

GUIDELINE FOR THE DIAGNOSIS, TREATMENT, AND FOLLOW-UP OF CUTANEOUS MELANOMA IN SECONDARY CARE



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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
AE	Adverse event
aHR	Adjusted hazard ratio
AJCC	American Joint Committee on Cancer
BCR	Belgian Cancer Registry
BT	Breslow thickness
CI	Confidence Interval
CLND	Complete lymph node dissection
CM	Cutaneous melanoma
CoI	Conflict of Interest
CT	Computed tomography
CTC	Common toxicity criteria
DFI	Disease-free interval
DMFS	Distant metastasis-free survival
DTA	Diagnostic test accuracy
ESMO	European Society of Medical Oncology
FNAC	Fine needle aspiration cytology
FOD SZ – SPF SS	Federal Public Service of Social Security
FOD VVVL – SPF SPSCAE	Federal Public Service Health, Food Chain Safety and Environment
F/U	Follow-up
GCP	Good Clinical Practice
GDG	Guideline development group
GP	General Practitioner
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HCP	Health care professional
HR	Hazard ratio
HRQoL	Health-related quality of life
IQR	Interquartile range
IV	Intravenous
LDH	Lactate deshydrogenase
M	Distant Metastasis
max	Maximum
MRI	Magnetic resonance imaging
MSS	Melanoma specific survival
N	Regional Lymph node
NED	No evidence of disease
NICE	National Institute for Health and Care Excellence
NMFS	Nodal metastatic free survival

NS	Non-significant
OS	Overall survival
PET	Positron emission tomography
PICO	Participants–Interventions–Comparator–Outcomes framework
PPV	Positive Predictive Value
pT	Pathological examination (T-category)
QoL	Quality of life
QUADAS-2	Quality Assessment of Diagnostic Accuracy Studies-2 tool
RCT	Randomised controlled trial
RFS	Recurrence-free survival
RIZIV – INAMI	National Institute for Health and Disability Insurance
RR	Relative risk; risk ratio
SAE	Serious adverse event
SLNB	Sentinel lymph node biopsy
SR	Systematic review
SSE	Skin self-examination
TNM staging	Tumour Nodule Metastasis staging
UK	United Kingdom
US	Ultrasound
vs.	versus
y	year
y.o.	Years old



■ SCIENTIFIC REPORT

1 INTRODUCTION

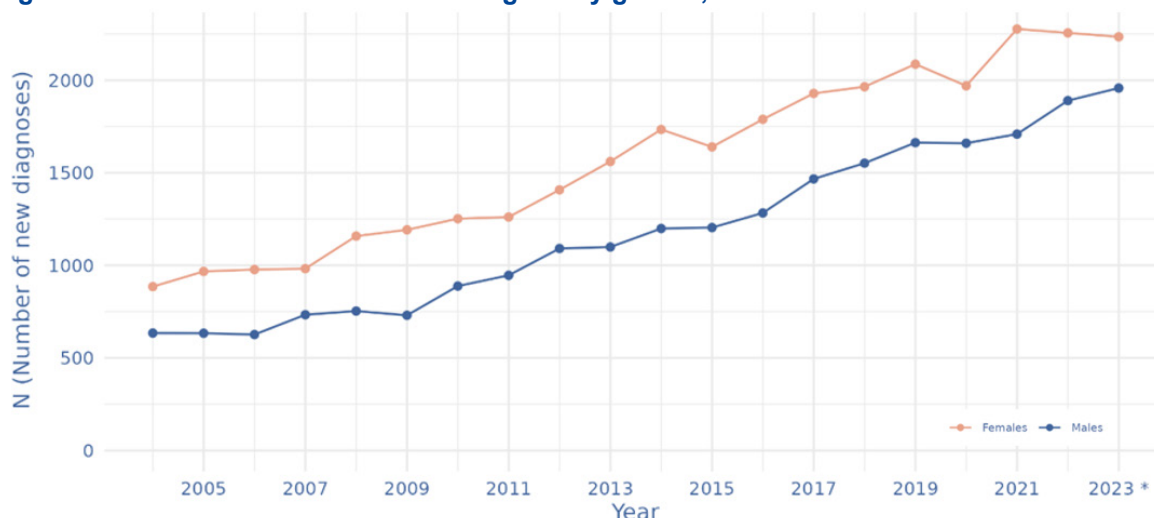
1.1 Background

Cutaneous melanoma is a malignancy arising from melanocytes of the skin that are often darkly pigmented. Exposure to ultraviolet radiation from natural sunlight and indoor tanning is a typical risk factor, although there are subtypes that are not related to ultraviolet radiation exposure. Hence, primary prevention of melanoma focuses on reducing ultraviolet radiation exposure and increasing sun-protective behaviours. High naevus count and the presence of clinically atypical moles are risk factors for melanomas in sun-protected skin, such as the trunk.(Long 2023)

Worldwide, the incidence of cutaneous melanoma has steadily risen since the 1950s with increasing sunlight exposure, but also overdiagnosis due to screening and histological overcalling may play a role.(Long 2023)

The number of new diagnoses of cutaneous melanoma in Belgium has increased over the past two decades and more than doubled from 1518 cases in 2004 to 4146 cases in 2022 (Figure 1). Belgium ranks high in incidence, with 35.9 cases per 100 000 persons, after Denmark, Sweden, the Netherlands, and Finland (age-standardised incidence rate for Europe 21.4/100000).(European Cancer Information System (ECIS) 2024)

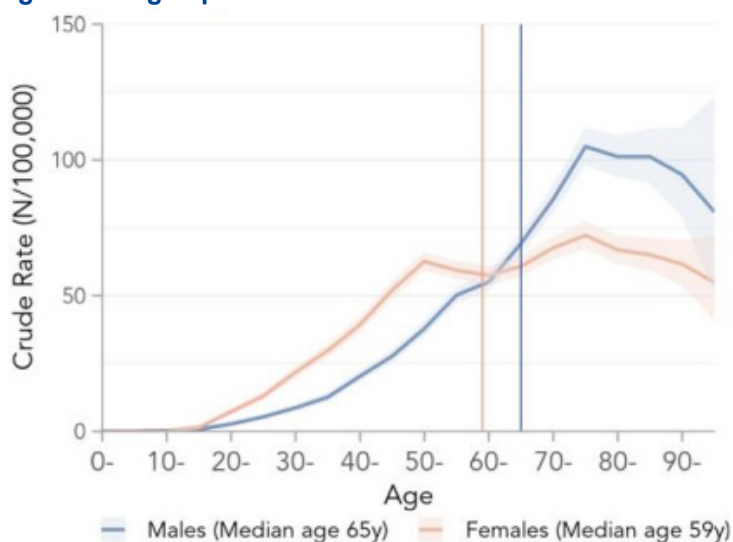
Figure 1 – Incidence of melanoma in Belgium by gender, 2004-2023



Source: Belgian Cancer Registry September 2024; *Data for 2023 are estimates

The median age at diagnosis of cutaneous melanoma in Belgium in 2022 was lower for women (59 years) than for men (65 years), with a rising incidence with age (Figure 2).(Belgian Cancer Registry (BCR) 2024)

Figure 2 – Age-specific incidence of melanoma 2018-2022



Source: Belgian Cancer Registry September 2024

Prognosis highly depends on the stage of the tumour at diagnosis.(Gershenwald JE 2017) A correct staging is based on the Tumour, Nodes, Metastasis (TNM) classification and stage grouping criteria according to the eighth edition of the American Joint Committee on Cancer (AJCC) staging system.(Gershenwald JE 2017) The staging system guides patient treatment and informs prognostic assessment and clinical decision-making. The extent of the primary tumour is classified after excision and pathological examination (pT or T-category Table 1). Clinical staging of regional lymph nodes (N) and distant metastasis (M) is based on physical examination and imaging. The clinical staging can be supplemented with further pathological staging, most often performed for the regional lymph nodes. For melanoma, satellite and in-transit lesions are included in the N-classification.

Table 1 – 8th AJCC TNM staging system

Stage	T-category ¹	N-category ²	M-category ³
Stage 0	Tis	N0	M0
Stage IA	T1a	N0	M0
Stage IB	T1b		
	T2a		
Stage IIA	T2b	N0	M0
	T3a		
Stage IIB	T3b		
	T4a		
Stage IIC	T4b		
Stage III	Any T	≥N1	M0
Stage IIIA	T1a T1b T2a	N1a or N2a	M0
Stage IIIB	T0	N1b or N1c	
	T1a T1b T2a	N1b or N1c or N2b	
	T2b T3a	N1a-2b	
Stage IIIC	T0	N2b-c or N3b-c	
	T1a-T3a	N2c or N3a-c	
	T3b-T4a	Any N≥N1	
	T4b	N1a-N2c	
Stage IIID	T4b	N3a-c	
Stage IV	Any T	Any N	M1

¹*The melanoma thickness of the primary tumour: Tis=melanoma in situ, T1a=nonulcerated <0.8 mm thickness, T1b= 0.8–1.0 mm thickness regardless of ulceration status OR ulcerated melanomas <0.8 mm thickness, T2= >1.0–2.0 mm thickness, T3= >2.0–4.0 mm thickness, T4= >4.0 mm thickness, a=nonulcerated and b=ulceration, T0= no evidence of a primary tumour OR site primary tumour unknown, TX= tumour thickness cannot be determined*

Measurements are recorded to the nearest 0.1 mm, not the nearest 0.01 mm, particularly for tumours >1 mm thick; tumours ≤1 mm may be measured to the nearest 0.01 mm when practical but should be reported rounded to the nearest 0.1 mm.

²*The melanoma regional lymph node category: N0= no regional nodes, N1-3= with 1 to 3 the number of metastatic lymph nodes; N1= 0-1 node, a=clinically occult no microsatellites, satellites, in-transit metastases (MSI), b=clinically detected (on palpation or ultrasound), c=0 nodes, MSI present; N2= 1-3 nodes, a=2-3 nodes clinically occult, no MSI, b=2-3 nodes clinically detected, no MSI, c=1 node clinical or occult, MSI present; N3= >1 node, a=>3 nodes, all clinically occult, no MSI, b=>3 nodes, ≥1 clinically detected or matted, no MSI, c=>1 node clinical or occult, MSI present*

³*The melanoma distant metastasis category: M0= no distant metastasis detected, M1=distant metastasis detected*

Women are more often diagnosed in stage I (81%) as compared to men (76%).(Belgian Cancer Registry (BCR) 2024) The 5-year (period 2013-2022) relative survival for men was 94.1% (95% CI 89.2%-99.3%) compared to 98.0% (95% CI 96.2%-100.0%) for women.(Belgian Cancer Registry (BCR) 2024) Survival has improved for both women and men and for all stages as shown in Table 2.

Table 2 – 5-year net survival in patients with cutaneous melanoma by stage diagnosed during 2008-2012 and 2018-2022

Combined stage	N at risk	Net survival probability (95% CI) period 2008-2012 Males	N at risk	Net survival probability (95% CI) period 2008-2012 Females	N at risk	Net survival probability (95% CI) period 2018-2022 Males	N at risk	Net survival probability (95% CI) period 2018-2022 Females
All stages	4313	86.0% (84.4%; 87.6%)	6183	92.5% (91.4%; 93.6%)	8205	95.3% (93.8%; 96.9%)	10306	96.8% (95.7%; 97.9%)
I	2280	100.8% (99.1%; 102.4%)	3663	100.4% (99.5%; 101.4%)	5941	104.3% (102.8%; 105.8%)	8121	102.6% (101.7%; 103.5%)
II	711	69.6% (64.7%; 74.7%)	832	76.3% (71.8%; 81.0%)	1257	83.8% (78.6%; 89.4%)	1322	83.5% (78.6%; 88.7%)
III	279	54.0% (47.7%; 61.2%)	288	70.9% (65.1%; 77.2%)	573	68.1% (62.1%; 74.6%)	510	80.9% (75.6%; 86.5%)
IV	133	19.2% (13.0%; 28.3%)	97	35.0% (25.8%; 47.5%)	178	29.2% (19.6%; 43.5%)	121	25.2% (14.9%; 42.4%)
X/NA	941	80.8% (77.2%; 84.6%)	1329	89.2% (86.5%; 92.0%)	325	56.7% (48.5%; 66.3%)	278	49.5% (41.9%; 58.5%)

Data provided by the BCR: Net survival may exceed 100%, this occurs when the observed survival probability for patients with the cancer type(s) under study is higher than the one for the matched general population (no excess mortality due to cancer). Stage NA: unknown primary tumour localisation. The stage is reported as a combination of both clinical and pathological stage with priority given to the pathological stage. If the stage is unknown or not submitted to the Belgian Cancer Registry, the stage is reported as 'unregistered stage' or X.

The overall survival by sub-stages for stage II and III is presented in Table 3.

Table 3 – 5-year overall survival in patients with cutaneous melanoma stage II and III diagnosed during 2015-2016, by substage

Combined stage	N at risk	Overall survival probability, 5yr
IIA	421	77.1 (72.8-80.9)
IIB	305	63.9 (58.2-69.0)
IIC	193	39.4 (32.5-46.3)
III*	134	63.3 (54.5-70.8)
IIIA	67	82.1 (70.6-89.4)
IIIB	78	67.5 (55.9-76.8)
IIIC%	67	49.3 (36.9-60.5)

Source: Belgian Cancer Registry September 2024; *missing data for this line to define a substage

The management of cutaneous melanoma has undergone several transformations over the past decade, resulting in decreasing mortality rates. Surgery remains the corner stone for treatment of non-metastatic melanoma, with wide excision of the primary tumour and lymphadenectomy of the regional lymph nodes only if indicated. New effective systemic therapies such as checkpoint immunotherapy and treatment targeting mutant BRAF were first introduced for metastatic disease and more recently, randomised trials in the adjuvant and neoadjuvant setting have been performed. (Long 2023)

The uptake of the new drugs has increased over the years in Belgium, especially for the advanced stages. Proportion of patients who received at least one dose of immunotherapy or targeted therapy during the first five years after diagnosis is shown in Table 4 for patients who were diagnosed with melanoma in 2021.

Table 4 – Uptake of drugs[§] for patients diagnosed with cutaneous melanoma, by combined stage in Belgium, incidence year 2021

Drug / stage (N)	stage I (3053)	stage II (528)	stage III (237)	stage IV (61)	stage X (38)	stage NA (68)
Nivolumab	0.5	9.1	43.9	47.5	2.6	51.5
Pembrolizumab	1.0	6.8	32.9	24.6	2.6	23.5
Ipilimumab	0.3	5.3	12.7	31.1	2.6	33.8
Vemurafenib*	-	-	-	-	-	-
Dabrafenib	0.2	2.5	22.4	18.0	-	13.2
Trametinib	0.2	2.5	22.4	18.0	-	13.2

Source: Belgian Cancer Registry September 2024. Numbers in the table are percentages.

*Vemurafenib use started in 2009 but use then declined as dabrafenib and trametinib were introduced.

[§]defined as proportion of patients who received at least one dose of the drug during the first 5 years after diagnosis.

1.2 Objective

To address the rising trend of melanoma and the changes of treatment of melanoma over the past decade, a Belgian guideline aims to inform healthcare providers involved in the management of patients with cutaneous melanoma to reduce variation in practice and improve survival. This



guideline provides recommendations on priority areas identified by stakeholders for the assessment and management of cutaneous melanoma in adults and is based on current scientific evidence.

1.3 Target users

This guideline is primarily developed for health professionals in secondary care. More specific, for dermatologists, oncologists, surgeons, radiologists and nuclear medicine specialists or medical doctors and their team caring for patients with cutaneous melanoma e.g., to inform clinical decisions, to inform standards of care.

1.4 Scope

This guideline covers:

- Primary cutaneous melanoma
- Diagnosis and initial treatment
- Follow-up after treatment

This guideline does not address:

- Mucosal melanoma, uveal melanoma and melanoma of other non-skin locations
- Non-melanoma skin cancer
- Screening
- Treatment of recurrent disease
- Palliative interventions

Priority topics for the scope of the guideline were first explored through an [online survey](#) with stakeholders and finalised at an expert and stakeholder group in April 2024. The survey was informed by a [review](#) of international guidelines.

The recommendations for adult patients with cutaneous melanoma in this guideline cover

- **Ultrasound use for primary N staging**
- **Whole-body [¹⁸F]FDG PET/CT use for primary N and M staging**
- **The surgical excision margins for stage 0 to II**
- **Adjuvant therapy for completely resected stage IIB, IIC, III or IV**
- **Neoadjuvant therapy for clinically detectable stage III melanoma and resectable stage IV melanoma**
- **Completion lymphadenectomy for micrometastatic nodal disease**
- **The surveillance strategy in the follow-up of patients who are clinically disease free after receiving treatment with curative intent**

2 METHODOLOGY

This guideline was developed based on scientific evidence in accordance with the KCE guideline development methodology (more detail can be found in the Good Clinical Practice methods melanoma supplement). To assure this guideline is of high quality before it is validated and implemented, the AGREE II checklist items are [deliberated](#). (AGREE 2017, Vernooij 2017)

2.1 Marking out the scope of the guideline

A search for [recent guidelines](#) on diagnosis, treatment and/or follow-up of melanoma was performed. The retrieved guidelines for this scoping phase were [appraised with AGREE II](#) by one reviewer (VIJ). (AGREE 2017, Brouwers 2010) A longlist of topics for research questions was compiled based on these guidelines, supplemented with other items found in the recent scientific literature.

The longlist was presented as a [survey](#) and was [largely distributed](#) to retrieve input on the priority of topics for research questions from experts and stakeholders. Proposals for new topics were encouraged.

2.2 Development of the research questions

The development of the clinical research questions was in close collaboration with the members of the [Guideline Development Group](#) (GDG).

The results of the survey were presented to the GDG and final research questions were formulated:

On diagnosis of cutaneous melanoma

- Is an ultrasound the diagnostic test of choice for primary N staging for patients with cutaneous melanoma?
- Is whole-body ¹⁸F-FDG PET/CT the diagnostic test of choice for the detection of metastases for patients with cutaneous melanoma for N and M staging?

On treatment of cutaneous melanoma

- Which are the most effective surgical excision margins for stage 0 to II cutaneous melanoma?
- Does completion lymphadenectomy (lymph node dissection) for micro-metastatic disease in stage III cutaneous melanoma result in better survival and/or quality of life compared to no completion lymphadenectomy?
- What is the effectiveness of adjuvant therapy for completely resected stage IIB, IIC, III or IV cutaneous melanoma?
- What is the effectiveness of an neoadjuvant therapeutic strategy for completely resected stage IIB, IIC, III or IV cutaneous melanoma?

On follow-up of treated patients

- At what frequency and how long should follow up interventions be performed in patients who are clinically disease free after receiving curative-intent treatment for melanoma to improve patients' outcomes?

All clinical questions were translated to the PICO (Participants–Interventions–Comparator–Outcomes) framework and shared with the GDG. To decide on critical and important outcomes, general principles were followed.

- A balance between desirable and undesirable effects was aimed for.
- Clinically relevant patient-centred outcomes were prioritised.
- Surrogate outcomes were avoided as much as possible.



We applied the GRADE-ADOLOPMENT approach; we evaluated recommendations from existing recent evidence-based guidelines that fulfilled certain criteria for credibility and rigour of development. Recent evidence-based guidelines, developed following rigorous methods were considered to avoid duplication of work and save on time and resources. The two selected guidelines that were used for adapt/adopt are presented in Appendix 2.5.

As in general, the aim of oncological treatment is to prolong overall survival or improve quality of life, these two outcomes were selected as critical outcomes.(Eisenhauer 2025) (Severe) adverse events (AEs) were added as important outcome as a measure of the undesirable effects. Although progression-free survival (PFS), event-free survival (EFS) and disease-free survival (DFS) are no strong surrogate outcomes for overall survival or quality of life, they were added as an important outcome. They often serve as basis for reimbursement decisions and may have some value for patients in the adjuvant setting. DFS is considered by some as an interim outcome contributing directly to patients' benefit derived from time gained without disease or need for renewed medical treatment.(Cherny 2025,Eisenhauer 2025,Mittal 2024)

2.3 Evidence review

An iterative approach for systematic reviews identified the NICE guideline 2022 systematic reviews for the questions on ultrasound for primary N staging, PET/CT for primary N and M staging, surgical excision margins for stage 0 to II, and completion lymphadenectomy for micro-metastatic disease stage III.(NICE 2022) For the follow-up question the Canadian Ontario guideline 2024 with systematic review was identified.(Rajagopal 2024) A de novo search was set-up for the adjuvant and neoadjuvant therapy questions. The search methods and results for each of the evidence reviews are presented in the following chapters (and related appendices).

2.4 From evidence to recommendation

The evidence, evidence summaries, and the evidence to recommendations for each of the research questions are presented in the following chapters (and related appendices).

Recommendations were formulated as strong or conditional according to the certainty of the supporting evidence and the balance between desirable and undesirable consequences of the alternative management options, the patients' values and preferences, and estimated cost or resource utilisation (see supplement methodology 2.5). Equity aspects were also included.(Pottie 2017)

Good practice statements (for situations when a guideline panel might judge the certainty high that the desirable effects of an intervention clearly outweighs its undesirable effects but the body of supportive evidence is indirect) and clinical practice guidance (adding additional practical information for clinical practice identified by experts and stakeholders) were also developed.

The KCE researchers drafted the recommendations which were discussed with the GDG at the GDG meeting after a presentation of the evidence review. An agreement on the direction of the effect, the strength, and the wording of the recommendation was made by an informal consensus. If no consensus was reached at the time of the meeting, the recommendation was adapted based on the discussion at the meeting. Next, the new proposal was circulated via mail to the GDG. Experts were asked to provide arguments in case of disagreement or to add clarifications where needed. The final recommendations (and guidance) on all research questions was again circulated inclusive of the evidence to recommendation section and experts were asked for their final comments and agreement. The final recommendations were presented at a stakeholders meeting on May 27th 2025. The report was then reviewed by the validators. Based on the evaluation and discussion and the final comments received from the stakeholders and validators, final minor and major changes were made by the KCE team to improve transparency and the interpretation of the presented results.

3 PRIMARY STAGING WITH ULTRASOUND AND PET/CT

3.1 Recommendations primary staging with ultrasound and [¹⁸F]FDG PET/CT

International consensus states that a lymph node biopsy is to be performed for melanomas with pathological classification pT1b and higher for correct staging purposes.

<i>Recommendations on primary N and M staging with imaging by pathological classification (pT) for adult patients with a diagnosis of primary cutaneous melanoma</i>		Strength of recommendation	GRADE certainty of evidence
Recommendations for the use of ultrasound by pT classification for N staging			
Any pT stage	<i>Clinicians should not offer ultrasound for N staging</i>	Strong	Low to moderate
Recommendations for the use of PET/CT by pT classification for N staging			
Any pT stage	<i>Clinicians should not offer PET/CT for N staging</i>	Strong	Very low
Recommendations for the use of PET/CT by pT classification for M staging*			
0 in situ - pT3a	<i>Clinicians should not offer whole-body PET/CT for M staging</i>	Strong	Very low
pT3b - pT4b	<i>Clinicians may offer whole-body PET/CT for M staging</i>	Conditional [∞]	

The notation PET/CT stands for [¹⁸F]FDG PET/CT throughout. pT: pathological classification

[∞]Conditional on individual benefits and harms evaluation. The patients should be informed about the implications of false positives; and that a lymph node biopsy is performed for correct staging purposes.

Clinical practice guidance:

Technical aspects to be considered for PET/CT

- the integrated 3D PET/CT device is EANM/EARL accredited (https://earl.eanm.org/wp-content/uploads/2023/05/EARL_Manual_4.2.pdf)
- the CT is of diagnostic quality (not just for attenuation correction) and contrast is used
- scan from head to toes (not from head to thigh region as in most standard PET/CT protocols)
- the EANM guidelines are followed (Boellaard 2015)
- the location of the melanoma is checked prior to PET/CT imaging to adjust the patient's position and field of view of the PET/CT accordingly
 - melanoma on the lower legs, scan from head to toes
 - melanoma of the forearm or hand, the arms should be kept alongside the body
 - other locations scan from head to knee.

3.2 Introduction

This chapter addresses the research questions on diagnosing regional (N staging) and distant (M staging) metastases in patients with a primary cutaneous melanoma without clinical signs of N or M metastases. The questions focused on primary staging with ultrasound and PET/CT for patients with a defined T stage. The question of staging with PET/CT concerned both N and M staging. Guidelines currently indicate M staging from T stage T3b and higher. This question addresses the indication if M staging could be indicated at a lower T stage T1b to T3a.



Imaging before sentinel lymph node biopsy (SLNB) has been used to identify patients with macroscopic nodal metastatic disease that is not detectable on clinical examination by palpation (Table 5). A correct baseline staging for patients with cutaneous melanoma is necessary for the correct management of the patient as the detection of regional and distant metastases will affect the treatment plan and subsequent suitable therapeutic modalities. Therefore, a sentinel node scintigraphy with biopsy is always performed for stage $\geq pT1b$ melanomas (international consensus). (Amaral 2025, NICE 2022)

Table 5 – Definitions 8th edition AJCC

	8 th edition AJCC	7 th edition AJCC
Nodal metastasis	'clinically occult' nodal metastasis Patients without clinical or radiographic evidence of regional lymph node metastasis but who have tumour-involved regional nodal metastasis found at SLN biopsy are defined as having 'clinically occult' nodal metastasis	'microscopic' nodal metastasis
	'clinically detected' nodal metastasis	'macroscopic' nodal metastasis
Distant metastasis	No evidence of distant metastasis	No distant metastasis

References: 8th AJCC (Gershenwald JE 2017, Keung 2018)

A summary of international recommendations on imaging for staging of commonly used guidance internationally and in Belgium is presented in Table 6. Of note, the NICE 2022 guideline is GRADE based with a systematic review whereas the ESMO 2025 and EADO 2022 guidelines do not present a systematic review of the evidence.

Table 6 – Recommendations for routine imaging by T stage

T stage	NICE 2022 (NICE 2022)	ESMO 2025 (Amaral 2025)	EADO 2022 (Garbe 2022)
0 in situ	Do not offer imaging	Not recommended	Not necessary
pT1a	Do not offer imaging	Not recommended	Not necessary
pT1b	Not specified	Not recommended	US-FNAC regional
pT2a	Not specified	Not recommended	US-FNAC regional
pT2b-pT3a	Not specified	Not recommended	US-FNAC regional
pT3b-pT4a	Consider staging with whole-body and brain PET/CT	Offer US, whole-body CT and/or PET/CT and brain MRI	US-FNAC regional
pT4b	Offer staging with whole-body and brain PET/CT	Offer US, whole-body CT and/or PET/CT and brain MRI	US-FNAC regional

3.3 Research questions and search

The two research questions on N and M staging with imaging by ultrasound and PET/CT were gathered in one search. Both questions: 'Is an ultrasound the diagnostic test of choice for the detection of lymph node metastases in primary cutaneous melanoma?' and 'Is whole-body ¹⁸F-FDG PET/CT the diagnostic test of choice for the detection of metastases in primary cutaneous melanoma for N and M staging?' were translated into [PICO](#) (population - index test – comparator – outcome) for the literature search. Cost-effectiveness was included as 'other' outcome. No separate search was performed for cost-effectiveness.

STUDY IDENTIFICATION AND SELECTION

The search for systematic reviews (SRs) was performed in the Cochrane Library (Cochrane Reviews and Trials), Medline Ovid, and Embase (search dates July 26th, 2024, July 3th, 2024, and July 18th, 2024), respectively. Out of six identified SR, the review by Dinnes et al., covering the research questions on both ultrasound and PET/CT, was selected. (Dinnes 2019, Jiménez-Requena 2010, Rodríguez Rivera 2014, Schröder-Günther 2012, Xing 2011, Zamani-Siahkali 2024) The search of the selected SR by Dinnes et al. 2019 was updated for the staging with ultrasound and PET/CT (final search dates of the SR were 2016). (Dinnes 2019) Cochrane Library (Cochrane Reviews and Trials), Medline Ovid, and Embase (search dates July 26th, 2024, July 3th, 2024, and July 18th, 2024), respectively, were searched to identify studies on the diagnostic test accuracy of ultrasound and PET/CT in patients with primary melanoma pre-SLNB. The primary studies identified in the SR of Dinnes et al., 2019 for the ultrasound and PET/CT questions were also extracted. For this KCE review, two studies from the SR were excluded as they included patients with positive lymph nodes detected on clinical examination. Searches identified 2807 potentially relevant references (see Figure 8 in the Appendix).

After deduplication, 1957 references remained. Based on title and abstract 1893 references were excluded. Of the remaining 65 references 43 were excluded with reason (see Table 23 in the Appendix). A final 22 studies were included. Two studies concerned ultrasound as well as PET/CT. (Hinz 2013, Stahlie 2021) Thirteen studies described the use of ultrasound. (Chai 2012, Hinz 2013, Hinz 2011, Hocevar 2004, Kunte 2009, Olmedo 2017, Sanki 2009, Sibon 2007, Stahlie 2021, Thompson 2021, van Rijk 2006, Verver 2018, Voit 2014) Of the thirteen studies, 4 studies were newly identified. (Olmedo 2017, Stahlie 2021, Thompson 2021, Verver 2018) Eleven studies were selected for the use of PET/CT. (Arrangoiz 2012, Avilés Izquierdo 2020, Cheng 2021, Hinz 2013, Kell 2007, Klode 2010, Maubec 2007, Revel 2010, Singh 2008, Stahlie 2021, Wagner 2012) Of these 11 studies, three studies were new. (Avilés Izquierdo 2020, Cheng 2021, Stahlie 2021)

3.4 Evidence

3.4.1 Included studies and methodological quality

The 22 included studies provided data for a total of 6259 study participants. All studies reported on a per patient analysis (per lesion analysis excluded) as defined by the PICO. All studies considered the use of imaging for the detection of nodal or distant metastasis. Thirteen studies, including 5758 participants, considered the use of ultrasound for N staging. A total of 501 participants contributed data for the staging with PET/CT. The overall methodological quality of all included studies is summarised in Figure 9 for ultrasound and in Figure 10 for PET/CT studies (both available in Appendix). Studies were generally at low or unclear risk of bias with more unclarity for the PET/CT studies on the index test (PET/CT). This was mostly due to limited information on the criteria for the detection of metastases (qualitative or quantitative) and the interpretation of the PET/CT. The prospective ultrasound studies identified through the updated review were at low concern for bias and applicability. (Olmedo 2017, Stahlie 2021, Thompson 2021, Verver 2018)

The evidence tables for the newly included primary studies and the SR of Dinnes et al., 2019, are presented in Appendix 3.5.2. The primary studies evidence tables included in the SR can be



consulted directly in the SR.(Dinnes 2019) Evidence tables on outcomes not reported in the SR are presented in Appendix 3.5.3.

3.4.2 Primary N staging with imaging

3.4.2.1 N staging by ultrasound

The updated search included a large prospective study with 2263 participants, a medium sized retrospective study with 384 participants and two small studies, a prospective study with 58 patients (accrual was halted early due to low sensitivity at interim analysis), and a prospective study with 23 participants also addressing PET/CT.(Olmedo 2017,Stahlie 2021,Thompson 2021,Verver 2018)

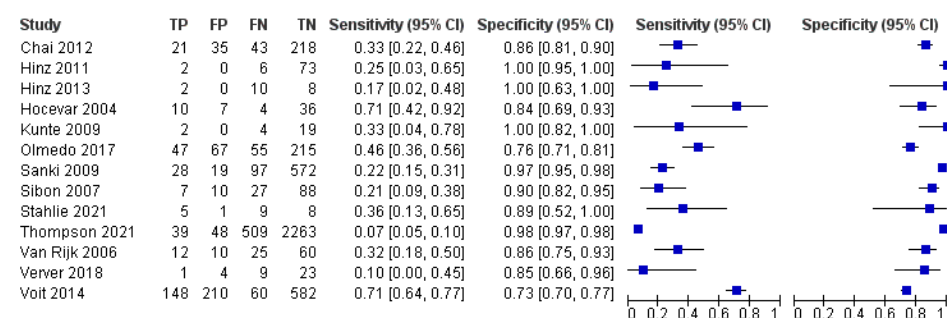
The combined results from the SR of Dinnes et al. 2019 for the detection of nodal metastasis by ultrasound (based on 11 studies), presented a sensitivity of 35.4% and a specificity of 93.9% (Table 29).(Dinnes 2019)

ACCURACY OF ULTRASOUND

The pooled estimates for the final 13 studies for the detection of any nodal metastases (including microscopic metastasis) with ultrasound versus histology in patients planned for SLNB gave a summary sensitivity of 28.8% (18.6%-41.7%) and a specificity of 91.7% (86.2%-95.2%)(Figure 3 and Figure 11).

Heterogeneity for sensitivity was large across the ultrasound studies from 7% to 71%. The sensitivity was below 40% for most studies and ranged from 7% in Thompson 2021, a prospective large study, to 36% in Stahlie 2021. Three studies had higher sensitivities, which cannot be explained by the data in the publications, 46% in Olmedo 2017, and 71% in Hocevar 2004 and Voit 2014. The study by Olmedo was retrospective and had a cost-evaluation focus. The older studies by Hocevar and Voit both had an unclear design. In terms of specificity, the studies applying ultrasound before and after the use of lymphoscintigraphy had the highest specificity (up to the 100% specificity observed).

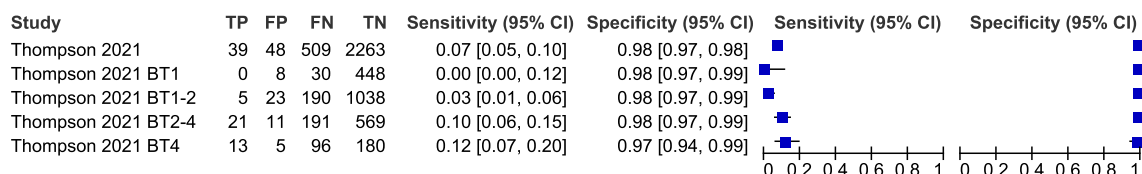
Figure 3 – Forest plot primary N staging (per patient) with ultrasound



ACCURACY OF ULTRASOUND BY BRESLOW THICKNESS (BT)

Results were only available for the large prospective study.(Thompson 2021) A total of 548 (17.4%) patients had nodal metastasis. The overall sensitivity was 7.1% (5.0%-9.3%) and specificity 97.9% (97.3%-98.5%)(Figure 4). The BT median value was 1.65 mm and the mean BT 2.24 mm. The prevalence of a nodal metastasis increased with the BT. In the BT1 (≤ 1.0 mm) 30 of the 486 (6.2%) participants had a nodal metastasis. In the BT1-2 (1.01 to 2mm) 195 of the 1256 (15.5%) had a nodal metastasis. For the BT2-4 (2.01 to 4mm) 222 of the 792 (28.0%) participants had a nodal metastasis, and for the BT4 (>4 mm) 109 of the 294 (37.1%) participants had a nodal metastasis. No true positive ultrasound results were present in the group of very thin (≤ 1 mm) melanomas. Ultrasound sensitivity for melanomas ≤ 2 mm in thickness was 2.2%. For melanomas >2 mm in thickness, sensitivity was 10.6%. Although still low, the sensitivity of ultrasound was considerably greater for thicker primary tumours (11.9% for tumours >4 mm, 0% for tumours ≤ 1 mm). The study also presented effectiveness of ultrasound for overall basins (3302 node basins in 2859 eligible patients) being very similar to the per patient analysis: sensitivity 6.6% (4.6%-8.7%) and specificity 98.0% (97.5%-98.5%).

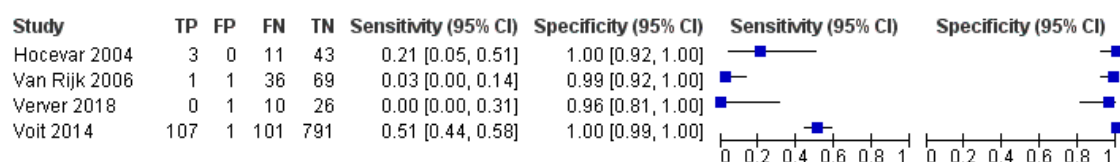
Figure 4 – Forest plot primary N staging (per patient) with ultrasound by Breslow thickness



ACCURACY ULTRASOUND COMBINED WITH FNAC

Four studies out of the 13 also presented (separate) accuracy data for ultrasound combined with FNAC (Figure 5 and Figure 12). (Hocevar 2004, van Rijk 2006, Verver 2018, Voit 2014) Only one study resulted from the updated search. (Verver 2018) This study did not detect any true-positive metastases and the sensitivity was 0%. The summary estimate therefore is the same as the SR, presenting a sensitivity of 18.0% (3.58 to 56.5) and a specificity of 99.8% (99.1 to 99.9) (Table 29).

Figure 5 – Forest plot primary N staging with US/FNAC (per patient)



TREATMENT CHANGES WITH ULTRASOUND USE

In one study, treatment was changed for five patients out of six patients for whom a lymph node was positive. The additional treatment were total lymph node dissection and/or adjuvant therapy. (Stahlie 2021)

SURVIVAL DATA

No evidence was available of the impact of ultrasound use on overall survival.

The studies confirmed that patients with macroscopic lymph node metastasis have a worse outcome than patients without macroscopic LN metastasis. Results on ultrasound-FNAC for survival from a large prospective study showed a 5-Year Kaplan–Meier estimated melanoma specific survival (MSS) of 95% for ultrasound-FNAC negative patients, compared to 59% for ultrasound-FNAC positive patients, respectively ($P < 0.001$). (Voit 2014) Balloon shape or complete loss of central echo yielded a 59% 5-year Kaplan–Meier estimated MSS, compared to 96% when no malignant or suspicious findings were seen on ultrasound ($P < 0.001$). (Voit 2014)

COST-EFFECTIVENESS OF ULTRASOUND USE

The medium sized retrospective study with 384 participants focused on cost-effectiveness. (Olmedo 2017) Nevertheless, the quality of the evidence was considered very poor e.g. the ICER is incorrectly measured and the negative incremental effectiveness is not explained.

RESULTS FOR ANY TEST BURDEN, COMPLICATIONS, QUALITY OF LIFE

No results were presented in the studies with ultrasound.



3.4.2.2 N staging by PET/CT

Three new small sized-studies were identified with the updated search.(Avilés Izquierdo 2020,Cheng 2021,Stahlie 2021) One prospective study with 23 participants, and two retrospective studies with 92 and 79 participants, respectively.

The SR by Dinnes et al. retrieved eight studies of PET-CT before SLNB, four were conducted in a population of '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).(Singh 2008)

A summary estimate for all eight included studies was not presented in the SR. Instead, the SR summary estimate only included the 4 studies with 'any participant eligible for SLNB' stating a sensitivity of 10.2% (4.3%-22.3%) with a summary specificity of 96.5% (87.1%-99.1%). Their analysis included 170 participants and 49 confirmed cases of nodal metastasis.

ACCURACY OF PET/CT

The pooled estimates for the 11 studies resulted in a sensitivity and specificity of 18.1% (9.9%-30.7%) and 95.4% (88.8%-98.2%)(Figure 6 and Figure 13). The accuracy by thickness was presented in one study (Figure 7).(Cheng 2021) The number of participants (n=92) was limited and no true positive results were detected in the thin melanoma groups.

Figure 6 – Forest plot primary N staging with PET/CT (per patient)

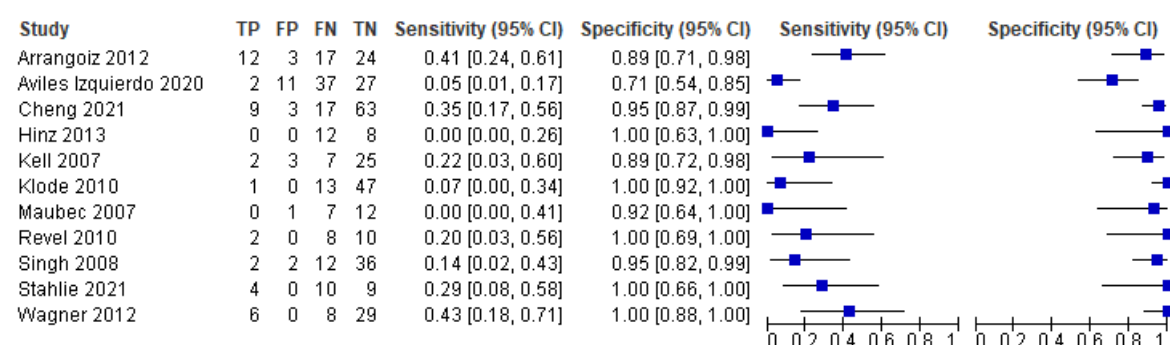
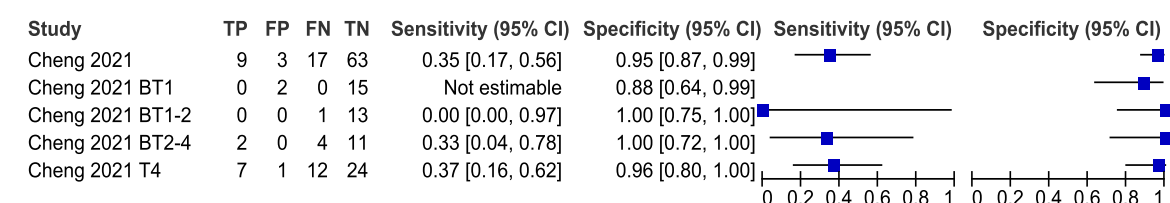


Figure 7 – Forest plot primary N staging with PET/CT (per patient) by Breslow thickness



TREATMENT CHANGES

For the small prospective study with 23 participants, all metastases were nodal (5 out of 6 detected by US and 4 out of 6 detected by PET/CT) and therefore treatment was altered to lymph node dissection and all but one also received adjuvant therapy.(Stahlie 2021) In a second study, six patients (11%) proceeded directly to therapeutic lymph node dissection due to the preoperative PET/CT findings.(Arrangoiz 2012)

SURVIVAL

No results were presented in the studies with PET/CT.

RESULTS FOR ANY TEST BURDEN, COMPLICATIONS, QUALITY OF LIFE, COST-EFFECTIVENESS

No results were presented in the studies with PET/CT.

3.4.2.3 Conclusions on N staging

The evidence reviewed showed that in a population of patients with a primary melanoma without signs of metastases on clinical examination, all imaging for N staging (ultrasound with or without FNAC, and PET/CT) had poor sensitivity (Table 7). Less than a third of people with nodal metastases diagnosed with lymph node biopsy were detected with the imaging modality. However, all summary specificities were higher than 90%. Heterogeneity of sensitivity was high between the studies on ultrasound. The visual interpretation of the forest plot might therefore be preferred over the summary statistic.

Only one study presented sensitivities by Breslow thickness; for the thin melanomas, the sensitivities were very low: 2.2% for melanoma ≤ 2 mm in thickness. Although still low, the sensitivity of ultrasound was considerably greater for thicker primary tumours, 10.6% for melanomas > 2 mm in thickness, 11.9% for > 4 mm thickness.

When the ultrasound data are translated to a hypothetical cohort of 1000 people eligible for SLNB, 246 of whom have nodal metastases (median prevalence), applying ultrasound potentially allows 71 people with nodal metastases to be identified directly (Table 31). For ultrasound with FNAC (N confirmation on biopsy), potentially 25 people with nodal metastases can be identified directly (Table 32). With PET/CT for N staging potentially two in eleven patients with a positive N will be identified (Table 33).

Table 7 – Summary of findings for ultrasound and PET/CT for N staging

Test	No. of studies (No. of patients)	Sensitivity (95% CI)	Specificity (95% CI)
<i>Ultrasound</i>	13 (5758)	28.8 (18.6-41.7)	91.7 (86.2-95.2)
<i>Ultrasound by BT</i>	1 (2828)	7.1 (5.0-10.0)	97.9 (97.0-98.0)
<i>BT1</i>	(486)	0.0 (0.0-12)	98.2 (97.0-99.0)
<i>BT1-2</i>	(1256)	2.6 (1.0-6.0)	97.8 (97.0-99.0)
<i>BT2-4</i>	(792)	9.9 (6.0-15.0)	98.1 (97.0-99.0)
<i>BT4</i>	(294)	11.9 (7.0-20.0)	97.3 (94.0-99.0)
<i>Ultrasound + FNAC</i>	4 (1201)	10.3 (1.5-46.3)	99.4 (97.0-99.9)
<i>PET-CT</i>	11 (501)	18.1 (9.9-30.7)	95.4 (88.8-98.2)

Conclusions on N staging:

For patients with a primary melanoma without signs of metastases on clinical examination (in a population with a N prevalence of 25%)

- Ultrasound for N staging has a high specificity of 92%. (moderate level of evidence)
- Ultrasound for N staging has low sensitivity and may detect 29% of patients with a positive N. (low to moderate level of evidence)
- Ultrasound with FNAC for N staging may detect one in ten patients with a positive N with a high specificity. (low level of evidence)
- PET/CT for N staging may detect two in eleven patients with a positive N with a high specificity. (very low level of evidence)



- The impact of N staging with ultrasound or PET/CT on the general burden, complications, quality of life, or survival was not described in the diagnostic studies.
- The impact of N staging with ultrasound or PET/CT on cost-effectiveness was not reliably described in the diagnostic studies.

3.4.3 Primary M staging with PET/CT

Of the eleven studies selected for PET/CT, five studies reported on the detection of distant M metastases. (Arrangoiz 2012, Avilés Izquierdo 2020, Maubec 2007, Stahlie 2021, Wagner 2012) Two studies were an update of the systematic review. (Avilés Izquierdo 2020, Maubec 2007, Stahlie 2021, Wagner 2012)

The prevalence of M metastasis was low or absent. Three studies did not detect a M: a small prospective studies (n=23) characterised by 48% pT4b (Stahlie 2021), another small prospective study (n= 25) with pT4 for 100% of participants (mean BT 6.6 mm (4.8-12.5))(Maubec 2007), and a retrospective study (n= 79) with pT4 for 25.3% (Avilés Izquierdo 2020). One M was detected in the retrospective study with 48 participants (pT4 60%)(Wagner 2012), and five M (8.9%) in a retrospective study with 56 participants (pT4 100% median BT 6 (4.1-40)). This last study included participants with melanomas of at least 4 mm thickness. (Arrangoiz 2012) The prevalence of N and M combined metastases in this study was 57% with five (8.9%) patients M-positive, identified at preoperative PET/CT.

ACCURACY

The sensitivity for detecting distant M metastases with PET/CT was 100% (48%-100%) and the specificity 94% (84%-99%)(reference standard was biopsy). This result is based on the one study with five M in a population of pT4 of at least 4 mm. (Arrangoiz 2012)

The systematic review by Dinnes et al studied the detection of metastasis at first diagnosis and at recurrence for CT and PET/CT. (Dinnes 2019) The authors concluded that results might not be reliable as studies were very small.

RESULTS FOR ANY BURDEN OF THE PET/CT

Results for investigations of false positives: in one study eight patients underwent invasive examinations (endoscopy, bronchoscopy, ultrasound guided biopsy) to determine the very cause of PET/CT findings. Four of these patients were incidentally diagnosed with another primary tumour (adenocarcinoma of the colon (2), lung carcinoma, neuroendocrine tumour). (Avilés Izquierdo 2020) Another study investigated three patients for positive foci in distant sites but none of these foci represented a true metastasis (MRI for orbital focus, two needle aspiration biopsies for a nodule of the thyroid gland, hepatic MRI for liver focal increased uptake). (Maubec 2007) In another study, a total of 14 incidental findings not suspicious of melanoma were detected. Three patients had non-specific nodes in the lung which required follow-up. (Stahlie 2021) In five other patients findings needed further diagnostic examination. (Stahlie 2021) Finally, PET/CT identified incidental findings in 35% (n=20) of participants that required further evaluation (mediastinal lymphadenopathy, lung, colon, and thyroid lesions). (Arrangoiz 2012)

TREATMENT CHANGES

Systemic chemotherapy (temozolomide) was added in 7% (n=5) of patients due to the finding of metastatic disease. (Arrangoiz 2012) Nowadays, with the available improved therapy, early detection of distant metastasis has become of more relevance.

3.4.3.1 Conclusions on M staging

The evidence retrieved on the detection of distant metastasis by PET/CT (M staging) in a population with a primary melanoma was very limited. None of the newly identified studies for this population detected true-positive distant metastases. The sole study (included in the SR) reporting more than 1

true-positive PET/CT metastases included participants with melanomas of at least 4 mm thickness. For this study in high risk patients, the sensitivity for detecting distant metastases with PET/CT was 100% (48%-100%) and the specificity 94% (84%-99%).

Conclusions on M staging:

For patients with a primary melanoma without signs of metastases on clinical examination

- **Whole-body PET/CT for M staging may have little benefit in patients with a primary melanoma of 4 mm thickness and more, and may have no benefit for thinner lesions but the evidence is very uncertain. (very low level of evidence)**
- **The impact of M staging with PET/CT on complications, quality of life, survival, or cost-effectiveness was not described in the diagnostic studies. False positive results for PET/CT were common and this will affect the quality of life of patients.**

3.5 Evidence to recommendations

3.5.1 Balance between clinical benefits and harms

A diagnostic test or strategy that improves patient-important outcomes will require the availability of effective treatment, reduction of test related adverse effects or anxiety, or improvement of patients' wellbeing from prognostic information. (Schünemann 2008)

A SLNB involving general anaesthesia and surgery may cause anxiety. The SLNB-procedure's complications that have been described are infections, seroma and lymphedema. (Moody 2017) Nevertheless, for a correct staging a confirmation biopsy is needed and currently performed for melanomas stage pT1b and higher. Adverse effects of ultrasound are limited and the procedure is easily planned within a short timeframe. Pathological confirmation by fine-needle aspiration can cause anxiety, pain, and infection. The GDG pathologists stated that a histology sample from a biopsy is preferred over a needle aspiration cytology sample as the quality is often insufficient.

PRIMARY N STAGING WITH ULTRASOUND

When staging 1000 patients with ultrasound based on a lymph node positivity prevalence of 24.6% (see Table 31 for the calculation of numbers), the following scenarios are hypothesised.

True Positives (71/1000)	The suspected lymph node on ultrasound is biopsied and is positive. Management changes because of upstaging to stage III: • a pathological confirmation is performed and is positive • neoadjuvant treatment may be offered • M staging is performed and immediate systemic treatment is started if positive.
False Positives (63/1000)	The suspected lymph node on ultrasound is biopsied and is negative. A sentinel node scintigraphy is performed for stage $\geq$ pT1b melanomas. The pathological confirmation is negative: final stage I-II. M staging may be considered for thick lesions. Test related anxiety will have been caused. Discomfort of biopsy.
True Negatives (691/1000)	A sentinel node scintigraphy with biopsy is performed for stage $\geq$ pT1b melanomas and is negative: Final stage I-II. Ultrasound was an unnecessary extra investigation. M staging may be considered for thick lesions.
False Negatives (175/1000)	A sentinel node procedure with biopsy is performed for stage $\geq$ pT1b melanomas and is positive. Ultrasound was an unnecessary extra investigation. False negatives are unavoidable as ultrasound will only identify macroscopic disease, for microscopic disease a SLNB is always needed.



The experts agreed that the balance between clinical benefits and harms was in favour of performing an ultrasound for N staging and this for stages from pT1b and higher but that a confirmation biopsy still had to be performed. Experts considered the clinical benefit for very thin lesions and thin lesions without ulceration (in situ and pT1a) very low because of the very low prevalence of radiologically detectable lymph node metastasis in this group. The validation review reinforced the need for correct staging by biopsy (as presented for each scenario in the table above) even after a positive ultrasound. The final recommendations by KCE was not to recommend ultrasound for N staging.

PRIMARY N STAGING WITH [¹⁸F]FDG PET/CT

The experts considered FDG-PET/CT not useful in the evaluation of regional metastases. The burden of the test is considerable with anxiety and psychological distress due to the high number of patients incorrectly classified as having a nodular metastasis and needing further investigations. The final recommendations by KCE was not to recommend ultrasound for N staging.

PRIMARY M STAGING WITH [¹⁸F]FDG PET/CT

The consensus advice for lesions with pT3b and pT4 in international practice guidelines is to offer whole-body PET-CT (and brain MRI).

The evidence reviewed showed that whole-body PET/CT for M staging may have little benefit in patients with a primary melanoma of at least 4 mm thickness and may have no benefit for thinner lesions but the evidence is very uncertain, which questions whether the reported results are in fact true. For the T stages up to pT3a and especially for the thinner lesions, performing whole-body PET/CT will lead to a high number of false positives and also result in a high number of investigations for incidental findings (benign and other lesions).

The experts stated that M staging with PET/CT can have some clinical benefit for stage pT2 and pT3 among patients with node-negative disease, especially when other risk factors are present such as ulceration, and advised a conditional recommendation in favour. Experts agreed that for lower stages PET/CT was considered not of clinical benefit. For the higher stages pT3b, pT4a, and pT4b, experts agreed that the balance was in favour of PET/CT.

Experts stressed the importance of checking the location of the melanoma prior to PET/CT imaging and to adjust the patient's position and field of view of the PET/CT accordingly (especially for acral melanomas). In the case of a melanoma on the lower legs, scanning should be done from head to toes; and in the case of a melanoma of the forearm or hand, the patient should keep the arms alongside the body during PET acquisition.

The final recommendations by KCE after the validation was to conditionally recommend whole-body PET/CT for M staging in line with the international consensus for stage pT3b and stage T4 as the evidence is very uncertain. The patients should be informed about the implications of false positives.

3.5.2 Quality of evidence

There was a disappointing lack of evidence on the accuracy of imaging in people with a diagnosis of primary melanoma at the time of staging. Studies were small in general except from the ultrasound-study by Johnson 2021 and Voit 2014, resulting in wide confidence intervals. Studies were generally at low or unclear risk of bias and of high or unclear concern regarding applicability of the evidence.

The PET/CT studies were often unclear on the index test (PET/CT). This was mostly due to limited information on the criteria for the detection of metastases (qualitative or quantitative) and the interpretation of the PET/CT. The prospective ultrasound studies identified through the updated review were at low concern for bias and applicability. (Stahlie 2021, Thompson 2021, Verver 2018)

The quality of the evidence can be summarised as follows: low to moderate for ultrasound; low for ultrasound-FNAC; very low for PET/CT.

3.5.3 *Patient preferences*

Ultrasound is accessible and patient-friendly.

3.5.4 *Cost and resource allocation*

The evidence presented on cost in one study for ultrasound was considered of serious limitations and of very low quality.

Providing an ultrasound is accessible and not costly. Nevertheless, the radiologist or clinician should be experienced as the interpretation of the examination is very dependent on the performer as well as his experience. Training will take time and might be costly.

A more intense use of PET/CT for staging at an earlier stage will be more costly to the healthcare system and to the patient. Transport cost to the hospital will vary depending on the distance and availability of public transport. This may vary by region and medical insurance of the patient.

In Belgium PET/CT for staging of a melanoma is reimbursed from stage IIC onwards. The Belgian law stipulates that a PET/CT provided to a patient for staging of a primary melanoma is reimbursed for stage IIC and higher (see website link [French](#) and [Dutch](#) article 2, point 1. 2) d). This translates to a tumour with a pathological stage T4= >4.0mm thickness and with ulceration.



4 SURGICAL RE-EXCISION MARGINS FOR STAGE I-II

4.1 Recommendations surgical re-excision margins

<i>Recommendations on surgical re-excision margin* for patients with a stage 0 – II primary melanoma</i>	Strength of recommendation	GRADE certainty of evidence
<i>Clinicians may apply a surgical margin* of 0.5 cm when excising melanoma in situ.</i>	Conditional [∞]	Low
<i>Clinicians may apply a surgical margin* of 1 cm when excising a melanoma with Breslow thickness up to 2 mm or when a 2 cm excision margin would cause unacceptable disfigurement or morbidity.</i>	Conditional [∞]	Low
<i>Clinicians should apply a surgical margin* of 2 cm when excising a melanoma with Breslow thickness above 2 mm.</i>	Strong	Moderate

[∞]Conditional on individual benefits and harms evaluation; *the re-excision margin includes the initial excision margin

Clinical practice guidance:

Histopathological margin reporting of the primary resection specimen

- For the primary excision specimens, the resection margins are reported as “excision complete” or “excision incomplete”, or as “margins cannot be evaluated” when assessment is not possible. Ideally, when histopathological margins are negative, the distance to the nearest margin should be specified in millimetres. Furthermore, if the resection margins are positive in an oriented specimen, the specific location of margin involvement should be documented.
- For future reference, a standardised national reporting system for histopathological assessments will become available for consultation on the Belgian Society of Pathology’s [website](#).

4.2 Introduction

Surgical resection of a primary melanoma remains the first step in the treatment and the staging of local disease. The wide local excision (re-excision after a first removal of a lesion for diagnosis) was designed to eliminate satellite cancer cells and reduce recurrences, ultimately to improve survival. The wide removal of the skin around the melanoma including the subcutis aimed to halt the progression of the cancer to the draining lymph nodes and further into the bloodstream. (van Akkooi 2025)

Seven RCTs (Table 8) studying the margins for surgical resection have been completed. None of these prospective RCTs have shown a benefit for overall survival of a wide margin over a small margin. (Balch 2001, Balch 1993, Bergenmar 2010, Cascinelli 1998, Cohn-Cedermark 2000, Gillgren 2011, Hayes 2016, Karakousis 1996, Khayat 2003, Moncrieff 2018, Newton-Bishop 2004, Ringborg 1996, Thomas 2004, Utjes 2019, Veronesi 1991, Veronesi 1988)

Several systematic reviews reviewed the data and reported no significant difference between narrow and wide excision margins for locoregional or distant recurrence, metastasis, death, or death due to melanoma. (Haigh 2003, Hanna 2021, Lens 2007, Sladden 2009, Wheatley 2016) Wide margins (2–5 cm), historically common, lead to complications and a higher need for surgical reconstruction. As a result, the interest in evidence for reducing margins as much as possible remains high.

Table 8 – RCTs on margins for resection of a primary melanoma

Trial	Year started	Thickness	Margins
WHO trial	1980	<2mm	1cm vs 3cm
European trial	1981	<2.1mm	2cm vs 5cm
Swedish trial I	1982	>0.8mm to ≤2mm	2cm vs 5cm
Intergroup trial	1983	1-4mm	2cm vs 4cm
Swedish trial II	1992	≥2mm	2cm vs 4cm
UK MSG trial	1993	>2mm	1cm vs 3cm
MelMarT trial	2015	>1mm	1cm vs 2cm

Currently, narrow margin excisions of not more than 2 cm are recommended by most national guidelines with smaller margins for thin lesions. International guidance for the surgical resection margins of a primary melanoma is presented in Table 9.

Table 9 – International recommendations surgical resection margins

Breslow thickness in mm	≤ 1	1.01 – 2.00	2.01 – 4.00	> 4
UK (NICE 2022)(NICE 2022)	1cm	1 – 2cm	≥ 2 m	≥ 2cm
US (NCCN 2025)(Swetter 2025)	1cm	1 – 2cm	2cm	2cm
Australia(Sladden 2018)	1cm	1 – 2cm	1 – 2cm	2cm
Canada(Wright 2019)	1cm	1 – 2cm	2cm	2 m
Belgium*	1cm	1 – 2cm	2cm	2cm
Netherlands(Veerbeek 2013)	1cm	1cm	2cm	2cm
Germany(Pflugfelder 2013)	1cm	1 m	2cm	2cm
France(Institut National du Cancer République Française 2024)	1cm	1-2cm	2cm	2cm
ESMO 2025(Amaral 2025)	1cm	1 m	2cm	2cm

*protocol UZ Brussel (UZ Brussel 2021)

New evidence will be forthcoming from the ongoing MelMarT-II trial which started in 2019 including patients with pT2b-pT4 comparing 2cm versus 1cm. This trial aims to answer if continued use of the 2cm wide excision margin for intermediate and high-risk primary cutaneous melanomas is appropriate. Two other studies (WoW in Sweden and NORMA in Australia) are exploring if a re-excision can be avoided for thin melanomas (≤1 mm Breslow thickness)(single- vs two-staged excisions).(van Akkooi 2025,Wennberg 2025,Zijlker 2023)

We identified the NICE 2022 guideline as a recent, relevant, and credible source that addressed the surgical excision margins for primary melanoma.(NICE 2022) Given the absence of new primary evidence since its publication (see evidence section below), we undertook an ADAPTE procedure to assess its relevance to the Belgian healthcare context and to formulate locally applicable, GRADE-based recommendations.

4.3 Research question and search

This chapter addresses the research questions on the width of surgical resection margins in patients with a primary cutaneous melanoma without clinical signs of N or M metastases. The experts were especially interested in new evidence to support the use for smaller margins. The research question was adopted from the NICE 2022 guideline: *What are the most effective surgical and histological excision margins for stage 0 to II melanoma?* The research question was translated into PICO (see Table 34 in the appendix).



STUDY IDENTIFICATION AND SELECTION

A search for recent systematic reviews addressing the research question, identified the evidence review for the NICE melanoma guideline 2022 update, and a SR published in 2021.(Hanna 2021,NICE 2022) The NICE search was performed at a more recent date than the SR by Hanna et al. and was selected for an update.

The search (final search dates of the NICE review was 3th January 2021) was updated for the Cochrane Library (Cochrane Reviews and Trials), Medline Ovid, and Embase (search dates 19th February 2025, 31th January 2025, 19th February 2025, respectively). New randomised primary studies on the resection margins for primary melanoma were not identified in this updated search (PRISMA in Figure 8, available in Appendix 4.2.4).

The evidence is based on the studies identified in the NICE guidelines review as no new studies were identified by the updated search. As a result, the recommendations from the guideline were adapted to the Belgian situation. Four studies compared a 2cm margin versus either 4cm or 5cm margins. As the larger margins are no longer clinical practice in Belgium and the interest of the experts was in evidence for reducing margins, the details of those 4 studies are not presented here. The full report can be consulted in the NICE evidence review.(NICE 2022)

4.4 Evidence

The seven primary studies identified by the NICE review are summarised in Table 10. The NICE review identified a further publication of a Swedish study on quality of life with limited details which they considered at very high risk of bias.(Bergenmar 2010) We evaluated this publication again. The presented data originated from the Swedish study described by Utjés et al.(Utjés 2019) It was therefore not included as primary study for this report but considered part of the study by Utjés et al.

The NICE review did not provide a meta-analysis of the 7 RCTs due to the heterogeneity of interventions ranging from 1 to 5cm margins. The evidence tables for each study are presented in the NICE evidence review summary. The quality of the RCTs ranged from very low to moderate (Table 10).

Table 10 – Trial characteristics surgical resection margins

Trial	Year started	Inclusion criteria	Margins	N patients	Follow-up time
WHO trial(Cascinelli 1998,Veronesi 1991,Veronesi 1988)	1980	Thickness ≤2mm; excluded: face, toes, fingers, excision > 6weeks, >65y, satellite nodule	1cm vs 3cm	612	5 years
European /French trial (Khayat 2003)	1981	Thickness <2mm; excluded toes, fingers, nails, >69y	2cm vs 5cm	337	16 years
Swedish trial I(Cohn-Cedermark 2000, Ringborg 1996)	1982	>0.8mm ≤2mm; excluded fingers, feet, face	2cm vs 5cm	989	11 years
Intergroup trial(Balch 2001,Balch 1993,Karakousis 1996)	1983	1-4mm, 2 groups: trunk or proximal extremity; distal extremity or head and neck	2cm vs 4cm	470	10 years (median)
Swedish trial II(Bergenmar 2010,Gillgren 2011,Utjés 2019)	1992	≥2mm; <75y, excluded hands and feet, head and neck	2cm vs 4cm	936	6.7 years (median)
UK MSG trial(Hayes 2016,Newton-Bishop 2004,Thomas 2004)	1993	≥2mm; excluded feet and hands	1cm vs 3cm	900	8.8 years (median)
MelMarT Pilot trial(Moncrieff 2018)	2015	>1mm; staged at the same operation with SLNB	1cm vs 2cm	400	Up to 12 months

Source: results adapted from the review by NICE

4.4.1 1cm versus 2cm surgical margins

The ongoing MelMarT trial, studying participants with a melanoma >1mm, reported early results on quality of life and adverse events at 12 months post-randomisation.(Moncrieff 2018) The MelMarT trial outcome assessment was unblinded and it was unclear how analysis was undertaken as details were not provided.

QUALITY OF LIFE

At 12 months, there was no difference in quality of life or neuropathic pain data in any domain between the 1 and 2cm groups (measured 'unblinded' using the FACT-M questionnaire). The quality was assessed as low.

ADVERSE EVENTS

Reconstruction surgery was significantly less common in the narrow margin group (Table 11). There were no differences for adverse events between the two margins (Table 11). The results for local and regional recurrence and overall survival have as yet not been reported.

Table 11 – Summary of findings MelMarT trial at 12 months*

GRADE quality	Summary of findings
Moderate	Reconstruction surgery at 12 months post-randomisation (OR<1 favours narrow excision margin): OR 0.29 [0.18, 0.49]
Very Low	Total surgical adverse events including: wound dehiscence; haematoma; haemorrhage; wound infection; or wound necrosis post-intervention (OR<1 favours narrow excision margin): OR 0.89 [0.46, 1.70]
Very Low	Wound dehiscence post intervention (OR<1 favours narrow excision margin): OR 1.04 [0.26, 4.24]
Very Low	Haematoma (Grade I or IIIa) post intervention (OR<1 favours narrow excision margin): OR 1.57 [0.26, 9.53]
Very Low	Haemorrhage post intervention (OR<1 favours narrow excision margin): No participants experienced haemorrhage (effect size not estimable)
Very Low	Wound infection (Grade I or II) post intervention (OR<1 favours narrow excision margin): OR 1.29 [0.52, 3.20]
Low	Wound necrosis (including partial/total loss of skin graft) post intervention (OR<1 favours narrow excision margin): OR 0.14 [0.02, 1.19]

*from NICE(NICE July 2022,NICE 2022)

Conclusions:

- 1cm versus 2cm surgical margins may result in no difference in quality of life at short term but the evidence is uncertain. (low level of evidence)
- The impact of 1cm versus 2cm surgical margins on recurrence and survival is not reported in one RCT.
- Reconstruction surgery was significantly less common in the narrow margin group. (moderate level of evidence)
- 1cm versus 2cm surgical margins may result in no difference in adverse events at short term but the evidence is very uncertain. (very low level of evidence)

4.4.2 1cm versus 3cm surgical margins

Two trials studied 1cm versus 3cm surgical margins.(Cascinelli 1998,Hayes 2016,Newton-Bishop 2004,Thomas 2004,Veronesi 1991,Veronesi 1988) The UK trial studying a single, primary, localised cutaneous melanoma 2 mm or greater in thickness on the trunk or limbs (excluding the palms of the hands or the soles of the feet), where a 3-cm excision margin was possible, was considered of



moderate quality with moderate risk of bias for most outcomes. The quality of the evidence in the UK study was considered low due to protocol violation in 14% of participants.

The WHO trial studying primary melanoma on trunk or limbs (excluding fingers, toes, face) with ≤ 2 mm thickness was considered at high risk of bias and of very low GRADE quality for all outcomes reported. 12% of participants were excluded following randomisation (75/612). The outcome assessors were not blinded to study arms.

SURVIVAL

Patients with melanomas of ≥ 2 mm thickness

The overall survival for the UK trial at 68 months [IQR 35–103]) was similar in the two groups (HR for death 1.07; 95%CI 0.85 to 1.36; $P=0.6$). There were 144 deaths in the group with 1-cm margins of excision, as compared with 137 in the group with 3-cm margins of excision. The melanoma-specific survival favoured the 3-cm margin. There were 128 deaths attributable to melanoma in the group with 1-cm margins, as compared with 105 in the group with 3-cm margins (HR 1.24; 95%CI 0.96 to 1.61; $P=0.1$). At a median follow-up of 8.8 years (106 months [IQR 76-135], 494 patients had died, with 359 of these deaths attributed to melanoma. 194 deaths were attributed to melanoma in the 1cm group compared with 165 in the 3cm group (unadjusted hazard ratio [HR] 1.24 [95%CI 1.01-1.53]; $p=0.041$). A higher number of deaths overall occurred in the 1cm group compared with the 3cm group (253 vs 241), unadjusted HR 1.14 (95%CI 0.96-1.36; $p=0.14$).

Patients with melanomas of ≤ 2 mm thickness

The overall survival at 8 years in the WHO study favoured the smaller margins (OR of 0.92 95%CI 0.55, 1.56; and the larger margins at 12 years (OR 1.20 95%CI 0.76, 1.90).

RECURRENCE

The overall relative rate of locoregional recurrence in the UK trial (median follow up 60 months) was 26% higher in the narrow excision margin: HR 1.26 (95%CI 1.00 to 1.59; $p=0.05$). There were 168 locoregional recurrences (as first events) in the group with 1-cm margins of excision, as compared with 142 in the group with 3-cm margins. Sentinel node biopsy was not performed; bias arising from different rates of positive sentinel node between treatment arms was not assessed. A recurrence was within 2cm of the scar or graft; In-transit recurrence was defined as a recurrence from beyond the first 2cm of the scar or graft to the regional nodes; all locoregional recurrences were detected clinically and confirmed by biopsy. The calculation combined the rates of local or in-transit recurrence with the rate of nodal recurrence into the single primary end point measured at three years. Beyond three years it was 0.69 (95%CI 0.36 to 1.37; $P=0.30$), on the basis of only 36 events.

For the WHO study the OR of any recurrence at 8 years follow up favoured the wider excision margin: OR 1.13 (0.71, 1.78).

QUALITY OF LIFE

Quality of life was reported in the UK study and was assessed from the answers given to posted questionnaires at six time points during two years. The Hospital Anxiety and Depression (HAD), Psychosocial Adjustment of Illness Scale-Self-Report (PAIS-SR), Medical Outcomes Survey-Short Form 36 (MOS-SF36), and the Cassileth Scar questionnaires were used. The quality was rated as moderate by GRADE for all outcomes presented.

Significantly poorer mental and physical function was present one month after surgery for patients treated with the 3cm margin excision, which disappeared within 6 months. The greater difficulties experienced for the wider margin group were in their domestic (OR 3.11 (1.17–8.27)), and social roles (OR 4.22 (1.54–11.55)) but this improved over time. There were no significant differences in vocational role and extended family relations between the two margin groups at any time point. The wide and narrow margin groups did not differ in their attitude toward the quality of medical care, to treatment and to their illness ($p=0.4$). A negative perception of the scar was worse in the wider margin group compared to the narrow margin OR 5.55 (2.06–14.98).

In summary, use of a 3-cm margin of excision for melanoma is associated with significantly more morbidity than use of a 1-cm margin, but this effect disappears in 6 months. Patients treated by 3-cm excision were more likely, however, to have a persistent poor view of their scar.

The WHO study did not present results on quality of life.

ADVERSE EVENTS

The use of a 3-cm margin of excision was associated with longer hospital stay, greater use of skin grafts, and higher surgical complication rates in the UK study: total surgical complications OR 0.49 [0.32, 0.76](high quality), partial or complete graft loss post intervention OR 0.48 [0.22, 1.04](moderate quality), wound dehiscence post intervention OR 0.76 [0.28, 2.07](low quality).

The WHO study did not present results.

Conclusions:

- The use of a 3cm margin of excision is associated with significantly more morbidity than use of a 1cm margin, but this effect disappears in 6 months. (moderate level of evidence)
- The use of a 3cm margin of excision compared to 1cm is associated with significantly persistent poor view of the scar. (moderate level of evidence)
- The use of a 3cm surgical margin compared to a 1cm surgical margin probably results in no clinical meaningful benefit in overall survival. (moderate level of evidence)
- The use of a 1cm surgical margin compared to 3cm is associated with significantly less adverse events and reconstruction surgery. (moderate level of evidence)
- Overall locoregional recurrence may be higher at 3 years in the 1cm versus 3cm surgical margins group for melanomas of ≥ 2 mm thickness but not for thinner melanomas but the evidence is uncertain. (low level of evidence)

4.4.3 2cm versus 4cm surgical margins

Two studies looked at the 2cm versus 4cm margins.(Balch 2001,Balch 1993,Bergenmar 2010,Gillgren 2011,Karakousis 1996,Utjés 2019) The risk of bias for both studies was moderate.

As, the larger margins are no longer clinical practice and the interest of the experts was in evidence for reducing margins, the details of the studies is not presented here. The full report can be consulted in the evidence review for the NICE guideline.(NICE 2022)

4.4.4 2cm versus 5cm surgical margins

Two studies looked at the 2cm versus 5cm margins. The risk of bias for the studies was moderate to high.

As the larger margins are no longer clinical practice and the interest of the experts was in evidence for reducing margins, the details of the studies is not presented here. The full report can be consulted in the evidence review for the NICE guideline.(NICE 2022)



4.5 Evidence to recommendations

4.5.1 Balance between clinical benefits and harm

Wider excision margins of 4cm and 5cm were abandoned in Belgian clinical practice as the earlier studies found no significant difference for survival, disease recurrence, or metastases. At the same time, a significantly worse impact was seen of the surgery itself on outcomes in patients with wider excision margins. The experts agreed their interest was in evidence on the use of smaller margins.

The experts considered the uncertainty around the evidence (also presented in the NICE benefits and harms discussion section 1.1.11) which has resulted in varying guidelines for surgical margins of resection internationally (Table 9), from 1 to more than 2cm, depending on Breslow thickness of the primary, which translates into excision defects from 2 to 6 cm in diameter.

The experts considered the early evidence (12 months follow-up) from the pilot MelMarT trial which included patients with >1mm melanomas.(Moncrieff 2018) No significant difference was seen between those with 1cm and 2cm margins for quality of life scores or neuropathic pain. The need for reconstruction surgery was significantly greater in the 2cm excision group. The experts pointed to the ongoing MelMarT II trial including patients with pT2b-pT4, which will provide statistical powered results on long term follow-up.

The experts and patient representative agreed that narrower margins are favoured for patients in terms of cosmesis as the need for grafts and reconstructive surgery is lower. Functional and cosmetic constraints in head and neck region occasionally may lead to reduced margins.

The experts considered the NICE research recommendation on histopathological margins. Evidence might be forthcoming from the NORMA (Australia) and WoW (Sweden) trial. Standard reporting is not yet widespread in Belgium. The Belgian Society of Pathology (BSP) and the different BSP working groups with co-ordination of the [digitization working group](#) are developing a standardised national reporting system for histopathological assessments. Experts pointed out that the 'radicality' with the indication of the smallest lateral margin in mm is currently not commonly reported. The views differed between the histopathologists presented in the GDG whereas the dermatologist were in favour of reporting the margins in millimetres. The Belgian Society of Pathology representatives had started a discussion on the topic as Belgian guidance might be helpful in the future when results of the two studies become available. A prospective national RCT (named WoW=Wide or Wise) in Sweden is comparing single- vs two-staged excisions of thin melanomas ≤ 1 mm. Histopathological margins are used instead of a standardised surgical margin as the inclusion criteria. The hypothesis is that for well-defined melanomas, a clinical margin of 3-5 mm may be sufficient to ensure that the melanoma is removed with an acceptable histopathological margin (≥ 1.5 mm). Patients with a thin melanoma and a histopathological margin of ≥ 1.5 mm are enrolled. In view of the lack of evidence for the need for broader excisions in melanoma, the ongoing studies on this topic, and the importance to discuss broader excision margins case by case involving the interdisciplinary medical team and the patient, the GDG experts proposed the following options for histopathological reporting. For excision specimens, the resection margins are reported as "excision complete" or "excision incomplete", or as "margins cannot be evaluated" when assessment is not possible due to clinical, pre-analytical, or analytical factors. Ideally, when histopathological margins are negative, the distance to the nearest margin should be specified in millimetres. Furthermore, if the resection margins are positive in an oriented specimen, the specific location of margin involvement should be documented.

The experts decision agreed with the international consensus on excision margins and the NICE recommendations for re-excision for stages 0 to II melanoma were adapted as follows:

- Consider a clinical margin of at least 0.5cm when excising stage 0 melanoma. Recommendation adapted to 'excising melanoma in situ=Tis'.
- If excision for stage 0 melanoma does not achieve an adequate histological margin, discuss further management with the specialist skin cancer multidisciplinary team. Recommendation rejected.

- Use a clinical margin of:
 - 1cm when excising stage I melanoma or when a 2cm excision margin would cause unacceptable disfigurement or morbidity. Recommendation adapted to 'excising a melanoma with Breslow thickness up to 2mm'
 - 2cm when excising stage II melanoma. The clinical margin should be around the histological biopsy scar and take into account the primary melanoma margin. Recommendation adapted to 'excising a melanoma with Breslow thickness above 2.0mm'

Experts preferred the recommendations to be adapted to reflect the Breslow thickness.

4.5.2 *Quality of evidence*

All studies were RCTs. From the three RCTs considered by the experts, the UK study was of the highest quality. The MelMarT trial was marked down one level for bias because the outcome assessment was unblinded. It was also unclear how analysis was undertaken as details were not provided. Quality of life evidence was considered of low quality, evidence for reconstruction moderate quality, and adverse events of very low quality.

The WHO study was rated as high risk of bias (very low GRADE quality for all outcomes). The UK study was of moderate quality overall except for the evidence on recurrence which was of low quality, and the quality of life being of low or very low quality.

4.5.3 *Patient preferences*

The importance of patients' quality of life is considered a critical outcome. The patient representative on the GDG asked for an empathetic approach with attention to the patient's well-being in consultation with the patient, possibly in the presence of a confidant. Procedures known to cause long-term discomfort should be well considered and the pros and cons should definitely be discussed with the patient as this should also include the width of the surgical margin.

4.5.4 *Cost and resource allocation*

The NICE review did not identify evidence on cost. We did not perform a separate search for cost. The experts expressed that practice is changing fast with the introduction of neoadjuvant and adjuvant therapies. At present the uncertainty in estimates of cost-effectiveness would be high especially for the narrower margins of < 2cm. A proper cost-effectiveness estimate would need more evidence.



5 LYMPHADENECTOMY FOR MICROMETASTATIC NODAL DISEASE

5.1 Recommendation on lymphadenectomy for micrometastatic nodal disease

<i>Recommendation on completion lymphadenectomy for micrometastatic nodal disease in stage III primary melanoma</i>	Strength of recommendation	GRADE certainty of evidence
<i>Clinicians should not offer completion lymph node dissection to people with stage III melanoma and micrometastatic nodal disease detected by SLNB</i>	Strong	Low to very low

5.2 Introduction

The management of regional lymph nodes in patients with melanoma has evolved significantly over time. Sentinel lymph node biopsy (SLNB) has become the standard staging procedure for patients with clinically (including imaging) node-negative melanoma. However, the therapeutic benefit of immediate completion (or complete) lymph node dissection (CLND) following a positive SLNB has been increasingly questioned. Input from topic experts highlighted that international studies have shown no clear therapeutic advantage of CLND, while also reporting a higher risk of adverse events associated with the procedure. In this context, Belgian-specific recommendations were considered valuable to help harmonise clinical practices.

We identified the NICE 2022(NICE 2022) guideline as a recent, relevant, and credible source that addressed the indication for completion lymph node dissection in this setting. It was therefore taken as a starting point for possible adoption or adaptation of the recommendations.

5.3 Research question and search

The research question addressed in this guideline is adapted from the one present in NICE 2022 guideline(NICE 2022): *What is the effectiveness of completion lymphadenectomy for micrometastatic nodal disease in stage III melanoma?*

The PICO (see Appendix 5.1) were developed for the search.

5.4 Evidence

The NICE 2022 (NICE 2022) guideline on melanoma provided a synthesis of the available evidence regarding the research question. This included two randomised controlled trials, MSLT-II(Faries 2017) and DeCOG-SLT(Leiter 2016,Leiter 2019). To confirm the continued completeness of the evidence base, a targeted literature update was conducted as part of this ADAPTE process (see Appendix 5.2). The aim of this search was to identify any new RCTs published since the NICE 2022 guideline cut-off date. The update covered major databases, including Cochrane, MEDLINE and Embase, between April 2021 and January 2025. No new primary RCTs were found in the updated search.

5.4.1 MSLT II trial

The MSLTII(Faries 2017) trial included participants aged 18-75 years with tumour-positive SLNs identified by hematoxylin and eosin (H&E), immunohistochemistry (IHC), or reverse transcription polymerase chain reaction (RT-PCR). All participants had a life expectancy of at least 10 years and good performance status.

Randomisation was stratified based on key prognostic factors, (including Breslow thickness and presence of ulceration), method of metastasis detection (RT-PCR vs standard), and the enrolment centre.

A total of 3531 patients underwent screening, and 967 participants were randomised to the CLND group in the intention-to-treat (ITT) analysis, with 824 included in the per-protocol population (140 declined surgery). Among them, 80 patients (9.7%) were RT-PCR positive. The observation group also included 967 patients in ITT, with 931 included in the per-protocol analysis (29 declined observation).

In the observation group, patients received clinical examination every 4 months during the first 2 years, every 6 months during years 3 to 5, and annually thereafter, with ultrasound nodal assessment conducted during the first 5 years. In contrast, the CLND group underwent completion dissection within 140 days of biopsy, followed by the same clinical examination schedule, but without ultrasound nodal assessment.

The study's statistical design required 1925 participants to detect a 5% difference in melanoma-specific survival, but only 1655 patients were included in the per-protocol analysis.

REPORTED RESULTS BY OUTCOME

Melanoma-specific Survival : The MSLT-II trial found no significant difference in melanoma-specific survival at 3 years between observation and completion dissection groups (86% in both groups; adjusted hazard ratio (aHR) 1.08, 95% CI 0.88 to 1.34).

Quality of Life: No specific measurement of Quality of life is reported in the study.

Short term and long term complications: lymphoedema was substantially higher following completion dissection (24.1%) compared to observation alone (6.3%).

Disease free survival: Disease-free survival at 3 years was slightly higher in the completion dissection group (68%) compared to observation (63%) (no HR reported in the paper). Completion dissection notably improved the rate of nodal control in pathology-positive patients (92% vs. 77%; aHR 0.31, 95% CI 0.24 to 0.41) but did not significantly affect distant metastases-free survival (aHR 1.10, 95% CI 0.92 to 1.31)

5.4.2 DeCOG-SLT trial

The DeCOG-SLT trial (Leiter 2016, Leiter 2019) included patients aged 18 to 75 years with primary cutaneous melanoma of the torso, arms, or legs, and a tumour thickness of ≥ 1 mm. Inclusion required micrometastases in SLNs diagnosed by H&E or IHC, including isolated tumour cells. Patients were excluded if they had other regional or distant metastases, or nodal capsule perforation.

Randomisation was stratified by tumour thickness (≤ 2 mm vs > 2 mm), presence of ulceration, and planned adjuvant interferon therapy.

A total of 240 patients were assigned to the CLND arm (intention-to-treat), although 36 patients did not undergo the surgery. In the observation arm, 233 patients were included in ITT, of whom three ultimately received CLND. The median follow-up time reported in the initial publication was 35 months.

In both study arms, follow-up consisted of physical examination and nodal ultrasound every 3 months, along with imaging (whole-body CT, MRI, PET-CT, or chest X-ray and abdominal ultrasound) as appropriate. The CLND procedure was performed within 120 days of biopsy, and surgical complications were specifically assessed at 3 and 6 months postoperatively.

The trial was powered to detect a 10% difference in outcome, with 550 patients required, based on a one-sided 5% error margin. The primary analysis was performed on an intention-to-treat basis, with adjustments for sentinel node tumour load, Breslow thickness, ulceration, number of positive sentinel nodes, and interferon therapy.

The extended five-years follow-up results were reported in Leiter et al., 2019 (Leiter 2019), with a median follow-up of 72 months. The analytical approach remained consistent with the 2016 (Leiter 2016) publication, with continued adjustment for key prognostic variables.



REPORTED RESULTS BY OUTCOME

Survival: The DeCOG-SLT trial in 2016 and its follow-up in 2019 demonstrated no significant difference between observation and completion dissection in survival outcomes. At 3 years overall survival aHR was 1.02, 95% CI 0.68 to 1.52, at 5 years it was aHR 0.95, 95% CI 0.70 to 1.36.

Quality of life: No specific measurement of Quality of life is reported in the study.

Short term and long term complications: Serious adverse events are reported only for the CLND group (grade 3: 15/240; grade 4: 19/240),

Disease free survival: at 3 years, distant metastases-free survival (aHR 1.19, 95% CI 0.83 to 1.69), and recurrence-free survival (aHR 0.96, 95% CI 0.70 to 1.31) showed no significant difference. These findings were consistent at 5 years, with distant metastases-free survival (aHR 1.09, 95% CI 0.79 to 1.50), and recurrence-free survival (aHR 1.01, 95% CI 0.75 to 1.36) remaining comparable between groups.

Conclusions:

- **No significant difference in overall survival or melanoma-specific survival between observation (clinical, ultrasound, and other imaging when indicated) and completion lymph node dissection (CLND) at 3 or 5 years. (very low to low level of evidence)**
- **Quality of Life was not assessed in either trial.**
- **Complications were present with lymphoedema (24.1% CLND vs. 6.3% observation) in MSLT-II; adverse events were evaluated in CLND group only DeCOG-SLT. (moderate level of evidence)**
- **Slight improvement in disease-free survival with nodal control with CLND (MSLT-II) and no significant difference in distant metastases-free or recurrence-free survival in either trial. (very low to moderate level of evidence)**

5.5 Evidence to recommendations

5.5.1 Balance between clinical benefits and harms

We report on the NICE 2022 evaluation of balance between clinical benefits and harms, and the adaptation by our GDG.(NICE 2022)

5.5.1.1 NICE 2022 between benefits and harms evaluation

The NICE committee based its recommendations on evidence from two major trials (DeCOG-SLT and MSLT-II), which showed that completion lymph node dissection (CLND) did not improve overall or melanoma-specific survival in patients with micrometastatic nodal disease.(Faries 2017,Leiter 2016,Leiter 2019) While MSLT-II found a higher overall recurrence rate in the observation group, this was primarily due to increased nodal recurrences, which the committee considered an expected consequence of omitting CLND. However, they emphasised that nodal recurrences can generally be detected early through proper follow-up and managed surgically if needed, without compromising survival outcomes. The committee also highlighted the significant morbidity associated with CLND, particularly the high risk of lymphoedema (24.1% vs 6.3% at 3 years in MSLT-II). As a result, the NICE committee recommended against routine CLND, but proposed it could still be considered in specific situations—such as difficult follow-up scenarios, head and neck melanoma, or when adjuvant therapies are contraindicated.

5.5.1.2 ADAPTE of NICE 2022 benefits and harms evaluation

Our GDG agreed with the NICE assessment of the benefits and harms. However, the GDG did not support maintaining the suggestion to perform CLND in cases where follow-up is considered complex. This position is not supported by evidence and likely reflects early surgical hesitancy during initial implementation of the non-surgical approach. In current practice, the omission of CLND is well

accepted and broadly integrated into care pathways. In Belgium, structured follow-up can be adequately ensured, and CLND can still be performed if nodal recurrence is detected. Therefore, the GDG considered that follow-up complexity should no longer be a justification for upfront CLND.

5.5.2 *Quality of evidence*

Similarly to the NICE 2022 committee, we rated both the MSLT-II and DeCOG-SLT trials as having moderate risk of bias. Key concerns included significant treatment deviations—notably, a large proportion of participants in the MSLT-II surgery group did not undergo CLND, and similar though smaller crossovers occurred in DeCOG-SLT. Neither trial was blinded, which also contributed to the moderate rating, although blinding for surgery at a patient level is very complex to achieve. Additionally, differences in inclusion/exclusion criteria, particularly in DeCOG-SLT, were noted as potentially limiting generalisability.

According to NICE guidelines, GRADE quality of evidence for survival outcomes are low to very low.

5.5.3 *Patient preferences*

Patient preferences were not described in the studies used for evidence review. However, findings from the randomised controlled trials suggest a potential insight into patient values. In both trials, a substantial number of participants initially randomised to completion lymph node dissection (CLND) chose to forgo surgery and opted for observation instead, while crossover in the opposite direction was less frequent. This pattern may indicate that patients are generally more inclined to avoid CLND surgery when given the choice. The GDG patient representative approved that the removal of lymph nodes is kept to a minimum and that this procedure is only done after considering all other options, and after consultation with the patient.

5.5.4 *Cost and resource allocation*

Similarly to the NICE 2022 committee we did not identify any published economic evidence in our review. Since most surgical teams have already moved away from routine CLND following trial results, the recommendations are not expected to have a significant resource impact. The limited use of CLND could potentially lead to cost savings.



6 IMMUNOTHERAPY AND TARGETED THERAPY FOR RESECTABLE STAGE IIB-IV MELANOMA

6.1 Recommendations on (neo-)adjuvant immunotherapy and targeted therapy

In patients with stage IIB-C, III or resectable stage IV, surgery remains the cornerstone of treatment. However, to reduce the risk of recurrence, immunotherapy or targeted therapy have been suggested, in the adjuvant setting or, in case of clinically detectable lymph nodes or resectable stage IV disease, in the neoadjuvant setting.

Both adjuvant and neoadjuvant therapy have shown a benefit in recurrence-free survival. However, given the uncertainty around the effect on overall survival, the substantial toxicity and costs and the expected variability in patient preferences, we did not formulate a strong but a conditional recommendation in favour of (neo-) adjuvant immunotherapy and targeted therapy.

Recommendations on adjuvant immunotherapy for persons with completely resected stage IIB to IV primary melanoma	Strength of recommendation	GRADE certainty of evidence
Clinicians may prescribe adjuvant immunotherapy with nivolumab or pembrolizumab monotherapy in patients with completely resected stage IIB-C, stage III ¹ or stage IV cutaneous melanoma ^{2,3}	Conditional [∞]	Low
Clinicians should not use combination immunotherapy in the adjuvant setting for resected stage IIB-C, stage III or stage IV cutaneous melanoma	Strong	Moderate

¹Only applicable if at least one lymph node metastasis larger than 1mm.

²Ipilimumab is currently not reimbursed in the adjuvant setting in Belgium.

³In the adjuvant setting, nivolumab (monotherapy) is reimbursed in stage III or completely resected stage IV melanoma; pembrolizumab (monotherapy) is reimbursed for completely resected stage IIB-C or III melanoma.

[∞]Conditional on individual benefits and harms evaluation.

Recommendations on adjuvant targeted therapy for persons with a stage IIB/C or III primary melanoma with BRAF mutations	Strength of Recommendation	GRADE certainty of evidence
Clinicians should not offer vemurafenib as adjuvant therapy to patients with stage IIB/C or-III melanoma with BRAF mutations	Strong	Very low
Clinicians may prescribe ¹ dabrafenib plus trametinib in patients with resected stage III ² cutaneous melanoma with BRAF V600E mutations ³	Conditional [∞]	Moderate

¹In Belgium, dabrafenib plus trametinib in the adjuvant setting is only reimbursed for stage III melanoma.

²Only applicable if at least one lymph node metastasis larger than 1mm.

³For other BRAF mutations, the evidence is more uncertain.

[∞]Conditional on individual benefits and harms evaluation.

Recommendations on neoadjuvant therapy for persons with clinically detectable resectable stage III or resectable stage IV melanoma	Strength of Recommendation	GRADE certainty of evidence
<i>In patients with clinically detectable stage III melanoma, clinicians may prescribe neoadjuvant treatment with ipilimumab plus nivolumab¹, followed by surgery and response-driven adjuvant therapy:</i> <i>no further adjuvant therapy in patients with major pathological response²</i> <i>subsequent adjuvant nivolumab or dabrafenib plus trametinib (in case of BRAF V600E mutation) in patients without major pathological response[*]</i>	Conditional [∞]	Low
<i>In patients with clinically detectable stage III or resectable stage IV melanoma, clinicians may prescribe neoadjuvant pembrolizumab, followed by surgery and adjuvant pembrolizumab</i>	Conditional [∞]	Low

¹The dosing used in the phase III RCT was ipilimumab 80mg and nivolumab 240mg.

²Major pathological response is defined as ≤ 10% residual viable tumour.

[∞]Conditional on individual benefits and harms evaluation.

POLICY RECOMMENDATION



To RIZIV/INAMI

We advise the Commissie toegemoetkoming geneesmiddelen / La Commission de remboursement des médicaments to take reimbursement of neoadjuvant ipilimumab plus nivolumab, and pembrolizumab into consideration for patients with clinically detectable resectable stage III or resectable stage IV melanoma. We refer to KCE report 252 on the use of off-label drugs.

6.2 Introduction

Although complete surgical resection of primary melanoma has curative intent, patients with stage IIB-C, III or resectable stage IV disease have a high risk of local or distant recurrence. To prevent recurrence and prolong overall survival, several immunotherapeutic agents and targeted therapies have been tested in the adjuvant setting in this group of patients.

Subsequently, neoadjuvant treatment before surgery has been suggested to further improve outcomes for clinically detectable stage III and resectable stage IV melanoma, as pre-clinical data suggest a stronger T cell checkpoint blockade activity when macroscopic tumour is still in place. In addition, immediate systemic treatment may avoid early recurrence after surgery, before adjuvant therapy has even started. Lastly, reduction of tumour burden pre-operatively may facilitate surgery.(Versluis 2023) Neoadjuvant treatment may also have disadvantages however, such as progression of disease before surgery can take place. Toxicity due to immunotherapy may delay or preclude patients from having surgery.(Olivier 2024) Hence, several recent randomised trials have investigated the possible clinical benefit of neoadjuvant therapy in clinically detectable resectable stage III and resectable stage IV melanoma.

6.3 Adjuvant Immunotherapy

6.3.1 Research question and search

What is the effectiveness of adjuvant immunotherapy for completely resected stage IIB, IIC, III or IV cutaneous melanoma? The PICO were developed for the search (see Appendix 6.1).

A common search from inception to 23 July 2024 for SR and RCTs on adjuvant or neoadjuvant immunotherapy or targeted therapy for melanoma resulted in 1742 citations. First we screened



records published 2021-2024. After screening 408 records based on title and abstract, 277 were excluded and 131 were screened based on full text. As a high-quality SR with search date in 2021 was identified for both research questions, records published before 2021 were not screened for inclusion. Further selection based on full text, excluded 96 more records. Reasons for inclusion and exclusion are listed in Appendix 6.2.4 (Table 41).

The following 35 papers were included:

- Adjuvant immunotherapy or targeted therapy:
 - SR: Ba 2023(Ba 2023), Lai-Kwon 2023(Lai-Kwon 2023), Sheng 2023(Sheng 2023)
 - RCTs: Long 2024(Long 2024), Luke 2024(Luke 2024), Schadendorf 2024(Schadendorf 2024), Ascierto 2023(Ascierto 2023), Kirkwood 2023(Kirkwood 2023), Larkin 2023(Larkin 2023), McLouth 2023(McLouth 2023), Unger 2023(Unger 2023), Weber 2023(Weber 2023), Eggermont 2022(Eggermont 2022), Grossmann 2022(Grossmann 2022), Larkin 2022(Larkin 2022), Livingstone 2022(Livingstone 2022), Long 2022(Long 2022), Luke 2022(Luke 2022), Weber 2022(Weber 2022), Schadendorf 2022(Schadendorf 2022), Schadendorf 2022(Schadendorf 2022), Bottomley 2021(Bottomley 2021), Eggermont 2021(Eggermont 2021), Long 2021(Long 2021), Mandala 2021(Mandala 2021)
- Neoadjuvant immunotherapy or targeted therapy:
 - SR: Gorry 2023(Boulva 2021, Gorry 2023)
 - RCTs: Blank 2024(Blank 2024), Long 2024(Long 2024), Lowe 2023(Lowe 2023), Lucas 2023(Lucas 2023), Patel 2023(Patel 2023), Versluis 2023(Versluis 2023), Patel 2022(Patel 2022), Rozeman 2021(Rozeman)

If applicable, additional publications related to the identified trials were taken from the references.

For the research question on adjuvant immunotherapy, included papers related to 9 RCTs. The following nine international multicentre randomised trials were included:

Ipilimumab vs placebo or interferon alfa:

- EORTC 18071(Coens 2017, Eggermont 2015, Eggermont 2019)
- Intergroup E1609(McLouth 2023, Tarhini 2021, Tarhini 2020)

Nivolumab vs placebo or interferon alfa:

- IMMUNED (also includes a combination arm ipilimumab + nivolumab)(Livingstone 2022, Zimmer 2020)
- Checkmate 76K(Kirkwood 2023)

Pembrolizumab vs placebo or interferon alfa

- EORTC 1325/KEYNOTE 054(Bottomley 2021, Buhrer 2024, Eggermont 2021, Eggermont 2020, Eggermont 2021, Eggermont 2022)
- KEYNOTE 716(Khattak 2022, Luke 2024, Luke 2022)
- SWOG S4104(Grossmann 2022, Unger 2023)

Nivolumab vs ipilimumab

- Checkmate 238(Ascierto 2020, Ascierto 2023, Larkin 2023, Mandala 2021, Weber 2024, Weber 2017)

Nivolumab + ipilimumab vs nivolumab

- Checkmate 915(Weber 2023)
- IMMUNED (see higher)

6.3.2 Evidence

6.3.2.1 Ipilimumab vs placebo/ interferon alpha

The Intergroup E1609 (Tahini 2019) was a three-arm trial which randomised 1670 patients with completely resected stage IIIB-IIIC or IV melanoma to ipilimumab 3mg/kg or ipilimumab 10mg/kg or high-dose interferon alfa. (Tahini 2018, Tahini 2021)

The EORTC 18071 trial (Eggermont 2015, 2019, Coens 2017) randomised 951 patients with stage IIIA-C melanoma to ipilimumab 10mg/kg or placebo. (Coens 2017, Eggermont 2015) Eligible patients with stage IIIA melanoma needed to have at least one micro-metastasis measuring > 1mm in the greatest diameter, according to the Rotterdam criteria of sentinel node tumour load.

Trial characteristics and results are summarised in Appendix 6.3 Table 42.

OVERALL SURVIVAL

Both studies showed a survival benefit for the ipilimumab arm, although the Intergroup E1609 trial only for the low-dose ipilimumab group. In an exploratory analysis of the Intergroup E1609 trial, no survival differences were seen between high-dose and low-dose ipilimumab.

In the EORTC 18071 study, 7-year overall survival rate was 60% in the ipilimumab group vs 51.3% in the placebo group, with a HR of 0.73 (95%CI 0.60-0.89).

In terms of absolute effects, that would translate as follows:

For resected stage IV melanoma without adjuvant therapy a 4-year survival of 63.1% is reported in the IMMUNED trial. (Zimmer 2020) Taking a HR of 0.73 into account, that would translate into a 4-year survival of 71.4% (95%CI 66.3-75.8%) with adjuvant ipilimumab or a survival benefit of 8% (95%CI 3-13%). (Skoetz 2020)

For stage IIB, 5-year overall survival in Belgium was 63.9% for patients diagnosed in 2015-2016 when no adjuvant immunotherapy was available. Taking a HR of 0.73 into account, that translates into a 5-year OS of 72.1% (95%CI 67.1-76.4%) with adjuvant ipilimumab. Calculated absolute effects on 5-year OS for stage IIB, IIC, IIIA, IIIB and IIIC can be found in Table 12. (Skoetz 2020)

Table 12 – Absolute effects of adjuvant ipilimumab 10 mg/kg on 5-year OS

Stage	5-y OS for patients diagnosed in 2015-2016 % (95%CI)*	Calculated 5-y OS with adjuvant ipilimumab % (95%CI)	5-y OS benefit % (95%CI)
IIB	63.9 (58.2-69.0)	72.1 (67.1-76.4)	8.2 (3.2-12.5)
IIC	39.4 (32.5-46.3)	50.7 (43.7-57.2)	11.3 (4.3-17.8)
IIIA	82.1 (70.6-89.4)	86.8 (83.9-88.8)	4.5 (1.8-6.70)
IIIB	67.5 (55.9-76.8)	75.1 (70.5-79.0)	7.6 (3.0-11.5)
IIIC	49.3 (36.9-60.5)	59.7 (53.3-65.4)	10.4 (4.0-16.1)

*Source: Belgian Cancer Registry

QUALITY OF LIFE

In the EORTC 18071 trial, no clinically important differences were seen between the two arms for general health-related quality of life (HRQoL). However, median HRQoL scores differed by more than 10 points at week 10 between treatment groups for diarrhoea and insomnia. Fatigue in the ipilimumab group had a clinically relevant deterioration at week 10 compared to baseline.

The Intergroup E1609 reported a higher proportion of worsening treatment bother (patient-reported outcome) at three months in the interferon and high-dose ipilimumab group compared to the low-dose ipilimumab arm.



SEVERE ADVERSE EVENTS

In the EORTC 18071 trial, using ipilimumab at a dose of 10mg/kg, 54% of patients in the intervention arm experienced a grade 3 or 4 adverse event, compared to 25% in the placebo arm.

For the Intergroup trial, the proportion of patients with a grade 3 or higher adverse event was 38.6% and 57.9% in the low-dose and high-dose ipilimumab respectively. That was lower than in the patient group treated with interferon.

RECURRENCE-FREE SURVIVAL

The EORTC 18071 study shows a prolonged RFS with ipilimumab versus placebo, with a HR of 0.75 (95%CI 0.63-0.88).

In the Intergroup E1609, no clearly prolonged RFS was demonstrated compared with interferon alfa. The HR for RFS was 0.85 (99.4%CI 0.66-1.09) and 0.84 (99.4%CI 0.65-1.09) for low-dose (3mg/kg) and high-dose (10mg/kg) respectively.

Conclusions:

- In completely resected high risk melanoma, adjuvant ipilimumab (10mg/kg) likely improves overall survival compared to placebo or adjuvant high-dose interferon alfa. (moderate level of evidence)
- Adjuvant high-dose ipilimumab (10mg/kg) is likely associated with reduced QoL related to symptoms of diarrhoea and insomnia, but probably not with a clinically meaningful reduction in general HRQoL, compared to placebo. (moderate level of evidence)
- In RCTs, adjuvant high-dose ipilimumab (10mg/kg) is associated with grade 3 or higher adverse events in 54-58% of patients. (high level of evidence)
- In completely resected high risk melanoma, adjuvant ipilimumab (10mg/kg) likely improves recurrence-free survival compared to placebo. (moderate level of evidence)

6.3.2.2 Nivolumab vs placebo

The IMMUNED trial (Zimmer 2020) randomised 167 patients with completely resected stage IV melanoma (or no evidence of disease after radiotherapy) in a 3-arm trial that compared nivolumab monotherapy with placebo and with the combination nivolumab and ipilimumab (3mg/kg). (Livingstone 2022, Zimmer 2020)

The Checkmate 76K (Kirkwood 2023) randomised 986 patients with stage IIB or IIC to nivolumab or placebo. (Kirkwood 2023)

Trial characteristics and results are summarised in Appendix 6.3 in Table 43.

OVERALL SURVIVAL

Only the IMMUNED trial reported on overall survival. Overall survival may be in favour of nivolumab, but a clear survival benefit could not be demonstrated (HR 0.75; 95%CI 0.36-1.56, wide confidence interval). (Livingstone 2022)

SEVERE ADVERSE EVENTS

In the IMMUNED trial, 43% of patients suffered from a grade 3-4 AE in the nivolumab group versus 25% in the placebo group. Treatment-related grade 3-4 event occurred in 29% and 6% respectively. (Livingstone 2022)

In the Checkmate 76K trial, rates of grade 3-4 events were 21.9% and 12.1% in the nivolumab and placebo arm respectively. Treatment-related SAE occurred in 10% and 2.3% respectively. There was one treatment-related death in the nivolumab group. (Kirkwood 2023)

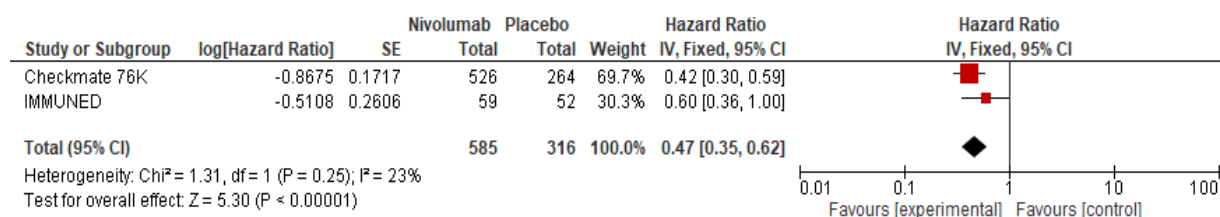
Meta-analysis for serious adverse events results in a RR of 1.78 (95%CI 1.31-2.42) to experience at least one severe adverse event when receiving adjuvant nivolumab.

QUALITY OF LIFE

No QoL outcomes were reported in the IMMUNED or Checkmate 76K trial.

RECURRENCE-FREE SURVIVAL

Both trials show a beneficial recurrence-free survival for the nivolumab arm. Meta-analysis of the two trials results in a HR of 0.47 (95%CI 0.35-0.62).(Kirkwood 2023,Livingstone 2022)



Conclusions:

- Adjuvant nivolumab may be associated with a benefit in overall survival compared to placebo (but the confidence interval also includes no or a harmful effect). (low level of evidence)
- The impact of adjuvant nivolumab on HRQoL is not reported in RCTs.
- Adjuvant nivolumab is associated with an increase of severe adverse events compared to placebo. (high level of evidence)
- Adjuvant nivolumab prolongs recurrence-free survival in resected cutaneous melanoma. (high level of evidence)

6.3.2.3 Pembrolizumab vs placebo or interferon alfa/ipilimumab

Three trials compared pembrolizumab with placebo or interferon/ipilimumab (physician's choice).

The EORTC1325/KEYNOTE-054 trial (Eggermont 2021) randomised 1019 patients with resected high-risk stage III melanoma to adjuvant pembrolizumab or placebo. Patients with N1a or N2a had to have at least one micro-metastasis measuring $> 1\text{mm}$ in greatest diameter. (Eggermont 2021)

The KEYNOTE-716 trial (Luke 2022) had the same treatment arms and randomised 1182 patients with resected stage IIB or IIC melanoma. (Khattak 2022,Luke 2024,Luke 2022)

Finally, the SWOG S4104 trial (Grossman 2022) randomised 1301 patients with resected stage III or IV melanoma to adjuvant pembrolizumab or high-dose interferon or ipilimumab according physician's choice.(Grossmann 2022)

Trial characteristics and results are summarised in Appendix 6.3 in Table 44.

OVERALL SURVIVAL

Only the SWOG S4104 trial already reported overall survival results. Overall survival may be in favour of pembrolizumab compared to the interferon/ipilimumab arm, but a clear survival benefit could not be demonstrated (HR 0.82; 96.3%CI 0.61-1.09, wide confidence interval).(Luke 2024)



QUALITY OF LIFE

In the EORTC 1325/KEYNOTE-054 trial, no clinically relevant differences in general HRQoL scores were seen during treatment or during (long term) follow-up.(Bottomley 2021,Buhrer 2024)

In the KEYNOTE-716 trial, there was no clinically meaningful difference in change from baseline. The proportion of patients with non-deteriorated global health status was 68.5% (64.2-72.7%) with pembrolizumab and 76.3% (73.2-80%) with placebo, meaning a difference of 7.8% (95% CI 2.2-13.4%).(Khattak 2022)

In the SWOG S4104 trial, differences were in favour of pembrolizumab at each assessment and exceeded clinically meaningful differences, compared to the interferon/ipilimumab group.(Unger 2023)

SEVERE ADVERSE EVENTS

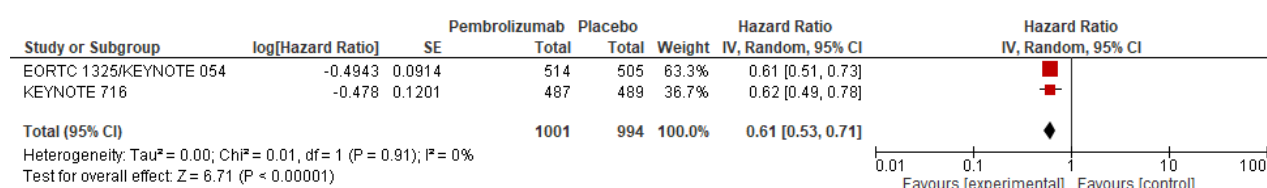
The EORTC1325 trial, treatment-related grade 3-5 adverse events occurred in 14.7% of patients in the pembrolizumab group and in 3.4% in the placebo group. When all SAEs were taken into account, proportion of patients who suffered from an SAE were 31.6% and 18.5% respectively. There was one pembrolizumab-related death due to myositis. Immune-related adverse events of any grade occurred in 37.3% of patients in the pembrolizumab group and in 9.0% of patients in the placebo group. The incidence of grade 3-4 immune-related AEs was 7.1% and 0.6% respectively.(Eggermont 2018)

In the KEYNOTE-716 trial, 17.2% of patients in the pembrolizumab arm experienced a grade 3 or higher treatment-related event, compared to 5.1% in the placebo arm.(Luke 2024)

In the SWOG S4104 arm, 17% of patients in the pembrolizumab group suffered from grade 3 or higher adverse events, compared to 43% and 65% with ipilimumab and interferon respectively.(Grossmann 2022)

RECURRENCE-FREE SURVIVAL

A meta-analysis was performed for the two trials that compared pembrolizumab, showing a HR of 0.61 (95%CI 0.53-0.71) for recurrence-free survival. In an absolute effect, this translates into a 5-year recurrence-free survival of 55% with adjuvant pembrolizumab vs 38% with placebo (taken from EORTC 1325).



Conclusions:

- Adjuvant pembrolizumab is likely not associated with a clinically meaningful benefit in overall survival compared to interferon/ipilimumab. (moderate level of evidence)
- There is no published evidence from RCTs on the effect of pembrolizumab on overall survival, compared to placebo.
- Adjuvant pembrolizumab is likely not associated with reduced general HRQoL, compared to placebo. (moderate level of evidence)
- Adjuvant pembrolizumab is associated with an increase of (treatment-related) serious adverse events compared to placebo. (high level of evidence)
- Adjuvant pembrolizumab is associated with improved RFS, compared to placebo. (high level of evidence)

6.3.2.4 Nivolumab vs ipilimumab

In the Checkmate 238 trial (Weber 2017), 906 patients with stage IIIB-C or resected stage IV melanoma were randomised between Nivolumab (3mg/kg) or Ipilimumab (10mg/kg). (Weber 2017)

Trial characteristics and results are summarised in Appendix 6.3 Appendix 6.4.4 in Table 45.

OVERALL SURVIVAL

No significant difference in overall survival was seen between the 2 treatment arms (HR 0.86; 95%CI 0.66-1.12 at 5-year FU). (Larkin 2023)

QUALITY OF LIFE

No results on QoL were reported.

SERIOUS ADVERSE EVENTS

Fewer patients in the nivolumab arm suffered from a grade 3 or higher adverse event: 25.4% vs 55.2% in the ipilimumab arm (calculated RR 0.46; 95%CI 0.39-0.55). (Weber 2017)

RECURRENCE-FREE SURVIVAL

An improved recurrence-free survival was seen in the nivolumab arm, compared to ipilimumab, with a HR of 0.72 (95%CI 0.60-0.86). Five-year recurrence-free survival was 50% in the group treated with nivolumab and 39% in the ipilimumab group.

Conclusions:

- Adjuvant nivolumab may be associated with a limited benefit in overall survival compared to ipilimumab (but the confidence interval also includes no effect or a harmful effect). (low level of evidence)
- The impact of adjuvant nivolumab compared to ipilimumab on HRQoL is not reported in RCTs.
- Adjuvant ipilimumab is associated with an increase in serious adverse events compared to adjuvant nivolumab. (high level of evidence)
- Adjuvant nivolumab may be associated with a recurrence-free survival benefit compared to ipilimumab. (low level of evidence)



6.3.2.5 Nivolumab vs nivolumab + ipilimumab

In the Checkmate 915 trial, 1844 patients with completely resected stage IIIB-D or IV melanoma were randomised between nivolumab-ipilimumab combination therapy or nivolumab monotherapy (+placebo). (Weber 2023) Trial characteristics and results are summarised in Appendix 6.3 in Table 46.

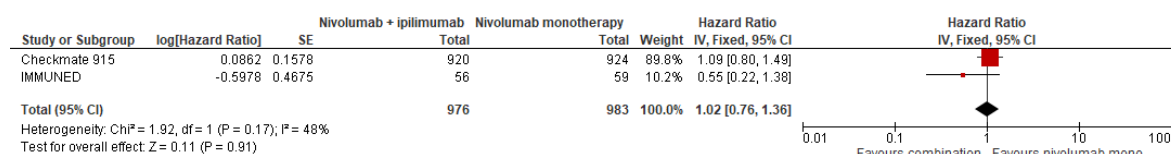
Also the IMMUNED trial (see Table 43) compared the combination nivolumab-ipilimumab with nivolumab monotherapy. (Livingstone 2022)

OVERALL SURVIVAL

In the Checkmate 915 trial, no significant difference in overall survival was seen between the 2 treatment arms (HR 1.09 (95%CI 0.80-1.32)). (Weber 2023)

The IMMUNED trial suggested a survival benefit for the combination arm but that survival benefit could not be proven (HR 0.55; 95%CI 0.22-1.38, wide confidence interval). (Livingstone 2022)

Meta-analysis of the two studies showed a HR of 1.02 (95%CI 0.76-1.36).



QUALITY OF LIFE

In the Checkmate 915 trial, HRQoL in both treatment groups remained within the cutoff for the clinically defined minimally important difference.

IMMUNED did not report on QoL outcomes.

SERIOUS ADVERSE EVENTS

In the Checkmate 915 trial, Grade 3-4 treatment related AEs were reported in 32.6% of patients in the combination group vs 12.8% in the monotherapy group.

In the IMMUNED trial, the respective proportions for treatment-related SAEs were 71% and 29%. (Livingstone 2022)

Meta-analysis showed a RR of 2.55 (95%CI 2.13 – 3.05) to experience a grade 3-4 adverse event with the combination therapy compared to nivolumab monotherapy.

RECURRENCE-FREE SURVIVAL

The Checkmate 915 trial reports a HR of 0.92 (97.3%CI 0.77-1.09) for RFS after minimum 24 months of FU. After 24 months, RFS was 64.6% in the combination group and 63.2% in the monotherapy group. (Weber 2023)

In the IMMUNED trial, an exploratory analysis showed a HR of 0.41 (97.5%CI 0.22-0.78) in favour of the combination treatment. (Livingstone 2022)

No meta-analysis was performed as 95%CI were not reported.

Conclusions:

- Adding ipilimumab to nivolumab does likely not result in a survival benefit in the adjuvant setting. (moderate level of evidence)
- Adding ipilimumab to nivolumab does likely not result in clinically important differences in HRQoL. (moderate level of evidence)
- Adding ipilimumab to nivolumab in the adjuvant setting leads to an increase of treatment-related serious adverse events. (high level of evidence)
- Adding ipilimumab to nivolumab does likely not result in improved RFS in the adjuvant setting. (moderate level of evidence)

6.3.3 Evidence to recommendations

6.3.3.1 Balance between clinical benefits and harms

Adjuvant immunotherapy has been welcomed for resected melanoma at high risk for recurrence, as for several drugs (ipilimumab, nivolumab and pembrolizumab) a benefit in terms of recurrence-free survival (HR 0.47 for nivolumab; HR 0.61 for pembrolizumab) has been shown in high quality RCTs. However, only for ipilimumab a benefit in overall survival has been demonstrated so far but adjuvant treatment of melanoma is currently not included in its approved indications, due to its excessive toxicity.

This has to be weighed against the risk of acute and of lifelong toxicities associated with treatment. In RCTs, often only acute toxicity during treatment is systematically collected. In a real-world study, Goodman et al noted chronic adverse events (> 3 months after therapy) in nearly half of the patients treated with anti-PD-1 therapy. 29% had persistent immune-related AEs present at last follow-up. (Goodman 2023)

The disadvantage of adjuvant therapy is that many patients are exposed to therapy and possible side effects, also the patients that would not have recurrence without adjuvant treatment and patients that would have the same survival benefit of treatment at the time of recurrence. If treatment can be safely started in the case of disease relapse, with the same overall survival outcomes as with adjuvant treatment, starting immunotherapy at the time of relapse would thus be the preferred option. Therefore, it is important to take the overall survival results of RCTs on adjuvant treatment into account. At present, no survival benefit has been proven for adjuvant nivolumab and pembrolizumab. (Ochendusko 2024)

Some GDG members were of the opinion that the strong benefit in RFS justifies a strong recommendation in favour of adjuvant immunotherapy. Others felt that the side effects and limitations regarding the effect on overall survival weighed more strongly (also see patient preferences). We concluded that the differences in opinions were best reflected in a conditional recommendation in favour of adjuvant immunotherapy.

As there is no proof of a beneficial effect on OS, DFS or QoL for the combination ipilimumab – nivolumab, combination therapy is not recommended in the adjuvant setting for melanoma.

6.3.3.2 Quality of evidence

We consider the overall quality of the evidence as low, mainly due to the absence of data on overall survival.



6.3.3.3 Patient preferences

Given the substantial toxicity that is associated with immunotherapy, possibly severe or chronic, individual patient's judgements about the balance between benefits and risks may vary. The uncertainty regarding the effect on overall survival may add to this variability. Also the individual risk for recurrence, based on (sub)stage of the tumour may result in differences in treatment decisions. The GDG patient representative, having experienced severe side effects of immunotherapy, would not choose immunotherapy and favoured follow-up with starting immunotherapy (or other therapy) in case of relapse.

The (sub)stage of the tumour at diagnosis will have an impact on the absolute number of people who potentially will benefit from adjuvant treatment. The UK based charity 'Focus on melanoma' has published an overview of absolute effects on their website www.melanomafocus.org by substage. For stage IIIA for example, if 100 patients take adjuvant treatment, only 3 to 4 fewer people would have recurrence after 5 years. Other people would have a favourable outcome even without adjuvant treatment and another 3 to 4 people would have recurrence within 5 years in spite of adjuvant treatment. For stage IIIC, the absolute effect would be more substantial as 15 to 16 fewer people would have recurrence within 5 years. Note that the effect on overall survival is not included in the information sheets as the results are still uncertain.

6.3.3.4 Cost and resource allocation

No literature search related to cost-effectivity of adjuvant therapy was performed.

We note that immunotherapy is expensive and costs may be an additional argument to further await OS results to make a final judgement on adjuvant immunotherapy. Hence, it is important that overall survival results of the RCTs are reported as soon as they are available.

Ipilimumab is currently not reimbursed in the adjuvant setting in Belgium.

6.4 Adjuvant targeted therapy for completely resected melanoma

6.4.1 Research question and search

A combined search for SRs and RCTs on adjuvant and neoadjuvant therapy in melanoma resulted in 1742 citations. The details of paper selection are described in the chapter on adjuvant immunotherapy.

Two studies were included in the most recent SRs (Ba 2023, Sheng 2023)(Ba 2023,Sheng 2023); the BRIM8 and the COMBI-AD study.

For the research question on adjuvant targeted therapy, two papers (including abstracts) related to one RCT were included. Both publications were updates of the COMBI-AD study. Additional publications related to the identified trials were taken from the references.

The BRIM8 study evaluated adjuvant vemurafenib in resected stage IIC-IIIC BRAF-V600 mutation-positive melanoma, while the COMBI-AD study evaluated the efficacy of adjuvant dabrafenib + trametinib in resected stage III cutaneous melanoma with BRAF mutations.

Details of both studies can be found in Table 47 and Table 48.

Reasons for inclusion and exclusion are listed joined with the immunotherapy publications in Appendix 6.2.4 (Table 41).

6.4.2 Evidence

6.4.2.1 Adjuvant vemurafenib

The BRIM8 study (Maio 2018, Schadendorf 2019) randomised patients with stage IIC-IIIB and IIIC cutaneous melanoma in two separate cohorts between adjuvant vemurafenib and placebo. Patients with stage IIIA disease needed to have one or more nodal metastases greater than 1mm in diameter.

OVERALL SURVIVAL

An overall survival benefit could not be proven (HR 0.76; 95%CI 0.49-1.18). Taking a 2-year survival of 86% with placebo and a HR of 0.76 into account, overall survival may increase with 3% (95%CI 6% higher to 3% lower). (Maio 2018)

QUALITY OF LIFE

A clinically meaningful decline in QoL and functional scales (except cognitive function) was seen during treatment with vemurafenib. (Schadendorf 2019)

SEVERE ADVERSE EVENTS

Serious adverse events occurred in 57% of patients treated with vemurafenib and in 15% of patients in the placebo group (Calculated RR 3.81; 95%CI 2.78-5.23). (Maio 2018)

DISEASE-FREE SURVIVAL

For the statistical analysis, a hierarchical approach was planned. DFS in the cohort with stage IIC-IIIB patients would only be performed if results for the stage IIIC patients were positive. However, the result for stage IIIC patients showed a HR of 0.80 (95%CI 0.54-1.18). Result for all patients was HR 0.65 (95%CI 0.50-0.85), however due to the hierarchical approach this result could not be considered statistically significant. (Maio 2018)

Conclusions:

- Adjuvant vemurafenib may results in little to no difference in overall survival compared to placebo, but the evidence is uncertain. (very low level of evidence)
- Adjuvant vemurafenib may have a clinically important negative impact on QoL and functional scores. (low level of evidence)
- Adjuvant vemurafenib likely results in a large increase of serious adverse events. (moderate level of evidence)
- Adjuvant vemurafenib may be associated with prolonged DFS compared to placebo, but the evidence is very uncertain. (very low level of evidence)

6.4.2.2 Adjuvant dabrafenib plus trametinib

In the COMBI-AD study, 870 patients with stage IIIA-IIIC cutaneous melanoma with BRAF V600E or V600K mutations were randomised between oral dabrafenib plus trametinib or placebo for 12 months. Stage IIIA disease was only eligible of lymph node metastasis larger than 1mm. (Long 2017, Long 2024)

OVERALL SURVIVAL

Observed survival after 7 years of follow-up was 73% (95%CI 68-77%) in the treated group and 66% (95%CI 62-71%) in the placebo group (HR 0.80; 95%CI 0.62-1.01). (Long 2024)

Subgroup analysis by type of BRAF V600 mutation, suggested a survival benefit for tumours with a BRAF V600E mutation (HR 0.75; 95%CI 0.58-0.96) but a reversed effect for tumours with BRAF V600K, but the latter group contained only 78 patients. (Long 2024)



QUALITY OF LIFE

During and after treatment, no significant differences in QoL were seen, based on EQ-5D-3L.

However, at 12 months, a higher proportion of patients with adjuvant dabrafenib plus trametinib reported problems in mobility (15% vs 8%) and usual activities (19 % vs 13%). A higher proportion in the placebo group reported problems in anxiety or depression (27% vs 22%).

SEVERE ADVERSE EVENTS

SAEs occurred in 36% in the combination-therapy group and in 10% in the placebo group.

RECURRENCE-FREE SURVIVAL

Recurrence-free survival was longer with the combination adjuvant treatment, with a HR of 0.52 (95%CI 0.43-0.63). Five-year recurrence-free survival was 52% in the treatment arm and 36% in the placebo arm. After 10 years, the proportions were 48% and 32% respectively.

Conclusions:

- **Adjuvant treatment with dabrafenib and trametinib may have a clinically meaningful effect on overall survival in stage III BRAF-mutated cutaneous melanoma but the evidence is uncertain. (low level of evidence)**
- **Adjuvant dabrafenib and trametinib has no important effect on general quality of life. (high level of evidence)**
- **Adjuvant dabrafenib and trametinib results in an important increase of serious adverse events. (high level of evidence)**
- **Adjuvant treatment with dabrafenib and trametinib results in prolonged recurrence-free survival. (high level of evidence)**

6.4.3 Evidence to recommendations

6.4.3.1 Balance between clinical benefits and harms

As adjuvant vemurafenib in BRAF mutated tumours may have a clinically important negative effect on QoL and the effect on RFS and OS remains uncertain, the benefit /harms balance does not support adjuvant treatment with vemurafenib.

For adjuvant therapy with dabrafenib and trametinib, the risk/benefit balance is more favourable. The therapy has a positive effect on recurrence-free survival and may have a beneficial effect on overall survival in BRAF-mutated tumours, but the results remain uncertain. On the other hand, although in RCTs dabrafenib and trametinib have no important impact on general QoL, the adverse events and the negative effect on mobility and usual activities also have to be taken into account. The GDG noted that adverse events from dabrafenib and trametinib are almost always reversible.

As for adjuvant immunotherapy, the benefits that can be expected will differ by (sub)stage of the tumour. In real-world data, it has been noted that patients with a melanoma substage IIIA according to the 8th edition of the AJCC classification probably only have very limited or even no benefit from adjuvant targeted therapy or immunotherapy in the adjuvant setting.(Grover 2023) In addition, the type of BRAF mutation may be taken into account when taking individual treatment decisions. In the COMBI-AD study, a survival benefit was seen only for tumours with the BRAF V600E mutation, but not in tumours with BRAF V600K mutations. Therefore, the GDG decided to limit the recommendation to tumours with BRAF V600E mutation.(Long 2024)

6.4.3.2 *Quality of evidence*

Very low level of evidence for Vemurafenib

Moderate level of evidence for dabrafenib and trametinib

6.4.3.3 *Patient preferences*

When deciding on adjuvant therapy with dabrafenib and trametinib judgements about the balance between benefits in (overall or recurrence-free) survival and the risks for adverse events may vary between patients. Therefore, a conditional recommendation was considered the most appropriate.

6.4.3.4 *Cost and resource allocation*

No literature search related to cost-effectivity of adjuvant therapy was performed.

Vemurafenib is currently not reimbursed in the adjuvant setting in Belgium.

We note that targeted therapy is expensive, which can be considered an argument against use in the adjuvant setting, given the uncertain effect on overall survival.

6.5 Neoadjuvant therapy for resectable clinically detectable stage III or stage IV primary melanoma

6.5.1 *Research question and search*

A common search for SR and RCTs on adjuvant or neoadjuvant immunotherapy or targeted therapy for melanoma was performed, see chapter 6.3. The reasons for inclusion and exclusion of retrieved publications are listed in Appendix 6.2.4 (Table 41).

For the research question on neoadjuvant therapy, 10 papers (including abstracts) were included. The most recent high-quality SR was published by Gorry et al. in 2023.(Gorry 2023) Five relevant RCTs were included in that review; our search identified 3 new RCTs.

The following studies compared neoadjuvant therapy with adjuvant therapy in resectable clinically detectable stage III or resectable stage IV melanoma:

- OpACIN (Versluis 2023(Versluis 2023), Lucas 2023(Lucas 2023), Rozeman 2021(Rozeman), Blank 2018(Blank 2018))
- NADINA (Blank 2024)(Blank 2024)
- SWOG S1801 (Patel 2023(Patel 2023), Patel 2022(Patel 2022), Lowe 2023(Lowe 2023))

One small trial (n=21) by Amaria et al. compared neoadjuvant treatment with adjuvant treatment or no systemic treatment. As finally only one patient in the comparator arm received adjuvant treatment (interferon and chemotherapy), this trial is not discussed in detail.(Amaria 2018)

Four trials compared different neoadjuvant treatment regimens: Tarhini 2018, Amaria 2018, the OpACIN-neo trial (Rozeman 2019) and the 2NeoTrio trial (Long 2024).

The OpACIN-neo trial (Rozeman 2019) compared three dosing schedules of neoadjuvant ipilimumab plus nivolumab: ipilimumab 3 mg/kg plus nivolumab 1 mg/kg or ipilimumab 1mg/kg plus nivolumab 3 mg/kg or sequential ipilimumab 3mg/kg and nivolumab 3mg/kg.(Rozeman 2019) In the large phase III NADINA trial, a dosing schedule resembling the ipilimumab 1mg/kg plus nivolumab 3 mg/kg schedule was used: 80mg ipilimumab plus 240mg nivolumab.(Blank 2024)

The study published by Amaria et al. randomised 23 patients to neoadjuvant treatment with combination therapy with ipilimumab (3mg/kg) and nivolumab (1mg/kg) or neoadjuvant therapy with nivolumab monotherapy (3mg/kg). The trial was closed early by the data safety monitoring board due to disease progression preventing surgery in the nivolumab monotherapy arm (2/12 pts) and the



high toxicity in the ipilimumab arm (grade 3 treatment related adverse events in 73% of patients).(Amaria 2018)

The study published by Tarhini et al. in 2018 compared two neoadjuvant treatment schedules of high- or low dose ipilimumab plus interferon.(Tarhini 2018)

As interferon and ipilimumab at a dose of 3mg/kg are no longer used in the (neo)adjuvant setting, these studies are not further discussed in detail.

Finally, the 2NeoTriotrial randomised 60 patients to neoadjuvant pembrolizumab monotherapy, sequential therapy of dabrafenib plus trametinib followed by pembrolizumab or concurrent triple therapy. Recurrences after major pathological response were more common in the target therapy arms. The authors concluded that immunotherapy and targeted therapy should not be combined in the neoadjuvant setting.(Long 2024) This trial is also not further discussed in detail.

6.5.2 Evidence

6.5.2.1 Neoadjuvant ipilimumab and nivolumab versus adjuvant treatment

Two studies used combination therapy of ipilimumab and nivolumab in the neoadjuvant arm.

The OpACIN trial randomised 20 patients with clinically detectable stage III melanoma to four cycles ipilimumab (3mg/kg) plus nivolumab (1mg/kg) given either as neoadjuvant (two cycles before and two cycles after surgery) or as adjuvant (four cycles after surgery).

The NADINA trial randomized 423 patients with clinically detectable stage III melanoma to two cycles ipilimumab (80mg) plus nivolumab (240mg) followed by surgery and adjuvant therapy (dabrafenib plus trametinib or nivolumab) in patients without major pathological response in the intervention arm or twelve cycles of adjuvant nivolumab after surgery in the control arm. Patients who had major pathological response after neoadjuvant therapy received no further postoperative therapy.(Blank 2024)

OVERALL SURVIVAL

Long-term follow-up of the OpACIN study showed a 6-year OS of 90% (95%CI 73-100%) in the neoadjuvant arm and 70% (95%CI 47-100%) in the adjuvant arm. No HR was reported, and the calculated RR is 0.33 (95%CI 0.04 – 2.69).(Versluis 2023)

The NADINA study did not yet report on the results for OS.

QUALITY OF LIFE

The OpACIN study did not include QoL outcomes.

QoL was included as a secondary outcome in the NADINA study but the results have not yet been reported.

ADVERSE EVENTS

In the OpACIN trial, grade 3 or higher adverse events were noted in 9 out of 10 patients in each arm. Two patients in each arm developed clinically severe treatment related adverse events (Steven-Johnson syndrome, severe colitis, polyradiculitis, diabetes type I). Eight patients needed chronic hormonal replacement therapy.(Blank 2018)

In the NADINA study, grade 3 or higher adverse events were reported in 47.2% of patients in the neoadjuvant group and in 34.1% in the adjuvant group. Surgery-related adverse events were similar in both groups, 14.1% and 14.4% in the neoadjuvant group and the adjuvant group respectively. In the neoadjuvant group, 23.1% of patients had an adverse event grade 3 or higher that was related to systemic treatment within the first 12 weeks and was therefore attributable solely to the neoadjuvant treatment.(Blank 2024)

EVENT-FREE SURVIVAL

After a median follow-up of 84 months, the OpACIN trial reports a 6-year EFS of 60% (95%CI 36-100%) in both arms.(Versluis 2023)

In the NADINA trial, at a median follow-up of 10.0 months, the estimated event-free survival at 12 months was 83.7% (99.9%CI 73.8 – 94.8%) and 57.2% (99.9%CI 45.1-72.7%) in the neoadjuvant and adjuvant group respectively. The overall adjusted hazard ratio was 0.32 (99.9%CI 0.15-0.66). Note that only melanoma or treatment related death were taken into account in the EFS analysis, deaths of other causes were censored.(Blank 2024)

Conclusions:

- **Neoadjuvant therapy with ipilimumab plus nivolumab may improve overall survival in clinically detectable stage III melanoma compared to adjuvant treatment with nivolumab, but the evidence is very uncertain. (low level of evidence)**
- **There is no evidence from RCTS on the effect of neoadjuvant therapy with ipilimumab plus nivolumab on QoL.**
- **Neoadjuvant therapy with ipilimumab plus nivolumab probably increases the occurrence of grade 3 or higher adverse events compared to adjuvant nivolumab alone. (moderate level of evidence)**
- **After a median follow-up of 10 months, neoadjuvant therapy with ipilimumab plus nivolumab followed by adjuvant treatment in patients without major pathological response improves event-free survival compared to adjuvant nivolumab alone. (high level of evidence)**

6.5.2.2 Neoadjuvant pembrolizumab versus adjuvant pembrolizumab

One RCT investigated the benefit of neoadjuvant pembrolizumab compared to adjuvant pembrolizumab. The SWOG S1801 randomised patients with clinically detectable stage IIIB to IIID or oligometastatic resectable stage IV melanoma to neoadjuvant pembrolizumab (200mg; 3 cycles before surgery and 15 cycles after surgery) or adjuvant pembrolizumab (200mg; 18 cycles after surgery).(Lowe 2023,Patel 2022,Patel 2023)

OVERALL SURVIVAL

After a median follow-up of 14.7 months, the HR for OS was 0.63 (95%CI 0.32 - 1.24). }(Patel 2022)

QUALITY OF LIFE

QoL was not measured in the SWOG S1801 trial.

ADVERSE EVENTS

The number of treatment-related grade 3-4 adverse events was higher in the neoadjuvant arm compared to the adjuvant arm. Of the patients who started pre-operative pembrolizumab, 7% had at least one grade 3 or 4 event that was deemed related to pembrolizumab. Surgery-related grade 3-4 AEs occurred in 7% of patients who underwent surgery after neoadjuvant pembrolizumab and 4% of the operated patients in the adjuvant arm had a grade 3 AE. Incidence of grade 3-4 AEs during adjuvant therapy was 12% in the neoadjuvant group and 14% in the adjuvant-only group.(Patel 2023)

As the overall number of patients that suffered from at least one grade 3-4 AE was not reported in the publication, we calculated the RR based on the number of grade 3-4 events per 100 patients. The RR was 1.73 (95%CI 1.23 – 2.43), or 17 (95%CI 5 – 33) grade 3-4 AEs more per 100 patients in the neoadjuvant arm.



EVENT-FREE SURVIVAL

After a median follow-up of 14.7 months, the HR for EFS was 0.58 (95%CI 0.39-0.87). (Lowe 2023) A 2-year EFS of 72% (95%CI 64 – 80%) was reported in the neoadjuvant group; for the adjuvant group reported 2-year EFS was 49% (95%CI 41-59%). (Patel 2023)

Note however that to calculate EFS, all events that occurred before the start of the adjuvant therapy were assigned the event time of day 84. This may have biased the results by artificially improving the results of patients that had progressive disease early during treatment or, in the neoadjuvant arm, events happening after day 84 could have been assigned an earlier date. (Olivier 2024)

Conclusions:

- **Neoadjuvant treatment with pembrolizumab may improve overall survival compared to adjuvant pembrolizumab in resectable clinically detectable stage III or resectable stage IV melanoma but the evidence is very uncertain. (low level of evidence)**
- **There is no evidence from RCTS on the effect of neoadjuvant therapy with pembrolizumab on QoL.**
- **Neoadjuvant treatment with pembrolizumab is probably associated with an increase of grade 3 or higher AEs compared to adjuvant pembrolizumab in resectable clinically detectable stage III or stage IV melanoma. (moderate level of evidence)**
- **Neoadjuvant treatment with pembrolizumab may improve overall survival compared to adjuvant pembrolizumab in resectable clinically detectable stage III or stage IV melanoma. (low level of evidence)**

6.5.3 Evidence to recommendations

6.5.3.1 Balance between clinical benefits and harms

NEOADJUVANT IPILIMUMAB PLUS NIVOLUMAB

The available evidence focusses on event-free survival. There is not yet published evidence available from RCTs regarding QoL and the evidence on OS is currently not yet available. The current evidence shows that, after a median follow-up of 10 months, neoadjuvant treatment with ipilimumab plus nivolumab followed by surgery and adjuvant nivolumab in patients without major pathological response improves event-free survival at the cost of an increase in grade ≥ 3 adverse events, compared to adjuvant nivolumab alone. An additional advantage of the neoadjuvant treatment schedule is that patients with major pathological response should not continue with adjuvant nivolumab and can thus reduce the dose and time of systemic treatment. Patients without major pathological response will not have the benefit of a reduced adjuvant schedule and are treated with adjuvant nivolumab if BRAF V600 wild-type and with adjuvant dabrafenib/trametinib if a BRAF V600E mutant.

NEOADJUVANT PEMBROLIZUMAB

More uncertainties remain regarding the benefits of neoadjuvant pembrolizumab compared to adjuvant pembrolizumab. As for neoadjuvant treatment with ipilimumab and nivolumab, there is not yet published evidence available from RCTs regarding QoL and the evidence on OS remains very unprecise. The results of the RCT show a benefit in terms of EFS, but the decision to assign events occurring before adjuvant treatment to time point of 84 days, may bias the results. An increase of grade ≥ 3 adverse events is noted in the neoadjuvant arm. In this trial, both treatment arms consisted of 18 cycles of pembrolizumab, so there was no advantage of shortened treatment for patients who had a major pathological response after neoadjuvant treatment.



6.5.3.2 *Quality of evidence*

Low level of evidence for neoadjuvant ipilimumab plus nivolumab

Low Level of evidence for neoadjuvant pembrolizumab

6.5.3.3 *Patient preferences*

Judgements about the balance between benefits in (overall or recurrence-free) survival and the uncertainties versus the risks for adverse events may vary between patients. Therefore, a conditional recommendation is formulated to point out that shared decision making is important in this case.

6.5.3.4 *Cost and resource allocation*

No literature search related to cost-effectivity of adjuvant therapy was performed.

Neoadjuvant treatment with ipilimumab and nivolumab may be cost-effective compared to adjuvant treatment if patients with major pathological response don't receive adjuvant treatment. However, the costs of the increased number of adverse events have also to be taken into account.

For neoadjuvant pembrolizumab, the uncertainty around the effect on EFS and OS and the increase in adverse events, may render the neoadjuvant treatment option not a favourable option in terms of cost-effectiveness.

A hurdle for implementing neoadjuvant treatment in stage III-IV melanoma may be the current reimbursement criteria for ipilimumab, nivolumab and pembrolizumab in Belgium. Neoadjuvant therapy is also considered an off-label indication for the studied drugs.



7 ROUTINE FOLLOW-UP OF PATIENTS WITH NO EVIDENCE OF DISEASE AFTER CURATIVE-INTENT TREATMENT HAS BEEN CONCLUDED

7.1 Recommendations for follow-up of patients with no evidence of disease after curative-intent treatment has been concluded

Scheduled surveillance interventions, for patients diagnosed with a cutaneous melanoma clinically disease free after receiving and concluding curative-intent treatment, aim to improve survival through early detection of recurrences and subsequent primary melanomas. A scheduled surveillance is defined by a system where all patients with the same melanoma stage have a routine follow-up planned from the start of follow-up.

There is no evidence that a more intense follow-up improves overall survival, at the same time harms in terms of false positive and resource use are apparent. Therefore, the strength of the recommendations are mostly conditional; and an intense follow-up is not recommended for thinner melanomas. A conditional recommendation implies that the patient should be informed of the evidence and the decisions should be based on an individual benefits and harms evaluation performed together with the patient.

Recommendations for follow-up of patients with no evidence of disease after curative-intent treatment has been concluded	Strength of recommendation⁹⁰	GRADE certainty of evidence
Recommendations for stage IA and IB primary melanoma		
<i>A dermatologist may provide a clinical follow-up with history and physical examination with full skin and lymph node examination (with photo-surveillance and dermoscopy if indicated) annually for 5 years.</i>	Conditional	Moderate for stage IB No evidence for stage IA
<i>Clinicians should not provide routine biomarker or blood tests to screen for asymptomatic recurrence or metastatic disease.</i>	Strong	No evidence
<i>Clinicians should not provide imaging to screen for asymptomatic recurrence or metastatic disease.</i>	Strong	Very low
Recommendations for stage IIA primary melanoma		
<i>A dermatologist may provide a clinical follow-up with history and physical examination with full skin and lymph node examination (with photo-surveillance and dermoscopy if indicated) every 6 months for 3 years, then annually for 2 years.</i>	Conditional	Moderate
<i>Clinicians should not provide routine biomarker or blood tests to screen for asymptomatic recurrence or metastatic disease.</i>	Strong	No evidence
<i>Clinicians should not provide imaging to screen for asymptomatic recurrence or metastatic disease.</i>	Strong	Very low
Recommendations for stage IIB primary melanoma		
<i>Clinicians may provide a clinical follow-up with history and physical examination with full skin and lymph node examination by a dermatologist (with photo-surveillance and dermoscopy if indicated) and an oncologist in case of previous adjuvant therapy, every 4 months in years 1-2, then every 6 months in years 3, and annually in year 4-5.</i>	Conditional	Moderate
<i>Clinicians should not provide routine biomarker or blood test to screen for asymptomatic recurrence or metastatic disease.</i>	Strong	No evidence

Clinicians may provide a PET/CT scans every 6 months to screen for asymptomatic recurrence or metastatic disease in years 1-2, then annually in years 3-5.	Conditional	Low
Clinicians may provide a brain MRI every 6 months to screen for asymptomatic recurrence or metastatic disease in years 1-2, then annually in years 3-5.	Conditional	No evidence
Recommendations for stage IIC primary melanoma		
Clinicians may provide a clinical follow-up with history and physical examination with full skin and lymph node examination by a dermatologist (with photo-surveillance and dermoscopy if indicated) and an oncologist in case of previous adjuvant therapy, every 4 months in years 1-3, and annually in year 4-5.	Conditional	Moderate
Clinicians should not provide routine biomarker or blood test to screen for asymptomatic recurrence or metastatic disease.	Strong	No evidence
Clinicians may provide a PET/CT scans every 6 months to screen for asymptomatic recurrence or metastatic disease in years 1-3, then annually in years 4-5.	Conditional	Low
Clinicians may provide a brain MRI every 6 months to screen for asymptomatic recurrence or metastatic disease in years 1-3, then annually in years 4-5.	Conditional	No evidence
Recommendations for stage III and resectable stage IV primary melanoma		
Clinicians may provide a clinical follow-up with history and physical examination with full skin and lymph node examination by a dermatologist (with photo-surveillance and dermoscopy if indicated) and an oncologist in case of previous (neo)adjuvant therapy, every 3 months in years 1-3, then every 6 months in years 4-5.	Conditional	No evidence
Clinicians should not provide routine biomarker or blood tests to screen for asymptomatic recurrence or metastatic disease.	Strong	No evidence
Clinicians may provide a PET/CT scans every 6 months to screen for asymptomatic recurrence or metastatic disease in years 1-3, then annually in years 4-5.	Conditional	Low for stage III
Clinicians may provide a brain MRI every 6 months to screen for asymptomatic recurrence or metastatic disease in years 1-3, then annually in years 4-5.	Conditional	No evidence
For patients with a positive sentinel lymph node, ultrasound scans of the draining nodal basin may be carried out every 4-6 months for years 1-3, and then every 6 months for years 4-5. [£]	Conditional	No evidence
Recommendations for any stage primary melanoma		
As part of routine follow-up, clinicians should provide education on skin self-examination and sun safety to patients and patients' caregivers who are involved in decision making.	Strong	No evidence

∞ Strong recommendation: Most individuals in this situation would want the recommended course of action, and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences. Conditional recommendation: The majority of individuals in this situation would want the suggested course of action, but many would not. Conditional on individual benefits and harms evaluation. For example, false positive results for PET/CT and CT when added to clinical follow-up were reported to be common and may affect the quality of life of patients.

[£]Not applicable when a complete lymph node dissection was performed.

**Good practice statements*:**

- Patients should be explained how they can access the dermatology clinic in case of a suspicious skin lesion, either recurrence or new lesion.
- After 5 years, the routinely scheduled follow-up with the dermatologist ends. Further follow-up can be planned in consultation with the patient and should be based on the patient's risk factors for a new lesion or recurrence.

**Good practice statements are developed when there is high certainty that the desirable effects of an intervention clearly outweigh its undesirable effects, but the body of supportive evidence is indirect.*

Clinical practice guidance:

- Radiologists or clinicians should use clear criteria for determining which lymph nodes are pathological. The radiologist or clinician should be experienced as the interpretation of the examination is very dependent on the performer as well as his experience.
- Patients with unresectable stage IV melanoma should receive an individual follow-up plan.
- Education on skin self-examination with handouts and online material for example a teaching video can be provided by patient associations.

7.2 Introduction

This chapter addresses the research question on surveillance interventions for patients diagnosed with a cutaneous melanoma clinically disease free after receiving curative-intent treatment. The aim of follow-up is to improve survival of patients by early detection of recurrences and subsequent primary melanomas as 8% of all patients with melanoma develop a secondary melanoma within 2 years of their initial diagnosis.(Amaral 2025) Patients are also at increased risk for other skin tumours.

A recent analysis of the US National Cancer Database patient cohort 2012-2020 with >1.0mm Breslow thickness (n=74097) showed that for patients with a negative lymph node, the probability of having metastatic disease at initial presentation ranged from 0.001 to 0.5.(Boutros 2025) Male patients older than 70 years of age with mitogenic tumours, lymphovascular invasion, ulceration, Breslow thickness greater than 4 mm, lentigo maligna subtype, and unusual tumour location, had the highest risk.(Boutros 2025) The authors concluded that the use of whole-body PET/CT with or without brain MRI can be tailored taking into account these specific patient and tumour characteristics.(Boutros 2025)

The type of surveillance interventions and their frequency could be a combination of clinical follow-up visits, laboratory tests, and imaging.(Johnston 2023) The surveillance interventions can be performed by patients and healthcare professionals. Clinical follow-up consists of skin self-examination (SSE), and clinical examination by healthcare professionals (HCP) at the clinic in a scheduled (more or less intense), unscheduled or fast-track system. Dermatologists may proceed to non-invasive imaging techniques and/or computer-aided systems such as photo surveillance. A care plan may be set up for the individual patient. The examinations that have been described in the literature during clinic visits include measurement of biomarkers (S100B, LDH) with imaging consisting of ultrasound, X-ray, PET/CT (standard or extended field of view), whole-body CT, MRI (whole-body or brain). Psychosocial interventions are also recommended during follow-up in the United Kingdom.(NICE 2022)

Evidence on the utility of SSE as well as whole body clinical examination is more consensual compared to the utility of imaging and blood tests for patients with resected melanoma.(Amaral 2025) There is no consensus on an optimal schedule for either clinical examination, imaging, or blood tests.(Amaral 2025) The schedule is particularly not well established after 3 years of follow-up.(Amaral 2025)

There is no evidence nor consensus on the duration of follow up, and even less so on the best transition time from the active disease follow up phase to a screening phase of a new potential disease (including other types of skin cancers). The current guidelines recommend follow-up durations varying between 0, 1, 3, 5 and 10 years and sometimes even lifelong.(Amaral 2025,Johnston 2023,NICE 2022,Rajagopal 2024)

Inspired by the literature on risk assessment and the accuracy level of the actual staging system, the more recent, consensus or evidenced-based guidelines always based the follow-up schedules on the melanoma stage at diagnosis (before full curative-intent treatment).(Amaral 2025,NICE 2022,Rajagopal 2024)

Some guidelines propose a patient-tailored follow-up schedule taking into account the disease stage, individual risk and personal needs of the patient, and which includes the clinical-dermatological examinations, lymph node US, laboratory examinations and imaging.(Amaral 2025) The Ontario guideline advises a routine follow-up schedule for all patients who are clinically disease-free after curative-intent treatment has been concluded.(Rajagopal 2024) Whenever symptoms of recurrence appear, the patient should be seen in between visits.(Rajagopal 2024) The NICE guideline suggests to consider personalised follow-up for people who are at increased risk of further melanomas.(NICE 2022) In particular, they recommend to base the follow-up of patients with stage IIIA-IIID and resected stage IV receiving adjuvant therapy on the therapeutic follow-up requirements.(NICE 2022) Although, this could still be considered the 'curative-intent treatment' phase.

A comparison of surveillance schedules of asymptomatic patients i.e. no evidence of disease, according to the more recent, consensus or evidenced-based guidelines is presented in Appendix 7.2.(Amaral 2025,NICE 2022,Rajagopal 2024)

7.3 Research question and search

The research question was as follows: For adult patients (≥ 18 years old) with stage I, II, III, or resectable IV melanoma who are clinically disease-free after receiving curative-intent treatment, which follow-up evaluation or combination of clinical follow-up, laboratory tests, and imaging are optimal and at what frequency should these evaluations be performed to improve patient outcomes?

The Ontario guideline on surveillance strategies was the starting point for adaptation for the Belgian context.(Rajagopal 2024) The research question was translated into PICO (population - intervention – comparator – outcome)(see Appendix 7.1).The literature search strategy (see Appendix 7.3) from the systematic review conducted for the Ontario guideline was adapted for this research question and updated for the years 2022-2025.(Rajagopal 2024)

7.4 Evidence

7.4.1 Included studies and methodological quality

The included studies are a combination of the studies included in the SR of Rajagopal et al. and studies identified, selected and appraised by KCE. The SR was assessed by one KCE researcher with the AMSTAR-2 tool (see Table 64 in Appendix).(Shea 2017)

Two RCTs were included: the MELFO trial and the TRIM trial.(Moncrieff 2022,Naeser 2022) The MELFO trial was identified and rated by the SR (Rajagopal et al) at high risk of bias for the patient-reported outcomes and at some concern of bias for survival and recurrence rate.(Rajagopal 2024) The TRIM trial, an ongoing trial with one publication on patient-reported outcomes at one year, was identified and evaluated by KCE as some concern for risk of bias.(Naeser 2022) The methodological quality of the MELFO-trial is summarised in the SR of Rajagopal.(Rajagopal 2024) The methodological quality of the TRIM study is summarised in Table 65 in the Appendix.

Six comparative cohort studies were included. Five of them were identified in the SR.(Rajagopal 2024) They were all assessed by the authors at high risk of bias. An additional cohort study was retrieved by KCE, the cohort study of Helvind et al. which had no serious risk of bias.(Helvind 2023)



The methodological quality of the five older cohort studies is summarised in the SR and the newly identified study is summarised in Table 66.

An overview of the selected studies is given in Table 13. The tables of evidence of each study are available in section Appendix 3.5.

Table 13 – Overview of selected studies for routine follow-up

Study	Design	Identified by	Stage	Size	Comparison	Outcomes
MELFO	RCT	Rajagopal	IB-II	388	Clinical examination frequency	OS, DFS, QoL
Rueth et al.	Modelling retrospective data, comparative	Rajagopal	I-III	1600	Imaging frequency and type	Gain in life expectancy, DFS
Kurtz et al.	Retrospective, comparative	Rajagopal	II-III	247	Imaging frequency and type	OS stage II, DFS
Ribero et al.	Retrospective, comparative	Rajagopal	IB-IIA	1149	Addition of US	DFS, QoL
Broman et al.	Retrospective, comparative	Rajagopal	III	159	Imaging frequency	DFS, QoL
Dieng et al.	Retrospective, comparative	Rajagopal	III	473	Imaging frequency	OS, DFS, QoL
TRIM	RCT	KCE search	IIB-IIID	204	Full strategy intensity	QoL
Helvind et al.	Retrospective, comparative	KCE search	IIB-IIID	1480	Addition of PET/CT	DFS

OS overall survival, DFS disease free survival, QoL quality of life

7.4.2 Frequency of clinical follow-up schedule

Patients from the UK and The Netherlands with stage IB–IIC melanoma treated with curative intent were enrolled in the MELFO RCT. (Moncrieff 2022) Experimental and control group patients received the same content of clinical follow-up which was composed of history taking, a physical examination, and a structured SSE education at each visit. For suspicious (recurrent) disease, diagnostic imaging and laboratory testing, as advised in the national guidelines, was offered.

192 patients were enrolled in the intervention group (less intense F/U) with a frequency of routine clinical visits in the 1st, 2nd, 3rd, 4th, and 5th year after surgery for primary melanoma differing according to the stage of the disease as described in Table 14.

Table 14 – MELFO RCT Frequency of routine clinical visits after surgery by stage (times/year)

	Year 1	Year 2	Year 3	Year 4	Year 5
Intervention=less intense follow-up					
Stage IB	1	1	1	1	1
Stage IIA	2	2	1	1	1
Stage IIB-IIC	3	3	2	1	1
Control= intense follow-up following national guidelines					
UK IB-IIC	4	4	4	2	2
Netherlands IB-IIC	4	3	2	2	2

196 patients were enrolled in the comparator group (more intense F/U) with a frequency as advised in the national guidelines. The frequency of the visits was not adapted to the stage in the control group.

OVERALL SURVIVAL AND DISEASE-FREE SURVIVAL OUTCOMES

In the MELFO trial, the reported relative risk (HR) for overall survival was 0.9 (95%CI 0.49-1.66) favouring the less intense group. The proportions for each group are not available (patient numbers at risk in the survival curves do not match with numbers in the Consort flow diagram). The 5-year disease-free survival (DFS) reported was 80.3%, (95%CI 74.6%–86.5%) for the more intense group and 82.7% (95%CI 76.9%–88.9%) for the less intense group (HR 0.92; 95%CI 0.56-1.53). The calculated absolute risk difference for DFS is 2.4% favouring the less intense group (NNT=42) which is unlikely to be of clinical relevance.

The 5-year cumulative hazard reported for detection of recurrence (n=59) or new primary melanoma (n=16) was 22.3% (95%CI 15.8%–28.2%) for the more intense and 18.5% (95%CI 12.2%–24.3%) for the less intense arm, with a HR of 0.87 (95%CI 0.54–1.39); calculated absolute risk difference of 3.8% (NNT=26) favouring the more intense group in detecting more recurrences.

QUALITY OF LIFE RELATED-OUTCOMES

At five years in the MELFO trial, the patient-reported outcomes assessed for 240 patients (62%) did not show a statistically significant difference between intervention and comparison groups for scores on the Cancer Worry Scale, Impact of Event Scale, RAND-36, or State-Trait Anxiety Inventory in the MELFO RCT (stages IB-II). (Moncrieff 2022)

The authors concluded that a reduced follow-up schedule induces no differences in patient-related outcomes. (Moncrieff 2022)

ADVERSE EVENTS

No evidence was retrieved on adverse events related to the intervention(s) (e.g. comparison of AEs rate between imaging examinations and clinical follow up examinations).

Diagnostic delay as a result of fewer clinical visits was not seen in the MELFO trial as results of the DFS were not significantly different. In both groups of the MELFO trial, 75% or more of the detections were initially by the patient: self-examination was the method of detection for 25 experimental patients and 32 control patients (75.8% vs. 76.2%; p=0.41). (Moncrieff 2022)

The authors concluded that a reduced-intensity, AJCC stage-adjusted clinical follow-up schedule is a safe strategy. (Moncrieff 2022)

No significant differences between the groups were detected in terms of the number of unscheduled or missed follow-up appointments during the MELFO study. (Moncrieff 2022). In approximately half of the patients, the additional visit was confined to one isolated episode in 5 years. The authors conclude that patients' acceptance was very high.

Conclusions:

- **A more intense clinical follow-up schedule probably results in no clinical meaningful benefit in overall survival or disease-free survival compared to a less intense follow-up for patients with melanoma stage IB-II. (moderate level of evidence)**
- **A more intense clinical follow-up schedule probably results in no clinical meaningful benefit in the quality of life compared to a less intense follow-up for patients with melanoma stage IB-II. (moderate level of evidence)**
- **Evidence on adverse events related to the clinical examinations during follow-up was not reported in RCT or comparative cohort studies.**



7.4.3 Imaging during follow-up

7.4.3.1 Different intensities of imaging

Two studies were identified; one study with one or a combination of the following -CT, PET/CT, brain MRI and nodal basin ultrasound- and one study with the addition of CT or PET/CT.(Broman 2021,Dieng 2022)

The retrospective comparative study by Broman et al included 159 patients with stage IIIA-D melanoma with a positive SLN biopsy managed with nodal surveillance at Moffitt Cancer Center in US, with at least six months of disease-free follow-up.(Broman 2021) Patients with clinically involved lymph nodes at presentation or evidence of distant disease on pre-operative or post-operative staging studies were excluded.

This retrospective cohort study looked at surveillance strategies consisting of clinical assessments with or without imaging. The type of imaging F/U interventions were CT, PET/CT, brain MRI, and nodal basin ultrasound and was determined by the treating oncologist. The comparison was based on average individual patients' surveillance regimens of PET/CT and CT only: low intensity (n=70) with CT or PET/CT less than once a year; moderate intensity (n=42) meaning a CT or PET/CT every year, and high intensity (n=47) with CT or PET/CT every six months.

The median age was 65 years (IQR 53-75). The median follow-up time was 24 months (IQR, 17 to 33) with a follow-up rate of 90%. On average patients were seen in clinic approximately once every two months, underwent nodal basin ultrasound once every six months, had one PET/CT per year, and one brain MRI per year. More patients on adjuvant therapy compared to those without therapy had intense follow-up: 58% versus 14%, respectively ($p<0.01$).

The study by Dieng et al compared intensive versus less intensive CT or PET/CT imaging follow-up strategies in stage IIIA–D patients with intensive follow-up defined by a frequency of imaging every 3–4 months (n=141), versus biannual (n=47) or annual (n=285) frequency imaging as the less intensive regimen. The frequency of the imaging schedule was determined by clinician preference which lead to serious selection bias.

Patients selected for intensive follow-up had worse clinical characteristics than those in the other two groups and patients in the biannual group had worse clinical characteristics than those in the annual group. The median age was 54 years with significant variation between the groups: (more older patients in the 3-monthly group $p<0.001$). The mean Breslow thickness also statistically differed between groups ($p<0.001$). The median follow-up time was 6.2 years.

OVERALL SURVIVAL

The overall survival was reported in Dieng et al. and was highest in the annual CT or PET/CT follow-up strategy group (intensive vs annual imaging HR 5.20; 95%CI 3.53 to 7.66, $p<0.01$; biannual vs annual imaging HR 1.21; 95%CI 0.65 to 2.28; $p=0.55$).(Dieng 2022) Because of the selection bias, these results can be questioned and are considered unreliable.

DISEASE-FREE SURVIVAL

In the study by Broman et al. DFS was reported as recurrence-free survival.(Broman 2021) Forty-eight patients (27%) had a recurrence. Most distant recurrences were detected by CT or PET/CT while most nodal recurrences were detected by ultrasound and loco-regional recurrences by clinical assessment. The recurrence-free survival was not different for the moderate vs low intensity (HR 1.21 95%CI 0.53-2.74) and the high vs low intensity (HR 1.05 95%CI 0.47-2.32) surveillance groups or between the 3 groups (low 27% vs. moderate 24% vs. high 30%; $p=0.33$). No difference in recurrence was seen by adjuvant systemic therapy ($p=0.76$). The authors concluded that, compared to moderate- and low-intensity surveillance regimens, high intensity translated to similar rates of recurrences that were able to be treated definitively.(Broman 2021) The authors concluded also that most nodal recurrences occurred within the first year and were initially detected by clinical

assessment or ultrasound, supporting continued use of physical exam and nodal basin ultrasound alongside cross-sectional imaging in stage III.

In the study by Dieng et al., the DFS was reported as distant disease-free survival and was highest in the annual CT or PET/CT follow-up strategy (intensive vs annual HR 4.57; 95%CI 3.25-6.45). The global recurrence rate was 53% for all patients (n=252). A higher distant recurrence rate was seen for patients in the intensive group compared to biannual or annual imaging with 84% vs. 51% vs. 38% recurrences, respectively (p<0.001).

QUALITY OF LIFE

No evidence was retrieved.

ADVERSE EVENTS

No evidence was retrieved on adverse events related to the intervention(s) (e.g. comparison of AEs rate between imaging examinations and clinical follow up examinations).

COST

This outcome, not part of the PICO, was added for the evidence to recommendations information. The retrospective comparative study of Broman et al. studied cost which was proportional to the surveillance intensity.(Broman 2021) From \$4,240 to \$24,838 for a patient with median recurrence-free follow-up receiving low-intensity versus high-intensity surveillance. The cost per detected recurrence was also proportional to surveillance intensity with \$15,688 to \$82,792 with low-intensity versus high-intensity surveillance. Median nodal basin ultrasound cost was \$1,123 whereas the lowest cross-sectional imaging charge was for PET/CT at \$5,772.

The authors conclude that, while earlier detection and management of nodal recurrence has not been clearly linked to improved long-term outcomes, potential utility and minimal increased cost support continued use of clinical assessment and nodal basin ultrasound even in adjuvant patients for whom cross-sectional imaging is planned, at least for first year of surveillance when nodal recurrence risk is highest.(Broman 2021)

7.4.3.2 Adding imaging to clinical follow-up

The TRIM study is an ongoing nationwide prospective randomised study with multiples aims for stage IIB-III.(Naeser 2022) Half of the patients are randomised to whole-body imaging in addition to physical examinations. Three imaging procedures are performed during the first year. First aim is to investigate whether imaging improves survival by earlier detection of recurrence (results not available yet). The second aim was to investigate if imaging during the first year of follow-up affected the patients' well-being.

Helvind et al. published the results of a retrospective analysis of prospectively collected data from two consecutive nationwide population-based cohorts of Danish patients with stage IIB to IIID melanoma.(Helvind 2023) The year of primary diagnosis was used by the authors as a proxy for two different surveillance programs. Patients with cutaneous melanoma diagnosed in 2008–2010 (cohort 1) were followed only with clinical examinations and patients with cutaneous melanoma diagnosed in 2016–2017 (cohort 2) were followed with clinical examinations and routine PET/CT at 6, 12, 24, and 36 months. The clinical schedule was 3-monthly for 2 years, then 6-monthly for 3 years.

The retrospective study by Kurtz et al. included patients with stage II and III melanoma followed for a minimum of 6 months after surgical resection to achieve no evidence of disease status.(Kurtz 2017) A comparison was made between clinical examination only and clinical examination with imaging. For patients with stage IIA-IIB a clinical examination plus at least 2 serial chest X-rays, and for patients stage IIC-IIIA-IIIB-IIIC a clinical examination plus some combination of chest X-rays, CT scans (including chest, abdomen, pelvis, and neck for head and neck primary), magnetic resonance imaging (MRIs), whole body PET/CTs, or other directed imaging (ultrasound).(Kurtz 2017) In total 181 patients (IIA-B: n=76 and IIC/IIIA-C: n=105) were included receiving clinical examination and



imaging. The comparison group with clinical examination only, included 66 patients (IIA-B: n=49, IIC: n=0, IIIA-C: n=17).(Kurtz 2017) The impact of the MRI imaging was not reported.

The Rueth et al. study modelled retrospective patient-level data (n=1600) from a single-institution and simulated the natural history of patients with stage I–III melanoma.(Rueth 2014) A 5-year imaging strategy with CT or PET/CT (chest/abdomen/pelvis) performed every 6 or 12 months was compared to clinical examination every three months for different stages. The population included children (age range 8 to 95 years). An adult subgroup analysis was not conducted. This modelling study calculated gain in life expectancy for ‘surgically treatable’ detected regional and distant metastasis with scanning, and disease-specific survival.

The retrospective study by Ribero et al. included patients with stage IB and IIA melanoma after negative lymph node biopsy.(Ribero 2017) A comparison was made between clinical examination only and clinical examination with ultrasound imaging by looking at two historical cohorts in two settings, one in Barcelona Spain and one in Turin Italy.

The historical cohorts ran before adjuvant therapy. The intervention cohort (1998-2014) was the Italian cohort (N=595) with ultrasound regional lymph node basins and F/U examinations every 6 months for 5 years. An abdominal US was performed every 12 months for 5 years. The control group (1998-2014) was the Spanish cohort (N=554) with clinical F/U examination every 4 months for the first 2 years, then every 6 months for the remaining 3 years and a laboratory tests (S100B) every 6 months for 5 years. The median age was 53.8 years with a median follow-up time of 4.14 years. The Breslow thickness of the primary melanoma was on average 1.39 mm in the Spanish cohort and 1.45 mm in the Italian cohort (NS). The median follow-up of patients without relapse was 3.8 years (IQR 1.1-7.3).

OVERALL SURVIVAL AND MELANOMA SPECIFIC SURVIVAL

In the study by Kurtz et al., the overall survival was presented for the lower stages only (median follow-up of 31.2 months).(Kurtz 2017) No survival analysis was performed for the higher stages because the majority (87%) of patients in the stage IIC/IIIA-C was followed with imaging. For stage IIA-IIIB patients (at least 2 serial chest X-rays), there was no difference in the overall survival rate between the intervention and comparison groups, 96% (95%CI 0.89-0.98) and 95% (95%CI 0.88-0.99), respectively. This outcome result is not relevant for Belgium as X-rays are not used for follow-up purposes.

The modelling study reported gain in life expectancy by stage I–III.(Rueth 2014) The assumptions were that 80% of early imaging-detected regional recurrences and 20% of early imaging-detected distant recurrences could be treated with curative intent. For all stage patients, life expectancy overall gains were ≤ 2 months. For stage I patients, life expectancy was 52 months without surveillance imaging. With PET/CT imaging every six months, the life expectancy increased by 0.4 months, with a 0.7 % relative survival increase. The NNT was 252 PET/CT scans every 6 months to detect one treatable recurrence. For stage II overall life expectancy increased with 1.1 month with biannual PET/CT versus without; resulting in a NNT of 79. For stage IIIA overall life expectancy increased with 0.9 month with biannual PET/CT versus without; resulting in a NNT of 78. For stage IIIB overall life expectancy increased with 1.7 month with biannual PET/CT versus without; resulting in a NNT of 33. Life expectancy for stage IIIC patients was 30 months without surveillance imaging. With PET/CT imaging every six months, life expectancy increased by two months, with a 6.8 % relative survival increase.

The benefit in long-term survival was limited to absent and not considered as clinically relevant except for the highest stages IIIB and C. This was explained by the lower average life expectancy for this population compared to stage I and II patients; an absolute gain of 2 months translates to a more substantial relative increase.

The Ribero study in stage IB-IIA, showed no statistical difference in MSS (Kaplan-Meier analysis) for the group with ultrasound compared to clinical only (p=0.19)(no further data presented).(Ribero 2017)

QUALITY OF LIFE

For the TRIM trial, Naeser et al 2022 reported results on the HRQoL at 1 year. During this first year of follow-up, patients in the intervention arm underwent laboratory tests and whole-body imaging at baseline, 6 and 12 months. The HRQoL assessments took place prior to the clinical visit on a web-based device administered by a research nurse. Validated HRQoL-instruments were used (EORTC QLQ-30 and HAD-scale).

The authors concluded that the addition of technical investigations to clinical examinations did not affect the melanoma patients' HRQoL or levels of anxiety or depression during the first year after radical surgery for stage IIB-C or III. One limitation of the study is that the levels of anxiety and especially depressive symptoms were globally low in the study group in comparison with the general population. The TRIM study was still recruiting, and future analyses might change the conclusion which are now limited to year 1.

High false positive rates of CT and PET/CT were common (see section 'other' below).(Rueth 2014)

DISEASE-FREE SURVIVAL

In the Helvind study, the overall recurrence for the total study period was the same for both cohorts HR 1.01; 95%CI 0.85-1.21.(Helvind 2023) Within the first two years of surveillance after diagnosis, a 51% greater hazard of distant recurrence (HR 1.51; 95%CI 1.16–1.96) and a tendency toward a higher hazard of overall recurrence (HR 1.16; 95%CI 0.93–1.44) for patients followed with clinical examinations and whole-body PET/CT compared to patients followed with clinical examinations alone was seen. The authors concluded that, because distant recurrences are not as readily detected by clinical examination as locoregional metastases, the data confirms the yield of routine PET/CT in melanoma surveillance.(Helvind 2023)

The progression-free survival (stage II-III) was not different between clinical only or with imaging ($p=0.75$). (Kurtz 2017) For stage IIC and IIIA-C routine whole body imaging detected recurrences that were not found on clinical examination in 50%. (Kurtz 2017)

In the modelling study, disease-specific survival was reported comparing CT or PET/CT in the biannual or the annual schedule.(Rueth 2014) Whatever the schedule or stage, the disease-specific survival was always similar (details on percentages for each stage and schedule are in Appendix 7.5.2). The 'surgically treatable' detection rates for regional and distant metastasis was calculated.(Rueth 2014) At 5-year follow-up, CT or PET/CT at 6-month intervals detected surgically treatable regional or distant recurrence in 6.4% of patients with stage I, 18.5% of stage II, and 33.1% of stage III disease; 12-month intervals decreased the rates to 3.0%, 7.9%, and 13.0%, respectively.

For stage IB-IIA, the median time to first recurrence was 2.32 years for clinical with ultrasound vs 2.97 years for clinical only, resulting in a hazard ratio for disease-free interval of 0.81 (95%CI 0.58-1.14) (overall median follow-up of patients without relapse was 3.8 years (IQR 1.1-7.3)).(Ribero 2017) Recurrences were detected in 69 (12.5%) in the no-ultrasound group versus 72 (12.1%) in the US-imaging group.

ADVERSE EVENTS

No evidence was retrieved on adverse events related to the intervention(s).

OTHER

In the modelling study, the positive predictive value (PPV) for both imaging modalities (CT or PET/CT) and for both intervals (annual or biannual) were low due to the high false positive rates of CT (20%) and PET/CT (9%) for any stage patients for the five-year period.(Rueth 2014) The PPV was highest in stage IIIC for PET/CT with 32 % (CT 13%). Both CT and PET/CT effectively predicted absence of disease. With a negative predictive value nearing 100%, routine imaging can effectively rule out recurrence.(Rueth 2014) With 12-month imaging intervals, 362 CT scans or 249 PET/CT scans would have to be performed during the course of 5 years to diagnose 1 treatable recurrence



for patients with stage I melanoma. With 12-month imaging intervals, 1 of every 34 CT scans or 1 of every 26 PET/CT scans detected a treatable recurrence for patients with stage IIIC melanoma.

The authors concluded that, with a negative predictive value nearing 100%, routine imaging can effectively rule out recurrence; however, the high rate of false-positives and the low positive predictive value means that a large number of imaging must be performed to detect a small number of treatable recurrences. For 10,000 patients, routine annual surveillance imaging for patients with stage I melanoma would result in a 5-year total of 45,296 CT scans and 45,314 PET/CT scans. (Rueth 2014)

Conclusions:

- There was no evidence on 'overall survival' from RCTs and cohort studies on adding imaging to the clinical examination schedule compared to clinical examination alone during follow-up of patients with melanoma.
- Adding a 6 or 12-monthly PET/CT to the clinical examination schedule may have little to no benefit on 'gain in life expectancy' for patients with stage I-III melanoma, but the evidence is very uncertain. (very low level of evidence)
- Adding a 6-monthly ultrasound to the clinical examination schedule for patients with stage IB-IIA melanoma may have little to no benefit for 'melanoma specific survival', but the evidence is very uncertain. (very low level of evidence)
- Adding PET/CT to the clinical follow-up schedule may have little to no effect on the 'quality of life' for patients with melanoma stage IIB-IIC, but the evidence is very uncertain. (very low level of evidence) False positive results for PET/CT and CT when added to clinical follow-up are common and may affect the quality of life of patients.
- Evidence on the 'adverse events' related to adding imaging to clinical follow-up was not reported in RCTs or cohort studies.
- An intense imaging schedule during follow-up may have no effect on 'disease-free survival' compared to a less frequent imaging schedule for patients with melanoma stage III, but the evidence is very uncertain. (very low level of evidence)
- Adding PET/CT imaging to a clinical examination schedule compared to clinical examination alone results in little to no difference in the 'detection of overall recurrences' during a 5-year follow-up period but may increase the detection of overall recurrences the first 2 years of patients with melanoma stage IIB-IIID. (low level of evidence)

7.5 Evidence to recommendations

7.5.1 Balance between clinical benefits and harms

MORE INTENSE VERSUS LESS INTENSE CLINICAL FOLLOW-UP SCHEDULE

The available evidence focusses on survival and quality of life during follow-up for stage IB-IIC. The current evidence shows that after a follow-up of 5 years, a more intense clinical follow-up schedule probably results in no clinical meaningful benefit in overall survival or disease-free survival compared to a less intense follow-up for patients with melanoma stage IB-II. For stage IB the frequency schedule was decreased from 4-4-4-2-2 (each number stands for the frequency in the order of the 5 years) to 1-1-1-1-1, for stage IIA the frequency was decreased from 4-3-2-2-2 to 2-2-1-1-1. For stage IIB-C the following two frequencies 4-4-4-2-2 or 4-3-2-2-2 were decreased to 3-3-2-1-1.

The current evidence on quality of life shows that a more intense clinical follow-up schedule probably results in no clinical meaningful benefit in quality of life compared to a less intense follow-up for patients with melanoma stage IB-II.

In a real life setting, the negative effect on mobility and usual activities of a more intense schedule have to be taken into account. A reduced schedule would therefore benefit the patient but also the Belgian health system by reducing medical costs, requiring less resources, and freeing clinic appointment which might result in reducing possible waiting list. A less intense schedule might also reduce the number of skin biopsies of very thin non-malignant lesions and the number of false positives will be reduced in general.

Reducing the follow-up schedule might cause harm by the later detection of a recurrence or a new primary malignant lesion. Early detection of recurrent disease, when tumour burden is lowest, might theoretically be beneficial because of treatment which has become available in the past decade. especially for higher stage disease IIB and IIC. This theoretical advantage is not shown in the RCTs.

According to the GDG, in Belgian practice, surgeons, family physicians and nurses specialised in skin cancer are not involved in the routine surveillance of melanoma patients. Experts explained that the use of dermoscopy is necessary for an optimal clinical F/U. Although some GPs are nowadays trained in dermoscopy, the expertise mostly lies with dermatologists. Care may be impacted by regional availability of healthcare resources, including specialist physicians and surveillance imaging modalities.

ADDING PET/CT OR ULTRASOUND TO THE CLINICAL FOLLOW-UP SCHEDULE

When considering the balance between benefits and harms for PET/CT, the available evidence showed that by adding a 6-monthly PET/CT to the clinical examination schedule the overall 'gain in life expectancy' was ≤ 2 months. The benefit was considered not clinically relevant for the lower stages. For stage III, an increased life expectancy of two months or a 6.8 % relative survival increase, might be considered clinically relevant because of the lower average life expectancy for this population. Another minor benefit was the earlier detection of recurrent disease (theoretically beneficial) in the first two years of follow-up. This benefit was no longer present for the total 5-year study period.

Benefits of surveillance imaging that were described by the experts were the detection of treatable recurrences, regional and distant, which may have important implications for improving patient outcomes. Secondly, reassurance and emotional support can be given to patients who remain disease free. The use of surveillance imaging is widely practiced in Belgium which might for some patients be beneficial and improve adherence to follow-up and for other cause 'scanxiety'. (Derry-Vick 2023)

Harm will be present as a result of frequent tests for the patients and the large number of tests required to detect a single treatable recurrence. For society, the use of surveillance imaging after melanoma surgery has important financial and resource implications. For the patient, anxiety or 'iatrogenic uncertainty' induced by surveillance imaging is commonly reported, and is related to the scan results and the scan procedures. (Derry-Vick 2023) The high false-positive rates of PET/CT might result in further examinations with related stress.

For the balance between benefits and harms for ultrasound, the evidence showed that ultrasound was not beneficial for patients with stage IB-IIA melanoma for 'melanoma specific survival'. Although ultrasound is currently often practised, accessible and safe, it does not weigh against the cost and time for the patient (including quality of life and false positives), and the cost and resources for the hospital and the Belgian system.



DECIDING ON A FOLLOW-UP SCHEDULE BY STAGE FOR BELGIUM

At the GDG meeting, a summary of the current guidelines was presented and discussed (Appendix 7.2). The Ontario guideline presented the recommendations by stage similar to the majority of guidelines on surveillance to reflect the risk of recurrence. Commonly, a more intense surveillance starts from stage IIB, while some guidelines select stage IIC and few guidelines stage III. In general, the schedule in Belgium is mostly based on the more intense schedule from the ESMO guidance, which is not in line with the evidence from the MELFO trial.

The GDG patient representative expressed the importance of patients' quality of life during the follow-up. Examples of factors negatively affecting quality of life were, travel related to the repeat visits (poor planning of visits between specialties), and limited time for counselling during and after the illness. The use of onco-coaches and social assistants to guide patients through the treatment and follow-up was limited but considered important. Patients felt empowered by learning about their skin and knowing how to deal with suspicion. This is in agreement with the consistent international recommendation on providing regular SSE and sun safety patient education at the clinic visits. (Johnston 2023)

STAGE IA-IB-IIA

GDG experts explained that an intense schedule is currently offered in Belgium including for stage IA (see ESMO guidance Table 51 to Table 53). The schedule proposed by the Ontario guideline (Rajagopal 2024) is less intense compared to ESMO and more intense than that of the MELFO study. KCE initially proposed to follow the Ontario schedule (6-12 months first three years, then yearly) for stage IA-IIA. This would probably mean a less intensive follow-up compared to current practice for most settings in Belgium, especially for stage IB and IIA. The GDG experts preferred a dermatologist clinic visit every 6 months for 3 years, then annually for 2 years. After exchange and discussion with the validators of the report, KCE decided to recommend yearly visits (MELFO schedule) without imaging, biomarkers or blood tests for stage IA and IB because the benefits do not weigh against the harms. Most patients would prefer a less intense follow-up compared to an intense follow-up (see benefit harm discussion above). Similarly, the MELFO schedule was followed by KCE for stage IIA except for year 3 (6-monthly instead of yearly).

Table 15 – Follow-up schedule IA-IIA for Belgium

	Year 1	Year 2	Year 3	Year 4	Year 5
Stage IA	1	1	1	1	1
Stage IB	1	1	1	1	1
Stage IIA	2	2	2	1	1

Experts of the GDG highlighted that ultrasounds of the lymph node basin is more sensitive than clinical follow-up for detecting nodal involvement and that US of the LN basin is current practice in Belgium although not everywhere as technical expertise is needed. The opinion of the GDG experts was not to use US of the LN basin for stage IA patient but from stage IB and IIA once a year during three years. After exchange with the stakeholders and the validators, the KCE team decided against recommending US once a year for patients stage IA, IB and IIA (and IIB-IIC) because the evidence to support this clinical action is lacking (see benefit harm discussion above).

Patients should be informed that a more intense schedule with or without imaging does probably not result in a clinical meaningful benefit in overall survival or disease-free survival compared to a less intense follow-up. The schedule should be discussed with the patient and the individual harms and benefits taken into account.

STAGE IIB-IIC

The follow-up schedule in Belgium is based on the more intense schedule from the ESMO guidance and is 3-monthly for the first 3 years and 6 monthly for another 2 years: 4-4-4-2-2. Nevertheless, the experts reported that variation across Belgium exists. KCE initially proposed to follow the Ontario schedule (3-3-2-1-1) for both stages. After exchange and discussion with the validators of the report, KCE decided to recommend the MELFO schedule 3-3-2-1-1 for stage IIB and schedule 3-3-3-1-1 for stage IIC, without biomarkers or blood tests because the benefits do not weigh against the harms (see benefit harm discussion above). Most patients would prefer a less intense follow-up compared to an intense follow-up.

The benefit to add surveillance imaging for stage IIB and IIC is limited to the detection of recurrences with important implications for clinical management, such as surgical resection of an isolated distant metastasis. A positive clinical impact for the melanoma survivor was calculated to be 1 month only (data from before 2014). Experts explained that meanwhile the opportunities for treatment have changed and would therefore apply surveillance imaging. Other aspects to consider are, the earlier detection of recurrent disease compared to clinical examination or symptoms in the first two years of follow-up and the lower average life expectancy for stage IIB and IIC in Belgium (and worse compared to IIIA). See data on the observed survival in Table 3. After exchange and discussion with the validators of the report, KCE decided to reduce the Ontario schedule for stage IIB for year 3 to annual surveillance imaging, and keep to the 6-monthly schedule for the first 3 years for imaging surveillance in stage IIC.

MRI of the brain is preferred over CT for routine screening by the authors of the Ontario guideline. The GDG experts confirmed a better soft tissue contrast and superior sensitivity for brain metastasis of MRI compared to CT. They suggested to align the frequency of the brain MRI with the frequency of PET/CT, acknowledging that evidence is lacking to support this.

STAGE III AND RESECTABLE IV

The experts explained that the practice in Belgium is 'intense clinical follow-up' based on the ESMO guidance: every 3 months during 5 years, then every 6 months for 5 years, and yearly after that. For planning purposes and to limit resources, some experts suggested alternating the clinical follow-up between dermatologist and oncologist but not all agreed.

Again, the limited evidence of an increased detection in the first 2 years for stage III by adding PET/CT, was supported by the experts. They suggested for PET/CT and brain MRI a frequency of 6 monthly for years 1-3, then yearly, acknowledging that evidence is lacking to support this schedule for MRI.

None of the reviewed studies presented data on the use of ultrasound in stage III. The experts said that the use of ultrasound is standard clinical practice nowadays for stage III as lymph node dissection is no longer indicated and performed (see chapter on lymphadenectomy). In Belgium, structured follow-up can be adequately ensured, and CLND can still be performed if nodal recurrence is detected.

The experts suggested the same schedule for patients with resectable stage IV as for stage III.

ADDITIONAL CONSIDERATIONS

There was no eligible evidence in this updated systematic review (and in the systematic review of Rajagopal) that investigated the role of photo-surveillance, dermoscopy or biomarkers in the target population. Amongst the ongoing studies (see Table 63 in Appendix 7.3.6), photo-surveillance and biomarkers are being investigated.

The duration of the follow-up surveillance and the transition between follow-up and lifelong screening of skin cancer by dermatologist is not discussed in the consulted guidelines, in which duration can vary from 1 year to 10 years, and even longer. In the ESMO guideline, lifelong self-examination of the skin and lymph nodes is mentioned as a recommendation. However, the ESMO committee refers clinicians to national guidelines for follow-up strategies after 3 years although they give an example



of lifelong follow-up strategies. The NICE committee recommends a 5-years follow-up duration except for stage IA but suggests to personalise follow-up surveillance for people who are at increased risk of further primary melanomas (for example, people with atypical mole syndrome, previous melanoma, multiple in-situ melanomas, or a history of melanoma in first degree relatives or other relevant familial cancer syndromes).

7.5.2 Quality of evidence

Moderate evidence for frequency of clinical follow-up schedule (one RCT).

Very low to low evidence for imaging during follow-up (one RCT and 6 cohort studies).

7.5.3 Patient preferences

The importance of patients' quality of life is considered a critical outcome. In the Ontario guideline patient's representatives stressed that decision-making by patients and carers is helped by education on SSE and sun safety. (Rajagopal 2024) The GDG patient representative agreed and explained that knowing how to deal with skin lesions empowers the patient who often is insecure, anxious and worried. This should entail giving an explanatory leaflet, reference to online-material including teaching video's on self-examination (avoiding Dr Google), clear verbal explanations on when to seek advice, and a low-threshold contact point. These tasks should be taken on by somebody who has the time, either a melanoma onco-coach, a dermatologist, oncologist, GP or trained nurse.

It is important that patients have somewhere accessible to go and that they are aware of their rights. Equity can be addressed through helping patients made aware of patient associations, who can help finding the right expert. The *Fight Against Cancer* website provides contact points of fellow patients and will explain about the rights of patients such as asking for a second opinion, to bring a confidant, and to get expert explanations.

7.5.4 Cost and resource allocation

A more intense follow-up requires more resources and will be more costly to the healthcare system and to the patient. The study of Broman et al. highlights that increasing surveillance intensity increased overall cost and cost per detected recurrence. (Broman 2021) Distance and transport costs to the hospital where imaging (PET/CT, CT, ultrasound, etc.) is available, may vary by region and insurance, respectively. In Belgium PET/CT is reimbursed from stage IIC onwards.

7.5.5 Adaptation of the Ontario recommendations to the Belgian situation

The recommendations from the Ontario guideline were adapted for Belgium as follows:

Stage I-IIA

1.1 a) A dermatologist may provide a clinical follow-up with history and physical examination with full skin and lymph node examination (with photo-surveillance and dermoscopy if indicated) ~~and a surgeon or a family physician/cancer nurse specialist~~ annually for stage IA and IB for 5 years. ~~as clinically indicated~~ [conditional recommendation].

1.1 b) A dermatologist may provide a clinical follow-up with history and physical examination with full skin and lymph node examination (with photo-surveillance and dermoscopy if indicated) ~~and a surgeon or a family physician/cancer nurse specialist~~ for stage IIA every 6-12 months for 3 years, then annually for 2 years. ~~or as clinically indicated~~ [conditional recommendation].

1.2 Clinicians should not provide imaging to screen for asymptomatic recurrence or metastatic disease. [strong recommendation].

1.3 Clinicians should not provide routine biomarker or blood tests to screen for asymptomatic recurrence or metastatic disease. [strong recommendation].

1.4 As part of routine follow-up, clinicians should provide education on SSE and sun safety to patients and patients' caregivers who are involved in decision making. [strong recommendation].

1.5 Patients should be explained how they can access the dermatology clinic in case of a suspicious skin lesion, either recurrence or new lesion. [good practice statement].

1.6 After 5 years, the routinely scheduled follow-up with the dermatologist ends. Further follow-up can be planned in consultation with the patient and should be based on the patient's risk factors for a new lesion or recurrence. [good practice statement].

Stage IIB-IIC

2.1 a) Clinicians may provide clinical follow-up with history and physical examination with full skin and lymph node examination by a dermatologist (with photo-surveillance and dermoscopy if indicated) and an ~~surgeon or a medical oncologist/cancer nurse specialist~~ **in case of previous adjuvant treatment maximum for stage IIB every 4 months in years 1-2, then every 6 months in year 3, and annually in year 4-5.** [conditional recommendation].

2.1 b) Clinicians may provide clinical follow-up with history and physical examination with full skin and lymph node examination by a dermatologist (with photo-surveillance and dermoscopy if indicated) and an ~~surgeon or a medical oncologist/cancer nurse specialist~~ **in case of previous adjuvant treatment maximum for stage IIC every 4 months in years 1-3, and annually in year 4-5.** [conditional recommendation].

2.2 Clinicians should not provide routine biomarker or blood tests to screen for asymptomatic recurrence or metastatic disease [strong recommendation].

2.3 a) ~~CT or~~ Clinicians may provide a PET/CT scan and a brain MRI every 6-12 months to screen for asymptomatic recurrence or metastatic disease in years 1-2, then annually in years 3-5 for patients with stage IIB. [conditional recommendation].

2.3 b). ~~CT or~~ Clinicians may provide a PET/CT scan and a brain MRI every 6-12 months to screen for asymptomatic recurrence or metastatic disease in years 1-3, then annually in years 4-5 for patients with stage IIC. [conditional recommendation].

2.4 As part of routine follow-up, clinicians should provide education on SSE and sun safety to patients and patients' caregivers who are involved in decision making. [strong recommendation].

2.5 Patients should be explained how they can access the dermatology clinic in case of a suspicious skin lesion, either recurrence or new lesion. [good practice statement].

2.6 After 5 years, the routinely scheduled follow-up with the dermatologist ends. Further follow-up can be planned in consultation with the patient and should be based on the patient's risk factors for a new lesion or recurrence. [good practice statement].

Stage III and resectable stage IV

3.1 Clinicians may provide a clinical follow-up with history and physical examination with full skin and lymph node examination by a dermatologist (with photo-surveillance and dermoscopy if indicated) and an ~~surgeon or a medical oncologist/cancer nurse specialist~~ **in case of previous adjuvant therapy every 3-6 months in years 1-3, then every 6 months in years 4-5** [conditional recommendation].

3.2 Clinicians should not provide routine biomarker or blood tests to screen for asymptomatic recurrence or metastatic disease [strong recommendation].

3.3. ~~CT or~~ Clinicians may provide a PET/CT scan every 6-12 months to screen for asymptomatic recurrence or metastatic disease in years 1-3, then annually in years 4-5. [conditional recommendation].

3.4. ~~Annual~~ Clinicians may consider a **6-monthly** brain MRI for **years 1-3**, then annually in years 4-5. ~~where available; otherwise, head CT may be considered after discussing with patients~~ [conditional recommendation].

3.5. For patients with a positive sentinel lymph node, ultrasound scans of the draining nodal basin should be carried out every 4-6 months for years 1-3, and then every 6 months for years 4-5 if no complete lymph node dissection was performed [conditional recommendation].



3.6 As part of routine follow-up, clinicians should provide education on SSE and sun safety to patients and patients' caregivers who are involved in decision making. [strong recommendation].

3.7 Patients should be explained how they can access the dermatology clinic in case of a suspicious skin lesion, either recurrence or new lesion. [good practice statement].

3.8 After 5 years, the routinely scheduled follow-up with the dermatologist ends. Further follow-up can be planned in consultation with the patient and should be based on the patient's risk factors for a new lesion or recurrence. [good practice statement].

8 DISSIMINATION AND IMPLEMENTATION

8.1 Discussion

A range of different methods to raise awareness of the guideline exist. These include standard approaches which are applied by KCE, such as:

- issuing a press release at the moment of publication on the KCE website;
- addressing questions from the press;
- notifying experts, stakeholders and patient organisations of the publication;
- presentation by GDG members at national meetings Belgian Association of Dermatology Oncology, (Belgian Society of Nuclear Medicine) BSMO (Belgian Society of Medical oncology)
- publicising the guideline through the KCE's alerts;
- using social media channels e.g. on melanoma awareness month in May;
- and publishing the guideline's main points of interest in a journal.

For the applicability of the guideline, we refer to the section on evidence to recommendation which discusses facilitators and barriers, such as resources, cost or patient's opinions on interventions. We did not 'officially' apply the GRADE Equity framework as described by Pottie et al. (Pottie 2017) The patient preferences and opinion were presented in the evidence to decision steps.

Barriers or enablers to the implementation of this guideline report include:

- Wait times and timely referrals.
- Access to diagnostics and treatment in a timely manner.
- Access to imaging for advanced stages.
- Cost and shortage of health care workers.

We refer to the KCE Report 334 (2020) "Health System Performance Assessment: how equitable is the Belgian health system?" for more background information on access and equity which are relevant for patients with melanoma. The potential resource implications of applying the recommendations on the use of PET/CT will be communicated to the NIHDI.

The field of melanoma research is very active and will very likely result in changes in treatment in the coming 10 years. Several trials are ongoing. The prognosis of thin lesions is entering the field of genetic testing probably soon. This will affect the identification of patients with thin lesions who need closer follow-up compared to those who can be reassured and follow-up can be less stringent. In this theme, the expert group already submitted a new [KCE project](#) which has been accepted for the year programme. Patient information and tools might be needed when the results become available. Experts are aware that if an update of this guideline is needed, a new project can be submitted to KCE.

This guideline does not present new tools. For the follow-up of patients with a melanoma an instructive video of self-examination for recurrence or new lesions such as existing in the Netherlands

might be welcomed. The patient organisation Melanoompunt (Dutch language) has a close working relationship with their sister organisation in the Netherlands, [Stichting Melanoom](#).

To evaluate whether the recommendations of this guideline are being adequately applied, the following elements can be examined:

- adjuvant and neoadjuvant treatment uptake can be followed-up by the Belgian Cancer Registry;
- to investigate the potential of quality indicators linked to the recommendations, an assessment of the available data is the first step;
- the number of times the report is accessed (and the summary in French and Dutch) and/or referred to in the literature.

8.2 The AGREE II checklist

The items list for this guideline is presented below. (AGREE 2017, Vernooij 2017)

	Reporting criteria	Page
Domain 1. Scope and Purpose		
1. Objectives	0 Health intent(s) (i.e., prevention, screening, diagnosis, treatment, etc.) 0 Expected benefit(s) or outcome(s) 0 Target(s) (e.g., patient population, society)	See overall objective and PICO for each question in the appendix
2. Question(s)	0 Target population 0 Intervention(s) or exposure(s) 0 Comparisons (if appropriate) 0 Outcome(s) 0 Health care setting or context	See development research questions and PICO for each question in the appendix
3. Population	0 Target population, sex and age 0 Clinical condition (if relevant) 0 Severity/stage of disease (if relevant) 0 Comorbidities (if relevant) 0 Excluded populations (if relevant)	See research question for each question and PICO for each question in the appendix
Domain 2. Stakeholder Involvement		
4. Group membership	0 Name of participant 0 Discipline/content expertise 0 Institution 0 Geographical location 0 A description of the member's role in the guideline development group	The details are presented in the appendix 1 and in the colophon. The role is described in the supplement methodology (1.4)
5. Target population views and preferences	0 Statement of type of strategy used to capture patients'/publics' views and preferences (e.g., participation in the guideline development group, literature review of values and preferences) 0 Methods by which preferences and views were sought (e.g., evidence from literature, surveys, focus groups) 0 Outcomes/information gathered on patient/public information 0 How the information gathered was used to inform the guideline development process and/or formation of the recommendations	The priorities were defined through a public survey (see appendix 2). The persons invited are in appendix 1.3. A stakeholder meeting was held to present the results. See also the supplement methodology (1.4.2).
6. Target users	0 The intended guideline audience 0 How the guideline may be used by its target audience (e.g., to inform clinical decisions, to inform policy, to inform standards of care)	Described in 1.3.
Domain 3. Rigour of Development		



	Reporting criteria	Page
7. Search methods	0 Named electronic database(s) or evidence source(s) where the search was performed 0 Time periods searched 0 Search terms used 0 Full search strategy included	The search strategies for each question are presented in the respective appendices'.
8. Selection criteria	0 Target population (patient, public, etc.) characteristics 0 Study design 0 Comparisons (if relevant) 0 Outcomes 0 Language (if relevant) 0 Context (if relevant)	The PICO are in the appendix.
9. Strengths and limitations of evidence	0 Study design(s) included in body of evidence 0 Study methodology limitations (sampling, blinding, allocation concealment, analytical methods) 0 Appropriateness/relevance of primary and secondary outcomes considered 0 Consistency of results across studies 0 Direction of results across studies 0 Magnitude of benefit versus magnitude of harm 0 Applicability to practice context	These items are in the PICO, the results section (including the appendices) and the evidence to recommendation for each question.
10. Formulation of recommendations	0 Recommendation development process 0 Outcomes of the recommendation development process 0 How the process influenced the recommendations	See 2.4.
11. Benefits, side effects and risks	0 Supporting data and report of benefits 0 Supporting data and report of harms/side effects/risks 0 Reporting of the balance/trade-off between benefits and harms/side effects/risks 0 Recommendations reflect considerations of both benefits and harms/side effects/risks	See 2.3 and the evidence to recommendation section for each question.
12. Explicit link	0 How the guideline development group linked and used the evidence to inform recommendations 0 Link between each recommendation and key evidence (text description and/or reference list) 0 Link between recommendations and evidence summaries and/or evidence tables in the results section of the guideline	See the evidence and de evidence to recommendation section for each question.
13. External review	0 Purpose and intent of the external review 0 Methods taken to undertake the external review 0 Description of the external reviewers 0 Outcomes/information gathered from the external review 0 How the information gathered was used to inform the guideline development process and/or formation of the recommendations	See supplement methodology 2.7 and the colophon and the appendix 1.
14. Update procedure	0 A statement that the guideline will be updated 0 Explicit time interval or explicit criteria to guide decisions about when an update will occur 0 Methodology for the updating procedure	See section 8.
Domain 4. Clarity of Presentation		
15. Specific and unambiguous	0 A statement of the recommended action	See recommendations for each question.

	Reporting criteria	Page
	0 Intent or purpose of the recommended action 0 Relevant population 0 Caveats or qualifying statements, if relevant 0 If there is uncertainty about the best care option(s), the uncertainty should be stated in the guideline	
16. Different options for management	Description of management options 0 Population or clinical situation most appropriate to each option	Presented as part of the recommendations.
17. Key recommendations	0 Recommendations in a summarised box, typed in bold, underlined, or presented as flow charts or algorithms 0 Specific recommendations grouped together in one section	Recommendations are at the start of each question/chapter.
Domain 5. Applicability		
18. Facilitators and barriers	0 Types of facilitators and barriers that were considered 0 Methods by which information regarding the facilitators and barriers to implementing recommendations were sought (e.g., feedback from key stakeholders, pilot testing of guidelines before widespread implementation) 0 Information/description of the types of facilitators and barriers that emerged from the inquiry (e.g., practitioners have the skills to deliver the recommended care, sufficient equipment is not available to ensure all eligible members of the population receive mammography) 0 How the information influenced the guideline development process and/or formation of the recommendations	See section 8.
19. Advice and tools	0 Additional materials to support the implementation of the guideline in practice. For example: - o Guideline summary documents - o Links to check lists, algorithms - o Links to how-to manuals - o Solutions linked to barrier analysis (see Item 18) - o Tools to capitalize on guideline facilitators (see Item 18) - o Outcome of pilot test and lessons learned	See section 8.
20. Possible resource implications	0 Types of cost information that were considered (e.g., economic evaluations, drug acquisition costs) 0 Methods by which the cost information was sought (e.g., a health economist was part of the guideline development panel, use of health technology assessments for specific drugs, etc.) 0 Information/description of the cost information that emerged from the inquiry (e.g., specific drug acquisition costs per treatment course) 0 How the information gathered was used to inform the guideline development process and/or formation of the recommendations	No explicit search for cost was performed. The Belgian law on reimbursement of PET/CT was consulted and one policy recommendations made.



	Reporting criteria	Page
21. Monitoring and/or auditing criteria	0 Criteria to assess guideline implementation or adherence to recommendations 0 Criteria for assessing impact of implementing the recommendations 0 Advice on the frequency and interval of measurement 0 Operational definitions of how the criteria should be measured	This is reported in 8.
Domain 6. Editorial Independence		
22. Editorially independent	0 The name of the funding body or source of funding (or explicit statement of no funding) 0 A statement that the funding body did not influence the content of the guideline	See methodology supplement chapter 1.
23. Conflicts of interest	0 Types of competing interests considered 0 Methods by which potential competing interests were sought 0 A description of the competing interests 0 How the competing interests influenced the guideline process and development of recommendations	Competing interest are summarised in the colophon with the description of each participant.

■ APPENDIX

APPENDIX 1. EXPERTS AND STAKEHOLDERS

Appendix 1.1. Guideline development group

At the start of the project, an information online session was held on two occasions. For this session 47 health care workers, mostly medical doctors, Domus Medica and SSMG, and the following Belgian Scientific Associations were invited:

- BADO: Belgian association of Dermato-oncology
- BDG: Belgian Dermoscopy Group
- BELNUC: Belgian Society of Nuclear Medicine
- BeSTRO: Belgian Society of RadioTherapy Oncology
- BRAVO: Belgian Radiation Oncology Awareness and Visibility Organization
- BSMO: Belgian Society of Medical oncology
- BSP: Belgian Society for Pathology, with the Dermatopathology Working Group
- BSR: Belgian Society of Radiology
- KBVDV: Koninklijke Belgische Vereniging voor Dermatologie en Venerologie
- Koninklijk Belgisch Genootschap Heelkunde - Royal Belgian Society of Surgery

The following patient and cancer organisations were also invited:

- AntiCancer Fund
- Kankerregister
- Kom op tegen kanker
- Ligue des Usagers des Services de Santé (LUSS)
- Melanoompunt
- PRT - Patienten Rat un Treff
- Stichting tegen kanker
- Vlaams Patienten Platform (VPP)

Interested persons for participation in the GDG were invited to contact the KCE team. Also, survey participants were able to express their interest to participate in the GDG. 25 medical experts agreed to start in the GDG, 5 did not attend and were excluded after the second meeting and after checking their interest by mail. Of the remaining 20, 4 dermatologists were covering for each other, 2 histopathologists (2 by 2) in case of absence. A patient representative from Melanoompunt agreed to join the GDG as well. The medical specialties presented were 3 histopathologists, 1 nuclear medicine, 6 dermatologist and 7 oncologist.



The Guideline Development Group met on June 17th 2024, October 24th 2024, February 11th 2025, and March 27th 2025.

Institution/Organisation	First Name	Name
UCL Saint Luc	Jean-François	Baurain
UZ Leuven	Francesca	Bosisio
UZ Gent	Lieve	Brochez
AZ Maria-Middelares (Gent)	Sam	Dekeyser
AZ Maria-Middelares (Gent)	Astrid	De Meulenaere
Vitaz	Ines	Deleu
BELNUC (Belgian Society of Nuclear Medicine)	Anne-Leen	Deleu
Melanoompunt	Diane	Denys
Jules Bordet Instituut	Annie	Drowart
UZLeuven	Marjan	Garmyn
UCLouvain	Evelyne	Harkemanne
Dermat	Marc	Haspeslagh
UZA	Niels	Horst
UZ Gent	Céline	Jacobs
UZ Brussel	Jolien	Kessels
BSMO (Belgian Society of Medical oncology)	Vibeke	Kruse
Bordet	Mireille	Langouo Fontsa
Dermat	Julie	Lemahieu
UZ Brussel	Bart	Neyns
GZA Sint-Augustinus	Annemie	Rutten
UCL Saint Luc	Vasiliki	Siozopoulou

Appendix 1.2. Stakeholders

After the information session and the survey, 12 persons wanted to participate as stakeholders. A final 5 attended the stakeholders meeting and gave feedback on the recommendations.

Institution/Organisation	First Name	Name
LUSS	Diane-Estelle	Ngatchou-Djomo
Domus Medica	Stefan	Teughels
Melanoompunt	Marianne	Bosman
Kom op tegen kanker	Els	Meerbergen
BADO	Arjan	Nikkels
Belgian Cancer Registry	Liesbet	Van Eycken

Appendix 1.3. Survey group

The following persons and/or institutions were invited for the survey or received the link via another person. The participation is indicated in the last column. Participation was open through an online link.

Institution/Organisation	First Name	Name	Response
CHU Liège	Françoise	Absil	
UCL Saint Luc	Jean-François	Baurain	yes
UZ Leuven	Oliver	Bechter	yes
UZ Gent	Hilde	Beele	
UZ Leuven	Veerle	Boecxstaens	
UZ Leuven	Francesca	Bosisio	yes
Imelda Bonheiden, VUB	Claire	Bourgain	yes
UZ Gent	Lieve	Brochez	yes
Emmaus	Jasper	Bruyneel	yes
CHU Liège	Corinne	Chapelier	
UZ Leuven	Melissa	Christiaens	
CHU Liège	Joëlle	Collignon	
CHU Liège	Patrick	Collins	yes
UCLouvain	Pierre	Coulie	
SSMG - Junior	Sarah	Cumps	
UZ Brussel	Jacques	De Grève	
UCL	An-Katrien	De Roo	yes
Virga Jesse, Hasselt	Petra	Dejeneffe	
Hôpital Erasme	Véronique	del Marmol	
Belgian Society of Nuclear Medicine	Anne-Leen	Deleu	yes
Vitaz	Ines	Deleu	yes
Melanoompunt	Diane	Denys	yes
Jules Bordet Instituut	Annie	Drowart	yes
UZ Brussel	Ramses	Forsyth	yes
UC Louvain	Bernard	Gallez	
UA CORE	Hanne	Goris	yes
UCLouvain	Evelyne	Harkemanne	yes
UZ Gent	Isabelle	Hoorens	yes
UZA	Niels	Horst	yes
UCL Saint Luc	Catherine	Hubert	
UZ Gent	Wouter	Huvenne	yes
UZ Gent	Céline	Jacobs	yes
Jules Bordet Instituut	Joseph	Kerger	yes
UZ Brussel	Jolien	Kessels	yes
Patienten Rat un Treff	Isabelle	Kniebs	
Belgian Society of Medical oncology	Vibeke	Kruse	yes
Bordet	Mireille	Langouo Fontsa	yes
U Antwerpen	Filip	Lardon	
Le Clef diagnostic pathology A'pen	Quentin	Le Clef	yes
Stichting tegen kanker	Veronique	Le Ray	
CHU Liège	Julie	Lemahieu	yes
UC Louvain	Sophie	Lucas	



Leuven kankerinstituut	Chris	Marine	
SSMG	Quentin	Mary	
Virga Jesse, Hasselt	Jeroen	Mebis	yes
UZA	Paul	Meijnders	
AZ Delta	Céline	Melis	yes
Belgian Society of RadioTherapy Oncology	Selma Ben	Mustapha	
UZ Brussel	Bart	Neyns	yes
Ligue des Usagers des Services de Santé	Diane-Estelle	Ngatchou-Djomo	yes
CHU Liège +BADO	Arjen	Nikkels	
U Antwerpen	Ken	Op de Beeck	
ULB	Martine	Piccart	
Belgian Society of Medical oncology	Kevin	Punie	
UZA	Marika	Rasschaert	
Kom op tegen kanker	Ward	Rommel	
CHU Liège	Andrée	Rorive	yes
GZA Sint-Augustinus	Annemie	Rutten	yes
Jules Bordet Instituut	François	Sales	
ASZ Aalst	Max	Schreuer	
GZA Wilrijk	Marleen	Segers	
UCL Saint Luc	Vasiliki	Siozopoulou	
Jessazh	Thomas	Steelandt	yes
Domus Medica	Stefan	Teughels	yes
UZ Leuven	Kathleen	Timmermans	
Dermpat Gent	Karolien	Van Den Bossche	yes
Hôpital Universitaire Bruxelles and Bordet	Dirk	Van Gestel	
UZA	Leon	Van Kempen	
UZA Iridium netwerk	Frederik	Vandaele	
Belgian Society of Radiology	Piet	Vanhoenacker	yes
Virga Jesse, Hasselt	Annelies	Vekemans	
UZ Gent	Evelien	Verhaeghe	
UZ Gent	Geert	Villeirs	
Belgian Dermoscopy Group			
Belgian Dermatology Nurse Association			

APPENDIX 2. METHODS SCOPING PHASE

Appendix 2.1. Review for the scoping phase

The aim was to identify guidelines published from 2018 onwards. A systematic search for guidelines on Melanoma was performed by VIJ in OVID Medline on February 8th 2024, the TRIP and G-I-N library database on April 24th, 2024. In addition, websites of professional organisations developing evidence-based guidelines and organisation with an oncology focus were searched in February 2024 to identify additional guidelines.

For Belgium: Cebam Digital Library for Health (CDLH vzw), Domus Medica,

For Europe: the European Society for Medical Oncology (ESMO), the European Dermatology Forum, The European Association of Dermato Oncology (EADO), the National Institute for Health and Care Excellence (NICE) UK, SIGN - Health Improvement Scotland, Federatie Medisch Specialisten (Nederlandse Melanoom Werkgroep Nederland), die Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften(AWMF) Leitlinienregister for Germany, Haute Autorité de Santé for France.

For the United States: the American Academy of Dermatology Association, the National Cancer Institute at NIH, the American Society of Clinical Oncology (ASCO), the Society for Immunotherapy of Cancer, the National comprehensive cancer network (NCCN), the U.S. Preventive Services Task Force.

For Canada: Cancer Care Alberta, the Annual Canadian Melanoma Conference of the Canadian Medical Oncologists, Ontario Health Care.

For Australia: Cancer Council Australia, the Royal Australian College of General Practitioners

The systematic search identified a total of 20 guidelines (see Table 16). The most recent guidelines were the UK NICE(NICE 2022), the Scottish SIGN(SIGN - Health Improvement Scotland), the ASCO guideline(Seth 2023), the Ontario surveillance guideline(Johnston 2023,Rajagopal 2024) and the ASCO-SNO-ASTRO Guideline(Vogelbaum 2022). Further, 13 consensus guides were retrieved (see Table 17). Finally, a update for the ESMO guideline was published in January 2025.

Appendix 2.1.1. OVID Medline

OVID Medline search on February 8th 2024 with database 2019 to January week 5 2024

1 exp Melanoma/

2 Skin Neoplasms/

3 (melanoma* or melanocarcinoma* or naevocarcinoma* or nevocarcinoma*).tw.

4 ((skin or derm* or cutaneous* or epitheli* or epiderm*) adj1 (adenocarcinoma* or cancer* or carcinoma* or malignan* or neoplas* or oncolog* or tumor* or tumour*)).tw.

5 ((maligna* or melano*) adj2 (freckle* or lesion* or mole* or nev* or naev*)).tw.

6 (hutchinson* adj2 (freckle* or melano*)).tw.

7 dubreuilh*.tw.

8 (maligna* adj2 lentigo*).tw.

9 LMM.tw.

10 or/1-9

Steps the same as the above search with in addition

11 practice guideline/ (5153)

12 10 and 11 (67)



The 67 retrieved references were extracted to endnote:

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45. Peris K, Fargnoli MC, Garbe C, Kaufmann R, Bastholt L, Seguin NB, et al. Diagnosis and treatment of basal cell carcinoma: European consensus-based interdisciplinary guidelines. *European Journal of Cancer*.118:10-34.
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49. Dessinioti C, Plaka M, Soura E, Mortaki D, Papaxoinis G, Gogas H, et al. A Practical Guide for the Follow-Up of Patients with Advanced Basal Cell Carcinoma During Treatment with Hedgehog Pathway Inhibitors. *Oncologist*.24(8):e755-e64.
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52. Lavoue V, Huchon C, Akladios C, Alfonsi P, Bakrin N, Ballester M, et al. Management of epithelial cancer of the ovary, fallopian tube, and primary peritoneum. Long text of the Joint French Clinical Practice Guidelines issued by FRANCOGYN, CNGOF, SFOG, and GINECO-ARCAGY, and endorsed by INCa. Part 1: Diagnostic exploration and staging, surgery, perioperative care, and pathology. *Journal of Gynecology Obstetrics and Human Reproduction*.48(6):369-78.
53. Lavoue V, Huchon C, Akladios C, Alfonsi P, Bakrin N, Ballester M, et al. Management of epithelial cancer of the ovary, fallopian tube, primary peritoneum. Long text of the joint French clinical practice guidelines issued by FRANCOGYN, CNGOF, SFOG, GINECO-ARCAGY, endorsed by INCa. (Part 2: systemic, intraperitoneal treatment, elderly patients, fertility preservation, follow-up). *Journal of Gynecology Obstetrics and Human Reproduction*.48(6):379-86.
54. Lavoue V, Huchon C, Akladios C, Alfonsi P, Bakrin N, Ballester M, et al. Management of epithelial cancer of the ovary, fallopian tube, and primary peritoneum. Short text of the French Clinical Practice Guidelines issued by FRANCOGYN, CNGOF, SFOG, and GINECO-ARCAGY, and endorsed by INCa. *European Journal of Obstetrics, Gynecology, & Reproductive Biology*.236:214-23.
55. Cook LB, Fuji S, Hermine O, Bazarbachi A, Ramos JC, Ratner L, et al. Revised Adult T-Cell Leukemia-Lymphoma International Consensus Meeting Report. *Journal of Clinical Oncology*.37(8):677-87.
56. Gilson D, Whittaker SJ, Child FJ, Scarisbrick JJ, Illidge TM, Parry EJ, et al. British Association of Dermatologists and U.K. Cutaneous Lymphoma Group guidelines for the management of primary cutaneous lymphomas 2018. *British Journal of Dermatology*.180(3):496-526.
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58. Swetter SM, Tsao H, Bichakjian CK, Curiel-Lewandrowski C, Elder DE, Gershenwald JE, et al. Guidelines of care for the management of primary cutaneous melanoma. *Journal of the American Academy of Dermatology*.80(1):208-50.
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61. Le Guern V, Rossignol M, Proust A. [Indirect causes of maternal deaths (except stroke, cardiovascular diseases and infections) in France 2013-2015]. *Gynecologie, Obstetrique, Fertilité & Senologie*.49(1):83-8.
62. Savoie PH, Morel-Journel N, Murez T, Ferretti L, Rocher L, Flechon A, et al. [French ccAFU guidelines - update 2020-2022: penile cancer]. *Progres en Urologie*.30(12S):S252-S79.
63. Cassoux N. [Management of ocular cancer during COVID-19 pandemic]. *Journal Francais d Ophthalmologie*.43(6):545-6.
64. Guillot B, Dupuy A, Pracht M, Jeudy G, Hindie E, Desmedt E, et al. [New guidelines for stage III melanoma (the French Cutaneous Oncology Group)]. *Annales de Dermatologie et de Venereologie*. 2019;146(3):204-14.
65. Bakrin N, Gladiéff L. [Malignant epithelial ovarian cancer: Role of intra peritoneal chemotherapy and hyperthermic intra peritoneal chemotherapy (HIPEC): Article drafted from the French Guidelines in oncology entitled "Initial management of patients with epithelial ovarian cancer" developed by FRANCOGYN, CNGOF, SFOG, GINECO-ARCAGY under the aegis of CNGOF and endorsed by INCa]. *Gynecologie, Obstetrique, Fertilité & Senologie*. 2019;47(2):214-21.
66. Bolze PA, Collinet P, Golfier F, Bourgin C. [Surgery in early-stage ovarian cancer: Article drafted from the French Guidelines in oncology entitled "Initial management of patients with epithelial ovarian cancer" developed by FRANCOGYN, CNGOF, SFOG, GINECO-ARCAGY under the aegis of CNGOF and endorsed by INCa]. *Gynecologie, Obstetrique, Fertilité & Senologie*.47(2):168-79.
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SELECTION OF GUIDELINES FROM ENDNOTE

From the 67 references a selection of 7 guidelines and 9 consensus guides was made. The remaining references were not selected for wrong design (6), wrong topic (41), new version available (4). The NCCN guideline by Swetter et al was not selected as a newer version was available online on their website (see below in the search of websites). The publication by Robinson et al was not selected as it was part of the Australian guideline (included in the website search).

Guidelines:

1. Botella-Estrada R, Boada-Garcia A, Carrera-Alvarez C, Fernandez-Figueras M, Gonzalez-Cao M, Moreno-Ramirez D, et al. Clinical Practice Guideline on Melanoma From the Spanish Academy of Dermatology and Venereology (AEDV). *Actas Dermo Sifiliograficas*. 2020;112(2):142-52.
2. Mangione CM, Barry MJ, Nicholson WK, Chelmow D, Coker TR, Davis EM, et al. Screening for Skin Cancer: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2023;329(15):1290-5.

3. Nakamura Y, Asai J, Igaki H, Inozume T, Namikawa K, Hayashi A, et al. Japanese Dermatological Association Guidelines: Outlines of guidelines for cutaneous melanoma 2019. *Journal of Dermatology*. 2019;47(2):89-103.
4. Seth R, Agarwala SS, Messersmith H, Alluri KC, Ascierto PA, Atkins MB, et al. Systemic Therapy for Melanoma: ASCO Guideline Update. *J Clin Oncol*. 2023;41(30):4794-820.
5. Smith HG, Bagwan I, Board RE, Capper S, Coupland SE, Glen J, et al. Ano-uro-genital mucosal melanoma UK national guidelines. *European Journal of Cancer*. 2020;135:22-30.
6. Swetter SM, Tsao H, Bichakjian CK, Curiel-Lewandrowski C, Elder DE, Gershenwald JE, et al. Guidelines of care for the management of primary cutaneous melanoma. *J Am Acad Dermatol*. 2019;80(1):208-50.
7. Vogelbaum MA, Brown PD, Messersmith H, Brastianos PK, Burri S, Cahill D, et al. Treatment for Brain Metastases: ASCO-SNO-ASTRO Guideline. *Journal of Clinical Oncology*. 2022;40(5):492-516.

Consensus:

1. Garbe C, Amaral T, Peris K, Hauschild A, Arenberger P, Basset-Seguin N, et al. European consensus-based interdisciplinary guideline for melanoma. Part 2: Treatment - Update 2022. *European Journal of Cancer*.170:256-84.
2. Gonzalez-Cao M, Puertolas T, Riveiro M, Munoz-Couselo E, Ortiz C, Paredes R, et al. Cancer immunotherapy in special challenging populations: recommendations of the Advisory Committee of Spanish Melanoma Group (GEM). *Journal for Immunotherapy of Cancer*. 2021;9(3):03.
3. Guillot B, Dupuy A, Pracht M, Jeudy G, Hindie E, Desmedt E, et al. [New guidelines for stage III melanoma (the French Cutaneous Oncology Group)]. *Annales de Dermatologie et de Venereologie*. 2019;146(3):204-14.
4. Keilholz U, Ascierto PA, Dummer R, Robert C, Lorigan P, van Akkooi A, et al. ESMO consensus conference recommendations on the management of metastatic melanoma: under the auspices of the ESMO Guidelines Committee. *Annals of Oncology*.31(11):1435-48.
5. Majem M, Manzano JL, Marquez-Rodas I, Mujika K, Munoz-Couselo E, Perez-Ruiz E, et al. SEOM clinical guideline for the management of cutaneous melanoma (2020). *Clinical & Translational Oncology: Official Publication of the Federation of Spanish Oncology Societies & of the National Cancer Institute of Mexico*.23(5):948-60.
6. Michielin O, van Akkooi A, Lorigan P, Ascierto PA, Dummer R, Robert C, et al. ESMO consensus conference recommendations on the management of locoregional melanoma: under the auspices of the ESMO Guidelines Committee. *Annals of Oncology*.31(11):1449-61.
7. Michielin O, van Akkooi ACJ, Ascierto PA, Dummer R, Keilholz U. Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*.30(12):1884-901.
8. Tejera-Vaquero A, Fernandez-Figueras MT, Santos-Briz A, Rios-Martin JJ, Monteagudo C, Fernandez-Flores A, et al. Protocol for the Histologic Diagnosis of Cutaneous Melanoma: Consensus Statement of the Spanish Society of Pathology and the Spanish Academy of Dermatology and Venereology (AEDV) for the National Cutaneous Melanoma Registry. *Actas Dermo Sifiliograficas*.112(1):32-43.
9. Wu CE, Liao YH, Wu CL, Yen RF, Lin CC, Yang MH, et al. Clinical practice consensus for the diagnosis and management of melanoma in Taiwan. *Journal of the Formosan Medical Association*.123(1):7-15.



Appendix 2.1.2. Websites

A search was performed with the terms 'guideline' and 'melanoma' on the websites by region:

Belgium

<https://www.domusmedica.be/>

<https://www.cdih.be/nl>

Europe

<https://www.esmo.org/guidelines/guidelines-by-topic/melanoma>

<https://www.edf.one/en/>

<https://eado.org/>

<https://www.nice.org.uk/guidance/ng14>

<https://www.sign.ac.uk/our-guidelines/cutaneous-melanoma/>

<https://melanomafocus.org/for-professionals/educational-resources/nice-sign-esmo-melanoma-guidelines/>

<https://richtlijndatabase.nl/zoek>

<https://register.awmf.org/de/start>

https://www.has-sante.fr/jcms/p_3229902/fr/recommandations-de-bonnes-pratiques-professionnelles-pour-le-secteur-social-et-medico-social

United States

<https://www.aad.org/member/clinical-quality/guidelines/melanoma>

<https://www.cancer.gov/types>

[ASCO Publications \(ascopubs.org\)](https://www.sitcancer.org/home)

<https://www.sitcancer.org/home>

<https://www.nccn.org/>

[Home page | United States Preventive Services Taskforce \(uspreventiveservicestaskforce.org\)](https://www.uspreventiveservicestaskforce.org/)

Canada

[Home | Alberta Health Services](https://www.albertahealthservices.ca/)

<https://camo-acom.ca/Overview>

<https://www.ontariohealth.ca/providing-health-care/clinical-standards-guidelines>

Australia

[Browse all Clinical Guidelines | Cancer Council](https://www.cancer.gov.au/clinical-guidelines)

[RACGP - Home](https://www.racgp.org.au/)

Results for website search

Guidelines:

1. Cancer Care Alberta. Management of In-Transit Disease. 2019. Available from: <https://www.albertahealthservices.ca/assets/info/hp/cancer/if-hp-cancer-guide-cu008-in-transit-disease.pdf>
2. Cancer Care Alberta. Biopsy of a Suspicious Pigmented Lesion. 2021. Available from: <https://www.albertahealthservices.ca/assets/info/hp/cancer/if-hp-cancer-guide-cu006-biop-susp-lesion-v7.pdf>
3. Cancer Council Australia. Clinical practice guidelines for the diagnosis and management of melanoma [Web page]. 2021. Available from: <https://wiki.cancer.org.au/australia/Guidelines:Melanoma>
4. Leitlinienprogramm Onkologie AWMF. S3-Leitlinie Prävention von Hautkrebs 032-052OL. 2021.
5. Leitlinienprogramm Onkologie Deutsche Krebsgesellschaft; Deutsche Krebshilfe AWMF. Diagnostik, Therapie und Nachsorge des Melanoms, version 3.3. (AWMF Registernummer: 032/024OL). 2020. Available from: <https://register.awmf.org/de/leitlinien/detail/032-024OL#anmeldung>
6. National Institute for Health and Care Excellence. Melanoma: assessment and management. NICE guideline [NG14] Published: 29 July 2015 Last updated. 2022.
7. Nederlandse Melanoom Werkgroep (NMW). Melanoom richtlijn. 2019.
8. RACGP. Guidelines for preventive activities in general practice. 2021. Available from: <https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/guidelines-for-preventive-activities-in-general-pr/early-detection-of-cancers/skin-cancer#ref-num-61>
9. Rajagopal S, Yao X, Abadir W, Baetz TD, Easson AM, Knight G, et al. An Ontario Health (Cancer Care Ontario) Clinical Practice Guideline: Surveillance Strategies in Patients with Stage I, II, III or Resectable IV Melanoma Who Were Treated with Curative Intent. Clin Oncol (R Coll Radiol). 2024.
10. SIGN - Health Improvement Scotland. Cutaneous melanoma. SIGN 146. First published Jan 2017 Last updated Aug 2023. 2023.
11. Swetter SM, Johnson D, Albertini MR, Barker CA, Bateni S, Baumgartner J, et al. NCCN Guidelines. Melanoma: Cutaneous, Version 2. April 2024. 2024. Available from: <https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1492>
12. Wong SL, Faries MB, Kennedy EB, Agarwala SS, Akhurst TJ, Ariyan C, et al. Sentinel Lymph Node Biopsy and Management of Regional Lymph Nodes in Melanoma: American Society of Clinical Oncology and Society of Surgical Oncology Clinical Practice Guideline Update. J Clin Oncol. 2018;36(4):399-413.
13. Wright FC, Souter LH, Kellett S, Easson A, Murray C, Toye J, et al. Primary excision margins, sentinel lymph node biopsy, and completion lymph node dissection in cutaneous melanoma: a clinical practice guideline. Curr Oncol. 2019;26(4):e541-e50.

Consensus guides:

1. Garbe C, Amaral T, Peris K, Hauschild A, Arenberger P, Basset-Seguín N, et al. European consensus-based interdisciplinary guideline for melanoma. Part 1: Diagnostics: Update 2022. Eur J Cancer. 2022;170:236-55.
2. Lee CW, McKinnon JG, Davis N. Canadian Melanoma Conference Recommendations on High-Risk Melanoma Surveillance: A Report from the 14th Annual Canadian Melanoma Conference; Banff, Alberta; 20-22 February 2020. Curr Oncol. 2021;28(3):2040-51.
3. Pavlick AC, Ariyan CE, Buchbinder EI, Davar D, Gibney GT, Hamid O, et al. Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immunotherapy for the



treatment of melanoma, version 3.0. Journal for ImmunoTherapy of Cancer. 2023;11(10):e006947.

Appendix 2.1.3. TRIP database

Search date: April 24th 2024 by VIJ

Search terms: (title:melanoma AND title:guideline) from_date:2017 to_date:2024

Selection of guidelines from endnote

From the 32 references a selection of 4 guidelines and 6 consensus guides was made. The remaining references were not selected for wrong design (11), wrong topic (4), new version available (7). The NCCN guideline by Swetter et al was not selected as a newer version was available online on their website (see below in the search of websites).

Guidelines:

1. Botella-Estrada R et al. Clinical Practice Guideline on Melanoma From the Spanish Academy of Dermatology and Venereology (AEDV). Spanish Clinical Guidelines. 2021:142-52.
2. Rajagopal S et al. An Ontario Health (Cancer Care Ontario) Clinical Practice Guideline: Surveillance Strategies in Patients with Stage I, II, III or Resectable IV Melanoma Who Were Treated with Curative Intent. Clinical oncology (Royal College of Radiologists (Great Britain)). 2024;36:243-53.
3. Seth R et al. Systemic Therapy for Melanoma: ASCO Guideline Update. Evidence Updates. 2023:JCO2301136.
4. Wright F et al. Primary excision margins, sentinel lymph node biopsy, and completion lymph node dissection in cutaneous melanoma: a clinical practice guideline. Current oncology (Toronto, Ont.). 2019:e541-e50.

Consensus:

1. Garbe C et al. European consensus-based interdisciplinary guideline for melanoma. Part 2: Treatment - Update 2022. European journal of cancer. 2022:256-84.
2. Garbe C et al. European consensus-based interdisciplinary guideline for melanoma. Part 1: Diagnostics: Update 2022. European Journal of Cancer. 2022:236-55.
3. Keilholz U et al. ESMO consensus conference recommendations on the management of metastatic melanoma: under the auspices of the ESMO Guidelines Committee. Annals of Oncology. 2020;31:1435-48.
4. Michielin O et al. ESMO consensus conference recommendations on the management of locoregional melanoma: under the auspices of the ESMO Guidelines Committee. Annals of Oncology. 2020;31:1449-61.
5. Health Commission Of The People's Republic Of China. National guidelines for diagnosis and treatment of melanoma 2022 in China (English version). Chinese Clinical Guidelines. 2022.
6. Pavlick A, al. e. Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immunotherapy for the treatment of melanoma, version 3.0. Society for Immunotherapy of Cancer.

Appendix 2.1.4. G-I-N library

Search date: April 24th 2024 by VIJ

Search terms: melanoma; no dates applied in the search.

Selection of guidelines from endnote

From the 19 references a selection of 2 guidelines and 0 consensus guides was made. Two guidelines had a newer reference. The remaining 15 references were not selected as the dates were before 2019 (between 2003 and 2018).

Guidelines:

1. Awmf DKG. Prävention von Hautkrebs. S3-LL (Leitlinienprogramm Onkologie von AWMF, DKG und DKH) [Web page].2021 [updated 2021].
2. Ontario Health. Surveillance of Patients with Stage I, II, III, or Resectable IV Melanoma Who Were Treated with Curative Intent [Web page].2023 [updated 2023].

Appendix 2.1.5. Final selection

After de-duplication of the previous 4 searches, 20 guidelines and 13 consensus guides were retrieved.

Guidelines:

1. Botella-Estrada R, Boada-Garcia A, Carrera-Alvarez C, Fernandez-Figueras M, Gonzalez-Cao M, Moreno-Ramirez D, et al. Clinical Practice Guideline on Melanoma From the Spanish Academy of Dermatology and Venereology (AEDV). Actas Dermo Sifiliograficas. 2020;112(2):142-52.
2. Cancer Care Alberta. Management of In-Transit Disease. 2019. Available from: <https://www.albertahealthservices.ca/assets/info/hp/cancer/if-hp-cancer-guide-cu008-in-transit-disease.pdf>
3. Cancer Care Alberta. Biopsy of a Suspicious Pigmented Lesion. 2021. Available from: <https://www.albertahealthservices.ca/assets/info/hp/cancer/if-hp-cancer-guide-cu006-biopsy-susp-lesion-v7.pdf>
4. Cancer Council Australia. Clinical practice guidelines for the diagnosis and management of melanoma [Web page].2021. Available from: <https://wiki.cancer.org.au/australia/Guidelines:Melanoma>
5. Leitlinienprogramm Onkologie AWMF. S3-Leitlinie Prävention von Hautkrebs 032-052OL. 2021.
6. Leitlinienprogramm Onkologie Deutsche Krebsgesellschaft; Deutsche Krebshilfe AWMF. Diagnostik, Therapie und Nachsorge des Melanoms, version 3.3. (AWMF Registernummer: 032/024OL). 2020. Available from: <https://register.awmf.org/de/leitlinien/detail/032-024OL#anmeldung>
7. Mangione CM, Barry MJ, Nicholson WK, Chelmow D, Coker TR, Davis EM, et al. Screening for Skin Cancer: US Preventive Services Task Force Recommendation Statement. JAMA. 2023;329(15):1290-5.
8. Nakamura Y, Asai J, Igaki H, Inozume T, Namikawa K, Hayashi A, et al. Japanese Dermatological Association Guidelines: Outlines of guidelines for cutaneous melanoma 2019. Journal of Dermatology. 2019;47(2):89-103.
9. National Institute for Health and Care Excellence. Melanoma: assessment and management. NICE guideline [NG14] Published: 29 July 2015 Last updated. 2022.
10. Nederlandse Melanoom Werkgroep (NMW). Melanoom richtlijn. 2019.



11. RACGP. Guidelines for preventive activities in general practice. 2021. Available from: <https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/guidelines-for-preventive-activities-in-general-pr/early-detection-of-cancers/skin-cancer#ref-num-61>
12. Rajagopal S, Yao X, Abadir W, Baetz TD, Easson AM, Knight G, et al. An Ontario Health (Cancer Care Ontario) Clinical Practice Guideline: Surveillance Strategies in Patients with Stage I, II, III or Resectable IV Melanoma Who Were Treated with Curative Intent. *Clin Oncol (R Coll Radiol)*. 2024.
13. Seth R, Agarwala SS, Messersmith H, Alluri KC, Ascierto PA, Atkins MB, et al. Systemic Therapy for Melanoma: ASCO Guideline Update. *J Clin Oncol*. 2023;41(30):4794-820.
14. SIGN - Health Improvement Scotland. Cutaneous melanoma. SIGN 146. First published Jan 2017 Last updated Aug 2023. 2023.
15. Smith HG, Bagwan I, Board RE, Capper S, Coupland SE, Glen J, et al. Ano-uro-genital mucosal melanoma UK national guidelines. *European Journal of Cancer*. 2020;135:22-30.
16. Swetter SM, Johnson D, Albertini MR, Barker CA, Bateni S, Baumgartner J, et al. NCCN Guidelines. Melanoma: Cutaneous, Version 2. April 2024. 2024.
Available from: <https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1492>
17. Swetter SM, Tsao H, Bichakjian CK, Curiel-Lewandrowski C, Elder DE, Gershenwald JE, et al. Guidelines of care for the management of primary cutaneous melanoma. *J Am Acad Dermatol*. 2019;80(1):208-50.
18. Vogelbaum MA, Brown PD, Messersmith H, Brastianos PK, Burri S, Cahill D, et al. Treatment for Brain Metastases: ASCO-SNO-ASTRO Guideline. *Journal of Clinical Oncology*. 2022;40(5):492-516.
19. Wong SL, Faries MB, Kennedy EB, Agarwala SS, Akhurst TJ, Ariyan C, et al. Sentinel Lymph Node Biopsy and Management of Regional Lymph Nodes in Melanoma: American Society of Clinical Oncology and Society of Surgical Oncology Clinical Practice Guideline Update. *J Clin Oncol*. 2018;36(4):399-413.
20. Wright FC, Souter LH, Kellett S, Easson A, Murray C, Toye J, et al. Primary excision margins, sentinel lymph node biopsy, and completion lymph node dissection in cutaneous melanoma: a clinical practice guideline. *Curr Oncol*. 2019;26(4):e541-e50.

Consensus:

1. Garbe C, Amaral T, Peris K, Hauschild A, Arenberger P, Basset-Seguin N, et al. European consensus-based interdisciplinary guideline for melanoma. Part 2: Treatment - Update 2022. *Eur J Cancer*. 2022;170:256-84.
2. Garbe C, Amaral T, Peris K, Hauschild A, Arenberger P, Basset-Seguin N, et al. European consensus-based interdisciplinary guideline for melanoma. Part 1: Diagnostics: Update 2022. *Eur J Cancer*. 2022;170:236-55.
3. Gonzalez-Cao M, Puertolas T, Riveiro M, Munoz-Couselo E, Ortiz C, Paredes R, et al. Cancer immunotherapy in special challenging populations: recommendations of the Advisory Committee of Spanish Melanoma Group (GEM). *Journal for Immunotherapy of Cancer*. 2021;9(3):03.
4. Guillot B, Dupuy A, Pracht M, Jeudy G, Hindie E, Desmedt E, et al. [New guidelines for stage III melanoma (the French Cutaneous Oncology Group)]. *Annales de Dermatologie et de Venereologie*. 2019;146(3):204-14.
5. Health Commission Of The People's Republic Of China. National guidelines for diagnosis and treatment of melanoma 2022 in China (English version). *Chinese Clinical Guidelines*. 2022.

6. Keilholz U, Ascierto PA, Dummer R, Robert C, Lorigan P, van Akkooi A, et al. ESMO consensus conference recommendations on the management of metastatic melanoma: under the auspices of the ESMO Guidelines Committee. *Ann Oncol.* 2020;31(11):1435-48.
7. Lee CW, McKinnon JG, Davis N. Canadian Melanoma Conference Recommendations on High-Risk Melanoma Surveillance: A Report from the 14th Annual Canadian Melanoma Conference; Banff, Alberta; 20-22 February 2020. *Curr Oncol.* 2021;28(3):2040-51.
8. Majem M, Manzano JL, Marquez-Rodas I, Mujika K, Muñoz-Couselo E, Pérez-Ruiz E, et al. SEOM clinical guideline for the management of cutaneous melanoma (2020). *Clin Transl Oncol.* 2021;23(5):948-60.
9. Michielin O, van Akkooi A, Lorigan P, Ascierto PA, Dummer R, Robert C, et al. ESMO consensus conference recommendations on the management of locoregional melanoma: under the auspices of the ESMO Guidelines Committee. *Ann Oncol.* 2020;31(11):1449-61.
10. Michielin O, van Akkooi ACJ, Ascierto PA, Dummer R, Keilholz U. Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. *Ann Oncol.* 2019;30(12):1884-901.
11. Pavlick AC, Ariyan CE, Buchbinder EI, Davar D, Gibney GT, Hamid O, et al. Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immunotherapy for the treatment of melanoma, version 3.0. *Journal for ImmunoTherapy of Cancer.* 2023;11(10):e006947.
12. Tejera-Vaquerizo A, Fernandez-Figueras MT, Santos-Briz A, Rios-Martin JJ, Monteagudo C, Fernandez-Flores A, et al. Protocol for the Histologic Diagnosis of Cutaneous Melanoma: Consensus Statement of the Spanish Society of Pathology and the Spanish Academy of Dermatology and Venereology (AEDV) for the National Cutaneous Melanoma Registry. *Actas Dermo Sifiliograficas.* 2021;112(1):32-43.
13. Wu CE, Liao YH, Wu CL, Yen RF, Lin CC, Yang MH, et al. Clinical practice consensus for the diagnosis and management of melanoma in Taiwan. *Journal of the Formosan Medical Association.* 2024. 123(1):7-15.

Appendix 2.2. Guidelines retrieved

Table 16 – Retrieved melanoma guidelines by date and presence of systematic search

Author	Title	Date	Systematic Search No 0 yes 1 no results 2	Dates search
Rajagopal(Johnston 2023,Rajagopal 2024)	Clinical Practice Guideline: Surveillance Strategies in Patients with Stage I, II, III or Resectable IV Melanoma Who Were Treated with Curative Intent.	2024	1	1/09/2022
Swetter(Swetter 2025)	NCCN guideline Melanoma Cutaneous	2024	0	NA
Mangione(Henrikson 2023,Mangione)	NB Screening for Skin Cancer: US Preventive Services Task Force Recommendation Statement	2023	1	1/01/2022
Seth(Seth 2023)	Systemic Therapy for Melanoma: ASCO Guideline Update.	2023	1	2018-2019
SIGN(SIGN - Health Improvement Scotland)	Cutaneous melanoma. SIGN 146.	2023	1	NICE and 2022
Vogelbaum(Vogelbaum)	Treatment for Brain Metastases: ASCO-SNO-ASTRO Guideline.	2022	1	1/09/2020
NICE(NICE 2022)	NICE guideline [NG14] Melanoma: assessment and management	2022	1	1/07/2021
Botella(Botella-Estrada 2020)	Guía de práctica clínica de melanoma de la Academia Española de Dermatología y Venereología	2021	1	2016-sept 2019



Cancer council Australia(Cancer Council Australia 2021)	Clinical practice guidelines for the diagnosis and management of melanoma	2021	1	2017-2018
Cancer Care Alberta(Cancer Care Alberta 2021)	Biopsy of a Suspicious Pigmented Lesion 2021	2021	2	NA
Leitlinienprogramm Onkologie(Leitlinienprogramm Onkologie AWMF 2021)	S3-Leitlinie Prävention von Hautkrebs 032 - 052OL	2021	0	NA
RACGP(RACGP 2021)	Guidelines for preventive activities in general practice	2021	0	NA
Smith(Smith)	Ano-uro-genital mucosal melanoma UK national guidelines.	2020	1	March 2017
Leitlinienprogramm Onkologie(Leitlinienprogramm Onkologie Deutsche Krebsgesellschaft; Deutsche Krebshilfe AWMF 2020)	S3-Leitlinie Diagnostik, Therapie und Nachsorge des Melanoms	2019	1	2016
Nederlandse Melanoom Werkgroep (NMW)(Nederlandse Melanoom Werkgroep (NMW) 2019)	Melanoom richtlijn	2019	2	2016
Wright(Wright 2019)	Primary excision margins, sentinel lymph node biopsy, and completion lymph node dissection in cutaneous melanoma: a clinical practice guideline.	2019	1	2017
Nakamura(Nakamura 2019)	Japanese Dermatological Association Guidelines: Outlines of guidelines for cutaneous melanoma	2019	1	30/11/2017
Swetter(Swetter 2019)	Guidelines of care for the management of primary cutaneous melanoma (from the AAD)	2019	1	oct 2017
Cancer Care Alberta(Cancer Care Alberta 2019)	Management of In-Transit Disease 2019	2019	2	NA
Wong(Wong 2018)	Sentinel Lymph Node Biopsy and Management of Regional Lymph Nodes in Melanoma: American Society of Clinical Oncology and Society of Surgical Oncology Clinical Practice Guideline Update	2018	1	June 2017

Table 17 – Retrieved melanoma consensus guides from scoping searches

Author	Title	Date	Systematic Search No 0 yes 1 no results 2	Dates search
Wu(Wu)	Clinical practice consensus for the diagnosis and management of melanoma in Taiwan	2024	0	NA
Pavlick(Pavlick 2023)	Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immunotherapy for the treatment of melanoma, version 3.0	2023	0	NA
Garbe(Garbe 2022)	European consensus-based interdisciplinary guideline for melanoma. Part 1: Diagnostics: Update 2022	2022	2	nov/21
Garbe(Garbe 2022)	European consensus-based interdisciplinary guideline for melanoma. Part 2: Treatment - Update 2022	2022	2	nov/21
Health Commission Of The People's Republic Of China(Health Commission Of The People's Republic Of China 2022)	National guidelines for diagnosis and treatment of melanoma 2022 in China (English version). Chinese Clinical Guidelines. 2022.	2022	0	NA
Gonzalez(Gonzalez-Cao 2021)	Cancer immunotherapy in special challenging populations: recommendations of the Advisory Committee of Spanish Melanoma Group (GEM)	2021	0	NA
Lee(Lee 2021)	Canadian Melanoma Conference Recommendations on High-Risk Melanoma Surveillance: A Report from the 14th Annual Canadian Melanoma Conference	2021	0	NA
Majem(Majem 2021)	SEOM clinical guideline for the management of cutaneous melanoma	2021	0	NA
Keilholz(Keilholz 2020)	ESMO consensus conference recommendations on the management of metastatic melanoma: under the auspices of the ESMO Guidelines Committee.	2020	0	NA
Michielin(Michielin 2020)	ESMO consensus conference recommendations on the management of locoregional melanoma: under the auspices of the ESMO Guidelines Committee.	2020	0	NA
Tejera(Tejera-Vaquerizo)	Protocol for the Histologic Diagnosis of Cutaneous Melanoma: Consensus Statement of the Spanish Society of Pathology and the Spanish Academy of Dermatology and Venereology (AEDV) for the National Cutaneous Melanoma Registry	2020	0	NA
Michielin(Michielin 2019)	Cutaneous Melanoma: ESMO Clinical Practice Guidelines	2019	0	NA
Guillot(Guillot)	Actualisation des données concernant le mélanome stade III : nouvelles recommandations du groupe français de cancérologie cutanée	2019	0	NA



Appendix 2.3. Quality evaluation

Table 18 – AGREE II evaluation rigour of development

Country/ Organisation	Title	Rigour of development								Domain score
		Systematic search	Selection criteria	Strengths and limitations of evidence	formulation of recommendations	Benefits, side effects and risks	Explicit link	External review	Update procedure	
Rajagopal(Johnston 2023,Rajagopal 2024)	Clinical Practice Guideline: Surveillance Strategies in Patients with Stage I, II, III or Resectable IV Melanoma Who Were Treated with Curative Intent. 2024	7	7	6	6	4	5	5	5	77.1
Swetter(Swetter 2025)	NCCN guideline Melanoma Cutaneous 2024 v2	1	4	5	7	7	4	5	7	72.9
Seth(Seth 2023)	Systemic Therapy for Melanoma: ASCO Guideline Update. 2023	6	6	6	7	5	5	6	4	77.1
SIGN(SIGN - Health Improvement Scotland)	Cutaneous melanoma. SIGN 146. 2023	7	7	5	7	4	4	6	5	77.1
Vogelbaum(Vogelbaum)	Treatment for Brain Metastases: ASCO-SNO-ASTRO Guideline. 2022	7	7	6	6	5	6	6	5	83.3
NICE(NICE 2022)	NICE guideline [NG14] Melanoma: assessment and management 2022	7	7	6	7	6	6	5	6	87.5
Cancer council Australia(Cancer Council Australia 2021)	Clinical practice guidelines for the diagnosis and management of melanoma	5	4	3	5	5	7	5	5	64.6
Garbe(Garbe 2022)	European consensus-based interdisciplinary guideline for melanoma. Part 1: Diagnostics: Update 2022	2	2	4	6	3	2	3	3	35.4
Garbe(Garbe 2022)	European consensus-based interdisciplinary guideline for melanoma. Part 2: Treatment - Update 2022	3	5	3	3	3	3	4	3	39.6



Garbe(Garbe 2025)*	European consensus-based interdisciplinary guideline for melanoma. Part 2: Treatment - Update 2024	3	5	3	3	3	3	4	3	39,6
Keilholz(Keilholz 2020)	ESMO consensus conference recommendations on the management of metastatic melanoma: under the auspices of the ESMO Guidelines Committee. 2020	4	4	5	5	4	3	2	2	43,8
Amaral(Amaral 2025)*	Cutaneous melanoma: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up	4	4	6	5	5	4	4	4	58,3
Michielin(Michielin 2020)	ESMO consensus conference recommendations on the management of locoregional melanoma: under the auspices of the ESMO Guidelines Committee.	4	5	5	5	4	3	3	2	47,9
Michielin(Michielin 2019)	Cutaneous Melanoma: ESMO Clinical Practice Guidelines	3	3	5	5	5	3	3	2	43,8

*Updates were added after search



Appendix 2.4. Survey

Appendix 2.4.1. Guidelines selected for survey topics / questions

Table 19 – Guidelines used for the survey preparation

Author	Title	Date	Systematic Search No 0 yes 1 no results 2	Dates search	Included for questions on scoping list	Reason included / excluded
Rajagopal(Johnston 2023,Rajagopal 2024)	Clinical Practice Guideline: Surveillance Strategies in Patients with Stage I, II, III or Resectable IV Melanoma Who Were Treated with Curative Intent.	2024	1	1/09/2022	1	Topic of surveillance
Swetter(Swetter 2025)	NCCN guideline Melanoma Cutaneous	2024	0	Continuous	1	Continuously updated
Mangione(Henrikson NB 2023,Mangione)	Screening for Skin Cancer: US Preventive Services Task Force Recommendation Statement	2023	1	1/01/2022	0	Topic excluded
Seth(Seth 2023)	Systemic Therapy for Melanoma: ASCO Guideline Update.	2023	1	2018-2019	1	Topic and recent
SIGN(SIGN - Health Improvement Scotland)	Cutaneous melanoma. SIGN 146.	2023	1	NICE and 2022	1	Expanded on NICE topics
Vogelbaum(Vogelbaum)	Treatment for Brain Metastases: ASCO-SNO-ASTRO Guideline.	2022	1	1/09/2020	1	Topic and date
NICE(NICE 2022)	NICE guideline [NG14] Melanoma: assessment and management	2022	1	1/07/2021	1	Broad topics and recent
Botella(Botella-Estrada 2020)	Guía de práctica clínica de melanoma de la Academia Española de Dermatología y Venereología	2021	1	2016-sept 2019	0	language and date
Cancer council Australia(Cancer Council Australia 2021)	Clinical practice guidelines for the diagnosis and management of melanoma	2021	1	2017-2018	1	Topics not yet covered
Cancer Care Alberta(Cancer Care Alberta 2021)	Biopsy of a Suspicious Pigmented Lesion 2021	2021	2	NA	0	no results systematic search
Leitlinienprogramm Onkologie(Leitlinienprogramm Onkologie AWMF 2021)	S3-Leitlinie Prävention von Hautkrebs 032 - 052OL	2021	0	NA	0	no systematic search
RACGP(RACGP 2021)	Guidelines for preventive activities in general practice	2021	0	NA	0	no systematic search
Smith(Smith)	Ano-uro-genital mucosal melanoma UK national guidelines.	2020	1	March 2017	0	Date / topic



Leitlinienprogramm Onkologie(Leitlinienprogramm Onkologie Deutsche Krebsgesellschaft; Deutsche Krebshilfe AWMF 2020)	S3-Leitlinie Diagnostik, Therapie und Nachsorge des Melanoms	2019	1	2016	0	date
Nederlandse Melanoom Werkgroep (NMW)(Nederlandse Melanoom Werkgroep (NMW) 2019)	Melanoom richtlijn	2019	2	2016	0	no results sytematic search - date
Wright(Wright 2019)	Primary excision margins, sentinel lymph node biopsy, and completion lymph node dissection in cutaneous melanoma: a clinical practice guideline.	2019	1	2017	0	date
Nakamura(Nakamura 2019)	Japanese Dermatological Association Guidelines: Outlines of guidelines for cutaneous melanoma	2019	1	30/11/2017	0	date
Swetter(Swetter 2019)	Guidelines of care for the management of primary cutaneous melanoma (from the AAD)	2019	1	oct 2017	1	topic
Cancer Care Alberta(Cancer Care Alberta 2019)	Management of In-Transit Disease 2019	2019	2		0	no results systematic search - date
Wong(Wong 2018)	Sentinel Lymph Node Biopsy and Management of Regional Lymph Nodes in Melanoma: American Society of Clinical Oncology and Society of Surgical Oncology Clinical Practice Guideline Update	2018	1	June 2017	0	date
Keilholz(Keilholz 2020)	ESMO consensus conference recommendations on the management of metastatic melanoma: under the auspices of the ESMO Guidelines Committee. 2020	2020	0	NA	1	European perspective
Michielin(Michielin 2020)	ESMO consensus conference recommendations on the management of locoregional melanoma: under the auspices of the ESMO Guidelines Committee.	2019	0	NA	1	European perspective
Michielin(Michielin 2019)	Cutaneous Melanoma: ESMO Clinical Practice Guidelines	2020	0	NA	1	European perspective



Appendix 2.4.2. Mail for survey

Dear expert, dear stakeholder,

KCE, the Belgian Healthcare Knowledge Centre, is starting to develop an evidence-based guideline on the **diagnosis and treatment of cutaneous melanoma**.

To define the **content of this guideline**, we would like to ask your input via an **online survey**.

This survey has a long list of proposed questions on seven topics. Could you indicate which questions are of **priority for clinical practice in Belgium**? Examples of priority are

- practice has recently changed,
- there is an ongoing debate in the clinical community or
- there is a large variability in clinical practice.

Important! If you have a question that needs to be listed, we invite you to add this new question to the text boxes and briefly explain why this is of interest.

To complete the survey follow this link [\[survey link\]](#). It will take you about fifteen minutes. Please **finalise** the survey by **10:00 a.m. on Monday, May 6th, 2024**.

Based on the responses received, the final scope of the KCE guideline on cutaneous melanoma will be defined. The guideline will be developed according to evidence-based principles in collaboration with experts from the guideline development group.

Please forward the survey if you know of other interested people who would like to give their input.

If you have any questions, do not hesitate to contact us.

Many thanks for your collaboration,

Kind regards,

Vicky Jespers for the KCE team

Appendix 2.4.3. Survey questions

Introduction

Many thanks for your input in defining the research questions to be studied in the KCE practice guideline on melanoma.

Text survey

Your name *[obligatory reply]*

Would you like to be member of the guideline development group (GDG)?

[yes OR no obligatory reply]

Members of the GDG assist in developing the clinical recommendations based on the evidence review provided by KCE. To this end, members of the GDG have to attend a maximum of 5 meetings.



The final composition of the GDG will be decided by KCE aiming at balanced representation of all clinical expertise and regions of the country.

Would you like to be member of the stakeholder group?

[yes OR no obligatory reply]

Stakeholders provide feedback on the clarity, completeness, acceptability of the clinical recommendations, comment on barriers and facilitators for the implementation. To this end, stakeholders have to attend one meeting.

What is your field of expertise? *[show all options – obligatory reply – more than one answer possible]*

- Dermatologist
- Oncologist
- Surgeon
- General Practitioner
- Radiologist
- Nuclear medicine
- Pathologist
- Nurse
- Oncology coach
- Therapist
- Patient
- Patient representative
- Dietician
- Other: specify

INSTRUCTIONS

The survey has 7 sections. For each section you are asked to rank the questions. At the end of the section you can suggest one or more new questions. Please explain shortly why this new question is important.

Please rank each question by giving a score. If the question is outside your field of expertise, tick “no expertise”.

Explanation scores:

5 = Top priority: should be included

4 = Moderate priority: can be included

3 = Some priority: inclusion unsure

2 = Little priority: likely not to be included

1 = No priority: should not be included

NE = No expertise

[show list of all questions – obligatory reply – possible answers: NE, 5, 4, 3, 2, 1]



The proposed research questions are based on the following guidelines:

- Keilholz U et al. ESMO consensus conference recommendations on the management of metastatic melanoma: under the auspices of the ESMO Guidelines Committee. *Ann Oncol.* 2020;31(11):1435-48.
- Michielin O et al. ESMO consensus conference recommendations on the management of locoregional melanoma: under the auspices of the ESMO Guidelines Committee. *Ann Oncol.* 2020;31(11):1449-61.
- Michielin O et al. Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2019;30(12):1884-901.
- Seth R et al. Systemic Therapy for Melanoma: ASCO Guideline Update. *J Clin Oncol.* 2023;41(30):4794-820.
- Swetter SM et al. Guidelines of care for the management of primary cutaneous melanoma. *J Am Acad Dermatol.* 2019;80(1):208-50.
- Vogelbaum MA et al. Treatment for Brain Metastases: ASCO-SNO-ASTRO Guideline. *Journal of Clinical Oncology.* 2022;40(5):492-516.
- Cancer Council Australia. Clinical practice guidelines for the diagnosis and management of melanoma [Web page]. 2021.
- National Institute for Health and Care Excellence. Melanoma: assessment and management. NICE guideline [NG14] Published: 29 July 2015 Last updated 2022.
- Rajagopal S et al. An Ontario Health (Cancer Care Ontario) Clinical Practice Guideline: Surveillance Strategies in Patients with Stage I, II, III or Resectable IV Melanoma Who Were Treated with Curative Intent. *Clin Oncol (R Coll Radiol).* 2024.
- SIGN - Health Improvement Scotland. Cutaneous melanoma. SIGN 146. First published Jan 2017 Last updated Aug 2023.
- Swetter SM et al. NCCN Guidelines. Melanoma: Cutaneous, Version 2. April 2024.

Topic 1: Managing vitamin D levels and concurrent drug treatment

[show list of all questions – obligatory reply – possible answers: NE, 5, 4, 3, 2, 1]

1 How should sub-optimal vitamin D levels be managed in people with melanoma (including supplements and monitoring)?

2 What is the most effective approach to the management of risks to patients associated with concurrent drug therapies used to treat other conditions, which may affect the prognosis from melanoma (for example, immunosuppressants, levodopa, metformin, HRT, COCP)

3 Please write any comments or specifications you have regarding the listed research questions of this section here.

[Open text]

4 Write here your new questions with an explanation why this question is important.

[Open text]

Topic 2: Identification and management of high-risk individuals

[show list of all questions – obligatory reply – possible answers: NE, 5, 4, 3, 2, 1]

1 What are the risk factors for development of single or multiple primary melanomas?

2 What are the genetic determinants of high risk for new primary melanomas?



3 What validated models integrate genetic and clinical risk factors into an overall measurement of (high) risk for new primary melanoma?

4 What interventions have been shown to provide clinical benefit in those assessed to be at high risk of new primary melanomas?

5 Please write any comments or specifications you have regarding the listed research questions of this section here.

[Open text]

6 Write here your new questions with an explanation why this question is important.

[Open text]

Topic 3: Assessing Melanoma

[show list of all questions – obligatory reply – possible answers: NE, 5, 4, 3, 2, 1]

1 To what extent can the diagnostic accuracy of history-taking and visual examination for the clinical identification of melanoma be improved by dermoscopy or/and new visualisation techniques?

2 Is photography an effective method of detecting progression of pigmented lesions, including dermoscopy pictures?

3 What are the steps when assessing a patient with a suspicious skin lesion (risk factors, biopsy, pathology report content, preliminary workup) to define clinical stage 0 in situ, IA, IB, II, III, or IV?

4 Which secondary tests should be used to diagnose indeterminate melanocytic neoplasms following histopathology?

5 Which imaging modalities should be used for the detection of involved lymph nodes and distant metastasis?

5a Is ultrasound of lymph nodes indicated in clinical stage I-II melanoma?

5b Is a PET-scan (or PET-CT) indicated in clinical stage I-II melanoma?

5c Is a PET-scan (or PET-CT) indicated in clinical stage III-IV melanoma?

6 What are the indications for MRI of the brain in melanoma?

7 Which is the most appropriate tumour sample (primary or secondary) on which to carry out genetic testing to identify people who might benefit from targeted therapies?

8 What is the role and optimal timing of (BRAF) genetic testing of the tumour after diagnosis for a person with melanoma?

9 Please write any comments or specifications you have regarding the listed research questions of this section here.

[Open text]

10 Write here your new questions with an explanation why this question is important.

[Open text]

Topic 4: Surgery

[show list of all questions – obligatory reply – possible answers: NE, 5, 4, 3, 2, 1]

1 Which are the most effective surgical and histological excision margins for stage 0 to II melanoma?

2 In people with a diagnosis of a thin melanoma (Breslow thickness $\leq 1\text{mm}$) which factors are predictive of sentinel lymph node biopsy positivity? (examples; Breslow thickness (0.8-1.0mm versus $<0.8\text{mm}$),



mitotic rate (≥ 2 versus < 2), ulceration (present versus absent), age (< 45 versus ≥ 45), lymphovascular invasion (present versus absent), tumour location (head, neck, or trunk versus extremities or other))

3 What is the utility of sentinel lymph node biopsy for people with stage III melanoma and micro-satellite lesions?

4 What is the effectiveness of completion lymphadenectomy for micro-metastatic nodal disease in stage III melanoma?

5 Which surgery should be offered to patients when the positive sentinel node was outside the nodal basin (aberrant), i.e. should the nodes in the nearest nodal basin also be removed?

6 In case of positive nodes in the groin, should resection of the iliac nodes be offered as well as the inguinal nodes?

7 Should wide local excision (WLE) be used for primary melanoma in the context of clinical stage IV disease?

8 Is surgery an effective treatment for in-transit metastasis?

9 Please write any comments or specifications you have regarding the listed research questions of this section here.

[Open text]

10 Write here your new questions with an explanation why this question is important.

[Open text]

Topic 5: Systemic treatment and radiotherapy

[show list of all questions – obligatory reply – possible answers: NE, 5, 4, 3, 2, 1]

IMPORTANT

1 Systematic treatment is changing rapidly. Please consider treatment(s) with recent / new evidence that has not yet been evaluated in guidelines. Write here your new questions with an explanation why this question is important.

[Open text]

2 What is the role of imiquimod or radiation in early-stage disease?

3 What are the indications for adjuvant therapy in early-stage disease?

4 Is there an indication for adjuvant radiotherapy after node dissection (stage IIIA, IIIB, IIIC)?

5 What is the role of adjuvant immune checkpoint inhibitors in resected stage III/IV disease?

6 In patients with completely resected stage II, III or IV melanoma with a BRAF V600 mutation what is the efficacy of BRAF inhibitors?

7 In patients with BRAF-mutated metastatic melanoma, which treatment should be used as first option: targeted therapy or immunotherapy?

8 For patients with metastatic disease who have progressed after targeted therapy and immunotherapy, can rechallenge with targeted therapy or immunotherapy be considered as a subsequent line of therapy?

9 What are the indications for neoadjuvant therapy in melanoma?

10 Please write any comments or specifications you have regarding the listed research questions of this section here.

[Open text]



11 Write here your new questions with an explanation why this question is important.

[Open text]

Topic 6: Treatment for brain metastasis

[show list of all questions – obligatory reply – possible answers: NE, 5, 4, 3, 2, 1]

1 What are the benefits and harms of surgery in adult patients with brain metastases? Do these benefits differ for patients with newly diagnosed disease versus recurrent disease? Are there subpopulations (eg, number of metastases and status of extracranial disease) of patients who do not benefit from surgery?

2 What are the benefits and harms of laser interstitial thermal therapy (LITT)?

3 What systemic therapy (chemotherapy, immunotherapy, and targeted agents) options, alone or in combination, have demonstrated clinical benefits in adults with brain metastases?

4 What are the benefits and harms of whole brain radiation therapy (WBRT) in adults with brain metastases?

5 What approaches have been found to mitigate the harms of WBRT (eg, radioprotectants, memantine, and hippocampal avoidance)?

6 What are the benefits and harms of stereotactic radiosurgery (SRS) or radiation therapy in adults with brain metastases?

7 What are the relative benefits and harms of SRS or radiation therapy compared to WBRT?

8 What are the benefits and harms of using radiation sensitizers?

9 How does the relative timing of surgery, radiation therapy, and systemic therapy affect the benefits and/or harms of those therapies?

10 Please write any comments or specifications you have regarding the listed research questions of this section here.

[Open text]

11 Write here your new questions with an explanation why this question is important.

[Open text]

Topic 7: Follow-up

[show list of all questions – obligatory reply – possible answers: NE, 5, 4, 3, 2, 1]

1 When can treated patients (with Curative Intent - disease free) be transitioned to primary care for follow-up?

2 What is the diagnostic accuracy of body imaging for re-staging during the follow-up of people with melanoma?

3 Should brain imaging be included for people with melanoma who are undergoing body imaging as part of follow-up, and who have no neurological signs or symptoms?

4 What is the effectiveness of body imaging for the follow-up of people with stage 4 (and unresectable stage 3) melanoma after concluding treatment, including the optimal frequency and duration?

5 Which follow-up evaluations (i.e. clinical follow-up, laboratory tests, photo-surveillance, dermoscopy and imaging), and at what frequency, are optimal to improve patient outcomes (e.g. survival, recurrence, side-effects from imaging examinations and patient-reported outcomes)?

6 Which follow-up evaluations (i.e. clinical follow-up, photo-surveillance and dermoscopy) to detect a new primary melanoma should be performed and at what frequency.



7 Please write any comments or specifications you have regarding the listed research questions of this section here.

[Open text]

8 Write here your new questions with an explanation why this question is important.

[Open text]

End

Appendix 2.5. Final choice of guidelines for Adapt or Adopt

	NICE England	Ontario Canada
Relevance	Topic melanoma; priority questions <u>On diagnosis of cutaneous melanoma</u> - Is an ultrasound the diagnostic test of choice for primary N staging for patients with cutaneous melanoma - Is whole-body ¹⁸F-FDG PET/CT the diagnostic test of choice for the detection of metastases for patients with cutaneous melanoma for N and M staging? <u>On treatment of cutaneous melanoma</u> - Which are the most effective surgical excision margins for stage 0 to II cutaneous melanoma? - Does completion lymphadenectomy (lymph node dissection) for micro-metastatic disease in stage III cutaneous melanoma result in better survival and/or quality of life compared to no completion lymphadenectomy?	Topic: Surveillance evaluations in patients with stage I, II, III, or resectable IV
Credibility	AGREE 87% for rigour of development*	AGREE 77% for rigour of development*
Recency	SR search July 2021	Published 2024; SR search up to March 2024 with extra study Dec 2024
GRADE based	Yes	Yes
Other		

*the rigour of development domain was defined as the most important factor for the credibility to Adapt or Adopt the recommendations of the guideline

APPENDIX 3. EVIDENCE REVIEW PRIMARY STAGING WITH ULTRASOUND AND PET/CT

Appendix 3.1. PICO

Table 20 – PICO diagnostic accuracy review of ultrasound for N staging

	Diagnostic accuracy review of ultrasound pre-SLNB for N staging
Objective	To determine the most accurate tests for diagnosing lymph nodes metastases before sentinel lymph node biopsy in melanoma for adults 18 years and above.
Review questions	Is an ultrasound the diagnostic test of choice for the detection of lymph node metastases in primary cutaneous melanoma?
Population	Included: Adults 18 years and above with a confirmed diagnosis of melanoma (any T stage) at baseline work-up before a sentinel lymph node biopsy (SLNB) Excluded:
Index test	Included: Ultrasound with or without subsequent fine needle aspiration cytology (FNAC) Excluded: -
Comparator test	none
Reference standard	Histology of lymph node with samples obtained from core biopsy, SLNB, or lymph node dissection Cytology of lymph node specimens, with samples obtained by core biopsy or fine needle aspiration
Target condition	Nodal metastases in participants scheduled for SLNB, any nodal metastases
Outcomes	Critical: Diagnostic accuracy Important: quality of life, any test burden, complications Other: treatment changes, survival, cost-effectiveness
Study design	Included: Good-quality systematic reviews, diagnostic randomised controlled trials, prospective and retrospective diagnostic cohort studies, in which the index test(s) and the reference standard test are applied to the same patients in a cross-sectional design. Articles in Dutch, English and French Excluded: Narrative reviews. Case reports. Studies presented as conference abstract only or if no full text was available. Studies in which it is not possible to calculate diagnostic characteristics of the tests.
Analysis	Per patient; By stage

**Table 21 – PICO diagnostic accuracy review of PET/CT for N staging and M staging**

	Diagnostic accuracy review of PET/CT pre-SLNB for N staging and M staging
Objective	To determine the most accurate tests for diagnosing metastases in primary melanoma for adults 18 years and above. Role of the test: Guidelines currently indicate M staging from T stage pT3b and higher and thus M staging might be indicated at lower T stage e.g. from pT2b or lower from pT1b or pT2a.
Review questions	Is whole-body ¹⁸ F-FDG PET/CT the diagnostic test of choice for the detection of metastases in primary cutaneous melanoma for N and M staging?
Population	Included: Adults 18 years and above with a confirmed diagnosis of melanoma (any T stage) at baseline work-up before a sentinel lymph node biopsy (SLNB)
Intervention	Included: (full body) ¹⁸ F-FDG PET/CT; Excluded: -
Comparator	Ce-CT; none
Reference standard	Histology of lymph node with samples obtained from core biopsy, SLNB, or lymph node dissection Histology, clinical examination or imaging at follow-up
Target condition	Detection of any metastasis, nodal (N staging) and/or distant (M staging)
Outcomes	Critical: Diagnostic accuracy Important: quality of life, any test burden, complications Other: treatment changes, survival, cost-effectiveness
Study design	Included: Good-quality systematic reviews, diagnostic randomised controlled trials, prospective and retrospective diagnostic cohort studies, in which the index test(s) and the reference standard test are applied to the same patients in a cross-sectional design. Articles in Dutch, English and French Excluded: Narrative reviews. Case reports. Studies presented as conference abstract only or if no full text was available. Studies in which it is not possible to calculate diagnostic characteristics of the tests.
Analyses	Per patient; By T stage; By N and M metastasis

Appendix 3.2. Search strategies

Appendix 3.2.1. Ovid Medline

Search date July 3th, 2024. Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions <1946 to July 02, 2024>

Search Strategy:

-
- 1 exp Melanoma/
 - 2 melanoma\$.tw.
 - 3 (maligna\$ adj1 lentigo\$).tw.
 - 4 (hutchinson\$ adj1 (freckle\$ or melano\$)).tw.
 - 5 dubreuilh.tw.
 - 6 LMM.tw.

- 7 or/1-6
- 8 exp neoplasm staging/
- 9 *cancer staging/
- 10 (stag\$ or restag\$ or re-stag\$ or upstag* or classif* or TNM or stratif*).tw.
- 11 or/8-10
- 12 7 and 11
- 13 exp Sentinel Lymph Node Biopsy/
- 14 ((sentinel and node) adj biops*).tw.
- 15 (sentinel adj1 lymphadenectom*).tw.
- 16 ((sentinel and node) adj dissect*).tw.
- 17 ((sentinel and node) adj procedure).tw.
- 18 ((sentinel and node) adj detection).tw.
- 19 (SLNB or SNB).tw.
- 20 or/13-19
- 21 exp Physical Examination/
- 22 ((clinical or physical) adj exam*).tw.
- 23 ((clinical or physical) adj assess*).tw.
- 24 *Palpation/
- 25 palpat*.tw.
- 26 or/21-25
- 27 exp Ultrasonography/
- 28 (ultraso* or sonogra* or echogra* or echotomogra*).tw.
- 29 27 or 28
- 30 *Diagnostic Imaging/
- 31 exp Radionuclide Imaging/
- 32 (radionuclide adj1 (scan* or imaging)).tw.
- 33 exp Magnetic Resonance Imaging/
- 34 magnet* resonance.tw.
- 35 (MRI or MRI*1 or NMR*1).tw.
- 36 (MR adj (imag* or scan*)).tw.
- 37 (magnet* adj (imag* or scan*)).tw.
- 38 (magneti?ation adj3 imaging).tw.
- 39 (wbmr* or whole body mr*).tw.
- 40 Whole Body Imaging/
- 41 exp Tomography/
- 42 exp Tomography, X-Ray Computed/



- 43 PET*1.tw.
- 44 PET-CT.tw.
- 45 (comput* adj1 tomogra*).tw.
- 46 ((diffusion or planar or echoplanar or functional or nuclear or radionuclide or radioisotope or conventional) adj2 (scan* or imag* or tomogra*)).tw.
- 47 (FDG-PET or FES-PET or 18F-FDG-PET or FLT-PET).tw.
- 48 ((CT or CAT) adj (scan* or imaging or examination)).tw.
- 49 (PET adj (scan* or imaging or examination)).tw.
- 50 positron emission tomograph.tw.
- 51 scintigraph*.tw.
- 52 or/30-51
- 53 exp Biopsy, Fine-Needle/
- 54 (fine needle adj1 (biops* or cytolog*)).tw.
- 55 (FNAC or FNA).tw.
- 56 53 or 54 or 55
- 57 20 or 26 or 29 or 52 or 56
- 58 12 and 57
- 59 ((systematic review or systematic literature review or systematic scoping review or systematic narrative review or systematic qualitative review or systematic evidence review or systematic quantitative review or systematic meta-review or systematic critical review or systematic mixed studies review or systematic mapping review or systematic cochrane review or "systematic search and review" or systematic integrative review).ti. not comment.pt. not (protocol or protocols).ti. not medline.st.) or (Cochrane Database Syst Rev.ja. and review.pt.) or systematic review.pt.
- 60 meta-analys*.ti.
- 61 meta-analysis.pt.
- 62 exp Technology Assessment, Biomedical/
- 63 health technology assessment.ti,kf.
- 64 HtA.ti,kf.
- 65 59 or 60 or 61 or 62 or 63 or 64
- 66 58 and 65
- 67 limit 66 to yr="2009-2024"
- 68 randomized controlled trial.pt.
- 69 controlled clinical trial.pt.
- 70 randomized.ti,ab.
- 71 placebo.ti,ab.
- 72 clinical trials as topic/
- 73 randomly.ti,ab.
- 74 trial?.ti.



75 68 or 69 or 70 or 71 or 72 or 73 or 74
76 exp animal/ not humans/
77 75 not 76
78 58 and 77
79 limit 78 to yr="2009-2024"
80 exp cohort studies/
81 cohort\$.tw.
82 controlled clinical trial.pt.
83 epidemiologic methods/
84 limit 83 to yr=1971-1988
85 80 or 81 or 82 or 84
86 58 and 85
87 limit 86 to yr="2009-2024"

Appendix 3.2.2. Embase

Search date July 18th, 2024

60 #58 AND (random*:ab,ti OR placebo*:de,ab,ti OR ((double NEXT/1 blind*):ab,ti)
#59 #58 AND ('meta-analysis'/exp OR 'meta-analysis' OR 'systematic review'/exp OR 'systematic review')
#58 #57 NOT ('conference abstract'/it OR 'conference paper'/it OR 'conference review'/it)
#57 #56 NOT [medline]/lim
#56 #55 AND [2009-2024]/py
#55 #11 AND #54
#54 #19 OR #24 OR #27 OR #49 OR #53
#53 #50 OR #51 OR #52
#52 fnac:ab,ti,kw OR fna:ab,ti,kw
#51 ('fine needle' NEAR/1 (biops* OR cytolog*)):ab,ti,kw
#50 'fine needle aspiration biopsy'/exp
#49 #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
#48 scintigraph*:ab,ti,kw
#47 ('positron emission' NEAR/5 tomograph*):ab,ti,kw
#46 (pet NEAR/5 (scan* OR imaging OR examination)):ab,ti,kw
#45 ((ct OR cat) NEAR/5 (scan* OR imaging OR examination\$)):ab,ti,kw
#44 'fdg pet':ab,ti,kw OR 'fes pet':ab,ti,kw OR '18f fdg pet':ab,ti,kw OR 'flt pet':ab,ti,kw
#43 ((diffusion OR planar OR echoplanar OR functional OR nuclear OR radionuclide OR radioisotope OR conventional) NEAR/2 (scan* OR imag* OR tomogra*)):ab,ti,kw
#42 (comput* NEAR/1 tomogra*):ab,ti,kw



- #41 pet*1:ab,ti,kw
- #40 'tomography'/exp
- #39 'whole body tomography':ab,ti,kw OR 'whole body tomographies':ab,ti,kw
- #38 'whole body imaging'/exp
- #37 wbm*:ab,ti,kw OR 'whole body mr':ab,ti,kw OR 'whole body mri':ab,ti,kw
- #36 (magnetisation NEAR/3 imaging):ab,ti,kw
- #35 (magnet* NEAR/5 (imag* OR scan*)):ab,ti,kw
- #34 (mr NEAR/5 (imag* OR scan*)):ab,ti,kw
- #33 mri:ab,ti,kw OR mri*1:ab,ti,kw OR nmr*1:ab,ti,kw
- #32 (magnet* NEAR/5 resonance):ab,ti,kw
- #31 'nuclear magnetic resonance imaging'/exp
- #30 (radionuclide NEAR/1 (scan* OR imaging)):ab,ti,kw
- #29 'scintiscanning'/exp
- #28 'diagnostic imaging'/exp/mj
- #27 #25 OR #26
- #26 ultraso*:ab,ti,kw OR sonogra*:ab,ti,kw OR echogra*:ab,ti,kw OR echotomogra*:ab,ti,kw
- #25 'echography'/exp
- #24 #20 OR #21 OR #22 OR #23
- #23 palpat*:ab,ti,kw
- #22 ((clinical OR physical) NEAR/10 assess*):ab,ti,kw
- #21 ((clinical OR physical) NEAR/10 exam*):ab,ti,kw
- #20 'physical examination'/exp
- #19 #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18
- #18 SLNB:ab,ti,kw OR snb:ab,ti,kw
- #17 (sentinel NEAR/10 detect*):ab,ti,kw
- #16 (sentinel NEAR/10 procedure\$):ab,ti,kw
- #15 (sentinel NEAR/10 dissect*):ab,ti,kw
- #14 (sentinel NEAR/1 lymphadenectom*):ab,ti,kw
- #13 ('sentinel node' NEAR/5 biops*):ab,ti,kw
- #12 'sentinel lymph node biopsy'/de
- #11 #7 AND #10
- #10 #8 OR #9
- #9 stag*:ab,ti,kw OR restag*:ab,ti,kw OR 're stag*':ab,ti,kw OR upstag*:ab,ti,kw OR
classif*:ab,ti,kw OR tnm:ab,ti,kw OR stratif*:ab,ti,kw
- #8 'cancer staging'/de
- #7 #1 OR #2 OR #3 OR #4 OR #5 OR #6
- #6 Imm:ab,ti,kw

- #5 dubreuilh:ab,ti,kw
- #4 (hutchinson* NEAR/1 (freckle* OR melano*)):ab,ti,kw
- #3 (maligna* NEAR/1 lentigo*):ab,ti,kw
- #2 melanoma*:ab,ti,kw
- #1 'melanoma'/de OR 'amelanotic melanoma'/de OR 'malignant lentigo'/de

Appendix 3.2.3. Cochrane

Search date 26/07/2024 22:19:57

- | ID | Search |
|-----|--|
| #1 | [mh Melanoma] |
| #2 | melanoma*:ti,ab |
| #3 | (maligna*:ti,ab NEAR/1 lentigo*:ti,ab) |
| #4 | (hutchinson*:ti,ab NEAR/1 (freckle*:ti,ab OR melano*:ti,ab)) |
| #5 | dubreuilh:ti,ab |
| #6 | LMM:ti,ab |
| #7 | #1 OR #2 OR #3 OR #4 OR #5 OR #6 |
| #8 | [mh "neoplasm staging"] |
| #9 | [mh ^"cancer staging"[mj]] |
| #10 | (stag*:ti,ab OR restag*:ti,ab OR re-stag*:ti,ab OR upstag*:ti,ab OR classif*:ti,ab OR TNM:ti,ab OR stratif*:ti,ab) |
| #11 | #8 OR #9 OR #10 |
| #12 | #7 AND #11 |
| #13 | [mh "Sentinel Lymph Node Biopsy"] |
| #14 | ((sentinel:ti,ab AND node:ti,ab) NEXT biops*:ti,ab) |
| #15 | (sentinel:ti,ab NEAR/1 lymphadenectom*:ti,ab) |
| #16 | ((sentinel:ti,ab AND node:ti,ab) NEXT dissect*:ti,ab) |
| #17 | ((sentinel:ti,ab AND node:ti,ab) NEXT procedure:ti,ab) |
| #18 | ((sentinel:ti,ab AND node:ti,ab) NEXT detection:ti,ab) |
| #19 | (SLNB:ti,ab OR SNB:ti,ab) |
| #20 | #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 |
| #21 | [mh "Physical Examination"] |
| #22 | ((clinical:ti,ab OR physical:ti,ab) NEXT exam*:ti,ab) |
| #23 | ((clinical:ti,ab OR physical:ti,ab) NEXT assess*:ti,ab) |
| #24 | [mh ^"Palpation"] |
| #25 | palpat*:ti,ab |
| #26 | #21 OR #22 OR #23 OR #24 OR #25 |
| #27 | [mh Ultrasonography] |



- #28 (ultraso*:ti,ab OR sonogra*:ti,ab OR echogra*:ti,ab OR echotomogra*:ti,ab)
- #29 #27 OR #28
- #30 [mh ^"Diagnostic Imaging"]
- #31 [mh "Radionuclide Imaging"]
- #32 (radionuclide:ti,ab NEAR/1 (scan*:ti,ab OR imaging:ti,ab))
- #33 [mh "Magnetic Resonance Imaging"]
- #34 (magnet* NEXT "resonance"):ti,ab
- #35 (MRI:ti,ab OR MRI*1:ti,ab OR NMR*1:ti,ab)
- #36 (MR:ti,ab NEXT (imag*:ti,ab OR scan*:ti,ab))
- #37 (magnet*:ti,ab NEXT (imag*:ti,ab OR scan*:ti,ab))
- #38 (magnet*ation:ti,ab NEAR/3 imaging:ti,ab)
- #39 (wbmr*:ti,ab OR ("whole body" NEXT mr*):ti,ab)
- #40 [mh ^"Whole Body Imaging"]
- #41 [mh Tomography]
- #42 [mh "Tomography, X-Ray Computed"]
- #43 PET*1:ti,ab
- #44 PET-CT:ti,ab
- #45 (comput*:ti,ab NEAR/1 tomogra*:ti,ab)
- #46 ((diffusion:ti,ab OR planar:ti,ab OR echoplanar:ti,ab OR functional:ti,ab OR nuclear:ti,ab OR radionuclide:ti,ab OR radioisotope:ti,ab OR conventional:ti,ab) NEAR/2 (scan*:ti,ab OR imag*:ti,ab OR tomogra*:ti,ab))
- #47 (FDG-PET:ti,ab OR FES-PET:ti,ab OR 18F-FDG-PET:ti,ab OR FLT-PET:ti,ab)
- #48 ((CT:ti,ab OR CAT:ti,ab) NEXT (scan*:ti,ab OR imaging:ti,ab OR examination:ti,ab))
- #49 (PET:ti,ab NEXT (scan*:ti,ab OR imaging:ti,ab OR examination:ti,ab))
- #50 "positron emission tomograph":ti,ab
- #51 scintigraph*:ti,ab
- #52 #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
- #53 [mh "Biopsy, Fine-Needle"]
- #54 ("fine needle":ti,ab NEAR/1 (biops*:ti,ab OR cytolog*:ti,ab))
- #55 (FNAC:ti,ab OR FNA:ti,ab)
- #56 #53 OR #54 OR #55
- #57 #20 OR #26 OR #29 OR #52 OR #56
- #58 #12 AND #57
- #59 #58 with Cochrane Library publication date Between Jan 2009 and Dec 2024
- #60 #59 in Cochrane Reviews
- #61 #59 in Trials

Appendix 3.2.4. Study selection

Figure 8 – Study flow selection of search staging with ultrasound and PET/CT

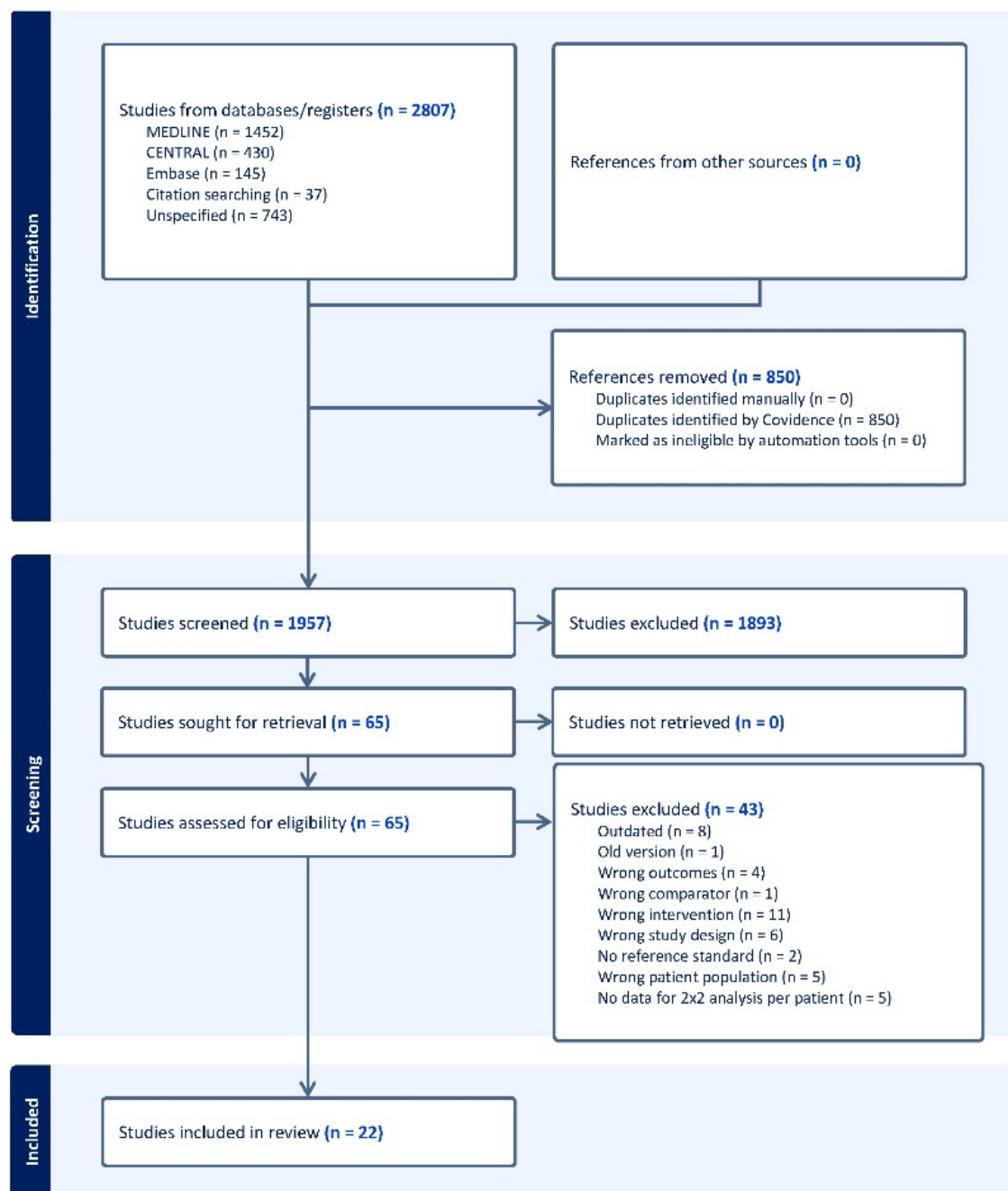


Figure provided by Covidence



Appendix 3.2.5. Studies excluded with reason

Table 22 – Not retained primary studies SR Dinnes 2019 staging ultrasound and PET/CT

Reference	Year	Reasons
Hafner(Hafner 2004)	2004	Wrong population: including all stages, clinically lymph node positive
Radzhabova	2009	Wrong population: including all stages, clinically lymph node positive
Kang(Kang 2011)	2011	Wrong population: including all stages, clinically lymph node positive
Veit-Heibach	2009	Wrong population: including all stages, clinically lymph node positive

Table 23 – Excluded primary studies for staging ultrasound and PET/CT

Reference	Year	Reasons
Abdel-Rahman(Abel-Rahman 2019)	2019	Wrong intervention
Bastiaannet(Bastiaannet 2009)	2009	Outdated
Blundo(Blundo 2021)	2021	Wrong intervention
Bohelay(Bohelay 2015)	2015	Wrong patient population
Borgognoni(Cancer Care Alberta 2019)	2019	Wrong intervention
Dinnes(Dinnes 2017)	2017	Wrong study design
Dinnes(Dinnes 2019)	2019	Wrong study design
Frary(Frary 2016)	2016	Outdated
Garcia-Rodrigo(García-Rodrigo 2017)	2017	Wrong intervention
Groen(Groen 2019)	2019	Wrong comparator
Gyorki(Gyorki 2017)	2017	Wrong intervention
Hafner(Hafner 2004)	2004	Outdated
Holtkamp(Holtkamp 2017)	2017	Wrong patient population
Izzo(Izzo 2023)	2023	Wrong intervention
Jimenez-Requena(Jiménez-Requena 2010)	2010	Wrong study design
Jouvet(Jouvet 2014)	2014	Wrong patient population
Kang(Kang 2011)	2011	Outdated
Marone(Marone 2012)	2012	No data for 2x2 analysis per patient
Niebling(Niebling 2016)	2016	Wrong intervention
Oude Ophuis(Oude Ophuis 2017)	2017	Wrong outcomes
Pfluger(Pfluger 2011)	2011	Outdated
Pflugfelder(Pflugfelder 2013)	2013	Old version
Plouznikoff(Plouznikoff 2017)	2017	Wrong outcomes
Prayer(Prayer 1990)	1990	Outdated
Ravichandran(Ravichandran 2020)	2020	No data for 2x2 analysis per patient



Rodriguez Rivera(Rodriguez Rivera 2014)	2014	Wrong study design
Rossi(Rossi 2003)	2003	No data for 2x2 analysis per patient
Schroer-Gunther(Schröer-Günther 2012)	2012	Outdated
Shimizu(Shimizu 2024)	2024	Wrong outcomes
Singnurkar(Singnurkar 2016)	2016	No reference standard
Ternov(Ternov 2018)	2018	No data for 2x2 analysis per patient
Testori(Testori 2005)	2005	No data for 2x2 analysis per patient
Valsecchi(Valsecchi 2011)	2011	Wrong intervention
Van Wissen(van Wissen 2016)	2016	Wrong patient population
Veit-Haibach(Veit-Haibach 2009)	2009	Outdated
Warycha(Warycha 2009)	2009	Wrong intervention
Weber(Weber 2022)	2022	Wrong outcomes
Wong(Wong)	2012	Wrong intervention
Wong(Wong 2018)	2018	Wrong intervention
Xing(Xing 2011)	2011	Wrong study design
Yan(Yan 2022)	2022	Wrong patient population
Yilmaz(Yilmaz 2020)	2020	No reference standard
Zamani-Siahkali(Zamani-Siahkali 2024)	2024	Wrong study design



Appendix 3.3. Appraisal

The selected systematic review was assessed by one researcher with the AMSTAR 2 (Assessing the methodological quality of systematic reviews). (Shea 2017)

Table 24 – Quality included systematic review staging ultrasound and PET/CT

Systematic review by Dinnes 2019 (Dinnes 2019)	
PICO included	yes
A priori study design	yes
Explanation selection study design inclusion	yes
Comprehensive literature search	yes
Duplicate study selection and data extraction	yes
List of in- and excluded studies	yes
Characteristics of included studies	yes
Study quality assessed	yes
Sources of funding studies reported	yes
Appropriate methods to combine findings	Yes
Bias consider in meta-analysis or summary estimates	yes
Heterogeneity discussed	n/a*
Likelihood of publication bias assessed	n/a*
Conflict of interest stated	yes

* 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), Dinnes et al. did not assess publication bias.

The QUADAS-2 checklist which had been tailored to the review topic by Dinnes et al was used for the assessment of the primary studies. (Whiting 2011) The questions that were not relevant for this review e.g. follow-up was included in the SR, were excluded. This is indicated and explained in the table below.

Table 25 – Methodology QUADAS-2 assessment staging ultrasound and PET/CT

Questions	Answers
<i>Participant selection - allocation</i>	
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 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 for melanoma 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)):	<u>This question was not included as no between person studies were identified.</u>
Could the selection of participants have introduced bias?	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
<i>Participant selection - applicability</i>	
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 ≤ 1 mm in thickness? <u>This question was modified as our research question was interested in specifically in Stage I-II results (clinical negative LN); thus inclusions restricted to stage I-II were considered as 'unrestricted'.</u>	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? <u>We included per patient analysis results and not per lesion.</u>	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



Questions	Answers
3) Does the study focus primarily on participants undergoing primary staging or those undergoing staging for disease recurrence? <u>We included primary staging only.</u>	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 – risk of bias	
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
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?	<u>This question was not included as no multiple threshold studies were identified.</u>
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?	<u>This question was not included as no within-person studies were identified.</u>
Could the conduct or interpretation of the index test have introduced bias?	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
Index test – applicability	
1) Were thresholds or criteria for diagnosis reported in sufficient detail to allow replication?	Yes – if the criteria for diagnosis of the target disorder were reported in sufficient detail to allow replication



Questions	Answers
<i>This item applies equally to studies using objective and more subjective approaches to test interpretation.</i>	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 mentioned in paper No – if the test was not interpreted by an experienced examiner 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?	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 – 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 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? <u>This question was not applied as all LN sent for histology are to be considered suspicious even if the US results are not known to the pathologist.</u>	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 <u>This question was excluded</u>



Questions	Answers
3) Were the reference standard results based on patient follow-up interpreted without knowledge of the results of the index test?	<u>This question was excluded as patient follow-up studies were not included.</u>
Could the reference standard, its conduct, or its interpretation have introduced bias?	If answers to questions 1a) and 1b) was 'Yes': Risk is Low If answers to questions 1a) and 1b) was 'No': Risk is High If answers to questions 1a) and 1b) was 'Unclear': Risk is Unclear
Reference standard - applicability	
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 ≤ 1 mm in thickness? <u>This question was modified as our research question was interested in specifically in Stage I-II results (clinical negative LN); thus inclusions restricted to stage I-II were considered as 'unrestricted'.</u>	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? <u>We included per patient data studies only.</u>	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
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 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
Flow and timing - risk of bias	
1) Was there an appropriate interval between index test and reference standard?	



Questions	Answers
• a) <i>For index test positive participants, was the interval between index test and histological reference standard ≤ 1 month?</i>	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 histological reference standard
• b) <i>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?</i>	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) <i>Did all participants receive the same reference standard?</i>	Yes – if all participants underwent the same reference standard; No – if some participants were excluded from the analysis Unclear – if not clearly reported
3) <i>Were all participants included in the analysis?</i>	Yes – if all participants were included in the analysis No – if some participants were excluded from the analysis Unclear – if not clearly reported
4) <i>For WITHIN-PERSON COMPARISON (WPC) of index tests: Was the interval between application of index tests ≤ 1 month?</i>	<u>Not included as not within-person studies.</u>
<i>Could the participant flow have introduced bias?</i>	<i>If answers to questions 1) and 2) and 3) was 'Yes': Risk is Low</i> <i>If answers to any one of questions 1) or 2) or 3) was 'No': Risk is High</i> <i>If answers to any one of questions 1) or 2) or 3) was 'Unclear': Risk is Unclear</i>

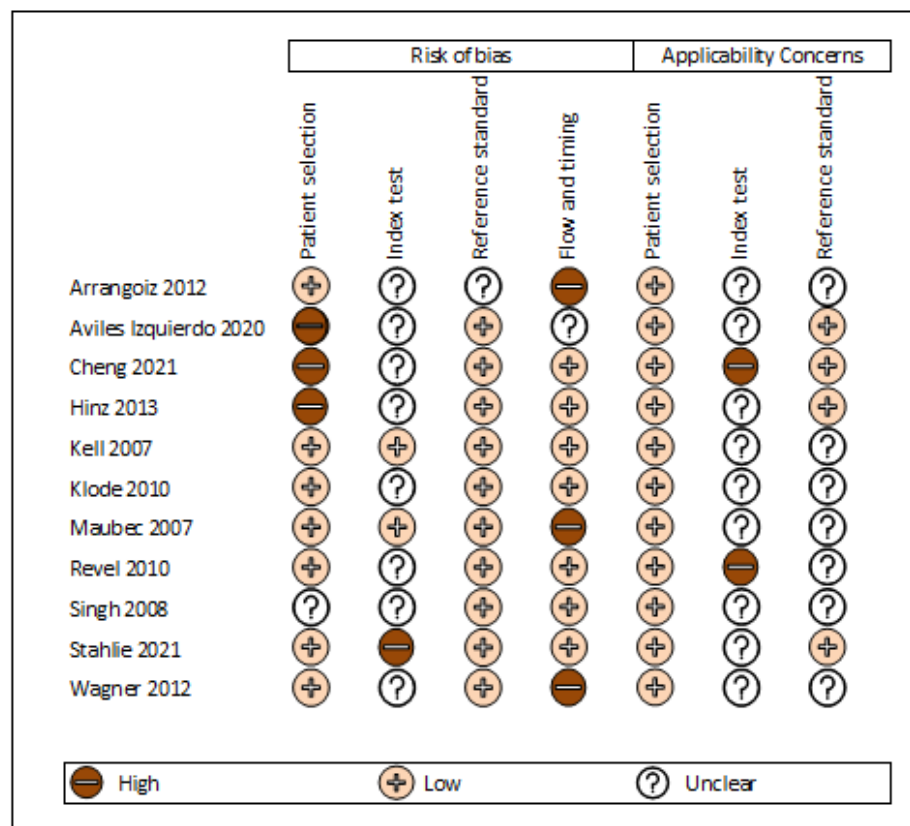


Figure 9 – Risk of bias and applicability concerns for the included studies on ultrasound

	Risk of bias				Applicability Concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Chai 2012	+	+	+	—	+	?	?
Hinz 2011	—	+	+	+	+	?	+
Hinz 2013	—	?	+	+	+	+	+
Hocevar 2004	?	?	+	?	+	?	?
Kunte 2009	+	+	+	+	+	?	?
Olmedo 2017	+	+	+	?	+	+	+
Sanki 2009	?	?	+	+	+	?	?
Sibon 2007	+	+	+	+	+	?	?
Stahlie 2021	+	+	+	+	+	+	+
Thompson 2021	+	+	+	+	+	+	+
Van Rijk 2006	+	?	+	+	+	?	?
Verver 2018	+	+	+	+	+	+	+
Voit 2014	+	+	+	+	+	?	?

	High		Low		Unclear
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Figure 10 – Risk of bias and applicability concerns for the included studies on PET/CT



Appendix 3.4. ROC curves

Summary diagnostic accuracy analysis with stata based on the Cochrane programme for diagnostics, appendix 3.(Takwoingi Y 2023)

Figure 11 – ROC primary N staging with ultrasound (per patient)

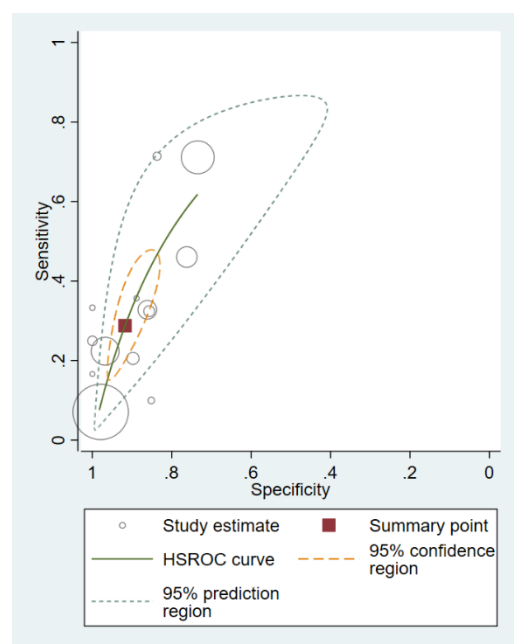




Figure 12 – ROC primary N staging with ultrasound/FNAC combination (per patient)

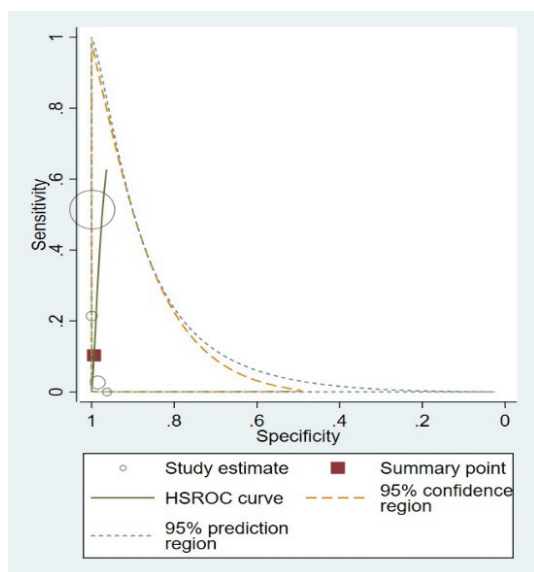
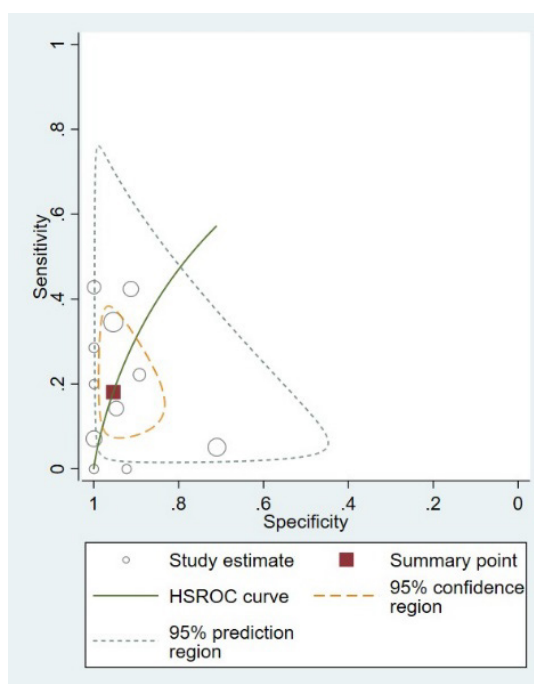


Figure 13 – ROC primary N staging with PET/CT (per patient)





Appendix 3.5. Evidence tables

Appendix 3.5.1. Systematic review Dinnes 2019

Table 26 – Evidence table SR ultrasound and PET/CT staging

<i>Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma(Dinnes 2019)</i>	
Methods	
Design	Cochrane systematic review
Source funding of and competing interest	National Institute for Health Research, via Cochrane Infrastructure funding to Cochrane Skin and Cochrane Programme Grant funding.
Search date	August 2016
Searched databases	MEDLINE via OVID (from 1946). MEDLINE In-Process & Other Non-Indexed Citations via OVID. Embase via OVID (from 1980). 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. 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-researchnetwork-portfolio/; searched 29 August 2016). • World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch/; searched 29 August 2016).
Included study designs	Test accuracy studies that allowed comparison of results of the index test versus a reference standard
Number of included studies	39 studies with 5204 study participants (34 studies with per patient data for 4980 patients). Not all studies were applicable to the research question e.g. disease recurrence.


Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma (Dinnes 2019)

Statistical analysis	Data from each study was summarised in two by two tables of TP, FP, TN, FN and used to calculate sensitivity and specificity. Univariate fixed or random models, where appropriate, were used for both sensitivity and specificity. Investigation of heterogeneity was performed. The 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.
Patient characteristics	
Eligibility criteria	Adults with cutaneous melanoma at any primary site who were undergoing staging, either following primary presentation of disease or following recurrence of disease. Studies with up to 10% of participants had other forms of melanoma such as ocular or mucosal melanoma were included. Studies with greater proportions of participants with non-cutaneous melanoma and studies including participants with other forms of cancer were only included if test results for participants with cutaneous melanoma could be differentiated.
Exclusion criteria	None
Patient & disease characteristics	Adults with cutaneous melanoma at any primary site who were undergoing staging
Interventions	
Index test	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 (¹⁸FDG only). • MRI (non-contrast-enhanced or contrast-enhanced). Any threshold for deciding test positivity, either qualitative or quantitative, was included. 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) were excluded.
Target condition	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

**Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma (Dinnes 2019)**

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

Reference standard

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.

Cross-sectional imaging-based reference standards (i.e. direct comparison of the index test vs an alternative reference standard imaging test) were excluded.

Results**Diagnostic accuracy (sensitivity, specificity)**

Summary of findings

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:	35.4	93.9	84	153	47	716
	2614 (542)	(17.0 to 59.4)	(86.1 to 97.5)	(40 to 141)	(197 to 96)	(106 to 19)	(657 to 744)
US + FNAC	3:	18.0	99.8	43	194	2	761
	1164 (259)	(3.58 to 56.5)	(99.1 to 99.9)	(8 to 134)	(229 to 103)	(7 to 1)	(756 to 762)
PET-CT	4:	10.2	96.5	24	213	27	736
	170 (49)	(4.31 to 22.3)	(87.1 to 99.1)	(10 to 53)	(227 to 184)	(98 to 7)	(665 to 756)



Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma (Dinnes 2019)

	Whole body imaging 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 ≥ 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%). The data for re-staging is not presented as it is not part of the KCE research question.			
Other	Layer 2: any test burden, complications Layer 3: quality of life, survival, cost-effectiveness			
Conclusions	<u>Ultrasound of regional lymph nodes before sentinel lymph node biopsy</u>: 11 relevant studies including 2614 people were identified with three of these studies comparing 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. 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.			

**Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma (Dinnes 2019)**

	<u>Whole body imaging (detection of any metastases):</u> 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.
Limitations	In most of the 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. 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: High or unclear concern for applicability for almost all domains.



Appendix 3.5.2. Primary studies updated search

Table 27 – Evidence table of primary studies ultrasound and PET/CT staging

<i>Olmedo D, Brotons-Seguí M, del Toro C, González M, Requena C, Traves V, et al. Valor de la ecografía ganglionar previa a la biopsia del ganglio centinela en 384 pacientes con melanoma: análisis de coste-efectividad. Actas Dermo-Sifiliográficas. 2017;108(10):931-8.</i>	
Design	Retrospective
Source of funding and competing interest	Funding not reported; no conflict of interests reported.
Setting	Spain January 2004 - December 2015
Sample size	384
Time interval between tests	Not reported
Statistical analysis	Contingency tables to calculate the sensitivity, specificity, positive predictive value, and negative predictive value were used. For purposes of the study, true positives were defined as indeterminate or positive ultrasound scans with histologic confirmation using either core-needle biopsy or SLNB. False positives were defined as indeterminate and positive ultrasound scans without lymph node metastasis, both in core-needle biopsy and in SLNB. True negatives were defined as normal ultrasound scans with negative SLNB results; false negatives were defined as normal ultrasound scans with positive SLNB results. Cost-effectiveness study from the health service perspective was performed.
Patient characteristics	
Eligibility criteria	Patients with Clinical stage I - II primary melanoma eligible for SLNB
Exclusion criteria	Lymph node metastasis had been detected during the physical examination
Patient & disease characteristics	Prevalence LN positive 26.5% =102/384
Interventions	
Index test	B-flow and Doppler lymph node ultrasound all covering all possible drainage territories; by experienced radiologists; Lymph nodes were classified as benign, indeterminate, or suspicious for melanoma according to standard criteria. (reference Ulrich J, van Akkooi AC, Eggermont AM, Voit CA. Sonographic criteria for diagnosing sentinel node metastases in melanoma patients. Ultraschall Med. 2015;36:149---53.)
Target condition	Primary target conditions were defined as detection of nodal metastases in participants scheduled for SLNB
Reference standard	Core-needle biopsy (n= 104) or/and SLNB (n=361) In the case of indeterminate or suspicious findings, an ultrasound-guided core-needle biopsy (Tru-cut) was performed.



	Histology with hematoxylin-eosin and immunohistochemistry (S100 and melan-A)																																		
Results																																			
Diagnostic accuracy (sensitivity, specificity)	Sens 0.46 [0.36, 0.56] Spec 0.76 [0.71, 0.81] <table><tr><th colspan="3">Reference standard</th><th colspan="2">Sensitivity</th><th colspan="2">Specificity</th></tr><tr><th></th><th>+</th><th>-</th><th>Total</th><th></th><th></th><th></th></tr><tr><th rowspan="2">Index test</th><th>+</th><td>TP 47</td><td>FP 67</td><td>Test+ 114</td><td>0.4608</td><td>0.7624</td></tr><tr><th>-</th><td>FN 55</td><td>TN 215</td><td>Test- 270</td><td>0.4123</td><td>0.7963</td></tr><tr><th>Total</th><td>D+ 102</td><td>D- 282</td><td>N 384</td><td>LR+ 1.9394</td><td>LR- 0.7073</td><td>Prevalence 0.2656</td></tr></table>	Reference standard			Sensitivity		Specificity			+	-	Total				Index test	+	TP 47	FP 67	Test+ 114	0.4608	0.7624	-	FN 55	TN 215	Test- 270	0.4123	0.7963	Total	D+ 102	D- 282	N 384	LR+ 1.9394	LR- 0.7073	Prevalence 0.2656
Reference standard			Sensitivity		Specificity																														
	+	-	Total																																
Index test	+	TP 47	FP 67	Test+ 114	0.4608	0.7624																													
	-	FN 55	TN 215	Test- 270	0.4123	0.7963																													
Total	D+ 102	D- 282	N 384	LR+ 1.9394	LR- 0.7073	Prevalence 0.2656																													
Cost-effectiveness	The authors state the following: SLNB was obviated in 23 patients (6%). The activity-based costing approach revealed a unit cost of € 1700.00 per patient staged by SLNB alone and € 1716.30 per patient staged by SLNB preceded by ultrasound. In terms of cost-effectiveness, the analysis revealed ultrasound followed by SLNB to be the dominant strategy, with a cost-effectiveness ratio lower than the alternative, ie, SLNB alone (€ 8095.24 vs € 28 605.00) The available data and analysis in table 4 is not always correct e.g. the ICER is incorrectly measured and the negative incremental effectiveness is not explained. The quality of this evidence is therefore considered very low.																																		
Other	No results for any test burden, complications, quality of life, treatment changes, survival																																		
Limitations and other comments																																			
Limitations and conclusions	Single center and retrospective. Ultrasound----including UGB when necessary----is a useful and cost-effective diagnostic tool for staging melanoma before SLNB.																																		



Verver D, Oude Ophuis CMC, Koppert LB, de Monyé C, van Deurzen CHM, Koljenović S, et al. Gamma probe and ultrasound-guided fine needle aspiration cytology of the sentinel node (GULF) trial. Eur J Nucl Med Mol Imaging. 2018;45(11):1926-33.

Design	Prospective two-centre, open-label, single-arm trial
Source of funding and competing interest	Stichting Coolsingel (pilot and start-up trial) and Stichting Theia (trial). No conflict of interest reported.
Setting	The Netherlands May 2015 - August 2017
Sample size	37
Time interval between tests	Same-day scintigraphy and SLNB
Statistical analysis	Sens, spec for ultrasound and for ultrasound with FNAC; per patient analysis
Patient characteristics	
Eligibility criteria	cT1b-4N0M0 cutaneous melanoma; Primary melanoma Stage I-II
Exclusion criteria	Unwilling or unable to give informed consent, or if they had a clinically suspicious lymph node, other known malignancy with potential to disseminate to the axillary or groin lymph node basins, prior lymph node biopsy, or no SN visible on lymphoscintigraphy.
Patient & disease characteristics	Prevalence LN positive 27% (10/37) Arm n=8, leg n=14, trunk n=15; male 18/37 BT 1.85 (1.13 - 4.00)
Interventions	
Index test	US following Berlin criteria. US aided by a hand-held gamma probe applied after lymphoscintigraphy; Hand-held gamma probe (16 mm Europrobe 3). US (Aloka ProSound alpha10) with a 1-15 MHz linear transducer US examination findings are reported according to the Berlin morphological criteria. Regarded as malignant when the lymph node appeared Bballoon shaped, and suspicious if peripheral perfusion, loss of central echoes, symmetrical broadening of the parenchyma, or an echo-poor island within an otherwise normal lymph node was present. Fine needle aspiration of all visualized assumed SN(s) was performed using a 21-gauge needle, regardless of suspicion of metastasis on US examination, with usually one or two cortical samples per SN (depending on the visual yield of each sample). A Mini 900 scintillation monitor with a sodium iodide crystal was used, when available, to measure radioactivity of the samples.



	Nuclear medicine specialist (scintigraphy); dedicated radiologist (US)																																																																																																																	
Target condition	Primary target conditions were defined as detection of nodal metastases in participants scheduled for SLNB.																																																																																																																	
Reference standard	Histology and FNAC. Cytological smears were prepared according to a standard protocol. Cytomorphology was assessed on haematoxylin and eosin (H&E) stained smears. The remainder of the aspirate was expressed into a CytoLyt solution from which a Cellient cell block was prepared, provided that an adequate amount of material was obtained. Cytomorphology was assessed again. In addition immunohistochemical staining was performed using S-100 and Melan-A for melanoma samples.																																																																																																																	
Results																																																																																																																		
Diagnostic accuracy (sensitivity, specificity)	Pre-SLNB US results: Sens: 0.10 [0.00, 0.45] Spec: 0.85 [0.66, 0.96] <table><tr><th colspan="3">Reference standard</th><th colspan="2">Sensitivity</th><th colspan="2">Specificity</th></tr><tr><th rowspan="4">Index test</th><th colspan="2">+</th><th colspan="2">+</th><th colspan="2">+</th></tr><tr><th colspan="2">-</th><th colspan="2">-</th><th colspan="2">-</th></tr><tr><th colspan="2">Total</th><th colspan="2">Total</th><th colspan="2">Total</th></tr><tr><th colspan="2">Test+</th><th colspan="2">Test+</th><th colspan="2">Test+</th></tr><tr><td>+</td><td>TP</td><td>FP</td><td>TP</td><td>FP</td><td>TP</td><td>FP</td></tr><tr><td></td><td>1</td><td>4</td><td>1</td><td>4</td><td>1</td><td>4</td></tr><tr><td>-</td><td>FN</td><td>TN</td><td>FN</td><td>TN</td><td>FN</td><td>TN</td></tr><tr><td></td><td>9</td><td>23</td><td>9</td><td>23</td><td>9</td><td>23</td></tr><tr><td>Total</td><td>D+</td><td>D-</td><td>D+</td><td>D-</td><td>D+</td><td>D-</td></tr><tr><td></td><td>10</td><td>27</td><td>10</td><td>27</td><td>10</td><td>27</td></tr><tr><td></td><td colspan="2">N</td><td colspan="2">N</td><td colspan="2">N</td></tr><tr><td></td><td colspan="2">37</td><td colspan="2">37</td><td colspan="2">37</td></tr></table><table><tr><th colspan="2">PPV</th><th colspan="2">NPV</th></tr><tr><td colspan="2">0.2000</td><td colspan="2">0.7188</td></tr><tr><th colspan="2">LR+</th><th colspan="2">LR-</th></tr><tr><td colspan="2">0.6750</td><td colspan="2">1.0565</td></tr><tr><th colspan="2">Prevalence</th><td colspan="2"></td></tr><tr><td colspan="2">0.2703</td><td colspan="2"></td></tr></table> Pre-SLNB US-FNAC results: No TP result with US-FNAC. One FP, 10 FN, 26 TN. Specificity 0.96 [0.81, 1.00]		Reference standard			Sensitivity		Specificity		Index test	+		+		+		-		-		-		Total		Total		Total		Test+		Test+		Test+		+	TP	FP	TP	FP	TP	FP		1	4	1	4	1	4	-	FN	TN	FN	TN	FN	TN		9	23	9	23	9	23	Total	D+	D-	D+	D-	D+	D-		10	27	10	27	10	27		N		N		N			37		37		37		PPV		NPV		0.2000		0.7188		LR+		LR-		0.6750		1.0565		Prevalence				0.2703			
Reference standard			Sensitivity		Specificity																																																																																																													
Index test	+		+		+																																																																																																													
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Other	No results for any test burden, complications, quality of life, treatment changes, survival, cost-effectiveness																																																																																																																	
Limitations and other comments																																																																																																																		
	This study included melanoma and breast cancer patients. Evaluation of the results indicated that even in the best case scenario a FNAC sensitivity of at least 80% could not be achieved, and planned accrual (n=116) was therefore terminated early.																																																																																																																	



Aviles Izquierdo 2020 Utility of PET/CT in patients with stage I-III melanoma	
Design	Retrospective review of clinic notes; non-comparative
Source of funding and competing interest	No financial support. One author declares the following conflict of interest: advisory role from BMS, MSD, Novartis, Roche, Pierre Fabre, Incyte, Amgen, Merck-Serono, Sanofi, Regeneron and Bioncotech.
Setting	Spain, September 2011 to November 2015
Sample size	79
Time interval between tests	Not reported
Statistical analysis	Per patient analysis for nodal and distant metastasis (no separate data).
Patient characteristics	
Eligibility criteria	Stage I-III followed up for at least three years or until their death; Staging patients with melanoma with a BT deeper than 1.5 mm or BT≤1.5 mm but with histological ulceration and no evidence of metastatic disease prior to SLNB.
Exclusion criteria	Patients with suspicious of malignancy findings in another image procedure previously performed were excluded. PET/CT reported as ambiguous were excluded.
Patient & disease characteristics	Prevalence of any metastasis for the included accuracy data participants 39/79=49% (39/83=47% reported) Mean age 56.36 (SD 15.77); median age 57 (25-88; Male 47 (56.6%), Head or neck 11 (13.3%), trunk 31 (37.3%), extremities 41 (49.4%); Breslow Thickness T1 (≤1 mm) 6 (7.2%), T2 (1.01–2 mm) 22 (26.5%), T3 (2.01–4 mm) 33 (39.8%), T4 (>4 mm) 21 (25.3%); BT Mean±SD 3.43±2.62, Median 2.80
Interventions	
Index test	PET/CT with results from whole body; Lesion was identified on CT and/or any pathological 18F-fluorodeoxy-glucose (FDG) uptake was detected: true positive (TP) when metastatic lesions were considered as malignant by the radiologist/nuclear medicine specialist report (2 observers: A nuclear medicine physician and a radiologist made the qualitative and semi-quantitative (SUVmax) analysis).
Target condition	Primary target conditions were defined as detection of nodal metastases in participants scheduled for SLNB and distant metastasis in patients scheduled for CLND.
Reference standard	Histology
Results	

**Diagnostic accuracy (sensitivity, specificity)**

Detection of distant and nodal metastasis by PET/CT:

Sens 0.05 [0.01, 0.17] and spec 0.72 [0.56, 0.85] The 2 true positive (TP) results were regional lymph nodes.

		Reference standard		Total		
		+	-		Sensitivity	Specificity
Index test	+	TP 2	FP 11	Test+ 13	0.0513	0.7250
	-	FN 37	TN 29	Test- 66	PPV 0.1538	NPV 0.4394
		D+ 39	D- 40	N 79	LR+ 0.1865	LR- 1.3086
					Prevalence 0.4937	

Other outcomes

Any test burden:

Investigations of false positives: Eight patients underwent invasive examinations (endoscopy, bronchoscopy, ultrasound guided biopsy) to determine the very cause of PET/CT findings. Four of these patients were incidentally diagnosed of another primary tumor (adenocarcinoma of the colon (2), lung carcinoma, neuroendocrine tumor).

Change of indication for SLNB: none

Survival: At the end of the study follow-up (max 3 years), 61 (73.5%) patients were alive and 22 (26.5%) had died because of melanoma.

No results complications, quality of life, treatment changes, cost-effectiveness

Limitations and other comments

Four patients with another incidental primary tumor in PET/CT were excluded. Characteristics are based on n=83. Accuracy reported based on 79 patients. Sens 5; spec 72.5; PPV 15.3; NPV 4



Stahlie EHA, van der Hiel B, Bruining A, van de Wiel B, Schrage YM, Wouters MWJM, et al. The value of lymph node ultrasound and whole body 18F-FDG PET/CT in stage IIB/C melanoma patients prior to SLNB. European Journal of Surgical Oncology. 2021;47(5):1157-62.

Design	Prospective non-comparative
Source of funding and competing interest	No funding received; WvH declares advisory board/consultancy agreement and research grant received from Amgen. MW declares a research grant received from Novartis. AvA declares advisory board/consultancy agreements for Amgen, Bristol-Myers Squibb, Novartis, MSD eMerck, Merck e Pfizer, Sanofi, Sirius Medical en 4SC and received a research grant from Amgen and Merck e Pfizer.
Setting	The Netherlands April 2019 - January 2021
Sample size	23
Time interval between tests	FNAC was performed at the time of US and PET/CT for suspicious lesions.
Statistical analysis	Per patient analysis for nodal metastasis for US and PET/CT; Sensitivity/true positive rate (TPR), specificity/true negative rate (TNR), positive- and negative predictive value (PPV, NPV) were determined using standard definitions.
Patient characteristics	
Eligibility criteria	Primary cutaneous melanoma Stage IIB and IIC planned for wide local excision. Stage IIB and IIC were defined as patients with a primary melanoma with a Breslow thickness >2 mm with ulceration and with a Breslow thickness >4 mm without ulceration. Thus, primary tumor staged as pT3b or pT4a (stage IIB) or pT4b (stage IIC).
Exclusion criteria	Exclusion of patients with palpable nodal metastases or symptomatic distant metastases detected by S100B prior to LSG and SLNB.
Patient & disease characteristics	14/23=61% nodal metastases and 0/23 (0%) distant metastasis 14: 6 N1b with imaging and 8 N1a with LNB (N category 8th edition staging system N1a=clinically occult detected with SLNB; N1b is clinically detected or with radiographic imaging) Median age 74 (37-85); male 16 (70%); Extremity 13 (57%), trunk 10 (44%), Head/neck 0; Breslow thickness pT3b 9 (39%), pT4a 3 (13%), pT4b 11 (48%); ulceration 20 (83%); Microsatellites 3 (13%)
Interventions	
Index test	US plus FNAC with Philips EPIQ 7 Ultrasound (Bothell, Washington, USA); coverage of the Regional lymph node basin; FNAC Used as confirmation of suspicious lesions n=6; Lymph nodes that presented with a loss of fatty hilum, cortical nodules, a short axis diameter of >1 cm, a convex aspect and/or blurred margins were considered suspicious. Whole body F-FDG PET/CT plus cytology FNAC or biopsy; Cross-calibrated Phillips Gemini TF time-of-flight 16 or Phillips Gemini TF big-bore PET/CT scanner (Cleveland, USA). Abnormal FDG accumulation was evaluated according to location, size and intensity. Experienced nuclear medicine physicians received clinical information from the treating surgeon.

Target condition	Primary target conditions were defined as detection of nodal metastases and distal metastases in participants scheduled for SLNB.																																																																										
Reference standard	Histology on biopsy and/or cytology (FNAC) for PET/CT suspicious lesions; FNAC for US suspicious lesions; SLNB for those without suspicious lesions or negative suspicious lesions. EORTC protocol (Cook et al 2019). FNAC was performed for 6 for US suspicious lesions and 1 extra for PET/CT suspicious lesion.																																																																										
Results																																																																											
Diagnostic accuracy (sensitivity, specificity)	Results for lymph node ultrasound <table><tr><th colspan="2"></th><th colspan="2">Reference standard</th><th rowspan="2">Total</th></tr><tr><th colspan="2"></th><th>+</th><th>-</th></tr><tr><th rowspan="2">Index test</th><th>+</th><td>TP 5</td><td>FP 1</td><td>Test+ 6</td></tr><tr><th>-</th><td>FN 9</td><td>TN 8</td><td>Test- 17</td></tr><tr><th colspan="2">Total</th><td>D+ 14</td><td>D- 9</td><td>N 23</td></tr></table><table><tr><td>Sensitivity</td><td>0.3571</td></tr><tr><td>Specificity</td><td>0.8889</td></tr><tr><td>PPV</td><td>0.8333</td></tr><tr><td>NPV</td><td>0.4706</td></tr><tr><td>LR+</td><td>3.2143</td></tr><tr><td>LR-</td><td>0.7232</td></tr><tr><td>Prevalence</td><td>0.6087</td></tr></table> Results for lymph node PET/CT <table><tr><th colspan="2"></th><th colspan="2">Reference standard</th><th rowspan="2">Total</th></tr><tr><th colspan="2"></th><th>+</th><th>-</th></tr><tr><th rowspan="2">Index test</th><th>+</th><td>TP 4</td><td>FP 0</td><td>Test+ 4</td></tr><tr><th>-</th><td>FN 10</td><td>TN 9</td><td>Test- 19</td></tr><tr><th colspan="2">Total</th><td>D+ 14</td><td>D- 9</td><td>N 23</td></tr></table><table><tr><td>Sensitivity</td><td>0.2857</td></tr><tr><td>Specificity</td><td>1.0000</td></tr><tr><td>PPV</td><td>1.0000</td></tr><tr><td>NPV</td><td>0.4737</td></tr><tr><td>LR+</td><td></td></tr><tr><td>LR-</td><td>0.7143</td></tr><tr><td>Prevalence</td><td>0.6087</td></tr></table> No distant metastases detected on whole body PET/CT.			Reference standard		Total			+	-	Index test	+	TP 5	FP 1	Test+ 6	-	FN 9	TN 8	Test- 17	Total		D+ 14	D- 9	N 23	Sensitivity	0.3571	Specificity	0.8889	PPV	0.8333	NPV	0.4706	LR+	3.2143	LR-	0.7232	Prevalence	0.6087			Reference standard		Total			+	-	Index test	+	TP 4	FP 0	Test+ 4	-	FN 10	TN 9	Test- 19	Total		D+ 14	D- 9	N 23	Sensitivity	0.2857	Specificity	1.0000	PPV	1.0000	NPV	0.4737	LR+		LR-	0.7143	Prevalence	0.6087
		Reference standard		Total																																																																							
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Prevalence	0.6087																																																																										
Other outcomes	Treatment changes: All metastases were nodal and therefore treatment was altered to lymph node dissection and all but one also received adjuvant therapy.																																																																										



	Incidental findings by PET/CT: Three patients had aspecific nodes in the lung which required follow-up. In five patients PET/CT revealed findings that needed further diagnostic examination. These were polyps in the colon, reactive changes in the gastric mucosa, a nonspecific cyst in the thyroid and for two patients benign follicular nodes in the thyroid. Six findings that did not need further examination were described: Schmorl's node, concrement in the kidney, synovitis of the femoral head, dilated aorta ascendens, adrenal adenoma and non-specific skin inflammation. No results for complications, quality of life, survival, cost-effectiveness
Limitations and other comments	
	Conclusions authors: US detected metastases in 22% of patients, altering their treatment, which suggests it is effective in the work-up of stage IIB/C melanoma. Staging with 18F-FDG PET/CT is not of added value prior to LSG and SLNB and should therefore not be used. SLNB cannot be replaced by the preoperative US we offer patients in our hospital, but we do think this imaging modality can be an adjunct to the procedure, in which it can save unnecessary anesthetics and surgery in 22% of pT3b or higher melanomas. Another advantage of detecting pathological lymph nodes prior to LSG and SLNB, lie in the possibility of foregoing SLNB and proceeding directly to LND or entering a neoadjuvant trial.

Thompson JF, Haydu LE, Uren RF, Andtbacka RH, Zager JS, Beitsch PD, et al. Preoperative Ultrasound Assessment of Regional Lymph Nodes in Melanoma Patients Does not Provide Reliable Nodal Staging: Results From a Large Multicenter Trial. *Annals of Surgery*. 2021;273(4).

Design	Prospective diagnostic international study
Source of funding and competing interest	Grant by the U.S. National Cancer Institute (NCI). No conflict of interest.
Setting	International with the PI from United State; December 2004 - May 2013
Sample size	2859
Time interval between tests	Interval less than a month
Statistical analysis	Per patient analysis for nodal metastasis; per basin analysis nodal metastasis.
Patient characteristics	



Eligibility criteria	Primary cutaneous melanoma patient clinically node-negative; Stage I-II
Exclusion criteria	In patients when no SN found n=12, LSG drainage to non-US basin n=2, or no documentation to confirm why SNB and US not in same basin n=3.
Patient & disease characteristics	Prevalence LN positive 19.2%=548/2859 patients (573/3302 basins (17.4%)) BT median 1.65 and mean 2.24 mm; 0 to 1.0 n=486 (17%), 1.01 to 2 n=1256 (43.9%), 2.01 to 4 n=792 (27.7%), and >4 mm n=294 (10.3%), unknown n=31 (1.1%) The median CSA of the tumor deposits in the SNs was 0.13 mm², but values ranged from 0.0001 to 143.2 mm². Tumor deposits in patients with true-positive US results (n ¼ 19) were significantly larger than those in patients with false-negative US results (n ¼ 335) (median CSA 6.84 vs 0.117 mm², Mann-Whitney U test, P < 0.001).
Interventions	
Index test	Preoperative US evaluation of the relevant regional lymph node basin for all patients, and a preoperative lymphoscintigram (LSG). In some centers, general US assessment of the entire node basin was performed before the LSG, while in other centers it was performed after the LSG, when the location of SNs was known, allowing focused US examination of them if the result of the LSG was known to the ultrasonographer. Abnormal node was characterized by the detection of either 1 or 2 of the following: (1) length:depth ratio <2; (2) a hypoechoic center; (3) inability to identify a nodal hilar vessel; (4) a focal rounded area of low-level echoes with increased vascularity in that area.
Target condition	Lymph node metastasis
Reference standard	Histologic examination of the SN(s) removed from each patient Detailed histologic assessment of SNs that were surgically removed; histopathology was assessed using standard hematoxylin and eosin (H&E) stained sections, and with immunohistochemistry (including S100, Mart-1, and HMB45), as previously described.(Morton DL, Cochran AJ, Thompson JF, et al. Sentinel node biopsy for early-stage melanoma: accuracy and morbidity in MSLT-I, an international multi-center trial. Ann Surg. 2005;242:302-311. discussion 311-313) (Cochran AJ, Roberts A, Wen DR, et al. Accurate evaluation of nodal tissues for the presence of tumor is central to the sentinel node approach. Cancer Treat Res. 2005;127:207-220" Local pathology report was reviewed by a central lab: Central pathology review of all SNs that had been reported by the contributing centers to contain metastatic disease was performed by one of the authors (AJC).)
Results	
Diagnostic accuracy (sensitivity, specificity)	Results US for analysis per patient, all patients



		Reference standard		Total		Sensitivity	Specificity
		+	-				
Index test	+	TP 39	FP 48	Test+	87	0.0712	0.9792
	-	FN 509	TN 2263	Test-	2772	PPV 0.4483	NPV 0.8164
Total		D+ 548	D- 2311	N	2859	LR+ 3.4264	LR- 0.9485
						Prevalence 0.1917	

Results by Breslow thickness and all patients, analysis per patient

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Thompson 2021	39	48	509	2263	0.07 [0.05, 0.10]	0.98 [0.97, 0.98]	■	■
Thompson 2021 BT1	0	8	30	448	0.00 [0.00, 0.12]	0.98 [0.97, 0.99]	■	■
Thompson 2021 BT1-2	5	23	190	1038	0.03 [0.01, 0.06]	0.98 [0.97, 0.99]	■	■
Thompson 2021 BT2-4	21	11	191	569	0.10 [0.06, 0.15]	0.98 [0.97, 0.99]	■	■
Thompson 2021 BT4	13	5	96	180	0.12 [0.07, 0.20]	0.97 [0.94, 0.99]	■	■

0 0.2 0.4 0.6 0.8 1 0 0.2 0.4 0.6 0.8 1

Results US for analysis per basin

		Reference standard		Total		Sensitivity	Specificity
		+	-				
Index test	+	TP 38	FP 55	Test+	93	0.0663	0.9798
	-	FN 535	TN 2674	Test-	3209	PPV 0.4086	NPV 0.8333
Total		D+ 573	D- 2729	N	3302	LR+ 3.2906	LR- 0.9529
						Prevalence 0.1735	

Other

No results for any test burden, complications, quality of life, treatment changes, survival, cost-effectiveness



Limitations and other comments	
	SN tumor volume was usually too small to be reliably detected by US. For accurate nodal staging to guide the management of melanoma patients, US is not an effective substitute for SN biopsy.

Cheng D, McNicoll CF, Kirgan D, Jones MS, Rivera MR, Doyle GM, et al. The role of FDG-PET-CT is limited in initial staging of nodal metastasis for thin cutaneous melanoma. The American Journal of Surgery. 2021;221(4):737-40.

Design	Retrospective; non-comparative
Source of funding and competing interest	No grants received; no conflicts of interest.
Setting	United States 2005 to 2015
Sample size	92
Time interval between tests	PET to surgery, median, IQR (days) 22.5, (8.5, 36.5)
Statistical analysis	Per patient analysis for nodal metastasis for PET/CT; Sensitivity/true positive rate (TPR), specificity/true negative rate (TNR), positive- and negative predictive value (PPV, NPV) were determined using standard definitions.
Patient characteristics	
Eligibility criteria	Primary pre-SLNB and/or CLND, Stage I-II PET-CT. (Of the 367 retrospectively identified cases; 95 obtained a PET-CT prior to lymphadenectomy)
Exclusion criteria	Patients who did not have a PET/CT were excluded.
Patient & disease characteristics	Prevalence LN positive 28%=26/92 patients Mean age 59.7 (SD 16.1); Male 62 (67%); Mean BT 4.57 (SD 5.0); 7 (18%) T1 cases, 14 (15%) T2 cases, 17 (18%) T3 cases, and 44 (48%) T4 cases; ulceration 38 (41%) ulceration by T1 1 (6%), T2 4 (29%), T3 5 (29%), T4 28 (64%)
Interventions	
Index test	A positive PET-CT result was defined as significant uptake, read as concerning for metastases, in the relevant nodal basin for the corresponding primary melanoma site.



Target condition	Primary target conditions were defined as detection of nodal metastases in participants scheduled for SLNB.																																																															
Reference standard	Positive lymph nodes were defined as any microscopic or macroscopic disease on pathologic analysis of the corresponding regional nodal basin on SLNB or CLND.																																																															
Results																																																																
Diagnostic accuracy (sensitivity, specificity)	<table><thead><tr><th>Study</th><th>TP</th><th>FP</th><th>FN</th><th>TN</th><th>Sensitivity (95% CI)</th><th>Specificity (95% CI)</th><th>Sensitivity (95% CI)</th><th>Specificity (95% CI)</th></tr></thead><tbody><tr><td>Cheng 2021</td><td>9</td><td>3</td><td>17</td><td>63</td><td>0.35 [0.17, 0.56]</td><td>0.95 [0.87, 0.99]</td><td></td><td></td></tr><tr><td>Cheng 2021 BT1</td><td>0</td><td>2</td><td>0</td><td>15</td><td>Not estimable</td><td>0.88 [0.64, 0.99]</td><td></td><td></td></tr><tr><td>Cheng 2021 BT1-2</td><td>0</td><td>0</td><td>1</td><td>13</td><td>0.00 [0.00, 0.97]</td><td>1.00 [0.75, 1.00]</td><td></td><td></td></tr><tr><td>Cheng 2021 BT2-4</td><td>2</td><td>0</td><td>4</td><td>11</td><td>0.33 [0.04, 0.78]</td><td>1.00 [0.72, 1.00]</td><td></td><td></td></tr><tr><td>Cheng 2021 T4</td><td>7</td><td>1</td><td>12</td><td>24</td><td>0.37 [0.16, 0.62]</td><td>0.96 [0.80, 1.00]</td><td></td><td></td></tr></tbody></table>										Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Cheng 2021	9	3	17	63	0.35 [0.17, 0.56]	0.95 [0.87, 0.99]			Cheng 2021 BT1	0	2	0	15	Not estimable	0.88 [0.64, 0.99]			Cheng 2021 BT1-2	0	0	1	13	0.00 [0.00, 0.97]	1.00 [0.75, 1.00]			Cheng 2021 BT2-4	2	0	4	11	0.33 [0.04, 0.78]	1.00 [0.72, 1.00]			Cheng 2021 T4	7	1	12	24	0.37 [0.16, 0.62]	0.96 [0.80, 1.00]		
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	For thin melanomas (n ¼ 17), the sensitivity of PET-CT was unable to be calculated since there were no positive lymph nodes.																																																															
Other	No results for any test burden, complications, quality of life, treatment changes, survival, cost-effectiveness																																																															
Limitations and other comments																																																																
	Our findings add to the literature that there is limited utility for PET-CT in the regional staging of nodal metastases in thin melanomas.																																																															



Appendix 3.5.3. Primary studies SR – other outcomes

Studies from the SR: Results for Outcomes not reported in the SR	
Arrangoiz 2012(Arrangoiz 2012)	PET/CT changed the treatment plan 18% of the time (T4 melanoma). Regional findings changed the surgical treatment plan in 11% and the adjuvant plan, systemic chemotherapy (temozolomide), in 7% due to the finding of metastatic disease. PET/CT identified incidental findings in 35% that required further evaluation (mediastinal lymphadenopathy, lung, colon, and thyroid lesions). No results for complications, quality of life, survival, cost-effectiveness
Chai 2012(Chai 2012)	No results for any test burden, complications, quality of life, treatment changes, survival, cost-effectiveness
Hinz 2011(Hinz 2011)	No results for any test burden, complications, quality of life, treatment changes, survival, cost-effectiveness
Hinz 2013(Hinz 2013)	No results for any test burden, complications, quality of life, treatment changes, survival, cost-effectiveness
Hocevar 2004(Hocevar 2004)	No results for any test burden, complications, quality of life, treatment changes, survival, cost-effectiveness
Kell 2007(Kell 2007)	No results for any test burden, complications, quality of life, treatment changes, survival, cost-effectiveness
Klode 2010(Klode 2010)	No results for any test burden, complications, quality of life, treatment changes, survival, cost-effectiveness
Kunte 2009(Kunte 2009)	No results for any test burden, complications, quality of life, treatment changes, survival, cost-effectiveness
Maubec 2007(Maubec 2007)	FP investigations: three patients with positive foci in distant sites but none of these foci represented a true metastasis (MRI for orbital focus, two needle aspiration biopsies for a nodule of the thyroid gland, hepatic MRI for liver focal increased uptake) No results for complications, quality of life, treatment changes, survival, cost-effectiveness
Revel 2010(Revel 2010)	No results for any test burden, complications, quality of life, treatment changes, survival, cost-effectiveness
Sanki 2009(Sanki 2009)	No results for any test burden, complications, quality of life, treatment changes, survival, cost-effectiveness
Sibon 2007(Sibon 2007)	No results for any test burden, complications, quality of life, treatment changes, survival, cost-effectiveness
Singh 2007(Singh 2008)	No results for any test burden, complications, quality of life, treatment changes, survival, cost-effectiveness
van Rijk 2006(van Rijk 2006)	No results for any test burden, complications, quality of life, treatment changes, survival, cost-effectiveness
Voit 2014(Voit 2014)	Survival: 5-Year Kaplan–Meier estimated melanoma specific survival (MSS) was 95% for US-FNAC negative patients, compared to 59% for US-FNAC positive patients, respectively (P < 0.001).



US was considered malignant if there was a total loss of central echoes or if the lymph node was enlarged and balloon shaped: Balloon shape or complete loss of central echo yielded a 59% 5-year Kaplan–Meier estimated MSS, compared to 96% when no malignant or suspicious findings were seen on US ($P < 0.001$).

No results for any test burden, complications, quality of life, treatment changes, cost-effectiveness

Appendix 3.6. Summary accuracy by imaging method

Table 28 – Summary of findings for ultrasound and PET/CT for N staging

Test	No. of studies (No. of patients)	Sensitivity (95% CI)	Specificity (95% CI)
<i>US</i>	13 (5758)	28.8 (18.6-41.7)	91.7 (86.2-95.2)
<i>US by BT</i>	1 (2859*)	7.1 (5.0-10.0)	97.9 (97.0-98.0)
<i>BT1</i>	(486)	0.0 (0.0-12)	98.2 (97.0-99.0)
<i>BT1-2</i>	(1256)	2.6 (1.0-6.0)	97.8 (97.0-99.0)
<i>BT2-4</i>	(792)	9.9 (6.0-15.0)	98.1 (97.0-99.0)
<i>BT4</i>	(294)	11.9 (7.0-20.0)	97.3 (94.0-99.0)
<i>US + FNAC</i>	4 (1201)	10.3 (1.5-46.3)	99.4 (97.0-99.9)
<i>PET-CT</i>	11 (501)	18.1 (9.9-30.7)	95.4 (88.8-98.2)

*31 patients unknown BT

Table 29 – Summary of findings Dinnes 2019 for ultrasound and PET/CT for N staging

Test	No. of studies (No. of patients)	Sensitivity (95% CI)	Specificity (95% CI)
<i>US</i>	11 (2614)	35.4 (17.0-59.4)	93.9 (86.1-97.5)
<i>US + FNAC</i>	4 (1201)	18.0 (3.58-56.5)	99.8 (99.1-99.9)
<i>PET-CT</i>	11 (501)	No result	No result
<i>Sub-analysis</i>	4 (170)	10.2 (4.31-22.3)	96.5 (87.1-99.1)



Appendix 3.7. Summary tables for GRADE

The GRADE for critical outcomes on accuracy are presented below.

Table 30 – Summary of findings for N staging: Numbers in a cohort of 1000 primary melanoma lesions

Test	No. of studies (No. of patients)	Median prevalence %	Sensitivity (95% CI)*	Specificity (95% CI)*	Predictive value of positive test (95% CI)*	Predictive value of negative test (95% CI)*	True positive	False negative	False positive	True negative	GRADE LoE ^{a,b,c}
<i>Ultrasound</i>	13 (5758)	24.6	28.8 (23.3-35.0)	91.6 (89.4-93.5)	53.0 (45.3-60.5)	79.8 (78.43-81.1)	71	175	63	691	Moderate to low
<i>Ultrasound + FNAC</i>	4 (1201)	24.6	10.2 (6.7-14.6)	99.7 (99.1-100)	92.6 (74.9-98.1)	77.3 (76.5-78.0)	25	221	2	752	Low
<i>PET/CT</i>	11 (501)	36.7	18.0 (14.2-22.3)	95.4 (93.5-96.9)	69.5 (60.0-77.6)	66.7 (65.6-67.9)	66	301	29	604	Very low

*https://www.medcalc.org/calc/diagnostic_test.php; ^aLow risk of bias in most studies; ^bLow concerns regarding applicability in most studies except for PET/CT studies; ^cImprecision due to low sample size(s) (wide confidence intervals) in half of the studies and heterogeneity across studies

Table 31 – GRADE table ultrasound for N staging

Sensitivity	28.9% (23.3-35.0)	Prevalences	24.6%	(22.0-27.4)					
Specificity	91.7% (89.4-93.5)								
Outcome	No. of studies of patients)	Study design	Factors that may decrease/increase quality of evidence					Effect per 1000 patients tested	Test accuracy QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 24.6%	
True positives (patients N+)	13 studies 1182 patients	Prospective (one large diagnostic study) and retrospective studies. No case-control type studies	low	not serious	very serious ^a	serious	none	71 (57-86)	⊕⊕○○ LOW
False negatives (patients incorrectly classified N-)								175 (160-189)	
True negatives (patients N-)	13 studies 4576 patients		low	not serious	not serious	not serious	none	691 (674-705))	⊕⊕⊕○ Moderate
False positives (patients incorrectly classified as N+)								63 (49-80)	

a. High unexplained heterogeneity of results



Table 32 – GRADE table ultrasound with FNAC for N staging

Sensitivity		10.2% (6.7-14.6)			Prevalences		24.6%	(22.0-27.4)	
Specificity		99.7% (99.1-100)							
Outcome	No. of studies (No. of patients)	Study design	Factors that may decrease/increase quality of evidence					Effect per 1000 patients tested	Test accuracy QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 24.6%	
True positives (patients N+)	4 studies 208 patients		low	not serious	very serious ^a	serious ^b	none	25 (16-36)	⊕⊕○○ LOW
False negatives (patients incorrectly classified N-)								221 (210-230)	
True negatives (patients N-)	4 studies 792 patients		low	serious	serious	not serious	none	752 (747-753)	⊕⊕○○ LOW
False positives (patients incorrectly classified as N+)								2 (1-7)	

a. High unexplained heterogeneity of results; b. 4 studies of which 3 very small

Table 33 – GRADE table PET/CT for N staging

Sensitivity		18.0% (14.2-22.3)		Prevalences		36.7%	(33.7-39.8)		
Specificity		95.4% (93.5-96.9)							
Outcome	No. of studies (No. of patients)	Study design	Factors that may decrease/increase quality of evidence					Effect per 1000 patients tested	Test accuracy QoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 24.6%	
True positives (patients N+)	11 studies 192 patients	Prospective (one large diagnostic study) and retrospective studies. No case-control type studies	low	serious	very serious ^a	very serious	none	66 (52-82)	⊕○○○ VERY LOW
False negatives (patients incorrectly classified N-)								301 (285-315)	
True negatives (patients N-)	11 studies 309 patients		serious	serious	not serious	very serious	none	604 (592-613)	⊕○○○ VERY LOW
False positives (patients incorrectly classified as N+)								29 (20-41)	

a. High unexplained heterogeneity of results



APPENDIX 4. EVIDENCE REVIEW RESECTION MARGINS PRIMARY CUTANEOUS MELANOMA

Appendix 4.1. PICO

Table 34 – PICO for surgical excision margins for stage 0 to II primary melanoma

	Intervention review of margins for stage 0 to II primary melanoma
Objective	To determine the most optimal extent of re-excision margins for primary melanoma in adults 18 years and above. Currently surgical margins of 1-2 cm are used for melanomas below 2 mm. Evidence for smaller margins would prevent the excess morbidity caused by larger excision defects.
Review questions	What are the most effective surgical re-excision margins for stage 0 to II primary melanoma?
Population	Included: Adults 18 years and above with a confirmed diagnosis of primary melanoma stage 0 - II
Intervention	Included: no wide re-excision; re-excision margin of ≤ 1 cm or 1 – 2 cm or 2 cm and above
Comparator	Compared to each other
Outcomes	Critical: Health-related quality of life, local recurrence, regional recurrence, overall survival Important: adverse events, inclusive of cosmetic reconstruction surgery
Study design	Included: Good-quality systematic reviews of RCTs, randomised controlled trials. Excluded: Narrative reviews, non-randomised studies, case reports. Studies presented as conference abstract only or if no full text was available.
Analysis	By stage

Appendix 4.2. Search strategies

Appendix 4.2.1. Ovid Medline

Search date Jan 30th 2025. Database: Ovid MEDLINE(R) <1946 to December 06, 2024>

1. exp melanoma/
2. ..nlpx"query=skin neoplasms","desiredResults=10000","minHitsDivisor=7","permitHyponyms=NO","lowestVocabularySearchLevel=none","phrasesBroken=NO","speedWanted=NoHypos","comment=Including Related Terms","elimEnable=NO","constraintMinTerms=2"
3. ((skin or derm* or cutaneous* or epitheli* or epiderm*) adj1 (cancer* or malignan* or neoplas* or oncolog* or tumor* or tumour*)).tw.
4. ((maligna* or melano*) adj2 (freckle* or lesion* or mole* or nev* or naev*)).tw.
5. (hutchinson* adj2 (freckle* or melano*)).tw.
6. dubreuilh*.tw.
7. (maligna* adj2 lentigo*).tw.
8. LMM.tw.
9. or/1-8
10. "margins of excision"/
11. (excis* or margin* or surg* or remov* or resect*).tw.
12. or/10-11
13. 9 and 12
14. animals/ not humans/

15. 13 not 14
16. limit 15 to "english language"
17. limit 16 to ed=20210301-20250131
18. randomized controlled trial.pt.
19. placebo.mp.
20. randomi?ed.mp.
21. or/18-20
22. 17 and 21 293

Appendix 4.2.2. Embase

Embase session results (19 Feb 2025)

No. Query Results

- | | | |
|-----|---|---|
| #19 | #17 AND (random*:ab,ti OR placebo*:de,ab,ti OR ((double NEXT/1 blind*):ab,ti)) | 5 |
| #18 | #17 AND ('meta-analysis'/exp OR 'meta-analysis' OR 'systematic review'/exp OR 'systematic review') 10 | |
| #17 | #16 NOT ('conference abstract'/it OR 'conference paper'/it OR 'conference review'/it) 153 | |
| #16 | #15 NOT [medline]/lim 405 | |
| #15 | #14 AND [09-12-2024]/sd NOT [19-02-2025]/sd 657 | |
| #14 | #10 AND #13 43010 | |
| #13 | #11 OR #12 4946922 | |
| #12 | excis*:ab,ti,kw OR margin*:ab,ti,kw OR surg*:ab,ti,kw OR remov*:ab,ti,kw OR resect*:ab,ti,kw 4943681 | |
| #11 | 'surgical margin'/exp 28497 | |
| #10 | #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 274379 | |
| #9 | (melanocytic NEAR/2 lesion?):ti,ab,kw 3279 | |
| #8 | melanocytom*:ti,ab,kw 1176 | |
| #7 | (melanotic NEAR/2 freckle*):ti,ab,kw 97 | |
| #6 | Imm:ab,ti,kw 2459 | |
| #5 | dubreuilh:ab,ti,kw 115 | |
| #4 | (hutchinson* NEAR/1 (freckle* OR melano*)):ab,ti,kw 23 | |
| #3 | (maligna* NEAR/1 lentigo*):ab,ti,kw 2136 | |
| #2 | melanoma*:ab,ti,kw 215884 | |
| #1 | 'melanoma'/exp 223219 | |



Appendix 4.2.3. Cochrane

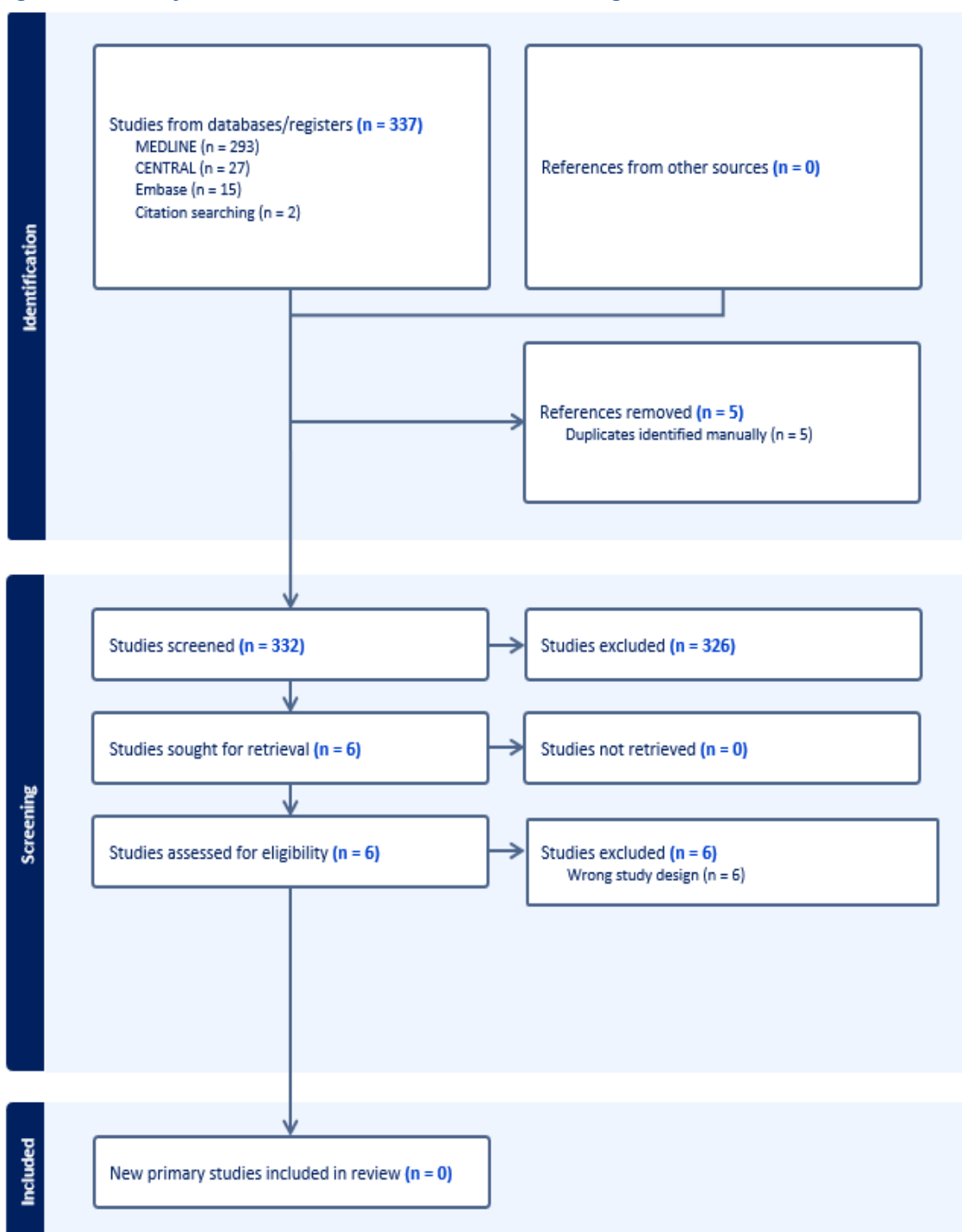
Date Run: 19/02/2025 04:58:32

ID Search Hits

- #1 [mh melanoma] 2757
- #2 [mh ^"Skin Neoplasms"] 2466
- #3 melanoma*:ab,ti 6419
- #4 ((skin or derm* or cutaneous* or epitheli* or epiderm*) NEAR/1 (adenocarcinoma* or cancer* or carcinoma* or malignan* or neoplas* or oncolog* or tumor* or tumour*)):ab,ti 3289
- #5 ((maligna* or melano*) NEAR/2 (freckle* or lesion* or mole* or nev* or naev*)):ab,ti 818
- #6 (hutchinson* NEAR/2 (freckle* or melano*)):ab,ti 2
- #7 dubreuilh*:ab,ti 0
- #8 (maligna* NEAR/2 lentigo):ti,ab 43
- #9 LMM:ab,ti 233
- #10 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 10393
- #11 [mh ^"margins of excision"] 192
- #12 (excis* or margin* or surg* or remov* or resect*):ab,ti 346140
- #13 #11 OR #12 346143
- #14 #10 AND #13 3022
- #15 #10 AND #14 3022
- #16 #15 with Cochrane Library publication date Between Dec 2024 and Dec 2025, in Trials 26
- #17 #15 with Cochrane Library publication date Between Dec 2024 and Dec 2025, in Cochrane Reviews 1

Appendix 4.2.4. Study selection

Figure 14 – Study flow selection of search resection margins re-excision





Appendix 4.2.5. Excluded full text

Table 35 – Full text excluded resection margins

Publication	Reason
Hanna 2021(Hanna 2021)	SR; no primary study
Elshot 2023(Elshot 2023)	SR; no primary study; topic incorrect
Friedman 2021(Friedman 2021)	SR; no primary study
Pisano 2024(Pisano 2024)	SR; no primary study
Williams 2025(Williams 2025)	SR; no primary study; wrong intervention
Zijlker 2023(Zijlker 2023)	No primary study

Appendix 4.3. Appraisal

The selected systematic review was assessed by one researcher with the AMSTAR 2.(Shea 2017)

Table 36 – Quality included systematic review re-excision margins

Systematic review NICE guideline NG 14. [C] Evidence review for surgical and histological excision margins for people with stage 0 to II melanoma	
PICO included	yes
A priori study design	yes
Explanation selection study design inclusion	yes
Comprehensive literature search	yes
Duplicate study selection and data extraction	yes
List of in- and excluded studies	yes
Characteristics of included studies	yes
Study quality assessed	yes
Sources of funding studies reported	yes
Appropriate methods to combine findings	Yes
Bias considered in meta-analysis or summary estimates	n/a*
Heterogeneity discussed	n/a*
Likelihood of publication bias assessed	no
Conflict of interest stated	yes

* A meta-analysis was not performed as "significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis".

The appraisal of the primary studies is presented in Appendix D of the NICE review page 38.

Appendix 4.4. Evidence tables

A summary of the clinical evidence is presented in the NICE Evidence review for surgical and histological excision margins for people with stage 0 to II melanoma page 10. The full clinical evidence tables for all the primary studies is presented in Appendix D of the NICE review page 38.

Appendix 4.5. Summary tables GRADE

The summary of findings tables are presented in Table 3 of the NICE review page 10. The outcomes defined in the PICO for this KCE review for the included trials with narrower margins are copied here.

Sample size	GRADE quality	Summary of findings
MelMarT 1cm versus 2cm excision		
400	Low	Quality of life 12 months post-randomisation (FACT-M) "there was no difference in quality of life or neuropathic pain data in any domain between the 1 and 2-cm groups. Similarly, there were no differences between the two margins in any subgroup analyses."
	Moderate	Reconstruction surgery at 12 months post-randomisation OR* 0.29 [0.18, 0.49]
	Very Low	Total surgical adverse events including: wound dehiscence, haematoma, haemorrhage; wound infection; or wound necrosis post-intervention OR* 0.89 [0.46, 1.70]
	Very Low	Wound dehiscence post intervention OR* 1.04 [0.26, 4.24]
	Very Low	Haematoma (Grade I or IIIa) post intervention OR* OR 1.57 [0.26, 9.53]
	Very Low	No participants experienced haemorrhage post-intervention
	Very Low	Wound infection (Grade I or II) post intervention OR* 1.29 [0.52, 3.20]
	Low	Wound necrosis (including partial/total loss of skin graft) post intervention OR* 0.14 [0.02, 1.19]
UK-MSG 1cm versus 3cm excision		
426	Moderate	Psychological adjustment to illness scale (PAIS); unclear how poor was defined; maximum follow up time = 2 years; OR>1 favours narrow excision margin Poor vocational adjustment to illness: OR 1.66 (0.68 to 4.08) Poor domestic adjustment to illness: OR 3.11 (1.17–8.27) Poor sexual adjustment to illness: OR 1.92 (0.70–5.31) Poor extended family adjustment to illness: OR 1.09 (0.43–2.75) Poor social adjustment to illness: OR 4.22 (1.54–11.55)
392	Moderate	Medical Outcomes Survey–Short Form (MOS-SF36); maximum follow up time = 2 years; coefficient<0 favours narrow excision margin Mental component summary score Coefficient= −133.1, SE=91.6, p=0.15 Physical component summary score Coefficient= −57.0, SE=83.5, p=0.06
128	Moderate	Perception of scar (maximum follow up time = 2 years; OR>1 favours narrow excision margin); measured using the last Cassileth Scar score on follow up: OR 5.55 (2.06–14.98)
900	High	Total surgical complications: not defined - OR 0.49 [0.32, 0.76]
	Moderate	Deaths due to any cause (follow up was 68 months [IQR 35–103]): HR 1.14 [95% CI 0.96–1.36] (highest in small margin)
	Moderate	Overall Survival over follow up (follow up was 68 months [IQR 35–103]) HR 1.19 (0.99–1.45) (highest in small margin)
	Moderate	Locoregional recurrence (median follow up 60 months): Local recurrence = recurrence within 2 cm of the scar or graft; In-transit recurrence = recurrence from beyond the first 2 cm of the scar or graft to the regional nodes; all locoregional recurrences were detected clinically and confirmed by biopsy: HR 1.26 (1.00 to 1.59) (highest in small margin)
WHO 1cm versus ≥3cm excision		
612	Very low	Overall survival at 12 years (lower in narrow excision margin): OR 1.20 [0.76, 1.90] Overall survival at 8 years: OR 0.92 [0.55, 1.56]



Very low	Local recurrence (first recurrence) at 8 years (OR<1 favours narrow excision margin): OR 9.18 [0.49, 171.23] In-transit metastases (first recurrence) at 8 years follow up: OR 1.01 (0.14-7.19) Regional nodal metastases (first recurrence) at 8 years follow up: OR 0.87 [0.47, 1.60]
NA	No data on quality of life

APPENDIX 5. EVIDENCE REVIEW LYMPHADENECTOMY

Appendix 5.1. PICO

Table 37 – PICO lymphadenectomy research question

Population	Included: Melanoma-patients 18 years and above with micrometastases detected by sentinel-node procedure Excluded: Children of less than 18 years
Intervention	Included: completion lymphadenectomy (+/- adjuvant therapy)
Comparator	No completion lymphadenectomy +/- adjuvant therapy
Outcomes	Critical: overall and melanoma-specific survival, quality of life Important: short-term and long-term adverse events, disease-free survival
Study design	Included: Good-quality systematic reviews of RCTs, RCTs Excluded: narrative reviews, non-randomised studies

Appendix 5.2. Search strategies

Search strategy of updated literature search, for NICE 2022 search strategy, see NICE 2022 guideline

Appendix 5.2.1. Cochrane

ID	Search Hits
#1	[mh melanoma] 2801
#2	[mh ^"Skin Neoplasms"] 2506
#3	(melanoma* or melanocarcinoma* or naevocarcinoma* or nevocarcinoma*):ab,ti,kw 7101
#4	((skin or derm* or cutaneous* or epitheli* or epiderm*) NEAR/1 (adenocarcinoma* or cancer* or carcinoma* or malignan* or neoplas* or oncolog* or tumor* or tumour*)):ab,ti,kw 5571
#5	((maligna* or melano*) NEAR/2 (freckle* or lesion* or mole* or nev* or naev*)):ab,ti,kw 935
#6	(hutchinson* NEAR/2 (freckle* or melano*)):ab,ti,kw 19
#7	(maligna* NEAR/2 lentigo):ti,ab,kw 51
#8	dubreuilh*:ab,ti,kw 0
#9	LMM:ab,ti,kw 236
#10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 11216
#11	[mh ^"Lymph Node Excision"] 1858
#12	[mh "Lymph Nodes"] 1491

#13 (surg* or resect* or remov* or ablat* or operat* or excision* or excised or dissection* or lymphadenectom* or CLND* or TLND*):ab,ti,kw 441281

#14 #11 OR #12 OR #13 441687

#15 #10 AND #14 3792

#16 #15 with Cochrane Library publication date Between Apr 2021 and Dec 2025, in Trials 911

#17 #15 with Cochrane Library publication date Between Apr 2021 and Dec 2025, in Cochrane Reviews

Appendix 5.2.2. Embase

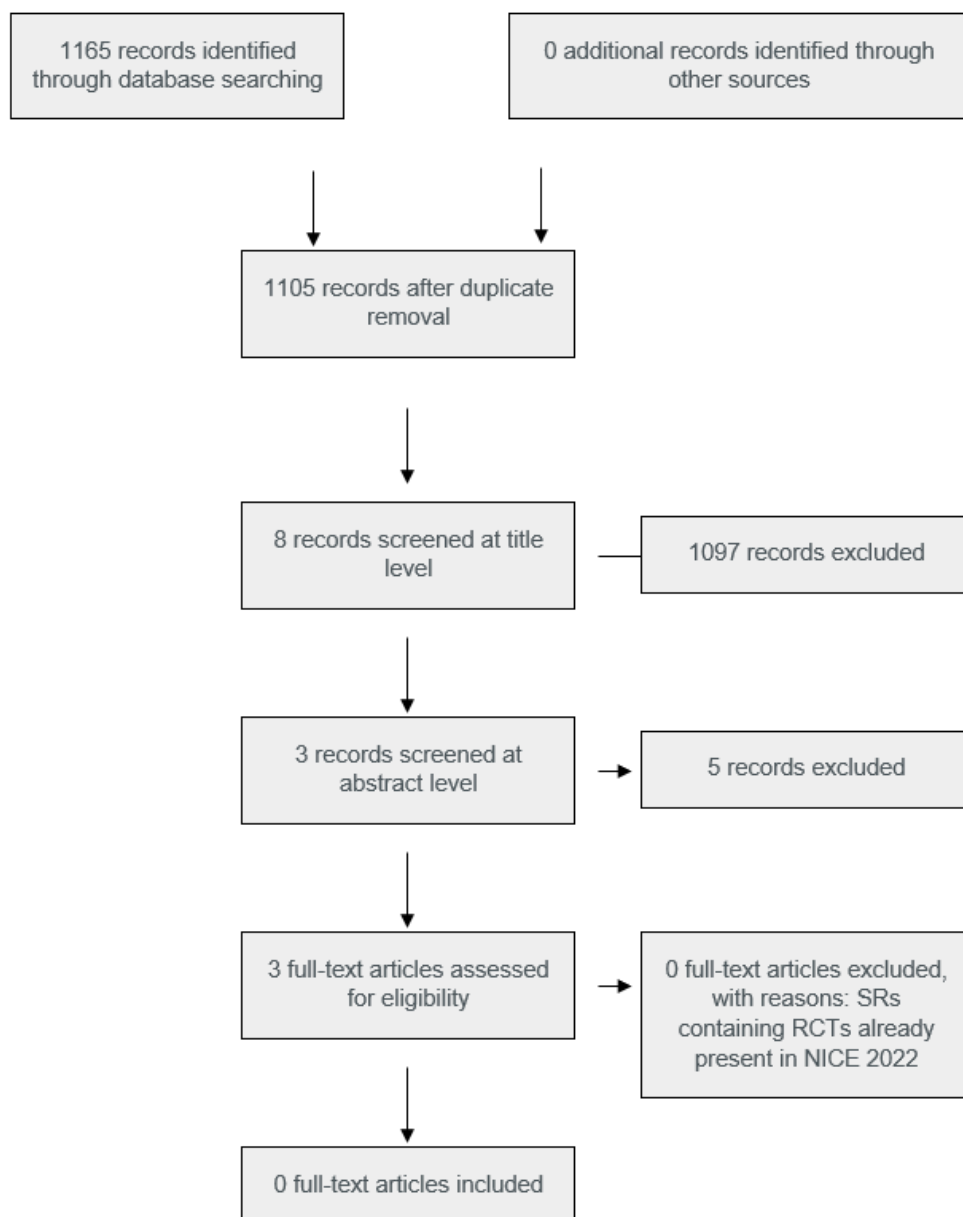
1. 'melanoma'/exp [222,761 results]
2. 'skin tumor'/exp [289,450 results]
3. melanoma*:ab,ti,kw OR melanocarcinoma*:ab,ti,kw OR naevocarcinoma*:ab,ti,kw OR nevocarcinoma*:ab,ti,kw [215,619 results]
4. ((skin OR derm* OR cutaneous* OR epitheli* OR epiderm*) NEAR/1 (adenocarcinoma* OR cancer* OR carcinoma* OR malignan* OR neoplas* OR oncolog* OR tumor* OR tumour*)):ab,ti,kw [124,401 results]
5. ((maligna* OR melano*) NEAR/2 (freckle* OR lesion* OR mole* OR nev* OR naev*)):ab,ti,kw [50,651 results]
6. (hutchinson* NEAR/2 (freckle* OR melano*)):ab,ti,kw [114 results]
7. dubreuilh*:ab,ti,kw [116 results]
8. (maligna* NEAR/2 lentigo*):ab,ti,kw [2,139 results]
9. Imm:ab,ti,kw [2,454 results]
10. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 [587,804 results]
11. 'lymph node dissection'/de [99,103 results]
12. 'lymph node'/de [127,394 results]
13. surg*:ab,ti,kw OR resect*:ab,ti,kw OR remov*:ab,ti,kw OR ablat*:ab,ti,kw OR operat*:ab,ti,kw OR excision*:ab,ti,kw OR excised:ab,ti,kw OR dissection*:ab,ti,kw OR lymphadenectom*:ab,ti,kw OR clnd*:ab,ti,kw OR tld*:ab,ti,kw [6,037,113 results]
14. #11 OR #12 OR #13 [6,136,572 results]
15. #10 AND #14 [126,394 results]
16. #15 AND (random*:ab,ti OR placebo*:de,ab,ti OR ((double NEXT/1 blind*):ab,ti)) [5,466 results]
17. #16 NOT ('animal'/exp NOT 'human'/de) [5,333 results]
18. #17 NOT [medline]/lim [2,433 results]
19. #18 NOT ('conference abstract'/it OR 'conference paper'/it OR 'conference review'/it) [688 results]
20. #19 AND [2021-2025]/py [274 results]
21. #20 AND [english]/lim [250 results]

Appendix 5.2.3. Medline

- 1 exp Melanoma/ (114429)
- 2 Skin Neoplasms/ (143635)



- 3 (melanoma* or melanocarcinoma* or naevocarcinoma* or nevocarcinoma*).tw. (147850)
- 4 ((skin or derm* or cutaneous* or epitheli* or epiderm*) adj1 (adenocarcinoma* or cancer* or carcinoma* or malignan* or neoplas* or oncolog* or tumor* or tumour*)).tw. (85423)
- 5 ((maligna* or melano*) adj2 (freckle* or lesion* or mole* or nev* or naev*)).tw. (35368)
- 6 (hutchinson* adj2 (freckle* or melano*)).tw. (76)
- 7 dubreuilh*.tw. (74)
- 8 (maligna* adj2 lentigo*).tw. (1441)
- 9 LMM.tw. (1754)
- 10 or/1-9 (332103)
- 11 Lymph Node Excision/ (39866)
- 12 exp Lymph Nodes/ (102831)
- 13 (surg* or resect* or remov* or ablat* or operat* or excision* or excised or dissection* or lymphadenectom* or CLND* or TLND*).tw. (4466225)
- 14 or/11-13 (4544176)
- 15 10 and 14 (67510)
- 16 animals/ not humans/ (5269977)
- 17 15 not 16 (64665)
- 18 limit 17 to "english language" (57260)
- 19 randomized controlled trial.pt. (632425)
- 20 randomi?ed.mp. (1168418)
- 21 placebo.mp. (264413)
- 22 or/19-21 (1236888)
- 23 18 and 22 (1984)
- 24 limit 23 to ed=20210423-20251231 (364)
- 25 remove duplicates from 24 (362)

*Appendix 5.2.4. Study selection***Figure 15 – Study flow selection of search lymphadenectomy**

The three full texts that were assessed for eligibility were all systematic reviews that did not include any new primary RCT.



Appendix 5.3. Appraisal

Adopted from NICE 2022 guideline

Risk of Bias assessment table

Domain	Question	Faries 2017	Leiter 2019	Risk of Bias Judgment
Domain 1: Bias arising from the randomisation process	Was the allocation sequence random?	Yes	Yes	Faries: Moderate (unclear allocation concealment) / Leiter: Low
	Was the allocation sequence concealed until participants were enrolled and assigned?	No information	Yes	
	Did baseline differences suggest a problem with randomisation?	No	Yes	
Domain 2a: Bias due to deviations from intended interventions (effect of assignment to intervention)	Were participants aware of assigned intervention?	Yes	Yes	Faries: Moderate / Leiter: Moderate
	Were carers/people delivering interventions aware?	Yes	Yes	
	Were there deviations from intended intervention due to experimental context?	Probably yes	Yes/Probably yes	
	Were deviations balanced between groups?	No	No	
	Were deviations likely to affect outcome?	No information	No information	
	Was appropriate analysis used (ITT)?	Yes	Yes	
	Was there substantial impact of failure to analyze correctly?	Not applicable	Not applicable	
Domain 2b: Bias due to deviations from intended interventions (effect of adhering to intervention)	Information on adherence to intervention	Little evidence provided	36 in CLND arm crossed over to observation, 3 vice versa (ITT used)	
Domain 3: Bias due to missing outcome data	Were outcome data available for all/nearly all participants?	No	Yes	Faries: Moderate / Leiter: Low



	Evidence that result was not biased by missing data?	No	Not applicable	
	Could missingness depend on true value?	Probably no	Not applicable	
	Difference in missing data between groups?	Not applicable	Not applicable	
	Likelihood of missingness depending on true value?	Not applicable	Not applicable	
Domain 4: Bias in measurement of the outcome	Was method of measuring the outcome inappropriate?	No	No	Faries: Moderate / Leiter: Low
	Could measurement differ between groups?	Probably no	Probably no	
	Were assessors aware of the intervention received?	Probably yes	Yes	
	Could assessment have been influenced?	Probably no	Probably no	
	Likelihood of assessment influence?	Not applicable	Probably no	
Domain 5: Bias in selection of the reported result	Was trial analysed per pre-specified plan?	Yes	Yes	Both Low
	Likely selective reporting of outcome measurements?	No/Probably no	No/Probably no	
	Likely selective reporting of data analyses?	No/Probably no	No/Probably no	
Overall	Overall Risk of Bias	Moderate	Moderate	
Overall	Overall Directness	Directly applicable	Directly applicable	



Appendix 5.4. Evidence tables

Study	Inclusion criteria	Randomization	Participants	Observation	Completion dissection	Statistical analysis	Size	Outcome	Point Estimate	95% CI
Faries 2017 (MSLT-II)	Tumor positive SLN by either H&E, IHC or RT-PCR. 18-75. At least 10 years life expectancy, good performance status	stratified: Breslow thickness, ulceration, methastasis detection (RT-PCR vs standard), enrollment MSLTI center	3531 underwent screening. Completion dissection : 967 in ITT . 824 per protocol (140 declined dissection) RTPCR positive 80(9.7%). Observation 967 in ITT analysis. 931 per protocol (29 declined observation) RT-PCR positive . Per protocol analysis reported	clinical examination every 4 months during the first 2 years, every 6 months during years 3 through 5, and then annually with US nodal assessment for the first 5 years	Completion dissection within 140 days from biopsy. clinical examination every 4 months during the first 2 years, every 6 months during years 3 through 5, and then annually without US nodal assessment	1925 needed to detect a 5% difference in melanoma specific survival. (1655 in per protocol analysis)	1655	Melanoma-specific survival at 3 years follow up	aHR 1.08	[0.88 to 1.34]
							1564	Rate of nodal recurrence at 3 years follow up (pathology positive)	aHR 0.31	[0.24 to 0.41]
							1564	Distant metastases-free survival at 3 years follow up (pathology?)	aHR 1.10	[0.92 to 1.31]
							1564	Recurrence-free survival at 3 years follow up (pathology positive)	OR 0.81	[0.66, 0.99]
							1564	Local-regional recurrence at 3 years follow up (pathology positive)	OR 0.94	[0.71, 1.24]
							1564	Distant recurrence at 3 years follow up (pathology positive)	OR 1.14	[0.92, 1.42]
							1655	Lymphedema		
Leiter 2016 (DeCOG-SLT)	Primary cutaneous melanoma of torso, arms, legs. 18-75 .Thickness 1mm or more. Micrometastases in SLN diagnosed with H&E and IHC, includes single cells	Stratified: Thickness (><2mm) ulceration, adjuvant interferon,	CLND : 240 ITT36 not receive CLND, , Observation 233ITT 3 patients received CLND. Median FU Time 35 months	PE and nodal US every 3 months. WB CT, MRI or PET-CT or chestXR and abdomen US.	Completion dissection within 120 days of biopsy. PE and nodal US every 3 months. WB CT, MRI or PET-CT or chestXR and abdomenUS. Surgical complications	550 needed to detect a 10% difference . One sided 5% error. ITT analysis. Adjustment: load in SN, thickness, ulceration, n positive SN , interferon	473	Distant metastases-free survival at 3 years follow up	aHR 1.19	(0.83 to 1.69)
							473	Overall survival at 3 years of follow up	aHR 1.02	(0.68 to 1.52)
							473	Recurrence-free survival at 3 years follow up	aHR 0.96	(0.7 to 1.31)
							473	Melanoma-specific death at 3 years follow up	OR 0.91	[0.55, 1.49]
							473	Satellite/in-transit recurrences at 3 years follow up	OR 0.97	[0.38, 2.49]
							473	Regional lymph node without distant metastases at 3 years follow up	OR 0.50	[0.21, 1.21]



	metastasis. Exclusion: any other regional/dista nt lesion. Perforation of the nodal capsule.				collected at 3 and 6 months		473	Regional and distant recurrences at 3 years follow up	OR 0.59 ?	[0.28, 1.25]
							473	Distant without regional lymph node recurrences at 3 years follow up	OR 1.24	[0.70, 2.20]
								Grade 3 AE		
								Grade 4 AE		
Leiter 2019 (DeCOG- SLT)	cfr 2016	cfr 2016	Median FU 72 months	cfr2016	cfr 2016	adjustment fro tumor thickness, , SN tumor load n of positive LN, ulceration, IFN therapy	473	Distant metastases-free survival at 5 years follow up	aHR 1,09	(0,79-1,5)
							473	Overall survival at 5-year follow up	aHR 0,95	[0,7-1,36]
							473	Recurrence-free survival at 5 years follow up	aHR 1,01	(0,75-1,36)



Appendix 5.5. Summary tables GRADE

Adopted from NICE 2022 guidelines

CLND versus observation: survival outcomes

Outcome	Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Overall survival at 3 years	Leiter 2016 (DeCOG-SLT)	473	N/A	aHR 1.02 (90%CI 0.68 to 1.52), p=0.95 (1)	Serious (2)	Not serious	N/A	NE (3)	Low
Overall survival at 5 years	Leiter 2019 (DeCOG-SLT)	473	N/A	aHR 0.95 (90%CI 0.70 to 1.36), p=0.80 (1)	Serious (2)	Not serious	N/A	NE (3)	Low
Melanoma-specific survival at 3 years	Faries 2017 (MSLT-II)	1939	N/A	aHR 1.08 [0.88 to 1.34] (4)	Serious (5)	Not serious	N/A	Serious (6)	Low
Melanoma-specific death at 3 years	Leiter 2016 (DeCOG-SLT)	473	N/A	OR 0.91 [0.55 to 1.49]	Serious (2)	Not serious	N/A	Very Serious (7)	Very Low
Melanoma-specific death at 5 years	Leiter 2019 (DeCOG-SLT)	473	N/A	OR 1.01 [0.66 to 1.53]	Serious (2)	Not serious	N/A	Very Serious (7)	Very Low

NE: no evidence; N/A: not applicable

- Adjusted for tumour load in sentinel lymph node biopsy, tumour thickness, ulceration, positive sentinel lymph node biopsy nodes, adjuvant interferon therapy
- Study was at serious risk of bias and was marked down one level: There was a lack of blinding procedures and some deviation from treatment which was unbalanced between experimental groups
- Study was downgraded one level as it was not possible to estimate imprecision since 90% confidence intervals were reported, rather than 95%CI.
- Unclear how adjusted but likely adjusted for sex, age, Breslow thickness, ulceration, primary site, number of positive sentinel nodes, and sentinel node positive
- Study was at serious risk of bias and was marked down one level: Unclear if allocation concealment. A large proportion of those randomised to the surgery group did no consent to receive Completion Lymphadenectomy - per protocol analysis may be high risk of bias. Unclear adherence to intervention. No blinding or blinded analysis performed. Overall survival was not reported in the study or appendix. Unclear how multivariable adjustments were made.
- Serious risk of imprecision as confidence intervals for study estimate crossed one line of minimum important effect (0.8 and 1.25 for hazard ratios and odds ratios)
- Study was downgraded two levels due to very serious imprecision as confidence intervals crossed two lines of minimum important difference (0.8 and 1.25 for hazard and odds ratios)

CLND versus observation: disease-free survival outcomes

Outcome	Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Recurrence-free survival at 3 years	Leiter 2016 (DeCOG-SLT)	483	N/A	HR 0.96 (90%CI 0.70 to 1.31), p=0.83 (1)	Serious(2)	Not serious	N/A	NE	Low
Recurrence-free survival at 3 years	Faries 2017 (MSLT-II)	1564	N/A	OR 0.81 [0.66 to 0.99] (4)	Very Serious (5)	Not serious	N/A	Serious	Very Low
Recurrence-free survival at 5 years	Leiter 2019 (DeCOG-SLT)	473	N/A	HR 1.01 (90%CI 0.75 to 1.36), p=0.94 (3)	Serious (2)	Not serious	N/A	NE	Low
Local-regional recurrence at 3 years	Faries 2017 (MSLT-II)	1564	N/A	OR 0.94 [0.71 to 1.24] (4)	Very Serious (5)	Not serious	N/A	Serious	Very Low
Satellite/in-transit recurrences at 3 years	Leiter 2016 (DeCOG-SLT)	483	N/A	OR 0.97 [0.38 to 2.49]	Serious (2)	Not serious	N/A	Very Serious	Very Low
Rate of nodal recurrence at 3 years	Faries 2017 (MSLT-II)	1564	N/A	aHR 0.31 [0.24 to 0.41] (8)	Serious (9)	Not serious	N/A	Not Serious	Moderate
Regional lymph node w/o distant metastases at 3 years	Leiter 2016 (DeCOG-SLT)	483	N/A	OR 0.50 [0.21 to 1.21]	Serious (2)	Not serious	N/A	Serious	Low
Regional lymph node recurrence at 5 years	Leiter 2019 (DeCOG-SLT)	473	N/A	OR 0.62 [0.37 to 1.06]	Serious(2)	Not serious	N/A	Serious	Low
Distant recurrence at 3 years	Faries 2017 (MSLT-II)	1564	N/A	OR 1.14 [0.92 to 1.42] (4)	Very Serious(5)	Not serious	N/A	Serious	Very Low
Distant metastases at 5 years	Leiter 2019 (DeCOG-SLT)	473	N/A	OR 1.21 [0.79 to 1.85]	Serious (2)	Not serious	N/A	Very Serious	Very Low
Distant metastases-free survival at 3 years	Faries 2017 (MSLT-II)	1564	N/A	HR 1.10 [0.92 to 1.31] (8)	Serious (5)	Not serious	N/A	Serious	Low
Distant metastases-free survival at 3 years	Leiter 2016 (DeCOG-SLT)	483	N/A	HR 1.19 (90%CI 0.83 to 1.69), p=0.43(1)	Serious (2)	Not serious	N/A	NE	Low
Distant metastases-free survival at 5 years	Leiter 2019 (DeCOG-SLT)	473	N/A	HR 1.09 (90%CI 0.79 to 1.50), p=0.62 (1)	Serious (2)	Not serious	N/A	NE	Low

NE: no evidence; N/A: not applicable;



1. Adjusted for tumour load in sentinel lymph node biopsy, tumour thickness, ulceration, positive sentinel lymph node biopsy nodes, adjuvant interferon therapy
2. Study was at serious risk of bias and was marked down one level: There was a lack of blinding procedures and some deviation from treatment which was unbalanced between experimental groups.
3. Study was downgraded one level as it was not possible to judge imprecision since study reported 90% confidence intervals.
4. Per-protocol analysis
5. Study was at very serious risk of bias and was marked down two levels: Unclear if allocation concealment. A large proportion of those randomised to the surgery group not consent to receive Completion Lymphadenectomy - per protocol analysis may be high risk of bias. Unclear adherence to intervention. No blinding or blinded analysis performed. Overall survival was not reported in the study or appendix. Unclear how multivariable adjustments were made.
6. Serious risk of imprecision as confidence intervals for study estimate crossed one line of minimum important effect (0.8 and 1.25 for hazard ratios and odds ratios)
7. Study was downgraded two levels due to very serious imprecision as confidence intervals crossed two lines of minimum important difference (0.8 and 1.25 for hazard and odds ratios)
8. Unclear how adjusted but likely adjusted for sex, age, Breslow thickness, ulceration, primary site, number of positive sentinel nodes, and sentinel node positive

CLND versus observation: adverse event outcomes

Outcome	Study	Sample size	Subgroup analysis	Effect size	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Lymphoedema at 3 years	Faries 2017 (MSLT-II)	1564	N/A	OR 4.71 [3.46 to 6.40] (1)	Serious (2)	Not serious	N/A	Not Serious	Moderate

1. Only percentages were reported, analyst used the total number of patients in each arm as the denominator to calculate the number with adverse events in each arm
2. Study was at serious risk of bias and was marked down one level: Outcome assessment was unblinded. Unclear how analysis was undertaken (e.g. per protocol or ITT participants were excluded for ineligibility but details not provided).

APPENDIX 6. EVIDENCE REVIEW IMMUNOTHERAPY AND TARGETED THERAPY FOR RESECTABLE STAGE IIB-IV MELANOMA

Appendix 6.1. PICO

Table 38 – Adjuvant immunotherapy for completely resected stage II–III–IV primary melanoma

	Adjuvant immunotherapy for completely resected stage II-III-IV primary melanoma
Review questions	What is the effectiveness of adjuvant immunotherapy for completely resected stage IIB, IIC, III or IV cutaneous melanoma?
Population	Included: patients with completely resected stage II, III or IV cutaneous melanoma Excluded: unresectable disease
Intervention	Included: immunotherapy (other than interferon) available in Belgium Excluded: adjuvant chemotherapy, adjuvant radiotherapy, adjuvant vaccine therapy, adjuvant target therapy
Comparator	A) No adjuvant treatment or adjuvant interferon B) 2 immunotherapeutic agents compared
Outcomes	Critical: Overall survival, health-related quality of life, adverse events (according to Common Toxicity Criteria (CTC)) Important: event-free survival, distant metastasis-free survival Other: overall cost of therapy
Study design	Included: systematic reviews of RCTs, RCTs. Articles in Dutch, English and French Excluded: Narrative reviews, non-randomised studies. Studies presented as conference abstract only (additional results published in abstract only are included) or if no full text was available.
Subgroup analyses	By stage

Table 39 – Adjuvant targeted therapy for completely resected stage II–III–IV primary melanoma

	Adjuvant targeted therapy for completely resected stage II-III-IV primary melanoma
Review questions	What is the effectiveness of adjuvant targeted therapy for completely resected stage IIB, IIC, III or IV cutaneous melanoma?
Population	Included: patients with completely resected stage II, III or IV cutaneous melanoma Excluded: unresectable disease
Intervention	Included: targeted therapy available in Belgium Excluded: adjuvant chemotherapy, adjuvant radiotherapy, adjuvant vaccine therapy, adjuvant immunotherapy
Comparator	A) No adjuvant treatment or adjuvant interferon B) Two targeted drugs compared
Outcomes	Critical: Overall survival, health-related quality of life, adverse events ((according to CTC) Important: event-free survival, distant metastasis-free survival Other: overall cost of therapy
Study design	Included: systematic reviews of RCTs, RCTs. Articles in Dutch, English and French Excluded: Narrative reviews, non-randomised studies. Studies presented as conference abstract only (additional results published in abstract only are included) or if no full text was available.
Subgroup analyses	By stage, if applicable



Table 40 – Neoadjuvant therapy for resectable clinically detectable stage III–IV primary melanoma

	Neoadjuvant therapy for resectable clinically detectable stage III or melanoma
Review question	What is the effectiveness of neoadjuvant therapy for resectable clinically detectable stage III or IV cutaneous melanoma?
Population	Included: patients with resectable clinically detectable stage III or IV cutaneous melanoma Excluded: unresectable disease
Intervention	Included: immunotherapy or targeted therapy available in Belgium Excluded: other types of neoadjuvant therapy
Comparator	Adjuvant immunotherapy of targeted therapy available in Belgium or other neoadjuvant treatment.
Outcomes	Critical: Overall survival, health-related quality of life, adverse events (according to CTC criteria) Important: event-free survival, Other: overall cost of therapy
Study design	Included: systematic reviews of RCTs, RCTs. Articles in Dutch, English and French Excluded: Narrative reviews, non-randomised studies. Studies presented as conference abstract only (additional results published in abstract only are included) or if no full text was available.
Subgroup analyses	By stage if applicable

Appendix 6.2. Search strategies

Appendix 6.2.1. Medline Ovid

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions <1946 to July 23, 2024> Search Strategy:

- 1 exp Melanoma/ (112615)
- 2 melanoma\$.tw. (143897)
- 3 (maligna\$ adj1 lentigo\$).tw. (1390)
- 4 (hutchinson\$ adj1 (freckle\$ or melano\$)).tw. (59)
- 5 dubreuilh.tw. (42)
- 6 LMM.tw. (1651)
- 7 or/1-6 (164137)
- 8 exp Adjuvants, Immunologic/ (185855)
- 9 exp Neoadjuvant Therapy/ (30895)
- 10 exp Chemotherapy, Adjuvant/ (47546)
- 11 exp Chemoradiotherapy, Adjuvant/ (4031)
- 12 8 or 9 or 10 or 11 (257236)
- 13 immunoadjuvant?.ab,ti,kf. (1112)
- 14 immunoactivator?.ab,ti,kf. (34)
- 15 immunopotentiator?.ab,ti,kf. (599)
- 16 immunostimulant?.ab,ti,kf. (2844)
- 17 neoadjuvant?.ab,ti,kf. (51508)

- 18 adjuvant?.ab,ti,kf. (190850)
- 19 13 or 14 or 15 or 16 or 17 or 18 (233395)
- 20 12 or 19 (416811)
- 21 7 and 20 (9050)
- 22 randomized controlled trial.pt. (618218)
- 23 controlled clinical trial.pt. (95582)
- 24 randomized.ti,ab. (712928)
- 25 placebo.ti,ab. (257172)
- 26 clinical trials as topic/ (202856)
- 27 randomly.ti,ab. (439371)
- 28 trial?.ti. (414604)
- 29 22 or 23 or 24 or 25 or 26 or 27 or 28 (1662128)
- 30 exp animal/ not humans/ (5242260)
- 31 29 not 30 (1533337)
- 32 21 and 31 (1213)
- 33 limit 32 to yr="2000-2024" (894)
- 34 ((systematic review or systematic literature review or systematic scoping review or systematic narrative review or systematic qualitative review or systematic evidence review or systematic quantitative review or systematic meta-review or systematic critical review or systematic mixed studies review or systematic mapping review or systematic cochrane review or "systematic search and review" or systematic integrative review).ti. not comment.pt. not (protocol or protocols).ti. not medline.st.) or (Cochrane Database Syst Rev.ja. and review.pt.) or systematic review.pt. (317634)
- 35 meta-analys*.ti. (207560)
- 36 meta-analysis.pt. (205075)
- 37 exp Technology Assessment, Biomedical/ (12402)
- 38 health technology assessment.ti,kf. (3075)
- 39 HtA.ti,kf. (934)
- 40 34 or 35 or 36 or 37 or 38 or 39 (447959)
- 41 21 and 40 (117)
- 42 limit 41 to yr="2000-2024" (115)

Appendix 6.2.2. Embase

Embase session results (29 Jul 2024)

No.	Query	Results
#26	#24 AND (random*:ab,ti OR placebo*:de,ab,ti OR ((double NEXT/1 blind*):ab,ti))	180
#25	#24 AND ('meta-analysis'/exp OR 'meta-analysis' OR 'systematic review'/exp OR 'systematic review')	96
#24	#23 NOT ('conference abstract'/it OR 'conference paper'/it OR 'conference review'/it)	1645



```

#23  #22 NOT [medline]/lim  4853
#22  #21 AND [2000-2024]/py  10826
#21  #7 AND #20  12021
#20  #12 OR #19  399675
#19  #13 OR #14 OR #15 OR #16 OR #17 OR #18  361422
#18  adjuvant$:ab,ti,kw  286598
#17  neoadjuvant$:ab,ti,kw  101086
#16  immunostimulant$:ab,ti,kw  3904
#15  immunopotentiator$:ab,ti,kw  759
#14  immunoactivator$:ab,ti,kw  51
#13  immunoadjuvant$:ab,ti,kw  1436
#12  #8 OR #9 OR #10 OR #11  160446
#11  'adjuvant chemoradiotherapy'/de  8081
#10  'adjuvant radiotherapy'/de  15537
#9   'neoadjuvant therapy'/exp  59895
#8   'adjuvant'/exp  86622
#7   #1 OR #2 OR #3 OR #4 OR #5 OR #6  258679
#6   Imm:ab,ti,kw  2315
#5   dubreuilh:ab,ti,kw  113
#4   (hutchinson* NEAR/1 (freckle* OR melano*)):ab,ti,kw  22
#3   (maligna* NEAR/1 lentigo*):ab,ti,kw  2070
#2   melanoma*:ab,ti,kw  209626
#1   'melanoma'/de OR 'amelanotic melanoma'/de OR 'malignant lentigo'/de  178068

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Appendix 6.2.3. Cochrane

(Neo)Adjuvants SR and RCT sensitive; Date Run: 29/07/2024 10:01:14

```

ID    Search Hits
#1    [mh Melanoma] 2738
#2    melanoma*:ti,ab  6254
#3    (maligna*:ti,ab NEAR/1 lentigo*:ti,ab)  41
#4    (hutchinson*:ti,ab NEAR/1 (freckle*:ti,ab OR melano*:ti,ab))  2
#5    dubreuilh:ti,ab  0
#6    LMM:ti,ab  212
#7    #1 OR #2 OR #3 OR #4 OR #5 OR #6  6653
#8    [mh "Adjuvants, Immunologic"]  2839
#9    [mh "Neoadjuvant Therapy"]  2641
#10   [mh "Chemotherapy, Adjuvant"]  5994
#11   [mh "Chemoradiotherapy, Adjuvant"]  338

```

#12 #8 or #9 or #10 or #11 10801
 #13 immunoadjuvant?:ab,ti 40
 #14 immunoactivator?:ab,ti 1
 #15 immunopotentiator?:ab,ti 27
 #16 immunostimulant?:ab,ti 170
 #17 neoadjuvant?:ab,ti 12194
 #18 adjuvant?:ab,ti 36578
 #19 #13 OR #14 OR #15 OR #16 OR #17 OR #18 44008
 #20 #12 or #19 47774
 #21 #7 AND #20 1248
 #22 #21 with Cochrane Library publication date Between Jan 2000 and Dec 2024 1133
 #23 #22 in Cochrane Reviews 5
 #24 #22 in Trials 1127

(Neo)Adjuvants 2000-2024 specific; Date Run: 29/07/2024 10:07:44

ID	Search Hits
#1	[mh Melanoma] 2738
#2	melanoma*:ti,ab 6254
#3	(maligna*:ti,ab NEAR/1 lentigo*:ti,ab) 41
#4	(hutchinson*:ti,ab NEAR/1 (freckle*:ti,ab OR melano*:ti,ab)) 2
#5	dubreuilh:ti,ab 0
#6	LMM:ti,ab 212
#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6 6653
#8	[mh "Adjuvants, Immunologic"[mj]] 1720
#9	[mh "Neoadjuvant Therapy"[mj]] 533
#10	[mh "Chemotherapy, Adjuvant"[mj]] 271
#11	[mh "Chemoradiotherapy, Adjuvant"[mj]] 104
#12	#8 or #9 or #10 or #11 2564
#13	immunoadjuvant?:ti 8
#14	immunoactivator?:ti 0
#15	immunopotentiator?:ti 13
#16	immunostimulant?:ti 43
#17	neoadjuvant?:ti 6471
#18	adjuvant?:ti 15918
#19	#13 OR #14 OR #15 OR #16 OR #17 OR #18 21516
#20	#12 or #19 23215
#21	#7 AND #20 759
#22	#21 with Cochrane Library publication date Between Jan 2000 and Dec 2024 677



#23	#22 in Cochrane Reviews	3
#24	#22 in Trials	673

Appendix 6.2.4. Citations excluded or included based on full text with reasons

Table 41 – (Neo)adjuvant therapy: citations excluded or included based on full text with reasons

	Year	Publication	Reason for exclusion
1	2024	Blank CU, Lucas MW, Scolyer RA, et al. Neoadjuvant Nivolumab and Ipilimumab in Resectable Stage III Melanoma N Engl J Med . 2024 Nov 7;391(18):1696-1708	Included neoadjuvant immunotherapy
2	2024	Bol KF, Schreibelt G, Bloemendal M, et al. Adjuvant dendritic cell therapy in stage IIB/C melanoma: the MIND-DC randomized phase III trial (213). Nat Commun 2024;15(1):1632	dendritic cell therapy
3	2024	Fuchs L, Gesierich A, Schummer P, Schilling B. Neoadjuvant therapy of melanoma (1048). Onkologie 2024;30(5):433-42	Narrative review
4	2024	Hieken TJ, Nelson GD, Flotte TJ, et al. Neoadjuvant cobimetinib and atezolizumab with or without vemurafenib for high-risk operable Stage III melanoma: the Phase II NeoACTIVATE trial (235). Nat Commun 2024;15(1):1430	Non-randomized study
5	2024	Kakish H, Xu K, Ahmed FA, et al. Preoperative therapy in melanoma: Evolving perspectives in clinical trials (237). Crit Rev Oncol Hematol 2024;193:104193	Narrative review
6	2024	Kirkwood JM, Del Vecchio M, Weber J, et al. Author Correction: Adjuvant nivolumab in resected stage IIB/C melanoma: primary results from the randomized, phase 3 CheckMate 76K trial (217). Nat Med 2024;30(3):906	Author correction without change of content
7	2024	Kirkwood JM, Del Vecchio M, Weber J, et al. Publisher Correction: Adjuvant nivolumab in resected stage IIB/C melanoma: primary results from the randomized, phase 3 CheckMate 76K trial (218). Nat Med 2024;30(2):607	publisher correction, no change to content
8	2024	Kirkwood JM, Vecchio MD, Weber J, et al. Plain language summary of the CheckMate 76K study results: nivolumab given after stage 2B/2C melanoma is removed by surgery (229). Future Oncol 2024;20(15):959-68	Summary, not original publication
9	2024	Kuijpers AMJ, van Akkooi ACJ. Neo-Adjuvant Therapy for Metastatic Melanoma (216). Cancers (Basel) 2024;16(7)	Narrative review
10	2024	Latifyan S, Haanen JB. Melanoma neoantigen vaccines: Are we getting more personal now? (226). Med 2024;5(4):288-90	Narrative review
11	2024	Long GV, Carlino MS, Au-Yeung G, et al. Neoadjuvant pembrolizumab, dabrafenib and trametinib in BRAFV600-mutant resectable melanoma: the randomized phase 2 NeoTrio trial	Included neoadjuvant targeted therapy
12	2024	Long GV, Hauschild A, Santinami M, et al. Final Results for Adjuvant Dabrafenib plus Trametinib in Stage III Melanoma (209). N Engl J Med 2024	Included adjuvant targeted therapy
13	2024	Luke JJ, Ascierto PA, Khattak MA et al. Pembrolizumab Versus Placebo as Adjuvant Therapy in Resected Stage IIB or IIC Melanoma: Final Analysis of Distant Metastasis-Free Survival in the Phase III KEYNOTE-716 Study. JCO 2024; 42(14):1619-1624	Included adjuvant immunotherapy
14	2024	Luke JJ, Long GV, Robert C et al. Safety of pembrolizumab as adjuvant therapy in a pooled analysis of phase 3 clinical trials of melanoma, non-small cell lung cancer, and renal cell carcinoma. J Cancer 2024; 207:114146	Not a SR, not specific for melanoma
15	2024	Mangla A, Lee C, Mirsky MM, et al. Neoadjuvant Dual Checkpoint Inhibitors vs Anti-PD1 Therapy in High-Risk Resectable Melanoma: A Pooled Analysis (6). JAMA Oncol 2024;10(5):612-20	Excluded SR (only one database searched)
16	2024	Biomarker Driven Patient Selection Neoadjuvant Anti-PD1 or Combinations for Locoregionally Advanced Melanoma (1439). 2024. https://clinicaltrials.gov/study/NCT06295159#study-overview	Ongoing study

	Year	Publication	Reason for exclusion
17	2024	Nimmer EK, Zhu H, Chianese-Bullock KA, von Mehren M et al. Multipartite vaccines for melanoma in the adjuvant setting: long-term survival outcomes and post-hoc analysis of a randomized phase II trial. Nature communications 2024, 14(1):2570	adjuvant vaccin
18	2024	Novis E, van Akooi ACJ. Management of Localized Melanoma in the Anti-PD-1 Era. Curr Oncol Rep . 2024 Jun 6. doi: 10.1007/s11912-024-01556-z. Online ahead of print	Narrative review
19	2024	Olivier T, Prasad V. Neoadjuvant followed by adjuvant pembrolizumab in melanoma: time biases in the data analysis of the SWOG S1801 trial. Translational Oncology 2024; 45:101959	Comment on RCT
20	2024	Ochendusko S, Puskulluoglu M, Pacholczak-Madej R, Ruiz-Millo O. Adjuvant anti-PD1 immunotherapy of resected skin melanoma: an example of non-personalized medicine with no overall survival benefit (207). Crit Rev Oncol Hematol 2024:104443.	Narrative review
21	2024	Schadendorf D, Luke JJ, Ascierto PA, et al. Pembrolizumab versus placebo as adjuvant therapy in resected stage IIB or IIC melanoma: Outcomes in histopathologic subgroups from the randomized, double-blind, phase 3 KEYNOTE-716 trial (223). J Immunother Cancer 2024;12(3)	Included adjuvant immunotherapy (secondary publication)
22	2024	Tarhini AA, Castellano E, Eljilany I. Treatment of Stage III Resectable Melanoma-Adjuvant and Neoadjuvant Approaches (231). Cancer J 2024;30(2):54-70	Narrative review
23	2024	Weber JS, Carlino MS, Khattak A, et al. Individualised neoantigen therapy mRNA-4157 (V940) plus pembrolizumab versus pembrolizumab monotherapy in resected melanoma (KEYNOTE-942): a randomised, phase 2b study (234). Lancet 2024;403(10427):632-44	vaccin
24	2023	Ascierto PA, Cioli E, Chiarion-Sileni V, et al. Neoadjuvant plus adjuvant combined or sequenced vemurafenib, cobimetinib and atezolizumab in patients with high-risk, resectable BRAF-mutated and wild-type melanoma: NEO-TIM, a phase II randomized non-comparative study	Protocol, no results
25	2023	Ascierto PA, Del Vecchio M, Merelli B, et al. 1089P Adjuvant nivolumab (NIVO) vs ipilimumab (IPI) in resected stage III/IV melanoma: 7-y results from CheckMate 238 Annal Oncol 2023; 34 Suppl2: S656 https://www.sciencedirect-com.gateway2.cdih.be/science/article/abs/pii/S0923753423030600?via%3Dihub	Included adjuvant immunotherapy
26	2023	Ascierto PA, Tarhini A, De Melo AC, et al. RELATIVITY-098: a phase 3, randomized, double-blind trial of adjuvant nivolumab (NIVO) + relatlimab (RELA) fixed-dose combination (FDC) versus (vs) NIVO after complete resection of stage III or IV melanoma (1621). 2023(1):90 https://onlinelibrary-wiley-com.gateway2.cdih.be/doi/10.1111/pcmr.13073	Trial design, no results
27	2023	Ba H, Zhu F, Zhang X, Mei Z, Zhu Y. Comparison of efficacy and tolerability of adjuvant therapy for resected high-risk stage III-IV cutaneous melanoma: a systemic review and Bayesian network meta-analysis (13). Ther Adv Med Oncol 2023;15:17588359221148918	Included adjuvant SR Search date November 2021
28	2023	Barron CC, Stefanova I, Cha Y, et al. Chronic immune-related adverse events in patients with cancer receiving immune checkpoint inhibitors: a systematic review (12). J Immunother Cancer 2023;11	Not in melanoma patients
29	2023	Burton E, Milton D, Simpson L, Tetzlaff M, Glitza IC, Ross MI, Gershenwald JE, McQuade J, Wong M, Patel S, Diab A, Postow M, Ariyan CE, Lee J, Fisher S, Prieto V, Davies M, Tawbi HA, Wargo J, Amaria R. Annals of oncology, 2023, 34, S659 added to CENTRAL: 29 February 2024 2024 Issue 2 1094P Relapse free survival (RFS) at 3	No comparative results

	Year	Publication	Reason for exclusion
		years by pathological (path) response to neoadjuvant systemic treatment (NST) in patients (pts) with surgically resectable, high-risk melanoma	
30	2023	ChiCtr. Adjuvant Carelizumab combined with Temozolomide for Stage IIIC-IIID Acral Melanoma (1342). 2023. https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02572632/full	Recruiting trial
31	2023	Ctri. Adjuvant MK-7684A vs Pembrolizumab for Resected High-Risk Melanoma (1343). 2023	Trial registry entry, closed to recruitment, no results posted
32	2023	Dummer R, Gyorki DE, Hyngstrom JR, Ning M, Lawrence T, Ross MI. Final 5-Year Follow-Up Results Evaluating Neoadjuvant Talimogene Laherparepvec Plus Surgery in Advanced Melanoma: A Randomized Clinical Trial. JAMA Oncol 2023;9(10):1457-9	Talimogene Laherparepvec not available in Belgium
33	2023	Eljilany R, Robert C, Scolyer RA, et al. KEYMAKER-U02 substudy 02C: neoadjuvant pembrolizumab (pembro) + vibostolimab (vibo) or gebasaxturev (geba) or pembro alone followed by adjuvant pembro for stage IIIB-D melanoma https://aacrjournals.org/cancerres/article/83/8_Supplement/CT002/725267/Abstract-CT002-KEYMAKER-U02-substudy-02C	Wrong outcomes
34	2023	Eljilany I, Castellano E, Tarhini AA. Adjuvant Therapy for High-Risk Melanoma: An In-Depth Examination of the State of the Field (257). Cancers (Basel) 2023;15(16)	Narrative review
35	2023	Eljilany I, Noor A, Paravathaneni M, et al. Granulomatous and Sarcoid-like Immune-Related Adverse Events following CTLA4 and PD1 Blockade Adjuvant Therapy of Melanoma: A Combined Analysis of ECOG-ACRIN E1609 and SWOG S1404 Phase III Trials and a Literature Review. Cancers 2023, 15, 2561	Specific AEs only (secondary publication)
36	2023	Jalovcic-Suljevic B, Long GV, Kirkwood JM, et al. Adjuvant Therapy With Nivolumab Versus Placebo in Patients With Resected Stage IIB/C Melanoma (Checkmate 76K). 2023:S36 Annals of Surgical Oncology 2023; 30:S36 Conference proceeding	Abstract with interim results only
37	2023	Gesierich A, Schilling B. Adjuvant therapy for melanoma (130). Onkologie 2023;29(8):671-9	Narrative review in German
38	2023	Gorry C, McCullagh L, O'Donnell H, et al. Neoadjuvant treatment for stage III and IV cutaneous melanoma (15). Cochrane Database Syst Rev 2023;1:CD012974	Included SR neoadjuvant Search date 10 August 2021
39	2023	Guyen DC, Erul E, Kaygusuz Y, et al. Immune checkpoint inhibitor-related hearing loss: a systematic review and analysis of individual patient data (10). Support Care Cancer 2023;31(12):624	Not specific for melanoma
40	2023	Huang S, Zheng G, Yang K. Neoadjuvant PD-1/PD-L1 combined with CTLA-4 inhibitors for solid malignancies: a systematic review and meta-analysis (125). World Journal of Surgical Oncology 2023;21(1)	No critical appraisal
41	2023	Jalovcic-Suljevic A. Neoadjuvant and/or adjuvant immunotherapy in malignant melanoma - the best approach (1175). 2023:30	Oral presentation at conference, no results
42	2023	Kirkwood JM, Del Vecchio M, Weber J, et al. Publisher Correction: adjuvant nivolumab in resected stage IIB/C melanoma: primary results from the randomized, phase 3 CheckMate 76K trial (Nature Medicine, (2023	Correction to author's name only
43	2023	Kirkwood JM, Del Vecchio M, Weber J, et al. Adjuvant nivolumab in resected stage IIB/C melanoma: primary results from the randomized, phase 3 CheckMate 76K trial (243). Nat Med 2023;29(11):2835-43	Included adjuvant immunotherapy
44	2023	Kirkwood JM, Strawderman MH, Ernstoff MS, Smith TJ, Borden EC, Blum RH. Interferon Alfa-2b Adjuvant Therapy of High-Risk Resected Cutaneous Melanoma: The Eastern Cooperative Oncology Group Trial EST 1684 (240). J Clin Oncol 2023;41(3):425-35	adjuvant interferon

	Year	Publication	Reason for exclusion
45	2023	Lai-Kwon J, Inderjeeth AJ, Lisy K, Sandhu S, Rutherford C, Jefford M. Impact of immune checkpoint inhibitors and targeted therapy on health-related quality of life of people with stage III and IV melanoma: a mixed-methods systematic review (17). Eur J Cancer 2023;184:83-105	Included adjuvant immunotherapy (SR) (QoL)
46	2023	Larkin J, Del Vecchio M, Mandalá M, et al. Adjuvant Nivolumab versus Ipilimumab in Resected Stage III/IV Melanoma: 5-Year Efficacy and Biomarker Results from CheckMate 238 (1394). 2023(17):3352-61	Included adjuvant immunotherapy
47	2023	Long GV, Menzies AM, Scolyer RA. Neoadjuvant Checkpoint Immunotherapy and Melanoma: The Time Is Now (273). J Clin Oncol 2023;41(17):3236-48	Narrative review
48	2023	Lowe MC, Hyngstrom JR, Wright GP, et al. Surgical Outcomes of SWOG1801: neoadjuvant/adjuvant Versus Adjuvant Pembrolizumab for Resectable Stage III-IV Melanoma (1171). 2023:S50 Annals of Surgical oncology 2023;30 (Suppl1):S49	Included neoadjuvant immunotherapy
49	2023	Lucas MW, Rozeman EA, Versluis JM, et al. 1096P Prolonged follow-up confirms durability of favorable outcomes after neoadjuvant ipilimumab plus nivolumab in melanoma (1657). 2023:S660-S1 Annals of Oncology 2023; 34(suppl 2):S660-S661	Included neoadjuvant immunotherapy
50	2023	Luke JJ, Ascierto PA, Khattak MA, et al. Pembrolizumab versus placebo as adjuvant therapy in stage IIB or IIC melanoma: final analysis of distant metastasis-free survival in the phase 3 KEYNOTE-716 study (1486). 2023(17)	Duplicate (13)
51	2023	Luke JJ, Long GV, Robert C, et al. Safety of Adjuvant Pembrolizumab (pembro) in a Pooled Analysis of Phase 3 Clinical Trials in Melanoma, Non-Small Cell Lung Cancer (NSCLC), and Renal Cell Carcinoma (1567). 2023:S187	Duplicate (14)
52	2023	Mandala M, Van Akkooi ACJ, Hauschild A, et al. Phase Iii Study of Adjuvant Encorafenib Plus Binimetinib Versus Placebo in Fully Resected Stage lib/C Brafv600-Mutated Melanoma: Columbus-Ad Study Design (1481). 2023:22	Study design only, no results
53	2023	McLouth LE, Zheng Y, Smith S, et al. Patient-reported tolerability of adjuvant ipilimumab (3 or 10 mg/kg) versus high-dose interferon alfa-2b for resected high-risk stage III-IV melanoma in phase III trial E1609 (261). Qual Life Res 2023;32(1):183-96	Included adjuvant immunotherapy
54	2023	Nct. A Study of Neoadjuvant Therapy With BCD-217 (Nurulimab + Prologolimab) in Patients With Resectable Stage III Skin Melanoma (1477). 2023 https://clinicaltrials.gov/study/NCT05751928	Ongoing trial
55	2023	Patel S, Othus M, Wright P, et al. LBA48 Pathologic response and exploratory analyses of neoadjuvant-adjuvant versus adjuvant pembrolizumab (PEM) for resectable stage IIIB-IV melanoma from SWOG S1801 (1178). 2023:S1288 https://www.sciencedirect-com.gateway2.cdih.be/science/article/abs/pii/S0923753423041868?via%3Dihub	Pathology data of NET arm only (abstract)
56	2023	Patel SP, Othus M, Chen Y, et al. Neoadjuvant-Adjuvant or Adjuvant-Only Pembrolizumab in Advanced Melanoma (262). N Engl J Med 2023;388(9):813-23	Included neoadjuvant immunotherapy
57	2023	Perez MC, Depalo DK, Zager JS. A safety review of recently approved and late-stage trial treatments for metastatic melanoma: systemic and regional therapies. Expert Opin Drug Saf 2023;22(9):789-97	Narrative Review
58	2023	Perez-Morales J, Broman KK, Bettampadi D, Haver MK, Zager JS, Schabath MB. Recurrence Patterns for Regionally Metastatic Melanoma Treated in the Era of Adjuvant Therapy: A Systematic Review and Meta-Analysis. Ann Surg Oncol 2023;30(4):2364-74	No OS or QoL outcomes
59	2023	Rutkowski P, Czarnecka AM. Pembrolizumab for the adjuvant treatment of IIB or IIC melanoma. Expert Rev Anticancer Ther 2023;23(9):897-902	Expert opinion

	Year	Publication	Reason for exclusion
60	2023	Saad M, Castellano E, Tarhini AA. Clinical updates in neoadjuvant immunotherapy for melanoma before surgery. Expert Rev Clin Immunol 2023;1-17	Expert opinion
61	2023	Saad M, Tarhini AA. Neoadjuvant Therapy in Melanoma: Where Are We Now? Curr Oncol Rep 2023;25(4):325-39	Narrative review
62	2023	Schadendorf D, Hauschild A, Mandala M, et al. Adjuvant dabrafenib + trametinib (DT) vs placebo (PBO) in patients (pts) with resected stage III BRAFV600-mutant melanoma: updated 5-year distant metastases-free survival (DMFS) analysis of COMBI-AD. 2023(1):176	Prognostic factors only (abstract)
63	2023	Sheng F, Yan Y, Zeng B. Efficacy and safety of immune checkpoint inhibitors and targeted therapies in resected melanoma: a systematic review and network meta-analysis. Front Pharmacol 2023;14:1284240	Included adjuvant immunotherapy + targeted therapy SR Search date: 6 June 2023
64	2023	Unger JM, Darke A, Othus M, et al. Effectiveness of Adjuvant Pembrolizumab vs High-Dose Interferon or Ipilimumab for Quality-of-Life Outcomes in Patients With Resected Melanoma: A Secondary Analysis of the SWOG S1404 Randomized Clinical Trial. JAMA Oncol 2023;9(2):251-60	Included adjuvant immunotherapy
65	2023	van Akkooi AC, Hauschild A, Long GV, et al. COLUMBUS-AD: phase III study of adjuvant encorafenib + binimetinib in resected stage IIB/IIC BRAF V600-mutated melanoma. Future Oncol 2023;19(30):2017-27	Study design, no results
66	2023	van Akkooi ACJ, Blank C, Eggermont AMM. Neo-adjuvant immunotherapy emerges as best medical practice, and will be the new standard of care for macroscopic stage III melanoma (268). Eur J Cancer 2023;182:38-42	Narrative review
67	2023	Versluis JM, Menzies AM, Sikorska K, et al. Survival update of neoadjuvant ipilimumab plus nivolumab in macroscopic stage III melanoma in the OpACIN and OpACIN-neo trials (269). Ann Oncol 2023;34(4):420-30	Included neoadjuvant immunotherapy
68	2023	Weber JS, Schadendorf D, Del Vecchio M, et al. Adjuvant Therapy of Nivolumab Combined With Ipilimumab Versus Nivolumab Alone in Patients With Resected Stage IIIB-D or Stage IV Melanoma (CheckMate 915) (280). J Clin Oncol 2023;41(3):517-27	Included adjuvant immunotherapy
69	2023	Yoon CH, Ross MI, Gastman B, et al. Adjuvant Pembrolizumab in Stage II Melanoma: outcomes by Tumor Location in the Phase 3 KEYNOTE-716 Study. 2023:S35 Annals of surgical oncology, 2023, 30, S35	Wrong outcomes (abstract)
70	2022	Bersanelli M, Petrelli F, Buti S, Stanganelli I. Immune checkpoint inhibitors in adjuvant setting after radical resection of melanoma: a meta-analysis of the pivotal trials (33). Hum Vaccin Immunother 2022;18(3):1902723	Searched only one database
71	2022	Bloemendal M, Bol KF, Boudewijns S, et al. Immunological responses to adjuvant vaccination with combined CD1c+ myeloid and plasmacytoid dendritic cells in stage III melanoma patients (289). Oncoimmunology 2022;11(1):2015113	vaccine therapy and dendritic cell therapy
72	2022	Braden J, Potter A, Paver E, et al. Neotrio trial - optimal neoadjuvant sequencing of anti-PD1 and BRAF targeting therapy in resectable BRAF mutant stage IIIB/C/D melanoma: results of histopathological analysis. 2022:50-1	Wrong outcomes (abstract)
73	2022	Braden J, Potter AJ, Paver EC, et al. NeoTrio – Optimal neoadjuvant (NAT) sequencing of anti-PD-1 and BRAF targeted therapy (TT) in BRAF mutant stage III melanoma: results of histopathological analysis. 2022:S909	Wrong outcomes

	Year	Publication	Reason for exclusion
74	2022	Dummer R, Gyorki D, Hyngstrom J, et al. LBA39 Final 5-year results of the phase II, multicenter, randomized, open-label trial of talimogene laherparepvec (T-VEC) neoadjuvant treatment (Tx) plus surgery vs immediate surgery in patients (pts) with resectable stage IIIB-IVM1a melanoma (MEL) (1715). 2022:S1406	Talimogene laherparepvec not available in Belgium
75	2022	Eggermont A, Kicinski M, Suci S. Association of selected (immune-related) adverse events and outcome in two adjuvant phase III trials, Checkmate-238 and EORTC1325/KEYNOTE-054 (315). J Immunother Cancer 2022;10(1)	Wrong outcomes, not a SR
76	2022	Eggermont AM, Ascierto PA, Khushalani NI, et al. PIVOT-12: a phase III study of adjuvant bimegaldesleukin plus nivolumab in resected stage III/IV melanoma at high risk for recurrence. Future Oncol 2022;18(8):903-13	Bimegaldesleukin not available in Belgium
77	2022	Eggermont AM, Kicinski M, Blank CU, et al. Five-Year Analysis of Adjuvant Pembrolizumab or Placebo in Stage III Melanoma (281). NEJM Evid 2022;1(11):EVIDoa2200214	Included adjuvant immunotherapy
78	2022	Grossmann KF, Othus M, Patel SP, et al. Adjuvant Pembrolizumab versus IFNalpha2b or Ipilimumab in Resected High-Risk Melanoma (319). Cancer Discov 2022;12(3):644-53	Included adjuvant immunotherapy
79	2022	Hooiveld-Noeken JS, Eggen AC, Racz E, de Vries EGE, Reyners AKL, Jalving M. Towards less mutilating treatments in patients with advanced non-melanoma skin cancers by earlier use of immune checkpoint inhibitors (27). Crit Rev Oncol Hematol 2022;180:103855	Narrative review
80	2022	Jin Y, Wei J, Weng Y, et al. Adjuvant Therapy With PD1/PDL1 Inhibitors for Human Cancers: A Systematic Review and Meta-Analysis (146). Frontiers in Oncology 2022;12	Multiple tumour types
8183	2022	Jing M, Cai Y, Shi J, et al. Adjuvant Treatments of Adult Melanoma: A Systematic Review and Network Meta-Analysis	not most recent SR
8284	2022	Khattak MA, Luke JJ, Long GV, et al. Adjuvant pembrolizumab versus placebo in resected high-risk stage II melanoma: Health-related quality of life from the randomized phase 3 KEYNOTE-716 study (290). Eur J Cancer 2022;176:207-17	Excluded: unresectable melanoma
85	2022	Larkin J, Weber J, Del Vecchio M, et al. Adjuvant nivolumab versus ipilimumab (CheckMate 238 trial): Reassessment of 4-year efficacy outcomes in patients with stage III melanoma per AJCC-8 staging criteria (291). Eur J Cancer 2022;173:285-96	Included adjuvant immunotherapy
86	2022	Lian B, Si L, Chi ZH, et al. Toripalimab (anti-PD-1) versus high-dose interferon-alpha2b as adjuvant therapy in resected mucosal melanoma: a phase II randomized trial (302). Ann Oncol 2022;33(10):1061-70	Mucosal melanoma
87	2022	Livingstone E, Zimmer L, Hassel JC, et al. Adjuvant nivolumab plus ipilimumab or nivolumab alone versus placebo in patients with resected stage IV melanoma with no evidence of disease (IMMUNED): final results of a randomised, double-blind, phase 2 trial. Lancet 2022;400(10358):1117-29	Included adjuvant immunotherapy
88	2022	Long GV, Carlino MS, Au-Yeung G, et al. NeoTrio: randomized trial of neoadjuvant (NAT) pembrolizumab (Pembro) alone, in sequence (SEQ) with, or concurrent (CON) with dabrafenib plus trametinib (D+T) in resectable BRAF-mutant stage III melanoma to determine optimal combination of therapy (1709). 2022(16). Journal of clinical oncology 2022, 40(16)	duplicate 11
89	2022	Long GV, Luke JJ, Khattak M, et al. Distant metastasis-free survival with pembrolizumab versus placebo as adjuvant therapy in stage IIB or IIC melanoma: the phase 3 KEYNOTE-716 study (1544). 2022(17) Journal of clinical oncology, 2022, 40(17)	Duplicate 13

	Year	Publication	Reason for exclusion
90	2022	Long GV, Luke JJ, Khattak MA, et al. Pembrolizumab versus placebo as adjuvant therapy in resected stage IIB or IIC melanoma (KEYNOTE-716): distant metastasis-free survival results of a multicentre, double-blind, randomised, phase 3 trial. <i>Lancet Oncol</i> 2022;23(11):1378-88	Included adjuvant immunotherapy
91	2022	Luke JJ, Rutkowski P, Queirolo P, et al. Pembrolizumab versus placebo as adjuvant therapy in completely resected stage IIB or IIC melanoma (KEYNOTE-716): a randomised, double-blind, phase 3 trial (309). <i>Lancet</i> 2022;399(10336):1718-29	Included adjuvant immunotherapy
92	2022	Lucas MW, Lijnsvelt J, Pulleman S, et al. The NADINA trial: a multicenter, randomised, phase 3 trial comparing the efficacy of neoadjuvant ipilimumab plus nivolumab with standard adjuvant nivolumab in macroscopic resectable stage III melanoma (1189). 2022(16).	Trial design, no results
93	2022	Mo DC, Liang ZY, Chen L, Huang JF, Luo PH, Wang HL. Efficacy and safety of adjuvant therapy with PD-1/PD-L1 inhibitors in cancer (136). <i>Experimental and Therapeutic Medicine</i> 2022;24(6)	SR other tumours also included
94	2022	Nct. Adjuvant Encorafenib and Binimetinib in High-risk Stage II Melanoma With a BRAF Mutation (1258). 2022. https://clinicaltrials.gov/show/NCT05270044	Ongoing trial
95	2022	Zhang N, Li S, Li J. Efficacy of immune checkpoint inhibitors and targeted therapy in adjuvant treatment of resectable melanoma: a network meta-analysis. <i>Chinese Journal of Dermatology</i> 2022;55(7):603-9.	Article in Chinese
96	2022	Witt RG, Erstad DJ, Wargo JA. Neoadjuvant therapy for melanoma: rationale for neoadjuvant therapy and pivotal clinical trials. <i>Ther Adv Med Oncol</i> 2022;14:17588359221083052	Narrative review
97	2022	Weber JS, Larkin J, Mandala M, et al. Five-year outcomes with adjuvant nivolumab (NIVO) versus ipilimumab (IPI) in resected stage IIIB-C or IV melanoma (CheckMate 238) (1502). 2022(1):177 Pigment cell & melanoma research, 2022, 35(1), 177	Included adjuvant immunotherapy
98	2022	Versluis JM, Sikorska K, Rozeman EA, et al. Survival update of neoadjuvant ipilimumab + nivolumab in macroscopic stage III melanoma: the OpACIN and OpACIN-neo trials (1692). 2022(16) <i>JCO</i> 2022; 40(16): Annual Meeting of the American Society of Clinical Oncology, ASCO 2022	Included neoadjuvant targeted therapy duplicate (67)
99	2022	Schadendorf D, Hauschild A, Mandala M, et al. Adjuvant dabrafenib plus trametinib (D + T) versus placebo in patients with resected stage III BRAFV600-mutant melanoma: updated 5-year distant metastases-free survival (DMFS) analysis of COMBI-AD. 2022 <i>Journal of clinical oncology</i> , 2022, 40(16)	Included adjuvant targeted treatment (2)
100	2022	Schadendorf D, Hassel JC, Fluck M, et al. Adjuvant nivolumab (NIVO) alone or in combination with ipilimumab (IPI) versus placebo in stage IV melanoma with no evidence of disease (NED): overall survival (OS) results of IMMUNED, a randomized, double-blind multi-center phase II DeCOG trial. 2022:S900 <i>Ann Oncol</i> 2022; 33(Suppl7):S900	Included adjuvant immunotherapy
101	2022	Saxena M, Burke A, Pavlick A, et al. Immunogenicity of Poly-ICLC matured dendritic cells as an adjuvant for NY-ESO-1 and Melan-AMART-1 peptide vaccination compared to Montanide® ISA-51 VG, in study subjects with melanoma in complete clinical remission but at high risk of disease recurrence (1670). 2022(12).	Wrong outcomes
102	2022	Rizzo A, Mollica V, Marchetti A, et al. Adjuvant PD-1 and PD-L1 Inhibitors and Relapse-Free Survival in Cancer Patients: The MOUSEION-04 Study (140). <i>Cancers</i> 2022;14(17)	Not most recent SR
103	2022	Reijers ILM, Menzies AM, Versluis JM, et al. Relapse-free survival (RFS) update and first translational analyses of DONIMI, a study testing personalized neoadjuvant domatinostat, nivolumab (NIVO) and ipilimumab (IPI) in stage III	Domatinostat not available in Belgium

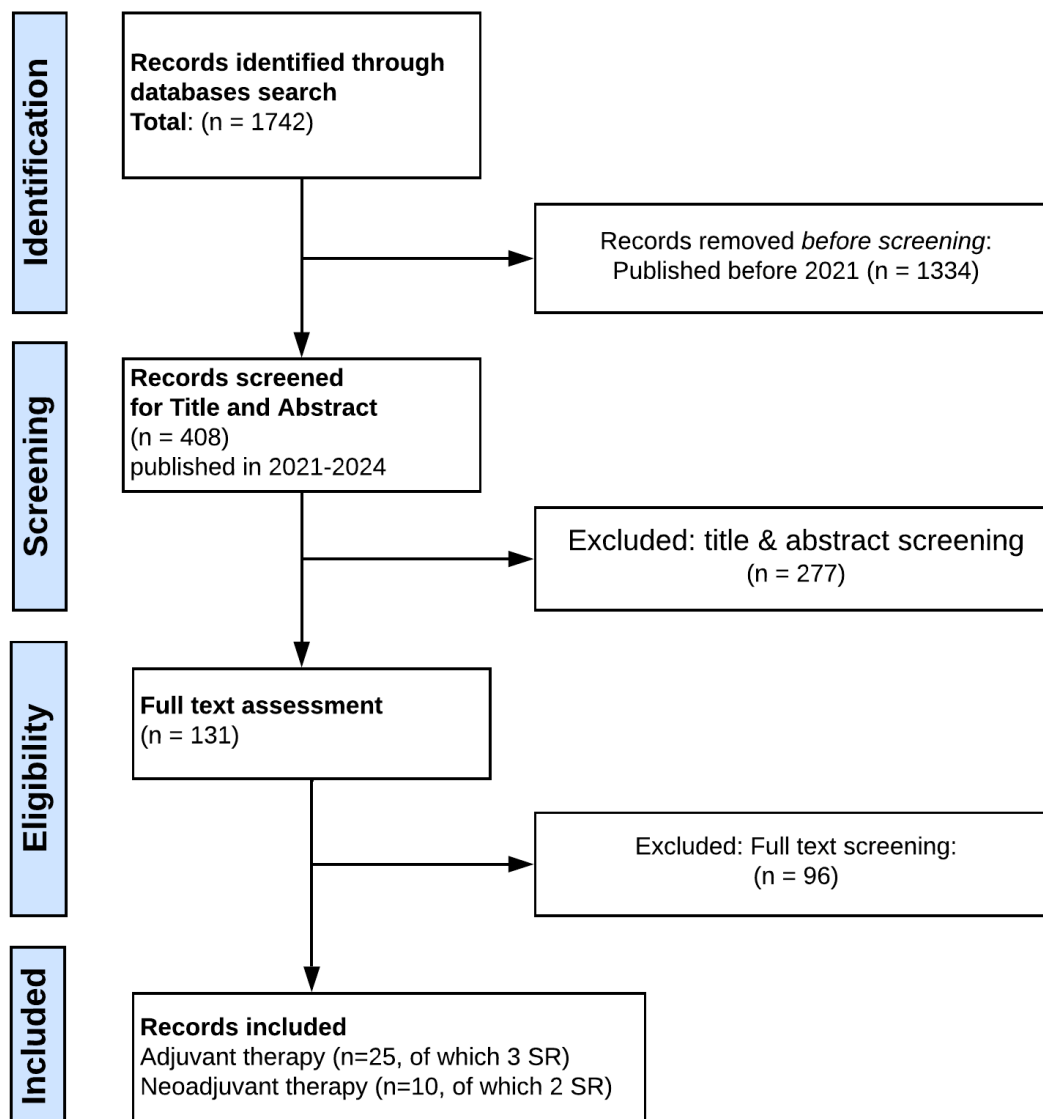
	Year	Publication	Reason for exclusion
		melanoma patients (pts) based on the interferon-gamma signature (IFN- γ sign) algorithm (1707). 2022:S908-S9 <i>Annals of oncology</i> , 2022, 33, S908-S909	
104	2022	Nct. A Study of Adjuvant Pembrolizumab/Vibostolimab (MK-7684A) Versus Pembrolizumab for Resected High-Risk Melanoma in Participants With High-Risk Stage II-IV Melanoma (MK-7684A-010/KEYVIBE-010) (1464). 2022 https://clinicaltrials.gov/study/NCT05665595	No results
105	2022	Niemi JVL, Sokolov AV, Schioth HB. Neoantigen Vaccines; Clinical Trials, Classes, Indications, Adjuvants and Combinatorial Treatments (284). <i>Cancers (Basel)</i> 2022;14(20)	Narrative review
106	2022	Notohardjo JCL, Veenstra S, Koster BD, et al. LBA43 Intradermal IMO-2125 versus placebo as adjuvant treatment in patients with stage II pT3-4/cN0 melanoma: interim efficacy and safety results of the randomized phase II INTRIM study (1599). 2022:S1410 <i>Annals of oncology</i> , 2022, 33, S1410	Wrong outcomes
107	2022	Patel A, Skitzki J. Melanoma trials that defined surgical management: Brief overview of current/upcoming adjuvant/neoadjuvant trials (313). <i>J Surg Oncol</i> 2022;125(1):38-45	Narrative review
108	2022	Patel S, Othus M, Prieto V, et al. LBA6 Neoadjuvant versus adjuvant pembrolizumab for resected stage III-IV melanoma (SWOG S1801) (1338). 2022:S1408 <i>Annals of oncology</i> , 2022, 33, S1408	Included neoadjuvant immunotherapy
109	2021	Correction to <i>Lancet Oncol</i> 2020; 21: 1465–77 (The <i>Lancet Oncology</i> (2020) 21(11) (1465–1477), (S1470204520304940), (10.1016/S1470-2045(20)30494-0)) (1066). The <i>Lancet Oncology</i> 2021;22(10):e428	Correction to affiliations only
110	2021	Bottomley A, Coens C, Mierzynska J, et al. Adjuvant pembrolizumab versus placebo in resected stage III melanoma (EORTC 1325-MG/KEYNOTE-054): health-related quality-of-life results from a double-blind, randomised, controlled, phase 3 trial (352). <i>Lancet Oncol</i> 2021;22(5):655-64	Included adjuvant immunotherapy
111	2021	Boulva K, Apte S, Yu A, et al. Contemporary Neoadjuvant Therapies for High-Risk Melanoma: A Systematic Review (37). <i>Cancers (Basel)</i> 2021;13(8)	Included neoadjuvant therapy SR
112	2021	Chick RC, Faries MB, Hale DF, et al. Multi-institutional, prospective, randomized, double-blind, placebo-controlled phase IIb trial of the tumor lysate, particle-loaded, dendritic cell (TLPLDC) vaccine to prevent recurrence in high-risk melanoma patients: A subgroup analysis (340). <i>Cancer Med</i> 2021;10(13):4302-11	Adjuvant vaccine
113	2021	Dummer R, Gyorki DE, Hyngstrom J, et al. Neoadjuvant talimogene laherparepvec plus surgery versus surgery alone for resectable stage IIIB-IVM1a melanoma: a randomized, open-label, phase 2 trial (329). <i>Nat Med</i> 2021;27(10):1789-96	Talimogene laherparepvec not available in Belgium
114	2021	Eggermont AMM, Blank CU, Mandala M, et al. Adjuvant pembrolizumab versus placebo in resected stage III melanoma (EORTC 1325-MG/KEYNOTE-054): distant metastasis-free survival results from a double-blind, randomised, controlled, phase 3 trial (353). <i>Lancet Oncol</i> 2021;22(5):643-54	Included adjuvant immunotherapy
115	2021	Euctr-001641-13-No. Adjuvant Immunotherapy with Relatlimab and Nivolumab Fixed-dose Combination versus Nivolumab Monotherapy after Complete Resection of Stage III-IV Melanoma (1523). 2021	No results available (Eudract 17/9/2024)
116	2021	Ghisoni E, Wicky A, Bouchaab H, et al. Late-onset and long-lasting immune-related adverse events from immune checkpoint-inhibitors: An overlooked aspect in immunotherapy (351). <i>Eur J Cancer</i> 2021;149:153-64	No SR of published trials
117	2021	Indini A, Grossi F. Adjuvant pembrolizumab for melanoma: update from the EORTC 1325-MG/KEYNOTE-054 trial (354). <i>Lancet Oncol</i> 2021;22(5):573-5	Comment
118	2021	Lau P, Shen M, Ma F, et al. A Bayesian network meta-analysis of comparison of cancer therapeutic vaccines for melanoma (38). <i>J Eur Acad Dermatol Venereol</i> 2021;35(10):1976-86	Adjuvant vaccine therapy (SR)

	Year	Publication	Reason for exclusion
119	2021	Lazarus HM, Ragsdale CE, Gale RP, Lyman GH. Sargramostim (rhu GM-CSF) as Cancer Therapy (Systematic Review) and An Immunomodulator. A Drug Before Its Time? (155). <i>Frontiers in Immunology</i> 2021;12	No focus on melanoma
120	2021	Long GV, Schadendorf D, Vecchio MD, et al. Adjuvant therapy with nivolumab (NIVO) combined with ipilimumab (IPI) vs NIVO alone in patients (pts) with resected stage IIIB-D/IV melanoma (CheckMate 915) (1496). 2021(13) <i>Cancer research</i> , 2021, 81(13 SUPPL)	Included adjuvant immunotherapy
121	2021	Mandala M, Larkin J, Ascierto PA, et al. Adjuvant nivolumab for stage III/IV melanoma: evaluation of safety outcomes and association with recurrence-free survival (1291). 2021(8) <i>J Immunother Cancer</i> . 2021 Aug;9(8):e003188	Included adjuvant immunotherapy
122	2021	Nct. Neoadjuvant Ipilimumab Plus Nivolumab Versus Standard Adjuvant Nivolumab in Macroscopic Stage III Melanoma (1174). 2021 https://clinicaltrials.gov/study/NCT04949113 (NADINA trial)	No results available (2028)
123	2021	Nct. A Study to Assess Adjuvant Immunotherapy With Nivolumab Plus Relatlimab Versus Nivolumab Alone After Complete Resection of Stage III-IV Melanoma (1389). 2021 https://clinicaltrials.gov/study/NCT05002569	No results (2029)
124	2021	Ridolfi L, Bulgarelli J, Piccinini C, et al. 49P A phase II randomized trial with adjuvant autologous tumor lysate-pulsed dendritic cells (DC) in resected stage III-IV melanoma patients: preliminary immunological results (1510). 2021:S1394 <i>Annals of oncology</i> , 2021, 32, S1394	No OS or QoL outcomes, dendritic cell therapy
125	2021	Rozeman EA, Hoefsmit EP, Reijers ILM, et al. Survival and biomarker analyses from the OpACIN-neo and OpACIN neoadjuvant immunotherapy trials in stage III melanoma (366). <i>Nat Med</i> 2021;27(2):256-63	Included neoadjuvant immunotherapy
126	2021	Slingsluff CL, Lewis KD, Andtbacka R, et al. Multicenter, double-blind, placebo-controlled trial of seviprotimut-L polyvalent melanoma vaccine in patients with post-resection melanoma at high risk of recurrence (331). <i>J Immunother Cancer</i> 2021;9(10)	Adjuvant vaccine therapy
127	2021	Tarhini AA, Kang N, Lee SJ, et al. Immune adverse events (irAEs) with adjuvant ipilimumab in melanoma, use of immunosuppressants and association with outcome: ECOG-ACRIN E1609 study analysis (341). <i>J Immunother Cancer</i> 2021;9(5)	No comparative outcomes
128	2021	Toor K, Middleton MR, Chan K, Amadi A, Moshyk A, Kotapati S. Comparative efficacy and safety of adjuvant nivolumab versus other treatments in adults with resected melanoma: a systematic literature review and network meta-analysis (42). <i>BMC Cancer</i> 2021;21(1):3	Not most recent SR (search date 2018)
F129	2021	Van Den Heuvel NMJ, Reijers ILM, Versluis JM, et al. 1500P Health-related quality of life in melanoma patients treated with neoadjuvant nivolumab and domatinostat: preliminary results (1658). 2021:S1100-S1 <i>Annals of oncology</i> , 2021, 32, S1100-S1101	Non-randomised extension of RCT
130	2021	Vreeland TJ, Clifton GT, Hale DF, et al. A Phase IIb Randomized Controlled Trial of the TLPLDC Vaccine as Adjuvant Therapy After Surgical Resection of Stage III/IV Melanoma: A Primary Analysis (364). <i>Ann Surg Oncol</i> 2021;28(11):6126-37	Adjuvant vaccine therapy
131	2021	Yamazaki N. Adjuvant therapy for melanoma. 2021(2):503 <i>Pigment cell & melanoma research</i> , 2021, 34(2), 503	Abstract of a narrative review



Appendix 6.2.5. Study selection

Figure 16 – Study flow selection of search adjuvant and neoadjuvant therapy



Appendix 6.3. Evidence tables

Table 42 – Ipilimumab vs placebo/interferon: evidence table

	Methodology	Patient characteristics	Intervention(s)	Results critical outcomes	Results important other outcomes	Critical appraisal
EORTC 18071 Eggermont 2015 Eggermont 2019 Coens 2017	• RCT • Funding: BMS • Setting: 19 centres in North America, Europe, Australia • Sample size: N=951 • Duration: 2008-2011	• ≥ 18 y.o. • Primary cutaneous melanoma metastatic to lymph nodes only • Stage IIIA, IIIB, IIIC with no in-transit metastasis • Completely excised with adequate surgical margins + complete regional lymphadenectomy	IV ipilimumab 10mg/kg every 3 weeks OR IV placebo every 3 weeks	• OS: HR 0.73 (95%CI 0.60-0.89) • 7-year OS rate was 60.0% vs 51.3% • Grade 3-4 AEs during treatment: 54% vs 25% • QoL: statistically significant treatment effect on global health status score, but the observed differences remain lower than the threshold for clinical relevance • Median HRQoL scores differed by more than 10 points at week 10 between treatment groups for diarrhoea and insomnia. In general, worse scores were reported in the ipilimumab group compared with the placebo group, which peaked around week 10, for most other symptom and	• RFS: HR 0.75 (95%CI 0.63-0.88) Median RFS 26.1 vs 17.1 months 7-y RFS 39.2 vs 30.9% • DMFS: HR 0.76 (95%CI 0.64-0.90) • 1% of participants died because of drug-related adverse events	Low risk of bias



	Methodology	Patient characteristics	Intervention(s)	Results critical outcomes	Results important other outcomes	Critical appraisal
				functioning scales, but none of these exceeded the clinically relevant threshold		
191Intergroup E1609 Tarhini 2019 McLouth 2023	- RCT - Funding: National Cancer Institute, BMS - Setting: 850 sites in USA and Canada - Sample size: N=1670 - Duration: 2011-2014	- Adult patients with completely resected melanoma of cutaneous or unknown origin, stage IIIB, IIIC or IV - Patients with stage IIIB or IIIC should have had complete lymph node dissection	IV ipilimumab 3mg/kg every 3 weeks (max 60 weeks) OR IV ipilimumab 10mg/kg every 3 weeks (max 60 weeks) OR High-dose interferon alfa (20 million units/m ² of body surface area per day, 5 days a week during induction phase) (max 52 weeks)	Ipi3 vs interferon - OS: HR 0.78 (95.6% RCI 0.61-0.99) - AEs ≥ grade 3: 38.6%(95%CI 34.3-42.9%) with Ipi3 vs 78.8% (95%CI 75.1-82.3%) Ipi10 vs interferon - OS : HR 0.88 (95.6%CI 0.69-1.12) Ipi3 vs Ipi10 (exploratory analysis) - OS: no significant differences - AEs ≥ grade 3: 28.5% (95%CI 24.6-32.6%) vs 46.3% (95%CI 41.9-50.8%) for Ipi3 and Ipi10 QoL - At 3 months, better overall HRQoL in Ipi arms compared to interferon; no significant	Ipi3 vs interferon - RFS: HR 0.85 (99.4% CI 0.66-1.09) Ipi10 vs interferon - RFS: HR 0.84 (99.4% CI 0.65-1.09) Ipi3 vs Ipi10 (exploratory analysis) - RFS: no significant differences	Low risk of bias

	Methodology	Patient characteristics	Intervention(s)	Results critical outcomes	Results important other outcomes	Critical appraisal
				differences between Ipi3 and Ipi10 - GI symptoms: at 3 months worse scores on the FACOT-D diarrhoea subscale in the Ipi arms - PROs: a higher proportion of patients on <interferon and ipi10 reported worsening treatment bother at 3 months compared to ipi3.		

Table 43 – Nivolumab vs placebo: evidence table

	Methodology	Patient characteristics	Intervention(s)	Results critical outcomes	Results important other outcomes	Critical appraisal
IMMUNED Zimmer 2020 Livingstone 2022 (Schadendorf 2022)	- RCT - Funding: BMS - Setting: 20 academic centres in Germany - Sample size: N=167 - Duration: 2015-2018	Stage IV cutaneous or unknown primary melanoma with no evidence of disease after surgery or radiotherapy	IV nivolumab 1mg/kg + IV Ipilimumab 3mg/kg every 3 weeks (induction phase) followed by nivolumab every 2 weeks OR IV nivolumab 1mg/kg + ipilimumab-matching placebo every 3 weeks (induction phase) followed by nivolumab every 2 weeks	Nivolumab + Ipi vs placebo - OS HR 0.41 (95%CI 0.17-0.99) Nivolumab vs placebo - OS: HR 0.75 (95%CI 0.36-1.56) Nivolumab + ipi vs nivolumab - OS: HR 0.55 (95%CI 0.22-1.38)	Nivolumab + Ipi vs placebo - RFS: HR 0.25 (97.5%CI 0.13-0.48) Nivolumab vs placebo - RFS: HR 0.60 (97.5%CI 0.36-1.00) Nivolumab + ipi vs nivolumab (exploratory analysis)	Low risk of bias



	Methodology	Patient characteristics	Intervention(s)	Results critical outcomes	Results important other outcomes	Critical appraisal
			OR Nivolumab-matching and ipilimumab- matching placebo	Grade 3-4 treatment-related AEs: 71% (95%CI 57-82%) in the Nivolumab-Ipi group, 27% (95%CI 16-40%) in the nivolumab group and 6% (95%CI 1-166%) in the placebo group	RFS: HR 0.41 (97.5%CI 0.22-0.78)	
Checkmate 76K Kirkwood 2023	- RCT - Funding: not reported - Setting: 129 sites in 20 countries worldwide - Sample size: N=986 - Duration: 2019-2021	Resected stage IIB/C melanoma	Adjuvant Nivolumab OR Placebo	- OS: not reported - Grade 3-4 AEs: 10.3% vs 2.3% 1 treatment-related death in the nivolumab group.	- RFS: HR 0.42 (95%CI 0.30-0.59) 12-month RFS rate 89% (95%CI 85.6-91.6%) vs 79.4% (95%CI 73.5-84.1)	Low risk of bias

Table 44 – Pembrolizumab vs placebo/interferon: evidence table

	Methodology	Patient characteristics	Intervention(s)	Results critical outcomes	Results important other outcomes	Critical appraisal
EORTC 1325-MG/KEYNOTE-054) Eggermont 2022 Eggermont 2021 Bottomley 2021 Buhner 2024	- RCT - Funding: Merck Sharp & Dohme - Setting: 123 academic centres in 23 countries - Sample size: N=1019 - Duration: 2015-2016	Adult patients with resected cutaneous melanoma with metastasis to regional lymph nodes (stage IIIA, IIIB or IIIC)	IV pembrolizumab 200mg every 3 weeks during 12 months OR placebo	- OS: not reported - HRQoL during treatment: difference in average score was -1 to 1 points during and -2 to 2 points after treatment (below clinical relevance threshold) - Long-term HRQoL (between 108	5 years RFS: 55.4% (95%CI 50.8-59.8%) vs 38.3% (95%CI 33.9-42.7%) HR 0.61 (95%CI 0.51-0.72) - DMFS: HR 0.60 (95%CI 0.49-0.43)	Low risk of bias

	Methodology	Patient characteristics	Intervention(s)	Results critical outcomes	Results important outcomes	Critical appraisal
				weeks and 48 months after randomisation): no clinically relevant differences		
KEYNOTE-716 Luke 2024 Luke 2022 Schadendorf 2024	• RCT • Funding: merck Sharp & Dohme • Setting: 160 academic centres in 16 countries • Sample size: N=1182 • Duration: 2018-2020	• Patients who are 12 y or older, with newly diagnosed completely resected (including at least 1 sentinel LN) cutaneous melanoma without regional lymph node involvement: stage IIB (T3b or T4a) or stage IIC	IV pembrolizumab 200mg every 3 weeks during 12 months OR placebo	• OS: not reported • QoL: not reported • Grade 3-4 treatment-related AEs: 17.2% vs 5.1%	• RFS: HR 0.62 (95%CI 0.49-0.79) • DMFS: HR 0.59 (95%CI 0.44-0.79)	Low risk of bias (but fixed block sizes)
SWOG S4104 Unger 2023 Grossmann 2022	• RCT • Funding: NIH/NCI and MSD • Setting: 211 sites in USA, Canada and Ireland • Sample size: N=1301 • Duration:	• Patients with completely resected melanoma at high risk of recurrence (stage IIIA(N2a), IIB, IIIC, IV)	Adjuvant pembrolizumab OR High-dose interferon or ipilimumab (physician/patient choice)	• OS: HR 0.82 (96.3%CI 0.61-1.09) • Grade 3 or higher AEs: 17% with pembrolizumab, 43% ipilimumab, 65% with interferon • QoL: Differences were in favour of pembrolizumab at each assessment time and exceeded the clinically meaningful difference (except cycle 9)	• RFS: HR 0.76 (99.62%CI 0.59-0.99)	Low risk of bias



Table 45 – Nivolumab vs Ipilimumab: evidence table

	Methodology	Patient characteristics	Intervention(s)	Results critical outcomes	Results important other outcomes	Critical appraisal
Checkmate 238 Ascierto 2020 Ascierto 2023 Weber 2017	- RCT - Funding: BMS and Ono Pharmaceutical - Setting: 130 academic centres in 25 countries - Sample size: N=906 - Duration: 2015	Patients at least 15y.o. completely resected stage IIIB, IIIC or IV non-ocular melanoma	IV Nivolumab 3mg/kg every 2 weeks (induction and then every 12 weeks) OR IV Ipilimumab 10mg/kg every 3 weeks (induction) and then every 12 weeks Each arm with matching placebo	- OS: 71% (95%CI 66-75%) with nivolumab vs 69% (95%CI 64-63%) with ipilimumab HR 0.89 (95%CI 0.70-1.14) - QoL: not reported - Grade 3-4 AEs: 17.5% with nivolumab vs 40.4% with ipilimumab	- RFS: HR 0.71 (95%CI 0.46-0.56.3%) RFS at 4 years 51.7% (95%CI 46.8-56.3%) vs 41.2% (95%CI 36.4-45.9) - DMFS: HR 0.79 (95%CI 0.63-0.99)	Low risk of bias

Table 46 – Nivolumab + ipilimumab vs nivolumab monotherapy: evidence table

	Methodology	Patient characteristics	Intervention(s)	Results critical outcomes	Results important other outcomes	Critical appraisal
Checkmate 915 Weber 2022 Long 2021	- RCT - Funding: BMS - Setting: 123 centres in 19 countries - Sample size: N=1844 - Duration: 2017-2018	Patients ≥ 12 y.o. with completely resected stage IIIB-D or IV melanoma. Complete lymph node dissection not required.	Nivolumab 240mg every 2 weeks + ipilimumab 1mg/kg every 6 weeks OR Nivolumab 480mg every 4 weeks + appropriate placebos	- OS: HR 1.09 (95%CI 0.80-1.32) - QoL: HRQoL in both treatment groups remained within the cutoff for the clinically defined minimally important difference. - Grade 3- treatment related AEs were reported in 32.6% in the combination group vs 12.8% in the monotherapy group	- RFS: HR 0.92 (95%CI 0.77-1.09) - DMFS: HR 1.01 (95%CI 0.83-1.23)	Low risk of bias

Table 47 – Adjuvant vemurafenib vs placebo: evidence table

	Methodology	Patient characteristics	Intervention(s)	Results outcomes critical	Results important other outcomes	Critical appraisal
BRIM8 Maio 2018(Maio 2018) Schadendorf 2019(Schadendorf 2019)	• RCT • Funding: F Hoffman-La Roche • Setting: 124 centres, worldwide • Sample size: N=498 • Duration: 2012-2015	• completely resected cutaneous melanoma, BRAF-V600 mutation positive; Cohort 1: stage IIC-IIIB; Cohort 2: stage IIIC	Oral vemurafenib (960mg twice daily) during 1 year OR placebo	OS Cohort 1: HR 0.60 (95%CI 0.32-1.11) Cohort 2: HR 0.95 (95%CI 0.50-1.79) All patients: HR 0.76 (95%CI 0.49-1.18) QoL Treatment is one of the independent factors associated with changes in global health status/quality of life. A clinically meaningful decline in QoL and functional scales (except cognitive function) was seen during treatment. SAE (Gr 3-4) 57% with vemurafenib vs 15% with placebo	DFS Cohort 1: HR 0.54 (95%CI 0.37-0.78)* Cohort 2: HR 0.80 (95%CI 0.54-1.18) All patients: HR 0.65 (0.50-0.85)* *due to hierarchical testing, these analyses cannot be considered statistically significant.	Low risk of bias, but high rate of consent withdrawal, final OS analysis not published.



Table 48 – Adjuvant dabrafenib + trametinib vs placebo: evidence table

	Methodology	Patient characteristics	Intervention(s)	Results critical outcomes	Results important other outcomes	Critical appraisal
COMBI-AD Long 2017(Long 2017) Schadendorf 2019(Schadendorf 2019) Dummer 2020(Dummer 2020) Long 2024(Long 2024)	• RCT • Funding: GlaxoSmithKline + Novartis • Setting: 169 sites in 26 countries • Sample size: N=870 • Duration: 2013-2014	• Completely resected stage IIIA (limited to lymph-node metastasis of >1mm), IIIB or IIIC cutaneous melanoma with BRAF V600E or V600K mutations • All patients had complete lymphadenectomy	Oral dabrafenib (150mg twice daily) plus trametinib (2mg once daily) during 12 months OR Two matched placebos	OS 7-year survival 73% (95%CI 68-77) with adjuvant dabrafenib + trametinib vs 66% (95%CI 62-71)with placebo; HR 0.80 (95%CI 0.62-1.01) BRAF V600E mutation: HR 0.75 (95%CI 0.58-0.96) BRAF 600K mutation : HR 1.95 (95%CI 0.84-4.50) QoL No significant differences between groups during and after treatment based on EQ-5D-3L. At 12 months, a higher proportion of patients with adjuvant dabrafenib plus trametinib reported problems in mobility (15% vs 8%) and usual activities (19 % vs 13%), a higher proportion in the placebo group reported problems in anxiety or depression (27% vs 22%) SAE (Gr 3-4) SAEs occurred in 36% in the combination-therapy group and in 10% in the placebo group.	RFS HR 0.52 (95%CI 0.43-0.63) 5-year RFS was 52% (95%CI 48-58) in the treated group and 36% (95%CI 32-41) in the placebo group. 10-year RFS was 48% in the treated group and 32% in the placebo group.	Low risk of bias

Table 49 – Neoadjuvant treatment studies: evidence table

	Methodology	Patient characteristics	Intervention(s)	Results critical outcomes	Results important other outcomes	Critical appraisal
OpACIN Blank 2018 Rozeman 2021 Lucas 2023 Versluis 2023	- RCT - Funding: Bristol-Myers Squibb - Setting: single centre, the Netherlands - Sample size: N=20 - Duration: 2015-2016	Patients with palpable stage III melanoma	4 courses ipilimumab 3mg/kg + nivolumab 1mg/kg pre-surgery: 2 courses pre-operatively and 2 courses post-operatively OR 4 courses ipilimumab 3mg/kg + nivolumab 1mg/kg post-operatively	OS - 6-year OS was 90% (95%CI 73-100%) in the neoadjuvant arm and 70% (95%CI 47-100%) in the adjuvant arm QoL Not reported Grade 3-4 events - grade 3-4 events in 9/10 pts in each arm - 2 pts in each arm developed clinically severe treatment related adverse events (steven-Johnson, severe colitis, polyradiculitis, diabetes type I) - 8 pts need chronic hormonal replacement therapy	EFS 6-year EFS was 60% (95%CI 36-100%) in both arms.	Unclear risk of bias
NADINA Blank 2024	- RCT - Funding: Bristol Meyer Squid and multiple grants from NHMRC - Setting: multicentre trial in the Netherlands and Australia	- Pts with resectable, macroscopic stage III cutaneous or acral melanoma or melanoma of unknown primary - At least one pathologically proven lymph-node metastasis	<u>Neoadjuvant arm:</u> 2 cycles of 80mg ipilimumab plus 240mg nivolumab followed by surgery and, in patients who had pathological partial response or nonresponse, adjuvant dabrafenib plus trametinib for 46 weeks	OS Not (yet) reported QoL Not (yet) reported Grade 3-4 events Grade ≥ 3 AEs 47.2% in neoadjuvant group and 34.1% in adjuvant group Surgery-related Grade ≥ 3 AEs 14.1% and	EFS Overall adjusted HR 0.32 (99.9%CI 0.15-0.66) (note: only melanoma or treatment related death taken into account as an event)	Low risk of bias



	- Sample size: 423 - Duration: 2021-2023		or 11 cycles adjuvant nivolumab <u>Adjuvant</u> arm: therapeutic lymph node dissection followed by 12 cycles of adjuvant nivolumab	14.4% in neoadjuvant and adjuvant group respectively. In neoadjuvant group Grade ≥ 3 AEs in 23.1% during first 12 weeks. Serious AEs in 36.3% and 24.0% in neoadjuvant and adjuvant group respectively.		
SWOG S1801 Patel 2022 Lowe 2023 Patel 2023	- RCT - Funding: research grants from national cancer institute USA and MSD - Setting: multicentre study USA - Sample size: 313 - Duration: 2019-2022	- Cutaneous, acral or mucosal melanoma, clinically detectable and measurable according to RESIST, stage IIIB-IIID or oligometastatic resectable stage IV (8th edition) - Histological confirmation with non-excisional biopsy	<u>Neoadjuvant</u>: 3 cycles of pembrolizumab (200mg) before surgery, followed by surgery and 15 cycles of pembrolizumab after surgery OR <u>Adjuvant</u>: 18 doses of post-operative pembrolizumab (200mg)	OS HR 0.63 (95%CI 0.32-1.24) QoL Not (yet) reported Grade 3-4 events Incidence of grade 3 AEs or higher during adjuvant therapy was similar in both groups (12% and 14% in neoadjuvant and adjuvant group respectively). Grade 3-4 events related to surgery was 7% and 4% respectively.	EFS HR 0.58 (95%CI 0.39-0.87) 2-year EFS was 72% (95%CI 64-80%) in the neoadjuvant group and 49% (95%CI 41-59%) in the adjuvant group (note: all events that occurred before the start of adjuvant therapy were assigned an event date of 84 days)	Low risk of bias

Appendix 6.4. Summary tables GRADE

Appendix 6.4.1. Ipilimumab vs placebo

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Ipilimumab	Placebo/interferon alfa	Relative (95% CI)	Absolute (95% CI)		
Overall survival												
1	RCT	not serious	not serious	not serious	serious ^{1 c}	none	666	676	HR 0.75 (0.64, 0.87)	Resected Stage IV, 4-y OS: 63% with placebo, 71% with ipilimumab (95%CI 66%-76%)	⊕⊕⊕ ○ MODERATE	CRITICAL
Quality of Life: 10 weeks												
1	RCT	not serious	not serious	not serious	serious ²	none	475	476		Observed difference in mean global health at week 10: 7.89 points (95% CI 4.93-10.85)	⊕⊕⊕ ○ MODERATE	CRITICAL
Serious adverse events												
1	RCT	not serious	not serious	not serious	not serious	none	471	474	RR 2.17 (1.81-2.59)	54% of patients had SAE with ipilimumab vs 25% with placebo	⊕⊕⊕⊕ HIGH	IMPORTANT
Recurrence-free survival												
1	RCT	not serious	not serious	not serious	serious ¹	none	475	476	HR 0.75 (95%CI 0.63-0.88)	7-year RFS, stage III: 30.9% (95%CI 26.7-35.2%) with placebo and 39.2% with ipilimumab (95%CI 34.5-43.9%)	⊕⊕⊕ ○ MODERATE	IMPORTANT

¹ Confidence includes both values smaller and larger than the clinically meaningful difference (5%).

² Confidence includes both values smaller and larger than the clinically meaningful difference (10 points).



Appendix 6.4.2. Nivolumab vs placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Nivolumab	Placebo	Relative (95% CI)	Absolute (95% CI)		
Overall survival												
2	RCT	serious ¹	not serious	not serious	serious ^{2 c}	none	59	52	HR 0.75 (0.36-1.56)	Stage 4-year OS: 63.1% (46.9-75.6%) with placebo and 72.6% (57.4-83.2%) with nivolumab	⊕⊕○ ○ LOW	CRITICAL
Quality of Life: not reported												
0												CRITICAL
Serious adverse events												
2	RCT	not serious	not serious	not serious	not serious	none	580	315	RR 1.78 (1.31-2.42)	SAE in 21.9%% with placebo and in 12.1% with nivolumab (Checkmate 76K)	⊕⊕⊕⊕ high	IMPORTANT
Recurrence-free survival												
2	RCT	not serious	not serious	not serious	not serious	none	585	316	HR 0.47 (0.35-0.62)	Stage IIB-IIC, 1-year RFS 79.4% with placebo, 89.5% (95%CI 86.4-92.1%) with nivolumab	⊕⊕⊕⊕ high	IMPORTANT

¹ OS data not (yet) published for the Checkmate-076K; ² Confidence includes both values smaller and larger than the clinically meaningful difference.

Appendix 6.4.3. Pembrolizumab vs placebo or interferon alfa/ipilimumab

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Pembrolizumab	Placebo or active control	Relative (95% CI)	Absolute (95% CI)		
Overall survival (pembrolizumab versus interferon alfa/ipilimumab)												
1	RCT	not serious	not serious	not serious	serious ^{1 c}	none	647	654	HR 0.82 (96.3%CI 0.61-1.09)	Stage IV, 4-y OS 70% with interferon/ipilimumab and 74.6% (96.3%CI 67.8%-80.4%) with pembrolizumab	⊕⊕⊕ ○ Moderate	CRITICAL
Quality of Life (pembrolizumab vs placebo)												
2	RCT	not serious	serious ²	not serious	not serious	none	1001	994	No MA	NA	⊕⊕⊕ ○ Moderate	CRITICAL
Treatment-related serious adverse events (pembrolizumab vs placebo)												
2	RCT	not serious	not serious	not serious	not serious	none	992	988	RR 3.75 (2.70-5.21)	17.2% with adjuvant pembrolizumab vs 5.1% with placebo (taken from KEYNOTE-716)	⊕⊕⊕⊕ high	IMPORTANT
Recurrence-free survival (pembrolizumab vs placebo)												
2	RCT	not serious	not serious	not serious	not serious	none	1001	994	HR 0.61 (95%CI 0.53-0.71)	Stage IIB-IIC, 3-y RFS: 63% with placebo and 75% (95%CI with 72-78%) with pembrolizumab Stage III, 5y RFS: 38% with placebo and 55% (95%CI 50-60%) with pembrolizumab	⊕⊕⊕⊕ high	IMPORTANT

¹ Confidence includes both values smaller and larger than the clinically meaningful difference. ² Although no clinically meaningful changes were seen in general HRQoL, significant differences were seen in symptom scales or responder rates and proportion of patients with non-deteriorated global health status.



Appendix 6.4.4. Nivolumab vs ipilimumab

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Nivolumab	Ipilimumab	Relative (95% CI)	Absolute (95% CI)		
Overall survival												
1	RCT	serious ¹	not serious	not serious	serious ²	none	453	453	HR 0.89 (0.70-1.14)	Stage IIIB-C, IV, 5y OS: 76% with nivolumab and 72% with ipilimumab	⊕⊕⊖ ⊖ Low	CRITICAL
Quality of Life: not reported												
0	RCT											CRITICAL
Serious adverse events												
1	RCT	not serious	not serious	not serious	not serious	none	452	453	RR 0.46 (0.39-0.55)	25.4% of pts with SAE in nivolumab group, 55.2% in the ipilimumab group	⊕⊕⊕⊕ High	IMPORTANT
Recurrence-free survival												
1	RCT	serious ¹	not serious	not serious	serious ²	none	483	453	HR 0.72 (0.72 0.60-0.86)	Stage IIIB-C, IV, 5y RFS: 76% with nivolumab and 72% with ipilimumab	⊕⊕⊖ ⊖ Low	IMPORTANT

¹ Quality of life listed as secondary outcome but not yet reported; ² Confidence includes both values smaller and larger than the clinically meaningful difference

Appendix 6.4.5. Nivolumab monotherapy vs nivolumab + ipilimumab

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Nivolumab	Nivolumab + Ipilimumab	Relative (95% CI)	Absolute (95% CI)		
Overall survival												
2	RCT	not serious	not serious	not serious	serious ¹	None	983	976	HR 1.02 (95%CI 0.76-1.36)	Stage IIIB-D, IV 2y OS: 89.8% with combination therapy and 89.6% (95%CI 86.4-92.1%) with nivolumab	⊕⊕⊕ ○ Moderate	CRITICAL
Quality of Life												
1	RCT	not serious	not serious	not serious	serious ²	none	924	920	NA	No clinically important differences	⊕⊕⊕ ○ Moderate	CRITICAL
Serious adverse events (treatment-related)												
2	RCT	not serious	not serious	not serious	not serious	none	971	973	RR 2.55 (2.13 – 3.05)	32.6% of pts with SAE in combination group, 12.8% in monotherapy group	⊕⊕⊕⊕ High	IMPORTANT
Recurrence-free survival												
2	RCT	not serious	serious ³	not serious	serious ¹	none	983	976	HR 0.92 (97.3%CI 0.77-1.09)	Stage IIIB-D, IV 2y RFS: 64.6% with combination therapy and 63.2% with nivolumab monotherapy	⊕⊕○ ○ Low	IMPORTANT

¹ Confidence includes values that mean no difference or a clinically meaningful difference for one of the treatment arms; ² Possibly clinically meaningful difference between two treatment arms at some timepoint; ³ One trial showing a clear benefit for the combination therapy, one trial doesn't



Appendix 6.4.6. Vemurafenib vs placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Vemurafenib	placebo	Relative (95% CI)	Absolute (95% CI)		
Overall survival												
1	randomised trials	Serious ¹	Not serious	Not serious	Very Serious ²	None	250	248	HR 0.76 (95%CI 0.49-1.18)	2y survival 86% with placebo, 3% higher with vemurafenib (6% higher to 3% lower)	⊕○○○ Very Low	CRITICAL
Quality of Life												
1	randomised trials	Serious ¹	Not serious	Not serious	Serious ³	None	250	248		Mean decline in the global health score of 17.4 (+/- 22.9) and 17.3 (+/- 24.1) points at days 15 and 22 of cycle 1	⊕⊕○○ Low	CRITICAL
Serious adverse events												
1	randomised trials	Serious ¹	Not serious	Not serious	Not serious	None	247	247	RR 3.81 (95%CI 2.78-5.23)	15% with placebo, 42% more with vemurafenib (27% more to 63% more)%	⊕⊕⊕○ Moderate	
Recurrence-free survival												
1	randomised trials	Serious ¹	Serious ⁴	Not serious	Serious ³	None	250	248	HR 0.65 (95%CI 0.50-0.85)	2y PFS 62% with placebo, 11% higher with vemurafenib (5% higher to 17% higher)	⊕○○○ Very Low	IMPORTANT

¹ Second planned OS analysis not published, high number of consent withdrawal

² Results include clinically significant effect and no effect and harm

³ Results include clinically significant effect and no effect

⁴ Results are inconsistent between the two cohorts and the overall results (+ no statistical power due to hierarchical approach)

Appendix 6.4.7. Dabrafenib + trametinib vs placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Dabrafenib + trametinib	placebo	Relative (95% CI)	Absolute (95% CI)		
Overall survival												
1	RCT	Not serious	Not serious	Not serious	Very Serious ¹	None	438	432	HR 0.80 (95%CI 0.62-1.01)	8y OS 71% with dabrafenib + trametinib and 65% with placebo	⊕⊕○○ Low	CRITICAL
Quality of Life												
1	RCT	Not serious	Not serious	Not serious	Not serious	None	438	432		No clinically important differences in QoL between groups	⊕⊕⊕⊕ High	CRITICAL
Serious adverse events												
1	RCT	Not serious	Not serious	Not serious	Not serious	None	435	432	RR 3.5 (95%CI 2.47-4.76)	10% with placebo, 25% more with (15% more to 38% more)%	⊕⊕⊕⊕ High	IMPORTANT
Recurrence-free survival												
1	RCT	Not serious	Not serious	Not serious	Not serious	None	438	432	HR 0.51 (95%CI 0.42-0.61)	5y-RFS 52% with adjuvant dabrafenib + trametinib and 36% with placebo	⊕⊕⊕⊕ High	IMPORTANT

¹ Confidence interval includes clinically significant effect and no effect.



Appendix 6.4.8. Neoadjuvant ipilimumab plus nivolumab

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Neoadjuvant	adjuvant	Relative (95% CI)	Absolute (95% CI)		
Overall survival												
1	RCT	not serious	not serious	not serious	very Serious ¹	none	20	20	6-y OS RR 0.33 (95%CI 0.04-2.69)	6-y OS 20% higher (29% higher to 51% lower)	⊕⊕○○ LOW	CRITICAL
Quality of Life												
0	RCT										NO EVIDENCE FROM RCTS	CRITICAL
Serious adverse events												
1 ²	RCT	not serious	not serious	not serious	serious ³	none	212	211	RR 1.38 (95%CI 1.09-1.75)	% pts with ≥ Gr3-5 AE 13% more (3 to 26% more)	⊕⊕⊕○ MODERATE	IMPORTANT
Event-free survival												
1 ³	RCT	not serious	not serious	not serious	not serious	None ⁴	212	211	HR 0.32 (99.9%CI 0.15-0.66)		⊕⊕⊕⊕ HIGH	IMPORTANT

¹Very small sample size; CI includes considerable benefit and considerable harm. ²Results OpACIN not taken into account as a high-dose schedule of ipilimumab is used in that trial. ³The CI contains a minimal and a clinically important difference. ⁴In the NADINA study, only melanoma or treatment related deaths were considered as an event in the EFS analysis. As a sensitivity analysis accounting for competing risks yielded similar results; no downgrading was done.

Appendix 6.4.9. Neoadjuvant pembrolizumab

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Neoadjuvant	Adjuvant	Relative (95% CI)	Absolute (95% CI)		
Overall survival												
1	RCT	not serious	not serious	not serious	very serious ¹ _c	none	154	159	HR 0.63 (95%CI 0.32-1.24)	5-y OS stage IIIB* : 68% with adjuvant therapy; 78% (62%-88%) with neoadjuvant therapy	⊕⊕○○ LOW	CRITICAL
Quality of Life: not reported												
0											NO EVIDENCE FROM RCTS	CRITICAL
Adverse events grade 3 or higher (total number of events)												
1	RCT	not serious	not serious	not serious	Serious ²	none	154	159	RR 1.73 (1.23 – 2.43)	17 (95%CI 5 – 33) events more per 100 patients	⊕⊕⊕○ MODERATE	IMPORTANT
Recurrence-free survival												
1	randomised trials	Not serious	not serious	not serious	Serious ²	Serious: statistical bias possible ³	154	159	HR 0.58 (95%CI 0.39-0.87)	2y EFS 17% higher (5% to 27% higher)	⊕⊕○○ LOW	IMPORTANT

¹Confidence interval includes both considerable benefit and considerable harm.

²Confidence includes a minimal difference and clinically important difference.

³Statistical rule to attribute all events happening before the start of adjuvant therapy to time point 84 days

*calculated taking a 5-year survival of 68% as baseline (trial was analysed with one-sided testing)



APPENDIX 7. EVIDENCE REVIEW FOLLOW-UP

Appendix 7.1. PICO

Table 50 – Surveillance interventions to be performed during the follow-up

	Surveillance interventions to be performed during the follow-up
Objective	To define the surveillance interventions and their frequency for, the duration of and the involved HCP in the follow-up of patients who are clinically disease free after receiving curative-intent treatment.
Review question	For adult patients (≥18 years old) with stage I, II, III, or resectable IV melanoma who are clinically disease-free after receiving curative-intent treatment, which follow-up evaluation or combination of clinical follow-up, laboratory tests, and imaging are optimal and at what frequency should these evaluations be performed to improve patient outcomes?
Population	Included: adults 18 years and above with stage I, II, III or resectable IV melanoma who are clinically disease free after receiving curative-intent treatment Excluded: paediatric age; uveal, mucosal, or acral melanoma; Spizoid lesions
Intervention	Included: any surveillance intervention (e.g. clinical follow-up, laboratory tests, imaging (e.g. ultrasound, PET-CT, MRI), patient education e.g. self-examination, sun safety), or combination of interventions at any schedule. Excluded: psychosocial interventions
Comparator	Any intervention or combination compared to another intervention or combination
Outcomes	Critical: Overall survival, health-related quality of life Important: disease-free survival*, adverse events related to the intervention(s) (e.g. imaging examinations/ from follow up examinations)
Study design	Included: - Systematic reviews - Randomised controlled trials - Comparative prospective and retrospective cohort studies - If minimum sample size of 30 per group - If articles in Dutch, English and French - If at least one critical or important outcome is reported Excluded: - Descriptive (without comparison) prospective and retrospective cohort studies - Narrative reviews - Case reports - Studies presented as conference abstract only (additional results published in abstract only are included) or if no full text was available - Studies in which the primary outcome is not stated, or no data are available for calculation
Analysis	By stage

* or reported as melanoma-specific survival, progression-free survival, disease-free interval, distant metastasis-free survival, or recurrence free survival (including detection of recurrences)

Appendix 7.2. Comparison of surveillance schedules according to recent, consensus or evidence-based guidelines

The following tables compare the surveillance schedules by stage for asymptomatic patients (i.e. no evidence of disease) according to the most recent, consensus or evidenced-based guidelines. (Amaral 2025, NICE 2022, Rajagopal 2024)

Table 51 – Follow-up schedule for stage IA melanoma patients according to Ontario Health, ESMO and the NICE guidelines

Stage IA	Scientific institution	Intervention	Frequency	Duration	Setting/HCP	Level/ Grade*
Patient education	Ontario 2024	SSE + sun safety	Q6-12mo Q12mo	1-3y 4-5y	HCP	recommended
	ESMO 2025	SSE and peripheral LNs + sun safety	Regular	Lifelong	Patient	IIIA
	NICE 2022(1.9.3)	reinforcing advice about self examination + sun safety	No mention	No mention	No mention	Ensure that
Clinical F/U	Ontario 2024	History, PE of full skin and LN	Q6-12mo Q12mo	1-3y 4-5y	Dermatologist (with photo-surveillance and dermoscopy if indicated) and a surgeon or a family physician/cancer nurse specialist	recommended
	ESMO 2025	Whole body examination (III,B)	Q6mo Q12mo Q12mo	1-3y 4-10y >10y	Preferentially a dermatologist (III,B)	V,B
	NICE 2022 (1.9.11 1.9.15)	Full examination of skin and LN	2x/y	1y	HCP skilled and expertised in skin kc and LN examination with access to dermoscopy and medical photography	Consider
Laboratory examination	Ontario 2024	Routine biomarker or blood tests	NA	NA	NA	Not recommended
	ESMO 2025		NA	NA	NA	V,B
	NICE 2022		Do not	NA	NA	Do not
Imaging	Ontario 2024	Imaging	NA	NA	NA	Not recommended
	ESMO 2025	LN US	NA	NA	NA	V,B
	NICE 2022	US scan of draining nodal basin	Do not	NA	NA	Do not
	Ontario 2024	Imaging	NA	NA	NA	Not recommended
	ESMO 2025	CT (or PET-CT) of neck, thorax, abdomen, pelvis	NA	NA	NA	V,B
	NICE 2022	CE-CT scan	Do not	NA	NA	Do not
	Ontario 2024	Imaging	NA	NA	NA	Not recommended
	ESMO 2025	Brain MRI	NA	/	/	V,B
	NICE 2022	Brain CE-CT	Do not	NA	NA	Do not

*The level of evidence and the grade of recommendation mentioned in the last column apply to the previous 4 columns except for advice between brackets.



Table 52 – Follow-up recommended schedule for stage IB melanoma patients according to Ontario Health, ESMO and NICE clinical practice guidelines on cutaneous melanoma

Stage IB	Scientific institution	Intervention	Frequency	Duration	Setting	Levels/ Grade*
Patient education	Ontario 2024	SSE + sun safety	Q6-12mo Q12mo	1-3y 4-5y	HCP	recommended
	ESMO 2025	SSE and peripheral LNs + sun safety	Regular	Lifelong	No mention	IIIA
	NICE 2022 (1.9.3)	reinforcing advice about self examination + sun safety	No mention	No mention	No mention	Ensure that
Clinical F/U:	Ontario 2024	History, PE of full skin and LN	Q6-12mo Q12mo	1-3y 4-5y	Dermatologist (with photo-surveillance and dermoscopy if indicated) and a surgeon or a family physician/cancer nurse specialist	recommended
	ESMO 2025	Whole body examination (III,B)	Q3-6mo Q6mo Q12mo	1-3y 4-10y >10y	Preferentially a dermatologist (III,B)	V,B
	NICE 2022 (1.9.11 1.9.15)	Full examination of skin and LN	2x/y 1x/y	1y 2-5y	HCP skilled and expertised in skin kc and LN examination with access to dermoscopy and medical photography	Offer
Laboratory examination	Ontario 2024	Routine biomarker or blood tests	NA	NA	NA	Not recommended
	ESMO 2025		Q3-6mo	1-3y	No mention	V,B
	NICE 2022		No mention	NA	NA	
Imaging	Ontario 2024	Imaging	NA	NA	NA	Not recommended
	ESMO 2025	LN US	Q6mo	1-3y	No mention	V,B
	NICE 2022	US scan of draining nodal basin if SLNB was considered but not done	2x/y 1x/y	1y 2-3y	No mention No mention	Consider
	Ontario 2024	Imaging	NA	NA	NA	Not recommended
	ESMO 2025	CT (or PET-CT) of neck, thorax, abdomen, pelvis	NA	NA	NA	V,B
	NICE 2022	CE-CT scan	Do not	NA	NA	Do not
	Ontario 2024	Imaging	NA	NA	NA	Not recommended
	ESMO 2025	Brain MRI	NA	NA	NA	V,B
	NICE 2022	Brain CE-CT	Do not	NA	NA	Do not

*The level of evidence and the grade of recommendation mentioned in the last column apply to the all line except mentioned otherwise between brackets.

Table 53 – Follow-up recommended schedule for stage IIA melanoma patients according to Ontario Health, ESMO and NICE clinical practice guidelines on cutaneous melanoma

Stage IIA	Scientific institution	Intervention	Frequency	Duration	Setting	Grade/Level*
Patient education	Ontario 2024	SSE + sun safety	Q6-12mo Q12mo	1-3y 4-5y	HCP	recommended
	ESMO 2025	SSE and peripheral LNs + sun safety	Regular	Lifelong	Patient	IIIA
	NICE 2022 (1.9.3)	reinforcing advice about self examination + sun safety	No mention	No mention	No mention	Ensure that
Clinical F/U	Ontario 2024	History, PE of full skin and LN	Q6-12mo Q12mo	1-3y 4-5y	Dermatologist (with photo-surveillance and dermoscopy if indicated) and a surgeon or a family physician/cancer nurse specialist	recommended
	ESMO 2025	Whole body examination (III,B)	Q3-6mo Q6mo Q12mo	1-3y 4-10y >10y	Preferentially a dermatologist (III,B)	V,B
	NICE 2022 (1.9.11 1.9.15)	Full examination of skin and LN	2x/y 1x/y	1-2y 3-5y	HCP skilled and expertised in skin kc and LN examination with access to dermoscopy and medical photography	Offer
Laboratory examination	Ontario 2024	Routine biomarker or blood tests	NA	NA	NA	Not recommended
	ESMO 2025		Q3-6mo	1-3y	No mention	V,B
	NICE 2022		No mention	NA	NA	
Imaging	Ontario 2024	Imaging	NA	NA	NA	Not recommended
	ESMO 2025	LN US	Q6mo	1-3y	No mention	V,B
	NICE 2022	US scan of draining nodal basin if SLNB was considered but not done	2x/y 1x/y	1-2y 3y	No mention No mention	Consider
	Ontario 2024	Imaging	NA	NA	NA	Not recommended
	ESMO 2025	CT or PET-CT of neck, thorax, abdomen, pelvis	NA	NA	NA	V,B
	NICE 2022 (1.9.7, 1.9.8, 1.9.12)	CE-CT scan	No mention	NA	NA	
	Ontario 2024	Imaging	NA	NA	NA	Not recommended
	ESMO 2025		NA	NA	NA	V,B
	NICE 2022	Brain CE-CT	No mention	NA	NA	

*The level of evidence and the grade of recommendation mentioned in the last column apply to the all line except mentioned otherwise between brackets.



Table 54 – Follow-up recommended schedule for stage IIB melanoma patients according to Ontario Health, ESMO and NICE clinical practice guidelines on cutaneous melanoma

Stage IIB	Scientific institution	Intervention	Frequency	Duration	Setting	Grade/Level*
Patient education	Ontario 2024	SSE + sun safety	Q3-6mo Q6mo	1-3y 4-5y	HCP	recommended
	ESMO 2025	SSE and peripheral LNs + sun safety	Regular	Lifelong	Patient	IIIA
	NICE 2022 (1.9.3)	reinforcing advice about self examination + sun safety	No mention	No mention	No mention	Ensure that
Clinical F/U:	Ontario 2024	History, PE of full skin and LN	Q3-6mo Q6mo	1-3y 4-5y	Dermatologist (with photo-surveillance and dermoscopy if indicated) and a surgeon or a medical oncologist/cancer nurse specialist	recommended
	ESMO 2025	Whole body examination (III,B)	Q3mo Q6mo Q12mo	1-3y 4-10y >10y	Preferentially a dermatologist (III,B)	V,B
	NICE 2022 (1.9.11 1.9.15)	Full examination of skin and LN	4x/y 2x/y 1x/y	1-2y 3y 4-5y	HCP skilled and expertised in skin kc and LN examination with access to dermoscopy and medical photography	Offer
Laboratory examination	Ontario 2024	Routine biomarker or blood tests	NA	NA	NA	Not recommended
	ESMO 2025		Q3-6mo	1-3y	No mention	V,B
	NICE 2022		No mention	NA	NA	
Imaging	Ontario 2024	LN US	No mention	NA	NA	
	ESMO 2025	LN US	Q3-6mo	1-3y	No mention	V,B
	NICE 2022	US scan of draining nodal basin if SLNB was considered but not done Alternate US scan with CE-CT scan	2x/y	1-3y	No mention	Consider
	Ontario 2024	CT or PET/CT scans	Q6-12mo Q12mo	1-3y 4-5y	No mention	Recommended
	ESMO 2025	CT or PET-CT of neck, thorax, abdomen, pelvis	Q6mo	1-3y	No mention	V,B
	NICE 2022 (1.9.7, 1.9.8, 1.9.12)	Whole-body CT scan(thorax, abdomen, pelvis – neck if indicated) Alternate CE-CT scan with US scan Whole body MRI if pregnancy or less than 25y	2x/y 2x/y 1x/y	1-2y 3y 4-5y	No mention	Consider
	NICE 2022 (1.9.13)	PET-CT	NA	NA	NA	Do not routinely
	Ontario 2024	Prefer Brain MRI or, instead, head CT after discussing with patient	Q12mo	1-5y		Weakly recommended
	ESMO 2025 MRI (no CT)	Brain MRI	Q6mo	1-3y	No mention	V,B
	NICE 2022 (1.9.7, 1.9.8, 1.9.12)	Brain CT scan Alternate CE-CT scan with US scan Brain MRI if pregnancy or less than 25y	2x/y 2x/y 1x/y	1-2y 3y 4-5y	No mention	Consider

*The level of evidence and the grade of recommendation mentioned in the last column apply to the all line except mentioned otherwise between brackets.

Table 55 – Follow-up recommended schedule for stage IIC melanoma patients according to Ontario Health, ESMO and NICE clinical practice guidelines on cutaneous melanoma

Stage IIC	Scientific institution	Intervention	Frequency	Duration	Setting	Grade/Level*
Patient education	Ontario 2024	SSE + sun safety	Q3-6mo Q6mo	1-3y 4-5y	HCP	recommended
	ESMO 2025	SSE and peripheral LNs + sun safety	Regular	Lifelong	Patient	IIIA
	NICE 2022 (1.9.3)	reinforcing advice about self examination + sun safety	No mention	No mention	No mention	Ensure that
Clinical F/U:	Ontario 2024	History, PE of full skin and LN	Q3-6mo Q6mo	1-3y 4-5y	Dermatologist (with photo-surveillance and dermoscopy if indicated) and a surgeon or a medical oncologist/cancer nurse specialist	recommended
	ESMO 2025	Whole body examination (III,B)	Q3mo Q6mo Q12mo	1-3y 4-10y >10y	Preferentially a dermatologist (III,B)	V,B
	NICE 2022 (1.9.11 1.9.15)	Full examination of skin and LN	4x/y 2x/y 1x/y	1-2y 3y 4-5y	HCP skilled and expertised in skin kc and LN examination with access to dermoscopy and medical photography	Offer
Laboratory examination	Ontario 2024	Routine biomarker or blood tests	NA	NA	NA	Not recommended
	ESMO 2025		Q3-6mo	1-3y	No mention	V,B
	NICE 2022		No mention	NA	NA	
Imaging	Ontario 2024	LN US	No mention	NA	NA	
	ESMO 2025	LN US	Q3-6mo	1-3y	No mention	V,B
	NICE 2022	US scan of draining nodal basin if SLNB was considered but not done Alternate US scan with CE-CT scan	2x/y	1-3y	No mention	Consider
	Ontario 2024	CT or PET/CT scans	Q6-12mo Q12mo	1-3y 4-5y	No mention	Recommended
	ESMO 2025	CT or PET-CT of neck, thorax, abdomen, pelvis	Q6mo	1-3y	No mention	V,B
	NICE 2022 (1.9.7, 1.9.8, 1.9.12)	Whole-body CT scan(thorax, abdomen, pelvis – neck if indicated) Alternate CE-CT scan with US scan Whole body MRI if pregnancy or less than 25y	2x/y 2x/y 1x/y	1-2y 3y 4-5y	No mention	Offer
	NICE 2022 (1.9.13)	PET-CT	NA	NA	NA	Do not routinely
	Ontario 2024(MRI)	Prefer Brain MRI or, instead, head CT after discussing with patient	Q12mo	1-5y		Weakly recommended
	ESMO 2025(V,B) MRI (no CT)	Brain MRI	Q6mo	1-3y	No mention	V,B
	NICE 2022 (1.9.7, 1.9.8, 1.9.12)	Brain CT scan Alternate CE-CT scan with US scan Brain MRI if pregnancy or less than 25y	2x/y 2x/y 1x/y	1-2y 3y 4-5y	No mention	Offer

*The level of evidence and the grade of recommendation mentioned in the last column apply to the all line except mentioned otherwise between brackets.



Table 56 – Follow-up recommended schedule for stage IIIA melanoma patients according to Ontario Health, ESMO and NICE clinical practice guidelines on cutaneous melanoma

Stage IIIA	Scientific institution	Intervention	Frequency	Duration	Setting	Grade/Level*
Patient education	Ontario 2024	SSE + sun safety	Q3-6mo Q6mo	1-3y 4-5y	HCP	recommended
	ESMO 2025	SSE and peripheral LNs + sun safety	Regular	Lifelong	Patient	IIIA
	NICE 2022 (1.9.3)	reinforcing advice about self examination + sun safety	No mention	No mention	No mention	Ensure that
Clinical F/U:	Ontario 2024	History, PE of full skin and LN	Q3-6mo Q6mo	1-3y 4-5y	Dermatologist (with photo-surveillance and dermoscopy if indicated) and a surgeon or a medical oncologist/cancer nurse specialist	recommended
	ESMO 2025	Whole body examination (III,B)	Q3mo Q6mo Q12mo	1-3y 4-10y >10y	Preferentially a dermatologist (III,B)	V,B
	NICE 2022 (1.9.11 1.9.15)	Full examination of skin and LN	4x/y 2x/y	1-3y 4-5y	HCP skilled and expertised in skin kc and LN examination with access to dermoscopy and medical photography	Offer
Laboratory examination	Ontario 2024	Routine biomarker or blood tests	NA	NA	NA	Not recommended
	ESMO 2025		Q3-6mo	1-3y	No mention	V,B
	NICE 2022		No mention	NA	NA	
Imaging	Ontario 2024	positive SLN without CLND, US of draining nodal basin	4-6mo 6mo	1-3 4-5	NA	recommended
	ESMO 2025	LN US	Q3-6mo	1-3y	No mention	V,B
	NICE 2022	US scan of draining nodal basin if SLNB was considered but not done Alternate US scan with CE-CT scan	2x/y	1-3y	No mention No mention	Consider
	Ontario 2024	CT or PET/CT scans	Q6-12mo Q12mo	1-3y 4-5y	No mention	Recommended
	ESMO 2025	CT or PET-CT of neck, thorax, abdomen, pelvis	Q6mo	1-3y	No mention	V,B
	NICE 2022 (1.9.7, 1.9.8, 1.9.12)	Whole-body CT scan(thorax, abdomen, pelvis – neck if indicated) Alternate CE-CT scan with US scan Whole body MRI if pregnancy or less than 25y	2x/y 1x/y	1-3y 4-5y	No mention	Offer
	NICE 2022 (1.9.13)	PET-CT	NA	NA	NA	Do not routinely
	Ontario 2024(MRI)	Prefer Brain MRI or, instead, head CT after discussing with patient	Q12mo	1-5y		Weakly recommended
	ESMO 2025 MRI (no CT)	Brain MRI	Q6mo	1-3y	No mention	V,B
	NICE 2022 (1.9.7, 1.9.8, 1.9.12)	Brain CT scan Alternate CE-CT scan with US scan Brain MRI if pregnancy or less than 25y	2x/y 1x/y	1-3y 4-5y	No mention	Offer

*The level of evidence and the grade of recommendation mentioned in the last column apply to the all line except mentioned otherwise between brackets.

Table 57 – Follow-up recommended schedule for stage IIIB melanoma patients according to Ontario Health, ESMO and NICE clinical practice guidelines on cutaneous melanoma

Stage IIIB	Scientific institution	Intervention	Frequency	Duration	Setting	Grade/Level*
Patient education	Ontario 2024	SSE + sun safety	Q3-6mo Q6mo	1-3y 4-5y	HCP	recommended
	ESMO 2025	SSE and peripheral LNs + sun safety	Regular	Lifelong	Patient	IIIA
	NICE 2022 (1.9.3)	reinforcing advice about self examination + sun safety	No mention	No mention	No mention	Ensure that
Clinical F/U:	Ontario 2024	History, PE of full skin and LN	Q3-6mo Q6mo	1-3y 4-5y	Dermatologist (with photo-surveillance and dermoscopy if indicated) and a surgeon or a medical oncologist/cancer nurse specialist	recommended
	ESMO 2025	Whole body examination (III,B)	Q3mo Q6mo Q12mo	1-3y 4-10y >10y	Preferentially a dermatologist (III,B)	V,B
	NICE 2022 (1.9.11 1.9.15)	Full examination of skin and LN	4x/y 2x/y	1-3y 4-5y	HCP skilled and expertised in skin kc and LN examination with access to dermoscopy and medical photography	Offer
	Ontario 2024	Routine biomarker or blood tests	NA	NA	NA	Not recommended
Laboratory examination	ESMO 2025		Q3-6mo	1-3y	No mention	V,B
	NICE 2022		No mention	NA	NA	
	Ontario 2024	positive SLN without CLND, US of draining nodal basin	4-6mo 6mo	1-3 4-5	NA	recommended
Imaging	ESMO 2025	LN US	Q3-6mo	1-3y	No mention	V,B
	NICE 2022	US scan of draining nodal basin if SLNB was considered but not done Alternate US scan with CE-CT scan	2x/y	1-3y	No mention No mention	Consider
	Ontario 2024	CT or PET/CT scans	Q6-12mo Q12mo	1-3y 4-5y	No mention	Recommended
	ESMO 2025	CT or PET-CT of neck, thorax, abdomen, pelvis	Q6mo	1-3y	No mention	V,B
	NICE 2022 (1.9.7, 1.9.8, 1.9.12)	Whole-body CT scan(thorax, abdomen, pelvis – neck if indicated) Alternate CE-CT scan with US scan Whole body MRI if pregnancy or less than 25y	2x/y 1x/y	1-3y 4-5y	No mention	Offer
	NICE 2022 (1.9.13)	PET-CT	NA	NA	NA	Do not routinely
	Ontario 2024(MRI)	Prefer Brain MRI or, instead, head CT after discussing with patient	Q12mo	1-5y		Weakly recommended
	ESMO 2025 MRI (no CT)	Brain MRI	Q6mo	1-3y	No mention	V,B
	NICE 2022 (1.9.7, 1.9.8, 1.9.12)	Brain CT scan Alternate CE-CT scan with US scan Brain MRI if pregnancy or less than 25y	2x/y 1x/y	1-3y 4-5y	No mention	Offer

*The level of evidence and the grade of recommendation mentioned in the last column apply to the all line except mentioned otherwise between brackets.



Table 58 – Follow-up recommended schedule for stage IIIC melanoma patients according to Ontario Health, ESMO and NICE clinical practice guidelines on cutaneous melanoma

Stage IIIC	Scientific institution	Intervention	Frequency	Duration	Setting	Grade/Level*
Patient education	Ontario 2024	SSE + sun safety	Q3-6mo Q6mo	1-3y 4-5y	HCP	recommended
	ESMO 2025	SSE and peripheral LNs + sun safety	Regular	Lifelong	Patient	IIIA
	NICE 2022 (1.9.3)	reinforcing advice about self examination + sun safety	No mention	No mention	No mention	Ensure that
Clinical F/U:	Ontario 2024	History, PE of full skin and LN	Q3-6mo Q6mo	1-3y 4-5y	Dermatologist (with photo-surveillance and dermoscopy if indicated) and a surgeon or a medical oncologist/cancer nurse specialist	recommended
	ESMO 2025	Whole body examination (III,B)	Q3mo Q6mo Q12mo	1-3y 4-10y >10y	Preferentially a dermatologist (III,B)	V,B
	NICE 2022 (1.9.11 1.9.15)	Full examination of skin and LN	4x/y 2x/y	1-3y 4-5y	HCP skilled and expertised in skin kc and LN examination with access to dermoscopy and medical photography	Offer
Laboratory examination	Ontario 2024	Routine biomarker or blood tests	NA	NA	NA	Not recommended
	ESMO 2025		Q3-6mo	1-3y	No mention	V,B
	NICE 2022		No mention	NA	NA	
Imaging	Ontario 2024	positive SLN without CLND, US of draining nodal basin	4-6mo 6mo	1-3 4-5	NA	recommended
	ESMO 2025	LN US	Q3-6mo	1-3y	No mention	V,B
	NICE 2022	US scan of draining nodal basin if SLNB was considered but not done Alternate US scan with CE-CT scan	2x/y	1-3y	No mention No mention	Consider
	Ontario 2024	CT or PET/CT scans	Q6-12mo Q12mo	1-3y 4-5y	No mention	Recommended
	ESMO 2025	CT or PET-CT of neck, thorax, abdomen, pelvis	Q6mo	1-3y	No mention	V,B
	NICE 2022 (1.9.7, 1.9.8, 1.9.12)	Whole-body CT scan(thorax, abdomen, pelvis – neck if indicated) Alternate CE-CT scan with US scan Whole body MRI if pregnancy or less than 25y	2x/y 1x/y	1-3y 4-5y	No mention	Offer
	NICE 2022 (1.9.13)	PET-CT	NA	NA	NA	Do not routinely
	Ontario 2024	Prefer Brain MRI or, instead, head CT after discussing with patient	Q12mo	1-5y		Weakly recommended
	ESMO 2025	Brain MRI	Q6mo	1-3y	No mention	V,B
	NICE 2022 (1.9.7, 1.9.8, 1.9.12)	Brain CT scan Alternate CE-CT scan with US scan Brain MRI if pregnancy or less than 25y	2x/y 1x/y	1-3y 4-5y	No mention	Offer

*The level of evidence and the grade of recommendation mentioned in the last column apply to the all line except mentioned otherwise between brackets.

Table 59 – Follow-up recommended schedule for stage IIID melanoma patients according to Ontario Health, ESMO and NICE clinical practice guidelines on cutaneous melanoma

Stage IIID	Scientific institution	Intervention	Frequency	Duration	Setting	Grade/Level*
Patient education	Ontario 2024	SSE + sun safety	Q3-6mo Q6mo	1-3y 4-5y	HCP	recommended
	ESMO 2025	SSE and peripheral LNs + sun safety	Regular	Lifelong	Patient	IIIA
	NICE 2022 (1.9.3)	reinforcing advice about self examination + sun safety	No mention	No mention	No mention	Ensure that
Clinical F/U:	Ontario 2024	History, PE of full skin and LN	Q3-6mo Q6mo	1-3y 4-5y	Dermatologist (with photo-surveillance and dermoscopy if indicated) and a surgeon or a medical oncologist/cancer nurse specialist	recommended
	ESMO 2025	Whole body examination (III,B)	Q3mo Q6mo Q12mo	1-3y 4-10y >10y	Preferentially a dermatologist (III,B)	V,B
	NICE 2022 (1.9.11 1.9.15)	Full examination of skin and LN	4x/y 2x/y	1-3y 4-5y	HCP skilled and expertised in skin kc and LN examination with access to dermoscopy and medical photography	Offer
Laboratory examination	Ontario 2024	Routine biomarker or blood tests	NA	NA	NA	Not recommended
	ESMO 2025		Q3-6mo	1-3y	No mention	V,B
	NICE 2022		No mention	NA	NA	
Imaging	Ontario 2024	positive SLN without CLND, US of draining nodal basin	4-6mo 6mo	1-3 4-5	NA	recommended
	ESMO 2025	LN US	Q3-6mo	1-3y	No mention	V,B
	NICE 2022	US scan of draining nodal basin	No mention	NA	NA	
	Ontario 2024	CT or PET/CT scans	Q6-12mo Q12mo	1-3y 4-5y	No mention	Recommended
	ESMO 2025	CT or PET-CT of neck, thorax, abdomen, pelvis	Q3-6mo	1-3y	No mention	V,B
	NICE 2022 (1.9.7, 1.9.8, 1.9.12)	Whole-body CT scan(thorax, abdomen, pelvis – neck if indicated) Whole body MRI if pregnancy or less than 25y	4x/y 2x/y	1-3y 4-5y	No mention	Offer
	NICE 2022 (1.9.13)	PET-CT	NA	NA	NA	Do not routinely
	Ontario 2024(MRI)	Prefer Brain MRI or, instead, head CT after discussing with patient	Q12mo	1-5y		Weakly recommended
	ESMO 2025(V,B) MRI (no CT)	Brain MRI	Q3-6mo	1-3y	No mention	V,B
	NICE 2022 (1.9.7, 1.9.8, 1.9.12)	Brain CT scan Brain MRI if pregnancy or less than 25y	4x/y 2x/y	1-3y 4-5y	No mention	Offer

*The level of evidence and the grade of recommendation mentioned in the last column apply to the all line except mentioned otherwise between brackets.

Table 60 – Follow-up recommended schedule for stage IV melanoma patients with no evidence of disease according to Ontario Health, ESMO and NICE clinical practice guidelines on cutaneous melanoma

Stage IV NED	Scientific institution	Intervention	Frequency	Duration	Setting	Grade/Level*
Patient education	Ontario 2024	SSE + sun safety	Q3-6mo Q6mo	1-3y 4-5y	HCP	recommended
	ESMO 2025	SSE and peripheral LNs + sun safety	Regular	Lifelong	Patient	IIIA
	NICE 2022 (1.9.3)	reinforcing advice about self examination + sun safety	No mention	No mention	No mention	Ensure that
Clinical F/U:	Ontario 2024	History, PE of full skin and LN	Q3-6mo Q6mo	1-3y 4-5y	Dermatologist (with photo-surveillance and dermoscopy if indicated) and a surgeon or a medical oncologist/cancer nurse specialist	recommended
	ESMO 2025	Whole body examination (III,B)	Q3mo Q6mo Q12mo	1-3y 4-10y >10y	Preferentially a dermatologist (III,B)	V,B
	NICE 2022 (1.9.11 1.9.15)	Full examination of skin and LN	4x/y 2x/y	1-3y 4-5y	HCP skilled and expertised in skin kc and LN examination with access to dermoscopy and medical photography	Offer
Laboratory examination	Ontario 2024	Routine biomarker or blood tests	NA	NA	NA	Not recommended
	ESMO 2025		Q3-6mo	1-3y	No mention	V,B
	NICE 2022		No mention	NA	NA	
Imaging	Ontario 2024	positive SLN without CLND, US of draining nodal basin	4-6mo 6mo	1-3 4-5	NA	recommended
	ESMO 2025	LN US	Q3-6mo	1-3y	No mention	V,B
	NICE 2022	US scan of draining nodal basin	No mention	NA	NA	
	Ontario 2024	CT or PET/CT scans	Q6-12mo Q12mo	1-3y 4-5y	No mention	Recommended
	ESMO 2025	CT or PET-CT of neck, thorax, abdomen, pelvis	Q3mo	1-3y	No mention	V,B
	NICE 2022 (1.9.7, 1.9.8, 1.9.12)	Whole-body CT scan (thorax, abdomen, pelvis – neck if indicated) Whole body MRI if pregnancy or less than 25y	4x/y 2x/y	1-3y 4-5y	No mention	Offer
	NICE 2022 (1.9.13)	PET-CT	NA	NA	NA	Do not routinely
	Ontario 2024	Prefer Brain MRI or, instead, head CT after discussing with patient	Q12mo	1-5y		Weakly recommended
	ESMO 2025	Brain MRI	Q3mo	1-3y	No mention	V,B
	NICE 2022 (1.9.7, 1.9.8, 1.9.12)	Brain CT scan Brain MRI if pregnancy or less than 25y	4x/y 2x/y	1-3y 4-5y	No mention	Offer

*The level of evidence and the grade of recommendation mentioned in the last column apply to the all line except mentioned otherwise between brackets.; NED= No Evidence of Disease

Appendix 7.3. Search strategies

The search strategy is adapted from the strategy developed by Rajagopal et al. for a systematic review on the same research question than ours. (Rajagopal 2024) The search did not include patient education on sun safety as an international consensus to include this intervention during follow-up already exists. The search strategy was adapted by the KCE information specialist to the three searched databases: Medline, Embase and Cochrane. Our search strategy slightly differs between cohort studies, RCT, and systematic reviews and guidelines.

First, a sensitive search strategy was used in Medline, Embase and Cochrane for RCT, SR and Guideline (see Figure 8). But, as Rajagopal et al. included an update on RCT in March 2024 but does not update the search for cohort studies, systematic reviews and guidelines, we secondly restricted the number of RCTs retrieved by the search strategy for the years 2024-2025 by using an Endnote filter on publication year before exporting to the Rayyan screening tool. The PRISMA chart below takes into account the effect of this restriction on the final numbers of identified studies.

Second, as a cohort studies exploratory search shows a high amount of background, it was decided to apply a more specific strategy for cohort studies. The lines 1 to 14 of the sensitive strategy, concerning the Melanoma concept, were adapted to make them more specific. This adaptation was made in Medline and Embase but not in Cochrane as this database does not include cohort studies. The sensitive and specific strategies were executed sequentially.



Appendix 7.3.1. Medline: sensitive strategy for RCT, SR and Guideline

Date	February 06, 2025	
Database	Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions <1946 to February 06, 2025>	
Search strategy		
1	exp melanoma/	114400
2	exp Hutchinson's Melanotic Freckle/	848
3	exp malignant lentigo/	848
4	1 or 2 or 3	114400
5	melanoma\$.mp.	168654
6	(melanotic adj2 freckle\$).mp.	902
7	(malignan\$ adj2 lentigo).mp.	77
8	melanocytom*.ab,ti,kf.	933
9	(melanocytic adj2 lesion?).ab,ti,kf.	2713
10	(hutchinson\$ adj1 (freckle\$ or melano\$)).tw.	59
11	dubreuilh.tw.	42
12	LMM.tw.	1754
13	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	171106
14	4 or 13	171106
15	exp Magnetic Resonance Imaging/	566319
16	exp Magnetic Resonance Spectroscopy/	226499
17	15 or 16	780151
18	bone scan\$.tw,kw.	9540
19	(magnetic resonance imag\$ or magnetic resonance spectroscop\$).tw,kw.	361679
20	(dynamic adj4 (MRI or magnet\$)).tw,kw.	13002
21	(diffusion weight\$ adj3 (MRI or magnet\$)).tw,kw.	11629
22	(MPMRI or MP-MRI or MR\$2 or DWI\$ or DW-MRI or DCE\$ or NMR\$ or fmri).tw,kw.	1500075
23	((T1-weighted or T2-weighted) adj3 imag\$).tw,kw.	31970
24	(MR\$1 adj (imag\$ or spectroscop\$ or scan\$ or tomograph\$)).tw,kw.	112834
25	(magnet\$ adj (imag\$ or spectroscop\$ or scan\$ or resonance)).tw,kw.	454708
26	18 or 19 or 20 or 21 or 22 or 23 or 24 or 25	1708775
27	17 or 26	1954487
28	exp Tomography, Emission-Computed/	140804
29	fluorodeoxyglucose f 18/	39105
30	28 or 29	143323
31	(spect or spect?ct).tw,kw.	34216
32	(emission and tomograph\$).tw.	98442
33	pet.tw,kw.	142187
34	PET-CT.tw,kw.	44942
35	PET?CT.tw,kw.	5288
36	PET-FDG.tw.	505
37	fluorodeoxyglucose.tw,kw.	22344
38	31 or 32 or 33 or 34 or 35 or 36 or 37	200874
39	30 or 38	227883
40	exp ultrasonography/	506277
41	ultrasound\$.tw,kw.	347441
42	ultrasonic\$.tw,kw.	72964
43	ultrasonog\$.tw,kw.	137229
44	nodal basin.tw,kw.	316
45	41 or 42 or 43 or 44	501195



46	40 or 45	779386
47	dermoscopy/	6301
48	dermoscop*.ab,ti,kf.	7943
49	dermatoscop*.ab,ti,kf.	1871
50	(epiluminescence adj2 microscop*).ab,ti,kf.	231
51	(skin surface adj2 microscop*).ab,ti,kf.	43
52	48 or 49 or 50 or 51	9281
53	47 or 52	11073
54	skin imaging.ab,ti,kf.	543
55	(LDH or lactate dehydrogenase or S100* or TSH or thyroid-stimulating hormone or ACTH or adrenocorticotrophic hormone cortisol or CBC or complete blood count or FBC or full blood count or Circulating DNA or Melanoma Dx or blood test* or blood work* or (lab adj2 test*) or (lab* adj2 exam*) or Electrolyte* or blood cell count or (liver adj function*) or LFTs or LFs or hepatic function*).ti,kw.	95268
56	photography/	28125
57	Photo*.tw,kw.	855582
58	Physicians, Primary Care/	4699
59	General Practitioners/	11777
60	Physicians, Family/	17574
61	58 or 59 or 60	33777
62	family doctor*.tw,kw.	5579
63	physician*.tw,kw.	493300
64	practitioner*.tw,kw.	197007
65	primary care.ti,kw.	69715
66	62 or 63 or 64 or 65	715094
67	61 or 66	722254
68	(Dermoscop\$ or electrical impedance spectroscopy or Raman spectroscopy).tw,kw.	46173
69	monitor\$.ti. or (asymptomatic and (recurrence or recurrent or high-risk)).tw.	193938
70	(follow-up or follow up or followup or following up or followed up).ti,kw.	131273
71	Surveillanc\$.mp.	319335
72	((transfer or transit\$ or model\$ or multidisciplinary) adj5 (care or team\$)).tw,kw.	112609
73	27 or 39 or 46 or 53 or 54 or 55 or 56 or 57 or 67 or 68 or 69 or 70 or 71 or 72	5047356
74	case reports/	2460720
75	Letter/	1286806
76	74 or 75	3515925
77	(comment or letter or editorial or note or erratum or letter erratum or abstract or short survey or news or newspaper article or patient education handout or case report or historical article).pt.	2890588
78	76 or 77	5113573
79	exp animal/ not human/	5304610
80	78 or 79	10284472
81	14 and 73	31099
82	81 not 80	22929
83	limit 82 to yr="2022 -Current"	4018
84	randomized controlled trial.pt.	631944
85	controlled clinical trial.pt.	95679
86	randomized.ti,ab.	740751
87	placebo.ti,ab.	262928
88	clinical trials as topic/	204305
89	randomly.ti,ab.	453777
90	trial?.ti.	433133



91	84 or 85 or 86 or 87 or 88 or 89 or 90	1709162
92	exp animal/ not humans/	5304610
93	91 not 92	1577589
94	83 and 93	170
95	((systematic review or systematic literature review or systematic scoping review or systematic narrative review or systematic qualitative review or systematic evidence review or systematic quantitative review or systematic meta-review or systematic critical review or systematic mixed studies review or systematic mapping review or systematic cochrane review or "systematic search and review" or systematic integrative review).ti. not comment.pt. not (protocol or protocols).ti. not medline.st.) or (Cochrane Database Syst Rev.ja. and review.pt.) or systematic review.pt.	338064
96	meta-analys*.ti.	222623
97	meta-analysis.pt.	212413
98	exp Technology Assessment, Biomedical/	12624
99	health technology assessment.ti,kf.	3268
100	HtA.ti,kf.	1003
101	95 or 96 or 97 or 98 or 99 or 100	470051
102	83 and 101	113
103	exp clinical pathway/	8231
104	exp clinical protocol/	198924
105	exp consensus/	24583
106	exp consensus development conference/	13009
107	exp consensus development conferences as topic/	3014
108	critical pathways/	8231
109	exp guideline/	40112
110	guidelines as topic/	42473
111	exp practice guideline/	33050
112	practice guidelines as topic/	131305
113	health planning guidelines/	4169
114	(guideline or practice guideline or consensus development conference or consensus development conference, NIH).pt.	50254
115	(position statement* or policy statement* or practice parameter* or best practice*).ti,ab,kf,kw.	53944
116	(standards or guideline or guidelines).ti,kf,kw.	149494
117	((practice or treatment* or clinical) adj guideline*).ab.	60727
118	(CPG or CPGs).ti.	6734
119	consensus*.ti,kf,kw.	40177
120	consensus*.ab. /freq=2	39855
121	((critical or clinical or practice) adj2 (path or paths or pathway or pathways or protocol*)).ti,ab,kf,kw.	30683
122	recommenda*.ti,kf,kw.	60255
123	(care adj2 (standard or path or paths or pathway or pathways or map or maps or plan or plans)).ti,ab,kf,kw.	98528
124	(algorithm* adj2 (screening or examination or test or tested or testing or assessment* or diagnosis or diagnoses or diagnosed or diagnosing)).ti,ab,kf,kw.	11753
125	(algorithm* adj2 (pharmacotherap* or chemotherap* or chemotreatment* or therap* or treatment* or intervention*)).ti,ab,kf,kw.	14530
126	or/103-125	814468
127	83 and 126	166
Comments		



Appendix 7.3.2. Medline: specific strategy for cohort studies

Date	February 06, 2025	
Database	Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions <1946 to February 06, 2025>	
Search strategy		
1	exp *melanoma/	93702
2	exp *Hutchinson's Melanotic Freckle/	678
3	exp *malignant lentigo/	678
4	1 or 2 or 3	93702
5	melanoma\$.ti,kf.	95346
6	(melanotic adj2 freckle\$).ti,kf.	31
7	(malignan\$ adj2 lentigo).ti,kf.	24
8	melanocytom*.ti,kf.	683
9	(melanocytic adj2 lesion?).ti,kf.	912
10	(hutchinson\$ adj1 (freckle\$ or melano\$)).ti,kf.	31
11	dubreuilh.ti,kf.	24
12	LMM.ti,kf.	80
13	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	96640
14	4 or 13	114076
15	exp Magnetic Resonance Imaging/	566319
16	exp Magnetic Resonance Spectroscopy/	226499
17	15 or 16	780151
18	bone scan\$.tw,kw.	9540
19	(magnetic resonance imag\$ or magnetic resonance spectroscop\$).tw,kw.	361679
20	(dynamic adj4 (MRI or magnet\$)).tw,kw.	13002
21	(diffusion weight\$ adj3 (MRI or magnet\$)).tw,kw.	11629
22	(MPMRI or MP-MRI or MR\$2 or DWI\$ or DW-MRI or DCE\$ or NMR\$ or fmri).tw,kw.	1500075
23	((T1-weighted or T2-weighted) adj3 imag\$).tw,kw.	31970
24	(MR\$1 adj (imag\$ or spectroscop\$ or scan\$ or tomograph\$)).tw,kw.	112834
25	(magnet\$ adj (imag\$ or spectroscop\$ or scan\$ or resonance)).tw,kw.	454708
26	18 or 19 or 20 or 21 or 22 or 23 or 24 or 25	1708775
27	17 or 26	1954487
28	exp Tomography, Emission-Computed/	140804
29	fluorodeoxyglucose f 18/	39105
30	28 or 29	143323
31	(spect or spect?ct).tw,kw.	34216
32	(emission and tomograph\$).tw.	98442
33	pet.tw,kw.	142187
34	PET-CT.tw,kw.	44942
35	PET?CT.tw,kw.	5288
36	PET-FDG.tw.	505
37	fluorodeoxyglucose.tw,kw.	22344
38	31 or 32 or 33 or 34 or 35 or 36 or 37	200874
39	30 or 38	227883
40	exp ultrasonography/	506277
41	ultrasound\$.tw,kw.	347441
42	ultrasonic\$.tw,kw.	72964
43	ultrasonog\$.tw,kw.	137229
44	nodal basin.tw,kw.	316
45	41 or 42 or 43 or 44	501195



46	40 or 45	779386
47	dermoscopy/	6301
48	dermoscop*.ab,ti,kf.	7943
49	dermatoscop*.ab,ti,kf.	1871
50	(epiluminescence adj2 microscop*).ab,ti,kf.	231
51	(skin surface adj2 microscop*).ab,ti,kf.	43
52	48 or 49 or 50 or 51	9281
53	47 or 52	11073
54	skin imaging.ab,ti,kf.	543
55	(LDH or lactate dehydrogenase or S100* or TSH or thyroid-stimulating hormone or ACTH or adrenocorticotrophic hormone cortisol or CBC or complete blood count or FBC or full blood count or Circulating DNA or Melanoma Dx or blood test* or blood work* or (lab adj2 test*) or (lab* adj2 exam*) or Electrolyte* or blood cell count or (liver adj function*) or LFTs or LFs or hepatic function*).ti,kw.	95268
56	photography/	28125
57	Photo*.tw,kw.	855582
58	Physicians, Primary Care/	4699
59	General Practitioners/	11777
60	Physicians, Family/	17574
61	58 or 59 or 60	33777
62	family doctor*.tw,kw.	5579
63	physician*.tw,kw.	493300
64	practitioner*.tw,kw.	197007
65	primary care.ti,kw.	69715
66	62 or 63 or 64 or 65	715094
67	61 or 66	722254
68	(Dermoscop\$ or electrical impedance spectroscopy or Raman spectroscopy).tw,kw.	46173
69	monitor\$.ti. or (asymptomatic and (recurrence or recurrent or high-risk)).tw.	193938
70	(follow-up or follow up or followup or following up or followed up).ti,kw.	131273
71	Surveillanc\$.mp.	319335
72	((transfer or transit\$ or model\$ or multidisciplinary) adj5 (care or team\$)).tw,kw.	112609
73	27 or 39 or 46 or 53 or 54 or 55 or 56 or 57 or 67 or 68 or 69 or 70 or 71 or 72	5047356
74	case reports/	2460720
75	Letter/	1286806
76	74 or 75	3515925
77	(comment or letter or editorial or note or erratum or letter erratum or abstract or short survey or news or newspaper article or patient education handout or case report or historical article).pt.	2890588
78	76 or 77	5113573
79	exp animal/ not human/	5304610
80	78 or 79	10284472
81	14 and 73	20350
82	81 not 80	14380
83	limit 82 to yr="2022 -Current"	2766
84	randomized controlled trial.pt.	631944
85	controlled clinical trial.pt.	95679
86	randomized.ti,ab.	740751
87	placebo.ti,ab.	262928
88	clinical trials as topic/	204305
89	randomly.ti,ab.	453777
90	trial?.ti.	433133



91	84 or 85 or 86 or 87 or 88 or 89 or 90	1709162
92	exp animal/ not humans/	5304610
93	91 not 92	1577589
94	83 and 93	121
95	((systematic review or systematic literature review or systematic scoping review or systematic narrative review or systematic qualitative review or systematic evidence review or systematic quantitative review or systematic meta-review or systematic critical review or systematic mixed studies review or systematic mapping review or systematic cochrane review or "systematic search and review" or systematic integrative review).ti. not comment.pt. not (protocol or protocols).ti. not medline.st.) or (Cochrane Database Syst Rev.ja. and review.pt.) or systematic review.pt.	338064
96	meta-analys*.ti.	222623
97	meta-analysis.pt.	212413
98	exp Technology Assessment, Biomedical/	12624
99	health technology assessment.ti,kf.	3268
100	HtA.ti,kf.	1003
101	95 or 96 or 97 or 98 or 99 or 100	470051
102	83 and 101	76
103	exp clinical pathway/	8231
104	exp clinical protocol/	198924
105	exp consensus/	24583
106	exp consensus development conference/	13009
107	exp consensus development conferences as topic/	3014
108	critical pathways/	8231
109	exp guideline/	40112
110	guidelines as topic/	42473
111	exp practice guideline/	33050
112	practice guidelines as topic/	131305
113	health planning guidelines/	4169
114	(guideline or practice guideline or consensus development conference or consensus development conference, NIH).pt.	50254
115	(position statement* or policy statement* or practice parameter* or best practice*).ti,ab,kf,kw.	53944
116	(standards or guideline or guidelines).ti,kf,kw.	149494
117	((practice or treatment* or clinical) adj guideline*).ab.	60727
118	(CPG or CPGs).ti.	6734
119	consensus*.ti,kf,kw.	40177
120	consensus*.ab. /freq=2	39855
121	((critical or clinical or practice) adj2 (path or paths or pathway or pathways or protocol*)).ti,ab,kf,kw.	30683
122	recommenda*.ti,kf,kw.	60255
123	(care adj2 (standard or path or paths or pathway or pathways or map or maps or plan or plans)).ti,ab,kf,kw.	98528
124	(algorithm* adj2 (screening or examination or test or tested or testing or assessment* or diagnosis or diagnoses or diagnosed or diagnosing)).ti,ab,kf,kw.	11753
125	(algorithm* adj2 (pharmacotherap* or chemotherap* or chemotreatment* or therap* or treatment* or intervention*)).ti,ab,kf,kw.	14530
126	or/103-125	814468
127	83 and 126	124
128	Epidemiologic studies/	9653
129	exp case control studies/	1575067
130	exp cohort studies/	2705522
131	Case control.tw.	169036
132	(cohort adj (study or studies)).tw.	383146



133	Cohort analy\$.tw.	14312
134	(Follow up adj (study or studies)).tw.	59724
135	(observational adj (study or studies)).tw.	193949
136	Longitudinal.tw.	366519
137	Retrospective.tw.	874572
138	Cross sectional.tw.	608155
139	Cross-sectional studies/	531664
140	128 or 129 or 130 or 131 or 132 or 133 or 134 or 135 or 136 or 137 or 138 or 139	4192537
141	83 and 140	726
142	141 not (94 or 102 or 127)	646
Comments		

Appendix 7.3.3. Embase: sensitive strategy for RCT, SR and guidelines

Date	7 Feb 2025	
Database	Embase	
Search strategy		
#1	'melanoma'/de	180959
#2	'amelanotic melanoma'/de	1831
#3	'malignant lentigo'/de	2883
#4	#1 OR #2 OR #3	183503
#5	melanoma*:ab,ti,kw	215580
#6	(maligna* NEAR/1 lentigo*):ab,ti,kw	2134
#7	(hutchinson* NEAR/1 (freckle* OR melano*)):ab,ti,kw	23
#8	dubreuilh:ab,ti,kw	115
#9	lmm:ab,ti,kw	2455
#10	(melanotic NEAR/2 freckle*):ti,ab,kw	97
#11	melanocytom*:ti,ab,kw	1175
#12	(melanocytic NEAR/2 lesion?):ti,ab,kw	3279
#13	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12	219271
#14	#4 OR #13	267099
#15	'nuclear magnetic resonance imaging'/exp	1370501
#16	'nuclear magnetic resonance spectroscopy'/exp	147441
#17	#15 OR #16	1502692
#18	'bone scan*:ab,ti,kw	15511
#19	('magnetic resonance' NEXT/2 (imag* OR spectroscop*)):ti,ab,kw	498044
#20	(dynamic NEAR/4 (mri OR magnet*)):ab,ti,kw	17285
#21	('diffusion weight*' NEAR/3 (mri OR magnet*)):ti,ab,kw	15251
#22	mpmri:ab,ti,kw OR 'mp-mri':ab,ti,kw OR dwi*:ab,ti,kw OR mri\$:ab,ti,kf OR 'dw-mri':ab,ti,kw OR dce*:ab,ti,kw OR nmr*:ab,ti,kw OR fmri:ab,ti,kw	392518
#23	((('t1-weighted' OR 't2-weighted') NEAR/3 imag*)):ti,ab,kw	38913
#24	(mr\$ NEAR/1 (imag* OR spectroscop* OR scan* OR tomograph*)):ti,ab,kw	303976
#25	(magnet* NEAR/1 (imag* OR spectroscop* OR scan* OR resonance)):ab,ti,kw	614163
#26	#18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25	1023535
#27	#17 OR #26	1805343
#28	'computer assisted emission tomography'/exp	352315
#29	'fluorodeoxyglucose f 18'/exp	85077
#30	'fluorodeoxyglucose f 18 positron emission tomography computed tomography'/exp	12
#31	#28 OR #29 OR #30	362618
#32	spect:ab,ti,kw OR "spect\$ct":ab,ti,kw	59772
#33	emission:ti,ab,kw AND tomograph*:ti,ab,kw	137937



#34	pet:ti,ab,kw	251773
#35	'pet ct':ti,ab,kw	91479
#36	pet?ct:ti,ab,kw	19593
#37	'pet fdg':ti,ab,kw	1040
#38	fluorodeoxyglucose:ti,ab,kw	31265
#39	#32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38	335430
#40	#31 OR #39	449828
#41	'echography'/exp	1147931
#42	ultrasound*:ti,ab,kw	553621
#43	ultrasonic*:ti,ab,kw	84434
#44	ultrasonog*:ti,ab,kw	202783
#45	'nodal basin':ti,ab,kw	506
#46	#42 OR #43 OR #44 OR #45	752963
#47	#41 OR #46	1505639
#48	'dermatoscopy'/exp	16064
#49	dermatoscop*:ti,ab,kw	2641
#50	dermoscop*:ti,ab,kw	9837
#51	(epiluminescence NEAR/2 microscop*):ti,ab,kw	313
#52	('skin surface' NEAR/2 microscop*):ti,ab,kw	61
#53	#49 OR #50 OR #51 OR #52	11744
#54	#48 OR #53	18057
#55	'skin imaging':ti,ab,kw	696
#56	ldh:ti OR 'lactate dehydrogenase':ti OR s100*:ti OR tsh:ti OR 'thyroid-stimulating hormone':ti OR acth:ti OR 'adrenocorticotrophic hormone cortisol':ti OR cbc:ti OR 'complete blood count':ti OR fbc:ti OR 'full blood count':ti OR 'circulating dna':ti OR 'melanoma dx':ti OR 'blood test':ti OR 'blood work*':ti OR ((lab NEAR/2 test*):ti) OR ((lab* NEAR/2 exam*):ti) OR electrolyte*:ti OR 'blood cell count':ti OR 'liver function*':ti OR lfts:ti OR lfs:ti OR 'hepatic function*':ti	98867
#57	'photography'/exp	110102
#58	photo*:ti,ab,kw	885319
#59	'general practitioner'/exp	128729
#60	'family doctor*':ti,ab,kw	8304
#61	physician*:ti,ab,kw	718038
#62	practitioner*:ti,ab,kw	252787
#63	'primary care':ti	73437
#64	#60 OR #61 OR #62 OR #63	988564
#65	#59 OR #64	1025500
#66	dermoscop*:ti,ab,kw OR 'electrical impedance spectroscopy':ti,ab,kw OR 'raman spectroscopy':ti,ab,kw	43932
#67	monitor*:ti,ab,kw OR (asymptomatic:ti,ab,kw AND (recurrence:ti,ab,kw OR recurrent:ti,ab,kw OR 'high risk':ti,ab,kw))	1560448
#68	'follow up':ti,kw OR followup:ti,kw OR 'following up':ti,kw OR 'followed up':ti,kw	195837
#69	surveillanc*:ti,ab,kw	366772
#70	((transfer OR transit? OR model? OR multidisciplinary) NEAR/5 (care OR team?)):ti,ab,kw	70479
#71	#27 OR #40 OR #47 OR #54 OR #55 OR #56 OR #57 OR #58 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70	7050041
#72	#14 AND #71	52463
#73	#72 AND 2022-2025/py	10255
#74	#73 NOT ('conference abstract'/it OR 'conference paper'/it OR 'conference review'/it)	7784
#75	#74 NOT medline/lim	2753



#76	#75 AND ('meta-analysis'/exp OR 'meta-analysis' OR 'systematic review'/exp OR 'systematic review')	156
#77	#75 AND (random*:ab,ti OR placebo*:de,ab,ti OR ((double NEXT/1 blind*):ab,ti))	93
#78	'clinical pathway'/de	10756
#79	'clinical protocol'/exp	131307
#80	'consensus'/exp	110130
#81	'consensus development'/de	30346
#82	'practice guideline'/exp	782971
#83	'guideline'/de	142
#84	'health care planning'/de	118062
#85	'position statement*':ab,ti,kw OR 'policy statement*':ab,ti,kw OR 'practice parameter*':ab,ti,kw OR 'best practice*':ab,ti,kw	76572
#86	standards:ti,kw OR guideline:ti,kw OR guidelines:ti,kw	203586
#87	((practice OR treatment*) NEAR/3 guideline*):ab	94579
#88	cpg:ti,kw OR cpgs:ti,kw	11447
#89	consensus*:ti,kw	49899
#90	((critical OR clinical OR practice) NEAR/3 (path OR paths OR pathway OR pathways OR protocol*)):ab,ti,kw	63117
#91	recommendat*:ti,kw	75541
#92	(care NEAR/3 (standard OR path OR paths OR pathway OR pathways OR map OR maps OR plan OR plans)):ab,ti,kw	184660
#93	(algorithm* NEAR/3 (screening OR examination OR test OR tested OR testing OR assessment* OR diagnosis OR diagnoses OR diagnosed OR diagnosing)):ab,ti,kw	24541
#94	(algorithm* NEAR/3 (pharmacotherap* OR chemotherap* OR chemotreatment* OR therap* OR treatment* OR intervention*)):ab,ti,kw	24995
#95	#78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #93 OR #94	1468378
#96	#75 AND #95	128
#97	#75 NOT (#76 OR #77 OR #96)	2412
#98	'clinical study'/de	169159
#99	'case control study'/de	227798
#100	'family study'/de	26477
#101	'longitudinal study'/de	230440
#102	'retrospective study'/de	1748745
#103	'prospective study'/de	957914
#104	'randomized controlled trials'/de	288055
#105	#103 NOT #104	946120
#106	'cohort analysis'/de	1279175
#107	(cohort NEAR/3 (study OR studies)):ab,ti,kw	626033
#108	('case control' NEAR/3 (study OR studies)):ab,ti,kw	196708
#109	('follow up' NEAR/3 (study OR studies)):ab,ti,kw	132180
#110	('observational' NEAR/3 (study OR studies)):ab,ti,kw	395042
#111	('epidemiologic\$' NEAR/3 (study OR studies)):ab,ti,kw	44400
#112	('cross sectional' NEAR/3 (study OR studies)):ab,ti,kw	507451
#113	#98 OR #99 OR #100 OR #101 OR #102 OR #105 OR #106 OR #107 OR #108 OR #109 OR #110 OR #111 OR #112	4195756
#114	#75 AND #113	613
#115	#114 NOT (#76 OR #77 OR #96)	538
#116	#75 NOT (#76 OR #77 OR #96 OR #115)	2412
Comments	:	

Appendix 7.3.4. Embase: specific strategy for cohort studies

Date	7 Feb 2025	
Database	Embase	
Search strategy		
#1	'melanoma'/mj	180959
#2	'amelanotic melanoma'/mj	1831
#3	'malignant lentigo'/mj	2883
#4	#1 OR #2 OR #3	183503
#5	melanoma*:ti,kw	215580
#6	(maligna* NEAR/1 lentigo*):ti,kw	2134
#7	(hutchinson* NEAR/1 (freckle* OR melano*)):ti,kw	23
#8	dubreuilh:ti,kw	115
#9	Imm:ti,kw	2455
#10	(melanotic NEAR/2 freckle*):ti,kw	97
#11	melanocytom*:ti,kw	1175
#12	(melanocytic NEAR/2 lesion?):ti,kw	3279
#13	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12	219271
#14	#4 OR #13	267099
#15	'nuclear magnetic resonance imaging'/exp	1370501
#16	'nuclear magnetic resonance spectroscopy'/exp	147441
#17	#15 OR #16	1502692
#18	'bone scan*:ab,ti,kw	15511
#19	('magnetic resonance' NEXT/2 (imag* OR spectroscop*)):ti,ab,kw	498044
#20	(dynamic NEAR/4 (mri OR magnet*)):ab,ti,kw	17285
#21	('diffusion weight*' NEAR/3 (mri OR magnet*)):ti,ab,kw	15251
#22	mpmri:ab,ti,kw OR 'mp-mri':ab,ti,kw OR dwi*:ab,ti,kw OR mri\$:ab,ti,kf OR 'dw-mri':ab,ti,kw OR dce*:ab,ti,kw OR nmr*:ab,ti,kw OR fmri:ab,ti,kw	392518
#23	((('t1-weighted' OR 't2-weighted') NEAR/3 imag*)):ti,ab,kw	38913
#24	(mr\$ NEAR/1 (imag* OR spectroscop* OR scan* OR tomograph*)):ti,ab,kw	303976
#25	(magnet* NEAR/1 (imag* OR spectroscop* OR scan* OR resonance)):ab,ti,kw	614163
#26	#18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25	1023535
#27	#17 OR #26	1805343
#28	'computer assisted emission tomography'/exp	352315
#29	'fluorodeoxyglucose f 18'/exp	85077
#30	'fluorodeoxyglucose f 18 positron emission tomography computed tomography'/exp	12
#31	#28 OR #29 OR #30	362618
#32	spect:ab,ti,kw OR "spect\$ct":ab,ti,kw	59772
#33	emission:ti,ab,kw AND tomograph*:ti,ab,kw	137937
#34	pet:ti,ab,kw	251773
#35	'pet ct':ti,ab,kw	91479
#36	pet?ct:ti,ab,kw	19593
#37	'pet fdg':ti,ab,kw	1040
#38	fluorodeoxyglucose:ti,ab,kw	31265
#39	#32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38	335430
#40	#31 OR #39	449828
#41	'echography'/exp	1147931
#42	ultrasound*:ti,ab,kw	553621
#43	ultrasonic*:ti,ab,kw	84434
#44	ultrasonog*:ti,ab,kw	202783
#45	'nodal basin':ti,ab,kw	506



#46	#42 OR #43 OR #44 OR #45	752963
#47	#41 OR #46	1505639
#48	'dermatoscopy'/exp	16064
#49	dermatoscop*:ti,ab,kw	2641
#50	dermoscop*:ti,ab,kw	9837
#51	(epiluminescence NEAR/2 microscop*):ti,ab,kw	313
#52	('skin surface' NEAR/2 microscop*):ti,ab,kw	61
#53	#49 OR #50 OR #51 OR #52	11744
#54	#48 OR #53	18057
#55	'skin imaging':ti,ab,kw	696
#56	ldh:ti OR 'lactate dehydrogenase':ti OR s100*:ti OR tsh:ti OR 'thyroid-stimulating hormone':ti OR acth:ti OR 'adrenocorticotrophic hormone cortisol':ti OR cbc:ti OR 'complete blood count':ti OR fbc:ti OR 'full blood count':ti OR 'circulating dna':ti OR 'melanoma dx':ti OR 'blood test':ti OR 'blood work':ti OR ((lab NEAR/2 test*):ti) OR ((lab* NEAR/2 exam*):ti) OR electrolyte*:ti OR 'blood cell count':ti OR 'liver function':ti OR lfts:ti OR lfs:ti OR 'hepatic function':ti	98867
#57	'photography'/exp	110102
#58	photo*:ti,ab,kw	885319
#59	'general practitioner'/exp	128729
#60	'family doctor':ti,ab,kw	8304
#61	physician*:ti,ab,kw	718038
#62	practitioner*:ti,ab,kw	252787
#63	'primary care':ti	73437
#64	#60 OR #61 OR #62 OR #63	988564
#65	#59 OR #64	1025500
#66	dermoscop*:ti,ab,kw OR 'electrical impedance spectroscopy':ti,ab,kw OR 'raman spectroscopy':ti,ab,kw	43932
#67	monitor*:ti,ab,kw OR (asymptomatic:ti,ab,kw AND (recurrence:ti,ab,kw OR recurrent:ti,ab,kw OR 'high risk':ti,ab,kw))	1560448
#68	'follow up':ti,kw OR followup:ti,kw OR 'following up':ti,kw OR 'followed up':ti,kw	195837
#69	surveillanc*:ti,ab,kw	366772
#70	((transfer OR transit? OR model? OR multidisciplinary) NEAR/5 (care OR team?):ti,ab,kw	70479
#71	#27 OR #40 OR #47 OR #54 OR #55 OR #56 OR #57 OR #58 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70	7050041
#72	#14 AND #71	52463
#73	#72 AND 2022-2025/py	10255
#74	#73 NOT ('conference abstract'/it OR 'conference paper'/it OR 'conference review'/it)	7784
#75	#74 NOT medline/lim	2753
#76	#75 AND ('meta-analysis'/exp OR 'meta-analysis' OR 'systematic review'/exp OR 'systematic review')	156
#77	#75 AND (random*:ab,ti OR placebo*:de,ab,ti OR ((double NEXT/1 blind*):ab,ti))	93
#78	'clinical pathway'/de	10756
#79	'clinical protocol'/exp	131307
#80	'consensus'/exp	110130
#81	'consensus development'/de	30346
#82	'practice guideline'/exp	782971
#83	'guideline'/de	142
#84	'health care planning'/de	118062
#85	'position statement':ab,ti,kw OR 'policy statement':ab,ti,kw OR 'practice parameter':ab,ti,kw OR 'best practice':ab,ti,kw	76572
#86	standards:ti,kw OR guideline:ti,kw OR guidelines:ti,kw	203586
#87	((practice OR treatment*) NEAR/3 guideline*):ab	94579



#88	cpg:ti,kw OR cpgs:ti,kw	11447
#89	consensus*:ti,kw	49899
#90	((critical OR clinical OR practice) NEAR/3 (path OR paths OR pathway OR pathways OR protocol*)):ab,ti,kw	63117
#91	recommendat*:ti,kw	75541
#92	(care NEAR/3 (standard OR path OR paths OR pathway OR pathways OR map OR maps OR plan OR plans)):ab,ti,kw	184660
#93	(algorithm* NEAR/3 (screening OR examination OR test OR tested OR testing OR assessment* OR diagnosis OR diagnoses OR diagnosed OR diagnosing)):ab,ti,kw	24541
#94	(algorithm* NEAR/3 (pharmacotherap* OR chemotherap* OR chemotreatment* OR therap* OR treatment* OR intervention*)):ab,ti,kw	24995
#95	#78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #93 OR #94	1468378
#96	#75 AND #95	128
#97	#75 NOT (#76 OR #77 OR #96)	2412
#98	'clinical study'/de	169159
#99	'case control study'/de	227798
#100	'family study'/de	26477
#101	'longitudinal study'/de	230440
#102	'retrospective study'/de	1748745
#103	'prospective study'/de	957914
#104	'randomized controlled trials'/de	288055
#105	#103 NOT #104	946120
#106	'cohort analysis'/de	1279175
#107	(cohort NEAR/3 (study OR studies)):ab,ti,kw	626033
#108	('case control' NEAR/3 (study OR studies)):ab,ti,kw	196708
#109	('follow up' NEAR/3 (study OR studies)):ab,ti,kw	132180
#110	('observational' NEAR/3 (study OR studies)):ab,ti,kw	395042
#111	('epidemiologic\$' NEAR/3 (study OR studies)):ab,ti,kw	44400
#112	('cross sectional' NEAR/3 (study OR studies)):ab,ti,kw	507451
#113	#98 OR #99 OR #100 OR #101 OR #102 OR #105 OR #106 OR #107 OR #108 OR #109 OR #110 OR #111 OR #112	4195756
#114	#75 AND #113	613
#115	#114 NOT (#76 OR #77 OR #96)	538
#116	#75 NOT (#76 OR #77 OR #96 OR #115)	2412
Comments	The sensitive and specific strategies were executed sequentially by adapting lines 1 to 14 to make them more specific. However, the Embase interface did not update the number of hits accordingly, resulting in identical hit counts for each line across both strategies, despite the modifications.	



Appendix 7.3.5. Cochrane: sensitive strategy for RCT, SR and guidelines

Date	16/01/2025 06:10:16	
Database	Cochrane	
Search strategy		
#1	mh melanoma	2801
#2	mh "Hutchinson's Melanotic Freckle"	16
#3	mh "malignant lentigo"	16
#4	#1 OR #2 OR #3	2801
#5	melanoma?:ti,ab	6459
#6	(melanotic NEAR/2 freckle*):ti,ab	2
#7	(malignan* NEAR/2 lentigo):ti,ab	3
#8	melanocytom*:ti,ab	0
#9	(melanocytic NEAR/2 lesion?):ti,ab	32
#10	(hutchinson? NEAR/1 (freckle? OR melano*)):ti,ab	2
#11	dubreuilh:ti,ab	0
#12	LMM:ti,ab	236
#13	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12	6698
#14	#4 OR #13	6889
#15	#14 with Cochrane Library publication date Between Jan 2022 and Jan 2025	1255
#16	#15 in Cochrane Reviews	1
#17	mh "Magnetic Resonance Imaging"	13327
#18	mh "Magnetic Resonance Spectroscopy"	978
#19	#17 or #18	14085
#20	(bone NEXT scan*):ti,ab	909
#21	("magnetic resonance" NEXT (imag* OR spectroscop*)):ti,ab	19897
#22	(dynamic NEAR/4 (MRI OR magnet*)):ab,ti	535
#23	((diffusion NEXT weight*) NEAR/3 (MRI OR magnet*)):ti,ab	515
#24	(MPMRI or "MP-MRI" or MR?? or DWI* or "DW-MRI" or DCE* or NMR* or fmri):ab,ti	28214
#25	("T1-weighted" or "T2-weighted") NEAR/3 imag*):ti,ab	846
#26	(MR? NEAR/1 (imag* OR spectroscop* OR scan* OR tomograph*)):ti,ab	14039
#27	(magnet* NEAR/1 (imag* or spectroscop* or scan* or resonance)):ab,ti	23522
#28	#18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25	49634
#29	#19 OR #28	49634
#30	mh "Tomography, Emission-Computed"	3750
#31	mh ^"fluorodeoxyglucose f 18"	968
#32	#30 OR #31	3852
#33	(spect OR spect?ct):ab,ti	2041
#34	(emission AND tomograph*):ti,ab	5014
#35	pet:ti,ab	9337
#36	PET-CT:ti,ab	3014
#37	PET?CT:ti,ab	2510
#38	PET-FDG:ti,ab	40
#39	fluorodeoxyglucose:ti,ab	1005
#40	#33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39	12627
#41	#32 OR #40	13049
#42	mh ultrasonography	19740
#43	ultrasound*:ti,ab	47027
#44	ultrasonic*:ti,ab	4076
#45	ultrasonog*:ti,ab	10973
#46	"nodal basin":ti,ab	25



#47	#43 OR #44 OR #45 OR #46	58428
#48	#42 OR #47	67565
#49	mh ^dermoscopy	120
#50	dermoscop*:ti,ab	437
#51	dermatoscop*:ti,ab	126
#52	(epiluminescence NEAR/2 microscop*):ti,ab	5
#53	("skin surface" NEAR/2 microscop*):ti,ab	6
#54	#51 or #52 or #53	134
#55	#49 or #54	242
#56	(LDH OR "lactate dehydrogenase" OR S100* OR TSH OR "thyroid-stimulating hormone" OR ACTH OR "adrenocorticotrophic hormone cortisol" OR CBC OR "complete blood count" OR FBC OR "full blood count" OR "Circulating DNA" OR "Melanoma Dx" OR ("blood" NEXT test*) OR ("blood" NEXT work*) OR (lab NEAR/2 test*) OR (lab* NEAR/2 exam*) OR Electrolyte* OR "blood cell count" OR (liver NEXT function*) OR LFTs OR LFs OR ("hepatic" NEXT function*)):ti	3456
#57	mh ^photography	905
#58	Photo*:ti,ab	29819
#59	mh ^"Physicians, Primary Care"	250
#60	mh ^"General Practitioners"	619
#61	mh ^"Physicians, Family"	542
#62	#59 or #60 or #61	1400
#63	("family" NEXT doctor*):ti,ab	460
#64	physician*:ti,ab	53822
#65	practitioner*:ti,ab	15786
#66	"primary care":ti	8731
#67	#63 OR #64 OR #65 OR #66	73783
#68	#62 or #67	73902
#69	(Dermoscop* OR "electrical impedance spectroscopy" OR "Raman spectroscopy"):ti,ab	556
#70	(monitor* OR (asymptomatic AND (recurrence OR recurrent OR high-risk))):ti,ab	121428
#71	(follow-up OR "follow up" OR followup OR "following up" OR "followed up"):ti	21802
#72	Surveillanc*:ti,ab	9851
#73	((transfer OR transit* OR model* OR multidisciplinary) NEAR/5 (care OR team?)):ti,ab	12152
#74	#29 or #41 or #48 or #55 or #56 or #57 or #58 or #68 or #69 or #70 or #71 or #72 or #73	360644
#75	#15 AND #74	311
#76	#75 with Publication Year from 2024 to 2025, in Trials	82
#77	#75 with Publication Year from 2022 to 2025, in Trials	239



Appendix 7.3.6. Study selection

For the primary studies selected by Rajagopal et al. through a search covering the 2015-2022 period for cohort studies and the 2015-2024 period for RCT, the reader can consult the flow chart in the publication of Rajagopal 2024.(Rajagopal 2024)

For the primary studies identified by our updated literature search, Figure 17 illustrates the PRISMA flow chart of selection of primary studies. Among the systematic reviews identified by the strategy search in the three databases, the screening of the selected primary studies by the authors of those systematic reviews allowed to identify one additional reference.

Selected RCT and cohort studies were included for the analysis process while systematic reviews were only used to identify additional primary studies to be included (for excluded studies see Table 61 and Table 62).

Figure 17 – Study flow selection of search surveillance interventions follow-up

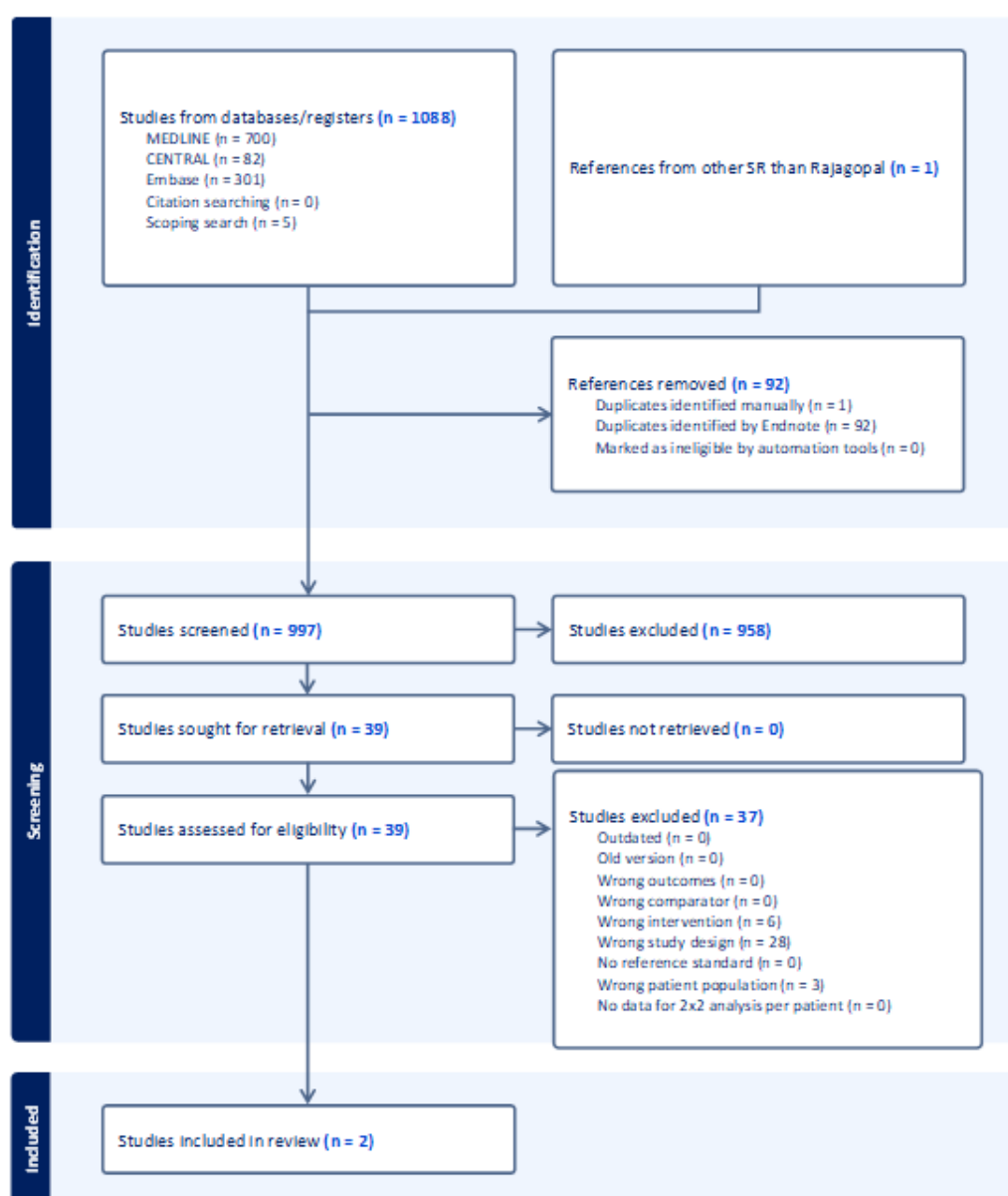


Table 61 – Not retained primary studies SR Dinnes 2019 for follow-up

Reference	Year	Reasons
Hafner(Hafner et al., 2004)	2004	Wrong population: including all stages, clinically lymph node positive
Radzhabova	2009	Wrong population: including all stages, clinically lymph node positive
Kang(Kang et al., 2011)	2011	Wrong population: including all stages, clinically lymph node positive
Veit-Heibach	2009	Wrong population: including all stages, clinically lymph node positive

Table 62 – Excluded references for the selection of primary studies for follow-up

Reference	Year	Reasons
Ackermann(Ackermann 2024)	2024	Wrong study design
Hobelsberger(Hobelsberger 2024)	2024	Wrong patient population
Huang(Huang 2024)	2024	Wrong study design
Ladjevardi(Ladjevardi 2024)	2024	Wrong study design
Absil(Absil 2023)	2023	Wrong intervention
Johannessen(Johannessen 2023)	2023	Wrong study design
Ziętek(Ziętek 2023)	2023	Wrong study design
Martos-Cabrera(Martos-Cabrera 2024)	2024	Wrong study design
Savage(Savage 2024)	2024	Wrong study design
Lucci(Lucci 2023)	2023	Wrong study design
Jaeger(Jaeger 2022)	2022	Wrong study design
Everdell(Everdell 2024)	2024	Wrong study design
Andersen(Andersen 2022)	2022	Wrong study design
Toia(Toia 2022)	2022	Wrong study design
Minor(Minor 2023)	2023	Wrong study design
Brunsgaard(Brunsgaard 2023)	2023	Wrong patient population
Montgomery(Montgomery 2024)	2024	Wrong intervention
Van Not(van Not 2024)	2024	Wrong intervention
Derks(Derks 2022)	2022	Wrong study design
Gyurdzhyan(Gyurdzhyan 2024)	2023	Wrong study design
Jansen(Jansen 2024)	2024	Wrong study design
Gjorup(Gjorup 2024)	2024	Wrong study design
Yan(Yan 2023)	2023	Wrong study design
Dhillon(Dhillon 2023)	2023	Wrong patient population
Briatico(Briatico 2024)	2024	Wrong study design
Palacios-Diaz(Palacios-Diaz 2022)	2022	Wrong study design
Çınar(Çınar 2022)	2022	Wrong study design
Bartlett(Bartlett 2022)	2022	Wrong study design
Weber(Weber 2022)	2022	Wrong intervention
Avilés-Izquierdo(Avilés-Izquierdo 2023)	2023	Wrong intervention
Geoffrois(Geoffrois 2023)	2023	Wrong study design
Tutic-Sorrentino(Tutic-Sorrentino 2024)	2024	Wrong study design



Bellinato(Bellinato 2022)	2022	Wrong intervention
Kim(Kim 2022)	2024	Wrong study design
Sullivan(Sullivan 2024)	2024	Wrong study design
Helvind(Helvind 2023)	2023	Wrong study design
Hansen(Hansen 2024)	2024	Wrong study design

Table 63 – Follow-up: Ongoing studies

Name, type and code of the study	Status - planned year of study completion	Interventions compared	Estimated participants	Ref if any published protocol
TRIM study, RCT NCT03116412	Recruiting - 2028	Addition of PET/CT to usual care	1300	Naeser et al. BMC cancer 2020(Naeser 2020)
IMAGE study, RCT NCT04385732	Active, not recruiting - 2025	Addition of surveillance photography to usual care	670	Yan et al. Trials 2023(Yan 2023)
MELVEC study, Prospective cohort study NCT04605822	Completed - 2024	Compare 2D- and 3D-imaging and routine clinical care	455	Publication of the protocol not retrieved
MELAcare study, RCT NCT05253872	Recruiting - 2028	Compare patient support and education tools combined with SSE to the current standard-of-care	378	Hansen et al. 2024, Acta Oncologica(Hansen 2024)
MELSELF, RCT ACTRN12621000176864	Active, not recruiting - 2025	Patient-led surveillance compared to clinician-led surveillance	504	Ackermann et al. 2021, Trials, (Ackermann 2021)
RCT ANZCTR12618000267257	Completed in 2021- Last update on the registration website in 2024	Addition of 3D full body imaging, genomic risk assessment and functional testing of gene variants	314	Primiero et al. 2019, BMJ open (Primiero 2019)

Appendix 7.4. Appraisal

The systematic review of Rajagopal et al., on which our search strategy was based, was assessed by one researcher with the AMSTAR-2 (Assessing the methodological quality of systematic reviews) tool.(Shea 2017)

Table 64 – Follow-up: Quality of the systematic review of Rajagopal

Systematic review by Rajagopal(Rajagopal 2024)	Score	Rationale
PICO included	Yes	
A priori study design	Partial yes	No plan for investigating causes of heterogeneity
Explanation selection study design inclusion	No	No explanation for including both RCTs and NRSI
Comprehensive literature search	Yes	
Duplicate study selection	No	It was planned in the protocol but time restriction prevent the selection in duplicate
Duplicate study data extraction	Yes	At least 2 reviewers achieved consensus on which data to extract from included studies
List of included and excluded studies	Yes	Prisma diagram has reasons for exclusion
Characteristics of included studies	Yes	
Study quality assessed	Yes	For RCTs and NRSI
Sources of funding studies reported	No	
Appropriate methods to combine findings	N/A	No meta-analysis performed due to heterogeneity of interventions and outcomes
Bias consider in meta-analysis	N/A	No meta-analysis performed due to heterogeneity of interventions and outcomes
Bias consider summary estimates	Yes	
Heterogeneity discussed	N/A	No meta-analysis performed
Likelihood of publication bias assessed	Yes	As part of the GRADE approach
Conflict of interest stated	No/Yes	Mentioned in the appendix but results are removed temporarily for publication process



Among the two studies identified by our search, there was TRIM RCT and cohort study by Helvind et al. (Helvind 2023, Naeser 2020) The risk of bias is presented in the tables below.

Table 65 – Follow-up: Risk of bias for the patient-reported outcome in the TRIM RCT

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk of bias	Randomization 1:1 was performed in the electronic data capture (EDC) system (Viedoc) at each site
Allocation concealment (selection bias)	Low risk of bias	Electronic data capture (EDC) system (Viedoc) at each site
Blinding of participants and personnel (performance bias)	High risk of bias	Non blinded trail
Blinding of outcome assessment (detection bias)	Unclear risk of bias	Patient answers by themselves but could answer with a mean aim related to the arm he is in
Incomplete outcome data (attrition bias)	Unclear risk of bias	All the available data was analysed but some data was missing
Selective reporting (reporting bias)	Low risk of bias	Protocol was very clear and respected
Other bias: deviations from the intended interventions	High risk of bias	No information on additional diagnostic intervention: Number? Type? Reason (symptoms or else?)

Table 66 – Follow-up: Risk of bias comparative cohort study Helvind

SELECTION BIAS	Helvind et al, 2023
Can selection bias sufficiently be excluded? Yes	Allocation of participants to the exposure group is not the result of clinician or patient choice. Inclusion is consecutive Because all patients in the current study were enrolled in a national surveillance program, and because Danish health care is tax-funded and freely available to all, the risk of selection bias was minimal. Strict adherence to national treatment and surveillance guidelines for which registration is mandatory, ensures that all patients were treated and followed uniformly and that data were registered prospectively with excellent data completion and report rates Participation rates is around 100% in both arms
Are the most important confounding factors identified, are they adequately measured and are they adequately taken into account in the study design and/or analysis? Yes	No matching for confounders in allocation but well considered in statistical analysis The statistical model used for analysis takes into account the following cofounders: age, sex, Charlston Comorbidity Index, histopathologic subtype of melanoma, and ICD-10 localization of primary tumor. Additional confounders not mentioned by researchers could be factors relevant to prognosis and responsiveness to treatment like genetics factors. Reporting and comparison of baseline characteristics are present. Because of unbalanced confounders between cohort 1 and cohort 2, patients in cohort 2 had a higher risk of death before recurrence (older patients with more comorbidities), which in turn lowered the cumulative incidence of recurrence. If patients had been more comparable, the differences in recurrence would likely have been greater. Co-intervention is possible in both arm, like in RCT on surveillance: Patients in cohort 1 were followed with clinical examinations alone but had access to cross-sectional imaging with FDG PET-CT (with CT in smaller centers) upon suspicion of recurrence. Patients in cohort 2 can be further referred to FDG PET-CT if recurrence was suspected between routine scans.
DETECTION BIAS	Support for judgement
Is the exposure clearly defined and is the method for assessment of exposure adequate and similar in study groups? Yes	All Danish melanoma patients are prospectively registered in the Danish Melanoma Database with information regarding primary treatment, surveillance, and recurrence. Primary treatment was unchanged throughout the study period.



	In all centers but one, whole-body FDG PET-CT is obtained with low-dose CT from base of skull to mid-thigh, with inclusion of extremities if relevant to primary tumor localization. In the last center, wherein approximately 18 % of patients are followed, FDG PET-CT is performed using diagnostic-dose CT with contrast enhancement.
Are the outcomes clearly defined and is the method for assessment of the outcomes adequate and similar in study groups? • Yes	The primary outcome of this study was the effect of surveillance with routine FDG PET-CT on the hazard of overall, locoregional, and distant recurrence. The secondary outcomes were differences in estimated cumulative incidence and absolute risk of overall, locoregional, or distant recurrence at six months and at 1, 2, 3, and 5 years post-treatment for patients followed with routine FDG PET-CT versus patients followed with clinical examinations only. To determine the cohort effect on the hazard of recurrence, cause-specific proportional hazards models (CSH) for overall, locoregional, and distant recurrence were fitted, and hazard ratios (HRs) with corresponding 95 % CIs were estimated comparing cohort 2 with cohort 1. The impact of surveillance with routine FDG PET-CT on recurrence detection, cumulative incidences of overall, locoregional, and distant recurrence six months and one, two, three, and five years after primary treatment were estimated for each cohort using the Aalen-Johansen estimator, with recurrence as the primary event and death before recurrence (death from all causes) as a competing event.
Is the likelihood that some eligible subjects might have the outcome at the time of enrolment assessed and taken into account in the analysis? • Yes	Patients were followed until recurrence, death, or end of the follow-up period on 31 December 2021.
Is the assessment of outcome made blind to exposure status? • Yes	The analysis in the databases comes after the exposure occurred
Is the follow-up sufficiently long to measure all relevant outcomes? • Yes	Although the sample size was sufficiently large to show an effect of routine FDG PET-CT on distant recurrence detection within the first two years of surveillance, significance was not reached for overall recurrence detection in the same period or for distant recurrence detection in individual pathologic stages.
ATTRITION BIAS	
Can selective loss-to-follow-up be sufficiently excluded? • Yes	Patients were censored in the event of emigration (loss to follow-up evaluation) or development of a new primary melanoma of a higher AJCC8 pathologic stage

Appendix 7.5. Evidence tables

Appendix 7.5.1. Systematic review

Evidence was extracted from the systematic review of Rajagopal et al.(Rajagopal 2024)

Table 67 – Follow-up: Evidence table of the systematic review of Rajagopal

<i>Rajagopal et al. 2024</i>	
Design	Systematic review including one RCT and 5 non-randomized comparative studies that investigated the follow-up strategies and their frequencies in adult patients with stage I, II, III, or resected IV melanoma who were clinically disease-free after receiving curative-intent treatment.
Methods	A comprehensive updated SR that followed PRISMA guidelines, without meta-analysis, registered at PROSPERO as CRD42021246482 Search terms are “melanoma”, “surveillance”, and “randomized trial” with their alternatives. Two methodologists reviewed the search strategies. One reviewer reviewed the titles and abstracts. For full-text review, selection was discussed with another review authors. The reference lists of included articles were hand-searched for further eligible papers. All included studies underwent data extraction by one researcher using a predefined data abstracting sheet, with all data audited subsequently by an independent auditor. Discrepancies were resolved through consensus with the other two review authors. The risk of bias per outcome of each comparison was assessed using the Cochrane Collaboration Risk of Bias 2.0 tool for randomized studies The Risk of Bias in Non-randomized Studies of Interventions tool was used to assess the risk of bias for each outcome for included non-randomized studies The certainty of the evidence, taking into account risk of bias, inconsistency, indirectness, imprecision, and publication bias was assessed using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach The results of each study were reported separately in a descriptive fashion A meta-analysis or traditional GRADE summary tables for each outcome were inappropriate to perform because of the large number of different interventions, patient populations, and outcomes among the included studies.
Source of funding and competing interest	Authors were supported by the Ontario Ministry of Health (OMH) but all work produced is editorially independent from the OMH. No grant from funding agencies in the public, commercial, or not-for-profit sectors
Search date	Published studies from January 1, 2015 to June 5, 2022 Ongoing studies on July 12, 2022 Update for RCT only: The MEDLINE and EMBASE databases were searched on March 14, 2024



Searched databases	Published studies: MEDLINE, EMBASE, PubMed, Cochrane Database of Systematic Reviews, Ongoing studies: the National Cancer Institute Clinical Trials Database and PROSPERO databases
Included study designs	Articles or conference abstracts reporting RCT or comparative study with a minimum analyzed sample size of 30 per group
Number of included studies	6 studies (1 RCT and 5 retrospective comparative studies) with 8 articles ultimately met the pre-planned study selection criteria 6 ongoing trials potentially meet the study selection criteria
Statistical analysis	Two-sided significance level of $\alpha = 0.05$
Eligibility criteria (PICO)	Included patients were clinically disease-free after receiving curative-intent treatment Any evaluations (e.g., clinical follow-up, laboratory tests, and imaging) with surveillance performed at any frequency, compared to another At least one outcome: survival, recurrence, side effect from imaging examinations, and patient-reported outcomes.
Exclusion criteria	Articles or abstracts not published in English Recruited >20 % or an uncertain percentage of non-target patients without subgroup analysis for the target patients
Patient & disease & interventions characteristics	See Rajagopal 2024
Results	See copy-paste below of the Table 4 from Rajagopal 2024 The reviewed RCT indicated that a reduced follow-up schedule, with clinical follow-up strategies alone, was safe and cost-effective for stage IA–IIC patients with melanoma. The results from one study showed that PET/CT had a higher PPV and lower false positive rate compared with CT alone in detecting recurrence in stage I–III patients. Surveillance strategies employing serial imaging examinations (chest x-rays, PET/CT or whole-body CT and brain MRI) detected about 40 % additional recurrences in stage IIA–IIIC patients with melanoma. In stage IIC and IIIA–C patients, these investigations, at five-year follow-up, detected 50 % more recurrences that led to additional management such as surgery. There was no clear evidence to support the use of ultrasound follow-up in stage IB–IIA melanoma to improve patient outcomes. The use of intensive or biannual imaging surveillance did not lead to better patient-related outcomes in comparison with annual imaging surveillance in stage IIIA–D patients.
Discussion	There were very few patients with stage IIB–C disease in the retrieved RCT, no subgroup analysis was conducted and the use of screening imaging strategies in this high risk IIB/C patient group was not clarified. The certainty of the evidence from the 5 comparative studies is very low due to potential confounders not being controlled for by performing a multivariable analysis or balancing for baseline characteristics in the comparative groups. All retrieved publications started recruiting patients prior to the advent of new therapies in the adjuvant and metastatic settings.

	- Given these novel therapies have been demonstrated to prolong OS in the metastatic setting, accurately identifying recurrent or metastatic disease is crucial, especially as data suggests that patients treated with a lower burden of disease have improved survival outcomes. - For patients having systemic treatment, the risk of continued ineffective treatment is higher due to side effects. So, more rather than less intensive surveillance with imaging follow-up to detect clinically occult disease may be needed. The potential false positive results from imaging evaluations should be considered and discussed with each patient. Patients should be informed of the potential risk of secondary cancer from CT or PET/CT examinations, although the risk remains very low.
Conclusions	Limited number of trials met the criteria It is important that surveillance protocols be based on individual risk of recurrence and established best practices. Future high-quality studies are needed to investigate the roles of new biomarkers in the surveillance of the target population and clarify the frequency of imaging follow-up strategies, especially in patients with high-risk stage II melanoma. The use of PET/CT vs. CT alone should also be explored on a larger scale with subgroup analysis by stage.
Limitations	The literature search was limited to English publications, which could potentially lead to missing relevant articles published in non-English journals. Only 4 literature databases were searched due to time limitations. Relevant papers in other medical databases may have been missed. One co-author instead of 2 independent reviewers screened titles and abstracts of the literature search, which could have potentially led to the inadvertent omission of a few relevant articles.



Appendix 7.5.2. Primary studies retrieved by the authors of the selected systematic review

Table 68 – Follow-up: Evidence tables of primary studies from the systematic review of Rajagopal

Moncrieff et al., 2022; Ann.Surg.(Moncrieff 2022); Moncrieff et al., 2020; Ann.Surg.Oncol(Moncrieff 2020); Deckers et al., 2020; Ann.Surg.Oncol(Deckers 2020)

MELFO study: Follow-up schedule for patients with sentinel node-negative cutaneous melanoma (the MELFO study): an international phase III randomized clinical trial

Methods	
• Design	Multicentre, nonblinded RCT
• Source of funding and competing interest	Research grant from the Groningen Melanoma Sarcoma Foundation. The Anthony Long Trust and Dutch Cancer Society funded the production of the patient self-examination videos that were used to educate patients in the United Kingdom & Netherlands cohorts, respectively. The funders played no role in the study design; nor in data collection, interpretation and analysis; nor in the writing of the report; nor in the decision to submit the article for publication. The authors report no conflicts of interest.
• Setting	UK, The Netherlands; 2006-2016; secondary/tertiary care melanoma referral centers
• Sample size	388, 1:1 randomisation in blocks of four in 2 groups
• Duration	10 years
• Follow-up	Median F/U time of 5 years. Surgical oncologists, dermatologists, or nurse practitioners undertook nonblinded follow-up in dedicated melanoma clinics. Diagnostic imaging was only performed in patients suspicious for recurrent disease, as appropriate.
• Statistical analysis	Full description available
Patient characteristics	
• Eligibility criteria	Stage I and II: patients with sentinel node-negative, cutaneous stage pT1b–pT4b (AJCC 7 th ed.), who had undergone surgery for their primary melanoma with curative intent. Adult patient 18-85 years
• Exclusion criteria	Stage III and IV Age below 18 or above 85 years, Unable to complete the questionnaires for reasons of comprehension Another malignancy or previous melanoma primary
• Patient & disease characteristics	Females n=192, males n=196. Median age: 61 years (IQR, 50 to 69); IA-IB: 64%, IIA:18%, IIB:15%, IIC:3%, (AJCC 8 th ed.)
Interventions	

- Intervention group (1) N= 192. Frequency of clinical F/U at 1st, 2nd, 3rd, 4th, 5th year after surgery for primary melanoma:
 - IA-IB: 1, 1, 1, 1, 1;
 - IIA: 2, 2, 1, 1, 1;
 - IIB-IIC: 3, 3, 2, 1, 1
 2015 NICE guideline or 2013 Netherland guideline was followed for type of interventions. This included the clinical following interventions: Patient history(PH), Physical examination(PE), Structured SSE education
- Comparator N= 196. Frequency of clinical F/U as per national guideline at 1st, 2nd, 3rd, 4th, 5th year after surgery: UK: IA-IIC: 4, 4, 4, 2, 2 and Netherlands: IA-IIC: 4, 3, 2, 2, 2

Results

- Outcome 1: patient reported outcome 240 patients (62%) (120 in each study arm; 135 patients from the United Kingdom and 95 from the Netherlands) completed their PROMs questionnaires. Groups were well matched except for gender (females 59%). Most patients in both groups were continuing to examine their skin and lymph node fields regularly, and both were performing this with a similar frequency.
At T₀, there were no significant differences between the 2 arms in terms of PROMs.
At 5 years, both arms expressed high satisfaction with their regimens (>97%).
At 5 years, both groups reported significantly improved mental and physical states of health compared with the baseline measurements.
At 5 years, no reported difference in PROMs between the 2 arms was found on the Impact of Event Scale(IES), the State-Trait Anxiety Inventory(STAI), Cancer Worry Scale(CWS), and RAND-36 scores indicating.

TABLE 2. Patient-reported QoL Outcome Measures at Baseline and After 5 Years—United Kingdom and The Netherlands Combined

Questionnaire	Study Group	Baseline [Mean (SD)]*	5 y [Mean (SD)]	Study Group (P†)		Baseline–5 y (P‡)	Effect Size§
				0 y	5 y		
STAI	Conventional	32.4 (7.6)	31.3 (8.2)	0.68	0.48	0.15 (conventional)	0.139
	Experimental	32.9 (8.2)	30.4 (7.9)			0.001 (experimental)	0.311
CWS	Conventional	7.8 (2.7)	6.3 (1.7)	0.11	0.56	<0.001 (conventional)	0.665
	Experimental	7.2 (3.1)	6.1 (2.1)			<0.001 (experimental)	0.415
IES	Conventional	27.7 (9.7)	20.2 (6.9)	0.13	0.60	<0.001 (conventional)	0.891
	Experimental	25.7 (9.8)	20.7 (8.0)			<0.001 (experimental)	0.559
RAND-36 Mental Component	Conventional	50.6 (9.9)	52.5 (8.5)	0.86	0.70	0.06 (conventional)	−0.206
	Experimental	50.4 (10.3)	52.9 (8.1)			0.003 (experimental)	−0.270
RAND-36 Physical Component	Conventional	49.1 (9.4)	51.6 (11.6)	0.12	0.19	0.02 (conventional)	−0.237
	Experimental	47.1 (10.6)	49.8 (10.1)			0.004 (experimental)	−0.261

*For patients who also filled in the questionnaire at 5 years.

†t test.

‡Paired t test.

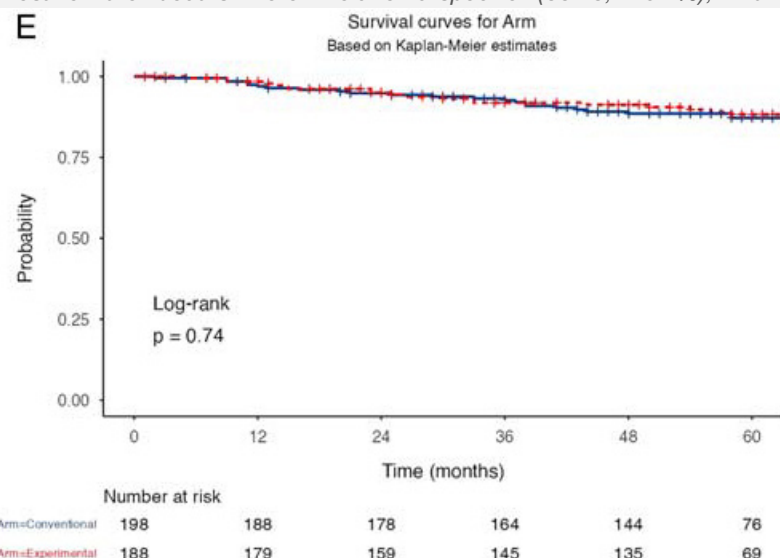
§Cohen d.

State-Trait Anxiety Inventory-state version (STAI-s) 20-items (Items could be scored on a 4-point scale ranging from “not at all” =1 to “very much” =4 (range 20–80). (Spielberger 2010) The 3-item Cancer Worry Scale (CWS), measuring concerns about developing cancer again and the impact on daily activities. Higher scores mean more worries (range 3–12). (Custers 2014) The 15-item Impact of Event Scale (IES) evaluating the extent to which patients suffer from life-hazards, in this case of having a melanoma, in terms of avoidance and intrusion. A higher score (range 0–75) corresponds to a higher level of stress response



	symptoms. (Horowitz 1979. The RAND-36, a 36-item health-related QoL questionnaire, of which the mental component and physical component summary scores were used. The summary scores are standardized with a mean of 50 and a SD of 10. A higher score defines a more favorable health state. {Hays, 2001 #727}) <i>Copied from Moncrieff et al 2022 (Moncrieff 2022)</i>
Outcome 2: recurrence or second primary melanoma	At 5 years follow-up, outcome data was available for 386 patients (99.5%). In total, 59 recurrences and 16 new melanoma primaries were detected during the study period. In both groups, 75% or more of the detections were initially by the patient: self-examination was the method of detection for 25 experimental patients and 32 control patients (75.8% vs. 76.2%; $p=0.41$). The 5-year cumulative hazard for detection of recurrence or new primary melanoma was 22.3% (95%CI : 15.8%–28.2%) for the control arm and 18.5% (95%CI : 12.2%–24.3%) for the experimental arm, with a HR of 0.86 (95%CI : 0.54–1.36; $p=0.51$). There was no significant difference between the 2 arms in terms of stage of detection nor subsequent first-line treatment of patients following tumor recurrence.
Outcome 3: melanoma-specific survival	There was no difference in DSS between the two arms: HR= 0.85, 95%CI 0.42–1.72, $p=0.66$ In multivariable analysis: HR 1.00; 95%CI 0.49-2.07; $p=0.99$
Outcome 4: disease-free survival	The 5-year DFS was 80.3%, 95%CI 74.6%–86.5% for the CSG and 82.7% (95%CI 76.9%–88.9% for the ESG In multivariable analysis: HR 0.92; 95%CI 0.56-1.53; $p=0.76$
Outcome 5: overall survival	There was no difference in OS: HR 0.9; 95%CI 0.49-1.66; $p=0.74$. Added by KCE: <i>The absolute numbers for OS are not presented by intervention and control: “During follow-up, 43 patients had died, including 20 patients in the ESG cohort and 23 patients in the CSG cohort.</i>

Most of the deaths were melanoma-specific (33/43; 76.7%), with 18/23 (78.3%) in the CSG and 15/20 (75%) in the ESG.”



- Outcome 6: distant metastasis-free survival
There is an identical 5-year DMFS of 87.1% for both study groups (HR =0.99, 95%CI 0.54–1.82, p=0.98)
- Adverse events and other
Overall compliance with the follow-up schedules at 5 years was 51.7% (61/120) for both groups. No significant differences between the groups were detected in terms of the number of unscheduled or missed follow-up appointments. In approximately half of the patients, the additional visit was confined to one isolated episode in 5 years.

Limitations and other comments

- Limitations
Adherence rate: 99.5% for recurrence and survival outcomes and 62% for patient-reported outcomes
- Conclusions authors
These results support the hypotheses that a reduced follow-up schedule induces no differences in PROMs, patient satisfaction, detection rates, recurrences, and deaths.
A reduced-intensity, AJCC stage-adjusted follow-up schedule for sentinel node–negative melanoma patients is a safe strategy
Patient self-examination is effective for recurrence detection with no evidence of diagnostic delay.
Patients' acceptance is very high.



Rueth et al., 2014, Ann Surg(Rueth 2014)

Is Surveillance Imaging Effective for Detecting Surgically Treatable Recurrences in Patients With Melanoma? A Comparative Analysis of Stage-Specific Surveillance Strategies

Methods	
• Design	Retrospective comparative study of single-institution, patient-level data, calculating transition probabilities based on a Markov model simulating the natural history of patients with stage I–III melanoma.
• Source of funding and competing interest	The authors declare no conflicts of interest. Supported in part by grant R01 CA127328-03, National Institutes of Health, National Cancer Institute. The University of Texas MD Anderson Cancer Center is supported in part by the National Institutes of Health through Cancer Center Support Grant CA016672.
• Setting	The University of Texas MD Anderson Cancer Center, US, Medical records of patients evaluated and surgically treated from 1992 to 2007
• Sample size	1600
• Duration	/ (retrospective)
• Follow-up	The regional or distant recurrence (that could be treated with surgical resection with curative intent) rate was estimated with a probabilistic Markov model based on the stage-specific natural history of real patients. The effects of disease recurrence were modeled as a sequence of transitions between mutually exclusive health states: NED, regional recurrence, distant recurrence, death from disease and death from other causes. Separate models were developed for patients with stage I, II, IIIA, IIIB, and IIIC disease, with transition probabilities calculated from contemporary patient-level data. Patient-level time-to-event data were used to determine the monthly transition probabilities, which were estimated using parametric survival models from the time of definitive local/regional treatment.
• Statistical analysis	As a base estimate, imaging was assumed to detect regional and distant recurrences of which 80% and 20% could be surgically treated with curative intent, respectively. Sensitivity analyses were conducted for all point estimates. For each disease stage, the number of surgically treatable regional or distant recurrence detected during 5 years per 10,000 patients undergoing computed tomography (CT) or positron emission tomography (PET)/CT scans at 6- or 12-month intervals was calculated. The associated positive and negative predictive values and life expectancy were also calculated and compared with clinical examination alone. Stage-specific Kaplan-Meier survival curves were constructed to ensure that the stage-specific survival estimates for this single-institution cohort were similar to those based on a large, multi-institutional cohort of patients.

	In each stage-specific model, a base-case analysis was performed for 50-year-old patients.
Patient characteristics	
Eligibility criteria	Model estimates for the natural history of patients were derived from 1600 patients with stage I–III melanoma treated with curative intent: surgical resection that rendered them free of disease without evidence of distant metastatic disease. So all patients were considered to be in the “no evidence of disease”(NED) health state after having completed surgical treatment for melanoma. Stage I-II patients has pathology negative LN. Staging is based on the AJCC 7th edition.
Exclusion criteria	Not NED
Patient & disease characteristics	Stage I: 45%, II: 4.5%, IIIA: 8.5%, IIIB: 23%, IIIC: 19%. A limited number of children was included: lower age range 13.5 years The single-institution stage-specific survival curves were compared with survival curves of patients in the AJCC melanoma staging database and demonstrated similar stage-specific survival ensuring generalizability of the results.
Interventions	
Intervention group (1)	F/U with imaging strategy CT chest/abdomen/pelvis performed every 6 months for 5 years or until recurrence
Intervention group (2)	F/U with imaging strategy CT chest/abdomen/pelvis performed every 12 months for 5 years or until recurrence
Intervention group (3)	F/U with imaging strategy PET/CT chest/abdomen/pelvis performed every 6 months for 5 years or until recurrence
Intervention group (4)	F/U with imaging strategy PET/CT chest/abdomen/pelvis performed every 12 months for 5 years or until recurrence
Comparator	clinical physical examination every 3 months
Results	



- Outcome 1: recurrence: number of surgically treatable regional or distant recurrence identified at 5 years per 10 000 patients

TABLE 3. Number of Surgically Treatable Regional and Distant Recurrences Detected in 5 Years per 10,000 Patients and the Number of Studies Needed to Detect a Single Treatable Recurrence

	6-mo Examination Interval				12-mo Examination Interval			
	Regional Recurrences (n)	Distant Recurrences (n)	Studies Performed (n)	NNT	Regional Recurrences (n)	Distant Recurrences (n)	Studies Performed (n)	NNT
Stage I								
CT	229	51	91,646	327	114	11	45,296	362
PET/CT	291	73	91,569	252	146	36	45,314	249
Stage II								
CT	660	146	81,888	102	271	75	39,823	115
PET/CT	852	189	82,174	79	363	87	39,939	89
Stage IIIA								
CT	582	146	79,065	109	273	70	38,831	113
PET/CT	793	218	78,865	78	357	99	39,003	86
Stage IIIB								
CT	1,093	260	60,448	45	474	107	28,877	50
PET/CT	1,459	349	60,386	33	612	166	28,931	37
Stage IIIC								
CT	1,269	301	46,312	29	501	136	21,743	34
PET/CT	1,683	398	46,529	22	680	161	21,945	26

The table represents data for each surveillance imaging strategy, by stage.

NNT indicates number needed to treat: the number of studies needed to detect 1 treatable recurrence.

-recurrence rate with biannual F/U (CT vs PET/CT): 4737/10 000=47.37% vs 6305/10 000=63.05%

-recurrence rate with annual F/U (CT vs PET/CT): 2032/10 000=20.32% vs 2707/10 000=27.07%

- more treatable recurrences were detected with PET/CT than with CT alone

- recurrence rates for patients with stage I melanoma were low: 87.7% of patients had no evidence of disease at 5 years,

-additional recurrence detection rate for stage I

- by any imaging at any schedule vs clinical only: regional 2.6%-5.2%, distant 1.8%-3.6%

- by CT annually: regional and distant, 1.3% of patients

- by PET/CT annually: regional and distant, 1.8% of patients

-additional recurrence detection rate for stage III by any imaging every 12 months vs clinical only: regional 4.6%, distant 14.8%.

-additional recurrence detection rate for stage IIIC by any imaging every 12 months vs clinical only: regional 6.4%, distant 8.4%;

- Outcome 2: 5-year disease specific survival

There were no differences in 5-year disease specific survival between CT and PET/CT, regardless of disease stage; and more frequent imaging was not associated with a substantial increase in disease specific survival, regardless of disease stage.

Disease-specific survival with biannual F/U (CT vs PET/CT): Stage I: 92% vs 92%; stage II: 77% vs 77%; stage IIIA: 76% vs 76%; stage IIIB: 53% vs 53%; stage IIIC: 37% vs 38%

Disease-specific survival with annual F/U (CT vs PET/CT): Stage I: 92% vs 92% stage II: 76% vs 76%; stage IIIA: 76% vs 76%; stage IIIB: 52% vs 53%; stage IIIC: 36% vs 37%

The greatest survival benefit was seen for patients with stage IIIB and stage IIIC disease. Even in these groups, the difference in 5-year disease specific survival when comparing a *less rigorous* imaging strategy of CT every 12 months and a *more rigorous* imaging strategy of PET/CT every 6 months was minimal.

TABLE 4. Unadjusted 5-Year Disease-Free Rates, Disease-Specific Survival, and Increase in Life Expectancy With Surveillance Imaging

	6-mo Examination Interval			12-mo Examination Interval		
	5-Year NED (%)	5-Year DSS (%)	Average Increase in Life Expectancy (mo)	5-Year NED (%)	5-Year DSS (%)	Average Increase in Life Expectancy (mo)
Stage I						
CT	87.7	91.8	0.3	87.7	91.5	0.2
PET/CT	87.7	91.9	0.4	87.7	91.5	0.2
Stage II						
CT	70.5	77.0	0.9	70.5	76.2	0.5
PET/CT	70.5	77.4	1.1	70.5	76.3	0.5
Stage IIIA						
CT	72.0	76.1	0.8	72.0	75.7	0.4
PET/CT	72.0	76.3	0.9	72.0	75.8	0.4
Stage IIIB						
CT	48.3	52.9	1.4	48.3	52.4	0.7
PET/CT	48.3	53.4	1.7	48.3	52.5	0.7
Stage IIIC						
CT	32.1	37.0	1.8	32.1	36.4	0.8
PET/CT	32.1	37.6	2.0	32.1	36.5	0.8

The table represents data for each surveillance imaging strategy, by stage.
NED indicates no evidence of disease; DSS, disease-specific survival.

- Outcome 3: life expectancy:

the mean increase in life expectancy gained as a result of detecting and successfully treating an early recurrence and the relative increase in life expectancy as a result of imaging surveillance:

routine surveillance imaging did not result in a substantial gain in life expectancy for any subgroup of patients with melanoma, regardless of imaging modality or frequency

-life expectancy at stage I (without imaging vs with PET/CT biannual): 52 months vs 52.4 months or 0.7% relative survival increase

-life expectancy at stage IIIC (without imaging vs with PET/CT biannual): 30 months vs 32 months or 6.8% relative survival increase

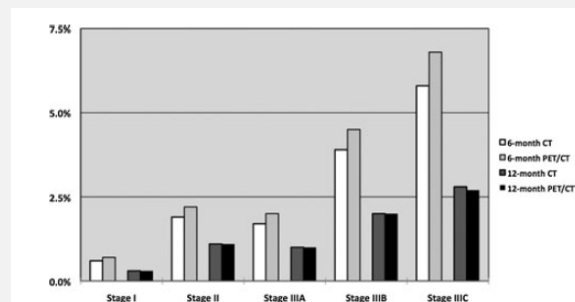


FIGURE 3. Stage-specific relative increase in life expectancy for surveillance imaging compared with clinical examination alone.



- Outcome 4: the total number of imaging studies required to detect and successfully treat an early regional or distant recurrence

- patients with stage I melanoma: with 12-month imaging intervals, 362 CT scans or 249 PET/CT scans would have to be performed during the course of 5 years to diagnose 1 treatable recurrence.

- patients with stage IIIC melanoma with 12-month imaging intervals, 1 of every 34 CT scans or 1 of every 26 PET/CT scans detected a treatable recurrence

- Outcome 5: the calculated positive and negative predictive values associated with each imaging strategy

TABLE 5. Positive and Negative Predictive Values of Surveillance Imaging

	6-mo Examination Interval		12-mo Examination Interval	
	PPV (%)	NPV (%)	PPV (%)	NPV (%)
Stage I				
CT	1.5	99.8	1.4	100.0
PET/CT	4.5	99.9	5.0	99.9
Stage II				
CT	4.6	99.2	4.5	99.2
PET/CT	13.1	99.8	12.7	99.7
Stage IIIA				
CT	4.1	99.3	4.2	99.4
PET/CT	13.0	99.8	12.2	99.8
Stage IIIB				
CT	9.7	98.4	9.0	98.5
PET/CT	25.8	99.5	24.7	99.6
Stage IIIC				
CT	14.3	97.3	12.8	97.6
PET/CT	34.8	99.1	32.3	99.2

The table represents data for each surveillance imaging strategy, by stage.
 PPV indicates positive predictive value for detecting regional or distant recurrences; NPV, negative predictive value for detecting regional or distant recurrences.

The high false-positive rates of CT (20%) and PET/CT (9%) resulted in low positive predictive values, particularly for patients with stage I disease, in whom recurrence rates were low.

As recurrence rates increased with each disease stage, the positive predictive values of CT and PET/CT increased as well.

For all stages of melanoma, the addition of PET to CT increased the positive predictive value of the study, thus adding diagnostic value.

Both CT and PET/CT were effective in predicting absence of disease, with negative predictive values exceeding 97% for all stages of melanoma.

- Adverse events

Not studied

For 10,000 patients, routine annual surveillance imaging for patients with stage I melanoma would result in a 5-year total of 45,296 CT scans and 45,314 PET/CT scans

Limitations and other comments

- Limitations

Modelling study

- Conclusions authors

With a negative predictive value nearing 100%, routine imaging can effectively rule out recurrence; however, the high rate of false-positive studies and low positive predictive value mean that a large number of imaging must be performed to detect a small number of treatable recurrences, likely with little impact on patient survival.

Kurtz et al. 2017, JSR(Kurtz 2017)**Surveillance strategies in the follow-up of melanoma patients: too much or not enough?**

Methods	
• Design	Retrospective comparative study
• Source of funding and competing interest	One researcher. has clinical trial support from Bristol-Myers Squibb and Karyopharm. Another researcher has clinical trial support from Pfizer, Bristol-Myers Squibb, and Tracon; and also serves on the advisory board for Genetech but received no financial benefits.
• Setting	Ohio State University USA, 2009-2015
• Sample size	247 (369 patient files reviewed of which 122 were lost to follow-up after the 6 months after surgery=exclusion/inclusion criteria)
• Duration	/ (retrospective)
• Follow-up	Some patients were followed up for 5 years and more but the analysis/data are based on the median FU time which is about 3 years. FU median follow-up of 35 months for patients with stage IIA/IIB and 31.2 months for patients with stage IIC/IIIA-C.
• Statistical analysis	Results for overall survival and recurrences are presented for the median follow up time of the intervention group. Kaplan-Meier survival curves were created using MedCalc software.
Patient characteristics	
• Eligibility criteria	patients with stage II and III melanoma who underwent surgery as primary therapy followed for a minimum of 6 months after surgical resection to achieve no evidence of disease status (NED)
• Exclusion criteria	F/U lasts for less than 6 months
• Patient & disease characteristics	Stage IIA-B (N=125) and stage IIC-IIIC (N=122) IIA: 19%, IIB: 31%, IIC: 9%, IIIA: 24%, IIIB:12%, IIIC: 5%



Table – Primary tumor characteristics and initial treatment of study patients.

Stage	No.	Median Breslow depth (range)	WLE only	WLE, SLNB	WLE, SLNB, and lymph node dissection	Additional adjuvant therapy
IIA	48	2.04 (0.9-3.5)	2 (4%)	46 (96%)	0	1 (2%)
IIB	77	3.78 (0.51-16)	3 (4%)	71 (92%)	3 (4%)	5 (6%)
IIC	21	7.83 (1.7-25)	1 (5%)	20 (95%)	0	2 (10%)
IIIA	59	2.77 (0.55-42)	0	13 (22%)	46 (78%)	15 (25%)
IIIB	30	2.7 (0.6-6.33)	0	10 (33%)	20 (67%)	13 (43%)
IIIC	12	4.06 (2.3-10)	0	2 (17%)	10 (83%)	5 (42%)
Total	247	3.43 (0.51-42)	6 (2%)	162 (66%)	79 (32%)	41 (17%)

WLE=wide local dissection; SLNB=sentinel lymph node dissection

Interventions	
Intervention group	Clinical examination with imaging (n=181)(73%) - IIA-B (n=76): clinical examination plus at least 2 serial chest x-rays - IIC/IIIA-C (n=105): clinical examination plus some combination of chest x-rays, CT scans (including chest, abdomen, pelvis, and neck for head and neck primary), magnetic resonance imaging (MRIs), whole body PET/CTs, or other directed imaging (ultrasound). The imaging modalities varied strongly between and within a patient.
Comparator	Clinical examination only (n=66) (27%): IIA-B (n=49), IIC (n=0), IIIA-C (n=17)
Results	
Outcome 1	recurrence detected in 42 of the 247 patients (17%) - for all stages: detection by clinical examination in 25/42 (60%) and by imaging 17/42 (40%) - by stage: - stage IIA-IIB: clinical exam 11/14 (79%) and chest x-rays imaging 3/14 (21%) - stage IIC-IIIC: clinical exam 14/28 (50%) and different types of imaging 14/28 (50%)
Outcome 2	At median follow-up of 35 mo, progression-free survival: stage IIA-IIB; comparison clinical only vs with imaging not significant p=0.75 at 5 years; presented as a figure without details of the results/data
Outcome 3	Overall survival at 35 months - stage IIA-B: with at least 2 serial X-rays: 96%; 95%CI 0.89-0.98 vs clinically 95%; 95%CI 0.88-0.99; p=NS - because a large majority (87%) of patients in the stage IIC/IIIA-C was in the intervention group, no survival comparison was done.
Adverse events and other	Median adherence time: IIA-B 35 months and IIC-IIIC 32 months

Limitations and other comments

• Limitations	the retrospective nature as well as the variety and inconsistent imaging modalities among patients
• Conclusion authors	We found wide variability among providers in approach to follow-up imaging for stage II and III melanoma. In stage IIA/B melanoma surveillance, chest x-rays did not improve survival compared to physical examination alone and detected a small percentage (21%) of asymptomatic recurrences. However, for stage IIC and IIIA-C melanoma where the recurrence rates are higher, routine whole body imaging detected recurrences not found on clinical examination in 50%.

Ribero et al. 2017(Ribero 2017)

Ultrasound-based follow-up does not increase survival in early-stage melanoma patients: a comparative cohort study

Methods	
• Design	Retrospective comparative study of 2 historical cohorts
• Source of funding and competing interest	Research grants: Fondo de Investigaciones Sanitarias; CIBER de Enfermedades Raras of the Instituto de Salud Carlos III; Fundacio' La Marato' de TV3; European Commission under the 6th Framework Programme; CERCA Programme/ Generalitat de Catalunya; Asociacion Espanola Contra el Cancer. No conflict of interests declared
• Setting	Italy and Spain, 1998-2015
• Sample size	Both cohort N=1149; Italy N=595 (1998-2013), intervention cohort; Spain N=554 (1998-2013), control cohort
• Duration	1998-2015 with median FU 4.14 years
• Follow-up	Yes, follow-up protocols at both centres were performed by trained dermatologists, who are specialist in skin cancers and melanoma follow-up
• Statistical analysis	Described fully; survival analysis Disease-specific survival (DSS) was calculated from the surgical excision date of the primary melanoma to the date of melanoma death or last checkup Distant metastasis-free survival (DMFS) was calculated from the surgical excision date to the appearance of the first metastasis in distal site primary melanoma or last check-up



	Nodal metastasis-free survival (NMFS) was calculated from the surgical excision date to the appearance of the first nodal metastasis in the regional basin or last check-up
Patient characteristics	
• Eligibility criteria	patients with stage IB and IIA melanoma; For patients with multiple melanomas, the most invasive melanoma tumour was included, as it is the one that drives the prognosis
• Exclusion criteria	Other stages: patients at AJCC stage IIB and IIC, as well as IA, were excluded from the present study because the follow-up was superimposable in the two which would make any comparison impossible
• Patient & disease characteristics	From both databases and electronic medical records were extracted the basal demographic characteristics of the patients, clinical and pathologic melanoma features, recurrence time and site, and survival. No statistical differences between cohorts, except for increased female prevalence in the C-FU cohort, whereas in the US-FU cohort there was a higher male prevalence. Median age was 53.8 years (IQR 41.5-65.2) with a median follow-up time of 4.14 years (IQR 1.2-7.6). Median follow-up of patients without relapse was 3.8 years (IQR 1.1-7.3). Breslow thickness of 1.39 mm in C-FU and 1.45 mm in US-FU (NS). No patients received target therapies and/or immunotherapy during the follow-up period
Interventions	
• Intervention group	US-FU: Italian cohort, N = 595. F/U: examination every 6 months for 5 years (+SSE education). US of the regional lymph node basins every 6 months for 5 years. Abdomen US every 12 months for 5 years."
• Comparator	C-FU: Spanish cohort, N =554. F/U: examination every 4 months (+SSE education) for the first 2 years, then every 6 months for the remaining 3 years. Laboratory tests (S100B) every 6 months for 5 years.
Results	
• Outcome 1	recurrence detected in 69 (12.5%) comparator and 72 (12.1%) in US group

Recurrence pattern divided for centre.

Recurrence site	C-FU	US-FU	Total
Skin	16	14	30
Skin, regional lymph node	3	0	3
Skin, regional lymph node, at distance	1	0	1
Skin, at distance	1	0	1
Regional lymph node	26	24	50
Regional lymph node, at distance	2	0	2
At distance	20	34	54
Total	69	72	141

C-FU, clinical follow-up; US-FU, ultrasound-based follow-up.

Median relapse time for the first metastatic site was 2.11 years (IQR 1.14-4.04) for skin metastases, 1.32 (IQR 0.57-3.29) for lymph node metastases and 2.84 (IQR 1.32-4.60) for distant metastases.

There was no significant difference in median time to detection of the first recurrence in the US-FU compared with the C-FU (median time 2.32 years versus 2.97 years, respectively, $p=0.23$).

- Outcome 2-5

Comparing clinical versus US follow up: 33 patients (6%) died in the C-FU cohort and 60 (10.1%) in the US-FU cohort. Distant metastases were detected in 47 (8.1%) patients of each cohort. 26 patients (4.7%) in the C-FU cohort and 29 (4.9%) in the US-FU group developed a nodal disease.

No statistically significant difference for the following outcomes:

disease-free interval (DFI), HR=0.81, $p=0.23$, 95%CI 0.58-1.14

melanoma-specific survival (MSS) HR=1.24, $p=0.32$, 95%CI 0.81-1.90

distant metastasis-free survival (DMFS), HR=0.78, $p=0.22$, 95%CI 0.51-1.16

nodal metastasis-free survival (NMFS), HR=0.88, $p=0.64$, 95%CI 0.51-1.50
- Adverse events and other

None

Melanoma has profound effects on patients both psychologically and emotionally, even at early stages, so regular follow-up may help patients cope with the idea of recurrence and offer opportunities for patient education.

The risk of nodal relapse, after a negative sentinel lymph node in the same basin has been described as a false-negative. False-negatives were less than 5% in both cohorts in stages IB and IIA.

Limitations and other comments

- Limitations

As a limitation of the study, gender and location of primary melanomas were not balanced between the two centres. We are conscious of the slight difference in survival related to sex differences and particularly in some body sites. Nevertheless, Breslow index and the presence of ulceration, which are the strongest prognostic factors, were balanced in both cohort.



	Further studies are required to evaluate the impact of early detections of metastasis by US and survival in patients identified as high risk by other methods, with the possibility of receiving immunotherapy. The implementation of new tests based on prognostic genetic signatures in low-risk melanomas, is promising for the identification of the patients who may relapse and die. Another limitation of this study is that during the 15 years of follow-up, many specialists and US equipment have changed during this time.
• Conclusion authors	US of the regional lymph nodes and US of the abdomen are not associated by an increase in DFI, DMFS, NMFS or MSS, at a time before the introduction of new treatments for melanoma. The absence of difference in any of the survival parameters suggests that survival is not improved by early detection of regional nodal metastasis by the practice of US. Our recommendation for patients in stage IBelIIA after negative SLNB is to perform clinical follow-up.

Broman et al. 2021(Broman 2021)

Surveillance of sentinel node positive melanoma patients who receive adjuvant therapy without undergoing completion lymph node dissection

Methods	
• Design	Retrospective comparative study based on a combination of cancer registry and institutional pathology database queries
• Source of funding and competing interest	Several fees/grants from companies. Research Program
• Setting	When ? 2014-2019: the period of practice-changing systemic immune and molecularly targeted therapies for the adjuvant setting, initially through clinical trials and later as standard of care Where? At Moffitt Cancer Center
• Sample size	N=159: a cohort of patients with SLN-positive melanoma managed with nodal surveillance with at least six months of disease-free follow-up
• Duration	Total study period: 5 years
• Follow-up	Median F/U time: 24 months (IQR, 17 to 33); FU rate 90 % Surveillance regimens were determined by treating medical and surgical oncologists. Surveillance consisted of scheduled clinical assessments with or without imaging including CT, PET/CT, brain MRI, and nodal basin ultrasound determined by treating oncologist. Levels of surveillance intensity were determined empirically by review of central tendencies of surveillance frequency for each clinical encounter or imaging study. Based on this average utilization, individual patients' surveillance regimens are low, moderate or high.
• Statistical analysis	Descriptive statistics included the number and location of recurrences, methods of recurrence detection, and time to first recurrence. Recurrent disease was identified by comparative review of clinical documentation, radiographic studies, and pathology reports. Extracranial recurrences were confirmed by biopsy when feasible. Recurrences were categorized by site of initial recurrence as local-regional (primary site or in-transit), nodal (SLN-positive basin), distant, or multiple sites. Methods of recurrence detection were determined using clinical documentation, imaging reports, and pathology reports. For each level of surveillance intensity, rates of image-detected versus clinically detected recurrence, the proportion of recurrences amenable to complete surgical resection, and recurrences that were able to be definitively treated were compared by using chi-squared tests for pairwise comparisons and Dunn's tests for multiple comparisons. Recurrence free survival was defined as patient alive without recurrence; patients were censored at loss to follow-up or death.



	Cost: Institutional billing data were obtained for each surveillance activity (clinic visits and imaging studies). Using median duration of recurrence-free follow-up, surveillance charges for each detected recurrence were estimated. Charges were used instead of cost to facilitate comparison across multiple payers.
Patient characteristics	
• Eligibility criteria	Patients with stage IIIA-D melanoma with biopsy SLN-positive melanoma managed with nodal surveillance with at least six months of disease-free follow-up
• Exclusion criteria	Patients with clinically involved lymph nodes at presentation or evidence of distant disease on pre-operative or post-operative staging studies
• Patient & disease characteristics	Median age: 65 years (IQR 53-75). Mean Breslow thickness: 2.4 mm (1.4-4.5) On average patients were seen in clinic approximately once every two months, underwent nodal basin ultrasound once every six months, had one PET/CT per year, and one brain MRI per year. 47 patients (30%) received high-intensity surveillance, 42 (26%) moderate-intensity, and 70 (44%) low-intensity or no surveillance. Recurrences were considered asymptomatic if the patient did not have signs or symptoms of recurrent disease during their most proximate clinical encounter to the imaging study. Salvage treatment for recurrent disease was categorized based on whether it was amenable to complete surgical resection and whether it was definitively treated by local therapy and/or radiographic complete response to systemic therapy.
Interventions	
• Intervention group	Moderate intensity N=42: CT or PET/CT every year High intensity N=47: CT or PET/CT every six months
• Comparator	Low intensity N=70: CT or PET/CT less than once a year
Results	
• Outcome 1	Among the patients with minimum 6 months disease-free follow-up (n=159), there were 33 recurrences (median follow-up 24 months). Recurrence rate: 20.7% In order of surveillance intensity, 33% with low-, 50% with moderate-, and 14% with high-intensity surveillance had recurrences amenable to complete resection (p=0.22). 33%, 60%, and 40% with low-, moderate-, and high-intensity surveillance achieved a disease-free interval after surgery or complete response to systemic therapy (p=0.28). No difference in recurrence risk among 3 groups: Low 0.27 vs. Moderate 0.25 vs. High 0.3 (p=0.33).

• Outcome 2	Recurrence-free survival: moderate vs low HR 1.21 (0.53-2.74) high vs low HR 1.05 (0.47-2.32)
• Cost	Estimated charges were proportional to surveillance intensity, ranging from \$4,240 to \$24,838 for a patient with median recurrence-free follow-up receiving low-intensity versus high-intensity surveillance. Charges per detected recurrence were also proportional to surveillance intensity, ranging from \$15,688 to \$82,792 with low-intensity versus high-intensity surveillance. The median charge for nodal basin ultrasound was \$1,123 whereas the lowest cross-sectional imaging charge was for PET/CT at \$5,772.
• Adverse events and other	None
Limitations and other comments	
• Limitations/other	Patients with higher risk primary tumors and higher burdens of nodal disease were more likely to receive adjuvant treatment. Recurrence was detected in 33% (22 of 66) of adjuvant therapy patients and 23% (26 of 111) of patients not receiving adjuvant treatment (p=0.15) due to selection bias because adjuvant patients had more high-risk primary tumor and nodal features.
• Conclusion authors	Compared to moderate- and low-intensity surveillance, high intensity translated to more image-detected recurrences but similar rates of recurrences that were able to be treated definitively. Most nodal recurrences occurred within the first year and were initially detected by clinical assessment or ultrasound, supporting continued use of physical exam and nodal basin ultrasound alongside cross-sectional imaging in stage III. While earlier detection and management of nodal recurrence has not been clearly linked to improved long-term outcomes, potential utility and minimal increased cost support continued use of clinical assessment and nodal basin ultrasound even in adjuvant patients for whom cross-sectional imaging is planned, at least for first year of surveillance when nodal recurrence risk is highest.


Dieng et al. 2022 (Dieng 2022)
The Impact of Surveillance Imaging Frequency on the Detection of Distant Disease for Patients with Resected Stage III Melanoma

Methods	
• Design	Longitudinal cohort – retrospective comparison
• Source of funding and competing interest	Research grants and disclosures presented; honoraria private companies
• Setting	Tertiary referral center Sydney
• Sample size	473
• Duration	median follow-up time of 6.2 years
• Follow-up	Yes
• Statistical analysis	The frequency of the imaging schedule was determined by clinician preference and was grouped as 3- to 4-monthly, 6-monthly, or 12-monthly. Survival status and deaths due to melanoma were confirmed using linkage to the National Death Index.
Patient characteristics	
• Eligibility criteria	patients with stage IIIA–D melanoma
• Exclusion criteria	No baseline imaging test or diagnosed with distant disease prior to their first scheduled surveillance imaging test (i.e. within 6–12 months of surgery). Patients underwent intermittent or ad hoc imaging that could not be categorized into one of the three schedules were excluded
• Patient & disease characteristics	median age was 54 years: annual 52 (14.8) biannual 54 (13.7) 3-monthly 60 (14.2) <0.001. Breslow thickness mean (SD) annual 3.3 (3.6) biannual 5.4 (6.1) 3-monthly 4.8 (3.8). Median follow-up of patients without relapse was 3.8 years (IQR 1.1–7.3).
Interventions	
• Intervention group	intensive (every 3–4 months) (n=141)
• Comparator	biannual (n=47) CT or PET/CT or annual (n=285) CT or PET/CT
Results	
• Outcome 1	distant recurrence was recorded in 252 patients (53%), with 40% detected by surveillance CT or PET/CT, 43% detected clinically, and 17% with another imaging modality.

	Median DDFS was 5.1 years (95%CI 3.9–6.6). Among 139 IIIC patients who developed distant disease, the median dMSS was 4.4 months shorter in those who underwent 3- to 4-monthly imaging than those who underwent 12-monthly imaging.
• Outcome 2	For substages IIIB and IIIC melanoma-specific survival (MSS) was higher for lower intensity; comparing: biannual imaging to annual imaging HR 1.25 95%CI 0.66, 2.40, p=0.495 intensive imaging to annual imaging HR 5.28 95%CI 3.55 to 7.87, p<0.001
• Outcome 3	For substages IIIB and IIIC overall survival was higher in lower intensity ; comparing: biannual imaging to annual imaging HR 1.21; 95%CI , 0.65 to 2.28; p=0.55 intensive imaging to annual imaging HR 5.20; 95%CI , 3.53 to 7.66, p<0.01
• Outcome 4	Distant disease-free survival (DDFS) comparing biannual imaging to annual imaging HR 1.69 95%CI 1.02, 2.78, p=0.040 intensive imaging to annual imaging HR 4.57 95%CI 3.25 to 6.45, p<0.001
• Adverse events and other	None
Limitations and other comments	
• Limitations/other	Results from before the era of adjuvant therapy. Selection bias: intensive surveillance had worse clinical characteristics compared to other two groups. And biannual group similarly worse clinical characteristics than annual group.
• Conclusion authors	“Selecting patients at higher risk of distant recurrence for more frequent surveillance imaging yields a higher proportion of imaging-detected distant recurrences but is not associated with improved survival. A randomized comparison of low versus high frequency imaging is needed.” Patients who underwent 3- to 4-monthly imaging had poorer prognostic characteristics than those who underwent 12-monthly imaging, with the impact of this evidenced in their median MSS and OS.

Primary studies retrieved by the KCE search to update the selected systematic study



Table 69 – Follow-up: Evidence tables of primary studies retrieved by the updated search

Naeser et al., 2022(Naeser 2022)	
Quality of Life in the First Year of Follow-Up in a Randomized Multicenter Trial Assessing the Role of Imaging after Radical Surgery of Stage IIB-C and III Cutaneous Melanoma (TRIM Study)	
Methods	
Design	Nationwide prospective randomized phase III study: quality of life assessment at 1 year F/U. Randomization 1:1 performed in the Electronic Data Capture system at each site and stratified according to tumor stage and radiological assessment method. Only persons at the main study center with defined roles will have access to the final trial data set. The baseline assessment is performed after the informed consent procedure but before randomization. The assessments are made at the study center, just before the study visits, preferably on a web-based device administered by a research nurse.
Source of funding and competing interest	The Research Foundation Stiftelsen Onkologiska Klinikens i Uppsala Forskningsfond; Uppsala University Hospital; Lion's Cancer Fund
Setting	10 oncology sites in Sweden
Sample size	220 patients (arm A = 116, arm B = 104) eligible for analysis but 16 patients not analyzed due to missing questionnaires or follow-up visit not performed according to protocol. 204 patients finally included in the analysis: arm A (standard arm) = 105 patients and arm B (experimental arm) = 99 patients.
Duration	Inclusion from June 2017 and January 2020;
Follow-up	Follow-up for 1 year
Statistical analysis	The questionnaires regarding symptoms of anxiety and depression and quality of life are validated self-reporting questionnaires. The values on the EORTC QLQ-C30 subscales is calculated and transformed to 100-points scales according to guidelines. The two subscales of the HAD-scale is calculated as in the original publication, and suggested cut-offs are implemented, making it possible to compare proportions of patients using the Chi2-test. Analyses of the EORTC QLQ-C30 and HAD subscales were performed by using linear mixed models with center as a random effect and including baseline scale scores in the models. Results from these models are presented as mean differences together with 99% confidence intervals (CI) between the study arms at 1 year. The level of significance was set to 1% to take multiple testing into account. Fisher's exact test was used to compare the study arms regarding number of patients at normal levels and possible and probable cases for anxiety and depression, respectively.
Patient characteristics	
Eligibility criteria	Age above 18 years; Signed and dated written informed consent; Radical surgery for stage IIB-C or III Cutaneous Malignant Melanoma; Sufficient renal function for iv contrast-enhanced CT.

• Exclusion criteria	Comorbidity or general condition prohibiting treatment in case of recurrent disease, current or previous malignancy within 5 years, and participation in other clinical studies interfering with the follow-up program
• Patient & disease characteristics	Overall, the clinical features in the two study arms were similar. Median age: 61 years (arm B), and 67 years (arm A) In both arms, about 60% men and the majority were diagnosed with Stage III melanoma (A = 53 %, B = 59%). Approximately 15% of patients had undergone a complete lymph node dissection, and about 20% received adjuvant systemic therapy after surgery. Only three patients in arm B and no patients in arm A received adjuvant radiotherapy.
Interventions	
• Intervention group (Arm B: n=99)	Clinical follow-up for 3 years (according to modified Swedish national guidelines): - <u>clinical examinations</u> every 12 months for stage II, with an additional visit at 6 months, and every 6 months for stage III patients. - <u>regional ultrasound</u> will only be performed at month 18 and 30 for stage III patients with a positive SLNB without subsequent lymph node dissection as US at baseline, 6, 12, 24 and 36 months are replaced by CT scan or iv contrast enhanced FDG-PET/CT including brain. - <u>laboratory tests</u> (creatinine, S100B protein, ALP, LDH, AST and ALT) at baseline, 6, 12, 24 and 36 months - <u>whole-body imaging</u> at baseline, 6, 12, 24 and 36 months (the modality of imaging (CT or FDG-PET/ CT) is chosen at baseline by the investigator and is kept the same for all examinations; CT of the thorax-abdomen and brain must be performed with iv contrast enhancement; in case of a positive SLNB without subsequent lymph node dissection, CT must include locoregional lymph nodes; whole-body FDG-PET/CT includes the brain to the proximal thighs and the concomitant CT is performed according to a diagnostic examination protocol with iv contrast-enhancement - if the melanoma was situated on a leg, the FDG-PET/CT field-of-view must also include the primary site).
• Comparator (Arm A: n=105)	Clinical follow-up for 3 years (according to Swedish national guidelines): - <u>clinical examinations</u> every 12 months for stage II, with an additional visit at 6 months, and every 6 months for stage III patients. - <u>ultrasound of regional lymph nodes</u> every 6 months for patients with a positive SLNB who have not undergone complete lymph node dissection. - for patients receiving systemic adjuvant treatment, <u>whole-body CT or FDG-PET/CT</u> at 6 months.
Results	
• Outcome 1: difference in HRQoL at 1 year between two arms	No differences in either level of anxiety/depression or quality of life were found at 1 year follow-up between the imaging and non-imaging group. No statistically significant differences were found in either HRQoL subscales or level of anxiety/depressive symptoms between the two study arms either at baseline or at 1-year follow-up. Levels of anxiety and especially depressive symptoms were generally low in the study group. At baseline assessments, 1.9 and 1.0% of study participants, respectively, were considered probable cases regarding depressive symptoms. Levels of anxiety at baseline were higher, with 6.1% probable cases in the experimental arm and 2.9% probable cases in the standard arm. At 1 year, anxiety rate and depression rate were similar to the rates at baseline.



• Outcome 2: recurrence rate	There was a higher rate of recurrence in the experimental arm during the first year. No number available as it is a publication on quality of life.
• Adverse events and other	None
Limitations and other comments	
• Limitations	The TRIM study is still recruiting, and future analyses in more patients and with longer follow-up are planned. Whether the results presented in the current study will change when more data are added remains to be seen. It is possible that HRQoL, anxiety and depressive symptoms would have been rated differently if the assessments had taken place during the months between follow-up visits. Our selection of oncology clinics means that differences in results between patients recruited at oncology as opposed to surgical centers cannot be ruled out. It is unclear whether our results might be generalized to follow-up programs in other cultural settings and for other types of cancer
• Conclusions authors	In conclusion, adding whole-body imaging to physical examinations did not affect the melanoma patients' HRQoL or levels of anxiety or depression.

Helvind et al., Ann. Surg. Oncol. 2023(Helvind 2023)

Earlier Recurrence Detection Using Routine FDG PET-CT Scans in Surveillance of Stage IIB to IIID Melanoma: A National Cohort Study of 1480 Patients

Methods	
• Design	Retrospective, population-based, nationwide cohort study Prospectively collected data from 2 consecutive nationwide population-based cohorts of Danish stage IIB to IIID melanoma patients. Each cohort was followed with a different nationwide surveillance program: the year of primary diagnosis is the proxy for the program used
• Source of funding and competing interest	Research grants from The Danish Cancer Society, The Danish Cancer Research Foundation, and the Research Foundation of Copenhagen University Hospital: Herlev and Gentofte
• Setting	Anywhere in Denmark
• Sample size	1480 patients: 765 patients in cohort 1 and 715 patients in cohort 2
• Duration	Cohort 1: patients with cutaneous melanoma diagnosed in 2008–2010

	Cohort 2: patients with cutaneous melanoma diagnosed in 2016–2017
Follow-up	Patients were followed for a median of 10.8 years in cohort 1 and 4.5 years in cohort 2 Patients were followed until recurrence, death, or end of the follow-up period on 31 December 2021 Patients were censored in the event of emigration (loss to follow-up evaluation) or development of a new primary melanoma of a higher AJCC8 pathologic stage.
Statistical analysis	Descriptive data were reported as means with 95 % CIs if distributed approximately normally or as medians with IQRs if not. Data were compared using the chi-square test for categorical data or Student's t test for continuous variables, with statistical significance set at the 95 % level. To determine the impact of surveillance with routine FDG PET-CT on recurrence detection, <u>cumulative incidences</u> of overall, locoregional, and distant recurrence six months and one, two, three, and five years were estimated using the Aalen-Johansen estimator, with recurrence as the primary event and death before recurrence (death from all causes) as a competing event. To determine the cohort effect on the hazard of recurrence, cause-specific proportional hazards models (CSH) for overall, locoregional, and distant recurrence were fitted, and <u>hazard ratios</u> (HRs) with corresponding 95 % CIs were estimated comparing cohort 2 with cohort 1. Potential confounders included in CSH models were age, sex, CCI, histopathologic subtype of melanoma, and ICD-10 localization of primary tumor. The proportional hazards assumption for the CSH models was tested by graphic evaluation of the scaled Schoenfeld residual plots for any trends. If the assumption of proportional hazards was violated for the cohort variable, models were fitted for appropriate time periods, and HRs were reported for these and for confounders by using separate baselines for each level of the offending variables. For sub-periods, cohort-specific and stage-specific absolute risk of overall, locoregional, and distant recurrence were estimated based on the CSH models. All outcomes were also presented with corresponding <u>cumulative incidences, HR, and absolute risk</u> for a competing event (death from all causes before overall, locoregional, and distant recurrence, respectively)
Patient characteristics	
Eligibility criteria	Patients prospectively registered in the Danish Melanoma Database (DMD) 18 years old or older with a first-time diagnosis of stage IIB to IIID melanoma (AJCC8) treated in 2008–2010 (cohort 1) or 2016–2017 (cohort 2). In case of synchronous melanomas, patients were included with data from the melanoma of highest AJCC8 stage
Exclusion criteria	Absence of pathology report corresponding to the primary tumor in the Danish Pathology Register (DPR)



Patient & disease characteristics	No patients received adjuvant therapy at the time of primary treatment (because adjuvant therapy was not implemented until early 2018 in Denmark) A higher proportion of male patients and patients of higher age and comorbidity index in cohort 2 A higher proportion of patients with nodular melanoma (NM) in cohort 1
Interventions	
Intervention group	Cohort 2 (715 patients): clinical examinations according to the surveillance-program for stage IIB to IIID patients and whole-body routine FDG PET-CT at 6, 12, 24, and 36 months Further referred to FDG PET-CT if recurrence was suspected between routine scans.
Comparator	Cohort 1 (765 patients): clinical examinations alone Access to cross-sectional imaging with FDG PET-CT (with CT in smaller centers) upon suspicion of recurrence
Results	
Primary outcome:	the effect of surveillance with routine FDG PET-CT on the hazard of overall, locoregional, and distant recurrence for patients followed with routine FDG PET-CT versus patients followed with clinical examinations only: Model-testing of the CSH models showed violation of the proportional hazards assumption, with a higher hazard of recurrence in cohort 2 for the first one to two years. A time cut for sub-analyses was set at two years based on graphic evaluation and consideration of timing of routine FDG PET-CT in the surveillance program.
Outcome 1: hazard of recurrence of overall recurrence	During all study period: HR:1.01; 95 % CI 0.85-1.21 During the first two years: HR: 1.16; 95 % CI 0.93–1.44 (hazard of overall recurrence higher for cohort with PET-CT F/U) After two years: HR: 0.81; 95 % CI 0.60–1.11 (hazard of overall recurrence lower for cohort with PET-CT F/U) Within the first two years of surveillance, patients in cohort 2 had a tendency toward a greater hazard of overall recurrence than in cohort 1
Outcome 2: hazard of recurrence of loco-regional recurrence	During all study period: HR:0.84; 95 % CI 0.66-1.06 During the first two years: HR: 1.05; 95 % CI 0.79–1.39 After two years: HR: 0.53; 95 % CI 0.33–0.84 (hazard of loco-regional recurrence significantly lower for cohort with PET-CT F/U) The hazard of locoregional recurrence was comparable between the cohorts. After two years, the hazard of locoregional recurrence was lower for cohort 2.
Outcome 3: hazard of recurrence of distant recurrence	During all study period: HR:1.20; 95 % CI 0.98-1.46 During the first two years: HR: 1.51; 95 % CI 1.16–1.96 (hazard of distant recurrence significantly higher for cohort with PET-CT F/U)

- Outcome 4: hazard of death before recurrence

After two years: HR: 0.86; 95 % CI 0.62–1.20 (hazard of loco-regional recurrence lower for cohort with PET-CT F/U)
51 % greater hazard of detection of distant recurrence in patients in cohort 2

In all the models, the hazard of death before recurrence was comparable between the two cohorts:

Death before overall rec: first 2y-HR: 1.01 0.69–1.47 ; after 2y-HR: 1.42 0.45–2.12

Death before loco-regional rec: first 2y-HR: 0.99 0.73–1.35 ; after 2y-HR: 0.81 0.60–1.11

Death before distant rec: first 2y-HR: 1.07 0.76–1.51 ; after 2y-HR: 1.28 0.90–1.82

Secondary outcome 1: differences in estimated cumulative incidence of overall, locoregional, or distant recurrence at six months and at 1, 2, 3, and 5 years post-treatment for patients followed with routine FDG PET-CT versus patients followed with clinical examinations only

Year of diagnosis	Time ^a	Overall recurrence	Death before event	Locoregional recurrence	Death before event	Distant recurrence	Death before event
2008–2010 <i>n</i> = 765	6 months	6.5 (4.8–8.3)	1.4 (0.6–2.3)	3.3 (2.0–4.5)	1.7 (7.8–2.6)	3.5 (2.2–4.8)	1.6 (0.7–2.5)
	1 Year	13.1 (10.7–15.5)	4.2 (2.8–5.6)	8.0 (6.1–9.9)	5.2 (3.7–6.8)	7.2 (5.4–9.0)	4.8 (3.3–6.4)
	2 Years	22.1 (19.2–25.1)	7.2 (5.4–9.0)	13.5 (11.1–15.9)	10.7 (8.5–12.9)	13.2 (10.8–15.6)	8.5 (6.5–10.5)
	3 Years	27.5 (24.3–30.7)	8.9 (6.9–10.9)	16.6 (14.0–19.3)	14.8 (12.3–17.3)	18.5 (15.7–21.2)	11.0 (8.8–13.2)
	5 Years	34.2 (30.8–37.5)	12.3 (10.0–14.6)	20.4 (17.6–23.3)	21.9 (18.9–24.8)	23.8 (20.8–26.8)	15.7 (13.1–18.3)
2016–2017 <i>n</i> = 715	6 Months	6.3 (4.5–8.1)	2.1 (1.0–3.1)	4.1 (2.6–5.5)	2.2 (1.2–3.3)	3.5 (2.2–4.8)	2.5 (1.4–3.7)
	1 Year	17.5 (14.7–20.3)	4.2 (2.7–5.7)	10.9 (8.6–13.2)	5.9 (4.2–7.6)	12.6 (10.2–15.0)	5.3 (3.7–7.0)
	2 Years	26.9 (23.6–30.1)	8.5 (6.5–10.6)	15.4 (12.8–18.0)	12.9 (10.4–15.3)	21.0 (18.0–24.0)	10.8 (8.5–13.1)
	3 Years	32.3 (28.9–35.8)	11.8 (9.4–14.1)	17.9 (15.1–20.7)	18.6 (15.8–21.5)	25.8 (22.6–29.0)	14.6 (12.0–17.2)
	5 Years	36.9 (33.3–40.5)	16.7 (13.9–19.5)	19.3 (16.4–22.2)	28.0 (24.6–31.4)	29.8 (26.4–33.2)	20.5 (17.5–23.6)

FDG PET-CT, positron emission tomography-computed tomography with fluorodeoxyglucose; CI, confidence interval
Cumulative incidences of overall recurrence: higher in cohort 2, with a peak difference at three years (32.3%vs 27.5%). The difference appeared greatest for the first two to three years after primary treatment (3-year rates: 27.5 % for cohort 1 and 32.3 % for cohort 2), after which the rates began to converge. The difference was less pronounced for locoregional recurrence. The cumulative incidences of distant recurrence is higher in cohort 2, with a peak difference at three years (25.8%vs. 18.5%). The difference was more pronounced for distant recurrence. The cumulative incidence of the competing event (death before recurrence) was higher in cohort 2.

Secondary outcome 2: differences in estimated absolute risk of overall, locoregional, or distant recurrence at 2 years post-treatment

At two years, we found a higher absolute risk of overall, locoregional, and distant recurrence for cohort 2 and comparable absolute risk of death before recurrence for the two cohorts.

- Outcome 9: absolute risk estimates of overall recurrence

Absolute risk of overall rec:

Cohort 2: 18.1 12.9–24.2

Cohort 1: 13.8 8.1–21.1

At two years, we found a higher absolute risk of overall recurrence for cohort 2.



Outcome 10: absolute risk estimates of locoregional recurrence	Absolute risk of locoregional rec: Cohort 2: 14.5 9.7-20.2 Cohort 1: 12.9 6.9-20.9 At two years, we found a higher absolute risk of locoregional recurrence for cohort 2.
Outcome 11: absolute risk estimates of distal recurrence	Absolute risk of distant rec: Cohort 2: 15.0 10.2-20.7 Cohort 1: 10.4 5.7-16.7 At two years, we found a higher absolute risk of distant recurrence for cohort 2.
Outcome 12: absolute risk estimates of death before recurrence	Absolute risk of death at 2 year before: Overall rec: cohort 2: 2.7 1.4–6.7 ; cohort 1: 3.3 1.3-4.8 Loco-regional rec: cohort 2: 2.2 1.0–4.1 ; cohort 1: 2.6 1.1–5.3 Distant rec: cohort 2: 1.4 0.6–2.8; cohort 1: 1.4 0.5–3.0 Comparable absolute risk of death before recurrence for the two cohorts.
Adverse events and other	None
Limitations and other comments	
Limitations/other	Results from before the era of adjuvant therapy. There is a differences in patient characteristics between the 2 cohorts. Patients in cohort 2 were generally older, had a higher comorbidity index, and were less likely to present with nodular melanoma. Consequently, patients in cohort 2 had a higher risk of death before recurrence, which in turn lowered the cumulative incidence of recurrence. If patients had been more comparable, the differences in recurrence would likely have been greater. There is a lack of information regarding the mode of recurrence detection: it is not known whether recurrences were detected by routine imaging, clinical examination, patient themselves, or imaging performed on other indications. So it is neither known whether the increase in recurrence detection was entirely attributable to routine imaging. The sample available is limited in size but sufficiently large to show an effect of routine FDG PET-CT on distant recurrence detection within the first two years of surveillance. However, significance was not reached for overall recurrence detection in the same period or for distant recurrence detection in individual pathologic stages.
Conclusion authors	Patients with stage IIB to IIID melanoma followed with routine FDG PET-CT had a 51 % increased hazard of distant recurrence detection within the first two years of surveillance. Because distant recurrences are not as readily detected by clinical examination as locoregional metastases, this demonstrates the yield of routine FDG PET-CT in melanoma surveillance. Future studies must determine whether this earlier recurrence detection translates into improved survival.

Appendix 7.6. Summary tables for GRADE

Appendix 7.6.1. More frequent versus less frequent follow-up

Table 70 – Follow-up: GRADE table for more frequent versus less frequent follow-up

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	More intensive	Less intensive	Relative (95%CI)	Absolute (95%CI)		
Overall survival stage IB-II												
1	RCT Melfo	Not serious	Not serious	Not serious	Serious*	-	196	192	5-y HR 0.9; 95%CI 0.49-1.66 favours less intense	No data to calculate proportions	⊕⊕⊕○ Moderate	CRITICAL
Disease-free survival stage IB-II												
1	RCT Melfo	Not serious	Not serious	Not serious	Serious*	-	196	192	5-y DFS HR 0.92; 95%CI 0.56-1.53 favours less intense	5-y DFS 80.3%, 95%CI 74.6%–86.5% intensive 82.7%, 95%CI 76.9%–88.9% less intensive Risk difference 2.4% ; NNT 42	⊕⊕⊕○ Moderate	IMPORTANT
Quality of life stage IB-II at 5 years												
1	RCT Melfo	Not serious	Not serious	Not serious	Serious*	-	196	192	Same score in both arms at 5y F/U	Same score in both arms at 5y F/U	⊕⊕⊕○ Moderate	CRITICAL

*downgraded 1 level; DFS disease free survival; F/U follow-up



Appendix 7.6.2. Different intensities of imaging during follow-up

Table 71 – Follow-up: GRADE table for different intensities of imaging during follow-up

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	More intensive	Less intensive	Relative (95%CI)	Absolute (95%CI)		
Overall survival stage III												
1	Longitudinal cohort – retrospective comparison Dieng	Very serious**	Not serious	Not serious	Serious*	-	141 (CT or PET-CT every 3-4 months)	47 biannual CT or PET-CT 285 annual CT or PET-CT	At 5-years biannual imaging vs annual imaging: HR 1.21; 95%CI 0.65-2.28; intensive imaging vs annual imaging: HR 5.20; 95%CI 3.53-7.66	Not calculated	⊕○○○ Very low	CRITICAL
Disease-free survival stage III												
Stage III - CT or PET-CT 3–4 months, versus biannual versus annual frequency												
1	Longitudinal cohort – retrospective comparison Dieng	Very serious**	Not serious	Not serious	Serious*	-	141 (CT or PET-CT every 3-4 months)	47 biannual CT or PET-CT 285 annual CT or PET-CT	5-y DDFS biannual imaging vs annual imaging: HR 1.69, 95%CI 1.02-2.78 intensive imaging vs annual imaging: HR 4.57, 95%CI 3.25-6.45	Stage IIIC median dMSS: 4.4 months shorter with intensive imaging compared to annual imaging	⊕○○○ Very low	IMPORTANT
Stage III – CT/PET/MRI/ultrasound frequency every 6 months, 12 months, >12 months												
1	Retrospective comparative study Broman	Very serious**	Not serious	Not serious	Serious*	-	42 (CT or PET-CT every year)= moderate intensive F/U 47 (CT or PET-CT every 6 month)= high intensive F/U	70 (CT or PET-CT less than every year)= Low intensive F/U	RFS moderate vs low HR 1.21 95%CI 0.53-2.74 high vs low HR 1.05 95%CI 0.47-2.32	No data available for calculation	⊕○○○ Very low	IMPORTANT

*downgraded 1 level; **downgraded 2 levels; DFS disease free survival; F/U follow-up; DDFS distant disease-free survival; RFS recurrence free survival; dMSS post distant recurrence melanoma specific survival

Appendix 7.6.3. Adding imaging to clinical follow-up

Table 72 – Follow-up: GRADE table for adding imaging to clinical follow-up

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	With imaging	Without imaging	Relative (95%CI)	Absolute (95%CI)		
Overall survival												
Stage IIA - X-ray added to clinical follow-up [∞]												
1	Retrospective comparative study Kurtz	Very serious*	Not serious	Serious*	Not serious	-	76 (only stage II)	66		At 35-months with imaging 96%; 95%CI 0.89-0.98 and without 95%; 95%CI 0.88-0.99	⊕○○○ Very low	CRITICAL
Stage I-III - Gain in life-expectancy at 5 years calculated by modelling PET/CT added to clinical follow-up												
1	Retrospective comparative study Rueth	Very serious*	Not serious	Serious*	Very serious**	-	Stage I n=724, stage II n=72, stage IIIA n=136, stage IIIB b=368, stage IIIC n=300	Idem	Stage I with PET/CT biannual imaging 0.7% relative survival increase vs without PET/CT Stage IIIC with PET/CT biannual imaging 6.8% relative survival increase vs without	life expectancy without imaging vs biannual PET/CT Stage I: 52 vs 52.4 months; NNT 252 Stage II: increase with 1.1 month; NNT 79 Stage IIIA: 0.9 month; NNT 78 Stage IIIB: 1.7 months; NNT 33 Stage IIIC: 30 vs 32 months; NNT 22	⊕○○○ Very low	CRITICAL
Melanoma specific survival												
Stage IB-IIA - Ultrasound added to clinical follow-up												
1	Retrospective comparative Ribero	Very serious*	Not serious	Not serious	Serious*	-	595 with ultrasound	554 without ultrasound	Kaplan-Meier curves for melanoma-specific survival no significant difference p=0.19	No data	⊕○○○ Very low	IMPORTANT
Quality of life Stage IIB-IIIC and III at 1 year												
1	RCT TRIM	Serious*	Not serious	Serious*	Serious*	-	99	105	Same score in both arms at 1y F/U	Same score in both arms at 1y F/U	⊕○○○ Very low	CRITICAL
Disease-free survival												



Stage IB-IIA - Ultrasound added to clinical follow-up												
1	Retrospective comparative Ribero	Very serious*	Not serious	Not serious	Serious*	-	595 with ultrasound	554 without ultrasound	Kaplan-Meier (median time to recurrence) DFI HR=0.81, 95%CI 0.58-1.14	US-FU compared with the C-FU (median time 2.32 years versus 2.97 years, respectively) P=0.23	⊕○○○ Very low	IMPORTANT
Stage IIA-IIB - X-ray added to clinical follow-up												
1	Retrospective comparative Kurtz	Very serious*	Not serious	Serious*	Not serious	-	181	66	5-y PFS stage IIA-IIB: clinical only vs with imaging not significant p=0.75		⊕○○○ Very low	IMPORTANT
Stage IIB-IIID – PET/CT at 6, 12, 24, and 36 months added to clinical examination												
1	Retrospective analyses cohorts Helvind	Not serious	Not serious	Not serious	Serious*	-	715 (with imaging)	765 (clinical F/U only)	Overall recurrence HR 1.01 95%CI 0.85-1.21 (first two years HR 1.16 95%CI 0.93–1.44). Distant recurrence HR 1.20 95%CI 0.98-1.46 (first two years HR 1.51 95%CI 1.16–1.96)		⊕⊕○○ Low	IMPORTANT

*downgraded 1 level; **downgraded 2 levels; DFI, disease free interval; NNT number needed to treat for 5-year follow-up with PET/CT at 6-month intervals

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