15 to 94 **Male:** 567 (57%) **Site:** NR **Mean BT** 2.58 mm; **median BT** 1.57 mm **BT** < 1 mm 288 29%; 1 to 2 mm 308 31%; 2 to 4 mm 231 23%; > 4 mm 173 17% **Clarks** II 32 3%; III 341 34%; IV 554 56%; V 54 6%, unknown 13 1%	**US.** B-mode & Doppler (1 to 18 MHz); LS before US **Scan coverage:** LNBs; patients first underwent a lymphoscintigraphy, which assists the ultrasonographist to better focus the examination **Contrast:** NA **US + FNAC for US positive**	Malignant if total loss of central echoes (LCE) or LN enlarged and balloon shaped (BS); suspicious if peripheral perfusion present or central echo wandering towards the rim **Info provided:** NR **No. observers:** 3; ultrasonographist (mixed; 1 expert and 2 trained but less expert) **Diagnosis:** unclear; likely single?	**Histology** (1000, 100%) **FNAC** (332, 33%; authors report as 342, including 10 US malignant as **FNAC** positive even though no **FNAC** was undertaken): **FU** (1000; 100%): mean 56 m; median 53 m; range 1 to 132 m **Histology interval:** NR **FU interval:** NR **Exclusions:** n = 0
Wagner 2012 France **Patients:** 48 **Primary lesions:** 48 **LNBs/ Metastases:** NR	**NC** **Retrospective** **Data:** per pt **Nodal mets:** 14/43 = 33%	**Primary (pre-SLNB)** **Stage of disease:** stage IIA 8, 16.7%; stage IIB 19, 39.6%; stage IIC 19, 39.6%; 2, 4.2% NR **Inclu-**	**Mean age:** NR; **Median age:** NR; **Range:** NR **Male:** 25 (52%). **Site:** NR **Mean BT** 7.6 mm (±4.5) (range 1.1 to 18 mm)	**PET-CT.** 2D; CT (NR) **Scan coverage:** WB; not further described **Contrast:** NR **CT parameters:** 140 kV, 200 mA (attenuation cor-	Abnormally increased ^{18}FDG uptake in a lymph node in the drainage territory of the melanoma **Info provided:** aware of all clin-	**Histology** (43, 89.6%; 2 CLND only, 1 SLNB + CLND, 40 SLNB only) **FNAC** (N/A) **FU** (1): min 12 months **Histology inter-**

(*Continued*)

		sion: SLNB candidates; BT ≥ 4 mm or BT > 1 mm with ulceration		rection and anatomical correlation); 7.5 mm **^{18}FDG:** 370MBq (Glucotep Cyclopharma, St Beauzire, France) **Breath hold:** normal breathing; "remain rested, to refrain from speaking, and to minimize swallowing" **CT used for:** attenuation correction and anatomical correlation **Reconstruction:** iterative OSEM (Ordered Subset Expectation Maximization) algorithm (3 iterations; 10 subsets)	ical findings **No. observers:** NR; nuclear medicine specialist (high) **Diagnosis:** unclear; 'at least one'	**val:** NR **FU interval:** NR **Exclusions:** n = 5; SLNB not performed for technical reasons

+: positive; AJCC: American Joint Cancer Committee; AWOSEM: attenuation weighted ordered subsets expectation maximisation; BT: Breslow thickness; CE: contrast enhanced; CLND: complete lymph node dissection; CT: computed tomography; 2D: two-dimensional; 3D: three-dimensional; EDV: end-diastolic volume; 18FDG: 2-deoxy-2-[18F]fluoro-D-glucose; FNAC: fine needle aspiration cytology; FORE: Fourier rebinning; FU: follow-up; HN: head and neck; LN: lymph node; LNB: lymph node basin; LND: lymph node dissection; LS: lymphoscintigraphy; mA: measure of tube current; mets: metastases; MM: malignant melanoma; NC: non-comparative; OSEM: ordered subsets expectation maximisation algorithm; PET: positron emission tomography; PI: pulse index; PSV: peak systolic volume; prosp: prospective; RF: risk factor; SD: standard deviation; SLN: sentinel lymph node; SLNB: sentinel lymph node biopsy; SSM: superficial spreading melanoma; SUV: standardised uptake value; U: unenhanced; US: ultrasound; WB: whole body

Appendix 9. Characteristics of studies of whole body imaging by population group (primary staging, re-staging, and mixed or unclear populations)

Study Country Pt/lesion numbers	Study design Outcome Prevalence	Presentation Inclusion criteria Imaging eligibility	Age, gender, site, BT, Clark	Index test	Threshold Observers	Reference Exclusions Other result
PRIMARY STAGING OF DISEASE						
Arrangoiz 2012 USA **Patients:** 56 **Primary lesions:** 56 **LNBs/ Metastases:** NR	NC **Retrospective** (Prosp database: NR) **Data:** per pt Any mets (NR; scan incl head): 32/56 = 57% Nodal: 29/56 = 52% Distant mets : 5/56 = 9%	**Primary** (N/A) **Stage of disease**: all T4 and clinically node negative and negative for distant metastases **Inclusion:** node negative; BT > 4 mm	**Mean age:** 67; **Median age:** NR; **Range:** 26 to 89 **Male:** 32 (57.1428571428571% **Site:** trunk 16, 29%; extremities 28, 50%; head and neck 12, 21% **BT** median 6 mm; mean 9 mm; range 4.1 to 40 mm	**PET-CT**. 2D or 3D; CT (U, helical, low dose) **Scan coverage:** WB; vertex of the head down to feet for all patients **Contrast:** U **CT parameters:** Discovery LS - 140 kVp, 90 mA; Siemens Biograph - 130 kVp, 100 mA; 5 mm **FDG:** 15 mCi (IV) **Breath hold:** normal breathing **CT used for:** attenuation correction; co-registered images **Reconstruction:** Discovery LS - OSEM algorithm with 28 subsets and 2 iterations Siemens Biograph - TrueX algorithm with 21 subsets and 2 iterations	SUV of 2.5 **Info provided:** NR **No. observers:** NR; 'in-house medical physicist' mentioned; NR; 'in-house medical physicist' mentioned (NR) **Diagnosis:** unclear	**Histology** (54, 96% (48 SNB and 6 LND)) **FNAC** (NR): FU (NR): NR **Histology interval:** NR; states that 6 "proceeded directly to therapeutic lymph node dissection" after PET **FU interval:** NR **Exclusions:** n = 0; N/A
Hafner 2004 Switzerland	**WPC** **Prospective**	**Primary** (N/A). **Stage of disease**:	**Mean age:** NR; **Median age:** 55;	US. B-mode (5 Mhz); US before	NR; 'radiologically suspect'	**Histology** (100; 100%)

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Patients: 101 **Primary lesions:** 101 **LNBs/Metastases:** 105 LNBs; 136 SLNs	**Data:** per pt Nodal mets: 26/100 = 26%	NR; stage IV (evidence of distant mets) excluded **Inclusion:** any cutaneous MM with BT ≥ 1 mm without evidence of detectable distant metastasis (includes clinically palpable)	**Range:** 18 to 79 **Male:** 55 (55%) **Site:** limbs 49, 49%, trunk 35, 35%, HN 16, 16% BT: 1.01 to 2 mm 38; 2.01 to 4 mm 43; > 4.0 mm 19	LS **Scan coverage:** regional lymph nodes of the groins, axillae, and neck (abdominal US also performed)	**Info provided:** unclear **No. observers:** 1; radiology resident (NR) **Diagnosis:** single (supervision by senior staff radiologist)	**FNAC** (NR (abstract reports 3 LN mets identified on physical exam, 2 of which were detected by US)): FU (NR): 20 months (8 to 39) **Histology interval:** 2 weeks **FU interval:** 6 months **Exclusions**: n = 1; sentinel node was not found intraoperatively No confirmed distant mets detected at time of imaging; 9 patients with suspicious findings on imaging were negative for progression/recurrence at 12 months
Kang 2011 S Korea **Patients:** 37 **Primary lesions:** 37 **LNBs/ Metastases:** NR	NC **Retrospective** (Prosp database: no; medical record review) **Data:** per pt Any mets (incl brain): 9/37 = 24%	**Primary** (N/A) **Stage of disease**: stage 0: 7 (18.9%); stage I: 6 (16.2%); stage II: 17 (45.9%); stage III: 6 (16.2%); stage IV: 1 (2.7%) **Inclusion:** newly diagnosed cutaneous MM undergoing staging work-up with PET-CT (any stage, including clinically node positive)	**Mean age:** 61.7 years; **Median age:** NR; **Range:** 48.1 to 75.3; ± 13.6 years **Male:** 17 (45.9%) **Site:** hand/foot 23 (62.1%), trunk 6 (16.2), head/neck 4 (10.8%), extremity 4 (10.8%) **BT** < 1.0 mm 8, 22%; ≥ 1 mm 15, 41%; NR 14, 38%	**PET-CT**. CT (U, 6 slice or 16 slice) (N/A) **Scan coverage:** vertex of skull to knees; plus lower limbs if with lower leg MM **Contrast:** U **CT parameters:** Reveal RT-HiRez: 130 kV, 95 mA Discovery ST: 140 kV, 160 mA; Reveal RT-HiRez: 2.5 mm Discovery ST: 3.	SUVmax ≥ 2.2 **Info provided:** NR **No. observers:** 2; nuclear physicians (experienced) **Diagnosis:** consensus of 2	**Histology** (6 (16.2%)) **FNAC** (0) FU (37 (100%)) : median follow-up 24.3 ± l l.7 months (range 8 to 55 months) **Histology interval:** NR **FU interval:** 3 months **Exclusions**: n = 0

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				75 mm **FDG:** 350 to 400 MBq **Breath hold:** NR; 'standard protocol' **CT used for:** unclear; combined PET-CT unit, mentions identification of anatomical location on fused PET-CT image **Reconstruction:** ordered subset expectation-maximisation		
Maubec 2007 France **Patients:** 25 **Primary lesions:** 26 **LNBs/ Metastases:** NR	**WPC** **Prospective** **Data:** per pt Any (incl brain): 7/25 = 28%	**Primary** (N/A). **Stage of disease**: all T4; 3 clinically node positive Post surgery: AJCC stage IIB 10, 40%; IIC 4, 16%; IIIA 4, 16%; IIIB 6, 24%; IIIC in 1, 4% **Inclusion:** any MM BT > 4 mm; SLNB planned if clinically node negative	**Mean age:** 60; **Range:** 14 to 87 **Male:** 15 (0.6%) . **Site:** trunk 8, 32%; limbs 8; 32%; head and neck 9, 36% **Mean BT** 6.6 mm, range 4.8 to 12.5 mm	**PET-CT**. 3D; CT (U) **Scan coverage:** WB; "top of the head to the mid-thigh and included if necessary, the lower limbs" **Contrast:** U **CT parameters:** 80 mA; 110 kV; 5 mm **FDG:** 5 MBq/kg **Breath hold:** normal breathing; "no breath hold instructions" **CT used for:** NR; integrated system **Reconstruction:** iterative algorithm (FORE and AWOSEM) with 2 iterations, 8 subsets, and	Uptake site suspicious for malignancy or not clearly explained by a benign etiology (SUV estimated but does not appear to formally contribute to diagnosis) **Info provided:** NR **No. observers:** NR; NR (NR) **Diagnosis:** NR	**Histology** (22, 88%; 3 node positive underwent CLND; 19 had SLNB; 3 no surgery) **FNAC** (N/A) FU (25, 100%): mean 11 months (2 to 19 months) **Histology interval:** NR **FU interval:** NR **Exclusions**: n = 0; all recruited pts can be included in analysis for any mets. 3 PET +ve for distant mets (1 orbital, 1 thyroid, 1 liver)

(*Continued*)

				a 5 mm full-width half maximum (FWHM) Gaussian postfilter		
Prayer 1990 Austria **Patients:** 217 **Primary lesions:** NR **LNBs/ Metastases:** NR	**WPC** Unclear (Prosp database: NR) **Data:** per pt Nodal mets: 29/217 = 13%	**Primary** **Stage of disease**: NR **Inclusion:** primary MM investigated either before or after removal of the primary melanoma in postoperative follow-up	**Mean age:** 56; **Median age:** NR; **Range:** 25 to 82 **Male:** 104 (47.926267281106%) **Site:** HN 42, 19%; arm 61, 28%; shoulder 23, 11%; leg 91, 42% **BT** < 0.75 mm 25, 12%; 0.75 to 1.5 mm 96, 44%; 1.5 to 3.00 mm 79, 36%; > 3 mm 17, 8% Clark level II 936, III 89, IV 33	**US.** B-mode (7.5 MHz); N/A **Scan coverage:** primary LNs depending on tumour localisation. Cervical (42); axillary (84); inguinal (91) **Contrast:** N/A	Suspicious - circular and oval masses with poor echo; longitudinally configurated LNs with echogenic eccentric hilum regarded as "enlarged reactively" **Info provided:** unclear; different clinicians for palpation (dermatologist) and for US (radiologist) **No. observers:** 1; radiologist (NR) **Diagnosis:** single	**Histology** (29, 13%) **FNAC** (0) FU (188, 87%): 6 months **Histology interval:** NR **FU interval:** 2 months **Exclusions**: n = 0 There were no false-negative sonographic results i.e. melanoma metastases did not occur within the following 6 months in any of the patients classified as having no suspect regional lymph nodes. The smallest metastasis detected by ultrasound was 11 mm in diameter
Veit-Haibach 2009 Germany **Patients:** 56 **Primary lesions:** 56 **LNBs/ Metastases:** NR	**WPC** **Prospective** **Data:** per pt Nodal: 13/56 = 23% Distant (brain NR): 12/56 = 21%	**Primary** (N/A) **Stage of disease**: on presentation: stage I or II 44, 79%; stage III or IV 12, 21% **Inclusion:** any primary MM referred for PET-CT **Excluded if** insufficient FU	**Mean age:** 62 years; **Median age: Range:** 23 to 86 years **Male:** 27 (48.2142857142857% **Site:** trunk 26, 46%; upper extremities 10, 18%; lower extremity 18, 32%; HN 2, 4%	**CT.** CE; two slice (N/A); NR **Scan coverage:** WB; no further detail, just states caudocranial direction **Contrast:** dual phase injection of 140 mL of 300 mmol/mL io-	**CT:** Lesion size and central necrosis for malignancy; fatty hilum and calcifications for benign. For size: short-axis diameter threshold of 1.5 cm for jugulodigastric and pre-	**Histology** (unclear; 14 with SLNB, 25%) **FNAC** (0) FU (56, 100%): mean 780 days (range 102 to 1390 days); roughly equivalent to 25.6 months (3.3 to 45.7 months)

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			NR	dinated contrast agent (90 mL at a rate of 3 mL/s, and 50 mL at a rate of 1.5 mL/s; dual phase used to ensure fully diagnostic (portal venous phase) CT data in the abdomen) **CT parameters:** NR; NR **Breath hold:** NR **PET-CT**. full ring-CT (CE; 2 slice) (N/A); NR **Scan coverage:** WB; no further detail, just states caudocranial direction **Contrast:** 140 mL of 300 mmol/mL iodinated contrast agent **CT parameters:** NR; NR **FDG:** 330 to 350 MBq **Breath hold:** NR **CT used for:** attenuation correction **Reconstruction:** reconstructed iteratively (FORE-OSEM, 2 iterations, 8 subsets, 128×128 matrix with 5 mm gaussian smoothing)	carinal LNs and threshold of 1 cm for all other LNs of the neck, thorax, and abdomen [16] **PET-CT:** increased glucose metabolism and independent of their size **Info provided:** provided patient-specific clinical background (first diagnosis of melanoma, post-surgical resection status, location of the resection site) but blinded to clinical exam and histopathology of primary tumour **No. observers:** 2; radiologists (NR). **Diagnosis:** consensus of 2	**Histology interval:** 4 weeks for SLNB **FU interval:** NR **Exclusions**: n = 0

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RE-STAGING OF DISEASE						
Iagaru 2007 USA **Patients:** 106 **Primary lesions:** NR **LNBs/ Metastases:** 139	**WPC** **Retrospective** (Prosp database: NR) **Data:** per pt Any mets (incl skin and brain): 56/106 = 53% (all tests) **Data:** per lesion Any mets (incl skin and brain): 87/139 = 63%	**Re-staging** (all patients had the study requested for disease re-staging) **Stage of disease**: NR; 76 stage I to IIIc and 30 stage IIIb to IV) **Inclusion:** PET-CT for MM re-staging **Excluded if** NR ORNR PET-CT for MM re-staging	**Mean age:** 56.8 ± 15.9 **Median age:** nr; **Range:** 20 to 87 **Male:** 68 (64.1%) **Site:** NR **BT** at initial diagnosis (n = 76) : mean 3.56 mm, 0.4 to 25 mm; < 1 mm in 6 (8%) , 1 to 4.0 mm 58 (76%), > 4 mm 12 (16%) **Clark's level** (n = 70): 3 (4%) , level II; 13 (19%), level III; 43 (61%), level IV; 11 (16%), level V	**CT**. U, multislice helical (N/A) **Scan coverage:** WB; top of the head to the ankles **Contrast:** N/A **CT parameters:** 140 kV, 40 mA; 5 mm **Breath hold:** no breath hold instructions reported **PET-CT**. 2D; CT (U, multislice helical) (N/A) **Scan coverage:** WB ; top of the head to the ankles **Contrast:** U **CT parameters:** 140 kV, 40 mA, 5 mm **FDG:** 15 mCi **Breath hold:** no breath hold instructions reported **CT used for:** attenuation correction and anatomical localisation **Reconstruction:** OSEM, 2 iterative steps, 28 subsets	**CT:** NR **PET-CT:** SUVmax ≥ 2.5 **Info provided:** NR for original interpretation or for re-interpretation **No. observers:** NR; board-certified nuclear medicine physicians and radiologists (board certified) **Diagnosis:** consensus	**Histology** (97, 91.5%) **FNAC** (N/A) FU (9, 8.5%): NR **Histology interval:** NR **FU interval:** NR **Exclusions**: n = 0; N/A
Rubaltelli 2011 Italy **Patients:** 436 **Primary lesions:** NR	**WPC** Unclear **Data:** per pt Nodal mets: 13/436 = 3%	**Re-staging** (all undergoing postoperative follow-up de-	**Mean age:** 54; **Median age:** 58; **Range:** 27 to 81 years **Male:** Full sam-	**US**. B-mode; linear array transducers (7.5 to 13 MHz) **Scan coverage:**	**US:** focal hypoechoic cortical thickening - a focal area of cortex at least	**Histology** (13, 3%) **FNAC** (436, 100%) FU (31/

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LNBs/ Metastases: NR		signed to ensure the early identification of lymph node metastases) **Stage of disease**: NR **Inclusion:** cutaneous MM with US of regional LNs as part of a follow-up; those with 'common signs of malignancy' on B-mode US were excluded	ple: 240 (52%) **Site:** NR	variable: axillary lymph nodes for MM of the upper limbs, inguinal lymph nodes for MM of the lower limbs, both axillary and inguinal lymph nodes for MM of the trunk, and cervical and supraclavicular lymph nodes for MM of the head and neck (72 neck, 248 axillary, and 354 inguinal LNBs were examined) **Contrast:** N/A **US.** contrast-enhanced US (7.5 to 13 MHz) **Scan coverage:** LNBs identified on B-mode US **Contrast:** sulfur hexafluoride microbubbles (SonoVue, Bracco)	twice as thick as the cortex in the remainder of the same lymph node **CE-US:** perfusion defects corresponding to the cortical focal thickening; homogeneous intense enhancement of the cortex considered benign **Info provided:** NR **No. observers:** 1 of 3; sonologist (high) **Diagnosis:** single	44 **FNAC** negative, 70%): 6 to 16 months (median, 10 months) **Histology interval:** NR **FU interval:** NR **Exclusions**: n = 24; definite signs of malignancy on B-mode US
Strobel 2007a Switzerland **Patients:** 47 **Primary lesions:** 47 **LNBs/ Metastases:** NR	NC **Retrospective** (Prosp database: NR) **Data:** per pt Any (incl brain): 39/47 = 83%	**Re-staging** (all pts followed up according to updated Swiss melanoma guidelines) **Stage of disease**: NR **Inclusion:** high risk melanoma (BT > 4 mm, or Clark level III or IV, or known resected metastases) and	**Mean age:** 58.4 years; **Median age: Range:** 20 to 83 years **Male:** 20 (42.5531914893617%) **Site:** NR **BT** 1.02 mm to 15 mm; unknown in 9	**PET-CT**. 2D PET, CT (CE, multi-slice, helical) **Scan coverage:** head to the knees with scanning of the lower legs for patients with primary tumours of the lower extremities **Contrast:** oral CT contrast agent given	FDG uptake clearly greater than background and established morphological CT criteria; if a focal FDG-active lesion was detected, the exact anatomical localisation was determined on the fused PET-CT	**Histology** (29, 62%; 20 distant mets and 9 LN mets) **FNAC** (4, 8.5%) FU (47, 100%) : minimum of 6 months (range 6 to 18 months in all patients **Histology interval:** **FU interval:** 3 months

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		raised S100 (> 0.2 μg/L) undergoing follow-up after primary treatment **Excluded if** PET-CT and S100B measurement > 2 weeks apart; treatment initiated between PET-CT and tumour marker measurement; or systemic therapy before the PET-CT investigation		15 minutes before injection of 18F-FDG **CT parameters:** 140 kV, 40 mAs, 4.25 mm **FDG:** 370 to 400 MBq **Breath hold:** CT: breath holding in the normal expiratory position **CT used for:** attenuation correction, fused **Reconstruction:** standard iterative algorithm (OSEM)	images. Lesions with 18F-FDG uptake in physiological sites or benign variants, e.g. muscles, brown fatty tissue or pulmonary infiltrations, were determined as benign **Info provided:** blinded to serum S100B **No. observers:** 2; nuclear radiology physicians (experienced) **Diagnosis:** consensus of 2	**Exclusions**: n = 0; N/A Reports characteristics of those with elevated S100 but not mets detected on imaging
STAGING IN MIXED OR UNCLEAR POPULATIONS						
Abbott 2011 UK **Patients:** 34 (microscopic group 20; macroscopic group 14) **Primary lesions:** 34 **LNBs/ Metastases:** NR	NC **Retrospective** (Prosp. database used) **Data:** per pt Any (excl brain): 7/34 = 21%	**Mixed** (primary/ FU) **Stage of disease**: IIIA 18, 53%; IIIB 10, 29%; IIIC 6, 18% **Inclusion:** stage III: micrometastases on SLNB or clinically detectable nodal metastases on diagnosis or FU	**Mean age:** NR; **Median age:** microscopic group: 50; macroscopic group: 63 **Range:** microscopic group: 19 to 74 years Macroscopic group: 48 to 79 years **Male:** microscopic group: 14 Macroscopic group: 6 (Microscopic group: 70% Macroscopic group: 43%%) **Site:** HN 1 (3%) , upper extremity 3 (9%) , trunk 20 (59%) , lower extremity	**PET-CT**. 2D; CT (NR) **Scan coverage:** skull base to upper thigh **Contrast:** NR **CT parameters:** NR; NR **FDG:** 400 MBq **Breath hold:** NR **CT used for:** attenuation correction and lesion localisation **Reconstruction:** iterative technique using an OSEM algorithm	Clearly indicative/highly suspicious for malignancy considered positive **Info provided:** clinical - NR; other tests - NR **No. observers:** NR; nuclear medicine consultants (experienced) **Diagnosis:** NR	Histology (5, 15%) **FNAC** (0) FU (34, 100%): microscopic mean 38 months (21 to 54 months); macroscopic mean 34 months (15 to 52 months) **Histology interval:** NR **FU interval:** 3 months **Exclusions:** n = 0

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			10 (29%) **BT (mean)**: microscopic group 2.27 mm (1.2 to 9.7 mm); macroscopic group 2. 01 mm (1.0 to 13 mm)			
Aukema 2010a Netherlands **Patients:** 46 **Primary lesions:** NR **LNBs/ Metastases:** NR	NC **Retrospective** (Prosp database: NR) **Data:** per pt Any (brain NR): 23/46 = 50%	**Mixed** (imaged on recurrence or after primary melanoma treatment) **Stage of disease**: NR; unfavorable primary tumour (n = 6); primary melanoma with simultaneous nodal metastases (n = 18) ; unknown primary melanoma with nodal metastasis (n = 2) ; locoregional recurrence (n = 15) ; distant recurrence (n = 5) **Inclusion:** raised S100 during FU after resection of nodal or distant metastases or with high risk primary tumour	**Mean age:** 59; **Median age:** ; **Range:** 25 to 93 years **Male:** NR (0%) **Site:** NR NR	**PET-CT**. NR; CT (U) (N/A) **Scan coverage:** whole body; not described **Contrast:** U **CT parameters:** kV NR; 40 mAs, 5 mm **FDG:** 180 to 240 MBq (4.9 to 6.5 mCi) **Breath hold:** No breath hold instructions reported **CT used for:** attenuation correction; PET fused to low-dose CT **Reconstruction:** NR	NR; "hypermetabolic lesions" **Info provided:** NR **No. observers:** 3; nuclear medicine physicians (experienced) **Diagnosis:** consensus of 3	**Histology** (13, 28.3%) **FNAC** (0) FU (33, 71.7%) : for D negative only (n = 19): median 12 months (4 to 32 months); NR for full sample **Histology interval:** NR **FU interval** **Exclusions:** n = NR **Other result:** "MRI revealed 2 brain metastases of 2 and 4 mm in 1 patient (2%). This patient also had other distant metastases that were detected by PET-CT"
Aukema 2010b Netherlands **Patients:** 70 **Primary lesions:** 70 **LNBs/ Metastases:** 73	**NC** **Prospective** **Data:** per pt Any mets: 30/70 = 43%	**Unclear** (N). **Stage of disease**: ≥ stage IIIb (all with clinically palpable nodes) **Inclusion:** clinically node positive with no sign of distant metas-	**Mean age:** 58; **Median age:** NR; **Range:** NR **Male:** 37 (0. 54%) **Site:** upper extremity 4, 6%; lower extremity 37, 53%; trunk 19, 27%; head/	**PET-CT**. 2D ; CT (U) (N/A) **Scan coverage:** WB according to primary lesion site (i.e. IRT inclusion of cranium or lower extremities) **Contrast:** U	NR; "metabolically active" **Info provided:** NR **No. observers:** 3; nuclear medicine physicians (NR) **Diagnosis:** consensus of 3	**Histology** (NR; 11 with histology or cytology) **FNAC** (NR; 11 with histology or cytology): FU (59; 84%): NR; ≥ 6 months **Histology interval:** N/A

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		tases; primary/ re-staging NR	neck 9, 13%; unknown primary 1, 1% BT: median 3 mm	**CT parameters:** kV NR; 40 mAs, 5 mm **FDG:** 180 to 240 MBq **Breath hold:** no breath hold instructions reported **CT used for:** attenuation correction; PET fused to low-dose CT **Reconstruction:** PET was fused with the low-dose CT after correction for attenuation		**FU interval:** NR **Exclusions**: n = 0 **Other result:** MRI detected brain mets in 5 pts, no reference standard reported
Bastiaannet 2009 Netherlands **Patients:** 251 **Primary lesions:** 251 **LNBs/ Metastases:** NR	**WPC** **Prospective** **Data:** per pt Distant mets: 78/251 = 31%	**Mixed** (primary (LN mets diagnosed at time of primary diagnosis) 39, 15.5%; recurrence (LN mets identified ≤ 3 years since primary dx) 145, 57.8%; recurrence > 3 years since primary dx 67, 26.7%) **Stage of disease**: III (100%) **Inclusion:** node positive (clinical or histology/ cytology proven) candidates for CLND; imaging to id further disease	**Mean age:** 56.9 years (n = 253) ; **Median age:** NR; **Range:** 19 to 93 years (reported in Bastiannet 2012) 76 (30.3%) < 50 years; 99 (39.4%) 50 to 65 years; 76 (30.3%) > 65 **Male:** 152 (0.606%) **Site:** HN 29, 11.6%; upper extremities 26, 10.4%; trunk 93, 37.0%; lower extremities 88, 35.0%; unknown primary 15, 6.0% **BT**: ≤ 1 mm 32, 12.8%; 1.0 to 2.0 73, 29.1%; ≥ 2.0	**CT**. CE, spiral, multi-slice **Scan coverage:** chest, abdomen plus neck for those with LN in the neck **Contrast:** oral and IV **CT parameters:** NR; NR; 'multi-slice' **Breath hold:** no breath hold instructions reported	NR (presence/ absence of mets) **Info provided:** NR **No. observers:** NR; attending staff nuclear medicine physicians (NR) **Diagnosis:** NR	**Histology** (NR) **FNAC** (NR) FU (251, 100%) : median 13.7 months; minimum 6 months stated for index test positive, NR for index test negative **Histology interval:** NR **FU interval:** NR **Exclusions**: n = 8; excluded due to follicular structure (n = 1), > 13 years between primary and lymph nodes (n = 3), incidence abroad (n = 1), mucosal melanoma (n = 2), and primary melanoma

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			129, 51.4%; unknown primary 15, 5.9%; missing 2, 0.8% **Clark level**: I/II/III (n = 84; 33.5%), IV/V (n = 144; 57.4%), unknown primary (n = 15; 5.9%), missing (n = 8; 3.2%)			treated as benign lesion (n = 1) (1) accuracy of PET alone, (2) change in treatment resulting from PET and/or CT
Cachin 2014 France **Patients:** 87 **Primary lesions:** 176 **LNBs/Metastases:** check entry	**NC** **Prospective** **Data:** per pt Any (incl brain, subcut mets): 39/67 = 58% **Data:** per lesion Any (incl brain): 85/176 = 48% Nodal: 20/39 = 51% Distant (incl brain): 65/137 = 47% Bone: 14/34 = 41% Lung: 10/27 = 37% Soft tissue: 16/25 = 64% Skin: 7/9 = 78% Brain: 7/9 = 78%	**Mixed** (states imaging was for staging or for re-staging). **Stage of disease**: NR; 45 (51% were diagnosed with melanoma mets on study Inclusion) **Inclusion:** prior history of cutaneous or ocular MM undergoing staging or restaging including: (a) newly diagnosed at any TNM stage, (b) known visceral or cutaneous MM metastases with unknown primary tumour, or (c) MM without metastases (included to assess test specificity)	**Mean age:** NR; **Median age:** NR; **Range:** NR **Male:** 42 (48.3%) **Site:** NR Breslow thickness (mm): < 1.0: 12, 13.8%; 1.0 to 2.0: 34, 39.1%; ≥ 2.0, 41, 47.1% Clark level: I 3, 3.4%; II 2, 2.3%; III 20, 23.0%; IV 46, 52.9%; V 3, 3.4%; not known 13, 14.9%	**PET-CT**. NR; SPECT used in 4 of 8 centres **Scan coverage:** WB (not further described) **Contrast:** NR **CT parameters:** SPECT; N/A **FDG:** 3 to 5 MBq/kg **Breath hold:** NR **CT used for:** PET 'correlated' with CT abnormalities **Reconstruction:** iterative in 6 of 8 centres; filtered backprojection in 2 of 8 centres	**PET.** Positive if there was focal uptake greater than mediastinal or liver uptake that could not clearly be related to physiological processes. Negative when a normal distribution of tracer was observed, even if the CT scan showed abnormalities. Bone accumulations were considered positive when the uptake was higher than in normal bone marrow. Any instance of equivocal PET uptake was considered positive **Info provided:** NR **No. observers:** NR; nuclear physician (experienced) **Diagnosis:** single	**Histology** (25; 28.7%) **FNAC** (N/A) FU (87, 100%): at least 6 months **Histology interval:** NR **FU interval:** NR **Exclusions**: n = 20; 12 did not undergo FDG PET due to imaging cancellation; 8 are unaccounted for (text describes 75 having PET but reports results for only 67)

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Dellestable 2011 France **Patients:** 40 **Primary lesions:** 40 **LNBs/ Metastases:** NR; 72 lesions	**WPC** Prospective **Data:** per lesion Any (incl brain): 72/119 = 61% (CT) 70/117 = 60% (MRI) 72/119 = 61% (PET-CT) Nodal: 31/39 = 79% (CT) 31/40 = 78% (MRI) 31/38 = 82% (PET-CT) Bone: 14/17 = 82% (CT) 14/16 = 88% (MRI) 14/17 = 82% (PET-CT) Liver: 4/21 = 19% (CT) 4/26 = 15% (MRI) 4/25 = 16% (PET-CT) Lung: 13/16 = 81% (CT) 13/14 = 93% (MRI) 13/15 = 87% (PET-CT)	**Mixed** (both primary staging and FU; breakdown reported but not legible on pdf) **Stage of disease**: AJCC I to II 11, 27. 5%; AJCC III to IV 29, 72.5% **Inclusion:** PET-CT for primary staging or follow-up of MM, regardless of AJCC stage or indication for examination	**Mean age:** 57 years; **Median age: Range:** 27 to 85 years **Male:** 20 (0.5%) . **Site:** NR **BT mean:** 3.2 mm, median 2.7 mm, range 0.6 to 11 mm	**CT**. CT (N/A); NR **Scan coverage:** skull, neck, thorax, abdomen, and pelvis **Contrast:** iodised injection was administered by the same venous route as for the previous examinations **CT parameters:** NR; NR **Breath hold:** no breath hold instructions reported **MRI**. WB, DW, T2STIR, CE 3D gradient echo (N/A); NR **Scan coverage:** WB; head to lower limbs **Contrast:** gadolinium injection **MRI parameters:** T2STIR, T1, diffusion and 3D gradient echo T1 after gadolinium injection; 1.5 T **Breath hold:** no breath hold instructions reported **PET-CT**. NR; CT (CE) (N/A); NR **Scan coverage:** WB; top of the	**CT:** NR **MRI:** NR **PET-CT**: focal uptake; unusual location or visual or quantitative intensity (SUV measurement) **Info provided:** NR **No. observers:** 3; NR (NR) **Diagnosis:** single with consensus if the results of any modality disagreed	**Histology** (36 lesions, 28% of 128) **FNAC** (0) FU (72, 56%): > 4 months **Histology interval:** NR **FU interval:** NR **Exclusions**: n = 20 lesions; 4 lesions with indeterminate reference and 16 not picked up by CT

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				skull to the feet **Contrast:** unclear; contrast is reported for CT; however CT component of **PET-CT** is not clear **CT parameters:** NR; NR **FDG:** 5.5 MBq/kg **Breath hold:** no breath hold instructions reported **CT used for:** attenuation correction and anatomical registration **Reconstruction:** NR		
Hausmann 2011 Germany **Patients:** 50 eligible; 33 included **Primary lesions:** 50 **LNBs/ Metastases:** NR	**WPC** **Prospective** **Data:** per lesion Any mets (excl brain): 455/824 = 55% (all tests) Nodal: 192/379 = 51% Distant: 263/445 = 59% Liver: 33/67 = 49% Lung: 145/197 = 74% Subcutaneous: 33/46 = 72% Other (authors' 'Other' category plus Adrenal, Kidney, Muscle and spleen sites): 51/118 = 43% Adrenal: 2/5 = 40% Bone: 1/17 = 6%	**Unclear** (Pts described as having undergone a previous assessment of tumour spread based on ADO (German) guidelines but staging/re-staging not described **Stage of disease**: full sample only: stage III (19); stage IV (31) **Inclusion:** AJCC stage III or IV MM; clinical indication for imaging was positive sentinel-node biopsy or suspicious lesions on ultrasound or X-ray studies	**Mean age:** full sample only: 59.6; **Median age:** **Range:** full sample only: 26 to 86 **Male:** full sample only: 32 (64%) **Site:** NR NR	**CT**. U + CE, multi-detector (N/A) **Scan coverage:** skull base to pelvis; CT and MR compared for "neck to the pelvis" only; sites imaged included lungs, liver, spleen, kidneys, adrenal glands, subcutaneous tissue, lymph nodes, muscle, bone marrow, and "other" **Contrast:** U + CE **CT parameters:** NR; NR **Breath hold:** no	**CT:** NR (presence/absence of mets) **MRI:** NR (presence/absence of mets) **Info provided:** diagnosis/age/sex **No. observers:** 4 (2 included); radiologist (high) **Diagnosis:** single	**Histology** (NR) **FNAC** (0) FU (33, 100%): ≥ 3 months **Histology interval:** N/A **FU interval:** minimum 3 months **Exclusions**: n = 17; no WB-CT follow-up undertaken. Results presented by region and for less experienced observers 3 and 4; also presented no. Mets detected by cranial MR but no 2×2 extractable

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	Kidney: 2/32 = 6% Muscle: 22/26 = 85% Spleen: 4/24 = 17%			breath hold instructions reported **MRI.** U + CE; 'standard sequences' (N/A) **Scan coverage:** WB; as above **Contrast:** U + CE **MRI parameters:** standard sequences with parallel imaging techniques; 1.5 T **Breath hold:** no breath hold instructions reported		
Jouvet 2014 France **Patients:** 37 **Primary lesions:** **LNBs/ Metastases:** 209 lesions (n varies per test)	**WPC** **Prospective** **Data:** per lesion Any mets (incl brain): 115/209 = 55% (CT) 125/218 = 57% (MRI) Any mets (excl brain): 95/186 = 51% (CT) 105/195 = 54% (MRI) 104/191 = 54% (PET-CT) Nodal: 23/53 = 43% (all tests) Bone: 15/33 = 45% (CT/MRI) 16/35 = 46% (PET-CT) Liver: 12/27 = 44% (all tests) Lung: 31/45 = 69% (all	**Unclear** (NR) **Stage of disease**: stage IV: 37 (100%) **Inclusion:** AJCC stage IV cutaneous MM referred for simultaneous staging by PET-CT, CT, superficial lymph node US, and MRI	**Mean age:** NR; **Median age:** NR; **Range:** NR **Male:** NR (0%) **Site:** NR NR	**CT**. CE; Helical; 16 row (N/A) **Scan coverage:** neck/ chest/ abdomen/ pelvis; "cervico-thoraco-abdomino-pelvic helicoidal acquisition"; then skull **Contrast:** iodinated IV injection **CT parameters:** 120 kV, 250 mAs (neck to pelvis); 140 kV, 120 mAs (skull), 1.25 mm (neck to pelvis), 2.5 mm (skull) **Breath hold:** no breath hold instructions reported **MRI.** (1) DW	**CT and MRI:** NR (presence/ absence of mets) **Info provided:** NR **No. observers:** 1; radiologist (experienced). **Diagnosis:** consensus of 2 (all images interp independently by 2 examiners, discordant results resolved by consensus)	**Histology** (0) **FNAC** (5, 13.5%) FU (32; 86.5%): > 9 months **Histology interval:** NR **FU interval:** NR **Exclusions**: n = 0; N/A Results are also presented by metastatic site. Provides K values for inter- and intra-observer agreements, but not the 2×2 tables for each observer

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	tests) Subcutaneous: 2/15 = 13% (CT) 10/22 = 45% (MRI) 7/15 = 47% (PET-CT)			alone (N/A); (2) DW, VIBE - 3D echo gradient CE, T1 - skull (N/A) **Scan coverage:** WB; top of skull to feet **Contrast:** U **MRI parameters:** echo-planar DW alone; 1.5 T **Breath hold:** no breath hold instructions reported		
Klebl 2003 Germany **Patients:** 83 **Primary lesions:** 83 **LNBs/ Metastases:** NR; 653 LNs examined	**WPC** **Prospective** **Data:** per pt Nodal mets: 17/79 = 22%	**Mixed** (primary (n = 8), follow-up (n = 75)) **Stage of disease**: NR **Inclusion:** MM Clark level IV or V undergoing FU after primary surgery	**Mean age:** NR; **Median age:** NR; **Range:** NR **Male:** 46 (55.421686746988%) **Site:** NR **Clark level** IV 68, 82%; level V 15, 18%	**US.** B-mode US; high resolution linear array (5 to 10 MHz); N/A **Scan coverage:** cervical, axillary, and inguinal LNBs **Contrast:** N/A	Suspicious/ indeterminate/ benign based on diameter, shape, echogenicity, and vascularisation pattern **Info provided:** unclear; could be same examiner as for LN palpation **No. observers:** NR; NR (NR) **Diagnosis:** NR	**Histology** (17, 20%) **FNAC** (0) FU (62, 75%): minimum 1 year; mean time since primary surgery 2.6 ± 2.3 years **Histology interval:** NR **FU interval:** 6 to 8 weeks for control visit, 6 to 12 months for FU visit **Exclusions**: n = 4; 4 were indeterminate on follow-up so that a final diagnosis could not be made No
Pfannenberg 2007 2007 Germany **Patients:** 64 **Primary lesions:** 420 **LNBs/ Metastases:** NR	**WPC** **Prospective** **Data:** per lesion Any metastases (excl brain): 297/420 = 71% (all tests)	**Mixed** (pre-surgery; investigation of abnormal findings; surveillance) **Stage of disease**: Stage III (25,	**Mean age:** 57.8 years; **Median age: Range:** 23.3 to 79.1 years **Male:** 41 (64.0625%) **Site:** NR	**CT**. CT (CE, 16 row multi-slice) (NA); N/A **Scan coverage:** base of the skull to the lower legs **Contrast:** Ultra-	**CT:** based on morphological characteristics and enhancement pattern; region-specific nodal size	**Histology** (65 (15%)) **FNAC** (N/A) FU (267 (64%) lesions by imaging follow-up, 88 (21%)

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	Nodal: 102/158 = 65% (CT) Distant (excl brain): 195/262 = 74% (all tests) Bone: 35/50 = 70% (all tests) Liver: 35/37 = 95% (all tests) Lung: 59/80 = 74% (all tests) Local: 53/70 = 76% (all tests) Other viscera: 13/25 = 52% (all tests)	39%); Stage IV (39, 61%) **Inclusion:** stage III or IV cutaneous MM undergoing imaging for exclusion of widespread disease and confirmation of local disease before surgical resection (n = 9); characterisation of abnormal radiological, clinical and laboratory findings (n = 48); routine melanoma surveillance in high risk patients (n = 7)	**Mean BT:** 2.69 mm (0.6 to 12 mm)	vist 370, Schering GmbH, Berlin, Germany, plus 1000 mL Mannitol 2% as a negative oral contrast agent before CT **CT parameters:** 120 kV, 120 to 160 mAs; 5 mm (axial, with an increment of 5 mm) and 3 mm (coronal with an increment of 2 mm) **Breath hold:** CT: patients were asked to stop breathing in normal expiration during the contrast-enhanced CT scans for optimal co-registration **MRI**. CE; multiple phased-array; axial and coronal (NA); N/A **Scan coverage:** head to toe **Contrast:** yes **PET-CT**. 3D; CT (CE, 16 row multi-slice) (NA); N/A **Scan coverage:** base of the skull to the lower legs **Contrast:** Ultravist 370, Schering GmbH, Berlin, Germany, plus	criteria based on measurement of the small axis diameter **MRI:** based on morphological characteristics and enhancement pattern; detected lymph nodes smaller than 10 mm but with brighter signal on T1 sequences, due to the paramagnetic effect of melanin, also were rated as suspicious **PET:** any focal tracer uptake exceeding normal regional tracer accumulation was assessed as a malignant lesion. Lesions rated malignant or probably malignant were considered to be malignant **Info provided:** aware of the clinical status **No. observers:** 6; 2 dermato-oncologists; 2 radiologists (2 specialists in nuclear medicine, 2 CT radiologists, and 2 MRI radiologists)	lesions by clinical follow-up): mean 252.5 days (range, 99 to 474 days) **Histology interval:** NR **FU interval:** every 3 months **Exclusions**: n = 36; no wbMRI (n = 25; due to metallic implants or claustrophobia (5 patients), refuse of a second whole body examination on the same day (17 patients) or abortion of the examination (3 patients); no evidence of tumour spread (3 patients) or lack of follow-up data for lesion characterisation (8 patients)

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				1000 mL mannitol 2% as a negative oral contrast agent before CT **CT parameters:** 120 kV, 120 to 160 mAs, 5 mm (axial, with an increment of 5 mm) and 3 mm (coronal with an increment of 2 mm) **FDG:** 370 MBq F-FDG IV 55 to 65 minutes before scanning **Breath hold:** CT: patients were asked to stop breathing in normal expiration during the contrast-enhanced CT scans for optimal co-registration **CT used for:** attenuation corrected and co-registered **Reconstruction:** iteratively reconstructed using commercial software (eSoft; Siemens., Erlangen, Germany)	**Diagnosis:** consensus of 2 or 4	
Pfluger 2011 Germany **Patients:** 50 **Primary lesions:** NR **LNBs/ Metastases:** NR; 232 lesions	**WPC** **Retrospective** (Prosp database: NR) **Data:** per lesion Any (incl brain) : 151/232 = 65% (CT)	**Mixed** (PET-CT was done for primary staging and for follow-up) **Stage of disease**: NR **Inclusion:** MM with regional LN	**Mean age:** 57; **Median age:** **Range:** 29 to 85 years **Male:** 36 (72%) **Site:** NR NR	**CT**. (1) CE, dual slice, helical (N/A); NR (2) U, dual slice, helical (N/A); NR **Scan coverage:** WB; from the skull including the legs	CT - abnormal soft tissue masses and/or enlarged LNs (diameter > 1.0 cm) plus degree of contrast enhancement for CE CT only PET alone - non-	**Histology** (41, 17.7%) **FNAC** (0) FU (191, 82.3%): ≥ 6 months; no further detail **Histology interval:** NR

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		metastases (NR if clinically detectable or micro-metastases) undergoing PET-CT either for primary staging or during follow-up. Only included lesions considered malignant by at least 1 of the 3 modalities (NECT, CECT, 18F-FDG PET)		**Contrast:** 120 mL (2.5 mL/s) of iodine-containing contrast medium **CT parameters:** 120 kV, 145 mAs, 2.5 mm **Breath hold:** CT expiration protocols for shallow free breathing during the emission scan **PET-CT** (1) 3D; CT (CE, dual slice, helical) (N/A); NR (2) 3D- CT (U, dual slice, helical) (N/A); NR **Scan coverage:** WB; from the skull including the legs **Contrast:** 120 mL (2.5 mL/s) of iodine-containing contrast medium **CT parameters:** 120 kV, 145 mAs, 2.5 mm **FDG:** 200 MBq **Breath hold:** CT expiration protocols for shallow free breathing during the emission scan **CT used for:** unclear; reports side	physiologically increased uptake of FDG with SUVmax > 2.5. For lesions with discrepant findings on both modalities, the finding of the modality with the higher diagnostic confidence score was accepted. If results from both modalities were discrepant and had the same diagnostic confidence score value, the lesion was judged positive **Info provided:** knowledge of clinical data **No. observers:** 2; NR (experienced) **Diagnosis:** consensus	**FU interval:** NR n = NR; ** In cases of new tumour lesions during the follow-up period, these lesions were not included in the study. The reason given for not including these lesions was the fact that non-detectable lesions in CT or 18F-FDG PET cannot be distinguished from non-existent lesions in the case of a newly detected tumour lesion during follow-up

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				by side PET-CT display with spatially synchronised images **Reconstruction:** NR; PET and CT interpreted side by side with spatially synchronised images to ensure that the identical lesion was assessed in both modalities		
Reinhardt 2006 Germany **Patients:** 250 **Primary lesions:** 250 **LNBs/ Metastases:** NR; 670 lesions identified	**WPC** **Retrospective** (Prosp database: NR) **Data:** per pt Any (excl brain): 116/250 = 46% Nodal mets: 78/250 = 31% Distant mets (excl brain): 84/250 = 34%	**Mixed** (primary staging after sentinel node biopsy (n = 75); therapy control after chemotherapy of metastatic disease (n = 42), staging of clinically suspected recurrent disease (n = 65), during follow-up within 5 years of primary treatment (n = 68) **Stage of disease**: initial pathology: stage I 22, 9%; stage II 88, 35%; stage III 108, 43%; stage IV 32, 13% **Inclusion:** cutaneous MM referred for PET-CT **Excluded if** inadequate reference standard (no histology or FU < 1	**Mean age:** 58; **Median age:** **Range:** ±16 **Male:** 145 (58%) **Site:** NR Tumor depth: ≤ 1.0 mm 29, 12%; 1.01 to 2.0 mm 68, 27%; 2.01 to 4.0 mm 66, 26%; > 4.0 mm 64, 26%	**CT**. CE, helical, dual detector (N/A); N/A **Scan coverage:** WB; base of skull to tip of toes in 3 parts **Contrast:** Peritrastoral-GI; Kohler Chemie GmbH, Alsbach, Germany **CT parameters:** 130 kV, 40 mAs, 5 mm **Breath hold:** limited breath hold for CT and shallow breathing for PET **PET-CT**. CT (CE), helical, dual detector (N/A); N/A **Scan coverage:** WB; base of skull to tip of toes in 3 parts **Contrast:** Peritrast-	NR for any test; states only that accuracy was assessed according to according to the current AJCC staging classification **Info provided:** routine clinical fashion; same clinical information about each patient **No. observers:** NR; NR; consensus by each of 2 experienced investigators (experienced) **Diagnosis:** consensus (of 2?)	**Histology** (100, 40% for N-staging (including 15 with SLNB) 20, 8% for M-staging) **FNAC** (N/A) FU (250, 100%) : NR; ≥ 1 year **Histology interval:** NR **FU interval:** NR **Exclusions**: n = 0 Reports data for differentiation by metastatic sites (M1A to M1C) and for detection of visceral and non-visceral mets. Gives Se/Sp by population group but prevalence per group not given to allow 2×2 to be included

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		year)		oral-GI; Kohler Chemie GmbH, Alsbach, Germany **CT parameters:** 130 kV, 40 mAs, 5 mm **FDG:** 371 ± 40 MBq FDG through an anterior cubital vein **Breath hold:** limited breath hold for CT and shallow breathing for PET **CT used for:** attenuation correction based on re-scaling of the CT image **Reconstruction:** iteratively reconstructed with attenuation correction on the basis of a re-scaling of the CT image as described elsewhere (Kinahan 2003)		
Strobel 2007b Switzerland **Patients:** 124 **Primary lesions:** NR **LNBs/ Metastases:** NR	NC **Prospective** **Data:** per pt Any (incl brain): 53/124 = 43%	**Unclear** (NR; PET-CT for depiction or exclusion of metastases) **Stage of disease**: NR **Inclusion:** high risk melanoma (BT > 4 mm, or Clark level III or IV, or known resected metastases) and	**Mean age:** 54.4 years; **Median age: Range:** 15 to 82 years **Male:** 59 (47.5806451612903% **Site:** NR NR	**PET-CT**. CT (CE, multislice, helical) (N/A); NR **Scan coverage:** head to the knees with scanning of the lower legs for patients with primary tumours of the lower extremities **Contrast:** oral CT contrast	Mets present if detected by 1 or both readers. FDG uptake clearly greater than background; if a focal FDG-active lesion was detected, the exact anatomical localisation was determined on the	**Histology** (20, 16.1%) **FNAC** (21, 16.9%) FU (124, 100%, 18 D+ and 61 D- had status confirmed by PET-CT or clinical FU, 4 D- had MRI to confirm absence of mets and 10/53 D+)

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		raised S100 (> 0.2 μg/L) undergoing follow-up after primary treatment **Excluded if** systemic therapy before the PET-CT investigation		agent given 15 minutes before injection of 18F-FDG **CT parameters:** 140 kV, 40 mAs, 4.25 mm **FDG:** 350 to 400 MBq **Breath hold:** CT: breath holding in the normal expiratory position **CT used for:** attenuation correction, fused **Reconstruction:** standard iterative algorithm (OSEM)	fused PET-CT images. Lesions with 18F-FDG uptake in physiological sites or benign variants, e.g. muscles, brown fatty tissue or pulmonary infiltrations, were determined as benign. Semi-quatitative analysis of FDG uptake in terms of SUVmax also conducted **Info provided:** blinded to serum S100B **No. observers:** 2; nuclear radiology physicians (experienced (13 years and 7 years)) **Diagnosis:** consensus of 2	: minimum of 6 months (range 6 to 18 months in all patients **Histology interval:** NR **FU interval:** NR **Exclusions**: n = 3; chemotherapy before PET-CT
van den Brekel 1998 Netherlands **Patients:** 26 **Primary lesions:** 26 **LNBs/ Metastases:** NR	NC **Retrospective** (Prosp database: NR) **Data:** per pt Nodal (neck): 21/26 = 81%	**Mixed** (NR; but interval between treatment of the primary and neck dissection ranged from 0 to 8.8 years (mean 21 months)) **Stage of disease**: stage III (palpable LN) 18, 69%; stage I and II 8, 31% **Inclusion:** HN MM with CT before neck dissection, including therapeutic and elective (negative on pal-	**Mean age:** 54. 5 years; **Median age: Range:** 55 to 83 years **Male:** 18 (0. 69230769230769. **Site:** scalp 6, 23%; temporal 3, 12%; ear 4, 15%; anterior face 4, 15%; neck 1, 4%; shoulder 1, 4%; upper limb 1, 4%; nasal mucosa 1, 4%; unknown primary 5, 19% **BT** 0.8 mm to 22 mm	**CT**. CE (N/A); NR **Scan coverage:** neck **Contrast:** IV bolus plus drip infusion of iodine contrast **CT parameters:** NR; 5 mm for 24 pts; 2 mm for 2 pts (both FN) **Breath hold:** NR	Presence of necrosis or axial diameter > 10 or > 11 mm **Info provided:** NR **No. observers:** 2; NR; co-authors (NR) **Diagnosis:** unclear	**Histology** (26, 100%) **FNAC** (0) FU (0): N/A **Histology interval:** 4 weeks **FU interval:** N/A **Exclusions**: n = 0 Both FN on CT used 8 mm CT thickness

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		pation). Also included primary and recurrence				
van Wissen 2016 Netherlands **Patients:** 70 **Primary lesions:** 70 **LNBs/ Metastases:** NR	NC **Retrospective** (Prosp database: no) **Data:** per pt Nodal (superficial groin mets only): 59/69 = 86% Nodal (deep groin mets only) : 24/67 = 36%	**Mixed** (NR. Discussion states "large proportion of our patients were initially treated for their primary tumour at other hospitals, and sometimes years prior to the current groin dissection") **Stage of disease**: only stage III B & C **Inclusion:** stage IIIB or IIIC MM with palpable groin metastases; selected for therapeutic CGD	**Mean age:** NR; **Median age:** 58; **Range:** 24 to 83 **Male:** 35 (0.5%) **Site:** leg 58, 83%; trunk 6, 9%; arm 0, 0%; unknown 6, 9% **BT mm:** ≤ 1. 00 6 (9%); ≤ 2.00 15 (21%) ; 2.01 to 4.00 15 (21%); > 4.00 12 (17%); missing/unknown 22 (31%)	**PET-CT**. CT (U) (NA) **Scan coverage:** WB; not further described **Contrast:** none **CT parameters:** Kv NR; 40 mAs, 2 to 5 mm **FDG:** 180 to 240 MBq **Breath hold:** standard acquisition protocols **CT used for:** attenuation correction; fused images **Reconstruction:** NR	FDG uptake (qualitative assessment) **Info provided:** NR **No. observers:** 1; nuclear medicine (nr) **Diagnosis:** single	**Histology** (70, 100%) **FNAC** (NA) FU (not for ref purposes): median 16 months (0 to 71 months) **Histology interval:** NR **FU interval:** NR **Exclusions**: n = 1; missing pathology 7/10 disease negative had a diagnos- tic resection of a lymph node before lymph node dissection potentially leading to FPs

+ - positive; AJCC: American Joint Cancer Committee; AWOSEM: attenuation weighted ordered subsets expectation maximisation; BT: Breslow thickness; CE: contrast enhanced; CLND: complete lymph node dissection; CT: computed tomography; 2D: two-dimensional; 3D: three-dimensional; DW: diffusion weighted; EDV: end-diastolic volume; 18FDG: 2-deoxy-2-[18F]fluoro-D-glucose; FNAC: fine needle aspiration cytology; FORE: Fourier rebinning; FU: follow-up; GE: gradient echo; HN: head and neck; LN: lymph node; LNB: lymph node basin; LND: lymph node dissection; LS: lymphoscintigraphy; mA: measure of tube current; mets: metastases; MM: malignant melanoma; MRI: magnetic resonance imaging; NC: non-comparative; OSEM: ordered subsets expectation maximisation algorithm; PET: positron emission tomography; PI: pulse index; PSV: peak systolic volume; prosp: RF: risk factor; SD: standard deviation; SLN: sentinel lymph node; SLNB: sentinel lymph node biopsy; SSM: superficial spreading melanoma; SUV: standardised uptake value; SUVmax: maximum standardised uptake value; U: unenhanced; US: ultrasound; WB: whole body

Appendix 10. Descriptive synthesis of all included studies of whole body imaging

Study design and setting

Twelve of the 24 studies (50%) were prospective case series (Aukema 2010b; Bastiaannet 2009; Cachin 2014; Dellestable 2011; Hafner 2004; Hausmann 2011; Jouvet 2014; Klebl 2003; Maubec 2007; Pfannenberg 2007; Strobel 2007b; Veit-Haibach 2009), ten (40%) were retrospective in design (Abbott 2011; Arrangoiz 2012; Aukema 2010a; Iagaru 2007; Kang 2011; Pfluger 2011; Reinhardt 2006; Strobel 2007a; van den Brekel 1998; van Wissen 2016), and in two, the direction of the design was not clear (Prayer 1990; Rubaltelli 2011). All studies were conducted in Europe apart from two US-based studies - Arrangoiz 2012; Iagaru 2007 - and one conducted in South Korea (Kang 2011).

Participants

Primary staging. Of the six studies conducted in participants undergoing primary staging, two included any participant following diagnosis of melanoma (Kang 2011; Veit-Haibach 2009); two excluded those with distant metastases on diagnosis (Hafner 2004; Maubec 2007) (Maubec 2007 was restricted to those with melanomas at least 4 mm in thickness); one included clinically node positive participants but did not report exclusion of those with distant metastases (Prayer 1990); and one included only clinically node negative participants with melanomas of at least 4 mm Breslow thickness (Arrangoiz 2012). Three studies also reported data for pre-SLNB imaging (Arrangoiz 2012; Hafner 2004; Maubec 2007), two of which reported subgroup data for clinically node negative participants who underwent SLNB (Hafner 2004; Maubec 2007). All six studies reported accuracy data on a per patient basis; no per lesion data were identified.

A total of 492 participants were included with sample sizes ranging from 25 in Maubec 2007 to 217 in Prayer 1990. When reported (n = 5), the ages of included participants ranged from 18 years in Hafner 2004 to 89 years in Arrangoiz 2012. The mean age of included participants was reported in five studies (the median of reported means was 61 years, range 56 to 67 years) and median age in one study (median 55 years in Hafner 2004). Fifty-two per cent of included participants were male. The percentage of participants with head and neck melanoma ranged from 4% in Veit-Haibach 2009 to 36% in Maubec 2007 (median 15%) and melanoma of the extremities, including the hands or feet where documented, from 32% in Maubec 2007 to 73% in Kang 2011 (median 50%).

Re-staging. Of the three studies conducted in participants undergoing re-staging of disease, one included any participant having imaging for re-staging purposes (Iagaru 2007); and two included clinically node negative participants either undergoing ultrasound of the regional lymph nodes as part of a follow-up program, as in Rubaltelli 2011, or with raised S100 during follow-up, as in Strobel 2007a. A total of 589 participants were included with sample sizes of 47 in Strobel 2007a, 106 in Iagaru 2007, and 460 in Rubaltelli 2011. The ages of included participants ranged from 20 years to 87 years. The median of reported mean ages was 55 years. Fifty-three per cent of included participants were male. The site of the primary melanoma was not reported in any study. All three studies reported accuracy data on a per patient basis, and one study also reported data per lesion (139 lesions identified in 30 participants; Iagaru 2007).

Mixed or unclear. The 15 studies conducted in mixed or not clearly described population groups are described in Table 3 according to the reported indication for imaging and participant stage of disease on recruitment.

Two studies clearly included participants at any stage of disease (Dellestable 2011; Reinhardt 2006). In Dellestable 2011, 27% of participants had stage I or II melanoma and 73% had stage III or IV disease; imaging was undertaken for primary staging or follow-up. In Reinhardt 2006, 44% of participants had stage I or II melanoma and the remaining participants had stage III or IV disease. Imaging was undertaken for primary staging after SLNB (30%); therapy control after chemotherapy of metastatic disease (17%), staging of clinically suspected recurrent disease (26%), and imaging during follow-up within five years of primary treatment (27%). Insufficient data were available from this study to allow 2×2 contingency tables to be estimated for each subgroup of participants, despite author contact.

Stage of disease on recruitment was not reported in four studies, and these were judged to have included 'any' stage of disease (Aukema 2010a; Cachin 2014; Klebl 2003; Strobel 2007b). Aukema 2010a included asymptomatic patients with raised S100 either judged to be high risk after primary melanoma treatment (56%) or undergoing follow-up after surgical treatment of regional (33%) or distant (11%) metastases. Cachin 2014 described imaging for staging or for re-staging but did not give a breakdown of the number of participants in each group. Klebl 2003 restricted inclusion to those with Clark level IV or V melanomas, with 10% of participants having primary staging and 90% undergoing follow-up, and Strobel 2007b included those with melanomas at least 4 mm in thickness, Clark level III or IV, or known resected metastases, further reporting only that imaging was used for depiction or exclusion of metastases.

The remaining nine studies in mixed or not clearly described population groups included only participants with stage III disease (Abbott 2011; Aukema 2010b; Bastiaannet 2009; Pfluger 2011; van den Brekel 1998; van Wissen 2016), stage IV disease (Jouvet 2014), or both (Hausmann 2011; Pfannenberg 2007) (Table 3). In the two studies including participants with stage III and IV melanoma, the percentage with stage III disease was 38% in Hausmann 2011 and 39% in Pfannenberg 2007. Four studies in mixed population groups included those having primary staging or follow-up but did not report the number of participants with each indication for imaging (Abbott 2011; Pfluger 2011; van den Brekel 1998; van Wissen 2016). Bastiaannet 2009 included those with nodal disease identified at the time of primary diagnosis (15%), or with recurrence up to three years from diagnosis (58%) or more than three years since primary diagnosis (27%). In Pfannenberg 2007, imaging was undertaken to exclude widespread disease and before surgical resection (14%); to characterise abnormal radiological, clinical, and laboratory findings (75%); or as part of routine surveillance in high-risk patients (11%). The remaining three studies did not clearly describe the indication for imaging and were conducted in patients with palpable and pathology proven lymph node metastases and no signs of distant metastases (Aukema 2010b); participants with positive sentinel node biopsy or suspicious lesions on ultrasound or X-ray studies (Hausmann 2011); or patients with stage IV melanoma (Jouvet 2014).

A total of 1265 participants were included in the 15 studies with sample sizes ranging from 26 in van den Brekel 1998 to 251 in Bastiaannet 2009. When reported (n = 10), the ages of included participants ranged from 15 years in Strobel 2007b to 93 years in

Aukema 2010a. The mean age of included participants was reported in nine studies (the median of reported means was 57 years, range 54 to 59 years) and median age in two studies (Abbott 2011 reporting a median age of 50 for those with microscopic disease and 63 for those with macroscopic disease; and van Wissen 2016 reporting a median age of 58 years). Forty-eight per cent of included participants were male. The site of the primary melanoma was reported in only five of the 16 studies (Abbott 2011; Aukema 2010b; Bastiaannet 2009; van den Brekel 1998; van Wissen 2016), one of which included only head and neck melanoma (van den Brekel 1998), and one of which included only those undergoing combined groin dissection for melanomas of the trunk (17%) or extremities (83%) (van Wissen 2016). Excluding van den Brekel 1998 and van Wissen 2016, the percentage of participants with head and neck melanoma ranged from 3% in Abbott 2011 to 13% in Aukema 2010b, and melanoma of the extremities, including the hands or feet where documented from 38% in Abbott 2011 to 59% in Aukema 2010b.

Index tests

Sixteen studies contributed data for a single index test (Abbott 2011; Arrangoiz 2012; Aukema 2010a; Aukema 2010b; Bastiaannet 2009; Cachin 2014; Hafner 2004; Kang 2011; Klebl 2003; Maubec 2007; Prayer 1990; Rubaltelli 2011; Strobel 2007a; Strobel 2007b; van den Brekel 1998; van Wissen 2016), and eight compared the accuracy of one or more index tests (Dellestable 2011; Hausmann 2011; Iagaru 2007; Jouvet 2014; Pfannenberg 2007; Pfluger 2011; Reinhardt 2006; Veit-Haibach 2009) (Table 1). Two studies also provided data for PET alone (ineligible index test) (Bastiaannet 2009; Hafner 2004), and two reported data for MRI of the brain in all patients but 2×2 contingency table data could not be included because of small patient or lesion numbers (Aukema 2010a; Aukema 2010b). However, available information on MRI of the brain has been separately summarised as an additional result.

Ultrasound. Five studies evaluated ultrasound as a staging tool (Hafner 2004; Jouvet 2014; Klebl 2003; Prayer 1990; Rubaltelli 2011). All studies employed B-mode ultrasound, three at single frequencies of 5 MHz (Hafner 2004), 7.5 MHz (Prayer 1990), and 12.5 MHz (Jouvet 2014), and two using variable frequencies of 5 to 10 MHz (Klebl 2003), and 7.5 to 13 MHz (Rubaltelli 2011). One study of ultrasound used in potential SLNB candidates performed ultrasound before lymphoscintigraphy. Lymph node basins were imaged according to the site of the primary melanoma in all studies. The criteria for the detection of nodal metastases were described in all studies apart from Hafner 2004 (Appendix 9). Ultrasound was performed by radiologists (Hafner 2004; Jouvet 2014; Prayer 1990), was performed by a sonologist (Rubaltelli 2011), or was not reported (Klebl 2003).

CT. Ten studies evaluated CT - unenhanced (Iagaru 2007), contrast enhanced (Bastiaannet 2009; Dellestable 2011; Jouvet 2014; Pfannenberg 2007; Pfluger 2011; Reinhardt 2006; van den Brekel 1998; Veit-Haibach 2009), or both (Hausmann 2011). CT parameters (tube current (mA), tube voltage (kV), and slice thickness (mm)) were not reported in four studies (Bastiaannet 2009; Dellestable 2011; Hausmann 2011; Veit-Haibach 2009), and ranged from 40 mA in Iagaru 2007 and Reinhardt 2006; to 250 mA in Jouvet 2014; 120 kV in Jouvet 2014, Pfannenberg 2007, and Pfluger 2011; to 140 kV in Iagaru 2007, with slice thicknesses from 1.25 mm in Jouvet 2014 to 5 mm in Iagaru 2007, Pfannenberg 2007, Reinhardt 2006, and van den Brekel 1998 (reported per study in Appendix 9).

Scan coverage included the skull (Dellestable 2011; Iagaru 2007; Jouvet 2014; Pfluger 2011), or specifically excluded the skull (Bastiaannet 2009; Hausmann 2011; Pfannenberg 2007; Reinhardt 2006), and it extended to the abdominal or pelvic area (Bastiaannet 2009; Dellestable 2011; Jouvet 2014; Pfluger 2011), or it also included the lower limbs (Iagaru 2007; Pfannenberg 2007; Pfluger 2011; Reinhardt 2006). van den Brekel 1998 imaged the neck area only, and Veit-Haibach 2009 did not clearly document the scan coverage, describing whole body imaging in a caudocranial direction. The criteria for the detection of metastases were not reported in six studies (Bastiaannet 2009; Dellestable 2011; Hausmann 2011; Iagaru 2007; Jouvet 2014; Reinhardt 2006). Four studies reported the use of morphological characteristics (Pfannenberg 2007; van den Brekel 1998), soft tissue masses (Pfluger 2011; Veit-Haibach 2009), contrast enhancement (Pfannenberg 2007; Pfluger 2011; Veit-Haibach 2009), and nodal size criteria (Pfannenberg 2007; Pfluger 2011; van den Brekel 1998).

Test interpretation was provided by radiologists (Hausmann 2011; Jouvet 2014; Veit-Haibach 2009), nuclear medicine physicians (Bastiaannet 2009), or both (Iagaru 2007), or by dermato-oncologists and radiologists (Pfannenberg 2007). Four studies did not report observer qualifications (Dellestable 2011; Pfluger 2011; Reinhardt 2006; van den Brekel 1998). Half of studies reported providing test interpreters with clinical information including the diagnosis, age, and sex of the patient (Hausmann 2011), clinical status (Pfannenberg 2007), clinical data (Pfluger 2011), routine clinical information (Reinhardt 2006), or patient-specific clinical background (Veit-Haibach 2009). All studies apart from two - Iagaru 2007 and van den Brekel 1998 - reported blinding to the results of other imaging tests.

MRI. Four studies evaluated 1.5 T MRI using a variety of different sequences before and after gadolinium contrast enhancement (Dellestable 2011; Hausmann 2011; Jouvet 2014; Pfannenberg 2007), including diffusion weighting (Dellestable 2011; Jouvet 2014), as well as ultrafast gradient echo (described as VIBE in the study reports) sequences (Jouvet 2014; Pfannenberg 2007). Scan coverage in three studies was from the head to the feet (Jouvet 2014; Pfannenberg 2007; Laurent 2010), and from the neck to the pelvis only in Hausmann 2011. Two studies did not report the criteria used to assess the presence of metastases (Hausmann 2011; Jouvet 2014); one reported a qualitative assessment of signal intensity (Dellestable 2011), and one reported use of morphological characteristics,

enhancement pattern, and lymph node size and signal (Pfannenberg 2007). Four studies reported test interpretation by radiologists (Dellestable 2011; Hausmann 2011; Jouvet 2014; Pfannenberg 2007). Two studies reported providing test interpreters with clinical information including the diagnosis, age, and sex of the patient (Hausmann 2011), or clinical status (Pfannenberg 2007). All studies reported blinding to the results of other imaging tests.

PET-CT. Seventeen studies examined the use of PET-CT for staging purposes, combining PET with unenhanced CT (Arrangoiz 2012; Aukema 2010a; Aukema 2010b; Dellestable 2011; Iagaru 2007; Kang 2011; Maubec 2007; van Wissen 2016), contrast enhanced CT (Jouvet 2014; Pfannenberg 2007; Reinhardt 2006; Strobel 2007a; Strobel 2007b; Veit-Haibach 2009), or evaluating both (Pfluger 2011). Two studies did not report whether or not the CT component was contrast enhanced (Abbott 2011; Cachin 2014). CT was clearly described as used for attenuation correction (Arrangoiz 2012; Aukema 2010a; Aukema 2010b; Pfannenberg 2007; Reinhardt 2006; Strobel 2007a; Strobel 2007b; van Wissen 2016; Veit-Haibach 2009), or for anatomical localisation (Cachin 2014; Kang 2011), or for both (Abbott 2011; Dellestable 2011; Iagaru 2007), or it was not clearly described (Jouvet 2014; Maubec 2007; Pfluger 2011). Where reported (n = 8), studies employed 2D PET (Abbott 2011; Aukema 2010b; Iagaru 2007; Strobel 2007a), 3D PET (Maubec 2007; Pfannenberg 2007; Pfluger 2011), or either 2D or 3D PET (Arrangoiz 2012). CT parameters were not reported in four studies (Abbott 2011; Cachin 2014; Dellestable 2011; Veit-Haibach 2009). In 14 studies, parameters ranged from 40 mA - Aukema 2010a; Aukema 2010b; Iagaru 2007; Reinhardt 2006; Strobel 2007a; Strobel 2007b; van Wissen 2016 - to 160 mA - Kang 2011; Pfannenberg 2007, or from 110 kV - Maubec 2007 - to 140 kV - Arrangoiz 2012; Iagaru 2007; Jouvet 2014; Kang 2011; Strobel 2007a; Strobel 2007b - and slice thickness from 2.5 mm - Kang 2011; Pfluger 2011 - to 6.5 mm - Jouvet 2014 - and are reported in Appendix 9.

Scan coverage included the skull (Arrangoiz 2012; Dellestable 2011; Iagaru 2007; Kang 2011; Maubec 2007; Pfluger 2011; Strobel 2007a; Strobel 2007b), or specifically excluded the skull (Abbott 2011; Jouvet 2014; Pfannenberg 2007; Reinhardt 2006), and it extended to the upper thigh (Abbott 2011), or to the lower limbs (Arrangoiz 2012; Dellestable 2011; Iagaru 2007; Jouvet 2014; Kang 2011; Maubec 2007; Pfannenberg 2007; Pfluger 2011; Reinhardt 2006; Strobel 2007a; Strobel 2007b). Five studies did not clearly document the scan coverage, describing whole body imaging (Aukema 2010a; Cachin 2014; van Wissen 2016), imaging according to the primary lesion site (Aukema 2010b), or imaging in a caudocranial direction (Veit-Haibach 2009).

The criteria for the detection of metastases were not reported in three studies (Abbott 2011; Jouvet 2014; Reinhardt 2006), or they were described as the presence of metabolically active lesions with no further detail in two (Aukema 2010a; Aukema 2010b). Six studies reported assessment of focal FDG uptake relative to background (Cachin 2014; Strobel 2007a), as supported by SUVmax assessment (Dellestable 2011; Maubec 2007; Pfannenberg 2007; Pfluger 2011; Strobel 2007b; van Wissen 2016; Veit-Haibach 2009). Three studies reported the use of SUVmax alone ($\geq$ 2.2 in Kang 2011 and $\geq$ 2.5 in Arrangoiz 2012 and Iagaru 2007).

Test interpretation was provided by nuclear medicine physicians alone (Abbott 2011; Arrangoiz 2012; Aukema 2010a; Aukema 2010b; Cachin 2014; Jouvet 2014; Kang 2011; Strobel 2007a; Strobel 2007b; van Wissen 2016), or teamed with radiologists (Iagaru 2007; Veit-Haibach 2009), or by dermato-oncologists and radiologists (Pfannenberg 2007). Four studies did not report observer qualifications (Dellestable 2011; Maubec 2007; Pfluger 2011; Reinhardt 2006). Four studies reported providing test interpreters with some form of clinical patient information (Pfannenberg 2007; Pfluger 2011; Reinhardt 2006; Veit-Haibach 2009). Seven studies reported blinding to the results of other imaging tests (Dellestable 2011; Jouvet 2014; Pfannenberg 2007; Reinhardt 2006; Strobel 2007a; Strobel 2007b; Veit-Haibach 2009).

Reference standards

Four of the 24 studies (17%) evaluated the accuracy of imaging in comparison to histology alone, using samples from SLNB or CLND (Hafner 2004; Maubec 2007), or from neck (van den Brekel 1998), or from groin (van Wissen 2016) dissection, and in two studies, the reference standard combined histology based on CLND or SLNB with follow-up to determine any false negative results on imaging (Arrangoiz 2012; Prayer 1990). The remaining studies used a combination of histology or follow-up (Abbott 2011; Bastiaannet 2009; Cachin 2014; Dellestable 2011; Hausmann 2011; Iagaru 2007; Kang 2011; Klebl 2003; Pfannenberg 2007; Pfluger 2011; Reinhardt 2006; Veit-Haibach 2009), FNAC or follow-up (Jouvet 2014), or histology, FNAC, or follow-up as a reference standard (Aukema 2010a; Aukema 2010b; Rubaltelli 2011; Strobel 2007a; Strobel 2007b).

Across the 20 studies reporting some form of follow-up, two did not report the length of follow-up, but more than 90% of included participants had a histological reference standard reported (Arrangoiz 2012; Iagaru 2007). Eighteen studies reported or required minimum follow-up periods of at least three months (n = 11) or reported the mean or median follow-up with a range that was at least three months (n = 7). Minimum follow-up was between three and six months (Aukema 2010a; Dellestable 2011; Hausmann 2011; Pfannenberg 2007; Veit-Haibach 2009), from six months to a year (Aukema 2010b; Bastiaannet 2009; Cachin 2014; Jouvet 2014; Kang 2011; Pfluger 2011; Prayer 1990; Rubaltelli 2011; Strobel 2007a; Strobel 2007b), or one year or longer (Abbott 2011; Klebl 2003; Reinhardt 2006). Where reported, median follow-up times ranged from 10 months in Rubaltelli 2011 to 24.3 months in Kang 2011, and mean follow-up from 8.3 months to 34 months (Abbott 2011).

Follow-up schedules were documented in eight studies (Abbott 2011; Hausmann 2011; Kang 2011; Klebl 2003; Pfannenberg 2007; Prayer 1990; Reinhardt 2006; Strobel 2007a). Tests used during follow-up were mentioned in 16 studies (Abbott 2011; Aukema 2010a; Aukema 2010b; Bastiaannet 2009; Cachin 2014; Dellestable 2011; Hausmann 2011; Jouvet 2014; Kang 2011; Pfannenberg 2007; Pfluger 2011; Reinhardt 2006; Rubaltelli 2011; Strobel 2007a; Strobel 2007b; Veit-Haibach 2009), although the detail provided varied considerably, for example from 'clinical or radiological follow-up' in Dellestable 2011 to 'physical examination, blood tests, ultrasound studies, X-rays, and CT scans of the body from the neck to the pelvis (WB-CT) as well as an MRI of the head (MRI-CR)' in Hausmann 2011 (Appendix 9).

Exclusions

Ten studies reported the exclusion of between 1 and 36 study participants (Bastiaannet 2009; Cachin 2014; Hausmann 2011; Klebl 2003; Pfannenberg 2007; Rubaltelli 2011; Strobel 2007b; van Wissen 2016), or lesions (Dellestable 2011). Pfluger 2011 further reported that new lesions detected during the follow-up period were not included as false negative on imaging on the basis that they may have been newly emergent lesions.

Appendix 11. Sensitivities and specificities of imaging tests from studies reporting data for more than one target condition

Test Study Population group No. patients/ cases [a] [Lesions/ cases]	Imaging detail	Sensitivity [95% CI] % TP/Diseased					Specificity [95% CI] % TN/Non-Diseased				
		Any metastasis		Nodal metastasis	Distant metastasis		Any metastasis		Nodal metastasis	Distant metastasis	
		Including brain	Excluding brain		Including brain	Excluding brain	Including brain	Excluding brain		Including brain	Excluding brain
CT											
Veit-Haibach 2009 **Primary Per patient data 56**	**CT (CE)**	**Not assessed**	**Not assessed**	**23 [5 to 54] 3/13**	**Not assessed**	**Brain NR 25 [5 to 57] 3/12**	**Not assessed**	**Not assessed**	**100 [92 to 100] 43/43**	**Not assessed**	**Brain NR 93 [81 to 99] 41/46**
Reinhardt 2006 **Mixed Per patient**	**CT (CE)**	**81 [73 to 88] 94/116**	**Not assessed**	**85 [75 to 92] 66/78**	**74 [63 to 83] 62/84**	**Not assessed**	**77 [69 to 84] 103/ 134**	**Not assessed**	**87 [81 to 92] 150/ 172**	**88 [82 to 92] 146/ 166**	**Not assessed**

(*Continued*)

data 250/ 116											
Dellestabl 2011 Mixed Per lesion data 40 [118 / 72]	CT (CE)	80 [69 to 89] 53/66	Not assessed	94 [79 to 99] 29/31	59 [42 to 74] 24/41	Not assessed	95 [84 to 99] 40/42	Not assessed	100 [63 to 100] 8/8	87 [73 to 96] 34/39	Not assessed
Hausmann 2011 Unclear Per lesion data 33 [824 /455]	CT (CE)	Not assessed	78 [74 to 82] 356/455	86 [81 to 91] 166 / 192	Not assessed	71 [65 to 76] 186/263	Not assessed	50 [44 to 55] 183/369	29 [22 to 36] 54/187	Not assessed	71 [64 to 77] 129/182
Jouvet 2014 Unclear Per lesion data 37 [218 / 125]	CT (CE)	90 [82 to 94] 103/115	88 [80 to 94] 84/95	96 [78 to 100] 22/23	88 [80 to 94] 81/92	86 [76 to 93] 62/72	70 [60 to 79] 66/94	69 [59 to 78] 63/91	63 [44 to 80] 19/30	73 [61 to 84] 47/63	72 [59 to 83] 44/61
Pfannenberg 2007 Mixed Per lesion data 64 [420/ 297]	CT (CE)	Not assessed	77 [72 to 82] 229/297	76 [67 to 84] 78/102	Not assessed	77 [71 to 83] 151/195	Not assessed	70 [61 to 78] 86/123	77 [64 to 87] 43/56	Not assessed	64 [52 to 76] 43/67
MRI											
Dellestabl 2011 Mixed Per lesion data 40 [118 / 72]	MRI (DW)	83 [72 to 91] 58/70	Not assessed	90 [74 to 98] 28/31	77 [61 to 89] 30/39	Not assessed	96 [85 to 99] 45/47	Not assessed	89 [52 to 100] 8/9	97 [86 to 100] 37/38	Not assessed

(*Continued*)

Hausmann 2011 Unclear Per lesion data 33 [824 / 455]	MRI (NR)	Not assessed	73 [69 to 77] 334/455	82 [76 to 87] 157/192	Not assessed	67 [61 to 73] 177/263	Not assessed	84 [80 to 87] 309/369	77 [70 to 83] 144/187	Not assessed	91 [85 to 94] 165/182
Jouvet 2014 Unclear Per lesion data 37 [218 / 125]	MRI (DW)	68 [59 to 76] 85/125	69 [59 to 77] 72/105	96 [78 to 100] 22/23	62 [52 to 71] 63/102	61 [50 to 72] 50/82	73 [63 to 82] 68/93	72 [62 to 81] 65/90	80 [61 to 92] 24/30	70 [57 to 81] 44/63	68 [55 to 80] 41/60
	MRI (DW+ VIBE)	84 [76 to 90] 105/125	81 [72 to 88] 85/105	87 [66 to 97] 20/23	83 [75 to 90] 85/102	79 [69 to 87] 65/82	87 [79 to 93] 81/93	87 [78 to 93] 78/90	100 [88 to 100] 30/30	81 [69 to 90] 51/63	80 [68 to 89] 48/60
Pfannenberg 2007 Mixed Per lesion data 64 [420/ 297]	MRI (DW+ VIBE)	Not assessed	80 [75 to 84] 237/297	66 [56 to 75] 67/102	Not assessed	87 [82 to 92] 170/195	Not assessed	76 [68 to 84] 94/123	77 [64 to 87] 43/56	Not assessed	76 [64 to 86] 51/67
PET-CT											
Arrangoiz 2012 **Primary 56/32**	**CT (NR)**	**47 [29 to 65] 15/32**	**Not assessed**	**Not assessed**	**100 [48 to 100] 5/0**	**Not assessed**	**88 [68 to 97] 21/24**	**Not assessed**	**Not assessed**	**94 [84 to 99] 48/51**	**Not assessed**
Reinhardt 2006 **Mixed Per patient data 250/ 116**	**CT (CE)**	**97 [91 to 99] 112/ 116**	**Not assessed**	**95 [87 to 99] 74/78**	**99 [94 to 100] 83/84**	**Not assessed**	**98 [94 to 100] 131/ 134**	**Not assessed**	**100 [98 to 100] 172/ 172**	**98 [94 to 99] 162/ 166**	**Not assessed**
Veit-Haibach 2009	CT (CE)			**38 [14 to 68]**		**Brain NR 42**			**100 [92 to 100]**		**Brain NR 93**

(*Continued*)

Primary Per patient data 56/13 Nodal; 12 Distant				**5/13**		**[15 to 72] 5/12**			**43/43**		**[81 to 99] 41/44**
Cachin 2014 Mixed Per lesion data 87 [176 / 85]	CT (NR)	80 [70 to 88] 68/85	Not assessed	85 [62 to 97] 17/20	78 [67 to 88] 51/65	Not assessed	54 [43 to 64] 49/91	Not assessed	37 [16 to 62] 7/19	58 [46 to 70] 42/72	Not assessed
Dellestabl 2011 Mixed Per lesion data 40 [118 / 72]	CT (CE)	74 [62 to 83] 53/72	Not assessed	84 [66 to 95] 26/31	66 [49 to 80] 27/45	Not assessed	89 [77 to 96] 42/47	Not assessed	100 [59 to 100] 7/7	88 [73 to 96] 35/40	Not assessed
Jouvet 2014 Unclear Per lesion data 37 [218 / 125]	CT (CE)	Not assessed	80 [71 to 87] 83/104	96 [78 to 100] 22/23	PET-CT did not cover skull	75 [64 to 84] 61/81	Not assessed	93 [86 to 97] 81/87	97 [83 to 100] 29/30	PET-CT did not cover skull	91 [81 to 97] 52/57
Pfannenberg 2007 Mixed Per lesion data 64 [420/ 297]	CT (CE)	Not assessed	91 [87 to 94] 269/297	85 [77 to 92] 87/102	PET-CT did not cover skull	93 [89 to 96] 182/195	Not assessed	77 [69 to 84] 95/123	89 [78 to 96] 50/56	PET-CT did not cover skull	67 [55 to 78] 45/67

a studies with per patient data denoted in bold type
CE: contrast enhanced; CT: computed tomography; DW: diffusion weighted; GE: gradient echo; MRI: magnetic resonance imaging; NR: not reported; PET: positron emission tomography; SLNB: sentinel lymph node biopsy; TN: true negative; TP: true positive; U: unenhanced; US: ultrasound; WB: whole body

Appendix 12. Findings from studies conducted in mixed or not clearly reported populations

Sensitivities and specificities from studies evaluating more than one target condition (any metastasis, nodal metastasis or distant metastasis) are tabulated in Appendix 11. Summary estimates of sensitivities and specificities are presented in Appendix 13.

Results: detection of any metastases

Eleven studies reported accuracy data for the detection of any metastasis in mixed study populations (Abbott 2011; Aukema 2010a; Aukema 2010b; Cachin 2014; Dellestable 2011; Hausmann 2011; Jouvet 2014; Pfannenberg 2007; Pfluger 2011; Reinhardt 2006; Strobel 2007b) (Table 1).

Forest plots of study data are provided in Figure 10 (per patient) and Figure 11 (per lesion). Summary estimates for indirect and direct comparisons of tests are presented in Appendix 13 and ROC plots of direct comparisons between tests in Figure 12, Figure 13, and Figure 14 (per lesion data only).

Figure 10. Forest plot of tests for the detection of any metastases (mixed populations - per patient data).

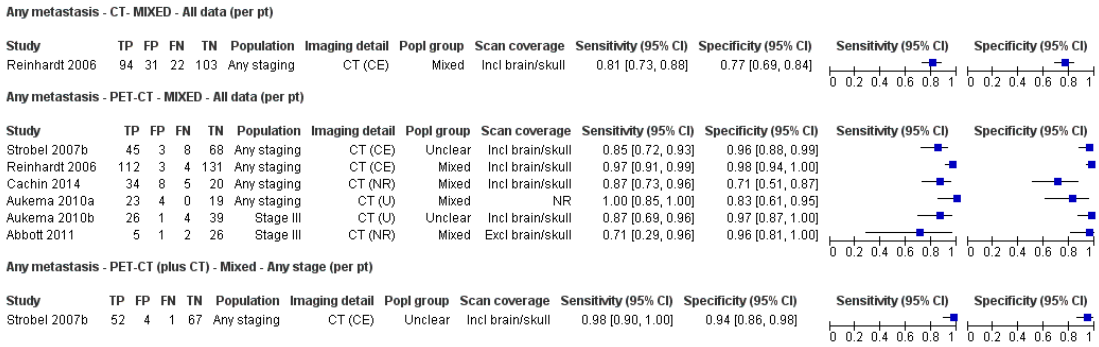


Figure 11. Forest plot of tests for the detection of any metastases (mixed populations - per lesion data).

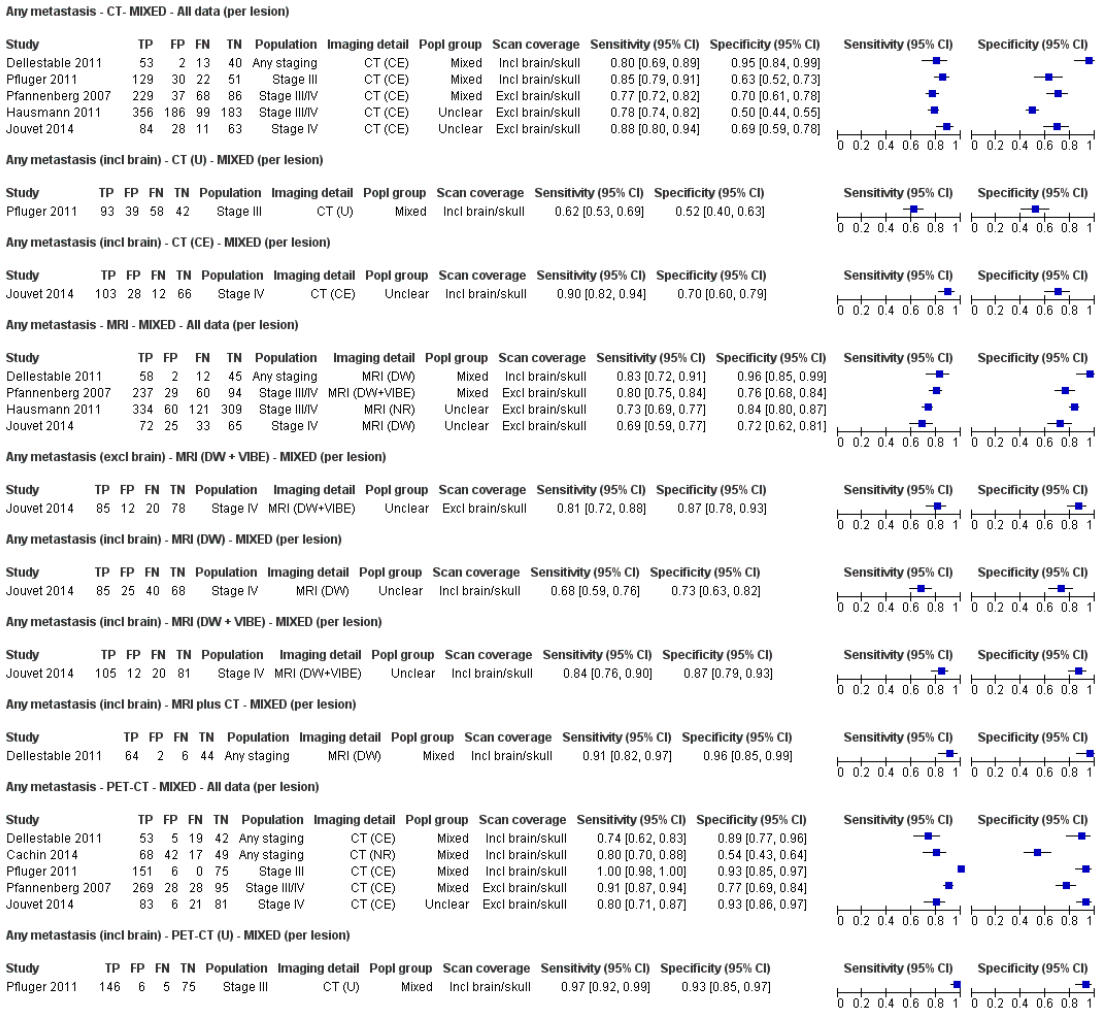


Figure 12. ROC plot of direct comparisons between CT and MRI for the detection of any metastases in mixed population group studies (per lesion data).

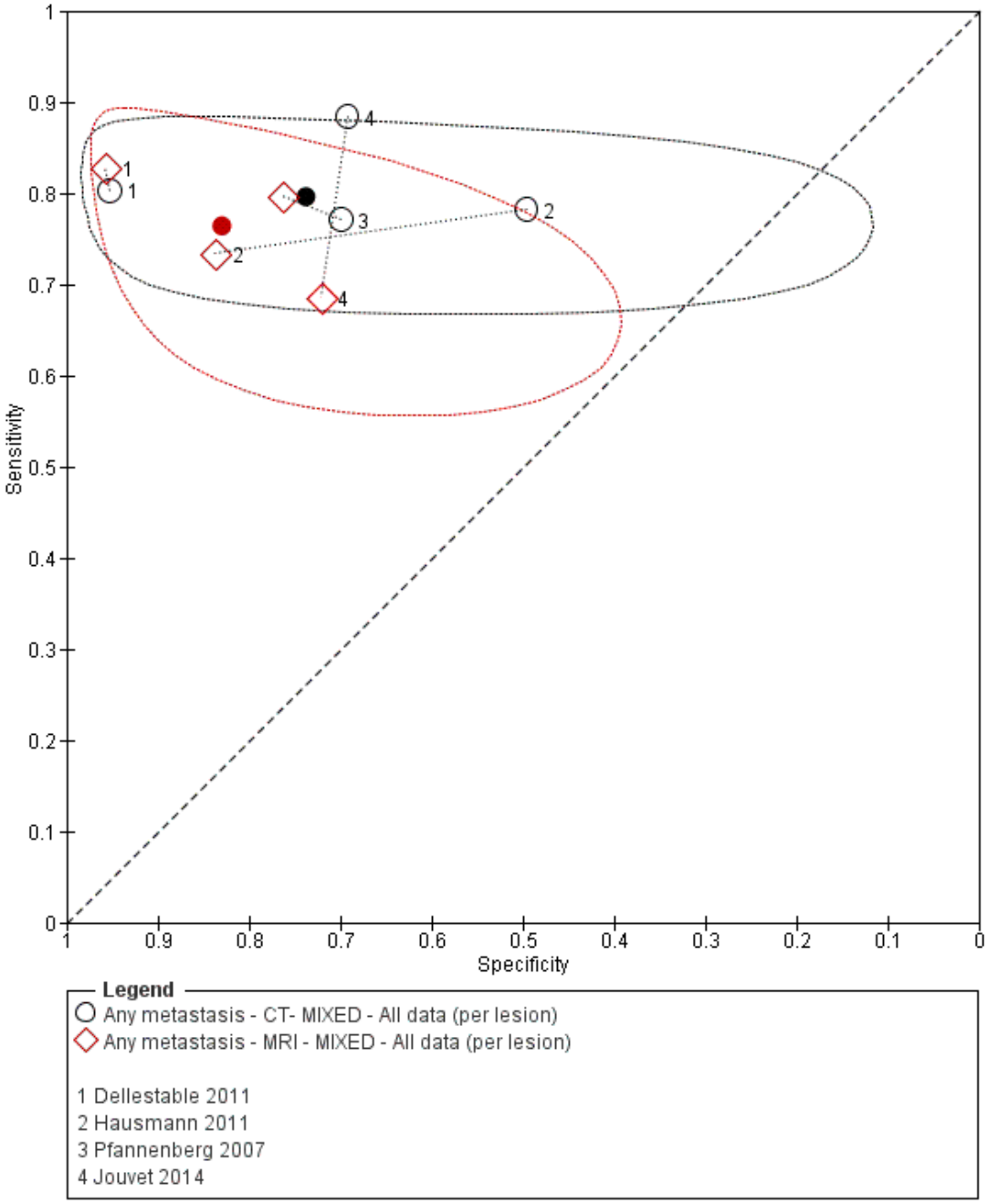


Figure 13. ROC plot of direct comparisons between CT and PET-CT for the detection of any metastases in mixed population group studies (per lesion data).

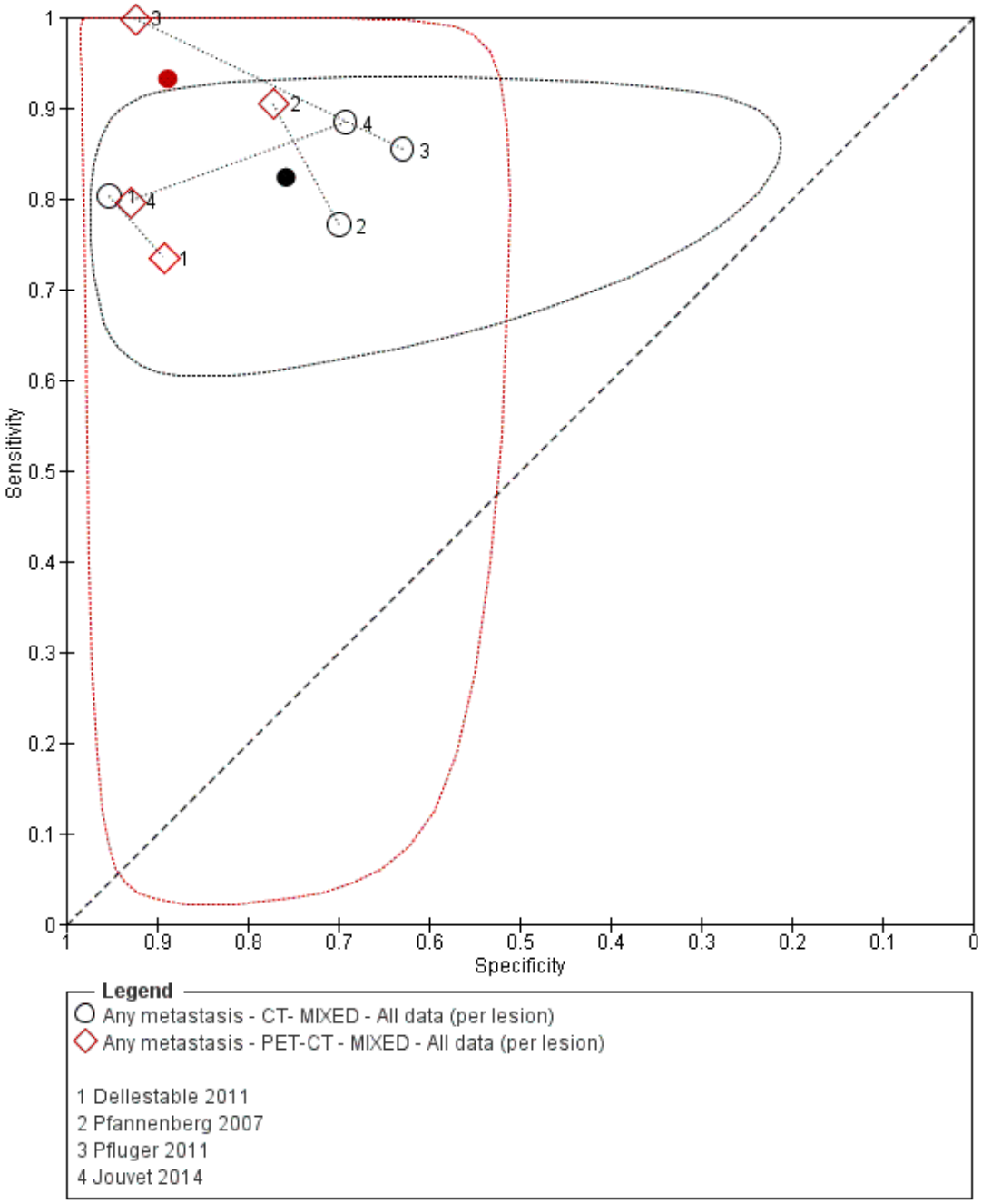
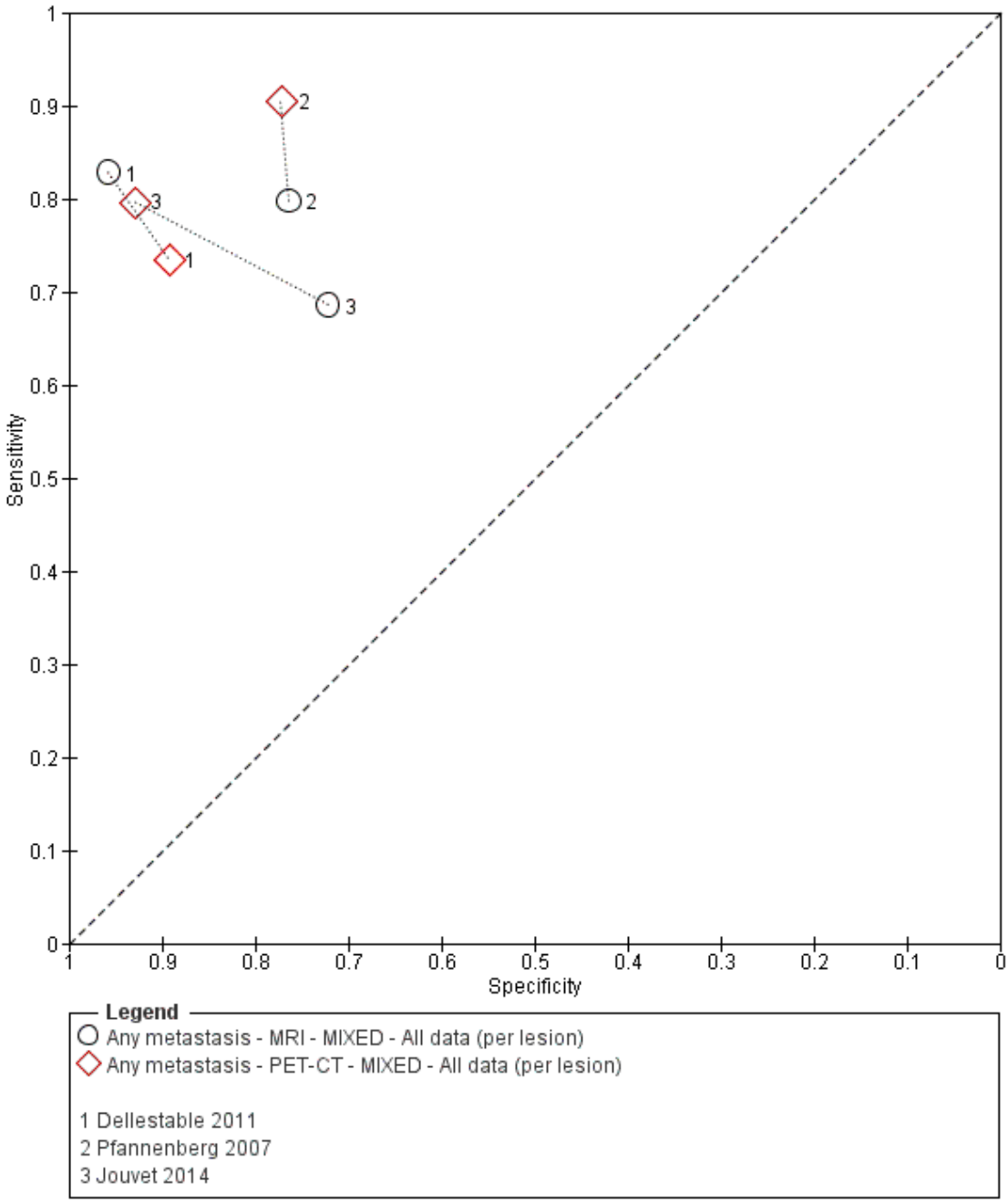


Figure 14. ROC plot of direct comparisons between MRI and PET-CT for the detection of any metastases in mixed population group studies (per lesion data).



Per patient data

Six studies reported per patient data for a total of 553 study participants and 268 cases of metastases (Abbott 2011; Aukema 2010a; Aukema 2010b Cachin 2014; Reinhardt 2006; Strobel 2007b) (Figure 10); prevalence ranged from 21% in Abbott 2011) to 58% in Cachin 2014.

CT. CT was evaluated in one study of 250 participants with mixed indications for imaging, including over 40% with stage I or II disease on presentation (Reinhardt 2006); scan coverage did not include the skull in this study. Observed sensitivity was 81% (95% CI 73, 88%) and specificity 77% (95% CI 69, 84%) (250 participants; 166 cases).

MRI. No per patient data for MRI were identified.

PET-CT. Six studies provided per patient data for PET-CT for the detection of any metastasis (Abbott 2011; Aukema 2010a; Aukema 2010b Cachin 2014; Reinhardt 2006; Strobel 2007b). The sensitivity of PET-CT ranged from 71% (95% CI 29% to 96%) in Abbott 2011 to 100% (95% CI 85% to 100%) in Aukema 2010a and specificity from 71% (95% CI 41% to 87%) in Cachin 2014 to 98% (95% CI 94% to 100%) in Reinhardt 2006.

Summary sensitivity from the six studies was 91.1% (95% CI 83.6% to 95.3%) and specificity 93.8% (95% CI 85.1% to 97.6%) (591 patients, 268 cases) (Appendix 13; Table A).

Observed sensitivity in Strobel 2007b increased from 85% (95% CI 72% to 93%) to 98% (95% CI 90% to 100%) (seven additional metastases detected) when PET-CT interpretation was combined with a separate dedicated CT interpretation, with one additional false positive result (specificities 96% and 94%, respectively).

Reinhardt 2006 provided a direct comparison of the accuracy of contrast enhanced CT with PET-CT, which found PET-CT to be significantly more sensitive (97%, 95% CI 91% to 99%) and specific (98%, 95% CI 94% to 100%) in comparison to CT alone (increases of 16% and 22%, respectively).

Per lesion data

Six studies reported per lesion data for a total of 311 study participants, 1989 lesions, and 1185 confirmed metastases (Cachin 2014; Dellestable 2011; Hausmann 2011; Jouvet 2014; Pfannenberg 2007; Pfluger 2011) (Figure 11). The prevalence of metastases on a lesion basis ranged from 48% in Cachin 2014 to 71% in Pfannenberg 2007. The average number of confirmed metastatic lesions per study participant ranged from 1 in Cachin 2014 to 14 in Hausmann 2011, with a median of 3.

CT. Five studies presented data for contrast enhanced CT for the detection of any metastases (Dellestable 2011; Hausmann 2011; Jouvet 2014; Pfannenberg 2007; Pfluger 2011). Sensitivity ranged from 77% (95% CI 72% to 82%) in Pfannenberg 2007 to 88% (95% CI 80% to 94%) in Jouvet 2014, and specificity from 50% (95% CI 44% to 55%) in Hausmann 2011 to 95% (95% CI 84% to 99%) in Dellestable 2011.

Summary sensitivity from the five studies was 81.3% (95% CI 76.8% to 85.1%) and specificity 71.2% (95% CI 53.9% to 83.9%) (1770 lesions, 1064 metastases) (Appendix 13; Table B).

A single study providing a direct comparison of the accuracy of contrast enhanced CT with unenhanced CT found contrast enhanced CT to be significantly more sensitive (85%, 95% CI 79% to 85%) compared to unenhanced CT (62%, 95% CI 53% to 69%), with a smaller decrease (11%) in specificity for unenhanced CT (52%, 95% CI 40% to 63%) (232 lesions, 151 confirmed metastases) (Figure 11) (Pfluger 2011).

MRI. Four studies presented data for MRI for the detection of any metastases (Dellestable 2011; Hausmann 2011; Jouvet 2014; Pfannenberg 2007). Sensitivity ranged from 69% (95% CI 59% to 77%) in Jouvet 2014 to 83% (95% CI 72% to 91%) in Dellestable 2011, and specificity from 72% (95% CI 62% to 81%) in Jouvet 2014 to 96% (95% CI 85% to 99%) in Dellestable 2011.

Summary sensitivity from the four studies was 76.4% (95% CI 70.6% to 81.4%) and specificity 83.0% (95% CI 71.9% to 90.3%) (1556 lesions, 927 metastases) (Appendix 13; Table B). Sensitivity and specificity in Jouvet 2014 were both increased (by 13% and 15%, respectively) with the addition of ultrafast gradient echo (VIBE) sequences to the MRI protocol.

PET-CT. Five studies evaluated PET-CT for the detection of any metastasis (Cachin 2014; Dellestable 2011; Jouvet 2014; Pfluger 2011; Pfannenberg 2007). Sensitivity ranged from 74% (95% CI 62% to 83%) in Dellestable 2011 to 100% (95% CI 98% to 100%) in Pfluger 2011, and specificity from 54% (95% CI 43% to 64%) in Cachin 2014 to 93% (95% CI 86% to 97%) in Jouvet 2014.

Summary sensitivity from the five studies was 90.7% (95% CI 69.0% to 97.7%) and specificity 84.5% (95% CI 69.7% to 92.9%) (1138 lesions, 709 metastases) (Appendix 13; Table B).

Pfluger 2011 showed only marginal differences in accuracy between PET-CT using contrast enhanced CT versus unenhanced CT; sensitivity for unenhanced PET-CT (97%, 95% CI 92% to 99%) compared to enhanced PET-CT (100%, 95% CI 98% to 100%) (232 lesions; 151 confirmed metastases).

Comparisons between tests. The statistical model comparing the three sets of pooled estimates showed no statistically significant differences in sensitivity (P = 0.17) or specificity (P = 0.29) between tests (Appendix 13; Table B).

Three of the studies provided a direct comparison of CT, MRI, and PET-CT (Dellestable 2011; Jouvet 2014; Pfannenberg 2007), Hausmann 2011 compared CT and MRI, and Pfluger 2011 compared CT and PET-CT. The direct comparisons between tests in these studies are plotted ROC space in Figure 12, Figure 13, and Figure 14. None of the differences in sensitivity and specificity between tests reached statistical significance (Appendix 13; Table C).

Results: detection of nodal metastases

Ten studies reported accuracy data for the detection of nodal metastases (Cachin 2014; Dellestable 2011; Hausmann 2011; Jouvet 2014; Klebl 2003; Pfannenberg 2007; Reinhardt 2006; Rubaltelli 2011; van den Brekel 1998; van Wissen 2016).
Forest plots of study data are provided in Figure 15 (per patient) and Figure 16 (per lesion).

Figure 15. Forest plot of tests for the detection of nodal metastases (mixed populations - per patient data).

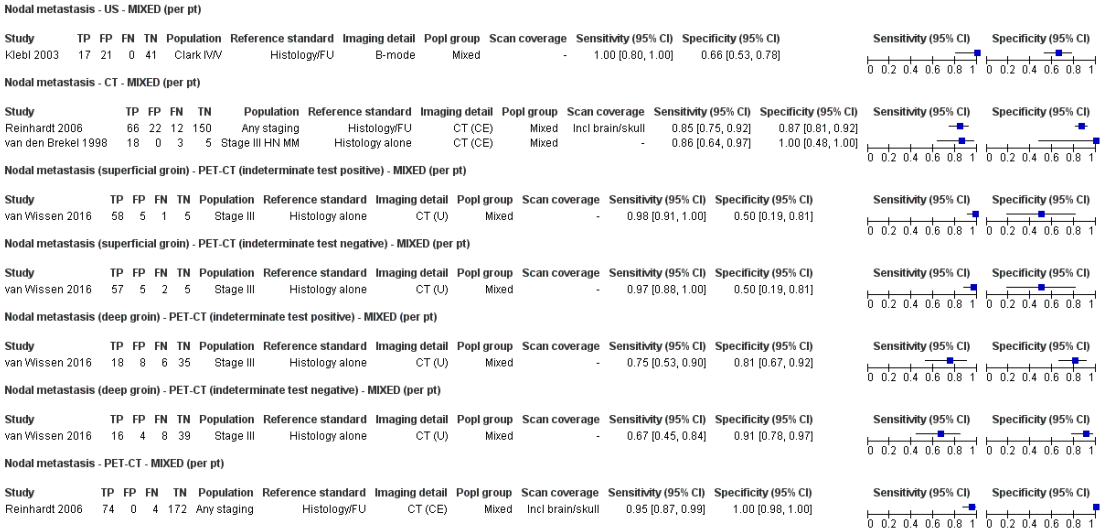
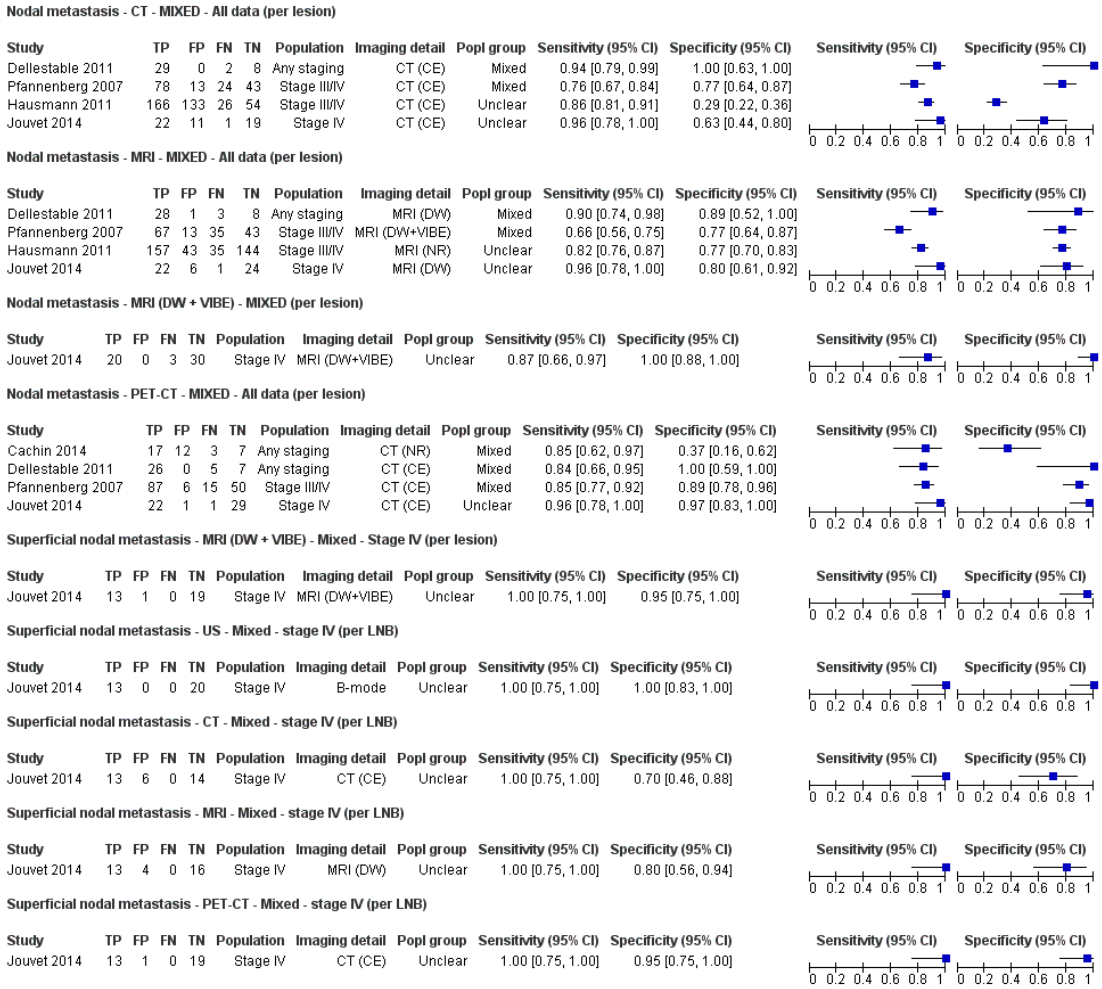


Figure 16. Forest plot of tests for the detection of nodal metastases (mixed populations - per lesion data).



Per patient data

Four studies reported per patient data for a total of 355 study participants and 175 cases of nodal metastases (Klebl 2003; Reinhardt 2006; Van den Brekel 1998; van Wissen 2016) (Figure 15); the prevalence of nodal metastases ranged from 22% in Klebl 2003 to 86% in van Wissen 2016.

Ultrasound. One study evaluated ultrasound for nodal metastases in participants with Clark level IV or V melanoma following primary treatment (n = 8) or during follow-up (n = 75) (Klebl 2003). All 17 participants with nodal metastases were identified on ultrasound (sensitivity 100%, 95% CI 80% to 100%) with 21 false positives (specificity 66%, 95% CI 53% to 78%); 11 of the 17 true positive results were also detected on palpation, with a total of 12 false positive results (Klebl 2003).

CT. CT was evaluated for the detection of nodal metastases in two studies. In Reinhardt 2006, 78 of the 166 participants with confirmed metastatic disease had nodal metastases (prevalence 78/250; 31%). Sensitivity was 85% (95% CI 75% to 92%) and specificity 87% (95% CI 81% to 92%). Similarly high sensitivity was reported in a high prevalence study of CT before therapeutic or elective dissection of the lymph nodes of the neck in participants with head and neck melanoma (86%, 95% CI 64% to 97%), with specificity of 100% (95% CI 48% to 100%) (26 participants; 21 cases of nodal metastases) (van den Brekel 1998).

MRI. No per patient data were identified for MRI in this patient group.

PET-CT. PET-CT was evaluated for the detection of nodal metastases in two studies. In a direct comparison with CT alone, PET-CT was more sensitive (95%, 95% CI 87% to 99%) than CT alone but with overlapping confidence intervals, and was significantly more specific (100%, 95% CI 98% to 100%) (250 participants; 78 cases of nodal metastases) (Reinhardt 2006).

van Wissen 2016 evaluated the use of PET-CT in 69 participants scheduled for combined superficial and deep groin dissection due to palpable groin metastases. Results showed that although PET-CT was highly sensitive for the detection of superficial groin metastases (98%, 95% CI 91% to 100%) (59 cases), six participants with deep groin metastases were missed by PET-CT even when indeterminate PET-CT results were considered test positive (sensitivity 75%, 95% CI 53% to 90%) (24 cases). Specificity was 81% (95% CI 76% to 92%), with eight false positive results.

Per lesion data

Per lesion data were reported in five studies for a total of 241 study participants, 669 lesions, and 338 confirmed metastases(Cachin 2014; Dellestable 2011; Hausmann 2011; Jouvet 2014; Pfannenberg 2007) (Figure 16). The prevalence of metastases on a lesion basis ranged from 43% in Hausmann 2011 to 78% in Dellestable 2011. Summary estimates for indirect and direct comparisons of tests are presented in Appendix 13, and ROC plots of direct comparisons between tests in Figure 17, Figure 18, and Figure 19 (per lesion data only).

Figure 17. ROC plot of direct comparisons between CT and MRI for the detection of nodal metastases in mixed population group studies (per lesion data).

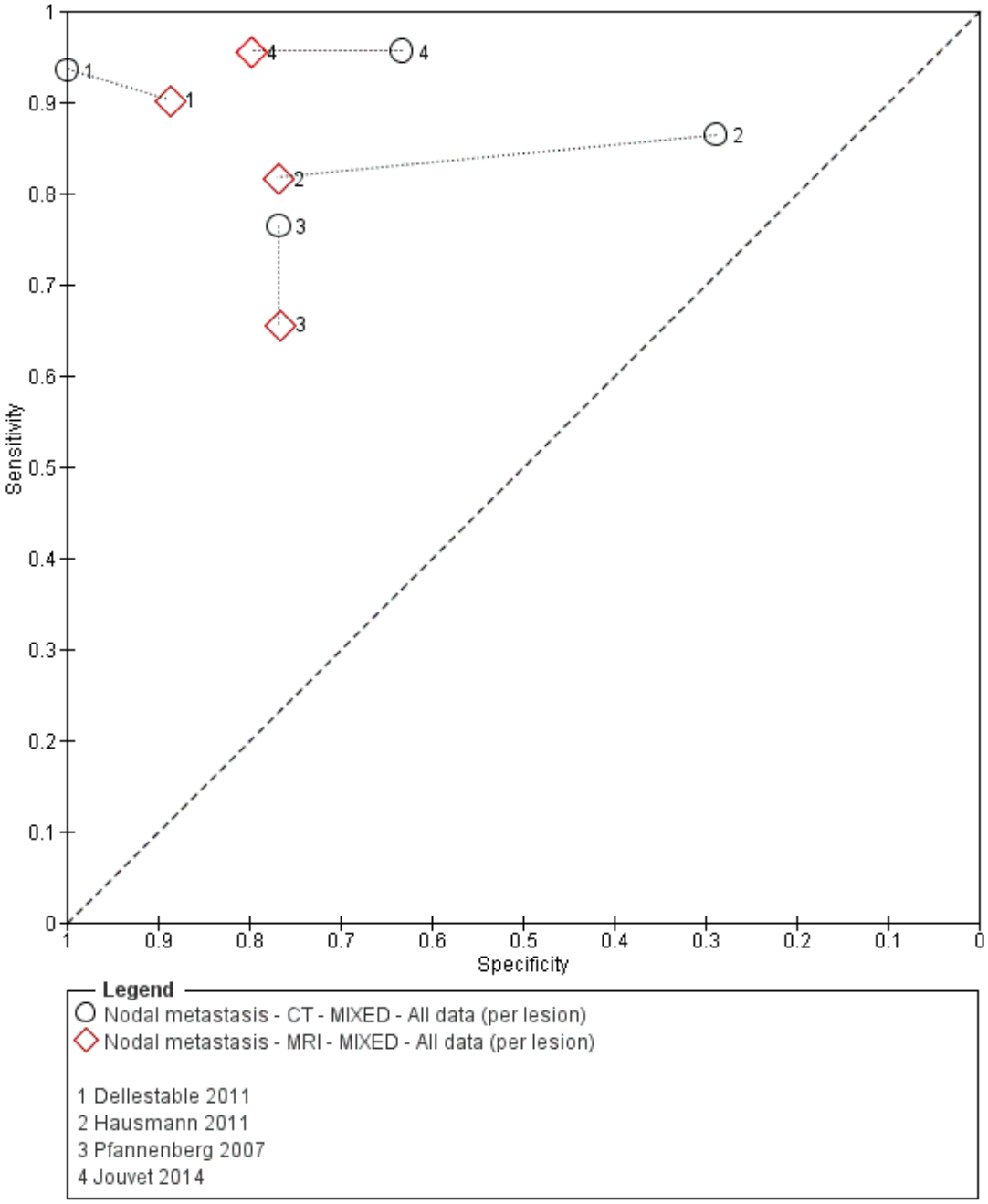


Figure 18. ROC plot of direct comparisons between CT and PET-CT for the detection of nodal metastases in mixed population group studies (per lesion data).

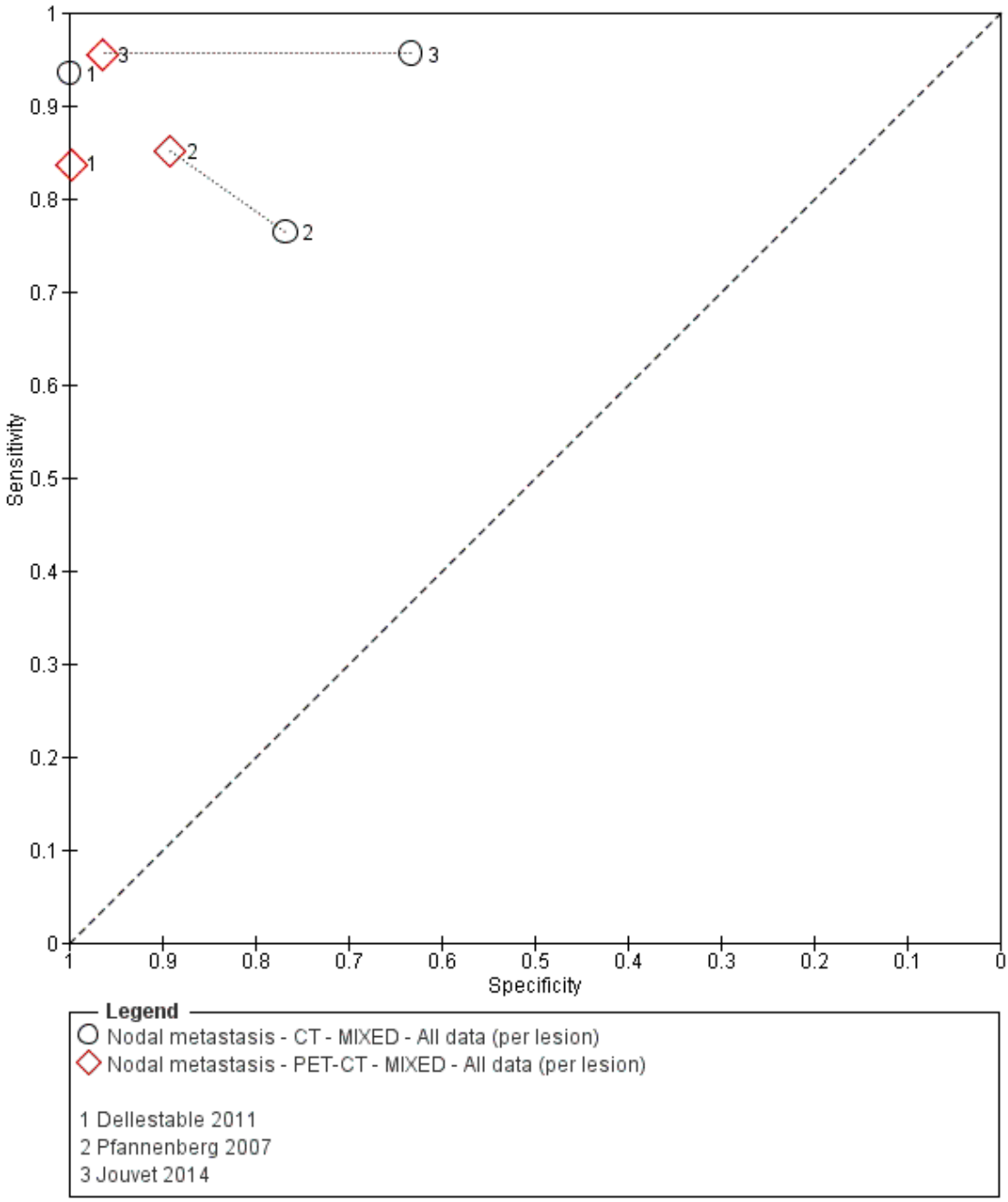
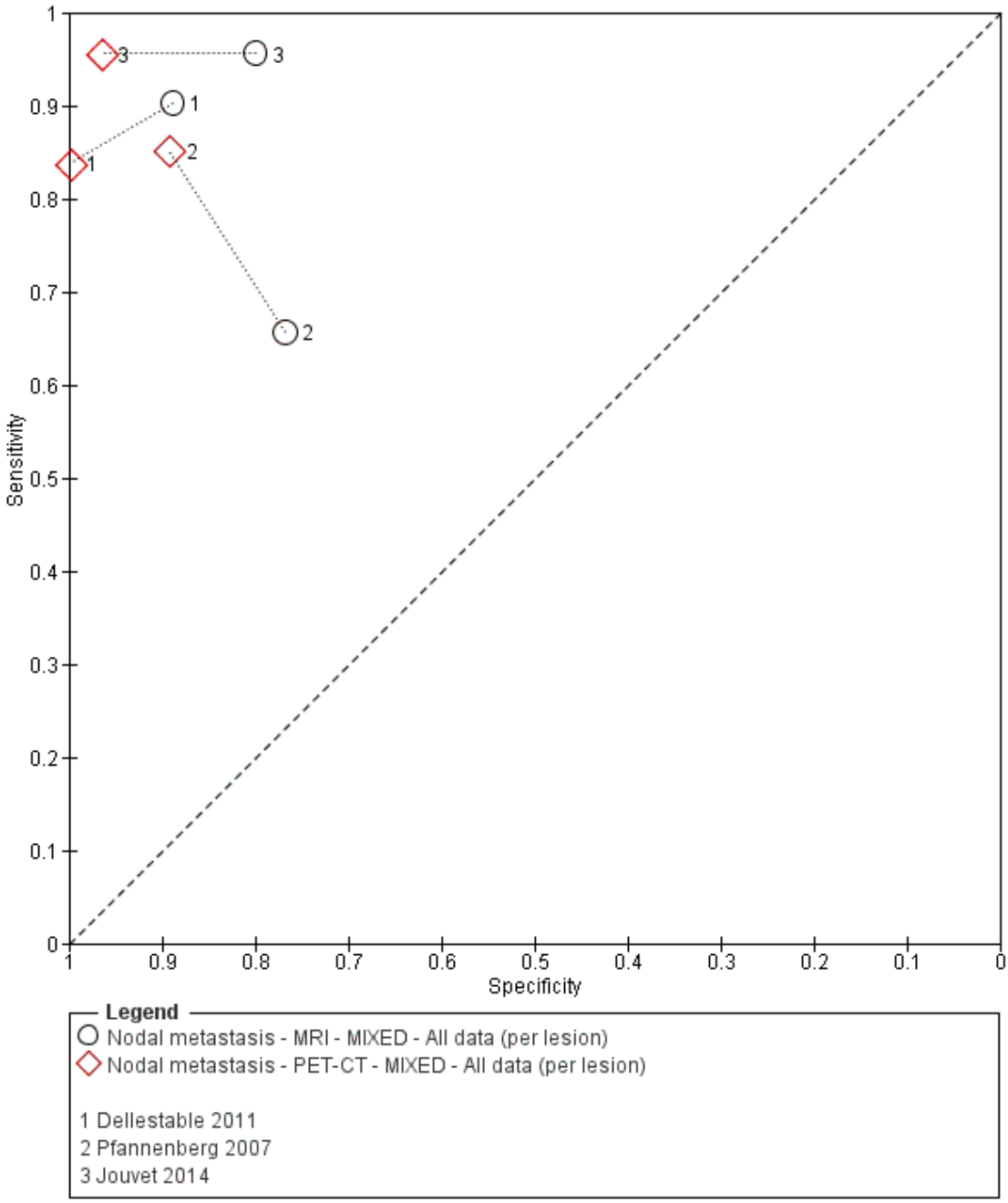


Figure 19. ROC plot of direct comparisons between MRI and PET-CT for the detection of nodal metastases in mixed population group studies (per lesion data).



CT. Four studies evaluated contrast enhanced CT for the detection of nodal metastasis (Dellestable 2011; Hausmann 2011; Jouvet 2014; Pfannenberg 2007). Sensitivity ranged from 76% (95% CI 67% to 84%) in Pfannenberg 2007 to 96% (95% CI 78% to 100%) in Jouvet 2014, and specificity from 29% (95% CI 22% to 36%) in Hausmann 2011 to 100% (95% CI 63% to 100%) in Dellestable 2011.

Summary sensitivity from the four studies was 87.2% (95% CI 76.5% to 93.4%) and specificity 69.2% (95% CI 34.6% to 90.5%) (629 lesions, 348 metastases) (Appendix 13; Table B).

MRI. The same four studies considered MRI for the detection of nodal metastasis using a number of different MRI protocols (Dellestable 2011; Hausmann 2011; Jouvet 2014; Pfannenberg 2007). Sensitivity ranged from 66% (95% CI 56% to 75%) in Pfannenberg 2007 to 96% (95% CI 78% to 100%) in Jouvet 2014, and specificity from 77% (95% CI 64% to 87%) in Pfannenberg 2007 to 77% (95% CI 70% to 83%) in Hausmann 2011 to 89% (95% CI 52% to 100%) in Dellestable 2011. Summary sensitivity from the four studies was 83.9% (95% CI 68.9% to 92.5%) and specificity 78.1% (95% CI 72.1% to 83.1%) (630 lesions, 348 metastases) (Appendix 13; Table B).

The direct comparison of diffusion weighted MRI compared with diffusion weighted plus VIBE sequences in Jouvet 2014 found the addition of VIBE to be less sensitive but more specific, but with small lesion numbers (53 nodal lesions and 23 malignancies), the differences were not statistically significant.

PET-CT. Four studies evaluated PET-CT for the detection of nodal metastasis (Cachin 2014; Dellestable 2011; Jouvet 2014; Pfannenberg 2007). Sensitivities ranged from 84% (95% CI 66% to 95%) in Dellestable 2011 to 96% (95% CI 83% to 100%) in Jouvet 2014, and specificities from 37% (95% CI 16% to 62%) in Cachin 2014 to 100% (95% CI 59% to 100%) in Dellestable 2011.

Summary sensitivity from the four studies was 86.4% (95% CI 80.5% to 90.7%) and specificity 89.1% (95% CI 53.1% to 98.3%) (288 lesions, 176 metastases) (Appendix 13; Table B).

Comparison between tests. The statistical model comparing the three sets of pooled estimates showed no statistically significant differences in sensitivity (P = 0.22) or specificity (P = 0.89) between tests (Appendix 13; Table B).

Three studies in mixed population groups provided a direct comparison of CT, MRI, and PET-CT (Dellestable 2011; Jouvet 2014; Pfannenberg 2007); Hausmann 2011 also compared CT and MRI. Three studies included the same total numbers of nodal lesions and metastases per test, while the number detected per test varied for Dellestable 2011. ROC plots show direct comparisons between tests in Figure 17, Figure 18, and Figure 19 (per lesion data only). No statistically significant differences in sensitivity were observed in any of the direct comparisons, but the specificity of PET-CT (92.5%, 95% CI 85.0% to 96.4%) was significantly higher than both MRI (by 13.5%, 95% CI 3.73% to 23.3%; P = 0.007) and CT alone (by 18.0%, 95% CI 7.69% to 28.3%; P = 0.001) (Appendix 13; Table C).

Results: detection of distant metastases

Nine studies considered the detection of distant metastases (Arrangoiz 2012; Bastiaannet 2009; Cachin 2014; Dellestable 2011; Hausmann 2011; Jouvet 2014; Pfannenberg 2007; Reinhardt 2006; Veit-Haibach 2009).

Forest plots of study data are provided in Figure 20 (per patient) and Figure 21 (per lesion).

Figure 20. Forest plot of tests for the detection of distant metastases (mixed populations - per patient data only).

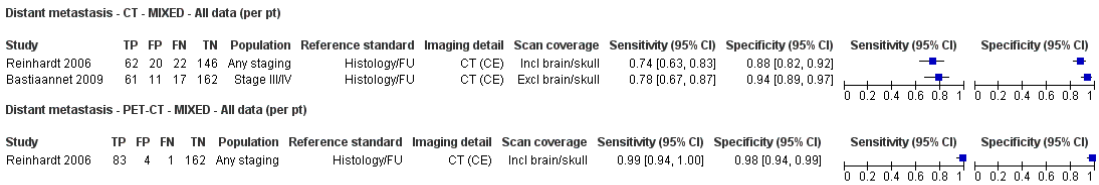
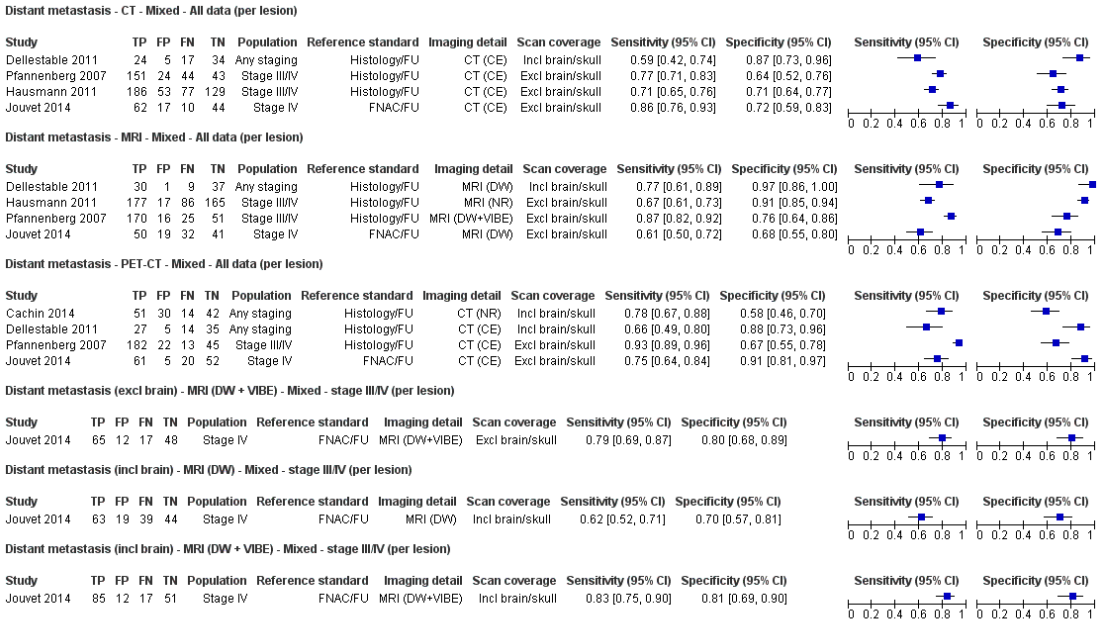


Figure 21. Forest plot of tests for the detection of distant metastases (per lesion data).



Per patient data

Two studies reported per patient data for a total of 501 study participants and 162 cases of distant metastases (Bastiaannet 2009; Reinhardt 2006) (Figure 20); the prevalence of nodal metastases was 31% (Bastiaannet 2009) and 34% (Reinhardt 2006).

CT. Reinhardt 2006 reported sensitivity of 74% (95% CI 63% to 83%) and specificity of 88% (95% CI 84% to 99%) in participants at any stage of disease and with mixed indications for imaging (250 participants; 84 cases of distant metastases). Bastiaannet 2009 included participants with palpable, confirmed lymph node metastases who were considered candidates for regional lymph node dissection. Sensitivity was 78% (95% CI 67% to 87%) and specificity 94% (95% CI 89% to 97%) (251 participants; 78 cases of distant metastases).

MRI. No per patient data were identified for MRI in this patient group.

PET-CT. Reinhardt 2006 reported a direct comparison of CT with PET-CT (Figure 20). Both sensitivity and specificity increased significantly with PET-CT (sensitivity 99%, 95% CI 94% to 100% and specificity 98%, 95% CI 94% to 99%).

Per lesion data

Per lesion data were reported in five studies for a total of 501 study participants, 1090 lesions, and 666 confirmed metastases (Cachin 2014; Dellestable 2011; Hausmann 2011; Jouvet 2014; Pfannenberg 2007) (Figure 21). The prevalence of distant metastases on a lesion basis ranged from 47% in Cachin 2014 to 74% in Pfannenberg 2007.

CT. Four studies evaluated contrast enhanced CT for the detection of distant metastasis (Dellestable 2011; Hausmann 2011; Jouvet 2014; Pfannenberg 2007). Sensitivity ranged from 59% (95% CI 42% to 74%) in Dellestable 2011 to 86% (95% CI 76% to 93%) in Jouvet 2014, and specificity from 64% (95% CI 52% to 76%) in Pfannenberg 2007 to 87% (95% CI 73% to 96%) in Dellestable 2011 (Figure 21).

Summary sensitivity from the four studies was 73.4% (95% CI 63.6% to 81.3%) and specificity 71.9% (95% CI 64.3% to 78.5%) (920 lesions, 571 metastases) (Appendix 13; Table B).

MRI. The same four studies considered MRI for the detection of distant metastasis (Dellestable 2011; Hausmann 2011; Jouvet 2014; Pfannenberg 2007). Sensitivity ranged from 61% (95% CI 50% to 72%) in Jouvet 2014, to 87% (95% CI 82% to 92%) in Pfannenberg 2007, and specificity from 68% (95% CI 64% to 87%) in Jouvet 2014 to 97% (95% CI 70% to 83%) in Dellestable 2011 (Figure 21).

Summary sensitivity from the four studies was 74.5% (95% CI 62.1% to 83.9%) and specificity 85.8% (95% CI 70.4% to 93.9%) (926 lesions, 579 metastases) (Appendix 13; Table B).

The low sensitivity and specificity observed in Jouvet 2014 were improved to 79% (95% CI 69% to 87%) and 80% (95% CI 68% to 89%) with the addition of VIBE sequences but with overlapping confidence intervals.

PET-CT. Four studies evaluated PET-CT for the detection of nodal metastasis (Cachin 2014; Dellestable 2011; Jouvet 2014; Pfannenberg 2007). Sensitivities ranged from 66% (95% CI 49% to 80%) in Dellestable 2011 to 93% (95% CI 89% to 96%) in Pfannenberg 2007, and specificities from 58% (95% CI 46% to 70%) in Cachin 2014 to 91% (95% CI 81% to 97%) in Jouvet 2014 (Figure 21).

Summary sensitivity from the four studies was 81.0% (95% CI 67.5% to 90.0%) and specificity 78.5% (95% CI 61.0% to 89.5%) (618 lesions, 382 metastases) (Appendix 13; Table B).

Comparison between tests. The statistical model comparing the three sets of pooled estimates showed no statistically significant differences in sensitivity (P = 0.22) or specificity (P = 0.89) between tests (Appendix 13; Table B).

Three studies in mixed population groups provided a direct comparison of CT, MRI, and PET-CT (Dellestable 2011; Jouvet 2014; Pfannenberg 2007); Hausmann 2011 also compared CT and MRI. Two studies included the same total numbers of lesions and metastases per test (Hausmann 2011; Pfannenberg 2007), and two included only those lesions detected by each test so that the number of lesions varied per test (Dellestable 2011; Jouvet 2014). The direct comparisons between tests in these studies are plotted as ROC space in Figure 22, Figure 23, and Figure 24. No statistically significant differences in sensitivity were observed in any of the direct comparisons, but the specificity of MRI (85.8%, 95% CI 70.4% to 93.9%) was significantly higher than CT (by 13.9%, 95% CI 0.43% to 27.3%; P = 0.043) (Appendix 13; Table C).

Figure 22. ROC plot of direct comparisons between CT and MRI for the detection of distant metastases in mixed population group studies (per lesion data).

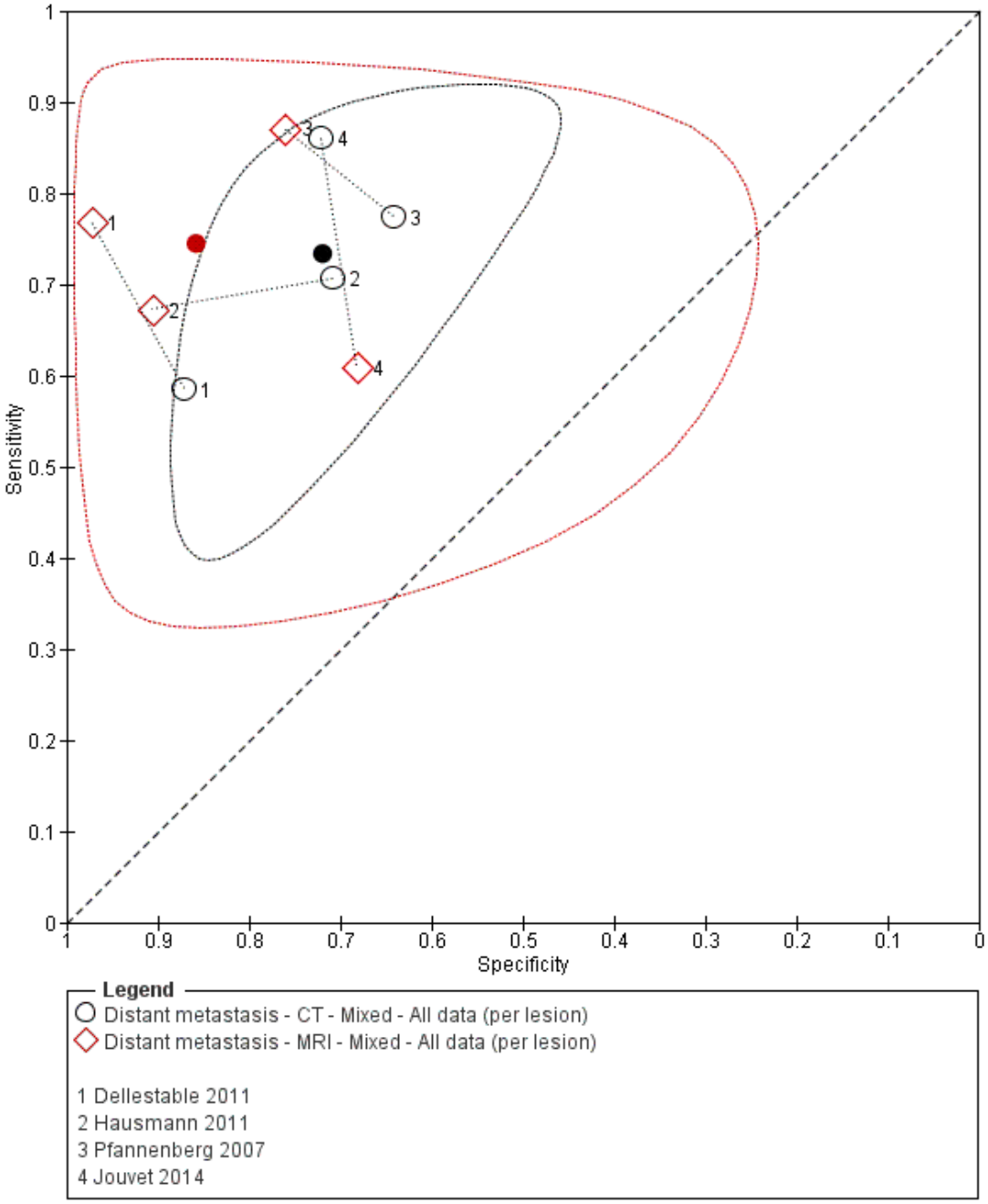


Figure 23. ROC plot of direct comparisons between CT and PET-CT for the detection of distant metastases in mixed population group studies (per lesion data).

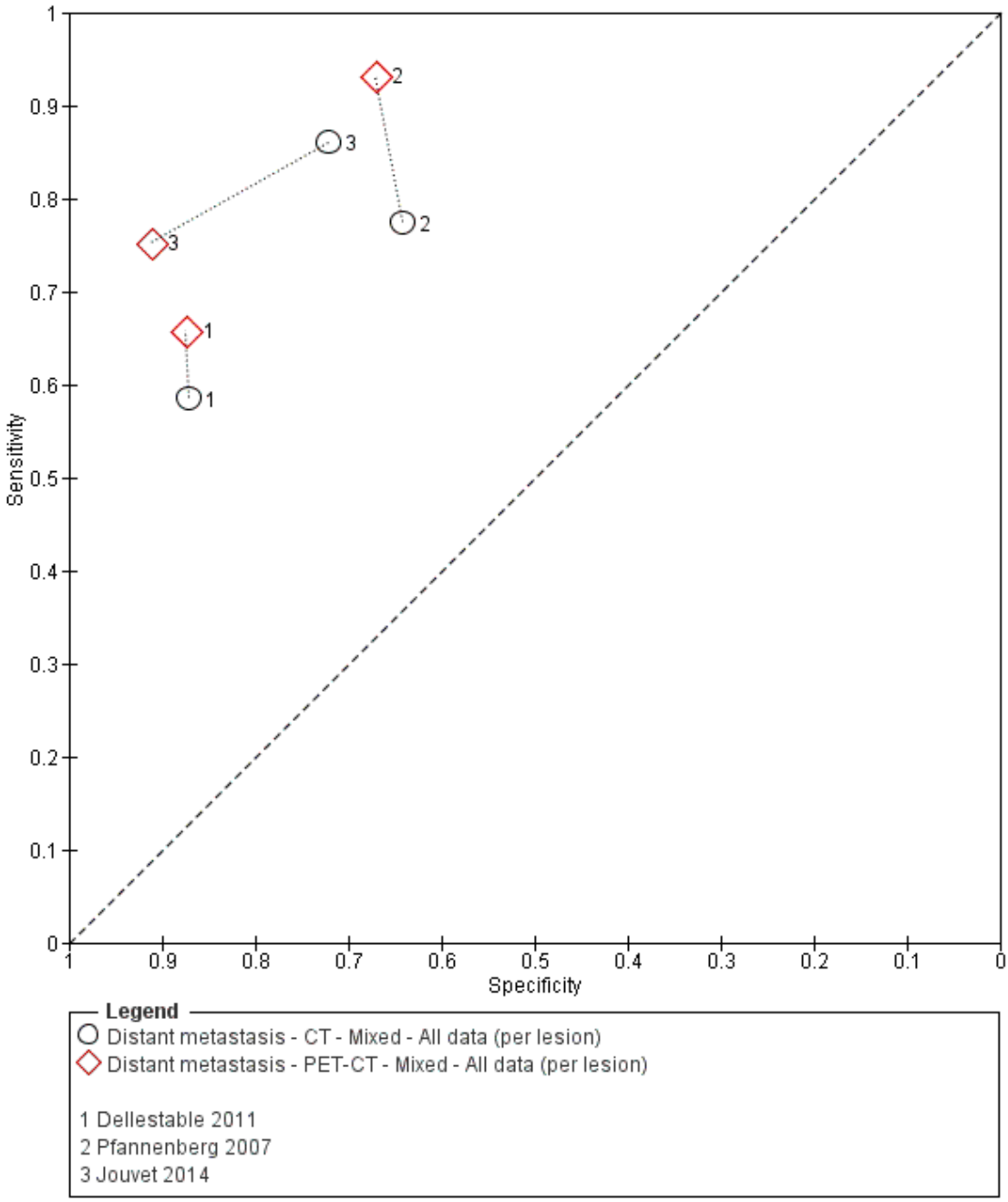
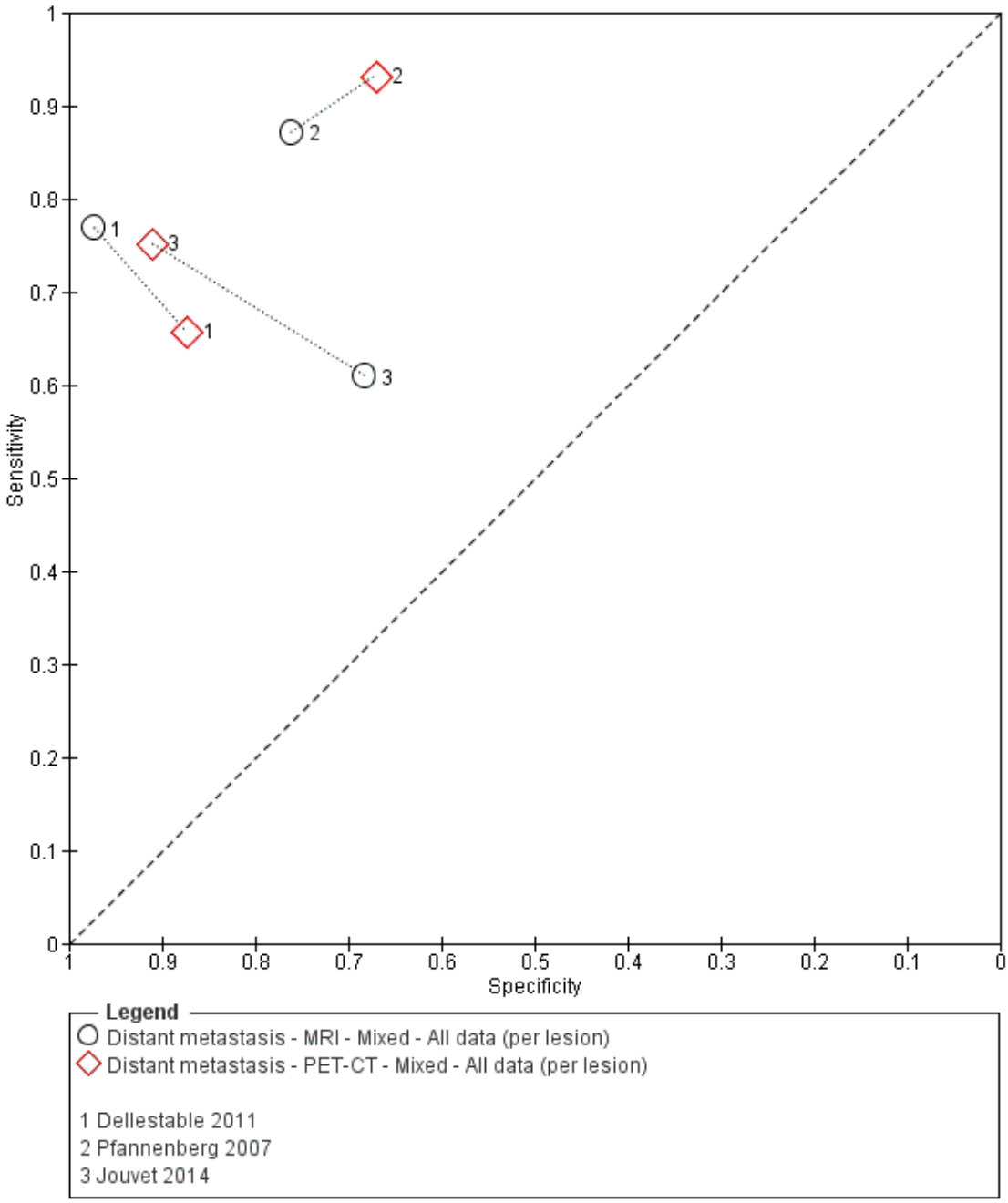


Figure 24. ROC plot of direct comparisons between MRI and PET-CT for the detection of distant metastases in mixed population group studies (per lesion data).



Results: detection of distant metastases by metastatic site

Four studies conducted in mixed or not clearly described population groups reported per lesion data according to metastatic site (Cachin 2014; Dellestable 2011; Jouvet 2014; Pfannenberg 2007). Appendix 14 presents sensitivities and specificities for all metastatic sites according to test for ease of comparison of accuracy across different sites. Sensitivity and specificity were not estimated for sites with fewer than five malignant or benign lesions. Forest plots of study data for each test by metastatic site are presented in Figure 25, Figure 26, Figure 27, and Figure 28. Summary estimates for indirect and direct comparisons of tests are presented in Appendix 13.

Figure 25. Forest plot of tests for the detection of bone metastasis in mixed population groups (per lesion data).

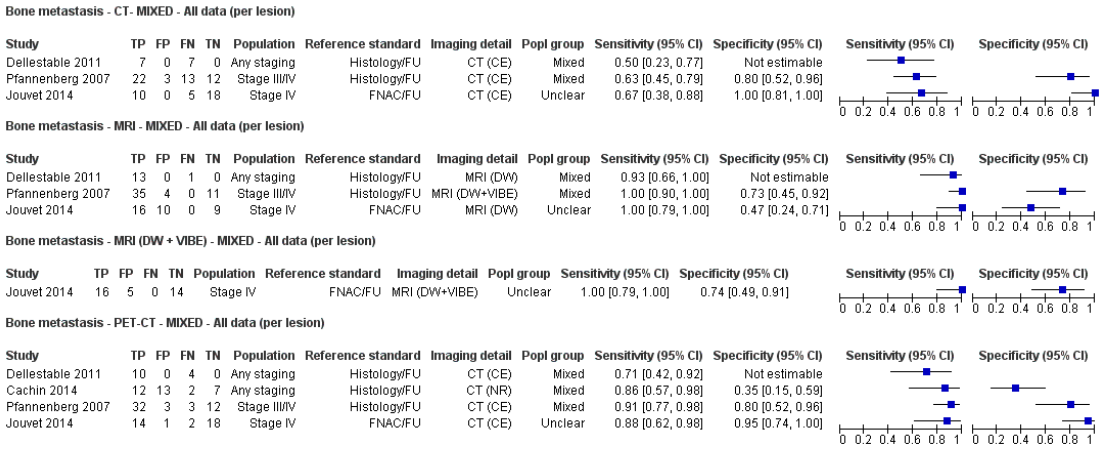


Figure 26. Forest plot of tests for the detection of lung metastasis in mixed population groups (per lesion data).

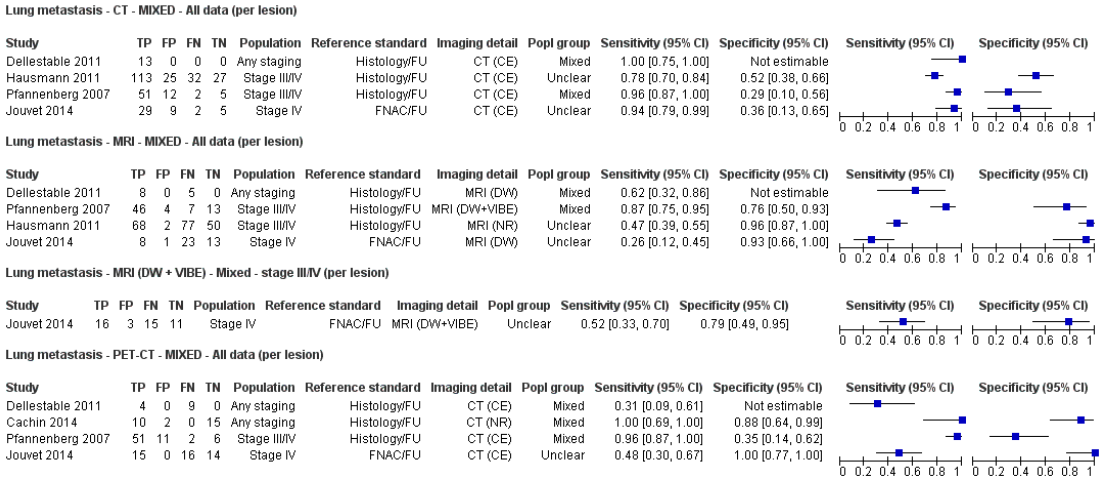


Figure 27. Forest plot of tests for the detection of liver metastasis in mixed population groups (per lesion data).

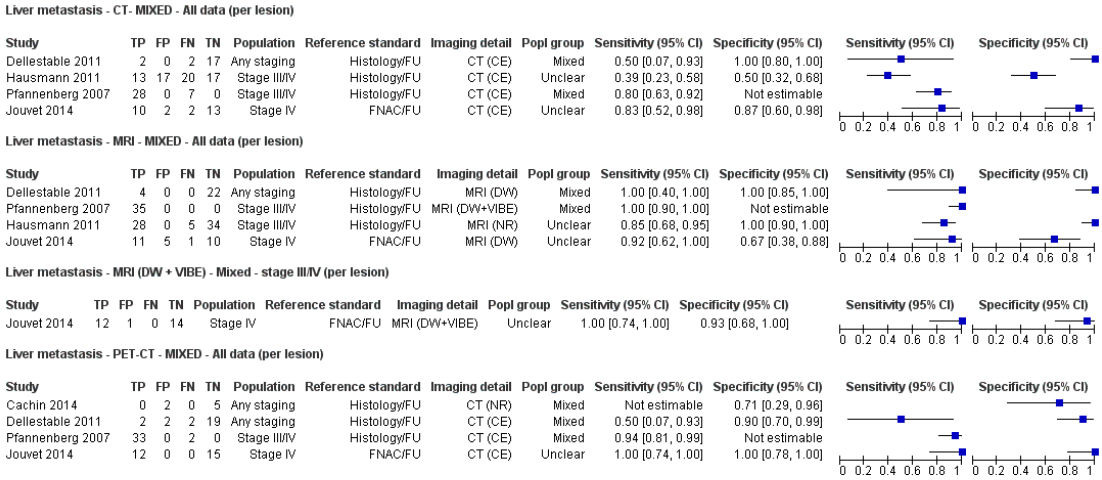
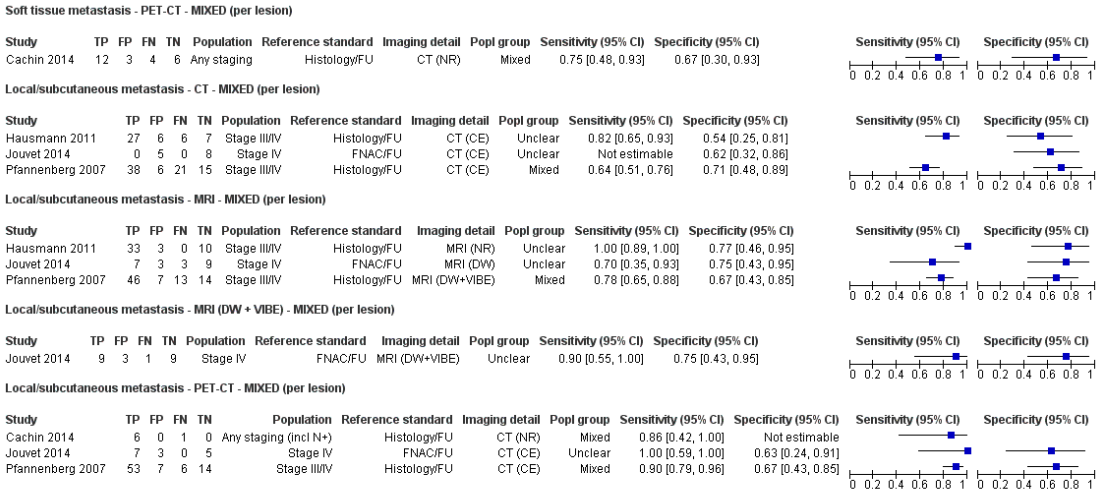


Figure 28. Forest plot of tests: 75 soft tissue metastasis - PET-CT - MIXED (per lesion), 76 local/subcutaneous metastasis - CT - MIXED (per lesion), 77 local/subcutaneous metastasis - MRI - MIXED (per lesion), 78 local/subcutaneous metastasis - MRI (DW + VIBE) - MIXED (per lesion), 79 local/subcutaneous metastasis - PET-CT - MIXED (per lesion).



Bone metastases

For the detection of metastases in the bone, CT performed the poorest in terms of sensitivity, which ranged from 50% (95% CI 23% to 77%) in Dellestable 2011 to 67% (95% CI 38% to 88%) in Jouvet 2014 in three studies, compared to 93% (95% CI 66% to 100%) in Dellestable 2011 to 100% in Jouvet 2014 and Pfannenberg 2007 for MRI, and 71% (95% CI 42% to 92%) in Dellestable 2011 to 91% (95% CI 77% to 98%) in Pfannenberg 2007 for PET-CT (Figure 25).

Data could be pooled for CT and PET-CT for two studies with more than five metastases and more than five benign lesions (Jouvet 2014; Pfannenberg 2007). For PET-CT (85 lesions and 51 metastases), summary sensitivity was 90.2% (95% CI 78.5% to 95.9%) and specificity 88.2% (95% CI 72.5% to 95.5%) (Appendix 13). Summary sensitivity for CT was 26.2% lower (P = 0.001) at 64.0% (95% CI 49.9% to 76.0%) and specificity non-significantly higher at 94.0% (95% CI 49.5% to 99.6%), (P = 0.56).

Lung metastases

For the detection of lung metastases (four studies), CT performed the best in terms of sensitivity, which ranged from 78% (95% CI 27% to 84%) in Hausmann 2011 to 100% (95% CI 75% to 100%) in Dellestable 2011 compared to 47% (95% CI 39% to 55%) in Hausmann 2011 to 87% (95% CI 75% to 95%) in Pfannenberg 2007 for MRI and 31% (95% CI 09% to 61%) in Dellestable 2011 to 100% (95% CI 69% to 100%) in Cachin 2014 for PET-CT (Figure 26). For those studies with more than five disease negative lesions identified, specificities were consistently poor for CT compared to MRI or PET-CT.

Data were pooled for CT and for MRI for three studies with more than five metastases and more than five benign lesions (Jouvet 2014; Pfannenberg 2007). For CT (312 lesions and 229 metastases), summary sensitivity was 90.6% (95% CI 75.7% to 96.8%) and specificity 43.8% (29.5% to 59.1%) (Appendix 13). Summary sensitivity for MRI was 34.9% lower (P = 0.054) at 55.7% (95% CI 24.0% to 83.4%) and specificity significantly higher at 91.3% (95% CI 77.3% to 97.0%) (P < 0.001).

Liver metastases

For liver metastases, only three studies included more than five metastatic lesions to allow comparison of sensitivities (Hausmann 2011; Jouvet 2014; Pfannenberg 2007). Both MRI - Hausmann 2011; Jouvet 2014; Pfannenberg 2007 - and PET-CT - Jouvet 2014; Pfannenberg 2007 - had higher sensitivities compared to CT, but differences were significant only for Hausmann 2011 due to small numbers (Figure 27).

Three studies included more than five benign lesions to allow comparison of specificities. Specificities were 90% or more for CT, MRI, and PET-CT in Dellestable 2011, but the number of benign lesions detected by each test varied from 17 (for CT) to 22 (for MRI). Hausmann 2011 reported specificity to be higher for MRI (100%) compared to CT (50%), but specificities were consistently high for CT, MRI, and PET-CT (87% to 100%) in Jouvet 2014.

No statistical pooling could be undertaken for this target condition.

Local or subcutaneous metastases and soft tissue metastases

The detection of local or subcutaneous metastases was reported in three studies. Overall PET-CT appeared more sensitive than MRI (sensitivities 90% - Pfannenberg 2007 - and 100% - Jouvet 2014 - compared to 70% and 78% for MRI, respectively) and MRI more sensitive in comparison to CT (sensitivities 78% - Pfannenberg 2007 - and 100% - Hausmann 2011 - compared to CT (sensitivities 64% - Pfannenberg 2007 - and 82% - Hausmann 2011), but lesion numbers were small and confidence intervals overlapping. No clear differences in specificities were observed (Figure 28).

Brain metastases

Only two studies included sufficient numbers of imaging abnormalities of the brain to allow sensitivity to be estimated for CT and MRI (Jouvet 2014), and for PET-CT (Cachin 2014). The lowest sensitivity was observed for diffusion weighted MRI (65%, 95% CI 41% to 85%); however the addition of VIBE sequences increased sensitivity to 100% (95% CI 83% to 100%) (23 lesions identified, 20 confirmed metastases). In comparison, the sensitivity of CT was 95% (95% CI 75% to 100%).

In Cachin 2014, the sensitivity of PET-CT for detection of brain metastases was 22% (95% CI 3% to 60%) (nine lesions identified, seven confirmed metastases).

Three additional studies conducted in mixed or unclear populations reported some data on the detection of brain metastases, but numbers were insufficient to include 2×2 contingency tables. In Strobel 2007b, a single confirmed brain metastasis was described as detected on PET-CT. Two studies evaluated whole body PET-CT in combination with MRI of the brain (Aukema 2010a; Aukema 2010b). In Aukema 2010a, MRI detected two confirmed brain metastases in one patient, and in Aukema 2010b, five confirmed brain metastases were detected - four in patients with multiple metastases detected by PET-CT and one solitary brain metastasis. Neither study reported the detection of any benign imaging abnormalities.

Appendix 13. Summary estimates of sensitivities and specificities from mixed or unclear population studies

Table A Summary estimates for tests evaluated in mixed study populations, per patient data

Test Target condition	Studies	Participants (cases)	Sensitivity (95% CI) %	Specificity (95% CI) %
Any metastasis				
PET-CT	6	591 (268)	91.1 (83.6 to 95.3)	93.8 (85.1 to 97.6)

Table B Indirect comparison of imaging tests from mixed study populations, per lesion data

Test Target condition	Studies	Participants (cases)	Sensitivity (95% CI) %	Specificity (95% CI) %
Detection of any metastasis				
CT	5	1770 (1064)	81.3 (76.8 to 85.1)	71.2 (53.9 to 83.9)
MRI	4	1556 (927)	76.4 (70.6 to 81.4)	83.0 (71.9 to 90.3)

(*Continued*)

PET-CT	5	1138 (709)	90.7 (69.0 to 97.7)	84.5 (69.7 to 92.9)
Difference (P value)			0.17	0.29
Detection of nodal metastasis				
CT	4	629 (348)	87.2 (76.5 to 93.4)	69.2 (34.6 to 90.5)
MRI	4	630 (348)	83.9 (68.9 to 92.5)	78.1 (72.1 to 83.1)
PET-CT	4	288 (176)	86.4 (80.5 to 90.7)	89.1 (53.1 to 98.3)
Difference (P value)			0.22	0.89
Detection of distant metastasis				
CT	4	920 (571)	73.4 (63.6 to 81.3)	71.9 (64.3 to 78.5)
MRI	4	926 (579)	74.5 (62.1 to 83.9)	85.8 (70.4 to 93.9)
PET-CT	4	618 (382)	81.0 (67.5 to 90.0)	78.5 (61.0 to 89.5)
Difference (P value)			0.58	0.21

Table C Direct comparisons of imaging tests from mixed study populations, per lesion data

Test Target condition	Studies	Participants (cases)	Sensitivity (95% CI) %	Specificity (95% CI) %
Detection of any metastasis				
CT	4	1538 (913)	79.6 (76.0 to 82.8)	73.8 (51.5 to 88.2)
MRI	4	1556 (927)	76.4 (70.6 to 81.4)	83.0 (71.9 to 90.3)
Difference % (95% CI), P value			3.19 (-3.25 to 9.64), P = 0.33	-9.21 (-30.1 to 11.7), P = 0.39
Detection of any metastasis				
PET-CT	4	962 (624)	93.2 (63.9 to 99.1)	88.8 (80.6 to 93.8)
CT	4	946 (609)	82.3 (76.6 to 86.9)	75.8 (58.9 to 87.2)

(*Continued*)

Difference % (95% CI), P value			10.9 (-3.08 to 24.8), P = 0.13	13.0 (-2.66 to 28.7), P = 0.10
Detection of any metastasis				
PET-CT	3	730 (473)	83.1 (65.3 to 92.8)	87.3 (76.7 to 93.5)
MRI	3	732 (472)	77.4 (70.6 to 82.9)	83.1 (72.9 to 90.0)
Difference % (95% CI), P value			5.79 (-4.67 to 16.3), P = 0.28	4.20 (-11.6 to 20.0), P = 0.60
Detection of nodal metastasis				
CT	4	629 (348)	87.2 (76.5 to 93.4)	69.2 (34.6 to 90.5)
MRI	4	630 (348)	83.7 (68.8 to 92.3)	77.7 (72.4 to 82.1)
Difference % (95% CI), P value			3.41 (-10.8 to 17.6), P = 0.64	-8.45 (-39.7 to 22.8), P = 0.60
Detection of nodal metastasis				
PET-CT	3	249 (156)	86.5 (80.2 to 91.1)	92.5 (85.0 to 96.4)
CT	3	250 (156)	89.0 (71.9 to 96.2)	74.5 (64.7 to 82.3)
Difference % (95% CI), P value			-2.44 (-14.9 to 10.0), P = 0.70	18.0 (7.69 to 28.3), P = 0.001
Detection of nodal metastasis				
PET-CT	3	249 (156)	86.5 (80.2 to 91.1)	92.5 (85.0 to 96.4)
MRI	3	251 (156)	86.1 (63.1 to 95.7)	78.9 (69.6 to 86.0)
Difference % (95% CI), P value			0.48 (-15.8 to 16.8), P = 0.95	13.5 (3.73 to 23.3), P = 0.007
Detection of distant metastasis				
CT	4	920 (571)	73.4 (63.6 to 81.3)	72.0 (64.3 to 78.5)
MRI	4	926 (579)	74.5 (62.1 to 83.9)	85.8 (70.4 to 93.9)
Difference % (95% CI), P value			-1.10 (-15.2 to 13.0), P = 0.88	-13.9 (-27.3 to -0.43), P = 0.043
Detection of distant metastasis				

(*Continued*)

PET-CT	3	481 (317)	81.8 (63.1 to 92.2)	83.5 (68.0 to 92.3)
CT	3	475 (308)	76.0 (62.6 to 85.7)	74.2 (61.9 to 83.6)
Difference % (95% CI), P value			5.77 (-12.7 to 24.2), P = 0.54	9.35 (-6.85 to 25.5), P = 0.26
Detection of distant metastasis				
PET-CT	3	481 (317)	81.8 (63.1 to 92.2)	83.5 (68.0 to 92.3)
MRI	3	481 (316)	77.0 (61.7 to 87.4)	83.8 (59.8 to 94.8)
Difference % (95% CI), P value			4.78 (-14.6 to 24.1), P = 0.63	-0.33 (-21.1 to 20.4), P = 0.98

Table D Direct comparisons of tests by metastatic site

Test	Studies	Participants (cases)	Sensitivity (95% CI) %	Specificity (95% CI) %
Detection of bone metastasis				
PET-CT	2	85 (51)	90.2(78.5 to 95.9)	88.2 (72.5 to 95.5)
CT	2	83 (50)	64.0 (49.9 to 76.0)	94.0 (49.5 to 99.6)
Difference % (95% CI), P value			26.2 (10.6 to 41.8), P=.001	-5.73(-24.8 to 13.3), P=0.56
Detection of lung metastasis				
CT	3	312 (229)	90.6 (75.7 to 96.8)	43.8 (29.5 to 59.1)
MRI	3	312 (229)	55.7 (24.0 to 83.4)	91.3 (77.3 to 97.0)
Difference % (95% CI), P value			34.9 (-0.61 to 70.4), P=0.054	-47.5 (-65.2 to -29.8), P<0.001
Detection of local or subcutaneous metastasis				
CT	2	126 (92)	71.8 (57.6 to.82.7)	64.7 (47.6 to 78.7)
MRI	2	126 (92)	96.2 (31.1 to 99.9)	70.6 (53.4 to 83.3)
Difference % (95% CI), P value			-24.4 (-43.9 to -4.86), P=0.01	-5.88 (-28.1 to 16.3), P=0.60
Detection of local or subcutaneous metastasis				

(*Continued*)

PET-CT	2	95 (66)	90.9 (81.2 to 95.9)	65.5 (46.9 to 80.3)
MRI	2	102 (69)	76.8 (65.4 to 85.2)	69.7 (52.3 to 82.9)
Difference % (95% CI), P value			14.1 (1.96 to 26.2), P=0.02	-4.18 (-27.5 to 19.2), P=0.73
Detection of local or subcutaneous metastasis				
MRI	3	148 (102)	89.7 (53.7-98.5)	71.7 (57.2-82.8)

Appendix 14. Sensitivity and specificity of imaging tests by metastatic site

Study Population group	No. pts Lesions/ cases	Test	Distant	Bone		Lung		Liver		Skin/ subcutaneous		Other
			Sensitivity: [95% CI]% TP/Dis Specificity: [95% CI]% TN/No Dis	Sensitivity [95% CI] % TP/Dis	Specificity [95% CI] % TN/No Dis	Sensitivity [95% CI] % TP/Dis	Specificity [95% CI] % TN/No Dis	Sensitivity [95% CI] % TP/Dis	Specificity [95% CI] % TN/No Dis	Sensitivity [95% CI] % TP/Dis	Specificity [95% CI] % TN/No Dis	Sensitivity: [95% CI] % TP/Dis Specificity: [95% CI]% TN/No Dis
CT												
Dellestab 2011 Mixed	40 118/ 72 (no. varies per test)	CT (CE)	Incl brain: Se: 59 [42 to 74] 24/41 Sp: 87 [73 to 96] 34/39	50 [23 to 77] 7/14	Insufficient data (3/3 detected)	100 [75 to 100] 13/13	Insufficient data (2/3 detected)	Insufficient data (2/4 detected)	100 [80 to 100] 17/17			Distant minus bone, lung, liver mets Se: 20 [3 to 56] 2/ 10 Sp: 75 [48 to 93] 12/ 16

(*Continued*)

Haus-mann 2011 Unclear	33 824/ 455 (all de-tected by ≥ 1 test)	CT (CE)	Excl brain: Se: 71 [65 to 76] 186/ 263 Sp: 71 [64 to 77] 129/ 182	(n = 1)	(n = 1)	78 [70 to 84] 113/ 145	52 [38 to 66] 27/52	39 [23 to 58] 13/33	50 [32 to 68] 17/34	Subcu-ta-neous: 82 [65 to 93] 27/33	Subcu-ta-neous: 54 [25 to 81] 7/13	Adrenal, spleen, muscle, kidney plus 'other' [a]: Se: 63 [49 to 76] 33/ 52 Sp: 94 [86 to 98] 78/ 83
Jouvet 2014 Unclear	37 218/ 125 (no. varies per test)	CT (CE)	Incl brain: Se: 88 [80 to 94] 81/92 Sp: 73 [61 to 84] 47/63 Excl brain: Se: 86 [76 to 93] 62/72 Sp: 72 [59 to 83] 44/61	67 [38 to 88] 10/15	100 [81 to 100] 18/18	94 [79 to 99] 29/31	36 [13 to 65] 5/14	83 [52 to 98] 10/12	87 [60 to 98] 13/15	Subcu-ta-neous: 2/2	Subcu-ta-neous: 62 [32 to 86] 8/13	Brain: Se: 95 [75 to 100] 19/20 Sp: 3/3 lesions cor-rectly iden-tified as benign Other[b]: 13/ 13 cor-rectly identi-fied; 1 (small bowel) missed by CT
Pfan-nen-berg 2007 Mixed	64 420/ 297 (all suspi-cious on ≥ 1 test)	CT (CE)	Excl brain: Se: 77 [71 to 83] 151/ 195 Sp: 64 [52	63 [45 to 79] 22/35	80 [52 to 96] 12/15	96 [87 to 100] 51/53	29 [10 to 56] 5/17	80 [63 to 92] 28/34	Insuffi-cient data (1/2 de-tected)	64 [51 to 76] 38/59	71 [48 to 89] 15/21	'Other viscera' [c]: Se: 92 [64 to 100] 12/13

(*Continued*)

			to 76] 43/67									Sp: 83 [52 to 98] 10/12 Brain metastases excluded[d]
MRI												
Dellestab 2011 Mixed	40 118/72 (no. varies per test)	MRI (DW)	Incl brain: Se: 77 [61 to 89] 30/39 Sp: 97 [86 to 100] 37/38	93 [66 to 100] 13/14	Insufficient data (2/0 detected)	62 [32 to 86] 8/13	Insufficient data (1/1 detected)	Insufficient data (4/4 detected)	100 [85 to 100] 22/22			Distant minus bone, lung, liver mets Se: 63 [24 to 91] 5/8 Sp: 92 [64 to 100] 12/13
Hausmann 2011 Unclear	33 824/455 (all detected by ≥ 1 test)	MRI (NR)	Excl brain: Se: 67 [61 to 73] 177/263 Sp: 91 [85 to 94] 165/182	Insufficient data (1/1 detected)	Insufficient data (1/1 detected)	47 [39 to 55] 68/145	96 [87 to 100] 50/52	85 [68 to 95] 28/33	100 [90 to 100] 34/34	Subcutaneous: 100 [89 to 100] 33/33	Subcutaneous: 77 [46 to 95] 10/13	Adrenal, spleen, muscle, kidney plus 'other' [a]: sensitivity: Se: 92 [81 to 98] 48/52 Sp: 86 [76 to 92] 71/83
Jouvet 2014 Unclear	37 218/125 (no. varies per test)	MRI (DW)	Incl brain: Se: 62 [52 to 71] 63/102	100 [79 to 100] 16/16	47 [24 to 71] 9/19	26 [12 to 45] 8/31	93 [66 to 100] 13/14	92 [62 to 100] 11/12	67 [38 to 88] 10/15	Subcutaneous: 70 [35 to	Subcutaneous: 75 [43 to	Brain: Se: 65 [41 to 85] 13/20

(*Continued*)

			Sp: 70 [57 to 81] 44/63 Excl brain: Se: 61[50 to 72] 50/82 Sp: 68 [55 to 80] 41/60							93] 7/10	95] 9/12	Sp: 3/3 benign correctly identified Other 2: 13/13 correctly identified; 1 (small bowel) missed by MRI
		MRI (DW + VIBE)	Incl brain: Se: 83 [75 to 90] 85/102 Sp: 81 [69 to 90] 51/63 Excl brain: Se: 79 [69 to 87] 65/82 Sp: 80 [68 to 89] 48/60	100 [79 to 100] 16/16	74 [49 to 91] 14/19	52 [33 to 70] 16/31	79 [49 to 95] 11/14	100 [74 to 100] 12/12	93 [68 to 100] 14/15	Subcutaneous: 90 [55 to 100] 9/10	Subcutaneous: 75 [43 to 95] 9/12	Brain: Se: 100 [83 to 100] 20/20 Sp: 3/3 benign correctly identified Other[b]: 13/13 correctly identified; 1 (small bowel) missed by MRI
Pfannenberg 2007 Mixed	64 420/297 (all suspicious on ≥ 1 test)	MRI (DW + VIBE)	Excl brain: Se: 87 [82 to 92] 170/195 Sp: 76 [64 to 86]	100 [90 to 100] 35/35	73 [45 to 92] 11/15	87 [75 to 95] 46/53	76 [50 to 93] 13/17	100 [90 to 100] 35/35	Insufficient data (2/2 detected)	78 [65 to 88] 46/59	67 [43 to 85] 14/21	'Other viscera: sensitivity: 62 [32 to 86] 8/13 Sp: 92 [62

(*Continued*)

			51/67									to 100] 11/12 Brain metastases excluded[d]
PET-CT												
Cachin 2014 Mixed	87 176/85	PET-CT (NR)	Incl brain: Se: 78 [67 to 88] 51/65 Sp: 58 [46 to 70] 42/72	86 [57 to 98] 12/14	86 [57 to 98] 12/14	100 [69 to 100] 10/10	100 [69 to 100] 10/10	2/2	71 [29 to 96] 5/7	Skin: 86 [42 to 100] 6/7	0/2	Brain: Se: 22 [3 to 60] 2/7 Sp: 2/7 Soft tissue metastasis: Sp: 75 [48 to 93] 12/16 Sp: 6/7
Dellestab 2011 Mixed	40 118/72 (no. varies per test)	PET-CT (CE)	Incl brain: Se: 66 [49 to 80] 27/45 Sp: 88 [73 to 96] 35/40	71 [42 to 92] 10/14	3/3	31 [9 to 61] 4/13	2/2	2/4	90 [70 to 99] 19/21			Distant minus bone, lung, liver mets: Se: 92 [62 to 100] 11/12 Sp: 79 [49 to 95] 11/14
Jouvet 2014 Unclear	37 218/125 (no. varies per test)	PET-CT (CE)	Excl brain: Se: 75 [64 to 84] 61/81 Sp: 91 [81 to 97] 52/57	88 [62 to 98] 14/16	75 [43 to 95] 18/19	48 [30 to 67] 15/31	100 [77 to 100] 14/14	100 [74 to 100] 12/12	100 [78 to 100] 15/15	100 [59 to 100]	63 [24 to 91] 5/8	Other[2]: 13/13 correctly identified; 1 (small bowel) missed by CT

(*Continued*)

Pfannenberg 2007 Mixed	64 420/297 (all suspicious on ≥ 1 test)	PET-CT (CE)	Excl brain: Se: 93[89 to 96] 182/195 Sp: 67 [55 to 78] 45/67	91 [77 to 98] 32/35	80 [52 to 96] 12/15	96 [87 to 100] 51/53	35 [14 to 62] 6/17	94 [81 to 99] 33/35	2/2	90 [79 to 96] 53/59	67 [43 to 85] 14/21	'Other viscera' [c]: Se: 100 [75 to 100 13/13 Sp: 92 [62 to 100] 11/12 Brain metastases excluded[d]

[a] 'Other' not further defined (Hausmann 2011).
[b] Fourteen 'other metastatic sites described', all assumed (by us) to be malignant adrenal (4), heart (2), spleen (2), peritoneal carcinosis (2), breast (1), pleura (1), vagina (1), and small intestine (1)
[c] other visceral metastases such as bowel or peritoneal lesion (Pfannenberg 2007).
[d] Brain metastases excluded from comparison of accuracy; reports 15 patients with cerebral metastases, "exclusively diagnosed by wbMRI" (Pfannenberg 2007).
CE: contrast enhanced; CI: confidence interval; CT: computed tomography; Dis: diseased group; DW: diffusion weighted; excl: excluding; GE: gradient echo; incl: including; MRI: magnetic resonance imaging; No Dis: non-diseased group; NR: not reported; PET: positron emission tomography; Se: sensitivity; Sp: specificity; TN: true negative; TP: true positive; U: unenhanced; US: ultrasound; WB: whole body

CONTRIBUTIONS OF AUTHORS

JD was the contact person with the editorial base.

JD co-ordinated contributions from the co-authors and wrote the final draft of the review.

SEB conducted the literature searches.

JD, NC, LFR, AD, AG, LP, and SAC screened papers against eligibility criteria.

JD, LFR, AD, AG, LP, and SAC appraised the quality of papers.

JD, LFR, AD, AG, LP, and SAC extracted data for the review and sought additional information about papers.

JD entered data into Review Manager 5 (Review Manager 2014).

JD and YT analysed and interpreted data.

JD, JJD, NC, LFR, YT, and CD worked on the methods sections.

JD, JNB, STC, PN, MS, ZT, RNM, and HCW drafted the clinical sections of the background and responded to clinical comments of the referees.

JD, JJD, CD, and YT responded to the methodology and statistics comments of the referees.

KG was the consumer co-author and checked the review for readability and clarity and ensured that outcomes were relevant to consumers.

JD is the guarantor of the update.

Disclaimer

This project was supported by the National Institute for Health Research via Cochrane Infrastructure funding to Cochrane Skin and Cochrane Programme Grant funding. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS, or the Department of Health.
This review presents independent research supported by the NIHR Birmingham Biomedical Research Centre at the University Hospitals Birmingham NHS Foundation Trust and the University of Birmingham. The views expressed are those of the author(s) and are not necessarily those of the NHS, the NIHR, or the Department of Health and Social Care.

DECLARATIONS OF INTEREST

Jacqueline Dinnes: I am employed by the University of Birmingham under an NIHR Cochrane Programme Grant (13-89-15) to produce the review.

Lavinia Ferrante di Ruffano: nothing to declare.

Yemisi Takwoingi: nothing to declare.

Seau Tak Cheung: nothing to declare.

Paul Nathan: I have received consultancy fees from Bristol Myers Squibb (BMS), Pfizer, Merck Sharp Dohme (MSD), Merck, and Immunocore to sit on advisory boards. I have received payment from BMS and Novartis for lectures at satellite symposia; payment from BMS for webcasts; payment of travel, accommodations, and meeting expenses from BMS and MSD for attending conferences of the American Society of Clinical Oncology, the Society for Melanoma Research, and the European Society of Medical Oncology.

Rubeta N Matin: my institution received a grant for a Barco NV commercially sponsored study to evaluate digital dermoscopy in the skin cancer clinic. My institution also received Oxfordshire Health Services Research Charitable Funds for carrying out a study of feasibility of using the Skin Cancer Quality of Life Impact Tool (SCQOLIT) in non-melanoma skin cancer, and ScARF funding for the melanoma unmet needs study. I have received payment from Public Health England for the "Be Clear on Cancer Skin Cancer" report; payment for development of educational presentations on skin toxicity for BMS; and royalties for the *Oxford Handbook of Medical Dermatology* (Oxford University Press). I have no conflicts of interest to declare that directly relate to the publication of this work.

Naomi Chuchu: nothing to declare.

Sue Ann Chan: nothing to declare.

Alana Durack: nothing to declare.

Susan E Bayliss: nothing to declare.

Abha Gulati: nothing to declare.

Lopa Patel: nothing to declare.

Clare Davenport: my employer (University of Birmingham) received funding for my participation in this review as part of an NIHR programme grant awarded to Jac Dinnes, the PI.

Kathie Godfrey: nothing to declare.

Manil Subsesinghe: nothing to declare.

Zoe Traill: nothing to declare.

Jonathan J Deeks: my employer (University of Birmingham) received funding for my participation in this review as part of an NIHR programme grant awarded to Jac Dinnes, the PI.

Hywel C Williams: I am director of the NIHR HTA Programme. HTA is part of the NIHR, which also supports the NIHR systematic reviews programme from which this work is funded.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- NIHR Systematic Review Programme, UK.

This project was funded by an NIHR Cochrane Systematic Reviews Programme Grant (13-89-15)

- National Institute for Health Research (NIHR), UK.

The NIHR, UK, is the largest single funder of Cochrane Skin

- NIHR Birmingham Biomedical Research Centre, UK.

JD, JJD, and YT receive support from the NIHR Birmingham Biomedical Research Centre

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We set out to separately review the evidence for ultrasound, CT, MRI, and PET-CT for staging of melanoma, and to bring the reviews together in a Cochrane Overview review; however, as our main focus is on the comparative accuracy of different imaging tests, the reviews were brought together into a single review.

A new primary objective was added: to determine the diagnostic accuracy of ultrasound or PET-CT for detection of nodal metastases before SLNB in adults with confirmed cutaneous invasive melanoma.

A new secondary objective was added: to determine the diagnostic accuracy of ultrasound, CT, MRI, or PET-CT for detection of any metastasis in the staging of disease in mixed or not clearly described populations of adults with cutaneous invasive melanoma. According to the protocol, the effect of mixed or not clearly reported populations was to be considered as a subgroup analysis.

We clarified that the primary objectives refer to *adults* with melanoma.

We amended the text to clarify that studies available only as conference abstracts would be excluded from the review; studies available only as conference abstracts do not allow a comprehensive assessment of study methods or methodological quality.

Sources of heterogeneity could not be formally investigated because of lack of data.

We allowed the inclusion of up to 10% of participants having non-cutaneous melanoma.

We excluded studies of PET alone as the technology is now considered obsolete, instead including only those that examined PET combined with CT.

Studies reporting multiple applications of the same test in more than 10% of study participants were excluded because of anticipated effects on test accuracy (multiple tests increasing the chance of metastases being detected), thereby increasing test sensitivity and reducing specificity.

Reference standard inclusion criteria were amended to allow malignancy to be confirmed by imaging follow-up (growth or regression of suspicious lesion on imaging) and to recognise that histology may be available for index negative (e.g. SLNB may be conducted in all those with ultrasound regardless of positive or negative). The minimum follow-up required was also dropped from six months to three months in accordance with the minimum required in diagnosis reviews.

We proposed to supplement the database searches by searching the annual meetings of appropriate organisations (e.g. British Association of Dermatologists' Annual Meeting, American Academy of Dermatology Annual Meeting, European Academy of Dermatology and Venereology Meeting, Society for Melanoma Research Congress, World Congress of Dermatology, European Association of Dermato Oncology), but because of the volume of evidence retrieved from database searches and time restrictions, we were unable to do this.

For quality assessment, we tailored the QUADAS-2 tool according to the review topic. In terms of analysis, we did not restrict analysis to per patient data due to lack of data.