Bijlage 10 Evidencetabellen

Uitgangsvraag 5: Wat is het effect van de schildwachtklier procedure bij patiënten met nieuw gediagnosticeerd melanoom met breslowdikte ≥ 1 mm op de (ziektevrije) overleving in vergelijking met een 'wait and see' aanpak?

Randomized controlled trials

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
Multicenter Selective Lymphadenectomy Trial (MSLT) (Morton, Cochran et al. 2005; Morton, Thompson et al. 2006)	RCT Supported by the National Cancer Institute Setting: international multicenter (United States, Europe, Australia) Sample size: N=1269 Recruitment: January1994 to March 2002; median follow-up 59.8 months	Invasive primary cutaneous melanoma, classified as Clark level III with a Breslow thickness of 1 mm or more, or as Clark level IV or V with any Breslow thickness Exclusion: operative procedure that could have disrupted lymphatic drainage patterns from the primary site; a history of melanoma or other invasive	Wide excision and SNB with immediate lymphadenectomy if nodal micrometastases were detected on biopsy vs. wide excision and postoperative observation of regional lymph nodes with lymphadenectomy if nodal relapse occurred	5-year melanoma-specific survival: 87.1% (95%CI: 85.8-88.4) vs. 86.6% (85.0-88.2)	5-year disease-free survival before a first recurrence at any site: 78.3% (76.7-79.9) vs. 73.1 (71.0-75.2) 5-year survival of subgroup of lymph node positive patients: 72.3% (67.7-76.9) vs. 52.4% (46.5-58.3)	Level of evidence: A2 Central randomisation Blinding of assessors not reported; blinding of patients not reported but unlikely No ITT analysis; reported that the results from the ITT analysis were consistent with the results of the patients that received the assigned treatments (94.2% of enrolled patients) Disease free survival before a first recurrence at any site is affected by trial design bias, as the intervention removes an important site of recurrence. Either nodal recurrence should be excluded as an event, or the end-point should be

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		malignancy within the previous 5 years; life expectancy less than 10 years; primary or secondary immune deficiency; pregnancy				expressed as distant disease free survival The subgroup analysis of node-positive patients carries a high risk of detection bias. Not all (micro) metastases in the observation group will be detected. The survival advantage of 20% is in contradiction to no survival advantage in the trial population as a whole.

Abbreviations: ITT; intention to treat; RCT: randomized controlled trial; SNB: sentinel node biopsy

Observationele studies

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
(Gutzmer, Al Ghazal et al. 2005)	Before-after study with retrospective data collection Support not reported; no conflicts of interest declared Setting: Hannover Medical University, Germany Sample size: N=673 January 1995-March 2000 (pre-SNB group) and April 2000 and March 2003 (SNB group)	Primary cutaneous melanoma with a Breslow thickness of 1 mm or more and no clinical or radiological evidence of melanoma metastasis at the time of diagnosis Median thickness 2.0 mm; 17.1% of patients > 4mm; 61% of melanoma´s in the control group were located on the extremities, vs. 49% in the intervention group (p=0.007)	Wide excision and SNB with completion lymphadenectomy if nodal micrometastases were detected vs. wide excision and postoperative observation of regional lymph nodes with lymphadenectomy if nodal relapse occurred	Melanoma related survival: similar in both groups (p=0.32)	SNB patients had significantly fewer recurrences (p=0.006) Locoregional cutaneous metastases (p=0.48) Regional lymph node metastases (p<0.001) Distant metastases (p=0.81)	Level of evidence: B Before-after design (no concurrent control group) Retrospective data collection Differential follow-up: median 59.7 months (range 5.6–118.1) in the control group and 35.5 months (range 5.8–59.6 months) in the SNB group No information on loss to follow-up Temporal trend of increased adjuvant interferon-α therapy: 10% of the control group vs. 32% of the SNB group Unadjusted survival analyses

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
(Koskivuo, Talvet et al. 2007)	Before-after study with partial retrospective and partial prospective data collection Support and conflicts of interest not reported Setting: university hospital in Finland Sample size: N=921 January 1983-September 2001 (pre-SNB group) and October 2001 and December 2006 (SNB group)	Cutaneous melanoma, clinical stage I–II, Clark level II–V, all Breslow thickness included 94 patients with undetermined Breslow thickness were excluded from the control group 47% tumour thickness 1 mm or less Patients in the control group had lower Clark levels more frequently	Wide excision and SNB with immediate lymphadenectomy if nodal micrometastases were detected on biopsy vs. wide excision and postoperative observation of regional lymph nodes with lymphadenectomy if nodal relapse occurred	5 Year melanoma related survival: 87.8% vs. 85.2% (hazard ratio: 0.88; 95%CI: 0.49–1.56; p=0.66)	5 year disease-free survival: 85.1% vs. 79.0% (hazard ratio: 0.84; 95%CI: 0.55–1.28; p=0.42) Locoregional disease-free survival (p=0.41) Nodal disease-free survival (p=0.004) Distal disease-free survival (p=0.44) Stratified analyses for thin melanomas and for intermediate and thick melanoma´s gave similar results for melanoma related survival and disease-free survival	Level of evidence: B Before-after design (no concurrent control group) Retrospective data collection of the ´before´ group; prospective data collection of the ´after´ group leads to a risk of detection bias, especially of recurrence, favouring the control group Differential follow-up: median 74 months (range 2–281) in the control group and 16 months (range 2-63 months) in the SNB group Temporal trend in resection margins: 0.4 to 10 cm in the control group vs. 0.5 to 3 cm in the intervention group Unadjusted survival analyses

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
(Leiter, Buettner et al. 2010)	Before-after study with retrospective data collection Support and conflicts of interest not reported Setting: university hospital of Tuebingen, Germany Sample size: N=879 January 1991-January 1995 (pre-SNB group) and January 1996 and January2000 (SNB group)	Primary cutaneous melanoma with a Breslow thickness of 1 mm or more Patients with a follow-up of less than 3 months were excluded There were more males in the intervention group, the level of invasion was higher and there were more ulcerated tumours	SNB procedure and completion lymph node dissection if SNB was positive vs. no SNB procedure	5 Year melanoma related survival: 85.58% (95%CI: 81.8-89.2%) vs. 81.5% (95%CI: 77.6-85.4%); p=0.28 Cox proportional hazard analysis - adjusted for age, gender, body site, tumor thickness, level of invasion, and histological subtype - for risk of overall death from melanoma: 0.74 (95%CI: 0.52–1.05); p=0.09	5-year recurrence-free survival : 76.9% (95%CI 72.6–81.2%) vs. 67.8% (95%CI: 63.1–72.5%); p=0.003 Satellite/in-transit disease-free survival: 90.8% (95%CI: 87.9–93.7%) vs. 89.9% (95%CI: 86.8–93.0%); p=0.66 Nodal disease-free survival: 91.8% (95%CI: 88.9–94.7%) vs. 82.0% (95%CI 78.1–85.9%); p<0.001 Distal disease-free survival: 93.2% (95%CI: 90.5–95.9%) vs. 92.9% (95%CI: 90.0–95.8%); p=0.91 Cox proportional hazard analysis - adjusted for age, gender, body site, tumor thickness, level of invasion, and histological subtype - for risk of recurrence: 0.65 (95%CI: 0.49–0.87); p=0.003	Level of evidence: B Before-after design (no concurrent control group) Unclear which criteria to select patients for SNB were used; article from same institute states that non-SNB was used up to 1999 (Mohrle, Schippert et al. 2004) Retrospective data collection from a systematic nationwide registry (Smaller) differential follow-up: median 57.6 months (IQR: 39.7–79.7) in the control group and 54.3 months (IQR: 41.2-69.1 months) in the SNB group Temporal trend not assessed Groups were not similar with regard to prognostic characteristics, in favour of control group. This was controlled for in some analyses

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
(Starz, Siedlecki et al. 2004)	Before-after study with retrospective data collection Support and conflicts of interest not reported Setting: university hospital of Augsburg, Germany Sample size: N=598 1987- 1993 (pre-SNB group) and 1995 and 2000 (SNB group)	Primary cutaneous melanoma with a Breslow thickness of 0.75 mm or more No evidence of metastasis at the time of diagnosis Groups were similar in the most important prognostic factors	SNB procedure and completion lymph node dissection if SNB was positive vs. no SNB procedure	Overall survival: better in SNB group (p=0.03) Multivariable Cox regression analysis – adjusted for gender, age, tumor site and tumor thickness- RR: 0.65 (95% CI: 0.42-0.998); p=0.49	Distal disease-free survival: better in the SNB group (p=0.006) Multivariable Cox regression analysis – adjusted for gender, age, tumor site and tumor thickness- RR: 0.58 (95% CI: 0.36-0.94); p=0.03	Level of evidence: B Before-after design (no concurrent control group) Retrospective data collection in a systematic nationwide registry 30% of SNB patients refused CLND; these were included in the SNB group for the analyses Differential follow-up: median 95 months in the control group and 45.5 months in the SNB group Temporal trend not assessed Melanoma-specific survival not assessed
(van Poll, Thompson et al. 2005)	Comparative cohort study Supported by the Melanoma Foundation of the University of Sydney, and conflicts of interest not reported Setting: university hospital of Sydney, Australia	Primary cutaneous melanoma with a Breslow thickness of 1 mm or more Exclusion: multiple or occult primary melanomas; evidence of metastasis at	SNB procedure and completion lymph node dissection if SNB was positive vs. no SNB procedure	In-transit recurrence: 3.6% vs. 4.9% (non-significant) In-transit recurrence as a first recurrence: 2.4% vs. 2.5% (non-significant)	-	Level of evidence: B 53% of patients participated in the MSLT trial; no separate analyses for those patients Data collected in a systematic registry Differential follow-up: median 35 months in the control group and 42 months in the SNB group The main analyses were not

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
	Sample size: N=1789 January 1991-December 2000 (no-SNB group) and February 1992-December 2000 (SNB group)	the time of diagnosis; adjuvant treatment by isolated limb perfusion, isolated limb infusion, or postoperative radiotherapy; therapeutic lymph node dissection not performed after histological evidence of metastasis was obtained by SNB; a failed SNB procedure; <12 months follow-up Groups were similar except for follow-up and location of the tumor. There were less head and neck melanoma´s in					adjusted; results from a multivariable regression analysis showed similar results however Only relevant results reported here

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
		the SNB group (12%) vs. the control group (20%)				

Abbreviations: 95%CI: 95 percent confidence intervals; RR: relative risk ; SNB: sentinel node biopsy

Uitgangsvraag 7.1: Wat is het effect en de diagnostische accuratesse van beeldvormend onderzoek naar metastasen bij patiënten met nieuw gediagnosticeerd melanoom stadium I-II op de overleving in vergelijking met een 'wait and see' aanpak?

Diagnosis
Primary studies

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
Reference: Cordova 2006{Cordova, 2006 #46}	Design: prospective cross sectional Source of funding: Not stated Setting: University Centre, Italy Sample size: N=25 Duration: 2002-2004, median follow-up 20 months (range 4-30)	Eligibility criteria: patients with a cutaneous melanoma with Breslow thickness ≥ 0.75 mm and no palpable regional lymph nodes, AJCC stage I-II Patient characteristics (e.g. age, tumour characteristics, stage, etc.): 15 men and 10 women, mean age 53.8 (range 24-72), primary lesions upper extremity 12%, lower extremity 24%, trunk 40%, head and neck 24% Prevalence of disease: 40%	Index test(s): FDG-PET Reference standard: Sentinel lymph node biopsy + follow-up	Sensitivity, specificity, PPV, NPV, LR+, LR- Sens 20% (95% CI 0-44.8) Spec 87% (95% CI 69.4-100) LR+ 1.50 (95% CI 0.25-8.98) LR- 0.92 (95% CI 0.64-1.33)	Effect size secondary outcome(s) Effect size all other outcomes	Level of evidence: A2 Dropouts: not reported Results critical appraisal (definition of positive and negative cases, completeness of verification) Consecutive, prospective, blinded interpretation
Reference: Fogarty 2006{Fogarty, 2006 #52}	Design: retrospective Source of funding: not stated Setting: one centre in Australia Sample size:	Eligibility criteria: performance of brain MRI for primary staging of cutaneous melanoma Patient characteristics (e.g. age, tumour characteristics, stage, etc.): stage I: N=3, stage II: N=12 Prevalence of disease: brain	Index test(s): brain MRI Reference standard: -	Sensitivity, specificity, PPV, NPV, LR+, LR-	Effect size secondary outcome(s) Effect size all other outcomes brain metastases found by brain MRI in 11 patients, all stage IV no metastases found	Level of evidence: B Dropouts: not reported Results critical appraisal (definition of positive and negative cases, completeness of verification): Retrospective, spectrum of disease

	N=100 of which 15 with stages I-II Duration: 1998-2002	metastases identified with MRI in 11% of all patients (all stage IV)			in patients with stages I-III including patients with symptoms suggestive of brain metastases	unclear, no comparison with reference standard
Reference: Hocevar 2004{Hocevar, 2004 #66}	Design: prospective cross-sectional Source of funding: Slovenian Ministry of Education, Science and Sport Setting: one centre in Slovenia Sample size: N=57 Duration: June 2002-August 2003	Eligibility criteria: malignant melanoma in whom SLN was planned Patient characteristics (e.g. age, tumour characteristics, stage, etc.): 21 men, 36 women Prevalence of disease: 24.6%	Index test(s): ultrasound Reference standard: FNAB and SLNB	Sensitivity, specificity, PPV, NPV, LR+, LR- Sens 71.4% (95% CI 47.8-95.1) Spec 83.7% (95% CI 72.7-94.8) LR+ 4.39 (95% CI 2.06-9.33) LR- 0.34 (95% CI 0.15-0.79)	Effect size secondary outcome(s) Effect size all other outcomes	Level of evidence: B Dropouts: none reported Results critical appraisal (definition of positive and negative cases, completeness of verification): Prospective, unclear selection process and differential verification
Reference: Kahle 2003{Kahle, 2003 #71}	Design: prospective cross-sectional Source of funding: : not stated Setting: University centre,	Eligibility criteria: malignant melanoma on trunk or extremities, Breslow ≥ 1.0 mm, Clark >III Patient characteristics (e.g. age, tumour characteristics, stage, etc.): 40 females, 27 males, average age 48.8	Index test(s): Ultrasound Reference standard: SLNB	Sensitivity, specificity, PPV, NPV, LR+, LR- No diagnostic accuracy measures reported 70/82 (85.4%) of sentinel lymph	Effect size secondary outcome(s) Effect size all other outcomes	Level of evidence: B Dropouts: none reported Results critical appraisal (definition of positive and negative cases, completeness of verification):

	Germany Sample size: N=67 Duration: not stated	years, Breslow range 1.08-5.5 Prevalence of disease: metastases to the SLN 16.4%		nodes identified by US compared to scintigraphy		Prospective, unclear selection process
Reference: Kell 2007{Kell, 2007 #12}	Design: retrospective Source of funding: not stated Setting: one centre in US Sample size: N= 37 Duration: 1 year	Eligibility criteria: malignant melanoma >0.75 mm, no evidence of systemic or regional metastases, undergoing SLNB and PET/CT Patient characteristics (e.g. age, tumour characteristics, stage, etc.): mean age 61.4 years, mean thickness 2.4 mm Prevalence of disease: 24.3%	Index test(s): PET/CT Reference standard: SLNB	Sensitivity, specificity, PPV, NPV, LR+, LR- Sens 22.2% (95% CI 0-49.4) Spec 89.3% (95% CI 77.8-100.0) LR+ 2.07 (95% CI 0.41-10.5) LR- 0.87 (95% CI 0.60-1.26)	Effect size secondary outcome(s) Effect size all other outcomes PET identified another occult tumour in 4 patients (10.8%)	Level of evidence: B Dropouts: none reported Results critical appraisal (definition of positive and negative cases, completeness of verification): Retrospective, unclear spectrum of disease
Reference: Klode 2010{Klode, 2010 #73}	Design: retrospective Source of funding: not stated Setting: one university centre, Germany Sample size: N=61 Duration: January 2004-December 2006	Eligibility criteria: primary malignant melanoma, Breslow >1.0mm, receiving SLNE Patient characteristics (e.g. age, tumour characteristics, stage, etc.): mean age 58.8 years (range 31-82), nodular melanoma 44.3%, superficially spreading melanoma 32.8%, acrolentiginous melanoma 9.8%; trunk or extremities 42.6%, mean thickness	Index test(s): PET/CT Reference standard: SLNB	Sensitivity, specificity, PPV, NPV, LR+, LR- Unit of analysis: lymph nodes Sens 5.7% (95% CI 0-17.1) Spec 100% (95% CI 100-100) LR+ 26.3 (95% CI 1.11-622.8) LR- 0.92 (95% CI 0.80-1.06) (AVDB: imputation	Effect size secondary outcome(s) Effect size all other outcomes	Level of evidence: B Dropouts: none reported Results critical appraisal (definition of positive and negative cases, completeness of verification): Retrospective, analyses per lymph node

		2.62mm (range 1.0-8.0), 24.6% ulcerated tumour Prevalence of disease: nodal metastases 23%; stage I: 11.5%, stage II: 11.5%		of 0.5 in every cell to account for 0 cell in calculation of likelihood ratios)		
Reference: Mansour 2010{Mansour, 2010 #82}	Design: retrospective Source of funding: not stated Setting: one tertiary referral centre, US Sample size: N=79 Duration: April 1999 – December 2007	Eligibility criteria: melanoma and PET/CT for initial staging or follow-up Patient characteristics (e.g. age, tumour characteristics, stage, etc.): mean age 54.3 years (range 16-93), 66.7% male Prevalence of disease: musculoskeletal metastases in AJCC stage II patients: not reported	Index test(s): PET/CT Reference standard: clinical follow-up including multiple imaging modalities and clinical records	Sensitivity, specificity, PPV, NPV, LR+, LR- Patients with stage II, scans unit of analysis: 3 true positive scans, 6 false positive scans – denominator not reported	Effect size secondary outcome(s) Effect size all other outcomes	Level of evidence: B Dropouts: none reported Results critical appraisal (definition of positive and negative cases, completeness of verification): Retrospective, unclear reference standard, incomplete analyses
Reference: Newton-Dunn 2007{Newton-Dunn, 2007 #91}	Design: retrospective Source of funding: not stated Setting: one centre, UK Sample size: N=115 Duration: October 2004-October 2006	Eligibility criteria: malignant melanoma scheduled for SLNB Patient characteristics (e.g. age, tumour characteristics, stage, etc.): age 16-84, 57% men, 1.7% T1, 52% T2, 30% T3, 16% T4 Prevalence of disease: distant disease 0% Incidental abnormalities 58%	Index test(s): CT Reference standard: not applicable	Sensitivity, specificity, PPV, NPV, LR+, LR-	Effect size secondary outcome(s) Effect size all other outcomes Distant disease: none identified. 58% had incidental abnormalities: 20 lung nodules, 29 liver lesions, 7 ovarian cysts, 4 adrenal lesions, 5 renal	Level of evidence: C Dropouts: none reported Results critical appraisal (definition of positive and negative cases, completeness of verification): Retrospective, outcomes not clearly defined

					lesions	
Reference: Sanki 2009{Sanki, 2009 #104}	Design: prospective cross-sectional Source of funding: None Setting: one centre, Australia Sample size: N=716 Duration: January 2001-August 2005	Eligibility criteria: no clinically detectable lymph nodes and Breslow > 1 mm or adverse histologic features (Clark IV-V, ulceration or high mitotic rate) Patient characteristics (e.g. age, tumour characteristics, stage, etc.): not reported Prevalence of disease: histologically positive SLN: 17.5%	Index test(s): US Reference standard: histology of SLNB	Sensitivity, specificity, PPV, NPV, LR+, LR- Patients unit of analysis: Sens 23.3% (95% CI 18.1-28.1) Spec 97.3% (95% CI 96.5-98.1) LR+ 8.57 (95% CI 4.80-15.29) LR- 0.79 (95% CI 0.72-0.87) Lymph nodes unit of analysis: Sens 24.3% (95% CI 19.5-28.7) Spec 96.8% (95% CI 95.9-97.7) LR+ 7.68 (95% CI 4.68-12.60) LR- 0.78 (95% CI 0.71-0.86) Sensitivity significantly greater for neck nodes	Effect size secondary outcome(s) Effect size all other outcomes regression tree analysis: 2 or more sonographic signs, rounded appearance and Breslow > 1.4 mm: Sens 88.3% (95% CI 81.8-92.8) spec 36.1% (95% CI 34.8-37.0)	Level of evidence: B Dropouts: none reported Results critical appraisal (definition of positive and negative cases, completeness of verification): Prospective, unclear selection process, total verification
Reference: Sawyer	Design:	Eligibility criteria: new cases	Index test(s): CT	Sensitivity,	Effect size	Level of evidence: B

2009{Sawyer, 2009 #105}	retrospective Source of funding: none reported Setting: single centre, UK Sample size: N=132 Duration: January 2000-August 2006	of melanoma with AJCC stages IIB/C Patient characteristics (e.g. age, tumour characteristics, stage, etc.): stage IIB: N=42, mean age 64 years (range 19-94), stage IIC: N=90, mean age 65 years (range 22-90) Prevalence of disease: 8.60%	Reference standard: follow-up including CT scans	specificity, PPV, NPV, LR+, LR- Initial scans with metastases: Chest 3/? Abdomen 2/? Pelvis 0/? Head 3/102 Neck 0/?	secondary outcome(s) Effect size all other outcomes Changes in management None in chest, abomen, pelvis and neck scans, In head scans: 0.7% at initial scan	Dropouts: none reported Results critical appraisal (definition of positive and negative cases, completeness of verification): Retrospective, follow-up CT scans part of the reference standard
Reference: Singh 2008{Singh, 2008 #110}	Design: prospective cross-sectional Source of funding: International Union Against Cancer, Switzerland Setting: single centre, Germany Sample size: N=52 Duration: not stated	Eligibility criteria: primary melanoma, Breslow > 1mm. stage I-II Patient characteristics (e.g. age, tumour characteristics, stage, etc.): 69% men, mean age 55 years (range 17-76), mean Breslow 2.87 mm (range 1-12), extremitie 44%, trunk 31%, heand and neck 25% Prevalence of disease: metastatic disease in sentinel node: 27%	Index test(s): PET/CT Reference standard: SLNB	Sensitivity, specificity, PPV, NPV, LR+, LR- Sens 14.3% (95% CI 0-32.6) Spec 94.7% (95% CI 87.6-100) LR+ 2.71 (95% CI 0.42-17.5) LR- 0.90 (95% CI 0.72-1.13)	Effect size secondary outcome(s) Effect size all other outcomes	Level of evidence: B Dropouts: not reported Results critical appraisal (definition of positive and negative cases, completeness of verification): Prospective, unclear inclusion process
Reference: Van Der Ploeg 2009{Van Der Ploeg, 2009 #119}	Design: prospective cross-sectional Source of funding: not stated	Eligibility criteria: melanoma patients undergoing both lymphoscintigraphy and SPECT/CT Patient characteristics (e.g. age, tumour characteristics,	Index test(s): SPECT/CT Reference standard: not applicable	Sensitivity, specificity, PPV, NPV, LR+, LR-	Effect size secondary outcome(s) Effect size all other outcomes Additional sentinel	Level of evidence: C Dropouts: none reported Results critical appraisal (definition of positive and negative

	Setting: single centre, the Netherlands Sample size: N=85 Duration: December 2006-? 	stage, etc.): mean age 54 years Prevalence of disease: patients with metastatic nodes 21.2%			nodes: 12 in 7 patients 3/22 metastatic nodes identified by SPECT/CT only Management changes in 30 patients (35%): longer incision 11 patients, smaller incision 6 patients, incision at another site 5 patients	cases, completeness of verification): Prospective, unclear selection process
Reference: Van Rijk 2006{Van Rijk, 2006 #121}	Design: prospective cross-sectional Source of funding: not stated Setting: single centre, the Netherlands Sample size: N=107 Duration: November 2000-December 2004	Eligibility criteria: clinically localised cutaneous melanoma, Breslow ≥ 1mm or Clark level ≥ IV, eligible for lymphatic mapping Patient characteristics (e.g. age, tumour characteristics, stage, etc.): 53% men, trunk 40%, leg 32%, arm 22%, head and neck 6%, median Breslow 2.0 mm (range 0.6-12.5) Prevalence of disease: patients with metastatic sentinel nodes: 34%	Index test(s): US Reference standard: lymphatic mapping and histology	Sensitivity, specificity, PPV, NPV, LR+, LR- US alone: sens 33.3% (95 %CI 17.9-48.7), spec 87% (95% CI 77.2-93.8) LR+ 2.3 (95% CI 1.10-4.80) LR- 0.78 (95% CI 0.61-1.00) US+FNAC: sens 4.7%, other outcome measures not reported nor calculable	Effect size secondary outcome(s) Effect size all other outcomes	Level of evidence: A2 Dropouts: none reported Results critical appraisal (definition of positive and negative cases, completeness of verification): Prospective, consecutive

Reference: Voit 2010{Voit, 2010 #125}	Design: prospective cross-sectional Source of funding: Deutsche Krebshilfe Setting: multicentre, Germany, the Netherlands Sample size: N=400 Duration: July 2001-December 2007	Eligibility criteria: melanoma patients scheduled to undergo sentinel node procedure Patient characteristics (e.g. age, tumour characteristics, stage, etc.): 55% male, median breslow 1.8 mm, 54% Clark IV, 32% ulcerated tumour, extremities 46%, trunk 43%, head and neck 11% Prevalence of disease: metastatic lymph nodes 20.6%	Index test(s): US Reference standard: sentinel node procedure	Sensitivity, specificity, PPV, NPV, LR+, LR- Unit of analysis: lymph nodes Hump structure: sens 20.8% (95% CI 11.7-29.8), spec 72% (95% CI 67.0-77.2) LR+ 0.74 (95% CI 0.46-1.19) LR- 1.10 (95% CI 0.96-1.26) Echo-poor islands Sens 20.8% (95% CI 11.7-29.8), Spec 96.0% (95% CI 93.7-98.2) LR+ 5.14 (95% CI 2.54-10.4) LR- 0.83 (95% CI 0.73-0.93) Cap structure Sens 7.8% (95% CI 1.8-13.8)	Effect size secondary outcome(s) Effect size all other outcomes	Level of evidence: A2 Dropouts: none reported Results critical appraisal (definition of positive and negative cases, completeness of verification): Prospective, consecutive inclusion

				Spec 87.2% (95% CI 83.4-91.0) LR+ 0.61 (95% CI 0.27-1.38) LR-1.06 (95% CI 0.98-1.14) Loss of central perfusion Sens 24.7% (95% CI 15.0-34.4) Spec 77.0% (95% CI 72.2-81.8) LR+ 1.07 (95% CI 0.69-1.67) LR- 0.98 (95% CI 0.85-1.13) Peripheral perfusion Sens 76.6% (95% CI 67.1-86.1) Spec 82.1% (95% CI 77.7-86.5) LR+ 4.28 (95% CI 3.26-5.62) LR- 0.28 (95% CI 0.19-0.43) Loss of central echoes Sens 90%, spec		

				92% (conflicting results, CI not calculated) Balloon-shaped lymph node Sens 29.9% (95% CI 19.6-40.1) Spec 100% (95% CI 100-100) LR+ 179.0 (95% CI 11.0-2913.9) LR- 0.70 (95% CI 0.60-0.81) Loss of central echoes and/or balloon shaped Sens 33.8% (95% CI 23.2-44.3) Spec 98.0% (95% CI 96.4-99.6) LR+ 16.7 (95% CI 7.11-39.03) LR- 0.68 (95% CI 0.58-0.79) Peripheral perfusion and/or loss of central echoes and/or balloon shaped		

				Sens 81.8% (95% CI 73.2-90.4) Spec 80.1% (95% CI 75.5-84.6) LR+ 4.10 (95% CI 3.19-5.28) LR- 0.23 (95% CI 0.14-0.37)		

Systematic reviews

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
Reference El-Maraghi J Am Coll Radiol 2008{El-Maraghi, 2008 #48}	Design: systematic review Source of funding: not stated Search date: not stated Searched databases: PubMed, UpToDate and SumSearch meta-enigne Included study designs: not specified, but mostly diagnostic accuracy studies Number of included studies: 20	Eligibility criteria: newly diagnosed melanoma Patient characteristics: not stated: not stated	Index test(s): PET and PET/CT Reference standard: SNLB	Sensitivity, specificity, PPV, NPV, LR+, LR-: sensitivity ranges from 0-92%, specificity ranges from 7-100%, PPV ranges from 0-100%, NPV ranges from 20-85%	Effect size secondary outcome(s) Effect size all other outcomes	Level of evidence: A2 Results critical appraisal (definition of positive and negative cases, completeness of verification): no clear inclusion/exclusion criteria, no quality assessment, no meta-analysis Included studies: Wagner 2005 Hafner Fink Longo Belhocine Acland Wagner Maubec

						Kell Vereecken Steinert Libberecht Havenga
Reference: Jimenez-Requena, Eur J Nucl Med Imaging 2010{Jimenez-Requena, 2010 #69}	Design: systematic review Source of funding: not stated Search date: 2006 only including studies published between 2000-2006 Searched databases: PubMed, Embase, Cancerlit Included study designs: diagnostic accuracy studies Number of included studies: 16 (+12 from previous meta-analysis were pooled in new meta-analysis)	Eligibility criteria: cutaneous melanoma, PET for regional or distant metastases, at least 12 patients, sufficient primary data Patient characteristics: stage I-IV, initial evaluation or recurrence	Index test(s): FDG-PET Reference standard: SNLB+clinical follow-up	Sensitivity, specificity, PPV, NPV, LR+, LR-: Regional metastases: pooled specificity 99% (97-99), I^2 51.9% (unit lymph nodes) Distant metastases: unit=lesions: diagnostic odds ratio 72.9 (27.3-194.4) ; unit=scans: pooled specificity 86% (77-92), I^2 0.0%; diagnostic odds ratio 37.9 (15.8-90.9), I2 0.0%	Effect size secondary outcome(s) Effect size all other outcomes	Level of evidence: A2 Results critical appraisal (definition of positive and negative cases, completeness of verification): good literature search, suboptimal pooling methods, results not reported per stage Included studies: Gritters Boni Steinert Blessing Valk Damian Wagner Hsueh Holder Macfarlane Rinne Wagner Dietlein Paquet Klein Crippa

						Eigtved Tyler Acland Acland Reinhardt Stas Sweeter Belhocine Longo Fink Hafner Finkelstein Vereecken Wagner
Reference Krug, Radiology 2008{Krug, 2008 #75}	Design: systematic review Source of funding: not stated Search date: March 2007 Searched databases: Medline, Embase, Web of Science, CDSR Included study designs: diagnostic accuracy studies Number of included studies: 28	Eligibility criteria: (clinical study evaluating FDG PET, at least 10 patients, histolopatho- logically proved CMM, per-patient or per-lesion statistics, and sufficient data to reconstruct contingency tables. Patient characteristics: median age 54 years (range, 42– 63), on average 60% men (range, 47%–78%), mean number of participants per study 54 (range, 12–257). Patients enrolled	Index test(s): PET and PET/CT Reference standard: not stated specifically but presumably histology+follow-up	Sensitivity, specificity, PPV, NPV, LR+, LR-: early stage subgroup (10 studies, 755 patients) pooled DOR 4.3 (1-18), sensitivity 60% (54-60). SNLB as reference standard: LR+ 1.33 (0.66-2.68), LR- 1.00 (0.83-1.19); Regional and distant metastases: LR+ 5.35 (3.64-7.98), LR- 0.13 (0.08-0.20), DOR 51.3 (24.9-105.6)	Effect size secondary outcome(s) Effect size all other outcomes disease management changes in 33% (15-64), analyses on patients with all stages	Level of evidence: A2 Results critical appraisal (definition of positive and negative cases, completeness of verification): thorough literature search, appropriate quality appraisal, suboptimal meta-analyses Included studies: Gritters Blessing Steinert Holder Macfarlane RInne Nguyen Crippa Eigtveld

		exclusively for initial staging: 17 studies. Other 11 studies: enrollment for initial staging: 18%–97%.				Paquet Tyles Acland Belhocine Swetter Havenga Fink Finkelstein Harris Vereecken Batiaannet Brady Clark Horn Reinhardt Romer Iagaru

Uitgangsvraag 7.2: Wat is het verschil in diagnostische accuratesse en therapeutische impact voor de vaststelling van metastasen tussen PET en CT bij patiënten met een bewezen melanoom van de huid?
Systematische reviews
Systematic reviews

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
Facey2007	Design: Health technology assessment Funding: NIHR HTA program Search date: August 2005 Searched databases: Medline, Embase, CDSR, DARE, INAHTA Included study designs: Systematic reviews and primary diagnostic studies	Eligibility criteria not specified (various designs and various cancer types) Patient characteristics: *EARLY STAGES:* *Acland*:patients with primary cutaneous melanoma (Breslow > 1mm) *Belhohine:*stage I/II patients *Fink:* patients with newly diagnosed stage I/II primary cutaneous melanoma *Hafner:*patients with newly diagnosed stage I/II primary cutaneous melanoma (Breslow > 1mm) *Havenga*: patients with primary cutaneous melanoma	Index test: PET/CT-scan for staging and/or restaging Reference standard: SLNB, MRI, histopathology	Staging: *Early stage disease* Twelve new PS's used PET for staging using SLNB as the comparator or reference standard ; Nine of these PSs showed highly consistentresults that PET had poor sensitivity (generally<20%) to detect regional lymph-node activityin early-stage patients. This appears to be dueto the small size of the micrometastases. *Later stage disease:* For later stage disease, comparative results arevaried. In one study PET was less sensitive thanMRI, but in another PET was superior toCT/MRI and led to more changes in treatment. PET sensitivity varied between 40 and 100% inthe three PSs in later stage disease. Again,sensitivity in small lesions was poor. *Distant metastases:* For distant metastases, there were several FPsand one		Level of evidence: A2 Well performed systematic review of systematic reviews and primary studies Quality of underlying studies highly variable Included studies: *SR*: Mijnhout 2001 DACEHTA 2001 MSAC 2000 *Primary studies:* Acland 2001 Belhocine 2002 Fink 2004 Hafner 2004 Havenga 2003 Kokoska 2001 Longo 2003 Reinhardt 2002 Wagner 2005 Ghanem 2005 Gulec 2003 Vereecken 2005 Finkelstein 2004 Jenicke 2001 Kurli 2005

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
		(Breslow >1mm and no palpable regional LNs) *Kokoska*: patients with melanoma of the head and neck (Breslow >1mm) *Longo*: patients with stage I and II cutaneous melanoma (Breslow > 1mm) *Reinhardt*: patients with cutaneous melanoma (Breslow > 0.75mm) *Wagner*: patients with early stage cutaneous melanoma (Breslow > 1mm) *LATER STAGE DISEASE* *Ghanem:* patients with malignant melanoma *Gulec:* patients with suspected metastatic		study in which the sensitivity wasonly 4%.		

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
		melanoma *Vereecken:* patients with melanoma at intermediate or high risk of recurrence, scheduled for SLNB and complementary excision *STAGING/RESTAGING* *Finkelstein*: patient with stages IV melanoma undergoing metastasectomy *Jenike:* patients with advanced melanoma *Kurli:* patients with suspected choroidal melanomas				

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
Xing 2010	Design: meta-analysis of patient-level data Funding: NCI, NIH Search date: January 1990-June 2009 Searched databases: Medline, Embase, Cancerlit, Cochrane Libary Included study designs: retrospective and prospective studies (more than 10 patients included and comparisons of single or multiple imaging modalities)	Eligibility criteria:patients with melanoma Patient characteristics: not specified	Index test: PET CT PET/CT Ultrasonography Reference standard: SLNB, minimum of 6 months follow-up	*N-staging (primary staging)* *US* *Se 60%*, Sp 97% CT Se 9%, Sp 92% PET Se 30%, Sp 96% PET/CT Se 11%, Sp 97% *M-staging(primary staging)* CT Se 51%, Sp 69% PET Se 74%, Sp 75% PET/CT Se 80%, Sp 87%	*N-staging(surveillance)* US Se 96%, Sp 99% CT Se 61%, Sp 97% PET Se 87%, Sp 98% PET/CT Se 65%, Sp 99% *M-staging (surveillance)* CT Se 63%, Sp 78% PET Se 82%, Sp 83% PET/CT Se 83%, Sp 91%	Level of evidence: A2 Well performed systematic review Quality of underlying studies highly variable Median Se and Sp reported Included studies: see table 1 and 2

Primaire studies

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
Bastiaannet 2009	Design: prospective multi centre study Source of funding: not stated Setting: 5 tertiary care	Eligibility criteria: Patients with melanoma with potentially resectable lymph node metastases Patient characteristics: >=	Index tests: FDG-PET CT Reference standard:	Distant metastases: PET: Se 86%, Sp 94% CT:	Diagnosis LN metastases: PET: Se 91% CT: Se 92%	Level of evidence: B Dropouts: none reported

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
	hospitals, the Netherlands Sample size: N=251 Duration: July 2003 through December 2007	18 years; Breslow thickness <= 1.0 mm: 12.8%, > 1.0mm: 80.5%; Prevalence of metastatic disease: 31%	Histology/cytology, other imaging modalities (bone scan, MRI) or 6 months follow-up	Se 78%, Sp 94%	Change in treatment: 19% of patients; in 79% as a result of both scans, in 17% exclusively by FDG-PET, and in 4% exclusively by CT; in 34 patients (14%), FDG-PET had an additional value over spiral CT, and in 23 patients (9%), CT had additional value over FDG-PET PET identified 133 metastatic sites vs. 112 with CT (p=0.03) PET identified more bone metastases (27 vs. 10, p<0.0001) and subcutaneous metastases (11 vs. 5, p=0.03)	Consecutive patients Differential verification Slightly discordant results (e.g. TP + FN for PET = 79, for CT = 78)
Iagaru 2006	Design: retrospective single centre study Source of funding: not stated Setting: University centre, US	Eligibility criteria: Patients with histopathologically confirmed malignant melanoma who had a whole body PET/CT at the instituteand	Index tests: FDG-PET CT Reference standard: Pathology results and	Disease restaging: PET: Se 89.5%(95%C.I. 78.9-95.1) , Sp 81.6% (95%C.I 68.6-90.1)	Best performance (100% Se (95%C.I 82.4-100) and 83.3% Sp (95%C.I 55.2-95.3)) of PET/CT in patients with stage III	Level of evidence: B Dropouts: none reported No clear definition

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
	Sample size: N=106 Duration: January 2003 – June 2005	availablescans Patient characteristics: mean age 56.7years (± 15.9 y); Prevalence of disease:56/106 = 53%	clinical follow-up	CT: Se 68.5% (95%C.I 55.3-79.3), SP 94.2% (95%C.I 84.4-98.1) PET/CT Se 89.3% (95%C.I 78.5-95.0), Sp 88% (95%C.I 76.2-94.4)	and IV melanoma PET/CT for patients with Breslow depth of < 1.0 mm Se 75.0% , Sp 66.7% PET/CT for patients with Breslow depth of 1.0 -4.0 mm Se 92.7%, Sp 87.5% PET/CT for patients with Breslow depth of >4.0 mm Se 81.3%, Sp 60.0% Change in disease management from surgery to chemotherapy for 4 of 30 patients with advanced disease	of clinical follow-up potential incorporation bias
Pfannenberg 2007	Design: prospective, blinded single centre study Source of funding: not stated Setting: University centre, Gemany	Eligibility criteria: Histologically proven cutaneous melanoma presenting with potential evidence of metastatic spread Patient characteristics:	Index test(s): PET PET/CT CT wbMRI Reference standard:	N and M staging: PET: Se 70.4%, Sp 83.7 CT Se 77.1%, Sp 69.9% PET/CT Se 90.6%, Sp 69,9%	PET/CT more sensitive in detecting skin and subcutaneous metastases than wbMRI	Level of evidence: B Consecutive patients Exclusion of 36 patients due to

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
	Sample size: N=64 Duration: September 2004 – September 2005	mean age : 57.8 (range 23.3-79.1); 25 patients were stage III and 39 patients were stage IV Prevalence of melanoma metastases: 297/420 lesions (70.7%)	pathology, , imaging follow-up and clinical follow-up lesions rated as malignant or probably malignant were confirmed by histology or progression on follow-up lesions rated as benign or probably benign were confirmed by histology or no progression at follow up	wbMRI: Se 79.8%, Sp 89.1%	PET/CT showed a significant higher accuracy ($p < 0.0001$) than wbMRI in N-staging the most accurate method to classify bone metastases is wbMRI (NS) Diagnostic accuracy in defindeing M1a-category is dignificantly higher for PET/CT than for wbMRI ($p< 0.0001$) See table 3 Impact on patient management: 75.% motivated by PET alone 73.2% motivated by CT alone 90.2% motivated by PET/CT 87.8% motivated by wbMRI	metallic implants or claustrophobia, refuse of a second whole-body examination on the same day or abortion of the examination (25 patients) and evidence of tumor spread, or lack to follow-up (11 patients) Incorporation bias Only per-lesion analysis
Reinhardt	Design: retrospective,	Eligibility criteria: patients	Index test(s):	initial N-staging:	Change in disease	Level of evidence :

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
2006	blinded single centre study Source of funding: not stated Setting: University hospital, Germany Sample size: N=250 Duration: November 2002 – June 2004	with cutaneous melanoma undergoing PET/CT Patient characteristics: mean age 58 ±16 years; stage I: 22 patients; stage II: 88 patients; stage II: 108 patients; stage IV: 32 patients Prevalence of metastatic disease: 46.4%	PET PET/CT CT <u>Reference standard</u>: primary malignant disease was confirmed by his pathologic verification; clinical follow-up	PET Se 94.7% (95%C.I 89.6-99.8) , Sp 100% (95%C.I 98-100) CT Se 84.2% (95%C.I76-92.4) , Sp 92.9% (95%C.I 87.1-89.7) PET/CT Se 100% (95%C.I 98-100), Sp 100% (95% C.I 98-100) <u>Initial M-staging:</u> PET Se 93.8% (95% C.I 88.3-99.3), Sp 96.6% (95%C.I 92.5-100) CT Se 93.8% (95% C.I 88.3-99.3), Sp 96.6% (95%C.I 92.5-100) PET/CT Se 93.8% (95% C.I 88.3-99.3), Sp 96.6% (95%C.I 92.5-100)	management : 48.4% of the patients after PET/CT	B Drop outs: 5 patients due to lack of confirming data of suspected metastatic disease or insufficient follow-up for at least 1 year Incorporation bias for CT Some patients received index tests for primary staging (N=75), therapy control (N=42), recurrence staging (N=65) or follow-up (N=68)

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
Romer 2006	Design: retrospective explorative study Source of funding: not stated Setting: University Centre, Germany Sample size: N= 34 Duration: September 2002 – January 2004	Eligibility criteria: Histological confirmation of malignant melanoma Confirmation of stage III and IV according to the revised version of the system established by AJCC Performance CT not earlier nor later than 30 days before, respectively after the PET-scan Availability of the digital data Clinical and radiological follow-up over at least 3 months or histopathological confirmation of malignancy in lesion detected Patients' characteristics: mean age 49 (range 20 – 78); 6 patients stage III and 28 patients stage IV; mean follow up in months: 7, range 3-21. Prevalence abnormalities: 82 out of 968 (extra)nodal areas (8,4%)	Index test(s): PET CT PET/CT Reference standard: Clinical and radiological follow-up (CT and MRI) for at least 3 months	Localization ofabnormalities PET Se 85%, Sp98% CT Se 88%, Sp 95% PET/CT Se 94%, 100%	Localization of nodal abnormalities PET Se 85%, Sp98% CT Se 79%, Sp 95% PET/CT Se 94%, 100% Localization of extra nodal abnormalities PET Se 86%, Sp99% CT Se 94%, Sp 95% PET/CT Se 94%, 100%	Level of evidence : B Exclusion of 19patients because they didn't meet the inclusion criteria CT part of the reference test: incorporation bias

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
Swetter 2002	Design: retrospective single centre study Source of funding: not stated Setting: University Centre, USA Sample size: N=104 Duration: June 1995 – June 2002; median follow-up after PET 24 months	Eligibility criteria: patients with primary or recurrent melanoma without concurrent internal nonmelanoma malignancies, and who underwent PET Patients characteristics: mean age 54 (range 19-87); stage I: 5%, stage II: 37%, stage III: 29%, stage IV: 29% Prevalence: 41/104 = 39% according to PET and 30/104 = 29% according to CT (unclear how many patients really had metastatic disease)	Index test: PET CT Reference test: Histological examination or disease progression confirmed with other imaging studies or patient death as result of melanoma	Detection of melanoma metastases PET (104 ptn, 199 meta's): Se 84%, Sp 97% CT (54 ptn, 133 meta's): Se 58%, Sp 70%	Direct comparison PET and CT PET Se 81% CT Se 57%	Level of evidence : B Exclusion of 4 patients with concurrent internal nonmelanoma malignancies No clear definition of clinical follow-up Comparison CT and PET only in 53 of the patients Differential verification Per-lesion-analysis
Veit-Haibach 2009	Design: prospective single centre study Source of funding: not stated Setting: University Centre, Germany Sample size: N=56 Duration: not mentioned; mean follow-up 780 days	Eligibility criteria: patients referred for combined PET/CT after surgical resection of primary MM, and with sufficient follow-up data Patients characteristics: mean age 62 (range 23-86); stage I: 41%, stage II: 27%, stage III: 11%, stage IV: 21% Prevalence of	Index test: PET CT PET/CT Reference test: Histopathological examination (if suspected metastases) or clinical follow-up (imaging, tumour markers,	N-staging: PET Se 38.5%, Sp 100% PET/CT Wat is het effect van de schildwachtklier procedure bij patiënten met nieuw gediagnosticeerd melanoom met breslowdikte ≥ 1 mm op de (ziektevrije)	PET/CT resulted in treatment change in 2 patients compared to PET and in 4 patients compared to CT	Level of evidence : B Consecutive patients Exclusion of 18patients with insufficient follow-up No clear definition of clinical follow-up: possible

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
		metastases: 12/56 = 21%	physical examination)	overleving in vergelijking met een 'wait and see' aanpak?<u>M-staging</u>: PET Se 33.3%, Sp 90.9% PET/CT Se 41.7%, Sp 93.2% CT Se 25.0%, Sp 93.2% No statistical differences between the imaging procedures		incorporation bias Differential verification
Brady 2006	Design: prospective single centre study Source of funding: not stated Setting: University Centre, USA Sample size: N=103 Duration: from 1999-2002	Eligibility criteria: clinical stage IIc, III or IV, suitable for curative surgery, no prior significant malignancies. Patients characteristics: mean age 60 (range 21-88; stage IIC: 12%, stage III: 72%, stage IV: 17% Prevalence: 44/103 = 43%	<u>Index test</u>: PET CT <u>Reference test</u>: histopathological examination clinical follow-up radiological follow-up	<u>Detection of melanoma metastases</u> PET: Se 68%, Sp 92% CT: Se 48%, Sp 95%	<u>Treatment changes</u> PET: 14% CT: 2% PET and CT: 20%	Level of evidence : B Drop outs: 13 patients logistical causes and tumour characteristics Very probable incorporation bias Differential verification

Uitgangsvraag 13.1: Op welke termijn kunnen nieuwe kankermanifestaties (locale of regionale recidieven, afstandsmetastasen dan wel tweede primaire tumoren) optreden?

Primaire studies

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
Bernengo 2005 (Bernengo, Quaglino et al. 2005)	Retrospective cohort study Funding/CoI: not reported Setting: University of Turin, Turin, Italy Sample size: N=3,174 Duration: 1975-2004	Eligibility criteria: Cutaneous melanoma patients, treated and followed at the study institute No incomplete histopathological data, in situ carcinoma, unknown primary or multiple primary carcinomas *A priori* patient characteristics: Male 46%, female 54% ⩽53 y 50%, >53 y 50% AJCC stage primary tumour: I 54%, II 46% 43% recurrence Follow-up: median 10.2 y Definition of DFS: time lapse from the definite surgery of the primary melanoma to either the	Not applicable	All recurrences (43%): 77% ⩽5y 12% 6-10 y 5% 11-15 y 7% 16-20 y AJCC stage IA (13%): 46% ⩽5y 8% 6-10 y 31% 11-15 y 15% 16-20 y AJCC stage IB (34%): 68% ⩽5y 18% 6-10 y 15% 11-15 y 0% 16-20 y AJCC stage IIA (61%): 74% ⩽5y 8% 6-10 y 3% 11-15 y 5% 16-20 y AJCC stage IIB (68%): 90% ⩽5y 6% 6-10 y 4% 11-15 y 0% 16-20 y	Breslow thickness ⩽ 1mm: 43% ⩽5y 14% 6-10 y 21% 11-15 y 21% 16-20 y Breslow thickness 1.01-2mm: 75% ⩽5y 15% 6-10 y 10% 11-15 y 0% 16-20 y Breslow thickness 2.01-4mm: 75% ⩽5y 9% 6-10 y 8% 11-15 y 8% 16-20 y Breslow thickness >4mm: 89% ⩽5y 7% 6-10 y 0% 11-15 y 4% 16-20 y	Level of evidence: C Consecutive patients 210/2100 (10%) of disease-free patients at the last visit were lost to follow-up

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
		date of relapse or last follow-up visit		AJCC stage IIC (89%): 89% ≤5y 8% 6-10 y 0% 11-15 y 3% 16-20 y	Regional recurrence rate: 1/6 <1 year # 1/20 ≥ 5 year # Visceral metastasis recurrence rate: 1/100 # from 0 to > 20 years	
Bradford 2010 (Bradford, Freedman et al. 2010)	Population-based registry study Funding/CoI: unspecified Setting: SEER registry, encompassing 10% of the USA population Sample size: N=89,515 Duration: 1973-2006	Eligibility criteria: Melanoma patients who survived at least 2 m after their initial diagnosis No new diagnosis within the first 2 m after primary diagnosis *A priori* patient characteristics: 53% male, 47% female Median age 54 y 3% second melanoma´s Follow-up: median 9.2 y	Not applicable	-	Hazard rate second melanoma (rate per person year at risk): 1/158 2 m-1 y 1/261 1-5 y 1/287 5-10 y 1/310 10-20 y 1/299 >20 y	Level of evidence: C Large population Retrospective study based on routinely collected cancer data Loss to follow-up not described
Francken 2008	Retrospective cohort study	Eligibility criteria: Cutaneous melanoma	Not applicable	All recurrences stage IA at 10 years (8%) #:	-	Level of evidence: C

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
(Francken, Accortt et al. 2008)	Funding/CoI: Stichting VSB Fonds, Stichting Dr Hendrik Muller's Vaderlandsch Fonds, Stichting Fonds Doctor Catherine van Tussenbroek, Nell Ongerboer Fonds, Stichting Groninger Universiteits Fonds, Stichting De Korintiërs, Nederlandse Kankerbestrijding-Koningin Wilhelmina Fonds, Marco Polo Fonds, The Melanoma Foundation of the University of Sydney and Integraal Kankercentrum Noord-Nederland Setting: Sydney Melanoma Unit, Sydney, Australia Sample size: N= 4,748 Duration: 1959-2002	AJCC stages I to II treated at the study centre No incomplete data for tumour thickness, ulceration or date of recurrence *A priori* patient characteristics: 52% male, 48% female AJCC stage primary tumour: IA 39%, IB 30%, IIA 16%, IIB 11%, IIC 4% Recurrence: 18.9% Follow-up: median 6 y		50% ≤5y 50% 6-10 y All recurrences stage IB at 10 years (22%) #: 68% ≤5y 32% 6-10 y All recurrences stage IIA at 10 years (34%) #: 74% ≤5y 26% 6-10 y All recurrences stage IIBA at 10 years (46%) #: 83% ≤5y 17% 6-10 y All recurrences stage IIC at 10 years (52%) #: 88% ≤5 y 12% 6-10 y		Consecutive patients Retrospective study based on routinely collected cancer data Loss to follow-up not specified

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
Hansel 2010 (Hansel, Schonlebe et al. 2010)	Retrospective cohort study Funding/CoI: not reported Setting: Academic Teaching HospitalDresden-Friedrichstadt, Dresden, Germany Sample size: N=1,881 Duration: 1972-2001	Eligibility criteria: Cutaneous melanoma AJCC stages I to II Follow-up of ≥ 10 years *A priori* patient characteristics: Stage I or II patients 1.1% late recurrence Follow-up: ≥ 10 y	Not applicable	1.1% of patients with a follow-up of at least 10 y had a recurrence (defined as a late recurrence)	-	Level of evidence: C Consecutive patients Patient characteristics not specified Retrospective study based on routinely collected cancer data Loss to follow-up not specified The % of late recurrence might be underestimated if the mean or median follow-up (which was not specified) was rather short, e.g. 12 years
Hohnheiser 2011 (Hohnheiser, Gefeller et al. 2011)	Retrospective cohort study Funding/CoI: not reported Setting: University Hospital Erlangen, Germany	Eligibility criteria: Cutaneous melanoma No non-curative resection, no distant metastasis at time of diagnosis	Not applicable	All recurrences (21%): 82% ⩽5y 12% 6-10 y 7% > 10 y	-	Level of evidence: C Consecutive patients Prospective data collection

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
	Sample size: N=2,487 Duration: 1978-1997	*A priori* patient characteristics: Male 43%, female 57% UICC stage primary tumour: I 52%, II 23%, III 8%, unknown 18% 21% recurrence Follow-up: median 13 y; 1.2% lost to follow-up				Low loss to follow-up (1.2%)
Leiter 2011 (Leiter, Buettner et al. 2011)	Retrospective cohort study Funding/CoI: none/84 centres in Germany, Austria and Switzerland Setting: German Central Malignant Melanoma Registry Sample size: N=33,384 Duration: 1976-2007	Eligibility criteria: Patients with primary cutaneous melanoma stage I to III and a follow-up of at least 3 months cutaneous melanoma AJCC stages I to III *A priori* patient characteristics: 45% male, 55% female Mean age 54 y Recurrence: stage I 7.1%, stage II 32.8%, stage II 51.0% 2.3% second	Not applicable	Hazard rate recurrence (per person -years) stage I: 1/ 71 at 1 year 1/78 at 3 years 1/100 at 5 years 1/91 at 10 years Hazard rate recurrence (per person -years) stage II: 1/7 at 1 year 1/13 at 3 years 1/23 at 5 years 1/79 at 10 years Hazard rate recurrence (per person	Hazard rate recurrence (per person -years) stage Ia: 1/ 152 at 1 year 1/167 at 3 years 1/167 at 5 years 1/115 at 10 years Hazard rate recurrence (per person -years) stage Ib: 1/ 37 at 1 year 1/40 at 3 years 1/58 at 5 years 1/67 at 10 years Hazard rate (per person -year) second	Level of evidence: C Large population Retrospective study based on routinely collected cancer data Loss to follow-up not described

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
		melanoma Follow-up: median 4.9 months		-years) stage III: 1/3 at 1 year 1/10 at 3 years 1/14 at 5 years 1/47 at 10 years	melanoma: 1/222 at 1 year 1/769 at 3 years 1/526 5 years 1/1000 at 10 years	
Leman 2003 (Leman and Mac Kie 2003)	Retrospective cohort study Funding/CoI: not reported on Setting: Scottish Melanoma Group Database Sample size: N= 3,822 Duration: not reported	Eligibility criteria: Registered melanoma patients with a follow-up of at least 10 y *A priori* patient characteristics: Mean age 58 y (men), 51 y (women) 0.65% late recurrence Follow-up: >10 y	Not applicable	0.65% of patients with a follow-up of at least 10 y had a recurrence (defined as a late recurrence)	-	Level of evidence: C No information on the characteristics of the cohort, loss to follow-up, patient characteristics The % of late recurrence might be underestimated if the mean or median follow-up (which was not specified) was rather short, e.g. 12 years
McCaul 2008 (McCaul, Fritschi et al. 2008)	Retrospective cohort study Funding/CoI: not reported Setting: Queensland Cancer Registry, Australia Sample size:	Eligibility criteria: Diagnosis of melanoma in the cancer registry No zero survival time, synchronous melanoma or incompatible coding of	Not applicable	The rate of second melanomawas relatively constant over 20 years of follow-up at 1/166 person years, except for the first year when it was 1/79	-	Level of evidence: C Large population Retrospective study based on routinely collected cancer data

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
	N=52,997 Duration: 1982-2003	level and behaviour *A priori* patient characteristics: 55% male, 45% female Mean age 57 y (males), 53 y (females) Invasive lentigo maligna 3.6%, in situ lentigo maligna 11.8%, all other invasive melanomas 61.5%, all other in situ melanomas 23.1% 3.8% second melanomas at 5 years and 6. 4% at 10 years Follow-up: mean 6.8 y		Rates did not differ by different types of melanoma		Loss to follow-up not described
Romano 2010 (Romano, Scordo et al. 2010)	Retrospective study of prospective database Funding/CoI: no potential conflicts of interest Setting: Single centre (MSKCC, US) Sample size: N=340 Duration: 12/1998-1/2004	Eligibility criteria: Patients with stage III melanoma who were rendered free of disease but later relapsed Sufficient information for evaluation *A priori* patient characteristics:	Not applicable	AJCC stage IIIA #: 40% ⩽1 y 64% ⩽ 2y 92% ⩽ 5 y AJCC stage IIIB #: 44% ⩽1 y 79% ⩽ 2y 98% ⩽ 5 y AJCC stage IIIC #:	Similar percentages were found for systemic, local and in-transit and for lymph node metastases per sub-stage	Level of evidence: C 149 patients lacked the required information and were excluded Consecutive patients

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
		Male 64%, female 36% Median age: 57y Stage primary tumour: IIIA 28%, IIIB 46%, IIIC 26% 100% recurrence Follow-up: median 77 months (for patients without recurrence)		70% ⩽1 y 92% ⩽ 2y 100% ⩽ 5 y		

Data read from relapse-free survival curves
When figures do not add up to 100% this may be due to rounding differences
Abbreviations: AJCC: American Joint Committee on Cancer; DFS: disease free survival; y: year(s); m: month(s); SEER: surveillance, epidemiology and end-results; UICC: International Union Against Cancer; USA: United States of America

Uitgangsvraag 13.2: Is de behandeleffectiviteit hoger naarmate de kanker eerder wordt gedetecteerd?

Primary studies

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
Francken AB 2007 [1]	Prospective study Funding/CoI: Supported in part by Stichting VSB Fonds, Stichting Dr. Hendrik Muller's Vaderlandsch Fonds, Stichting Fonds Doctor Catherine van Tussenbroek-Nell	Eligibility criteria: Previously treated for a single primary melanoma stage I-III Presenting to the SMU with a first melanoma recurrence at least 6 weeks after diagnosis of the primary tumour No occult primary	Detection of recurrence by patient, partner or relative (any symptom or signrelating to the recurrence resulting in a medical consultation)	No significant difference in survival between patient-detected and doctor-detected recurrence (p=0.54, no exact data provided)	No significant difference in survival between symptomatic and non-symptomatic recurrence (p=0.18, no exact data provided)	Level of evidence: B Patients were divided into 2 groups: 168 patients were interviewed by telephone regarding detection

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
	Ongerboer Fonds, Stichting Groninger Universiteits Fonds, Stichting De Korintiers, KWF Kankerbestrijding, Marco Polo Fonds, and the Melanoma Foundation of the University of Sydney Setting: Single centre (Sydney Melanoma Unit) Sample size: N=211 Duration: 7/2001-2/2003	melanoma *A priori* patient characteristics: Male 62%, female 38% Median age: male 58y, female 60y Stage primary tumour: male: I 29%, II 55%, III 16%; female: I 33%, II 45%, III 22% Group comparability (N=204): Male: 64% vs. 60% (NS) Age ≥ 70 at recurrence: 34% vs. 48% (NS) Recurrence symptoms: none 3% vs. 92%, lump swelling 71% vs. 8% (p<0.0001) Breslow (mm): ≤ 1.0 25% vs. 12%, > 4.0 16% vs. 28% (p=0.03) Clinical stage at primary diagnosis: NS	(N=154) vs. Detection of recurrence by doctor during routine follow-up visit (N=50)			of primary melanoma and recurrence, follow-up arrangements etc; for 43 patients this information was retrieved from the medical record. Median time between recurrence diagnosis and interview was 5.3 months: risk of recall bias. No clear risk adjustment for survival
Garbe C 2003[2], Leiter U 2010 [3]	Prospective study Funding/CoI: Supported by grant no. M3/95/Ga I from	Eligibility criteria: Referred for follow-up examinations of pathologically confirmed	Early discovery of metastasis/second	3-year survival (median follow-up of 43 months after detection of	Mode of detection of recurrence: Physical examination: 47%	Level of evidence: B Over 25-month

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
	the Deutsche Krebshilfe, Bonn,Germany Setting: Single centre (University of Tuebingen) Sample size: N=2008, of which 112 developed recurrence and 46 developed second primaries Duration: 8/1996-8/1998	stage I to IV melanoma Regular follow-up at the University Hospital No suspicion of recurrence at study entry *A priori* patient characteristics: Male 43%, female 57% Median age: male 56y, female 52y Stage primary tumour: I 73%, II 15%, III 10%, IV 2% Group comparability: not provided for early vs. late discovery	primary/recurrence (organ or lymph nodemetastases of no more than 2 cm in diameter, with less than 10 individual nodes being affected [mainly accounting for in-transit metastasis]. and,simultaneously, with an indication for surgery with a curative intent) vs. Late discovery of metastasis/second primary/recurrence	recurrence): Stage I/II: 76% vs. 38% (p<0.0001) Stage III: 60% vs. 18% (p<0.0001) 10-year survival (median follow-up of 65 months after detection of recurrence): 43% (95%CI 29.5-55.7) vs. 26% (12.5-38.7) (p=0.012) 10-year survival adjusted for lead time bias: 41% (27.4-53.6) vs. 26% (12.5-38.7) Multivariate Cox analysis: early phase vs. advanced phase detection of metastases was independent prognostic factor, adjusted for stage at diagnosis (p<0.001) (RR for dying of melanoma: 1.8, 95%CI 1.1-2.9, p=0.022)	CT: 24% LN sonography: 14% Chest X-ray: 6% Patients' self examinations detected 31% in early phase and 26% of late recurrences (Leiter 2010)	study period (Garbe 2003), 112 patients with stage I-III melanoma with recurrence: 48% were classified as early discoveries (although in Leiter 2010 it is reported 58%) Early vs. late detection was defined based on tumour characteristics and not based on the way it was detected Unclear if representative cohort (patients referred for follow-up)

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
Hofmann U 2002 [4]	Retrospective study Funding/CoI: not reported Setting: Single centre (University of Mannheim, Germany) Sample size: N=661, of which 127 developed recurrence Duration: 1/1983-11/1999	Eligibility criteria: Patients with stage I-III melanoma treated and followed for at least 6 months at the outpatients clinic Proper primary documentation *A priori* patient characteristics (N=630 stage I/II): only Breslow thickness: pT1 31%, pT2 28%, pT3 24%, pT4 7% Group comparability: not provided for patient-diagnosed vs. doctor-diagnosed relapse	Patient-diagnosed relapse (N=77, stage I/II) vs. Doctor-diagnosed relapse (N=48, stage I/II)	No significant difference in survival between patient-detected and doctor-detected recurrence (p=0.91, no exact data provided)	No significant difference in survival between symptomatic and non-symptomatic recurrence (p=0.64, no exact data provided)	Level of evidence: B Discordant information on inclusion of stage IV patients Exclusion of patients without sufficient follow-up or documentation No risk-adjustment for survival No clear definition of patient- or doctor-diagnosed relapse
Meyers MO 2009 [5]	Retrospective study of prospective database Funding/CoI: not reported Setting: Single centre (US) Sample size: N=118 of which 43 developed	Eligibility criteria: Patients undergoing surgical treatment for melanoma stage II/III Initially evaluated by SLN biopsy, clinically node negative Routine follow-up at centre	Patient-detected and/or symptomatic relapse (i.e. patients who sought care from their physician because of a new symptom	No significant difference in survivalbetween a self-detected recurrence and recurrence detectedby either a physician or by routine diagnostic scans (p=0.6, no exact data provided)	No difference in survivalamong patients who experienced a symptomatic recurrencecompared withthose who were asymptomatic (p=0.2, no exact data provided)	Level of evidence: B No risk-adjustment for survival

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
	recurrence Duration: 1997-2005	*A priori* patient characteristics: Male 65%, female 35% Median age: 63.5y Stage primary tumour: IIA 25%, IIB 26%, IIC 12%, III 30%, unknown 8% Group comparability: not provided for patient-diagnosed vs. doctor-diagnosed relapse	[e.g. neurologic deficit or decreased performance status]. and who were subsequently diagnosed with a recurrence) (N=29) vs. Doctor- or imaging-detected relapse (N=14)			
Moore Dalal K 2008 [6]	Retrospective study of prospective database Funding/CoI: not reported Setting: Single centre (MSKCC, US) Sample size: N=1062 of which 203 developed recurrence Duration: 1991-2004	Eligibility criteria: Patients with histologically confirmed clinical stage I or II melanoma whounderwent successful SLNB Clinically node negative, no evidence of distant metastasis at time of SLNB No multiple primaries	Patient-diagnosed relapse (awareness of symptoms or abnormal physicalfindings) (N=109) vs. Doctor-diagnosed	Patients whose recurrences were self-detected by physical findings had a significantly improved survival (median 37 months) compared with those detected by symptoms only (median 7 months), physician physicalexam (median 29 months), or	Adjusted for worst site of recurrence, method of detection remainedsignificantly associated with post-recurrence survival(p=0.02)	Level of evidence: B Five patients were excluded for unclear reasons

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
		A priori patient characteristics: Male 62%, female 38% Median age: 60y Stage primary tumour: IA 1%, IB 21%, IIA 33%, IIB 26%, IIC 19% Group comparability: not provided for patient-diagnosed vs. doctor-diagnosed relapse	relapse (discovered on routine physicalexam or scheduled test) (N=89)	screening radiologictests (median 9 months) (overall test p<0.001)		
Romano E 2010 [7]	Retrospective study of prospective database Funding/CoI: no potential conflicts of interest Setting: Single centre (MSKCC, US) Sample size: N=340 Duration: 12/1998-1/2002	Eligibility criteria: Patients with stage III melanoma who were rendered free of disease but later relapsed Sufficient information for evaluation *A priori* patient characteristics: Male 64%, female 36% Median age: 57y Stage primary tumour: IIIA 28%, IIIB 46%, IIIC 26% Group comparability: not provided for patient-	Symptomatic relapses vs. Relapses discovered by physical examination or imaging	Symptomatic relapses, as opposedto relapses discovered by physical examination or radiographic imaging,were associated with shorter survival: RR 0.67 (95%CI 0.50-0.88, p=0.004)		Level of evidence: B 149 patients lacked the required information and were excluded

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
		diagnosed vs. doctor-diagnosed relapse				

Abbreviations: 95%CI: 95% confidence intervals; CoI: conflicts of interest; CT: computed tomography; LN: lymph node; NS: not significant; RR: relative risk; SLN: sentinel lymph node; SLNB: sentinel lymph node biopsy; US: United States