## Evidence tabellen

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 |
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| Multicenter Selective Lymphadenectomy Trial (MSLT)  ([Morton, Cochran et al. 2005](#_ENREF_5); [Morton, Thompson et al. 2006](#_ENREF_6)) | 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 malignancy within the previous 5 years; life expectancy less than 10 years; primary or secondary immune deficiency; pregnancy | 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 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 |
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| ([Gutzmer, Al Ghazal et al. 2005](#_ENREF_1)) | 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 |
| ([Koskivuo, Talve et al. 2007](#_ENREF_2)) | 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 |
| ([Leiter, Buettner et al. 2010](#_ENREF_3)) | 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](#_ENREF_4))  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 |
| ([Starz, Siedlecki et al. 2004](#_ENREF_7)) | 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](#_ENREF_8)) | 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  Sample size: N=1789  January 1991-December 2000 (no-SNB group) and February 1992-December 2000 (SNB group) | Primary cutaneous melanoma with a Breslow thickness of 1 mm or more  Exclusion: multiple or occult primary melanomas; evidence of metastasis at 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 the SNB group (12%) vs. the control group (20%) | 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 adjusted; results from a multivariable regression analysis showed similar results however  Only relevant results reported here |

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: N=100 of which 15 with stages I-II  Duration: 1998-2002 | 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 metastases identified with MRI in 11% of all patients (all stage IV) | 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 in patients with stages I-III including patients with symptoms suggestive of brain metastases | Level of evidence: B  Dropouts: not reported  Results critical appraisal (definition of positive and negative cases, completeness of verification):  Retrospective, spectrum of disease 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, Germany  Sample size: N=67  Duration: not stated | 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 years, Breslow range 1.08-5.5  Prevalence of disease: metastases to the SLN 16.4% | 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 nodes identified by US compared to scintigraphy | 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 |
| 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 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% | 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 of 0.5 in every cell to account for 0 cell in calculation of likelihood ratios) | 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 |
| 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 lesions | Level of evidence: C  Dropouts: none reported  Results critical appraisal (definition of positive and negative cases, completeness of verification): Retrospective, outcomes not clearly defined |
| 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 2009{Sawyer, 2009 #105} | Design: retrospective  Source of funding: none reported  Setting: single centre, UK  Sample size: N=132  Duration: January 2000-August 2006 | Eligibility criteria: new cases 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% | Index test(s): CT  Reference standard: follow-up including CT scans | Sensitivity, specificity, PPV, NPV, LR+, LR-  Initial scans with metastases:  Chest 3/?  Abdomen 2/?  Pelvis 0/?  Head 3/102  Neck 0/? | Effect size  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 | Level of evidence: B  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  Setting: single centre, the Netherlands  Sample size: N=85  Duration: December 2006-? | Eligibility criteria: melanoma patients undergoing both lymphoscintigraphy and SPECT/CT  Patient characteristics (e.g. age, tumour characteristics, stage, etc.): mean age 54 years  Prevalence of disease: patients with metastatic nodes 21.2% | 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 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 | Level of evidence: C  Dropouts: none reported  Results critical appraisal (definition of positive and negative 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)  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) | 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 |

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), I2 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), I2 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 exclusively for initial staging: 17 studies. Other 11 studies: enrollment for initial staging: 18%–97%. | 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  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 |
| --- | --- | --- | --- | --- | --- | --- |
| 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 (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 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 | 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 study in which the sensitivity wasonly 4%. |  | 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 |
| 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 hospitals, the Netherlands  Sample size: N=251  Duration: July 2003 through December 2007 | Eligibility criteria: Patients with melanoma with potentially resectable lymph node metastases  Patient characteristics: >= 18 years; Breslow thickness <= 1.0 mm: 12.8%, > 1.0mm: 80.5%;  Prevalence of metastatic disease: 31% | Index tests:  FDG-PET  CT  Reference standard: Histology/cytology, other imaging modalities (bone scan, MRI) or 6 months follow-up | Distant metastases:  PET:  Se 86%, Sp 94%  CT:  Se 78%, Sp 94% | Diagnosis LN metastases:  PET: Se 91%  CT: Se 92%  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) | Level of evidence: B  Dropouts: none reported  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  Sample size: N=106  Duration: January 2003 – June 2005 | Eligibility criteria: Patients with histopathologically confirmed malignant melanoma who had a whole body PET/CT at the instituteand availablescans  Patient characteristics: mean age 56.7years (± 15.9 y);  Prevalence of disease:56/106 = 53% | Index tests:  FDG-PET  CT  Reference standard: Pathology results and clinical follow-up | Disease restaging:  PET:  Se 89.5%(95%C.I. 78.9-95.1) , Sp 81.6% (95%C.I 68.6-90.1)  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) | 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 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 | Level of evidence: B  Dropouts: none reported  No clear definition of clinical follow-up  potential incorporation bias |
| Pfannenberg 2007 | Design: prospective, blinded single centre study  Source of funding: not stated  Setting: University centre, Gemany  Sample size: N=64  Duration: September 2004 – September 2005 | Eligibility criteria: Histologically proven cutaneous melanoma presenting with potential evidence of metastatic spread  Patient characteristics: 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%) | Index test(s):  PET  PET/CT  CT  wbMRI  Reference standard:  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 | 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%  wbMRI:  Se 79.8%, Sp 89.1% | PET/CT more sensitive in detecting skin and subcutaneous metastases than wbMRI  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 | Level of evidence: B  Consecutive patients  Exclusion of 36 patients due to 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 2006 | Design: retrospective, blinded single centre study  Source of funding: not stated  Setting: University hospital, Germany  Sample size: N=250  Duration: November 2002 – June 2004 | Eligibility criteria: patients 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% | Index test(s):  PET  PET/CT  CT  Reference standard:  primary malignant disease was confirmed by his pathologic verification;  clinical follow-up | initial N-staging:  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)  Initial M-staging:  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) | Change in disease management : 48.4% of the patients after PET/CT | Level of evidence : 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) |
| 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 |
| 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 metastases: 12/56 = 21% | Index test:  PET  CT  PET/CT  Reference test:  Histopathological examination (if suspected metastases) or clinical follow-up (imaging, tumour markers, physical examination) | 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) overleving in vergelijking met een ‘wait and see’ aanpak?M-staging:  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 | 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 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% | Index test:  PET  CT  Reference test:  histopathological examination  clinical follow-up  radiological follow-up | Detection of melanoma metastases  PET:  Se 68%, Sp 92%  CT:  Se 48%, Sp 95% | Treatment changes  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](#_ENREF_1)) | 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 date of relapse or last follow-up visit | 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  AJCC stage IIC (89%):  89% ≤5y  8% 6-10 y  0% 11-15 y  3% 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  Regional recurrence rate:  1/6 <1 year #  1/20 ≥ 5 year #  Visceral metastasis recurrence rate:  1/100 # from 0 to > 20 years | Level of evidence: C  Consecutive patients  210/2100 (10%) of disease-free patients at the last visit were lost to follow-up |
| Bradford 2010 ([Bradford, Freedman et al. 2010](#_ENREF_2)) | 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 ([Francken, Accortt et al. 2008](#_ENREF_3)) | Retrospective cohort study  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 | Eligibility criteria:  Cutaneous melanoma 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 | Not applicable | All recurrences stage IA at 10 years (8%) #:  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 | - | Level of evidence: C  Consecutive patients  Retrospective study based on routinely collected cancer data  Loss to follow-up not specified |
| Hansel 2010 ([Hansel, Schonlebe et al. 2010](#_ENREF_4)) | 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](#_ENREF_5)) | Retrospective cohort study  Funding/CoI: not reported  Setting: University Hospital Erlangen, Germany  Sample size: N=2,487  Duration: 1978-1997 | Eligibility criteria:  Cutaneous melanoma  No non-curative resection, no distant metastasis at time of diagnosis  *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 | Not applicable | All recurrences (21%):  82% ≤5y  12% 6-10 y  7% > 10 y | - | Level of evidence: C  Consecutive patients  Prospective data collection  Low loss to follow-up (1.2%) |
| Leiter 2011 ([Leiter, Buettner et al. 2011](#_ENREF_6)) | 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 melanoma  Follow-up: median 4.9 months | 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 -years) stage III:  1/3 at 1 year  1/10 at 3 years  1/14 at 5 years  1/47 at 10 years | 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 melanoma:  1/222 at 1 year  1/769 at 3 years  1/526 5 years  1/1000 at 10 years | Level of evidence: C  Large population  Retrospective study based on routinely collected cancer data  Loss to follow-up not described |
| Leman 2003 ([Leman and Mac Kie 2003](#_ENREF_7)) | 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](#_ENREF_8)) | Retrospective cohort study  Funding/CoI: not reported  Setting: Queensland Cancer Registry, Australia  Sample size: N=52,997  Duration: 1982-2003 | Eligibility criteria:  Diagnosis of melanoma in the cancer registry  No zero survival time, synchronous melanoma or incompatible coding of 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 | 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  Rates did not differ by different types of melanoma | - | Level of evidence: C  Large population  Retrospective study based on routinely collected cancer data  Loss to follow-up not described |
| Romano 2010 ([Romano, Scordo et al. 2010](#_ENREF_9)) | 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:  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) | 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 #:  70% ≤1 y  92% ≤ 2y  100% ≤ 5 y | 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 |

# 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 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 | 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 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 | Detection of recurrence by patient, partner or relative (any symptom or signrelating to the recurrence resulting in a medical consultation) (N=154)  vs.  Detection of recurrence by doctor during routine follow-up visit (N=50) | 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 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 20032, Leiter U 2010 3 | Prospective study  Funding/CoI: Supported by grant no. M3/95/Ga I from 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 | Eligibility criteria:  Referred for follow-up examinations of pathologically confirmed 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 | Early discovery of metastasis/second 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 | 3-year survival (median follow-up of 43 months after detection of 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) | Mode of detection of recurrence:  Physical examination: 47%  CT: 24%  LN sonography: 14%  Chest X-ray: 6%  Patients’ self examinations detected 31% in early phase and 26% of late recurrences (Leiter 2010) | Level of evidence: B  Over 25-month 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) |
| 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 recurrence  Duration: 1997-2005 | Eligibility criteria:  Patients undergoing surgical treatment for melanoma stage II/III  Initially evaluated by SLN biopsy, clinically node negative  Routine follow-up at centre  *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 | Patient-detected and/or symptomatic relapse (i.e. patients who sought care from their physician because of a new symptom [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) | 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 |
| 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  *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 | Patient-diagnosed relapse (awareness of symptoms or abnormal physicalfindings) (N=109)  vs.  Doctor-diagnosed relapse (discovered on routine physicalexam or scheduled test) (N=89) | 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 screening radiologictests (median 9 months) (overall test p<0.001) | 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 |
| 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-diagnosed vs. doctor-diagnosed relapse | 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 |

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