2.3 Diagnostiek bij onbekende primaire tumor						
I Study ID	**II Method**	**III Patient Characteristics**	**IV Interventions**	**V Results primary outcome**	**VI Results secondary and other outcome**	**VII Critical appraisal**
1. Agazzi *et al*, The origin of brain metastases in patients with an undiagnosed primary tumour, Acta Neurochirurgica, 2004	**1.** Retrospective Cohort **2.** Not reported **3.** Lausanne University Hospital Switzerland **4.** 342 --> 15 lost to FU **5.** January 1983 - December 1998	**1.** Patients with brain metastases that has been diagnosed in the years after CT scan was introduced and became routinely in Lausanne University Hospital Switzerland. **2.** Sex, age, Karnofsky Performance Status, Discharge destination and clinical presentation of cerebral metastases. **3.** Not described	**1+2.**The difference in distribution between undiagnosed primary tumour (UDP) patients with BM versus diagnosed primary (DP) tumour patients with BM.	**1.** UDP: lung 59,8%, Non lung 14%, Unknown 26,2% . DP Lung 42,7%, Non lung 55,9, Unknown 1,4%	**1+2.** Not Reported	**1.** B. **2.** 15 Patients were lost to FU **3.** There is a large difference between the two groups of patients and therefore difficult to compare, difference in p value. Unclear how people were diagnosed for the category "undiagnosed". Not clear what happened with the lost to follow up. No description of possible blinding for patient examination
1. D'Ambrosio *et al*, Prognosis in patients presenting with brain metastasis from an undiagnosed primary tumor, Neurosurgical Focus, 2007	**1.** Retrospective Cohort **2.** Not reported **3.** Lausanne University Hospital Switzerland **4.** 342 --> 15 lost to FU **5.** January 1983 - December 1998	**1.** Patients with CT diagnosed brain metastases. **2.** Sex, age, clinical presentation, location of brain metastases, number of bm, presenceof systemic disease, location of primary tumour. **3.** Not described	**1+2.** Surgery+WBRT, Radiosurgery+WBRT,WBRT, corticosteroid.	**1.** UDP median surv. 6 months.DP median surv. 4,5 months	**1+2.** Treatment, age less than 65 yrs, discharge home, absence of sytemicmetast. And asymptomatic cerebral metastasis	**1.** B. **2.** 15 patients were lost to FU. **3.** Not checked for significance and a very long inclusion period
1. Drlicek *et al*, Immunohistochemical panel of antibodies in the diagnosis of brain metastases of the unknown primary, Pathology, Research & Practice, 2004	**1.** Retrospective case series **2.** Not reported **3.** Landes-Nervenklinik Wagner- Jauregg, Linz, Austria **4.** 54 cases **5.** 1 year (not specified)	**1.** Consecutive unselected BM **2.** Sex, site of prim tumour. **3.** Not described	**1+2.** Immunohistochemical investigation on unselected BM.	**1.** For 29 cases out of 40 specific immunohistochemical profiles were identified (for several primary tumour groups)	**1+2.** Not Reported	**1.** C. **2.** Not reported **3.** Very small sample size and no follow up
1. Giordana *et al*, Cerebral metastases as first symptom of cancer: a clinico-pathologic study, Journal of Neuro-Oncology, 2000	**1.** Retrospective case series **2.** Supported by AIRC, Milan, Italy **3.** Department of Neuroscience, University of Turin **4.** 181 patients **5.** 1985 - 1997	**1.** Patients were consecutively operated for single cerebral metastases of a carcinoma **2.** Sex, age. **3.** Not described	**1+2.**The primary site of BM can be identified by immunohistochemical study of the neurosurgical specimens.	**1.** Freq known =82 / unknown= 99	**1+2.** The immunohistochemical investigation helped to establish an antibody panel useful to identify the primary of a BM in daily routine. This panel succeeded to point of the correct primary in 29 out	**1.** C. **2.** Not reported **3.** No blinding and this study does not answer our question, valid?

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					of 40 cases	
1. Jeong *et al*, Usefulness of whole-body (18)F-FDG PET in patients with suspected metastatic brain tumors, Journal of Nuclear Medicine, 2002	**1.** Retrospective case series **2.** Not reported **3.** Not reported **4.** 127 patients **5.** May 1997 - May 2001	**1.** Patients were enrolled with brain masses who had suspected radiologic evidence of metastatic brain tumors **2.** 77 Male, 50 female, mean age 55+/-12years, 61 metastatic brain tumor **3.** Not described	**1+2.** Whole Body F-FDG PET.	**1.** 56 Of 70 patients primary tumours were identified by tje F-FDG PET.16 false negative cases. And 3 false positive cases	**1+2.** Not Reported	**1.** C **2.** Not reported **3.** Not clear what kind of setting is used and therefore difficult to interpret the results. No FU time reported
1. Kim DG *et al*, Whole-body [18F]FDG PET in the management of metastatic brain tumours, Acta Neurochirurgica, 1998	**1.** Retrospective case series **2.** In part supported by a grant from the Seoul University Hospital **3.** Department of Neurosurgery, Seoul National Hospital **4.** 20 patients **5.** November 1995 - November 1996	**1.** All patients were suffering or needing to be differentiated from metastatic brain tumours. **2.** 13 Male, 7 females, 57years, range 22-76 **3.** Not described	**1+2.**[18F]FDG PET can be used as a convenient and appropriate tool for the diagnosis and systemic evaluation of MB tumour.	**1.** In 11 from the 20 patients the F FDG PET could identify the primary tumour, this was 9 from the 20 for conventional work up. 15,4% false negative, no false positive for the FFDG-PET and 30,7% were false negative for the conventional work up.	**1+2.** Not Reported	**1.** C **2.** Not reported **3.** Small smaple size and low external validity due to a too specific setting
1. Klee *et al*, Detection of unknown primary tumours in patients with cerebral metastases using whole-body 18F-flouorodeoxyglucose positron emission tomography, European Journal of Neurology, 2002	**1.** Retrospective case series **2.** Danish NRC Grant / the National Female Research Cooperation: The diagnostic value of PET in relation to cancer. And the Brithe Meyer Foundation **3.** Department of Neurosurgery, Rigshospitalet, Copenhagen University Hospital **4.** 16 Patients	**1.** Histologically confirmed cerbral metastases and unknown primary tumours, who were investigated with a whole-body PET scan. **2.** 8 Male, 8 female, median age of 57 years (range 34-74), 14 patients were smokers. **3.** Not described	**1+2.** Whole body [18]FDG PET scanning is a sensitive tool in the search for unknown primary tumours of patients with confirmed cerebral metastases.	**1.** 8 Of 16 patients were true possitive. Non confirmed as false positive or false negative	**1+2.** Not Reported	**1.** C. **2.** Not reported **3.** Short inclusion period but small sample size. A low external validity due to the specific setting

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	5. March 1999 - March 2001					
1. Latief *et al*, Search for a primary lung neoplasm in patients with brain metastasis: is the chest radiograph sufficient?, AJR American Journal of Roentgenology, 1997	**1.** Retrospective case series **2.** Not reported **3.** University of Maryland Medical Centre, Baltimore **4.** 32 Patients --> 1 lost to FU **5.** 1991-1995	**1.** The patients had an initial presentation with symptomatic brain metastasis: the patient underwent a head CT or MR imaging study as part of the initial evaluation of CNS symptoms in the absence of other systemic clinical symptoms, cross-sectional imaging of the brain of the brain showed one or more lesions that were judged to be suggestive of metastatic disease. and no prior neoplasm was documented. **2.** 25 Male, 7 female mean age 57yrs, range 44-84yrs. 30 smokers **3.** Not described	**1+2.** Chest CT provides an advantage over chest radiography when diagnosing a primary lung neoplasm in a selected group of patients.	**1.** 1 Patient had no radiograph or CT that showed a primary lesion. 19 had a primary on radiograph and CT. 4 patients had a nonspecific radiograph and a positive CT. 8 patients had no pos radiologic diagn. And a positive CT	**1+2.** Cat 1. NA, Cat 2 4,2 cm Cat 3. 2.7 cm,Cat 4 2,4cm	**1.** C. **2.** 1 patient lost to FU. **3.** Short inclusion period but small sample size. A low external validity due to the specific setting

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I Study ID	**II Method**	**III Patient Characteristics**	**IV Interventions**	**V Results primary outcome**	**VI Results secondary and other outcome**	**VII Critical appraisal**
1. Nguyen *et al*, Brain metastases as the only manifestation of an undetected primary tumor, Cancer, 1998	**1.** Retrospective cohort **2.** Not reported **3.** The University of Texas M.D. Anderson Cancer Centre **4.** 39 **5.** 1977-1996	**1.** Brain metastasis from a undetected primary tumour. **2.** Male:female ratio 21:18, median age of 55yrs, range 41-76 yrs, 7 patients KPS≤60 **3.** Not described	**1+2.** Not reported	**1.** In 12 patients the primary site was eventually discovered	**1+2.** for extracranial diseases the minority will survive longer than 5 years	**1.** C. **2.** Not reported **3.** Very long inclusion period and no clear hypotheses tested which makes it difficult to interpret.
1. Perry *et al*, Metastatic adenocarcinoma to the brain: an immunohistochemical approach, Human Pathology, 1997	**1.** Retrospective case series **2.** Not reported **3.** Department of Anatomic Pathology, Mayo clinic, Rochester **4.** 68 consecutive biopsies **5.** 1990-1995	**1.** Consecutive biopsy specimens of metastatic adenocarcinomas to the brain of unknown primary tumours **2.** Not described. **3.** Not described	**1+2.** Immunohistochemical markers are usefull in the setting of metastatic adenocarcinomas to the brain.	**1.** CAM 5.2, WSK and GFAP are useful confirmatory stains in suspected metastatic adenocarcinoma of the brain. AE1/AE3, CAM 5.2 and WSK do not stain astrocytes. CK 7 is a reliable marker of the lung and breast. CK20 detects gastrointestinal prim. Strong staining reduces FP's for CK7 and CK20. GCDFP-15 and ER are of further help in separating breast from lung. PR is non specific to interpret. for all markers 88 were True Pos, 70 were False Pos, 221 Tue Neg, 30 False neg.	**1+2.** Not Reported	**1.** C. **2.** Not reported **3.** No patient characterisics available and no control group
1. Prok *et al*, Thyroid transcription factor-1 staining is useful in identifying brain metastases of pulmonary origin, Annals of Diagnostic Pathology, 2006	**1.** Retrospective case series **2.** Not reported **3.** Not reported **4.** 101 **5.** 1998-2005	**1.** Metastatic carcinoma involving the brain 1998-2005 **2.** Not reported **3.** Not reported	**1+2.** Thyroid transcription factor-1 staining is useful in identifying brain metastases of pulmonary origin.	**1.** 44 Were positive stained tumours for TTF-1. 1+ for 4 tumours, 2+ for 6 tumours, 3+ for 10 tumours and 4+ for 24 tumours.	**1+2.** Not Reported	**1.** C. **2.** Not reported. **3.** The immunohistochemical staining was assessed, blinded to knowledge of the primary site of origin / no patient characteristics. Described/ low external validity

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I Study ID	**II Method**	**III Patient Characteristics**	**IV Interventions**	**V Results primary outcome**	**VI Results secondary and other outcome**	**VII Critical appraisal**
1. Ruda *et al*, Brain metastases from unknown primary tumour: a prospective study, Journal of Neurology, 2001	**1.** Prospective case series **2.** Not reported **3.** University Hospital of Torino **4.** 33 **5.** 1987-1996 (screening time for inclussion was January 1987-December 1991	**1.** Patients with solitary brain metastases and the primay site still unknown, all patients were treated with WBRT, non had adjuvant chemotherapy. **2.** 28 Male, 5 female, median age 51 yrs, range 32-70 yrs **3.** Not described	**1+2.** In patients with both single and multiple brain metastases from undetected primary site, surgery and/or WBRT enable the control of the brain disease.	**1.** Median survival : Single (GTR+WBRT)= 13mnths, Multible (WBRT)= 6mnths, Multiple (GRT+WBRT)=8 mnths colon 11%, pancreas 8%,melanoma of the breast 0%	**1+2.** Not Reported	**1.** C. **2.** Not reported **3.** Small sample size and a long inclusion period but prospective study
1. Strickland *et al*, Utility of tissue-specific transcription factors thyroid transcription factor 1 and Cdx2 in determining the primary site of metastatic adenocarcinomas to the brain, Archives of Pathology & Laboratory Medicine, 2007	**1.** Retrospective case series **2.** Not reported **3.** H.Lee Moffit Center and Research Institute at the University of South Florida, Tampa **4.** 38 consecutive brain biopsies **5.** Not reported	**1.** Metastatic adenocarcinoma of known origin **2.** Not reported **3.** Not reported	**1+2.** It is usefull to characterize previously unpublished immunohistochemical expression of the relative new tissue specific Thyroid transcription factor 1 and Cdx2 in metastatic adenocarcinomas to the brain.	**1.** For the TTF-1 expression in lung, the sensitivity was 55%, specificity was 100%, PPV and NPV was 100% and 62% For the Cdx2 expression in gastrointestinal, sensitivity was 83%, specificity was 100%, PPV and NPV was 100% and 97% For the CK7 expression in lung or breast, sensitivity was 100%, specificity was 83%, PPV and NPV was 97% and 100% For the CK20 expression in gis primaries sensitivity was 83%, specificity was 97%, PPV and NPV was 83% and 97%	**1+2.** Not Reported	**1.** C. **2.** Not reported **3.** Descriptive, small sample size? Stained slides were reviewed by two pathologists with joint review and resolution of discrepancies

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I Study ID	**II Method**	**III Patient Characteristics**	**IV Interventions**	**V Results primary outcome**	**VI Results secondary and other outcome**	**VII Critical appraisal**
1. Taweevisit *et al*, Cytokeratin 7 and 20 as immunohistochemical markers in identification of primary tumors in craniospinal metastases: Do they have a significant role?, Neuropathology, 2003	**1.** Retrospective case series **2.** Reviewer is supported by the Development Grants for New Faculty Member/Researchers, Chulalonkorn university. **3.** King Chulalongkorn Hospital, Bangkok, Thailand **4.** 66 cases **5.** 1998-2002	**1.** Craniospinal metastasis with routine preoperative investigations, including physical examination and chest X-Ray film **2.** Not reported **3.** Not reported	**1+2.** Cytokeratin 7 and 20 as immunohistochemical markers in identification of primary tumors in craniospinal metastases do play a significant role.	**1.** CK7/CK20 the PPV was 82% and NPV was 75%. CK7/CK20 the sensitivity was 95% and specificity was 38%	**1+2.** Not Reported	**1.** C. **2.** Not reported **3.** No patient characteristics, small sample size and the specific setting gives a low external validity
1. Van der Pol *et al*, Brain metastases from an unknown primary tumour: Which diagnostic procedures are indicated?, Journal of Neurology Neurosurgery and Psychiatry, 1996	**1.** Retrospective cohort **2.** Not reported **3.** Maastricht University Hospital, Maastricht, The Netherlands **4.** 72 patients **5.** 1987-1994	**1.** Brain metastasis from an unkown primary cancer and had a MRI or CT scam. **2.** 46 Male, 26 female, median age of 65yrs, range 15-85yrs. **3.** Not reported	**1+2.** Guidelines for further diagnostic procedures are needed for brain metastases from an unknown primary tumour.	**1.** The PPV was 85%. no significant difference in survival between a treatable tumour and a undiagnosed tumour	**1+2.** No significant difference in survival between a treatable tumour and a undiagnosed tumour	**1.** B. **2.** Not reported **3.** Low external validity due to the specific setting but validity, specific for the Netherlands. Very long inclusion period