Bijlage 10 Evidence tabellen

Vraag 1a Bij patiënten met invasief cervixcarcinoom, welke diagnostische techniek resulteert in de meest accurate stadiëring?

Systematic reviews

Study ID	Method	Patiënt characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
(Bipat, Glas et al. 2003)	Design: systematic review with meta-analysis Funding: not reported on Search date:1985-2002 Searched databases: Medline and Embase Included study designs: not reported on 57 included studies	Eligibility criteria: English or German language studies; sample size ≥10 patiënts; histopathology as reference standard; sufficient data to construct a 2x2 contingency table Exclusion criteria: data reported elsewhere in more detail Patiënt characteristics: cervical carcinoma	Index test: CT, MRI or both Reference standard: histopathology	Meta-analysed (N=9) accuracy of CT to detect parametrial invasion: Se 55% (95%CI 44-66); Sp 76% (visual inspection forest plot) Meta-analysed (N=52) accuracy of MRI to detect parametrial invasion: Se 74% (95%CI 68-79); Sp 85% (visual inspection forest plot) Meta-analysed (N=3) accuracy of CT to detect bladder invasion: Se 64% (95%CI 39-82); Sp 73% (95%CI 52-87) Meta-analysed (N=16) accuracy of MRI to detect bladder invasion: Se 75% (95%CI 66-83); Sp 91% (95%CI 83-95) Meta-analysed (N=2) accuracy of CT to detect rectum invasion: Se 45% (95%CI 20-73); Sp 94% (visual inspection forest plot) Meta-analysed (N=9) accuracy of MRI to detect rectum invasion: Se 71% (95%CI 53-83); Sp 83% (visual inspection forest plot)	The sensitivity for parametrial invasion by MRI was significant higher compared with CT (P=0.0027) The sensitivity for bladder invasion and rectum invasion by MRI were higher compared with CT but these differences were not statistically significant The sensitivity for lymph node involvement by MRI was significantly higher compared to CT (P=0.047) Subgroup analyses for methodological criteria, coil usage, T1 vs. T2, type of magnetic field, year of publication or sample size did not reveal differences in accuracy. No data on cervical angulation technique	Level of evidence: B 30 prospective studies, 14 retrospective studies and in 13 studies data collection was unknown Blinded assessment in 29 studies; non blinded assessment in 28 studies Complete verification in 43 studies; partial verification in 14 studies Characteristics from the original studies were not described; clinical heterogeneity unknown Statistical heterogeneity partially taken into account Included studies: *Primary studies:* 53 studies published before 2001 Studies published from 2001 onwards: (Narayan, Hicks et al. 2001) (Reinhardt, Ehritt-Braun et al. 2001) (Sheu, Chang et al. 2001) (Wang, Wong et al. 2001)

Study ID	Method	Patiënt characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
				Meta-analysed (N=17) accuracy of CT to detect lymph node (unspecified) metastasis: Se 43% (95%CI 37-57); Sp 94% (visual inspection forest plot) Meta-analysed (N=25) accuracy of MRI to detect lymph node (unspecified) metastasis: Se 60% (95%CI 52-68); Sp 93% (visual inspection forest plot)		
(Havrilesky, Kulasingam et al. 2005)	Design: systematic review with meta-analysis Funding: Centers for Medicare and Medicaid Services Search date:1966-2003 Searched databases: Medline Included study designs: observational studies	Eligibility criteria: English language studies reporting primary data and published in a peer review journal with 12 or more included patiënts Patiënt characteristics: newly diagnosed cervical cancer	Index test: CT, MRI or PET Reference standard: histology or follow-up	Meta-analysed (N=2) accuracy of CT to detect pelvic lymph node metastasis (reference: histology or follow-up): Se 47% (95%CI: 21–73), Sp not enough data to calculate Meta-analysed (N=2) accuracy of MRI to detect pelvic lymph node metastasis (reference: histology or follow-up): Se 72% (95%CI: 53–87), Sp 96% (95%CI: 92–98) Meta-analysed (N=4) accuracy of PET to detect pelvic lymph node metastasis (reference: histology or follow-up): Se 79% (95%CI: 65–90), Sp 99 (95%CI: 96–99) Single study accuracy of MRI to detect para-aortic lymph node metastasis (reference: histology): Se 67% (95%CI: 9-99), Sp 100%	No data on T1 vs. T2 weighted or contrast enhanced MRI	Level of evidence: B Included studies were small (none included over 50 patiënts) and none reported blinded assessment Three studies were in selected subgroups, e.g. patiënts had to have negative MRI or CT findings Two studies used differential verification (histology or follow-up) Statistical heterogeneity was not assessed and there was clinical heterogeneity Included studies: *15 Primary studies:* 11 studies published before 2001 (Belhocine, Thille et al. 2002) (Lin, Hung et al. 2003) (Reinhardt, Ehritt-Braun et

Study ID	Method	Patiënt characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
				(95%CI: 66-100) Meta-analysed (N=4) accuracy of PET to detect para-aortic lymph node metastasis (reference: histology): Se 84% (95%CI: 68-94), Sp 95% (95%CI: 89-98)		al. 2001) (Yeh, Hung et al. 2002)
(Kang, Kim et al. 2010)	Design: systematic review with meta-analysis Funding: National Cancer Center, Korea Search date: 1980-2009 Searched databases: Medline, Embase Included study designs: retrospective and prospective studies	Eligibility criteria: diagnostic performance of PET or PET/CT specified for para-aortic lymph nodes; 2x2 tables could be constructed; 10 or more patiënts included; with histology as a reference standard Patiënt characteristics: *Boughanim*: IB2 or II *Choi*: IB-IVA *Lin*: IIB-IVA or IB/ IIA with a tumor diameter ≥5 cm or involvement of pelvic lymph nodes; negative abdominal CT finding *Narayan*: all operable patiënts without definitive CT evidence of para-aortic lymph node	Index test: PET or PET/CT Reference standard: histology	Meta-analysed (N=10) accuracy of PET or PET/CT to detect para-aortic lymph node metastasis: Se 34% (95%CI: 10-72) PET (N=5): 66% (95%CI: 33-89) PET/CT (N=5): 13% (95%CI: 2-56) Sp 97% (95%CI: 93-99%) PET (N=5): 97% (95%CI: 90-99) PET/CT (N=5): 98% (95%CI: 78-100) NLR 0.68 (95%CI: 0.40-1.15) PET (N=5): 0.35 (95%CI: 0.14-0.87) PET/CT (N=5): 0.89 (95%CI: 0.69-1.15) PLR 12.49 (95%CI: 4.64-33.62) PET (N=5): 19.9 (95%CI: 7.2-55.4) PET/CT (N=5): 7.0 (95%CI: 1.0-47.4)	Meta-analysed (N=5) accuracy of PET or PET/CT to detect para-aortic lymph node metastasis in studies with a low (≤15%) prevalence: Se 5% (95%CI: 0-55%); Sp 99% (95%CI: 90-100%); NLR 0.95 (95%CI: 0.82-1.11); PLR 9.15 (95%CI: 0.37-226.46) Meta-analysed (N=5) accuracy of PET or PET/CT to detect para-aortic lymph node metastasis in studies with a high (>15%) prevalence: Se 73% (95%CI: 53-87%); Sp 93% (95%CI: 86-97%); NLR 0.29 (95%CI: 0.15-0.55); PLR 10.62 (95%CI: 4.90-23.05)	Level of evidence: B 8/10 included studies were prospective in nature and 6/10 studies used blinded assessment of the index test Meta-analysed Se was extremely (unspecified) heterogeneous. Prevalence of para-aortic lymph node metastasis was the only statistically significant confounder in a multivariate regression analysis. The authors hypothesized selection bias or verification bias may have played a role in some studies 6 studies enrolled patiënts with negative results for para-aortic lymph nodes on prior CT, MRI, or PET Included studies: *10 Primary studies:* 11 studies published before 2001

Study ID	Method	Patiënt characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
		metastasis *Reinhardt*: cervical cancer patiënts *Roh*:IB-IVA *Vergote*: IB2-IIIB cervical cancer without para-aortic lymph node metastasis on PET and CT or PET/CT *Wright*: IA2-IIA *Yildirim*: locally advanced cervical cancer with negative CT findings for para-aortic lymph node metastasis Disease prevalence: a meta-analysed 14.2% of patiënts across all studies had para-aortic lymph node metastases				(Boughanim, Leboulleux et al. 2008) (Choi, Roh et al. 2006) (Lin, Hung et al. 2003) (Narayan, Hicks et al. 2001) (Reinhardt, Ehritt-Braun et al. 2001) (Roh, Seo et al. 2005) (Vergote, Tsolakidis et al. 2008) (Wright, Dehdashti et al. 2005) (Yildirim, Sehirali et al. 2008)
(van de Lande, Torrenga et al. 2007)	Design: systematic review with meta-analysis Funding: not reported on Search date: July 2006 Searched databases: Medline, Embase Included study designs: SNB studies	Eligibility criteria: majority (N80%) of included patiënts with early stage cervical cancer (FIGO I-IIA); English language studies; ≥ 10 patiënts included; sufficient data to reconstruct 2x2 tables Patiënt characteristics: see eligibility	Index test: SNB (Technetium, blue dye or both) Reference standard: histology	Meta-analysed (N=21) accuracy of SNB to detect lymph node metastasis: Se 89% (95%CI: 83-94) Technetium (N=5) 92% (95%CI: 79-98) Blue dye (N=4) 81% (95%CI: 67-92) Both (N=12) 92% (95%CI: 84-98)	Sentinel node detection rate: Technetium (N=7) 88% (95%CI: 82-92) Blue dye (N=5) 84% (95%CI: 79-89) Both (N=13) 97% (95%CI: 95-98)	Level of evidence: B Study quality: none of the studies used masked assessment of the reference standard; 19/22 studies were prospective; 17/22 studies used consecutive patiënts Meagre description of patiënt characteristics Included studies: *Primary studies*: 2 studies published before 2001

Study ID	Method	Patiënt characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
						(Angioli, Palaia et al. 2005) (Barranger, Cortez et al. 2004) (Chung, Kim et al. 2003) (Di Stefano, Acquaviva et al. 2005) (Gil-Moreno, Diaz-Feijoo et al. 2005) (Hubalewska, Sowa-Staszczak et al. 2003) (Lambaudie, Collinet et al. 2003) (Lantzsch, Wolters et al. 2001) (Levenback, Coleman et al. 2002) (Li, Zhang et al. 2004) (Lin, Tzeng et al. 2005) (Malur, Krause et al. 2001) (Marchiole, Buenerd et al. 2004) (Martinez-Palones, Gil-Moreno et al. 2004) (Niikura, Okamura et al. 2004) (Pijpers, Buist et al. 2004) (Rhim, Park et al. 2002) (Rob, Strnad et al. 2005) (Roca, Caresia et al. 2005) (Silva, Silva-Filho et al. 2005) (van Dam, Hauspy et al. 2003)

Study ID	Method	Patiënt characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
(Selman, Mann et al. 2008)	Design: systematic review with meta-analysis Funding: A Medical Research Council training fellowship Conflict of interest: none declared Search date and databases: Medline (1966-2006); Embase (1980-2006); Cochrane Library (Issue 2, 2006); Medion (1980-2006) Included study designs: not reported on 95 test results from 72 studies since some studies reported on more than one index test	Eligibility criteria: accuracy of index test compared with histological examination of lymph nodes in women with a primary presentation of cervical cancer of any histological type or stage; data could be used to create 2x2 tables. Exclusion criteria: fewer than 10 participants Patiënt characteristics: primary presentation of cervical cancer	Index test: CT, MRI, PET or SNB Reference standard: histology	Meta-analysed (N=32) accuracy of CT to detect pelvic &/ para-aortal lymph node metastasis: Se 57.5% (95%CI 53.5- 61.4); Sp 92.3% (95%CI 91.9-93.5); positive LR 4.3 (95%CI 3.0-6.2);negative LR 0.58 (95%CI 0.48-0.70) Meta-analysed (N=24) accuracy of MRI to detect pelvic &/ para-aortal lymph node metastasis: Se 55.5% (95%CI 49.2-61.7); Sp 93.2% (95%CI 91.4-94.0); positive LR 6.4 (95%CI 4.9-8.3); negative LR 0.50 (95%CI 0.39-0.64) Meta-analysed (N=8) accuracy of PET to detect pelvic &/ para-aortal lymph node metastasis: Se 74.7% (95%CI 63.3-84.0); Sp 97.6% (95%CI 95.4-98.9); positive LR 15.3 (95%CI 7.9-29.6); negative LR 0.27 (95%CI 0.11-0.66) Meta-analysed (N=31) accuracy of SNB to detect pelvic &/ para-aortal lymph node metastasis: Se 91.4% (95%CI 87.1-94.6); Sp 100% (95%CI 99.6-100); positive LR 40.8 (95%CI 24.6-67.6); negative LR 0.18 (95%CI 0.14-0.24)	Multivariable analysis of SNB versus MRI OR 18.49 (95%CI 3.59-95.17) PET versus MRI OR 3.84 (95%CI 1.22-12.12) CT versus MRI OR 0.63 (95%CI 0.36-1.12) Sentinel node detection rate: 89.1% (95%CI 72.6-98.5) Blue dye alone: 91.6% (95%CI 84.5-96.7) Blue dye and technetium: 95.6% (95%CI 92.3-98) No data on T1 vs. T2 weighted or contrast enhanced MRI In a multivariable analysis the type of lymph node (pelvic or para-aortal) did not influence the accuracy estimates	Level of evidence: B 29/95 test results reported blinded assessment of index test; 2/95 test results reported blinded assessment of reference test 58/95 studies reported whole or random sample verification Not all primary studies detected SN bilaterally, nor even reported if this was the case heterogeneity taken into account but not fully explained Included studies: *Primary studies:* 36 studies published before 2001 Studies published from 2001 onwards: (Altgassen, Gottschild et al. 2002) (Angioli, Palaia et al. 2005) (Barranger, Grahek et al. 2003) (Barranger, Cortez et al. 2004) (Belhocine, Thille et al. 2002) (Buist, Pijpers et al. 2003) (Chung, Kim et al. 2003) (Dargent and Enria 2003) (Di Stefano, Acquaviva et al. 2005)

Study ID	Method	Patiënt characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
						(Gil-Moreno, Diaz-Feijoo et al. 2005) (Hertel, Kohler et al. 2002) (Hubalewska, Sowa-Staszczak et al. 2003) (Kokka, Vorgias et al. 2003) (Kuhnel, Horn et al. 2001) (Lambaudie, Collinet et al. 2003) (Lantzsch, Wolters et al. 2001) (Levenback, Coleman et al. 2002) (Li, Zhang et al. 2004) (Lin, Hung et al. 2003) (Lin, Tzeng et al. 2005) (Malur, Krause et al. 2001) (Marchiole, Buenerd et al. 2004) (Martinez-Palones, Gil-Moreno et al. 2004) (Niikura, Okamura et al. 2004) (Ozsarlak, Tjalma et al. 2003) (Pijpers, Buist et al. 2004) (Reinhardt, Ehritt-Braun et al. 2001) (Rhim, Park et al. 2002) (Rob, Strnad et al. 2005) (Roh, Seo et al. 2005) (Silva, Silva-Filho et al. 2005) (van Dam, Hauspy et al. 2003) (Vorgias, Katsoulis et al. 2002)

Study ID	Method	Patiënt characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
						(Wang, Wong et al. 2001) (Wang, Sun et al. 2004) (Yeh, Hung et al. 2002)

Abbreviations: CI: confidence interval; NLR: negative likelihood ratio; NPV: negative predictive value; PLR: positive likelihood ratio; PPV: positive predictive value; Se: sensitivity, SE: spin echo; SN: sentinel node; SNB: sentinel node biopsy; Sp: specificity; y: year

Observational studies

Study ID	Method	Patiënt characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
(Akata, Kerimoglu et al. 2005)	Design: prospective cohort study Source of funding: not reported on Conflict of interest: not reported on Setting: University School of Medicine, Ankara, Turkey Sample size: N=28 Duration: not reported on	Eligibility criteria: referred for MRI after histological confirmation of cervical cancer; able to receive vaginal contrast medium; surgical or pathological staging Patiënt characteristics: mean age 53.4 y; stage IA:4%; IB:43%; IIA:18%; IIB:29%; IIIB:4%; IVB:4%	Index tests: MRI without and with vaginal opacification Reference standard: histopathology	Accuracy of MRI without vaginal opacification to detect stage I: Se 54%; Sp 60%; PPV 54%; NPV 60% Accuracy of MRI without vaginal opacification to detect ≥ stage IIA: Se 67% Accuracy of MRI with vaginal opacification to detect stage I: Se 100% Accuracy of MRI with vaginal opacification to detect ≥ stage IIA: Se		Level of evidence: B Dropouts: none reported Consecutive patiënts Exclusion of 20 patiënts who did not undergo surgery: partial verification bias exclusion of 2 patiënts who could not receive vaginal contrast medium Blinded assessment of index test; blinded assessment of reference test not reported on

Study ID	Method	Patiënt characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
				73%		
(Altgassen, Hertel et al. 2008)	Design: prospective multicenter cohort study Source of funding: in part by the Deutsche Krebshilfe (German Cancer Aid) Conflict of interest: no potential conflicts of interest Setting: 18 centres in Germany Sample size: N=590 Duration: 1998-2006	Eligibility criteria: invasive cervical cancer of all stages, intention of surgical staging, complete pelvic lymphadenectomy in case of negative SNB or one positive SLB, and appropriate tracer application. Exclusion criteria: neoadjuvant therapy, pregnancy, preoperatively detected metastatic disease, previous lymphadenectomy, tumor involvement of the adnexae, lymphoscintigraphy within 14 days before surgery, or allergy Patiënt characteristics: median age 41 y; 76% SCC. FIGO stage IA1: 8%; IA2: 8%; IB1: 52%; IB2: 11%; IIA/IIB: 18% Disease prevalence: 22% lymph node metastases	Index test: SNB (Technetium: 9%; patent blue: 31%; both: 60%) Reference standard: histopathology from pelvic lymphadenectomy (507 patiënts) and para-aortic lymphadenectomy (190 patiënts)	Accuracy of SNB to detect lymph node metastasis (N=507): Se 77% Technetium 71% Patent blue 73% Combined 80% Tumour ≤20 mm91% Tumour >20 mm73% Unilateral SN70% Bilateral SN87% NPV 94% Technetium 95% Patent blue 93% Combined 95% Tumour ≤20 mm99% Tumour >20 mm89% Unilateral SN91% Bilateral SN97%	One-sided sentinel node detection rate (N=590): 89% Technetium: 82% Patent blue: 82% Combined: 94% Two-sided sentinel node detection rate: not reported An anaphylactic reaction was seen in two patiënts which necessitated abandoning surgery. Surgery was performed 2 days later without any labelling	Level of evidence: B Dropouts: reported on. In 7 patiënts the reference standard was inconclusive or unknown; in 3 patiënts the index test was inconclusive Non-blinded study Consecutive patiënts
(Amit, Beck et al. 2006)	Design: not reported Source of funding: not reported on Conflict of interest: not reported on Setting: Israel Sample size: N=16 Duration: not reported	Eligibility criteria: patiënts with proven cervical cancer referred for hysterectomy and pelvic lymphadenectomy with a follow-up of >6 months (group 1) Patiënt characteristics: mean age: 45 y; all stage I patiënts Disease prevalence: 25% lymph node metastases	Index test: whole body PET/CT Reference standard: histology	Accuracy of PET/CT to detect extra cervical disease (N=16): Se 0%; Sp 92%, NPV 73%; PPV 0% PET/CT failed to detect 4 patiënts with positive lymph nodes	-	Level of evidence: B Dropouts: not reported on Risk of selection bias through eligibility criteria Unclear whether patiënts were consecutive

Study ID	Method	Patiënt characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
						Blinded assessment not reported
(Bentivegna, Uzan et al. 2010)	Design: retrospective cohort study Source of funding: not reported on Conflict of interest: not reported on Setting: Gustave Roussy Institute, Vullejuif, University Paris Sud, France Sample size: N= 16 Duration: 2005-2008	Eligibility criteria: early-stage (<4 cm) cervical cancer (stage IB1) with MRI and PET/CT imaging before surgery including at least a pelvic lymphadenectomy Patiënt characteristics: median age 43 y; 61% SCC; 17% AC; 17% ASC; 14 patiënts underwent preoperative utero-vaginal brachytherapy; 2 patiënts underwent upfront surgery Prevalence of disease: 12.5% lymph node metastasis	Index tests: PET/CT Reference standard: histopathology from pelvic lymphadenectomy (N=16) and para-aortic lymphadenectomy (N=1)	Accuracy of PET/CT to detect lymph node metastasis bilateral (N=16): Se 0%, NPV 88%	-	Level of evidence: B Consecutive patiënts Blinded assessment not reported on Long interval between index and reference test in which 14/16 patiënts had brachytherapy Selection bias through eligibility criteria
(Bjurberg, Kjellen et al. 2007)	Design: prospective study Source of funding: Berta Kamprad's Foundation for Research and Treatment of Cancer, Gunnar Nilsson's Cancer Foundation, The Donations Fund of Lund University Hospital and The Swedish Cancer Foundation Conflict of interest: not reported on Setting: Lund University Hospital, Sweden Sample size: N=17 Duration: 2004-2006	Eligibility criteria: locally advanced cervical cancer FIGO stage IB2-IVB scheduled for radical radiotherapy , with or without concomitant cisplatin, with curative intent (group 2 in article) Patiënt characteristics: mean age 56 y; 82% SCC; 12% AC; 6% ASC. FIGO stage IB2: 6%; stage IIA: 6%; stage IIB: 71%; stage IIIB: 6%; stage IVA: 12% Disease prevalence: 29% metastases not detected during routine work-up	Index test: PET Reference standard: histology	Accuracy of PET to detect metastasis not detected by a routine staging procedure, including CT and MRI (N=17): Se 83%; Sp 100%; NPV 92%; PPV 100%	-	Level of evidence: B Dropouts: none Consecutive patiënts Blinded assessment not reported The one false negative finding was detected by CT 5 weeks after PET (and then confirmed by histology)
(Chao, Ho et al. 2008)	Design: prospective cohort study	Eligibility criteria: newly diagnosed SCC cervical	Index test: PET (N=38) or PET/CT (N=9)	Accuracy of PET or PET/CT to detect para-	PET or PET/CT had positive clinical impact	Level of evidence: B

Study ID	Method	Patiënt characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
	Source of funding: research grants from Chang Gung Memorial Hospital Conflict of interest: no conflicts of interest to declare Setting: Chang Gung Memorial Hospital, Taiwan Sample size: N=47 Duration: 2001-2007	cancer patiënts with a suspicion of para-aortic lymph node metastasis based on CT/MRI, or inguinal or supraclavicular lymph node metastasis based on palpation or CT/MR; scheduled for curative-intent treatment such as concurrent chemoradiation or surgery Exclusion criteria: no previous cytotoxic therapy; concomitant or a past history of malignancy; histology-proven metastasis to pleura, peritoneum, mediastinal lymph node, lung, bone or liver parenchyma; malignant ascites or pleural effusion; intolerable to extended field irradiation Patiënt characteristics: mean age 55 y; FIGO stage I/IIA: 17%; IIB/IV: 83% Prevalence of disease: para-aortic lymph node metastasis: 79%; inguinal lymph node metastasis: 11%; supraclavicular lymph node metastasis: 26%; bone metastasis: 2%; other distant non skeletal sites: 4%	Reference standard: CT/MRI, biopsy or follow-up through imaging including PET	aortal lymph node metastasis (N=47): Se 97%; Sp 90%; NPV 90%; PPV 97% Accuracy of PET or PET/CT to detect inguinal lymph node metastasis (N=47): Se 80%; Sp 86%; NPV 97%; PPV 40% Accuracy of PET or PET/CT to detect supraclavicular lymph node metastasis (N=47): Se 85%; Sp 100%; NPV 94%; PPV 100% Accuracy of PET or PET/CT to detect bone metastasis (N=47): Se 100%; Sp 98%; NPV 100%; PPV 50% Accuracy of PET or PET/CT to detect other distant non skeletal sites (N=47): Se 100%; Sp 91%; NPV 100%; PPV 33%	in 21 of the 47 study patiënts, in 23 it had no impact, and in three it had negative impact. Positive impact included disclosing additional curable sites (n=8), down-staging (n=6), offering metabolic biopsy (n=4) or change to palliation (n=3)	Dropouts: not reported Unclear whether patiënts were consecutive Only patiënts with suspected metastasis to para-aortal, inguinal or supraclavicular lymph nodes included Blinded assessment not reported on Differential verification Incorporation bias Indeterminate PET or PET/CT positive findings were tentatively included with the false positives, as indeterminate lesions were defined as ´a biopsy of the lesion of interest was not feasible or yielded a negative result and a second assessment of both CT-MRI and PET imaging showed persistent regression or remission of the lesion after definitive treatment´
(Choi, Kim et	Design: prospective cohort	Eligibility criteria:	Index test: MRI	Accuracy of MRI to	Region-based analysis	Level of evidence: B

Study ID	Method	Patiënt characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
al. 2004)	study Source of funding: 2001 BK21 Project for Medicine, Dentistry, and Pharmacie Conflict of interest: not reported on Setting: Seoul National University Hospital, Seoul, Korea Sample size: N=115 Duration: January 2000 - June 2003	cervical carcinoma with proven histopathological staging and operable state Patiënt characteristics: mean age 52.3 y Prevalence of disease: 20.2% vaginal invasion	Reference standard: histopathology	detect vaginal invasion (N=114): Se 87%; Sp79%; PPV 51%; NPV 96%	of parametria and pelvic lymph node metastasis	Dropouts: 1 patiënt didn't undergo surgery due to confirmation of bladder invasion by cystoscopy Consecutive patiënts Exclusion of patiënts that did not have histopathological confirmation: partial verification bias Blinded assessment of index test; blinded assessment of reference test not reported on
(Choi, Roh et al. 2006)	Design: prospective cohort study Source of funding: National Cancer Center Conflict of interest: not reported on Setting: Research Institute and Hospital, National Cancer Center, Goyang. Korea Sample size: N=22 Duration: 2003-2005	Eligibility criteria: untreated patiënts with histopathologically confirmed FIGO stage IB-IVA invasive cervical carcinoma as determined by conventional workup that included MRI and PET/CT scans; no contraindications to the surgical procedure; no evidence of distant metastases; Eastern Cooperative Oncology Group performance status of 0-1 Exclusion criteria: patiënts who did not want to undergo PET/CT or laparoscopic lymphadenectomy (N=63) and tumours other than SCC	Index tests: MRI (T2 weighted, contrast enhanced) and PET/CT Reference standard: histopathology	Accuracy of MRI to detect PALN + pelvic lymph node metastasis (N=22): Se 39%; Sp 44%; PPV 50%; NPV 33% Accuracy 41% Accuracy of PET/CT to detect PALN + pelvic lymph node metastasis (N=22): Se 77%; Sp 56%; PPV 71%; NPV 63%; Accuracy 68%	-	Level of evidence: B Dropouts: none reported Consecutive patiënts Selective subgroup: high prevalence of lymph node metastasis Blinded assessment of index and reference test

Study ID	Method	Patiënt characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
		(N=10) Patiënt characteristics: mean age 50 y; 100% SCC Prevalence of disease: 59% lymph nodes metastasis				
(Chou, Chang et al. 2006)	Design: prospective study Source of funding: National Science Council and the Institute of Nuclear Energy Research, Chang Gung Memorial Hospital Conflict of interest: no conflicts of interest to declare Setting: Chang Gung Memorial Hospital, Taiwan Sample size: N=60 Duration: not reported	Eligibility criteria: cervical cancer patiënts scheduled for radical hysterectomy and pelvic lymphadenectomy; SCC≤ 4 cm by MRI or AD or ASC of any size; age 18-70 y Exclusion criteria: small-cell carcinoma; MRI showed suspicious lymph nodes; histologically proven metastasis to lymph nodes; ever received radiotherapy and/or chemotherapy for cervical cancer; history of allergy to the radiotracer; a previous diagnosis of cancer other than non-melanoma skin cancer; pregnancy Patiënt characteristics: median age: 48 y; 60% SCC; 33% AC; 7% ASC. FIGO staging: IA2: 2%; IB1: 90%; IB2: 5%; IIA:3% Disease prevalence: 18% lymph node metastases	Index test: PET Reference standard: histology	Accuracy of PET to detect pelvic lymph node metastasis not detected by MRI (N=60): Se 10%, Sp 94%, NPV 84%, PPV 25%	-	Level of evidence: B No dropouts Unclear if patiënts were consecutive Blinded assessment not reported Selective subgroup of MRI negative patiënts
(Chung, Kang et al. 2007)	Design: retrospective cohort study Source of funding: Korea Health 21 R&D Project, Ministry of Health & Welfare, Republic of Korea Conflict of interest: none	Eligibility criteria: histologically confirmed invasive carcinoma of the uterine cervix; FIGO stage IA, IB, IIA or IIB; no medical or surgical contra-indications to the primary treatment of	Index tests: MRI (T2 weighted, no contrast enhancement) Reference standard: histology	Accuracy of MRI to detect parametrial invasion (N=119): Se 100%; Sp 89%; PPV 62%; NPV 100%; accuracy 91%;	Cervical angulation not reported	Level of evidence: B Consecutive patiënts Blinded assessment of index test; blinded assessment of reference test not

Study ID	Method	Patiënt characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
	declared Setting: Seoul National University College of Medicine, Seoul, Korea Sample size: N=119 Duration: 2004-2006	radical hysterectomy and pelvic lymphadenectomy; no contra-indications to MRI; no evidence of distant metastases; Eastern Cooperative Oncology Group performance status of 0-1; written informed consent Exclusion criteria: histology of small cell carcinoma; histologically proven metastasis to para-aortic lymph nodes; ever received radiotherapy and/or chemotherapy for cervical cancer; contra-indication to MRI; previous diagnosis of cancer other than non-melanoma skin cancer; pregnancy Patiënt characteristics: median age 50 y; stage IA1:10%; IA2:4%; IB1:35%; IB2:12%; IIA:23%; IIB:16%; 83% SCC; 13% AC; 3% ASC; 2% undifferentiated carcinoma Prevalence of disease:15% parametrial invasion; 29% pelvic lymph node metastasis; 3% para-aortic lymph node metastasis		Accuracy of MRI to detect pelvic &/ para-aortic lymph node metastasis (N=119): Se 71%; Sp 69%; PPV 48%; NPV 86%; accuracy 70%		reported on Retrospective selection of patiënts who underwent MRI and surgery: risk of selection bias
(Chung, Kang et al. 2010)	Design: retrospective cohort study Source of funding: none stated Conflict of interest: not	Eligibility criteria: histopathologically confirmed FIGO stages IB-II invasive cervical cancer with no distant metastasis who	Index test: MRI (T2 weighted, contrast enhanced) and PET/CT Reference standard:	Accuracy of MRI to detect pelvic lymph node metastasis (N=83): Se 64.3%; Sp 69.1%; PPV 51.4%;	-	Level of evidence: B Consecutive patiënts Exclusion of 21 patiënts whom didn't

Study ID	Method	Patiënt characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
	reported on Setting: not stated Sample size: N=83 Duration: 2004-2008	underwent radical surgery and had undergone both preoperative MRI and PET/CT before radical surgery Patiënt characteristics: mean age 47 y; stage IBI:61%; IB2:14%; IIA:17%; IIB:7%; 72% SCC; 22% AC; 4% ASC; 2% other Prevalence of disease: 33.7% pelvic lymph node metastasis	histopathology	NPV 79.2%; Area under the ROC curve 0.667 (95%CI 0.542-0.792) Accuracy of PET/CT to detect pelvic lymph node metastasis (N=83): Se 28.6%; Sp 83.6%; PPV 47.1%; NPV 69.7%; Area under the ROC curve 0.561 (95% CI 0.427-0.695)		meet inclusion criteria: risk of selection bias Blinded assessment of index test; blinded assessment of reference test not reported on
(Chung, Park et al. 2009)	Design: retrospective cohort study Source of funding: Korea Health 21 R&D Project Conflict of interest: not reported on Setting: Seoul National University Hospital, Seoul, Korea Sample size: N=34 Duration: 2003 –2007	Eligibility criteria: FIGO stage IA2-IIB cervical cancer who underwent type II or III radical hysterectomy and pelvic lymphadenectomy as primary treatment; preoperative PET/CT Patiënt characteristics: median age 45.5 y; stage IA2:3%; IB1:44%; IB2:24%; IIA:18%; IIB:12%; 65% SCC; 21% AC; 6% ASC; 9% others Prevalence of disease: 50% pelvic lymph node metastasis	Index test: PET/CT Reference standard: histopathology	Accuracy of PET/CT to detect pelvic lymph node metastasis (N=34): Se 41.2%; Sp 94.1%; PPV 87.5%; NPV 61.5%	-	Level of evidence: B Consecutive patiënts Exclusion of 12 patiënts who didn't meet inclusion criteria Risk of selection bias (preoperative PET/CT and surgery) and selective subgroup (high prevalence of pelvic lymph node metastasis) Blinded assessment not reported on
(Darlin, Persson et al. 2010)	Design: cohort study Source of funding: not reported on Conflict of interest: none	Eligibility criteria: early stage (IA1-IIA) cervical cancer with SNB procedure and pelvic lymphadenectomy	Index test: SNB (Tc99 human-albumin nanocolloid injection, lymphoscintigram and	Accuracy of SNB to detect lymph node metastasis (N=94): Se 94% (95%CI 73-10);	One-sided sentinel node detection rate: 90% ≤ 20 mm 94% > 20 mm 83%	Level of evidence: B Dropouts: not reported on

Study ID	Method	Patiënt characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
	stated Setting: Lund University Hospital, Sweden. Sample size: N=105 Duration: 2005-2009	Patiënt characteristics: median age 40 y; stage IA1:10%; IA2:14%; IB1:66%; IB2:2%; IIA:9%; 57% SCC, 42% AC, 1% neuroendocrine Prevalence of disease: 17% lymph node metastasis	gamma probe) Reference standard: histopathology	NPV 99% (95%CI 93-100)	Two-sided sentinel node detection rate: 59% ≤ 20 mm 65% > 20 mm 50%	Consecutive patiënts Unclear if the design was prospective Blinded assessment not reported on
(deSouza, Dina et al. 2006)	Design: retrospective cohort study Source of funding: not reported on Conflict of interest: not reported on Setting: Hammersmith Hospital, United Kingdom Sample size: N= 119 Duration: 1993-2002	Eligibility criteria: cervical cancer on biopsy referred for MRI prior to radical hysterectomy and pelvic lymphadenectomy Patiënt characteristics: average age 43.5 y; 68% SC; 24% AC; 5% ASC;3% neuroendocrine. FIGO stage IA:3%; IB1:71%; IB2:21%; IIA:3%; IIB:3% Prevalence of disease: 13% parametrial invasion	Index tests: endovaginal followed by external phased array MR imaging (T2 weighted, no contrast enhancement) Reference standard: histopathology	Accuracy of MRI to detect parametrial invasion (N=119): Se 80% (95%CI: 51.9-95.7); Sp 91% (95%CI: 84.2-96.0); PPV 57%; NPV 97%	Cervical angulation not reported	Level of evidence: B Consecutive patiënts Risk of selection bias through retrospective application of eligibility criteria Blinded assessment of index test; blinded assessment of reference test not reported on
(Fader, Edwards et al. 2008)	Design: prospective study Source of funding: Scaife Foundation Conflict of interest: none declared Setting: two centres, New York, United States Sample size: N=38 Duration: not reported	Eligibility criteria: FIGO IA1–IIB cervical cancer patiënts, undergoing radical hysterectomy and pelvic/para-aortic lymphadenectomy Exclusion: prior history of chemotherapy, radiation therapy or retroperitoneal surgery Patiënt characteristics:68% SCC. FIGO stage IA1: 11%; IA2: 24%; IB1: 53%; IB2: 8%; IIA: 3%; IIB: 3% Disease prevalence: 16% lymph node metastases	Index test: SNB (technetium and/or isosulfan blue) Reference standard: histopathology (imprint cytology and H and E and IHC staining with anti-cytokeratin antibody cocktail)	Accuracy of SNB to detect lymph node metastasis N=38): Se 83% Intraoperative assessment 33% NPV 97% Intraoperative assessment: 89%	One-sided sentinel node detection rate: 92% Two-sided sentinel node detection rate: 47%	Level of evidence: B Dropouts: none Consecutive patiënts: not reported Blinded assessment not reported
(Fischerova,	Design: prospective cohort	Eligibility criteria: early-stage	Index tests: MRI	Accuracy of MRI to	-	Level of evidence: B

Study ID	Method	Patiënt characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
Cibula et al. 2008)	study Source of funding: not reported on Conflict of interest: not reported on Setting: General Teaching hospital, Charles University, Prague Sample size: N= 95 Duration: 2004-2006	cervical cancer (T1a1-T2a) examined by both TRUS and MRI and undergoing surgical treatment Patiënt characteristics: median age 47 y; Stage IA1:2%; IA2:2%; IB1:69%; IB2:16%; IIA:4%; IIB:6%; 76.8% SCC; 7.4% ASC; 15.8% AC Prevalence of disease: 6.3% parametrial invasion	Reference standard: histopathology	detect parametrial invasion (N=95): Se 50% (95%CI: 11.81-88.19); Sp 98% (95%CI 92.12-99.73); PPV 60% (95%CI 14.66-94.73); NPV 97% (95%CI 90.57-99.31); Accuracy 95% (95%CI 88.14-98.27)		Dropouts: 1 patiënt refused to undergo surgery Consecutive patiënts Only patiënts examined by both MRI and TRUS were included (selection bias) Exclusion of 22 patiënts due to more advanced disease on imaging and 2 patiënts due to contraindication for surgery: partial verification bias Blinded assessment not reported on
(Goyal, Singh et al. 2010)	Design: cohort study Source of funding: not reported on Conflict of interest: not reported on Setting: army hospital, New Delhi, India Sample size: N=80 Duration: 2007-2009	Eligibility criteria: clinically operable cervical cancer Exclusion criteria: uncontrolled diabetes mellitus, a known second malignancy; pregnancy Patiënt characteristics: mean age 48.5 y; FIGO stage IB1:64%; IB2:21%; IIA:15%; 81% SCC; 16% AC; 1% ASC; 1% Signet cell type Prevalence of disease: 30% pelvic lymph node metastasis	Index tests: PET/CT Reference standard: histopathology	Accuracy of PET/CT to detect pelvic lymph node metastasis (N=80): Se 58%; Sp 93%; PPV 78%; NPV 84%	Para-aortic lymph node sampling was performed in 46 patiënts (in 32 patiënts because of suspicious pelvic lymph nodes; in 14 patiënts routinely) and the one suspicious para-aortic lymph node on PET/CT was confirmed histologically	Level of evidence: B Dropouts: none Consecutive patiënts, unclear if the design was prospective Exclusion of 2 patiënts due to distant metastasis. Selection of operable patiënts only: risk of selection bias Blinded assessment of index test; blinded assessment of reference test not

Study ID	Method	Patiënt characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
						reported on
(Hertel, Kohler et al. 2002)	Design: prospective cohort study Source of funding: not reported on Conflict of interest: not reported on Setting: Friedrich-Schiller University, Jena, Germany Sample size: N=109 Duration: 1995-2001	Eligibility criteria: cervical cancer FIGO stage IB2 or higher Patiënt characteristics: median age 49.7 y; stage IB2:27%; IIA:13%; IIB:38%; IIIA:6%; IIIB:9%; IVA:6%; IVB:3%; 80.7% SC; 19.3% AC Prevalence of disease: 11% bladder wall invasion ; 6% invasion of rectal pillar	Index tests: CT (N=42) ; MRI (N=18); CT and MRI (N=49) Reference standard: histology, visual inspection or dissection (laparoscopy)	Accuracy of CT to detect bladder wall invasion (N=91): Se 9%; Sp 73% (95%CI 71-89); PPV 4%; NPV 85% (95%CI 77-93) Accuracy of MRI to detect bladder wall invasion (N=67): Se 64%; Sp 88% (95%CI 79-96); PPV 50%; NPV 92% Accuracy of CT to detect rectal pillar invasion (N=91): Se 0%; Sp 85% (95%CI 77-93); PPV 0%; NPV 92% (95%CI 86-98) Accuracy of MRI to detect rectal pillar invasion (N=67): Se 50%; Sp 86% (95%CI 77-95); PPV 18%; NPV 96% (95%CI 91-98)	Data of lymph node metastasis included in (Selman, Mann et al. 2008)	Level of evidence: B Dropouts: none Consecutive patiënts Subgroup of IB2 patiënts Differential verification Blinded assessment not reported on
(Hoon Chung, Lee et al. 2005)	Design: cohort study Source of funding: not reported on Conflict of interest: not reported on Setting: National Cancer Center, Korea Sample size: N=44 Duration: 2001-2004	Eligibility criteria: untreated histologically confirmed FIGO stage IB2-IVA (for IIA max tumor diameter >4cm); invasive cervical cancer as determined by conventional workup including MRI; age 20-75 y; no contraindications to the surgical procedure; no	Index tests: MRI (T2 weighted) Reference standard: histopathology (by laparoscopy)	Accuracy of MRI to detect para-aortic lymph node metastasis (N=44): Se 0%; Sp 100%; NPV 89%; accuracy 89%	-	Level of evidence: B Dropouts: none reported Consecutive patiënts, unclear if the design was prospective Exclusion of two

Study ID	Method	Patiënt characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
		evidence of distant metastasis; Eastern Cooperative Oncology Group performance status 0 or 1; informed consent Patiënt characteristics: median age 48.0 y (23-72); Stage IB2: 9.1%; IIA:6.8%; IIB:77%; IIIB:7%. 82% SCC; 11% AC; 7% ASC				patiënts due to severe intra-abdominal adhesion related to previous surgery No blinded assessment of index and reference test
(Hori, Kim et al. 2009)	Design: prospective cohort study Source of funding: not reported on Conflict of interest: no financial relationship disclosed Setting: Osaka University Hospital Sample size: N=31 Duration: 2006-2007	Eligibility criteria: biopsy-proved untreated cervical carcinoma Patiënt characteristics: mean age 51.1 y; 71% SCC; 13% mucinous AC; 6% serous AC; 6% endometrioid AC; 3% ASCC. Stage IA1:6%; IA2:3%; IB1:55%; IB2:10%; IIA:13%; IIB:13% Prevalence of disease: 13% parametrial invasion; 19% vaginal invasion; 23% lymph node metastasis	Index tests: 3.0-T MRI and 1.5-T MRI (T2 weighted, contrast enhanced with cervical angulation) Reference standard: Histopathology or follow-up CT	Accuracy of 3.0-T MRI to detect parametrial invasion (N=31): Se 75% (95%CI 33-100); Sp 70% (95%CI 53-88); PPV 27% (95%CI 1-54); NPV 95% (95%CI 85-100); accuracy 71% (95%CI 55-87); area under ROC curve=0.82 Accuracy of 1.5-T MRI to detect parametrial invasion (N=31): Se 75% (95%CI 33-100); Sp 70% (95%CI 53-88); PPV 27% (95%CI 1-54); NPV 95% (95%CI 85-100); accuracy 71% (95%CI 55-87); area under ROC curve 0.85 Accuracy of 3.0-T MRI to detect vaginal invasion (N=31): Se 67% (95%CI 29-100); Sp 68% (95%CI 50-86);	There were no significant differences between 3.0- and 1.5-T MR imaging in terms of the areas under the ROC curve, sensitivity or specificity (p>0.5 for all comparisons)	Level of evidence: B Consecutive patiënts Dropouts:16 patiënts did not agree to be included in the study: risk of selection bias 12 patiënts were excluded due to radiation therapy Differential verification: 1 patiënt did not undergo pelvic lymphadenectomy and follow-up CT findings 6 months after surgery were used as reference standard Blinded assessment of index test; blinded assessment of reference standard not reported on Data from reader 1 presented, data from

Study ID	Method	Patiënt characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
				PPV 33% (95%CI 7-60); NPV 89% (95%CI 76-100); accuracy 68% (95%CI 51-84); area under ROC curve 0.62 Accuracy of 1.5-T MRI to detect vaginal invasion (N=31): Se 67% (95%CI 29-100); Sp 72% (95%CI 54-90); PPV 36% (95%CI 8-65); NPV 90% (95%CI 77-100); accuracy 71% (95%CI 55-87); area under ROC curve 0.67 Accuracy of 3.0-T MRI to detect pelvic lymph node metastasis (N=31): Se 57% (95%CI 20-94); Sp 83% (95%CI 68-98); PPV 50% (95%CI 15-85); NPV 87% (95%CI 73-100); accuracy 77% (95%CI 63-92); area under ROC curve 0.72 Accuracy of 1.5-T MRI to detect pelvic lymph node metastasis (N=31): Se 57% (95%CI 20-94); Sp 88% (95%CI 74-100); PPV 57% (95%CI 20-94); NPV 88% (95%CI 74-100); accuracy 81%		reader 2 also shown in article

Study ID	Method	Patiënt characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
				(95%CI 67-95); area under ROC curve 0.78		
(Hricak, Gatsonis et al. 2005)	Design: prospective multicenter cohort study Source of funding: National Cancer Institute Conflict of interest: no potential conflicts of interest declared Setting: 25 centers, United States Sample size: N=208 Duration: 2000-2002	Eligibility criteria: untreated biopsy-confirmed cervical cancer of all cell types, scheduled for hysterectomy Patiënt characteristics: SCC: 72%; AC: 22%; other: 10%. FIGO staging: IA: 8%; IB: 65%; IIA: 3%; IIB: 9%; greater than IIB: 12%; not determined: 3% Disease prevalence: 21% surgicopathologic findings consistent with FIGO stage IIB or higher	Index test: CT, MRI Reference standard: surgicopathologic findings (data from the surgical report and pathologic analysis of specimens)	Accuracy of CT to detect stage IIB or higher (N=166): Se 42% (95%CI: 26-59); Sp 82% (95%CI: 75-88); NPV 84% (95%CI: 76-90); PPV 39% (95%CI: 24-57) Accuracy of MRI to detect stage IIB or higher (N=166): Se 53% (95%CI: 35-70); Sp 75% (95%CI: 67-83); NPV 85% (95%CI: 77-91); PPV 37% (95%CI: 24-52)	Four cases of rectal involvement (surgicopathological finding) were not detected by CT nor MRI There were 6 cases of bladder involvement, of whom none were detected by CT and two were detected by MRI See also (Mitchell, Snyder et al. 2006) and (Mitchell, Snyder et al. 2009)	Level of evidence: B Dropouts: 36 patiënts were excluded because of enrolment disqualification or missing data; including 13 patiënts who did not have surgery (risk of partial verification bias) Consecutive patiënts Blinded index test assessment. The prospective readings are presented here 2x2 tables could not be constructed so the accuracy data from the study are presented here
(Jung, Kim et al. 2010)	Design: retrospective cohort study Source of funding: National Cancer Center, Korea Conflict of interest: none declared Setting: Seoul National University Hospital and the National Cancer Center , Republic of Korea Sample size: N=251 Duration: 2006-2009	Eligibility criteria: stage IA2-IIA cervical cancer, confirmed by radical hysterectomy with lymph node dissection and preoperative MRI performed within 4 weeks before operation Exclusion criteria: receiving radiation or chemotherapy before surgery Patiënt characteristics: FIGO	Index test: MRI Reference standard: histopathology	Accuracy of MRI to detect parametrial invasion (n=251)(data from article): Se 43.2% (95%CI 28.3-59.0); Sp 92.7% (95%CI 86.6-96.6); NPV 82.0% (95%CI 74.6-88); negative LR 5.9; ROC area 0.679	-	Level of evidence: B Consecutive patiënts Risk of selection bias through retrospective application of selection criteria Blinded assessment of index test; blinded assessment of reference test not reported on

Study ID	Method	Patiënt characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
		stage IA2:3%; IB1:75%; IB2:6%; IIA:15%; 72% SCC; 28% AC/ASC. Prevalence of disease: 18% parametrial invasion				A 2x2 table could not be constructed
(Kim, Choi et al. 2009)	Design: retrospective cohort study Source of funding: not reported on Conflict of interest: none declared Setting: Republic of Korea Sample size: N=79 Duration: 2001-2007	Eligibility criteria: untreated histopathologically confirmed FIGO stage IB-IVA cervical cancer determined by conventional work-up that included MRI; no contraindication to surgical procedure; no evidence of distant metastasis; Eastern Cooperative Oncology Group performance status of 0-1. Exclusion criteria: small cell carcinoma and patiënts who did not undergo laparoscopic lymph node dissection Patiënt characteristics: not reported on Prevalence of disease: 38% metastatic lymph nodes	Index test: PET/CT and MRI/PET Reference standard: histopathology	Accuracy of PET/CT to detect para-aortic + pelvic lymph node metastasis (N=79): Se 47%; Sp 71%; PPV 50%; NPV 69%; ROC area 0.690 (95%CI :0.650-0.728) Accuracy of MRI/PET to detect para-aortic + pelvic lymph node metastasis (N=79): Se 57%; Sp 67%; PPV 52%; NPV 72%; ROC area 0.735 (0.696-0.771)	-	Level of evidence: B Consecutive patiënts Retrospective selection of patiënts with a MRI and PET/CT prior to surgery (risk of selection bias) Blinded assessment of index test; blinded assessment of reference standard not reported on
(Kokka, Vorgias et al. 2003)	Design: retrospective study of medical records Source of funding: not reported on Conflict of interest: not reported on Setting: Metaxa Memorial Cancer Hospital, Peiras Greece Sample size: N=309 Duration: 1986-2000	Eligibility criteria: early (IB-IIA clinical FIGO) untreated cervical cancer patiënts who completed pre-treatment evaluation at the institution Exclusion criteria: neoadjuvant treatment and/or radiotherapy Patiënt characteristics:mean age: 48 y; SCC: 86%; AC: 11%; ASC: 2%. FIGO surgicopathological staging IB: 65%; IIA: 34%; IV: 1%	Index test: CT Reference standard: histology or visual inspection (cystoscopy and/or urine cytology, barium enema with sigmoidoscopy)	Accuracy of CT to detect urinary tract invasion (N=309): Se 100%; Sp 99.7%; NPV 100%; PPV 75% Accuracy of CT to detect gastrointestinal tract invasion (N=307): Se 50%; Sp 99.7%; NPV 99.7%; PPV 50%	Accuracy of CT to detect lymph node metastasis: included in (Selman, Mann et al. 2008)	Level of evidence: B Consecutive patiënts Risk of selection bias through selection criteria Blinded assessment not reported Differential verification, and partial verification (307/309) for gastrointestinal tract

Study ID	Method	Patiënt characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
		Disease prevalence: urinary tract invasion: 1%; gastrointestinal tract invasion: 0.3%				invasion
(Leblanc, Gauthier et al. 2011)	Design: retrospective multicenter study Source of funding: not reported on Conflict of interest: not reported on Setting: 5 French tertiary-care centers Sample size: N=125 Duration: 2004-2008	Eligibility criteria: primary stage IB2-IVA locally advanced cervical cancer or a centropelvic recurrence after chemoradiation for locally advanced cervical cancer, without evidence of distant metastasis and enlarged para-aortic nodes (>10mm) at abdominopelvic MRI with or without CT scan Patiënt characteristics: median age 48.3 y; 87% SCC; 11% AC; 2% clear cell. Stage IB2:34%; IIA:7%; IIB:37%; IIIA:2%; IIIB:10%; IVA:8%; centropelvic recurrence: 2% Prevalence of disease:17% para-aortic lymph node metastasis	Index tests: PET completed by CT or hybrid PET/CT Reference standard: histopathology	Accuracy of PET/CT to detect para-aortic lymph node metastasis (N=125): Se 33%; Sp 94%; PPV 54%; NPV 88%	Accuracy of PET/CT to detect para-aortic lymph node metastasis ≤ 5 mm (data form article): Se 22%; Sp 91%; PPV 15%; NPV 94% Accuracy of PET/CT to detect para-aortic lymph node metastasis >5 mm (data form article): Se 42%; Sp 93%; PPV 38%; NPV 94%	Level of evidence: B Unclear if patiënts were consecutive Blinded assessment of index test; blinded assessment of reference test not reported on Selection bias through retrospective application of selection criteria 2/125 patiënts had centropelvic recurrence
(Liu, Yen et al. 2009)	Design: retrospective study Source of funding: not reported on Conflict of interest: no conflicts of interest declared Setting: Chang Gung Memorial Hospital, Taiwan Sample size: N=165 Duration: not reported	Eligibility criteria: invasive cervical cancer patiënts (stage III/IV or positive lymph node metastasis) who had had PET and either CT or MRI performed within 30 days Exclusion: history of other malignancy; follow-up <180 days after PET (except those who died of disease within 180 days)	Index tests: CT and PET (N=40), MRI and PET (N=146) Reference standard: PET and either CT or MRI positive, along with a concordant clinical course of progression, with or without a transient response to palliative treatment. In case of	CT and PET group: accuracy of CT to detect hematogenous bone metastasis (N=40): Se 25%; Sp 100%; NPV 92%; PPV 100% CT and PET group: accuracy of PET to detect hematogenous bone metastasis	-	Level of evidence: B Not reported whether patiënts were consecutive Risk of selection bias through retrospective application of selection criteria Blinded index test assessment Differential

Study ID	Method	Patiënt characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
		Patiënt characteristics: not described Disease prevalence: 7.3% hematogenous bone metastases	discordant imaging findings a bone biopsy was done if there would be clinical implications; otherwise visceral metastasis on imaging or new evidence of hematogenous bone metastasis within 180 days was considered proof	(N=40): Se 100%; Sp 100%; NPV 100%; PPV 100% MRI and PET group: accuracy of MRI to detect hematogenous bone metastasis (N=146): Se 80%; Sp 99%; NPV 99%; PPV 80% MRI and PET group: accuracy of PET to detect hematogenous bone metastasis (N=146): Se 100%; Sp 99%; NPV 100%; PPV 91%		verification Incorporation bias
(Loft, Berthelsen et al. 2007)	Design: prospective cohort study Source of funding: donation by The John and Birthe Meyer Doundation Conflict of interest: not reported on Setting: Rigshospitalet Copenhagen University Hospital, Denmark Sample size: N=119 Duration: 2002-2005	Eligibility criteria: newly diagnosed cervical cancer stage ≥1B Exclusion criteria: current previous or malignant disease of another type; diabetes mellitus; pregnancy; claustrophobia; extreme obesity or other reasons due to which the PET/CT scan could not be performed Patiënt characteristics: stage IB1:24%; IB2:3%; 2A:6%; 2B:26%; 3A:1%; 3B:36%; 4A:4%; 82% SCC; 11% AC; 8% others Disease prevalence: para-aortal lymph node	Index test: PET/CT Reference standard: To detect para-aortal lymph node metastasis: histopathology (N=12) and other imaging modalities or follow-up (N=107) To detect distant metastasis: histopathology (N=11) and other imaging modalities or follow-up (N=108)	Accuracy of PET/CT to detect para-aortal lymph node metastasis (N=119): Se 100%; Sp 99%; PPV 94%; NPV 100% Accuracy of PET/CT to detect distant metastasis (N=119): Se 100%; Sp 94%; PPV 53%; NPV 100%	-	Level of evidence: B Dropouts: none reported Consecutive patiënts 1 patiënt who had had a hysterectomy prior to PET/CT was excluded Differential verification: histology, other imaging modalities and follow-up Partial verification: 14 patiënts who had positive pelvic lymph nodes on PET and

Study ID	Method	Patiënt characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
		metastasis: 13%; distant metastasis: 8%				were not examined histologically were excluded for calculations concerning pelvic lymph node status Incorporation bias in some patiënts Blinded assessment not reported on
(Manfredi, Gui et al. 2009)	Design: prospective cohort study Source of funding: not reported on Conflict of interest: not reported on Setting: Italy Sample size: N=53 Duration: not reported on	Eligibility criteria: localised cervical carcinoma (FIGO stage <IIB) studied by MRI Patiënt characteristics: mean age 47.3 y; 73% SCC; 18% AC; 9% ASC. Grade I:9%; Grade II:32%; Grade III:59%. Prevalence of disease: 6% vaginal invasion; 13% tumour extension to the internal os	Index test: MRI Reference standard: histopathology	Accuracy of MRI to detect vaginal invasion (N=53): Se 67%; Sp 92%; PPV 33%; NPV 98%; accuracy 91% Accuracy of MRI to detect tumour extension to the internal os (N=53): Se 86%; Sp 93%; PPV 67%; NPV 98%;accuracy 92%	Lesion based analysis of pelvic and lumbo-aortic lymph node metastasis Accuracy of MRI to detect stromal invasion: data for 2x2 table were not shown	Level of evidence: B Consecutive patiënts Dropouts: 2 patiënts who refused MRI were not included in analysis: risk of selection bias Exclusion of 5 patiënts due to locally advanced disease on MRI (partial verification) No blinded assessment of index and reference test
(Matsushita, Kurata et al. 2001)	Design: retrospective cohort study Source of funding: not reported on Conflict of interest: not reported on Setting: Niigata University Faculty of Medicine, Niigata, Japan Sample size: N=23 Duration: 1991-2000	Eligibility criteria: primary adenocarcinoma of the uterine cervix and MRI before surgery Patiënt characteristics: mean age 53 y; stage IB:65%; IIB:26%; IIIB:4%; IVB:4%; 35% adenoma malignum; 30% endometrioid adenocarcinoma; 22% ASC; 9% clear cell carcinoma; 4%	Index test: T2-weighted MRI Reference standard: histopathology	Accuracy of MRI to detect parametrial invasion (N=23): Se 60%; Sp 100%; PPV 100%; NPV 90%	-	Level of evidence: B Consecutive patiënts Risk of selection bias through retrospective design where MRI is needed to be included Blinded assessment of index test; blinded assessment of

Study ID	Method	Patiënt characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
		serous AC; 6 patiënts received neoadjuvant chemotherapy Prevalence of disease: 22% parametrial invasion				reference test not reported on
(Mitchell, Snyder et al. 2006)	Design: prospective multicenter cohort study Source of funding: National Cancer Institute Conflict of interest: no potential conflicts of interest declared Setting: 25 centers, United States Sample size: N=208 Duration: 2000-2002	Eligibility criteria: untreated biopsy-confirmed cervical cancer of all cell types, scheduled for hysterectomy Patiënt characteristics: SCC: 72%; AC: 22%; other: 10%. FIGO staging: IA: 8%; IB: 65%; IIA: 3%; IIB: 9%; greater than IIB: 12%; not determined: 3% Disease prevalence: uterine involvement: 17% (32/172); stromal invasion: 44% had shallow (≤5mm) invasion, 22% had deep (>5mm) invasion	Index tests: CT, MRI Reference standard: histology	Accuracy of CT to detect uterine involvement (N=na): AUC 0.66 Accuracy of MRI to detect uterine involvement (N=na): AUC 0.80	Agreement between CT and histology on the tumor size: kappa coefficient 0.18 (95%CI: 0.06-0.30); weighted kappa coefficient 0.32 (95%CI: 0.20-0.43) Agreement between MRI and histology on the tumor size: kappa coefficient 0.30 (95%CI: 0.18-0.42); weighted kappa coefficient 0.41 (95%CI: 0.30-0.53) Accuracy of CT to detect stromal invasion (N=119): Se 29% (95%CI: 21-39); Sp 79% (95%CI: 59-92); NPV 23% (95%CI: 15-33); PPV 83% (95%CI: 67-94) Accuracy of MRI to detect stromal invasion (N=102): Se 65% (95%CI: 54-74); Sp 43% (95%CI: 23-66); NPV 23% (95%CI: 12-39); PPV 82% (95%CI: 72-	Level of evidence: B Dropouts: 36 patiënts were excluded because of enrolment disqualification or missing data including 13 patiënts who did not have surgery (risk of partial verification bias) Consecutive patiënts Blinded index test assessment. The prospective readings are presented here 2x2 tables could not be constructed so the accuracy data from the study are presented here

Study ID	Method	Patiënt characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
					90) Accuracy of CT to detect deep (>5mm) stromal invasion: Se 29% (95%CI: 15-47); Sp 73% (95%CI: 63-82); NPV 75% (95%CI: 65-83); PPV 28% (95%CI: 14-45) Accuracy of MRI to detect deep (>5mm) stromal invasion: Se 79% (95%CI: 59-92); Sp 42% (95%CI: 31-53); NPV 86% (95%CI: 72-95); PPV 830 (95%CI: 20-41) See also (Hricak, Gatsonis et al. 2005) and (Mitchell, Snyder et al. 2009)	
(Mitchell, Snyder et al. 2009)	Design: prospective multicenter cohort study Source of funding: National Cancer Institute Conflict of interest: no potential conflicts of interest declared Setting: 25 centers, United States Sample size: N=208 Duration: 2000-2002	Eligibility criteria: untreated biopsy-confirmed cervical cancer of all cell types, scheduled for hysterectomy Patiënt characteristics: SCC: 72%; AC: 22%; other: 10%. FIGO staging: IA: 8%; IB: 65%; IIA: 3%; IIB: 9%; greater than IIB: 12%; not determined: 3% Disease prevalence: lymphatic metastases: 34%; 13% common iliac nodal	Index tests: CT, MRI (T2 weighted) Reference standard: histology (pelvic lymph node dissection, para-aortic dissection was performed at the discretion of the surgeon)	Accuracy of CT to detect pelvic &/ para-aortic lymph node metastasis (N=161): Se 31%; Sp 86% Accuracy of MRI to detect pelvic &/ para-aortic lymph node metastasis (N=161): Se 37%; Sp 94%	See also (Hricak, Gatsonis et al. 2005) and (Mitchell, Snyder et al. 2006)	Level of evidence: B Dropouts: 47 patiënts were excluded because of enrolment disqualification or missing data (risk of partial verification bias) Consecutive patiënts Blinded index test assessment. The

Study ID	Method	Patiënt characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
		metastases; 9% para-aortic nodal metastases				prospective readings are presented here 2x2 tables could not be constructed so the accuracy data from the study are presented here
(Nam, Huh et al. 2010)	Design: retrospective cohort study Source of funding: not reported on Conflict of interest: not reported on Setting: Samsung Medical Centre, Seoul, South Korea Sample size: N=92 Duration: 1997-2007	Eligibility criteria: uterine cervical cancer patiënts (FIGO stage IIB-IVA), treated with radiotherapy with a curative intent, with or without chemotherapy, who had a pre-treatment MRI Patiënt characteristics: 37% > 60 y of age; 95% SCC; 5% AC. All patiënts were FIGO stage IIB-IVA Disease prevalence: 15% mucosal bladder invasion	Index test: MRI Reference standard: cystoscopy	Accuracy of MRI to detect bladder invasion (defined as wall invasion or mucosal invasion) (N=92): Se 93%; Sp 63%; NPV 98%; PPV 31% Accuracy of MRI to detect bladder invasion (defined as mucosal invasion) (N=92): Se 93%; Sp 94%; NPV 99%; PPV 72%	-	Level of evidence: B Dropouts: 4 patiënts were excluded because of missing follow-up data and 1 patiënt because of hysterectomy after radiotherapy Consecutive patiënts Risk of selection bias through selection criteria Blinded assessment not reported
(Oberoi, Vohra et al. 2002)	Design: retrospective cohort study Source of funding: not reported on Conflict of interest: not reported on Setting: Rajiv Gandhi Cancer Institute & Research Centre, New Delhi, India Sample size: N=105 Duration: 1997-2001	Eligibility criteria: surgery for primary carcinoma of the cervix Histological diagnosis of cervix carcinoma; FIGO stage IB or higher Patiënt characteristics: mean age 51 y; FIGO stage IB: 68%; IIA: 7%; IIB: 18%; IIIA: 6%; IVA: 2%; 98% SCC; 2% AC Prevalence of disease: parametrium invasion: 19%; vaginal invasion upper 2/3 rd: 18%; vaginal invasion lower	Index tests: MRI (T2 weighted) Reference standard: histopathology	Accuracy of MRI to detect stage IIB or higher (N=105): Se 85%; Sp; 92%; NPV: 92%; PPV: 79% Accuracy of MRI to detect parametrium invasion (N=105): Se 87%; Sp 93%; PPV 77%; NPV 96%; accuracy 91% Accuracy of MRI to detect vaginal invasion	Accuracy of MRI to detect surgico-pathological staging: stage IB: 90%; IIA: 57%; IIB: 84%; IIIA: 83%; IVA: 100%	Level of evidence: B Consecutive patiënts Risk of selection bias through retrospective selection of patiënts with available index test Blinded assessment of index and reference test not reported on

Study ID	Method	Patiënt characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
		1/3 rd: 7%; bladder invasion: 2%; rectum invasion: 1%; pelvic lymph node metastasis: 13%		upper 2/3rd (N=105): Se 83%; Sp 94%; PPV 79%; NPV 95%; accuracy 91% Accuracy of MRI to detect vaginal invasion lower 1/3rd (N=105): Se 78%; Sp 100%; PPV 100%; NPV 98%; accuracy 98% Accuracy of MRI to detect bladder invasion (N=105): Se 100%; Sp 100%; PPV 100%; NPV 100%; accuracy 100% Accuracy of MRI to detect rectum invasion (N=105): Se 100%; Sp 100%; PPV 100%; NPV 100%; accuracy 100% Accuracy of MRI to detect pelvic lymph node metastasis (N=105): Se 67%; Sp 96%; PPV 82%; NPV 92%; accuracy 90%		
(Ramirez, Jhingran et al. 2010)	Design: prospective study Source of funding: supported in part by a Cancer Center Support Grant Conflict of interest: not reported on	Eligibility criteria: stage IB2-IVA cervical cancer and a candidate for treatment with radiotherapy and concurrent chemotherapy; no evidence of para-aortic lymphadenopathy (all nodes	Index tests: PET/CT Reference standard: histology (laparoscopic staging)	The accuracy of PET/CT to detect para-aortic lymph node metastasis in CT or MRI negative patiënts (N=60): Se 36%; Sp 96%; NPV 83%; PPV	There was one conversion from laparoscopy to laparotomy because of uncontrolled bleeding The median length of	Level of evidence: B Dropouts: 1; another 4 patiënts were excluded because of too high blood glucose levels or

Study ID	Method	Patiënt characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
	Setting: University of Texas M. D. Anderson Cancer Center and Lyndon Baines Johnson General Hospital, Houston, United States Sample size: N=60 Duration: 2004-2009	<2 cm in diameter) on preoperative CT or MRI; adequate bone marrow, renal, and hepatic function; Zubrod performance status of 0, 1 or 2 Exclusion criteria: prior retroperitoneal surgery; prior pelvic or abdominal radiotherapy; upper abdominal intraperitoneal disease; evidence of ovarian metastases; pregnancy; had evidence of distant metastases on imaging studies or physical examination; contraindications to laparoscopy Patiënt characteristics: median age 48 y; 80% SCC; 15% AC; 5% other. FIGO stage IB1: 27%; IIA: 20%; IIB: 27%; IIIA: 6%; IIB: 20% Disease prevalence: 23% para-aortic lymph node metastases		71%	hospital stay was 1 day (range: 0-4 days). Five procedures were performed as an outpatiënt procedure Seven patiënts developed a lymphocyst postoperatively requiring drain placement 1/14 lymph node metastasis was found through ultrastaging	supraclavicular metastasis on PET/CT (N=2, partial verification) Unclear whether patiënts were consecutive Selected subgroup with negative para-aortic lymph nodes on CT or MRI Blinded assessment not reported
(Rockall, Ghosh et al. 2006)	Design: retrospective study Source of funding: not reported on Conflict of interest: not reported on Setting: St. Bartholomew's Hospital, London, United Kingdom Sample size: N=112 Duration: 1996-2004	Eligibility criteria: confirmed cervical cancer, clinical staging and MRI performed on-site and availability of clinical notes and MRI for review Patiënt characteristics: not described Disease prevalence: bladder invasion: 1%; rectal invasion:	Index test: MRI Reference standard: cystoscopy and endoscopic examination of the rectum	Accuracy of MRI to detect bladder invasion (N=112): Se 100%; Sp 88%; NPV 100%; PPV 7% Accuracy of MRI to detect rectal invasion (N=112): Se 100%; Sp 91%; NPV 100%; PPV	-	Level of evidence: B Consecutive patiënts Risk of selection bias through exclusion criteria Blinded assessment of index test

Study ID	Method	Patiënt characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
		2%		17%		
(Sahdev, Sohaib et al. 2007)	Design: retrospective study Source of funding: not reported on Conflict of interest: not reported on Setting: St. Bartholomew's Hospital, London, United Kingdom Sample size: N=150 Duration: 1995-2005	Eligibility criteria: early cervical cancer Exclusion: 223 patiënts were excluded because they had advanced cervical carcinoma involving parametrium or pelvic sidewall on imaging (including MRI) and/or on clinical examination, or if the MRI was inadequate Patiënt characteristics: 63% underwent radical hysterectomy (mean age 34 y) and 37% underwent radical vaginal trachelectomy (mean age 23 y) Disease prevalence: 12% internal os involvement; 5% myometrial invasion; 2% parametrial invasion; 13% lymph node metastases	Index test: MRI (T2 weighted) Reference standard: histology	Accuracy of MRI to detect involvement of the internal os (N=150): Se 90%; Sp 98%; NPV 98%; PPV 86% Accuracy of MRI to detect myometrial invasion (N=150): Se 100%; Sp 99%; NPV 100%; PPV 88% Agreement between MRI and histologic staging (N=150): kappa 0.56 (95%CI: 0.34–0.60) Accuracy of MRI to detect pelvic lymph node metastasis (N=150): Se 37%; Sp 95%; NPV 94%; PPV 39%	Accuracy of MRI to evaluate tumor size: mean difference in tumor size histology-MRI: -9 mm; 95% limits of agreement were 212.6-113 mm, thus, 95% of all tumors were within 13 mm of histologic size	Level of evidence: B Consecutive patiënts Risk of selection bias through exclusion criteria (81 patiënts were excluded) leaves a selective subgroup Blinded assessment of index test
(Sandvik, Jensen et al. 2011)	Design: retrospective cohort study Source of funding: not reported on Conflict of interest: none stated Setting: Herlev Hospital, Denmark Sample size: N=117	Eligibility criteria: Patiënt characteristics: 75% SCC; 17% AD; 6% ASC; 2% other. FIGO stage IA: 13%; IB: 43%; IIB: 24%; IIIB: 13%; IVA: 2%; IVB: 4% Disease prevalence: 14% (5/36)	Index test: PET/CT Reference standard: histology (biopsy for distant metastasis)	Accuracy of PET/CT to detect pelvic lymph node metastasis (N=36): Se 20%; Sp 90%; NPV 88%; PPV 25%	Accuracy of PET/CT to detect lymph node metastasis (unspecified), distant metastasis or other malignancies (N=42): Se 50%; Sp 91%; NPV 88%; PPV 57%	Level of evidence: B Consecutive patiënts 34 patiënts with early stage disease did not have PET because of limited capacity and were excluded (selection bias)

Study ID	Method	Patiënt characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
	Duration: 2006-2007					41 patiënts did not have the PET/CT findings verified (partial verification bias) Blinded assessment not reported
(Sharma, Thulkar et al. 2010)	Design: cohort study Source of funding: not reported on Conflict of interest: not reported on Setting: All India Institute of Medical Sciences, New Delhi, India Sample size: N=305 Duration: 2003-2005	Eligibility criteria: cervical cancer to be treated by radiotherapy with or without concurrent chemotherapy Patiënt characteristics: mean age 50 y; 93% SCC; 54% FIGO stage IIIB or higher Disease prevalence:5.5% bladder invasion	Index test: CT Reference standard: cystoscopy with biopsy or vesicovaginal fistula on clinical examination	Accuracy of CT to detect bladder invasion (N=305): Se 100%; Sp 92%; NPV 100%; PPV 40%	-	Level of evidence: B Dropouts: not reported on Consecutive patiënts, unclear if the design was prospective Double-blind assessment Differential verification (not reported how many patiënts had vesicovaginal fistulas and consequently did not undergo cystoscopy with biopsy)
(Sheu, Chang et al. 2001)	Design: prospective cohort study Source of funding: not reported on Conflict of interest: not reported on Setting: Veterans General Hospital-Taipei and School of Medicine, National Yang-Ming University, Taipei, Taiwan	Eligibility criteria: primary untreated cervix carcinoma; MRI-imaging and surgical treatment Patiënt characteristics: mean age 56.6 y; FIGO stage IA: 7%; IB: 49%; IIA: 10%; IIB: 29%; IIIA: 2%; IV: 2%; 83% SCC; 17% AC; MRI was performed in 2 patiënts after preoperative chemotherapy	Index tests: MRI Reference standard: histopathology	Accuracy of MRI to detect stage IIB or higher (N=41): Se 100%; Sp 89%; PPV 88%; NPV 100% Accuracy of MRI to detect vaginal invasion (N=41): Se 82%; Sp 80%; PPV 60%; NPV 92%	Accuracy of MRI to detect pathological staging: stage IB: 85%; IIA: 75%; IIB: 100%; IIIA: 100%; IVA: 100%; overall 83% Accuracy of MRI to differentiate between ≤stage IIA and ≥stage IIB: 93% (95%CI 86-	Level of evidence: B Dropouts: none Exclusion of 38 women who did not undergo surgical treatment because of high surgical risk, clinically advanced disease status, refusal of surgical

Study ID	Method	Patiënt characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
	Sample size: N=41 Duration: 1996-1999	and in 4 patiënts after preoperative radiation therapy Prevalence of disease: 27% vaginal invasion			100) Accuracy of MRI to detect tumor size > 1cm: Se 94%; Sp 57%; PPV 91%; NPV 67% Accuracy of MRI to detect tumor size < 0.5 cm: Se 71%; Sp 91%; PPV 63%; NPV 92% Data of parametrial invasion and lymph node metastases in (Bipat, Glas et al. 2003)	intervention (preferred radiotherapy) or did not undergo MRI due to pacemaker implantation, intracranial vascular clips or claustrophobia (partial verification bias) Consecutive patiënts Blinded assessment of index test; blinded assessment of reference test not reported on
(Sironi, Bellomi et al. 2002)	Design: prospective cohort study Source of funding: not reported on Conflict of interest: not reported on Setting: University of Milan, Italy Sample size: N=73 Duration: not reported	Eligibility criteria: invasive cervical carcinoma clinically considered < 3cm and confined to the cervix (FIGO stage IB1) Exclusion criteria: contraindications to MRI or use of intravenous gadolinium Mean age: 47 y Disease prevalence:37% parametrial invasion	Index test: MRI (FSE T2-W, SE T1-W Gd, SE T1-W Gd FS) Reference standard: histopathology	Accuracy of MRI FSE T2-W to detect parametrial invasion (N=73): Se 79% (95%CI: 61-84); Sp 81% (95%CI: 68-89); NPV 95% (95%CI: 75-98); PPV 73% (95%CI: 61-86) Accuracy of MRI SE T1-W Gd to detect parametrial invasion (N=73): Se 71% (95%CI: 59-83); Sp 23% (95%CI: -8-31); NPV 77% (95%CI: 59-79); PPV 53% (95%CI: 32-68)	-	Level of evidence: A2 Dropouts: 8 patiënts were excluded because they refused surgery Subgroup of IB1 patiënts Consecutive patiënts 2x2 tables could not be constructed: the reported outcomes are presented Double-blind assessment

Study ID	Method	Patiënt characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
				Accuracy of MRI SE T1-W Gd FS to detect parametrial invasion (N=73): Se 68% (95%CI: 59-79); Sp 63% (95%CI: 49-73); NPV 82% (95%CI: 73-92); PPV 74% (95%CI: 65-84)		
(Sironi, Buda et al. 2006)	Design: prospective cohort study Source of funding: not reported on Conflict of interest: none stated Setting: Milan, Italy Sample size: N=47 Duration: 2003-2004	Eligibility criteria: hisopathologically confirmed diagnosis of primary cervical carcinoma Exclusion criteria: FIGO stage IIB or higher; relative contraindications to PET scanning Patiënt characteristics: mean age 45.3 y; FIGO stage IA1: 9%; IB1: 74%; IB2: 17%; 79% SCC; 21% AC; 6 patiënts with stage IB2 underwent neoadjuvant chemotherapy before PET/CT Prevalence of disease: 32% pelvic lymph node metastasis	Index test: PET/CT Reference standard: histopathology	Accuracy of PET/CT to detect pelvic lymph node metastasis (N=47): Se 73% (95%CI 48.0-89.1); Sp 97% (95%CI 84.3-99.4); PPV 92%; NPV 89%; accuracy 89%	-	Level of evidence: B Dropouts: none Consecutive patiënts Double-blind assessment
(Testa, Ludovisi et al. 2009)	Design: prospective cohort study Source of funding: partially supported by I.R.I.S-PCR-OGONLUS Conflict of interest: not reported on Setting: Catholic University, Rome, Italy	Eligibility criteria: patiënts with early cervical cancer planned for primary surgery and patiënts with locally advanced cervical cancer planned for surgery after neoadjuvant treatment Exclusion: patiënts who underwent a cervical cone	Index test: MRI (T2 weighted) Reference standard: histopathology	Accuracy of MRI to detect parametrial invasion (N=68): Se 40%; Sp 89%; NPV 95%; PPV 22% Accuracy of MRI to detect vaginal invasion (N=68): Se 0%; Sp	Mean difference between histopathological measurements and MRI measurements of the craniocaudal diameter of the tumor: 1.49 mm (95% CI: −1.41 to 4.40 mm,	Level of evidence: B Dropouts: seven patiënts were not operated on because of no response to neoadjuvant treatment (partial verification bias)

Study ID	Method	Patiënt characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
	Sample size: N=75 Duration: 2002-2005	biopsy; patiënts who underwent surgery >7 days after MRI Patiënt characteristics: 78% SCC. FIGO stage IA2: 3%; IB1: 33%; IB2: 12%; IIA: 3%; IIB: 32%; IIIA: 3%; IIIB: 6%; IV: 5%. 33 patiënts were treated with primary surgery and 42 were planned for surgery after neoadjuvant treatment Disease prevalence: stromal invasion greater than two-thirds: 20.5%; parametrial invasion: 6.4; vaginal invasion: 3.8%; vesicovaginal septum invasion: 1.3%; rectovaginal septum invasion: 0%; lymph node metastases: 14.1%		95%; NPV 95%; PPV 0% Accuracy of MRI to detect vesicovaginal septum invasion (N=68): Se 100%; Sp 97%; NPV 100%; PPV 33% Accuracy of MRI to detect rectovaginal septum invasion (N=68): Sp 97%; PPV 33% Accuracy of MRI to detect pelvic lymph node metastasis (N=68): Se 27%; Sp 96%; NPV 87%; PPV 60%	limits of agreement −21.85 to 24.83 mm) Accuracy of MRI to detect stromal invasion greater than two-thirds (N=68): Se 94%; Sp 85%; NPV 98%; PPV 65%	Consecutive patiënts MRI assessor was blinded to FIGO staging, but not to patiënt history
(Wydra, Sawicki et al. 2006)	Design: prospective cohort study Source of funding: not reported on Conflict of interest: not reported on Setting: Medical University of Gdansk, Poland Sample size: N=100 Duration: 2002-2004	Eligibility criteria: early cervical cancer with radical hysterectomy and pelvic or para-aortic lymphadenectomy Patiënt characteristics: median age: 51 y; 94% SCC. FIGO stage IB1: 58%; IB2: 18%; IIA: 24% Disease prevalence: 22% lymph node metastases	Index test: SNB (blue-dye and hand-held gamma probe detection) Reference standard: histopathology from pelvic or para-aortic lymphadenectomy	Accuracy of SNB to detect lymph node metastasis (N=88): Se 86%; NPV 96%	One-sided sentinel node detection rate: 84%. According to FIGO stage: 96.6% IB1 66.7% IB2 62.5% IIA Two-sided sentinel node detection rate: 66%. According to FIGO stage: 86.2% IB1 38.9% IB2 37.5% IIA	Level of evidence: B Dropouts: none Consecutive patiënts Blinded assessment not reported Unclear which patiënts got a para-aortic lymphadenectomy and why Small discrepancy in number of patiënts with a one-sided sentinel node

Study ID	Method	Patiënt characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
						detected (84 vs. 88) in text vs. table
(Yamashita, Katayama et al. 2009)	Design: prospective study Source of funding: not reported on Conflict of interest: not reported on Setting: Asahikawa Medical College, Asahikawa, Japan Sample size: N=58 Duration: 2001-2007	Eligibility criteria: FIGO stages Ia to IIIb uterine cervical cancer Patiënt characteristics: mean age: 47 y; 88% SCC. FIGO stage: IA: 5%; IA1: 14%; Ia2: 3%; Ib1: 45%; IIA: 5%; IIB: 14%; IIIA: 2%; IIIB: 12% Disease prevalence: 8.6% lymph node metastases	Index test: SNB (blue dye and radioactive material) with intraoperative frozen section assessment Reference standard: histopathology from pelvic lymphadenectomy	Accuracy of SNB to detect lymph node metastasis (N=58): Se 100%; NPV 100%	One-sided sentinel node detection rate: 76% Two-sided sentinel node detection rate: 48%	Level of evidence: B Dropouts: none Unclear if patiënts were consecutive Blinded assessment not reported Unclear if patiënts got a para-aortic lymphadenectomy
(Yu, Jia et al. 2011)	Design: not reported on Source of funding: not reported on Conflict of interest: not reported on Setting: Affiliated Tumor Hospital of Harbin Medical University, Harbin, China Sample size: N=16 Duration: not reported	Eligibility criteria: not reported Patiënt characteristics: 88% SCC; 13% AC. FIGO stage IB1: 44%; IB2: 25%; IIA: 31% Disease prevalence: 6% lymph node metastases	Index test: PET/CT Reference standard: histopathology	Accuracy of PET/CT to detect lymph node metastasis (N=16): Se 0%; Sp 100%; NPV 94%	-	Level of evidence: B Dropouts: not reported on Study design was not described; nor was blinding. Unclear if patiënts were consecutive

Abbreviations: AC: adenocarcinoma; ASC: adenosquamous carcinoma; ASCC: adenosquamous cell carcinoma BMI: body mass index; CI: confidence interval; FS: fat suppressed; FSE: fast spin echo; Gd: gadolinium; na: not available; NLR: negative likelihood ratio; NPV: negative predictive value; PLR: positive likelihood ratio; PPV: positive predictive value; SCC: squamous cell carcinoma; Se: sensitivity, SE: spin echo; SN: sentinel node; SNB: sentinel node biopsy; Sp: specificity; y: year

Vraag 1B
Bij patiënten met invasief cervixcarcinoom, wat is het afkappunt van de tumormarkers SCC en CA125 voor het definiëren van een hoog risicogroep m.b.t. locale tumoruitbreiding, lymfekliermetastasen en metastasen op afstand?

Observational studies

Study ID	Method	Patiënt characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
(Bender, Sorosky et al. 2003)	Design: retrospective cohort study Source of funding: not reported on Conflicts of interest: not reported on Setting: University of Iowa Sample size: N=73 Duration: 1986-1998	Eligibility criteria: cervical adenocarcinoma or adenosquamous carcinoma treated at this centre, and a pre-treatment CA 125 (50% of all patiënts treated) Patiënt characteristics:mean age 45 y; 93% AC; 86% with low (I- IIA) FIGO stage; 52 patiënts underwent surgery and were included in the primary outcome Disease prevalence: 17% lymph node metastases	Index test: serum CA 125 Reference standard: histology	Accuracy of CA 125≥30 U/mL to predict positive lymph nodes (N=50): Se 67%; Sp 84%; NPV 92%; PPV 46%	-	Level of evidence: B Consecutive patiënts; risk of selection bias through eligibility criteria Partial verification: only patiënts with a radical hysterectomy could be verified by histology Uses the 1995 FIGO criteria The cut-off level for CA 125 was not predefined
(Chen, Liang et al. 2008)	Design: prospective study Source of funding: not reported on Conflicts of interest: not reported on Setting: China Medical University Hospital, China Sample size: N=148 Duration: 2001-2006	Eligibility criteria: untreated stage IB2–IVA squamous cell cancer of the uterine cervix, without evidence of enlarged para-aortic lymph nodes Patiënt characteristics: not specified. All patiënts went for concurrent chemoradiation Disease prevalence: tumor size >4 cm: 91 %; 15% lymph node metastases	Index tests: SSCA Reference standard: CT (lymph node positivity) and CT or pelvic examination (tumour size)	Accuracy of SSCA ≥2.0 ng/ml to predict a tumour size ≥4cm (N=148): Se 64%; Sp 31%; NPV 8%; PPV 91% Accuracy of SSCA ≥2.0 ng/ml to predict positive lymph nodes (N=148): Se 77%; Sp 38%; NPV 91%; PPV 18%	-	Level of evidence: B Dropouts: not reported Unclear if patiënts were consecutive Differential verification for the outcome tumour size The reference standard for parametrial invasion was not stated: not included as an outcome

Study ID	Method	Patiënt characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
						Concerns a subgroup of patiënts who did not receive surgery
(Kotowicz, Fuksiewicz et al. 2008)	Design: not reported Source of funding: not reported on Conflicts of interest: not reported on Setting: not stated Sample size: N=182 Duration: not stated	Eligibility criteria: not stated Patiënt characteristics: median age: 54 y; 13% AC; 87% SCC; 30% FIGO stage I-IIA Disease prevalence: 27% lymph node metastases	Index tests: CA 125, SCCA Reference standard: histology (N=55) or CT (N=127)	Accuracy of CA 125 ≥5.0 ng/ml to predict positive lymph nodes (N=182): Se 18%; Sp 60%; NPV 66%; PPV 15% Accuracy of SSCA ≥1.5 ng/ml to predict positive lymph nodes (N=182): Se 67%; Sp 84%; NPV 92%; PPV 46%	-	Level of evidence: B Dropouts: not reported Design is not reported on, nor is blinding Differential verification
(Takeda, Sakuragi et al. 2002)	Design: not reported Source of funding: not reported on Conflicts of interest: not reported on Setting: single institution study, Japan Sample size: N=103 Duration: 1988-2000	Eligibility criteria: invasive squamous cell cervical carcinoma treated with radical hysterectomy at the institution and whom had a preoperative SCCA, CA-125 and CA-19-9 available Patiënt characteristics: median age 52 y; 55% FIGO stage IB; 43% stage IIB Disease prevalence:27% lymph node metastases	Index tests: either SCCA or CA 125, or both combined Reference standard: histology	Accuracy of SSCA ≥1.5 ng/ml and/or CA 125 35 U/ml to predict positive lymph nodes (N=103): Se 79%; Sp 56%; NPV 88%; PPV 40%	-	Level of evidence: B Dropouts: not reported Unclear if patiënts were consecutive Design is not reported on, nor is blinding. Likely a retrospective study because preoperative tumour markers had to be available for inclusion Risk of selection bias through selection of hysterectomy patiënts with preoperative tumor markers available

Study ID	Method	Patiënt characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
(van de Lande, Davelaar et al. 2009)	Design: not reported Source of funding: Biocare foundation Conflict of interest: no conflicts of interest to declare Setting: VU University Medical Center, Amsterdam, the Netherlands Sample size: N=91 Duration: 1996-2006	Eligibility criteria: SSC Exclusion: prior or concomitant malignancy Patiënt characteristics: mean age: 42 y; FIGO stage IB1: 79%; IB2: 11%; IIA: 10% Disease prevalence: 31% lymph node metastases	Index tests: SCCA Reference standard: histology	Accuracy of SSCA ≥1.65 ng/ml to predict positive lymph nodes in patiënts with stage IB1 (N=72): Se 53%; Sp 84%; NPV 85%; PPV 50% Accuracy of SSCA ≥1.65 ng/ml to predict positive lymph nodes in patiënts with stage IB2 or IIA (N=19): Se 63%; Sp 46%; NPV 63%; PPV 40%	-	Level of evidence: No dropouts Unclear if patiënts were consecutive Design is not reported on, nor is blinding The cut off level for SSCA was not predefined Insufficient data to construct a 2x2 table; the accuracy data from the study are reported here

Abbreviations: AC: adenocarcinoma; CA 125: cancer antigen 125; NPV: negative predictive value; PPV: positive predictive value; ROC: receiver operating curve; SCC: squamous cell carcinoma; Se: sensitivity; Sp: specificity; SSC: squamous cell carcinoma; SSCA: squamous cell carcinoma antigen; y: year

Vraag 2: Wat is de plaats van fertiliteitsparende behandeling bij vrouwen met cervix carcinoom?

Reference	Search date	Recommendations	Evidence base	Level of evidence
SIGN 2008	2005	Women requesting fertility conservation should be offered radical trachelectomy and pelvic lymph node dissection, providing the tumour diameter is less than 2cm and no lymphatic-vascular space invasion is present	Case series	C
		Women with early stage disease and no LVSI (FIGO IA2 and microscopic IB1) requesting fertility conservation may be offered cold knife conisation or LLETZ combined with pelvic lymph node dissection	Case series	C

Primary studies

Conization

Reference	Methodology	Patiënt characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
Bisseling 2007	Retrospective cohort study Funding: not stated Setting: 2 university centres (1 in the Netherlands, 1 in Australia) Sample size: N=38 Duration: May 1987 – August 2004	Eligibility criteria: Patiënts with stage IA1 and IA2 cervical cancer Patiënt characteristics: Stage IA1: N=29, age 25-48 Stage IA2: N=9, age 30-45	Conization +/- PLND: stage IA1 N=16; stage IA2 N=2 vs. Hysterectomy +/- PLND: stage IA1 N=13; stage IA2 N=7 (8 radical hysterectomies, 8 simple (intrafascial) abdominal hysterectomies, and 4 vaginal hysterectomies)	No recurrence Excised parametria (N=8) and pelvic lymph nodes (N=17) were all free from disease	Number of women attempting to conceive not reported 18 fertility preserving treatment: 11 patiënts with 18 pregnancies resulting in 13 live births, 2 terminations and 3 spontaneous abortions	Level of evidence: very low B Average follow-up: 72 months No correction for confounders
Kim 2010	Retrospective cohort study Funding: not stated Setting: university hospital, Korea Sample size: N=108 Duration: Jan 1999 – Feb 2008	Eligibility criteria: Patiënts with stage IA1 cervical cancer undergoing conization Patiënt characteristics: Median age: 41 vs. 38 years	Simple hysterectomy (N=40) vs. Conisation (N=68)	No recurrence in hysterectomy group 7 recurrences in conization only group, all in patiënts with positive resection margins (N=40)	6 patiënts with recurrence were treated successfully with repeat conization or simple hysterectomy; pathology was primarily CIN 3 or microinvasive disease at most	Level of evidence: very low B Median follow-up: 67 months No correction for confounders 1 patiënts with recurrence lost to follow up for 6 years and subsequently

Reference	Methodology	Patiënt characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
						treated with CRT for advanced disease
Lee 2009	Retrospective cohort study Funding: not stated Setting: 3 tertiary hospitals, Korea Sample size: N=75 Duration: Jan 1997 – Dec 2006	Eligibility criteria: Patiënts with stage IA1 cervical cancer undergoing conization Patiënt characteristics: Mean age: 48 vs. 35 years (p<0.05)	Simple hysterectomy (N=53) vs. Conization (N=22)	No recurrence in the hysterectomy group In the conservative group, 10 patiënts underwent repeat conization; 2 patiënts underwent hysterectomy for abnormalities at second follow-up	Number of women attempting to conceive not reported 2 pregnancies and live births in conservative group	Level of evidence: very low B Mean follow-up: 34 vs. 37 months No correction for confounders Selection bias is possible, given the difference in mean age between the 2 groups
Reynolds 2010	Retrospective cohort study Funding: one author received a grant from the National Institutes of Health Setting: 2 tertiary hospitals, US Sample size: N=66 Duration: 1983 – 2008	Eligibility criteria: Patiënts with stage IA1 (N=52) or IA2 (N=14) cervical cancer Patiënt characteristics: Median age: 39 years	Conization (IA1: N=7 and IA2: N=1) Simple hysterectomy (IA1:N=16 and IA2:N=2) Radical hysterectomy (IA1:N=29 and IA2:N=9) Radical vaginal trachelectomy (IA1:N=0 and IA2:N=2) 34 and 12 patiënts respectively also underwent PLND	No recurrences No parametrial involvement in any of the 40 patiënts who underwent radical surgery One patiënt with positive lymph nodes in the group that underwent PLND (1/46, 2.2%)		Level of evidence: very low B No correction for confounders Mean follow-up: 71 months for IA1 group vs. 80 months for IA2 group
Yahata 2010	Retrospective cohort study Funding: not stated Setting: 2 hospitals, Japan Sample size: N=27 Duration: 1990 – 2004	Eligibility criteria: Patiënts with stage IA1 cervical cancer More than 5 years follow-up Patiënt characteristics: Mean age: 43 years	Hysterectomy (N=17) 15 radical, 2 simple. vs. Conisation (N=10)	No recurrence in both groups 2 second conizations for positive margins in conservative group 2 patiënts with positive margins underwent hysterectomy (are included in hysterectomy group)	3 pregnancies and live births in conservative group	Level of evidence: very low B No correction for confounders Mean follow-up: 75 months for conization group vs. 133 months for hysterectomy group

Radical trachelectomy

Reference	Methodology	Patiënt characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
Beiner 2008	Retrospective cohort study (matched) Funding: not stated Setting: Gynecologic Oncology at the University of Toronto Sample size: N=180 Duration: 1994 - 2007	Eligibility criteria: Patiënts with cervical cancer who sought preservation of fertility, tumor size ≤2 cm, and did not meet the Society of Gynecologic Oncologists' definition of microinvasive cancer (squamous cell carcinoma, less than 3 mm invasion, and no capillary lymphatic space invasion) Patiënts were matched with controls who underwent radical vaginal hysterectomy Patiënt characteristics: Median age: 34 vs. 31years (p<0.001)	Radical trachelectomy (LARVT) (n=90) vs. Radical vaginal hysterectomy (LARVH) (n=90) Both techniques were combined with laparoscopic pelvic lymph node dissection	5 and 1 recurrences were diagnosed in the RVT and radical hysterectomy groups, respectively Five-year recurrence-free survival: 95% vs. 100% (p=0.17) 3 vs. 1 deaths 5-year overall survival: 99% vs. 100% (p=0.55)	Similar length of operating time RVT patiënts experienced significantly less blood loss (300 vs. 600 ml, p<0.001, fewer blood transfusions (2% vs. 23%, p<0.0001), shorter postoperative hospital stay (1 vs. 6 days, p<0.001), and shorter time to normal urine residual (1 vs. 6 days, p<0.001) Significantly more intra-operative complications (13% vs. 2%, p<0.0001) in RVT group	Level of evidence: very low B Median follow-up of 51 and 58 months Matched 1:1 for age (±5 years), tumor size (±1mm), histology, grade, depth of invasion (±1mm), presence of capillary lymphatic space invasion (CLS), pelvic lymph node metastasis, and adjuvant radiotherapy Considerable risk of residual confounding No confidence intervals reported
Hertel 2006	Case series Funding: not stated Setting: multicentre Germany Sample size: N=108 Duration: March 1995 - November 2005	Eligibility criteria: Patiënts with cervical cancerExclusion criteria: Tumor size >2 cm, neuroendocrine tumor type, tumor-involved resection margins, or positive pelvic lymph nodes Patiënt characteristics: TNM stage 1A1, L1 n = 18, 1A2 n = 21, 1B1 n = 69	Radical vaginal trachelectomy (RVT) and pelvic lymphadenectomy	Three (3%) recurrences in 100 patiënts treated with RVT according to protocol Projected 5-year recurrence-free and overall survival rates: 97% and 98%	Average duration of surgery: 253 min (115–402) Perioperative complications: postoperative bleeding, embolism of the external iliac artery, retroperitoneal lymphocele, and paralytic ileus in one patiënt, respectively	Level of evidence: very low C Median follow-up time: 29 months (1-128) 8 patiënts excluded as the study criteria were not met after RVT
Kim 2011	Case series Funding: not stated Setting: Memorial Sloan–Kettering Cancer Center, New York	Eligibility criteria: Patiënts who attempted fertility-sparing surgery Patiënt characteristics:	Radical trachelectomy by either an abdominal (RAT), vaginal (RVT) or robotic approach (RRT) (49 RAT, 52 RVT, and	One patiënt recurred and died of disease 24 months after surgery. Two patiënts expired from non-oncologic causes	9% required an intervention for perioperative complications	Level of evidence: very low C Heterogeneous intervention in a

Reference	Methodology	Patiënt characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
	Sample size: N=105 Duration: November 2001 - September 2010	Preoperative stages: 12 stage IA1 (12%), 12 stage IA2 (12%), and 81 stage IB2 (77%)	4 RRT)	35 were actively attempting conception 6-12 months after surgery 22 patiënts (63%) successfully conceived		specialised centre Median follow-up: 29 months (range 0.1–99.8)
Li 2011	Case series Funding: not stated Setting: one centre Shangai Sample size: N=64 Duration: 04/2004 - 09/2010	Eligibility criteria: Confirmed invasive cervical cancer Tumor size < 4 cm FIGO stage IA1 disease with lymph vascular space invasion, or positive surgical margin and distorted cervicovaginal anatomy after conization; or stage IA2 or IB1 disease Desire to preserve fertility Patiënt characteristics: Median age: 29.5 years (range 11-41) Stage IA1 27%, IA2 12%, IB1 61% SCC 81%	Abdominal radical trachelectomy	No recurrences 14 patiënts tumor > 2 cm 10 patiënts attempted to conceive: 2 pregnancies, 1 delivery and one ongoing	Median blood loss: 362 ml (range 100–700 ml) Median length of postoperative hospital stay: 10.14 days (range 7–21 days) Postoperative cervical stenosis: 4/64 (6.25%)	Level of evidence: very low C Median follow-up: 22.8 months (range 1–78 months)
Marchiole 2007	Retrospective cohort study Funding: not stated Setting: Sample size: N=257 Duration: December 1986 - December 2003	Eligibility criteria: FIGO stage I–IIA carcinoma of the cervix Patiënt characteristics: Mean age: 32 vs. 47 years (p<0.001) Stage IA: 24.6% vs. 18%; stage IB1: 70.3% vs. 76.3%; stage IIA: 5.1% vs. 5.8% (NS) SCC: 76.3% vs. 73.4% (NS)	Radical trachelectomy (LARVT) (n=118) vs. Radical hysterectomy (n=139) Both combined with laparoscopic pelvic lymph node dissection	Risk of recurrence: 7 cases (5.2%) in patiënts treated with LAVRT and 9 cases (6.5%) in patiënts treated with LAVRH (p=NS) 6 recurrences in the LAVRT group had a tumor, giving on 21 interventions in the group size > 2 cm	Rate of intraoperative complications: 2.5% for LAVRT and 5.8% for LAVRH, p=NS Rate of postoperative complications: 21.2% for LAVRT and 19.4% for LAVRH, p=NS	Level of evidence: low B Median follow-up: 95 months (range 31–234) for LARVT and 113 months (range 36–249) for LARVH Statistical adjustment was done for risk factors in terms of recurrence-free survival: tumor size, nodal status, LVSI, histotype, age and type of operation and did not alter conclusions;

Reference	Methodology	Patiënt characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
						however, details of the adjustment were not reported
Nam 2011	Case series Funding: not stated Setting: four institutions in Korea Sample size: N=59 Duration: not mentioned	Eligibility criteria: Patiënts with early-stage cervical cancer who wanted to preserve fertility Patiënt characteristics: Median age: 29 years (range 22-44) Median tumour size: 1.8 cm	Laparoscopic radical trachelectomy	59 enrolled for LRT In 5 patiënts, LRT was abandoned because of lymph node metastasis or parametrial involvement 2 recurrences and 1 death from disease 16 patiënts attempted to conceive: 8 pregnancies, 3 healthy babies	Median estimated blood loss: 300 mL (range 50–1000) Perioperative transfusion in 15 patiënts 6 received adjuvant treatment 1 vesicovaginal fistula	Level of evidence: very low C Median follow-up was 31 months (range 7–70)
Nishio 2009	Case series Funding: not stated Setting: university hospital, Japan Sample size: N=61 Duration: September 2002 - March 2008	Eligibility criteria: Desire for fertility-sparing FIGO stage IA1 with lymph-vascular space involvement (LVSI) FIGO stage IA2 or stage IB1, no involvement of the upper endocervical canal and no Evidence of lymph node metastasis, as determined by MRI/CT Patiënt characteristics: Median age: 33 years (range 26-44) FIGO IA1 6.6%, IA2 13.1%, IB1 80.3% SCC 95.1%	Abdominal radical trachelectomy	Six recurrences (9.8%); none of the recurrences occurred in patiënts with a tumor diameter of <20 mm except in one case with adenocarcinoma among the 13 patiënts with a tumor diameter of ≥20 mm, five developed recurrent disease. Twenty-nine women attempted to conceive; four were successful. All four of these women had live births: two preterm deliveries, and two full-term deliveries	Median estimated blood loss (ml): 1160 (352–5568) Median length of stay (days): 23 (11–63) Median operative time (min): 436 (317–586) Median time to recovery of bladder dysfunction (days): 15 (7–35)	Level of evidence: very low C Median follow-up: 27 months (range 1-79 months)
Plante 2011	Case series Funding: not stated Setting: one centre in Quebec Sample size: N=140 Duration: not mentioned	Eligibility criteria: Patiënts with early-stage cervical cancer (stages IA, IB, and IIA) Desire to preserve fertility Patiënt characteristics: Median age: 31 years Stage IA2 21%, IB1 69%	Radical vaginal trachelectomy	6 recurrences (4.8%), 2 deaths (1.6%) Actuarial 5-year recurrence-free survival: 95.8% (95%CI 0.90–0.98) for the entire population, 79% (95%CI 0.49–0.93) in the group in which VRT was abandoned (p=0.001) Tumor size >2 cm was	Number of women attempting to conceive not reported 58 women conceived a total of 106 pregnancies The first- and second-trimester miscarriage rates	Level of evidence: very low C Mean follow-up was 93 months (range 4–225) RVT was abandoned in 15 patiënts (reasons not stated) Correction for confounders unclear

Reference	Methodology	Patiënt characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
		SCC 56%		associated with a higher risk of recurrence (p=0.002) 3 recurrences in 13 tumors > 2 cm	were 20 and 3% 77 (73%) pregnancies reached the third trimester 58 (75%) delivered at term	
Shepherd 2006	Case series Funding: not stated Setting: multicentre UK Sample size: N=123 Duration: August 1994 - 2005	Eligibility criteria: Patiënts with early-stage cervical cancer Patiënt characteristics: Mean age: 30.6 (SD 4.3) Stage IA2 1.6%, IB1 98.4% SCC 67.5%	Radical vaginal trachelectomy with pelvic lymphadenectomy Eleven women (8.9%) had completion treatment. Two had completion surgery and nine had chemoradiotherapy	Three recurrences (2.7%) among the women who did not have completion treatment and two (18.2%) in those who did Sixty-three women attempted pregnancy. There were 55 pregnancies in 26 women and 28 live births in 19.	6 perioperative and 26 postoperative complications	Level of evidence: very low C fertiliteitsparende

CLS: capillary lymphatic space invasion; FIGO International Federation of Gynecology and Obstetrics; LARVT laparoscopic-assisted radical vaginal trachelectomy ; LARVH laparoscopic-assisted radical vaginal hysterectomy; LVSI: lymphatic-vascular space invasion; LLETZ: large loop excision of the transformation zone; PLND: pelvic lymph node dissection; RCT: randomized controlled trial; RH: radical hysterectomy; RVT: radical vaginal trachelectomy; RRT: Robotic Radical trachelectomy
TNM: Tumor, Node, Metastasis system

Vraag 3: Bij patiënten met operatief behandeld cervixcarcinoom stadium 1B/IIA met aanwezigheid van lymfekliermetastasen, heeft postoperatieve chemoradiatie in vergelijking met postoperatieve radiotherapie een betere (ziektevrije) overleving?

Adjuvant chemoradiotherapy/radiotherapy

Reference	Search date	Recommendations	Evidence base	Level of evidence
SIGN 2008	2005	Patiënts who have undergone surgery for cervical carcinoma and have positive nodes should be considered for adjuvant treatment with concurrent chemoradiotherapy with platinum based chemotherapy	RCT's	B
		Patiënts who have undergone surgery for cervical carcinoma, have negative nodes and any two of the following risk factors should be considered for adjuvant treatment with radiotherapy, if fit enough: -greater than a third stromal invasion -lymphovascular space invasion -tumour diameter of > 4 cm	RCT's	B
		Concurrent chemoradiation should be considered in preference to radiation alone	RCT's	B

Systematic reviews

Reference	Methodology	Patiënt characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
Rosa 2009	Systematic Review Funding: CAPES, Brazil; Department of Health; UK NHS Cochrane Collaboration programme Grant Scheme CPG-506 Search date: January 2009 Databases: CENTRAL, Medline, EMBASE, LILACS, Biological Abstracts, CancerLit, trial registers, conference proceedings, references, experts Study designs: RCT N included studies: 3 (368 patiënts) Tattersall 1992 (n=71)(Tattersall, Ramirez et al. 1992) Peters 2000 (n=268 enrolled; 243 assessed)(Peters, Liu et al. 2000)	Eligibility criteria: Peters 2000 Patiënts with clinical stage IA2, IB, and IIA carcinoma of the cervix, initially treated with radical hysterectomy and pelvic lymphadenectomy, and who had positive pelvic lymph nodes and/or positive margins and/or microscopic involvement of the parametrium Median follow up : 42 months Protocol CE3005: Patiënts with clinical stage IB or IIA Median follow up : 29.5 months	Adjuvant platinum-based chemotherapy (in addition to radical hysterectomy, RT or both) Peters 2000: 4 cycles of CT with cisplatin and 5-fluorouracil. Protocol CE 3005: chemotherapy with bleomicin + ifosfamide + cisplatin vs. Adjuvant pelvic radiotherapy alone	CTRT vs. RT (N=2)		Level of evidence: B Allocation concealment: N=1 No blinding Peters 2000 and Tattersall 1992: Kaplan-Meier plots (max duration of follow-up) Peters 2000: based on an interim analysis of the data which rejected the null hypothesis of no benefit of CT Protocol CE3005: unpublished data
				Death from all causes (243 patiënts): HR 0.56 (95%CI 0.36-0.87; p=0.0096; I² 0%) in favour of chemotherapy	*Disease progression (243 patiënts):* HR 0.47 (0.30-0.74; p=0.0012; I² 0%) in favour of chemotherapy *Grade 4 toxicity (288 patiënts)*: HR 5.66 (2.14-14.98; p=0.00048; I² 0%) in favour of no chemotherapy	
		Tattersall 1992	3 cycles of CT with	Chemotherapy followed by RT vs. RT (N=1)		

Reference	Methodology	Patiënt characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
	Protocol CE3005 - UK Clinical Trials Register 2001 (n=57 enrolled; 54 assessed)(Cancer Research UK 2001)	Patiënts with clinical stage IB (87%) and IIA (13%) carcinoma of the cervix, initially treated with radical hysterectomy and pelvic lymphadenectomy, and who had positive pelvic lymph nodes (1 - >5) Median follow up : 30 months	cisplatin, vinblastine and bleomycin followed by pelvic RT Vs. RT only		*Disease progression (71 patiënts)*: HR 1.34 (0.24-7.66)	

Abbreviations: CT: chemotherapy; CTRT: chemoradiotherapy; HR: hazard ratio; RCT: randomized controlled trial; RT: radiotherapy

Primary studies

I Study ID	II Method	III Patiënt characteristics	IV Intervention(s)	V Results primary outcome	VI Results secondary and other outcome(s)	VII Critical appraisal of study quality
Monk 2005 retrospective analysis of Peters 2000 data	Design: RCT 2 arms Research funding: National Cancer Institute grants Setting: multicenter study Sample size: 268 patiënts enrolled in RCT 243 eligible patiënts Median follow-up: 5.2 years	Eligibility criteria: Patiënts with clinical stage IA2, IB, and IIA carcinoma of the cervix, initially treated with radical hysterectomy and pelvic lymphadenectomy, and who had positive pelvic lymph nodes and/or positive margins and/or microscopic involvement of the parametrium, SWOG performance status of 0–2, adequate bone marrow, renal and hepatic function. Median age: RT group 38 [20–64]; CTRT group 40 [19–74] No statistical differences in patiënts age, stage, tumour size and lymph nodes between groups	Intervention (n=127) Adjuvant platinum-based chemotherapy (in addition to radical hysterectomy, RT or both) - 4 cycles of CT with cisplatin and 5-fluorouracil. Control (n=116) Adjuvant pelvic radiotherapy alone	***5-year survival*** 80% (CTRT) vs. 66% (RT) ***5-year survival (%) by prognostic factor (RT, CTRT, p value)*** *Tumor size RT CTRT p* ≤2 cm 0.77 0.82 0.170 >2 cm 0.58 0.77 0.009 P value 0.09 0.53 *Histology RT CTRT p* Squamous 0.69 0.80 0.019 Nonsquam. 0.55 0.82 0.014 P value 0.17 0.76 *Grade RT CTRT p* Grades 1-2 0.66 0.80 0.007 Grade 3 0.67 0.80 0.091 P value 0.70 0.79 *Param.ext. RT CTRT p* Neg 0.78 0.84 0.052 Pos 0.49 0.73 0.009 P value 0.007 0.19 *Nodes RT CTRT p* 1 node 0.79 0.83 0.438 ≥2 nodes 0.55 0.75 0.006 P value 0.01 0.37		Level of evidence: B exploratory, hypothesis-generating analysis survival was estimated with Kaplan–Meier method with differences analyzed using a log-rank test

Abbreviations: CT: chemotherapy; CTRT: chemoradiotherapy; RCT: randomized controlled trial; RT: radiotherapy

Vraag 4 Bij patiënten met behandeld cervixcarcinoom, welke (frequentie van) follow-up zorgt voor een betere overleving en kwaliteit van leven?

Systematic reviews

Study ID	Method	Patiënt characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
(Elit, Fyles et al. 2009)	• Design: systematic review • Funding: Cancer Care Ontario, Ontario Ministry of Health and Long-term Care • Conflicts of interest: none to declare • Search date:1980-November 2007 • Searched databases: Medline, Embase, Cochrane databases, Canadian Medical Association Infobase, and the National Guideline Clearinghouse • Included study designs: randomized controlled trials, practice guidelines, meta-analyses, systematic reviews or cohort studies	• Eligibility criteria: studies were to report data relating to follow-up programs by the method of detection, the entry criteria for the study population, survival, and the number of recurrences found during screening, or on patiënt quality of life; >25 patiënts included and English language • Patiënt characteristics: 15/17 studies included patiënts with surgical stage IB or IIA; 6/17 studies included patiënts with all stages. The majority of included patiënts were IB or IIA. Treatment received: 4/17 studies surgery only; 3/17 studies radiotherapy alone; 9/17 studies combined treatment	• Index test: not applicable • Reference standard: not applicable	Follow-up visits typically occurred once every 3–4 months for the first 2 years, every 6 months for the next 3 years and then annually until year 10. There were no comparative studies on the frequency of follow-up visits Median time to recurrence ranged from 7–36 months after primary treatment. The % of recurrences detected per time period was: - 2 years 62-89% - 3 years 75-85% - 5 years 89- 99% For patiënts who were symptomatic at the time of recurrence detection, median overall survival after recurrence ranged from 8- 38 months, and for asymptomatic patiënts the range was 8 months to a median survival that was not reached after 53 months of follow-up	Rates of recurrence: ranged 8–26% - 14–57% in the pelvis - 15–61% at distant or multiple sites Asymptomatic recurrence was detected by (in % of patiënts with asymptomatic recurrence): - physical exam 29–71% - chest x-ray 20–47% - CT 0–34% - vaginal vault cytology 0–17% - ultrasound 0-2% - MRI 0-9% - intravenous pyelography 0% - tumour markers 0-26% - other 11-33%	Level of evidence: B (C voor uitkomst overleving) • All studies were retrospective, uncontrolled observational studies • Very heterogeneous patiënt populations • Included studies: *SRs*: None *Primary studies:* 11 published before 2001 (Duyn, Van Eijkeren et al. 2002) (Esajas, Duk et al. 2001) (Lim, Howells et al. 2004) (Morice, Deyrolle et al. 2004) (Sartori, Pasinetti et al. 2007) (Zola, Fuso et al. 2007)
(Havrilesky, Kulasingam et al. 2005)	• Design: systematic review with meta-analysis • Funding: Centers for Medicare and Medicaid Services • Search date:1966-2003 • Searched databases: Medline • Included study designs: observational studies	• Eligibility criteria: English language studies reporting primary data and published in a peer review journal with 12 or more included patiënts • Patiënt characteristics: not reported • Disease prevalence: not reported	• Index test: PET • Reference standard: histology or follow-up of 6 months or more	Meta-analysed (N=3) accuracy of PET to detect recurrence with clinical suspicion: Se 96% (95% CI: 87–99%), Sp 81% (95% CI: 58–94%) Meta-analysed (N=2) accuracy of PET to detect recurrence without clinical suspicion: Se 92% (95% CI: 77–98%), Sp 75% (95% CI: 69–80%) Single study accuracy of PET to detect recurrence (unspecified): Se 100%, Sp 77%	Recurrence was not reported separately for locoregional or distal recurrence	Level of evidence: B • All studies were retrospective and none of them reported blinded assessment • Included studies: *Primary studies:* 1 published before 2001 (Belhocine, Thille et al. 2002) (Chang, Hung et al. 2004) (Nakamoto, Eisbruch et al. 2002) (Ryu, Kim et al. 2003) (Sun, Chen et al. 2001)

Abbreviations: CI: confidence interval; NPV: negative predictive value; PPV: positive predictive value; Se: sensitivity, Sp: specificity; SRs: systematic reviews

Observational studies

Study ID	Method	Patiënt characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
	•	•				•
(Chan, Ng et al. 2002)	• Design: retrospective cohort study • Source of funding: not reported on • Conflicts of interest: not reported on • Setting: Queen Mary Hospital, Hong Kong SAR, China • Sample size: N=384 • Duration: 1994-1999	• Eligibility criteria: all patiënts with SCC and SCCA measurement • Patiënt characteristics: mean age 55 y; FIGO stage I: 49%; II: 30%; III:17%; IV:3%; 21 patiënts had persistent/progressive disease • Disease prevalence: 14% recurrence (3% locoregional and 12% distant)	Index test: SCCA Reference standard: blood tests, X rays, and CT scans	The accuracy of persistent SCCA ≥1.5 ng/mL to detect recurrence (N=309) before its detection: Se 71%; Sp 97%; NPV: 94%; PPV 85% Mean lead time: 9.8 months; median lead time: 7.8 months (range: 1-21 months)	7/10 patiënts with locoregional disease had elevated SSCA levels (not reported for the patiënts with a distant recurrence) 8% of patiënts had transient SCCA elevation which subsequently returned to normal without treatment. The magnitude of the transient elevation was small (mean and median: 1.7 ng/mL) All patiënts with SCCA>2.5 ng/mL had recurrent disease	Level of evidence: B • Consecutive patiënts • Risk of selection bias through selection criteria. 75 patiënts were excluded because of no SCCA monitoring • Blinded assessment not reported • Differential verification
(Chien, Ting et al. 2005)	• Design: retrospective cohort study • Source of funding: not reported on • Conflicts of interest: not reported on • Setting: National Taiwan University Hospital, Taipei, Taiwan • Sample size: N=46 • Duration: not reported	• Eligibility criteria: patiënts with cervical cancer (primary or recurrent) treated with curative radiotherapy in 1996 and available follow-up Pap smears • Patiënt characteristics: median age: 56 y; 85% SCC; 7% AD; 9% other. FIGO stage I: 37%; IIA: 20%; IIB: 20%; III: 7%; local recurrence: 17%. Median follow-up 34 months (range: 2-105 months) • Disease prevalence: 13% central recurrence; 57% recurrence	Index test: Pap smear Reference standard: Pap smear, histology, imaging, follow-up (clinically)	The accuracy of a Pap smear (malignancy) to detect central recurrence (N=46): Se 50%, Sp 100% The accuracy of a Pap smear (malignancy or high-grade squamous intraepithelial lesion) to detect central recurrence (N=46): Se 66%, Sp 95%	66% of Pap smears were within normal limits 25% had reactive changes or atrophy with inflammation; 3% had atypical cells	Level of evidence: B • Consecutive patiënts • 4 patiënts were excluded because they did not have follow-up Pap smears available • Blinded assessment not reported • Differential verification (10 by histology; 13 by imaging; 3 clinically) • Risk of incorporation bias as negative patiënts were followed with Pap smears
	•	•				•
	•	•				•
(Esajas, Duk et al. 2001)	• Design: retrospective cohort study • Source of funding: not reported on • Conflicts of interest: not reported on	• Eligibility criteria: FIGO stage IB and IIA patiënts with SCC • Exclusion: primary radiotherapy with or without chemotherapy, and not primary surgery	Index test: SCCA Reference standard: histology or follow-up	The accuracy of persistent SCCA >1.9 ng/mL to detect recurrence (N=225): Se 74%; Sp 96%; NPV 95%; PPV 79%	Of the 26 patiënts with elevated SCCA with a recurrence 16 patiënts recurred locoregional, 8 distal and 2 both. Of the nine patiënts without	Level of evidence: B • Consecutive patiënts with no loss to follow-up • Blinded assessment

Study ID	Method	Patiënt characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
	• Setting: University Hospital Groningen, the Netherlands • Sample size: N=225 • Duration: 1987-1998	• Patiënt characteristics: see eligibility • Disease prevalence: 16% recurrence (10% locoregional, 4% distant and 1% both)			elevated SCCA with a recurrence 6 patiënts had a locoregional recurrence, 2 patiënts had a distal recurrence and 1 a mixed recurrence 7% of patiënts had a transient rise in SCCA that normalised after 6 to 8 weeks False-positive serum SCCA could be related to benign skin disorders and to chronic obstructive pulmonary disease Also included in (Elit, Fyles et al. 2009)	not reported • Differential follow-up
(Forni, Ferrandina et al. 2007)	• Design: prospective cohort study • Source of funding: not reported on • Conflicts of interest: no conflicts of interest to report • Setting: Italy • Sample size: N=135 • Duration: not reported	• Eligibility criteria: all patiënts treated by the same team • Patiënt characteristics: median age: 57 y; 76% primary cervical carcinoma; 24% had already experienced disease recurrence that had been successfully treated • Disease prevalence: 32% recurrence or re-recurrence (21% locoregional and 11% both locoregional and distant)	Index test: SCCA Reference standard: physical and gynecologic examination (including Papanicolaou smear and colposcopy), complete blood analysis, chest X-ray and abdominopelvic MRI or CT plus transrectal ultrasonography	The accuracy of SCCA >1.4 ng/mL to detect recurrence before symptoms (N=135): Se 79%; Sp 96%; NPV 91%; PPV 90% The accuracy of SCCA 1.4 ng/mL + gynaecologic examination to detect recurrence (N=135): Se 95%; Sp 96%; NPV 98%; PPV 91%	No difference was found in the SCCA levels according to the site of recurrence 24/28 locoregional recurrences had elevated SCCA. 10/15 patiënts with both locoregional and distant recurrence had elevated SCCA In all patiënts, the elevation of SCCA levels preceded the appearance of any signs or symptoms of disease with a mean lead time of 4.7 months The total projected cost of the standard follow-up procedure, including CT or MRI, was 3,653.4 Euros per patiënt. The projected cost of the approach using only SCCA and gynaecologic examination was 298.5 Euros per patiënt	Level of evidence: B • Dropouts: none • Consecutive patiënts • Blinded assessment not reported • Differential verification
	•	•				•

Study ID	Method	Patiënt characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
	•	•				•
	•	•				•
(Yoon, Shin et al. 2010)	• Design: retrospective cohort study • Source of funding: not reported on • Conflict of interest: no conflicts of interest to declare • Setting: National Cancer Center Goyang, Gyeonggi, Republic of Korea • Sample size: N=112 • Duration: 2001-2004	• Eligibility criteria: cervical cancer stage IB-IV treated by concurrent chemoradiotherapy • Exclusion criteria: no SCCA determined in the follow-up period • Patiënt characteristics: median age 55 y. SCC: 91%; AD: 6%; ASC: 3%. FIGO stage IB: 10%; IIA: 12%; IIB: 59%; II/IV: 20%. 96% of patiënts had normalized SCCA levels at one month after treatment completion • Disease prevalence: 16% recurrent disease	Index test: SCCA Reference standard: histology or radiographic studies (unspecified)	The accuracy of two consecutive readings of SCCA 2.0 ng/mL to detect recurrence (N=112): Se 61%; Sp 98%; NPV 93%; PPV 85%	Locoregional or distant recurrence not reported separately	Level of evidence: B • Consecutive patiënts • Risk of selection bias • Blinded assessment not reported • Differential verification

Abbreviations: AD: adenocarcinoma; ASC: adenosquamous carcinoma; CEA: carcinoembryonic antigen; CI: confidence interval; NPV: negative predictive value; PPV: positive predictive value; SCC: squamous cell carcinoma; SCCA: squamous cell carcinoma antigen; Se: sensitivity, Sp: specificity; y: year

Observational studies

Study ID	Method	Patiënt characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
(Ansink, de Barros Lopes et al. 1996)	• Design: retrospective cohort study • Source of funding: not reported on • Conflict of interest: not reported on • Setting: Queen Elizabeth Hospital, Gateshead, United Kingdom • Sample size: N=112 • Duration: 1974-1995	• Eligibility criteria: stage IB cervical carcinoma patiënts whom had had hysterectomy and lymph node dissection. Patiënts with positive lymph nodes would get radiotherapy and during 1985-1988 adjuvant chemotherapy • Exclusion: no hysterectomy with lymph node dissection • Patiënt characteristics:112/674 (17%) developed a recurrence; mean age: 43 y; site of recurrence: not described	Routine follow-up: clinical history and physical examination 6 weeks post-operatively, then every 3 months during the first year, every 6 months during the second year and yearly thereafter up to ten years. Vault smears were taken as a routine up to 1988	Mean interval from primary treatment to recurrence: 25 months (range: 1-98 months) - 62% within 2 years - 75% within 3 years - 8% after 5 years Recurrence detected following: - 43% general practitioner referral - 26% routine follow-up - 13% self-referral - 10% other specialist - 8% not known Symptomatic vs. asymptomatic: - Symptomatic: 82% - Asymptomatic with signs: 13% - Unknown: 5%	Of the 8 patiënts who were alive and disease-free after recurrence, 3 were picked up during routine follow-up: at most 10% of recurrences detected during routine follow-up were cured	Level of evidence: B • Consecutive patiënts • No loss to follow-up • No data on diagnostic accuracy • No data on survival differences (follow-up detected vs. non-follow-up detected recurrence, symptomatic vs. asymptomatic recurrence)
(Bodurka-Bevers, Morris et al. 2000)	• Design: retrospective cohort study • Source of funding: not reported on • Conflict of interest: not reported on • Setting: University of Texas M. D. Anderson Cancer Center, Houston, United States • Sample size: N=133 • Duration: 1983-1993	• Eligibility criteria: FIGO stage IB cervical cancer patiënts treated at the centre • Exclusion: persistent disease (6 months or less from completion of treatment), and follow-up at another centre • Patiënt characteristics:133/993 (13%) developed a recurrence; 28% central pelvis; 16% pelvic wall; 16% lung; 17% lymph nodes; 13% multiple sites; 11% other sites	Routine follow-up: clinical history, physical examination and a PAP smear every 3 months in the first year, every 4 months in the second and third year and every 6 months thereafter up to 5 years. One chest X-ray in the first year	Mean interval from primary treatment to recurrence: - 16 months in asymptomatic patiënts - 17 months in symptomatic patiënts Symptomatic vs. asymptomatic: - Symptomatic: 86% - Asymptomatic 14% The median survival from initial diagnosis was 31 months for symptomatic and 83 months for asymptomatic patiënts (p< 0.001) The median survival from recurrence was 11 months for symptomatic and 42 months for asymptomatic patiënts (p<	In multivariate analysis symptomatic versus asymptomatic status at time of detection of recurrence was a significant predictor of overall survival, even when other standard prognostic factors including histology, grade, lesion size, and lymph node status were considered (p<0.01) There was a significant increase in median survival from time of recurrence for asymptomatic vs. symptomatic pulmonary recurrences, with asymptomatic patiënts living a median of almost 3 years and symptomatic patiënts surviving a median of only 1 year (p=0.02)	Level of evidence: B • Consecutive patiënts • No data on loss to follow-up

Study ID	Method	Patiënt characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
				0.001) All asymptomatic pelvic recurrences (N=8) were diagnosed by pelvic exam; all asymptomatic pulmonary recurrences (N=8) were detected by chest radiographs. Pap smears did not detect a single asymptomatic recurrence		
(Duyn, Van Eijkeren et al. 2002)	• Design: retrospective cohort study • Source of funding: not reported on • Conflict of interest: not reported on • Setting: three university hospitals, the Netherlands • Sample size: N=47 • Duration: 1992-1994	• Eligibility criteria: patiënts who achieved a complete remission after primary treatment for carcinoma of the cervix • Exclusion: more than one malignancy; an unknown cell type of the tumour; patiënts who were lost to follow-up; disease-free interval of less than 3months • Patiënt characteristics: 47/277 (17%) developed a recurrence; 34% central recurrence; 15% pelvic side wall; 51% distant or multiple recurrence	Routine follow-up: clinical history and physical examination, and in varying extent other investigations such as vaginal smears and blood tests (unspecified), every 3 months during the first year, every 4months in the second year, every 6months from 3 to 5 years and every year thereafter	Mean interval from primary treatment to recurrence: 18 months (range: 3-50 months) Recurrence detected following: - 45% self-referral - 32% routine follow-up - 13% general practitioner referral - 11% in another way Median survival after recurrence: - 12 months self-referral - 11 months routine follow-up - 5 months general practitioner referral - 2 months other (non-significant differences) Symptomatic vs. asymptomatic: - Symptomatic: 87% - Asymptomatic with signs: 9%	Treatment modalities for recurrence: surgery 13%, radiotherapy in 21%, chemotherapy 13%, combined treatment of chemotherapy and hyperthermia in 13% and palliative care only in 40% In univariate analysis, disease-free interval and treatment modality were significant prognostic factors for crude survival of recurrence	Level of evidence: B • Consecutive patiënts • Patiënts lost to follow-up were excluded • No data on diagnostic accuracy • No information on lead time bias or confounding factors for survival analysis • No multivariate analysis performed
(Esajas, Duk et al. 2001)	• Design: retrospective cohort study • Source of funding: not reported on • Conflicts of interest: not reported on	• Eligibility criteria: surgery treated FIGO stage IB and IIA patiënts with SCC • Exclusion: primary radiotherapy with or without chemotherapy, and not primary surgery	Index test: SCCA Reference standard: histology or follow-up Routine follow-up: clinical history, physical examination	Median interval from primary treatment to recurrence: 11 months (range: 3-126 months) The accuracy of persistent SCCA >1.9 ng/mL to	7% of patiënts had a transient rise in SCCA that normalised after 6 to 8 weeks False-positive serum SCCA could be related to benign	Level of evidence: B • Consecutive patiënts with no loss to follow-up • Blinded assessment not reported

Study ID	Method	Patiënt characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
	• Setting: University Hospital Groningen, the Netherlands • Sample size: N=225 (35 with recurrence) • Duration: 1987-1998	• Patiënt characteristics: see eligibility • Disease prevalence: 35/225 (16%) recurrence; 63% loco regional; 29% distant; 9% loco regional and distant	and blood analysis (haemoglobin count, erythrocyte sedimentation rate, and SCCA) starting 6 weeks post-operatively, then every 2 months for the first year, every 3 months in the second year, every 4 months in the third year, then every 6 months until the sixth year and yearly thereafter until 10 years after treatment	detect recurrence: Se 74%; Sp 96%; NPV 95%; PPV 79% Recurrence detected following: - 54% routine follow-up - 46% other doctor or self-referral Symptomatic vs. asymptomatic: - Symptomatic or signs: 86% - SCCA elevation as a first sign: 14% The complete remission rate after therapy for recurrence was significantly better if patiënts did not have radiotherapy as part of their primary therapy, had a normal SCCA at recurrence or had a loco - regional recurrence (univariate analyses). The mode of detection did not affect the complete remission rate	skin disorders and to chronic obstructive pulmonary disease Also included in (Elit, Fyles et al. 2009)	• No multivariate analyses performed
(Lim, Howells et al. 2004)	• Design: retrospective cohort study • Source of funding: not reported on • Conflict of interest: not reported on • Setting: University Hospital of Wales, Cardiff, United Kingdom • Sample size: N=53 • Duration: 1985-1999	• Eligibility criteria: patiënts who underwent surgery for cervical cancer • Patiënt characteristics:53/291 (18%) had recurrent disease	Routine follow-up: clinical history and physical examination every 3 months during the first year, every 6 months during the second year and yearly thereafter up to 5 years	Median interval from primary treatment to recurrence: 17.6 months (range: 3.0-60.0 months) - 63% within 2 years - 77% within 3 years Recurrence detected following: - 13% routine follow-up - 75% other doctor or self-referral - 11% unknown Symptomatic vs. asymptomatic: - Symptomatic: 96% - Asymptomatic: 4%%	Recurrence detection on routine follow up was not an independent prognostic factor for survival when compared with age, stage and whether the patiënt received post-operative adjuvant therapy	Level of evidence: B • Above the sample of 291 patiënts, 27 patiënts were lost to follow-up • Consecutive patiënts • From 18/291 (6%) of medical records it was unclear if the patiënt had had a recurrence • For 6/27 patiënts it was uncertain how the recurrence was detected • Unclear whether

Study ID	Method	Patiënt characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
				For the five patiënts with recurrent disease detected at routine follow-up who were symptomatic, the median survival was 37.5 months as opposed to only 8.3 months for the two patiënts with recurrent disease who were asymptomatic at the time of their clinic appointment When compared with the median survival for patiënts with a recurrence who self-presented (26.0 months), the differences were not statistically significant		time to recurrence was included in survival (risk of lead time bias) • Small sample size for a multivariate analyses
(Morice, Deyrolle et al. 2004)	• Design: retrospective cohort study • Source of funding: not reported on • Conflict of interest: not reported on • Setting: Institut Gustave-Roussy, Villejuif, France • Sample size: N=45 • Duration: 1986-1998	• Eligibility criteria: stage I and II cervical carcinoma treated with surgery and radiotherapy • Patiënt characteristics: 45/583 (8%) recurrence six months or later after primary treatment; 56% pelvic recurrence; 29% distant recurrence; 16% both distant and local recurrence	Routine follow-up: clinical history, physical examination, vaginal vault cytology, chest X-ray and abdominal pelvic ultrasound every 3 months in the first year, every 4 months during the second year, every 6 months during the third year, and every year thereafter	Median interval from primary treatment to recurrence: 16 months (range: 2-128 months) - Symptomatic: 16 months - Asymptomatic: 13 months - 89% within 5 years Recurrence detected following: - 9% routine follow-up - 84% self-referral - 7% radiologic examination for other reason Asymptomatic recurrence (N=7) detected by: - Physical examination: N=2 - Pap smear: N=1 - CT: N=2 - Chest X-ray: N=2 Symptomatic vs. asymptomatic: - Symptomatic: 84%	-	Level of evidence: B • Consecutive patiënts • 28/583 patiënts were lost to follow-up • Time to recurrence was not included in the survival analysis (risk of lead time bias) • No multivariate analyses

Study ID	Method	Patiënt characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
				- Asymptomatic: 16% The median survival since recurrence was 14 months for symptomatic and asymptomatic patiënts		
(Samlal, Van Der Velden et al. 1998)	• Design: retrospective cohort study • Source of funding: not reported on • Conflict of interest: not reported on • Setting: Academic Medical Centre, Amsterdam, the Netherlands • Sample size: N=27 • Duration: 1982-1991	• Eligibility criteria: cervical carcinoma IB and IIA treated at the study´s centre • Patiënt characteristics: 27/271 (10%) recurrence; 52% pelvic recurrence; 48% extra-pelvic recurrence	Routine follow-up: clinical history, physical examination and vaginal vault cytology, and in patiënts who had received radiotherapy also chest X-rays and ultrasound examinations of the kidneys, every 3 months in the first year, every 6 months up to three years and every year thereafter up to 10 years after treatment. From 1989 SCCA was included in routine follow-up	Median interval from primary treatment to recurrence: 14 months (range: 3-64 months) - 77% within 3 years - 14 months for a pelvic recurrence vs. 17 months for an extra-pelvic recurrence (p=0.03) Recurrence detected following: - 36% routine follow-up Symptomatic vs. asymptomatic: - Symptomatic: 65% - Asymptomatic: 33% The death rate in symptomatic patiënts was 94% vs. 56% in asymptomatic patiënts (significant difference). Two patiënts who survived a pulmonary recurrence were asymptomatic	41% of all recurrences were detected through physical examination and 52% through routine follow-up radiological examination	Level of evidence: B • Consecutive patiënts • Loss to follow-up not reported • Median follow-up 60 months • No multivariate analyses performed
(Sartori, Pasinetti et al. 2007)	• Design: retrospective cohort study • Source of funding: not reported on • Conflict of interest: none to declare • Setting: University of Brescia, Brescia, Italy • Sample size: N=63 • Duration: 1981-2004	• Eligibility criteria: stage IB–IIA cervical cancer, referred to the centre, with recurrence more than 3 months after primary treatment • Patiënt characteristics: median age 46 years (range: 18-72 years); 83% IB; 18% IIA; 57% pelvic recurrence; 43 distant recurrence	Routine follow-up: clinical history and physical examination every 3 months in the first year, every 4 months in the second year, every 6 months in the third to fifth year and annually thereafter. Pap smear from the vaginal vault and chest radiograph were taken annually	Diagnosis of recurrence was based on: - CT: 41% - Physical examination: 27% - Ultrasound: 10% - Histology: 8% - Chest X-ray: 6% - MRI: 5% - Cytology: 3% 53% of symptomatic recurrences was detected by physical examination	-	Level of evidence: B • Includes the same patiënts as (Zola, Fuso et al. 2007), so only additional information is described here • Consecutive patiënts

Study ID	Method	Patiënt characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
(Zola, Fuso et al. 2007)	• Design: retrospective cohort study • Source of funding: not reported on • Conflict of interest: none to declare • Setting: 8 Italian centers • Sample size: N=327 • Duration: 1980-2005	• Eligibility criteria: treated at one of the participating centers and recurrent cervical carcinoma • Patiënt characteristics: 327 patiënts with recurrence; mean age 49 years; 21% vaginal vault; 37% central pelvis; 10% pelvic wall; 5% lymph nodes; 24% distant (49% lung, 52% liver, 4% bone); 4% both distant and local recurrence	Routine follow-up: clinical history, physical examination and vaginal vault cytology in the first 2 years every 3 months, up to 5 years usually every 6 months and yearly thereafter. In some centres in addition ultrasound, chest X-ray, abdominal-pelvic CT, MRI and blood markers, at varying intervals	Symptomatic vs. asymptomatic: - Symptomatic: 50% - Asymptomatic: 50% In asymptomatic patiënts the first procedure was clinical visit for 51.8%, imaging for 36.6%, both clinical visit and imaging for 8.5% and in 3% it was cytology . The successful imaging consisted of CT (74%), MRI (20%) and ultrasound (5%) The median overall survival from primary treatment of symptomatic patiënts was 37 months versus 109 months for asymptomatic patiënts (Log rank, p=0.00001) The median survival since recurrence was 9 months for symptomatic patiënts and median was not reached for asymptomatic patiënts (p<0.0001) The median disease-free interval was 24 months for asymptomatic patiënts vs. 36 months for symptomatic patiënts (p=0.03)	In multivariate analysis symptomatic versus asymptomatic status at recurrence detection was a significant predictive factor in terms of overall survival (p=0.0001)	Level of evidence: B • Consecutive patiënts • Loss to follow-up not reported • Multivariate analysis performed

Abbreviations: SCCA: squamous cell carcinoma antigen

Vraag 5: De behandeling van patiënten met recidief cervixcarcinoom

Guidelines1

Treatment of recurrent, metastatic or persistent cervical cancer

Reference	Search date	Recommendations	Evidence base	Level of evidence
SIGN 2008	2005	Pelvic exenteration should be reserved as salvage surgery for women with recurrent cervical cancer in the central pelvis whose chemoradiotherapy has failed	Observational studies	C
		MRI or CT should be considered initially to assess potential clinical recurrence in symptomatic patiënts	Observational studies	B
		A whole body PET scan or PET-CT should be performed on all patiënts in whom recurrent or persistent disease has been demonstrated on MRI or CT and in whom salvage therapy (either pelvic exenteration or radiotherapy) is being considered	Observational studies	B
		Palliative chemotherapy should be offered to women with FIGO stage IVB or recurrent cervical carcinoma, after discussion of the relative benefits and risks, with either: • cisplatin 50 mg/m² on day 1 plus topotecan 0.75 mg/m² on days 1 to 3 every 3 weeks, or • cisplatin 50 mg/m² on day 1 plus paclitaxel 135 mg/m² every 3 weeks	RCT's	A2
CCO 2006	February 2006	It is recommended that all patiënts, particularly those who have been previously treated with cisplatin as a radiosensitizer, be offered the opportunity to participate in randomized trials, if available, that evaluate the efficacy and toxicity of other single-agent or combination chemotherapy regimens	Expert opinion	D
		Until further evidence becomes available, it is recommended that cisplatin in combination with topotecan should be offered to patiënts on the basis of improvements in response and survival outcomes when compared with single-agent cisplatin alone. (Note: The improvement in outcomes must be weighed against significant increases in adverse events, especially hematological toxicities, and the degree of the clinical benefit. Despite the increase in toxicity, no significant differences in quality of life were detected. Severe hematological toxicities were managed by dose modification and the use of granulocyte-colony–stimulating factors (G-CSFs) in subsequent cycles)	RCT's	A2

[1] The recommendations from the referenced guidelines are literally presented in this table. The level of evidence is attributed by the authors of this report.

Additional evidence

Chemotherapy for recurrent and stage IVB

Primary studies

Study ID	Method	Patiënt characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of study quality
Monk 2009 Cella 2010	• Design: RCT 4 arms • Research funding: none • Setting: one hospital • Sample size: ○ 513 patiënts enrolled in RCT with 2 arms → early closure for futility ○ 472 patiënts enrolled in RCT with 4 arms → 434 patiënts evaluable for efficacy • Duration: 12 months	• Eligibility criteria: ○ Stage IVB, recurrent, or persistent cervical cancer ○ Squamous, adenosquamous and adenocarcinoma ○ Confirmed by biopsy or CT/MRI if lesion > 3 cm ○ GOG performance status 0-1 ○ adequate hepatic, renal, and bone marrow function, no history of prior chemotherapy for metastatic disease	1. Intervention(s) • VC (n=108): vinorelbine 30mg/m^2 on days 1 and 8 plus cisplatin 50 mg/m^2 on day 1 every 3 weeks; • GC (n=112): gemcitabine 1,000 mg/m^2 on days 1 and 8 plus cisplatin 50 mg/m^2 on day 1 every 3 weeks; • TC (n=111): topotecan 0.75 mg/m^2 on days 1, 2, and 3 plus cisplatin 50 mg/m^2 on day 1 every 3 weeks. 2. Comparator(s) • PC (n=103): paclitaxel 135mg/m^2 over 24 hours plus cisplatin 50mg/m^2 on day 2 every 3 weeks;	*Median Overall survival* PC: 12.87 months (95%CI 10.02-16.76 months, unadjusted for multiplicity). VC: 9.99 months (95%CI 8.25-12.25 months) HR 1.15 (95%CI 0.79- 1.67) GC: 10.28 months (95%CI 7.62-11.60 months) HR 1.32 (95%CI 0.91-1.92) TC: 10.25 months (95%CI 8.61-11.66 months) HR 1.26 (95%CI 0.86-1.82) *Median progression-free survival* PC: 5.82 months (95%CI 4.53-7.59 months, unadjusted	*Toxicity* Comparable rates of adverse events between arms except for : Grade 3 leucopenia: 43% (GC), 63% (PC), 68% (VC), 71% (TC) ; p<0.0001 Grade 3 neutropenia: 42% (GC), 78% (PC), 78% (VC), 83% (TC); p<0.0001 Grade 3 thrombocytopenia: 28% (GC), 7% (PC), 7.5% (VC), 35% (TC); p<0.0001 Grade 3 anaemia : 34% (GC), 17% (PC), 29% (VC), 35% (TC); p=0.02	Level of evidence: B Results critical appraisal • No information about blinding • No information about comparability of treatments

Study ID	Method	Patiënt characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of study quality
				for multiplicity). VC: 3.98 months (95%CI 3.19-5.16 months) HR 1.36 (95%CI 0.97- 1.90) GC: 4.70 months (95%CI 3.58-5.59 months) HR 1.39 (95%CI 0.99-1.96) TC: 4.57 months (95%CI 3.71-5.75 months) HR 1.27 (95%CI 0.90-1.78)	Grade 3 infection: 9% (GC), 13% (PC), 7.5% (VC), 5% (TC); p=0.04 Grade 2 alopecia: 54% (PC), 9% (VC), 7% (GC) 26% (TC) (P<.0001). *Quality of life* No significant differences for QoL, neuropathy or pain between arms	
Mountzios 2009	• Design: RCT 2 arms • Setting: outpatiënt administration • Sample size: ○ 153 patiënts enrolled in RCT → 149 eligible patiënts • Median follow-up : 57.3 months (range 4–96 months)	• Eligibility criteria: histologically documented primary metastatic or recurrent carcinoma of the uterine cervix • No previous chemotherapy for advanced disease with the exception of prior cisplatin as radiation sensitizer • ECOG performance status 0-2 • Adequate hepatic, renal, and bone	1. Intervention ○ ITP : ifosfamide 1.5 g/m^2, daily, on days 1–3 + cisplatin 70 mg/m^2 on day 2 + paclitaxel 175 mg/m^2 on day 1 2. Comparator ○ IP : ifosfamide 1.5 g/m^2, daily, on days 1–3 + cisplatin 70 mg/m^2 on day 2	*Complete response* ITP: 25%; 95%CI 16%-36% IP: 11%; 95%CI 5%-20% P=0.033 *Partial response* ITP: 34%; 95%CI 24%-46% IP: 22%, 95%CI 13%-33% P = 0.105 *Overall response* ITP vs. IP: 59%	*Median PFS* ITP vs. IP: 7.9 (95%CI 6.1–9.8 months) vs. 6.3 months (95%CI 4.3–8.2 months), P = 0.023 *Median OS* ITP vs. IP: 15.4 (95%CI 8.6–22.3 months) vs.13.2 months (95%CI 10.9–15.5 months), P = 0.048	Level of evidence: B Results critical appraisal • No information about technique for randomisation • Blinding of outcome evaluation • ITT analysis • Phase II trial • No loss to follow-up

Study ID	Method	Patiënt characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of study quality
		marrow function • Exclusion criteria: brain metastases, active infection, serious concurrent medical illnesses and preexisting peripheral neuropathy • Characteristics of patiënts ○ Median age: 50-55 (range (28-75) ○ Majority: squamous cancer ○ FIGO Stage at diagnosis: I-IV		(95%CI 47%-70%) vs. 33% (95%CI 29%-45%) P = 0.002	HR for relapse or progression 0.70 (P = 0.046) HR for death 0.75 (P = 0.124) *Toxicity* Any grade stomatitis: 0% in IP vs. 10% in ITP P = 0.007 Any grade neurotoxicity: 11% in IP vs. 43% in ITP, P < 0.001	

Abbreviations: CI: confidence interval; CT/MRI: computed tomography/magnetic resonance imaging; ECOG: Eastern Cooperative Oncology Group; GOG: Gynecological Oncology Group; HR: hazard ratio; ITT: intent-to-treat; OS: overall survival; PFS: progression-free survival; RCT: randomized controlled trial

Vraag 6: Wat zijn de behandelingsmogelijkheden bij seksueel disfunctioneren na behandeling voor cervixcarcinoom

Guidelines

Reference	Search date	Recommendations	Evidence base	Level of evidence
SIGN 2008	2005	Women should be offered a vaginal stent or dilator to prevent post-radiotherapy vaginal complications	Case series	C
		Information about female sexual function should be offered to patiënts by a relevantly trained healthcare professional using a model of care that involves addressing motivational issues and teaching behavioural skills	RCT	A2
		Patiënts should be offered support sessions by a designated member of their care team, as soon as possible after treatment, which my include one or more of the following: - Relaxation - Personalised information about their disease and treatment - Emotional support and care	RCT of poor quality	B
		Topical oestrogens or benzydamine douches may be considered to alleviate postradiotherapy vaginal complications	RCT of poor quality	B

Systematic reviews

I Study ID	II Method	III Patiënt characteristics	IV Intervention(s)	V Results primary outcome	VI Results secondary outcome	VII Critical appraisal of review quality
Miles 2007	- Design: systematic review - Sources of funding: none mentioned - Search date: January 2007 - Searched databases: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, PsycINFO AMED, CINAHL National Health Service Research Register - Included study designs: RCT - Number of included studies: 1	- Eligibility criteria:patiënts undergoing interventions for sexual dysfunction following treatments for cancer	Vaginal oestrogen versus placebo	Sexual vaginal intercourse (self reported) (treatment N=26/44; control N=30/49) odds ratio(M-H, fixed, 95% CI) 0.91 [0.40, 2.10] Dyspareunia (self reported) (treatment N=20/26; control N=14/30) odds ratio (M-H, fixed, 95% CI) 3.81 [1.19, 12.16] Severe dyspareunia (self reported) (treatment N=0/26; control N=6/30) odds ratio (M-H, fixed, 95% CI) 0.07 [0.00, 1.33]		Level of evidence: B Most assessed interventions were for males treated for prostate carcinoma, only one study in women identified, same study as Flynn 2009 with a different presentation

I Study ID	II Method	III Patiënt characteristics	IV Intervention(s)	V Results primary outcome	VI Results secondary outcomes	VII Critical appraisal of review quality
Flynn 2009	- Design: systematic review - Sources of funding: none mentioned - Search date October 2008 - Searched databases: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, , and PsycINFO - Included study designs: RCT - Number of included studies: 5	- Eligibility criteria: primary malignancy of the female genital tract aged over 16 years - demonstrable psychosexual dysfunction or distress at entry to the study. These could include the DSM-IV diagnoses of Dyspareunia (302.76), Female Orgasmic Disorder (302.73), Female Sexual Arousal Disorder (302.72), Hypoactive Sexual Desire Disorder (302.71), Sexual Aversion Disorder (302.79) and Vaginismus (306.51)	Vaginal oestrogen versus placebo Brachytherapy 0.4Gy/Hr versus 0.8Gy/Hr Clinical nurse specialist versus standard care	Dyspareunia in all patiënts:(n = 93) odds ratio (M-H, fixed, 95% CI) 0.33 [0.11, 0.93] Dyspareunia in sexually active(n =56) odds ratio (M-H, fixed, 95% CI) 0.26 [0.08, 0.84] Dyspareunia in all patiënts (n=204) odds ratio (M-H, fixed, 95% CI) 0.37 [0.15, 0.93] Dyspareunia at 25 months post treatment (n=204) odds ratio (M-H, fixed, 95% CI) 0.39 [0.07, 2.05] Not sexually active (n=36) odds ratio (M-H, fixed, 95% CI) 0.63 [0.17, 2.36] Previously active, unsatisfactory now (n =20) odds ratio (M-H, fixed, 95% CI) 0.03 [0.00, 0.37]		Level of evidence: B One trial suggested a short-term benefit for the use of vaginal dienoestrol in women after pelvic radiotherapy (NNT = 4). Another trial suggested a short-term benefit for one regime of low dose-rate brachytherapy. Studies of a Clinical Nurse Specialist intervention, Psychoeducational Group Therapy and a Couple-Coping intervention did not show any significant benefit. All studies were of poor methodological quality. There was no convincing evidence to support the use of any intervention

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Miles 2010 Johnson 2010 (two reports of the same systematic review)	- Design: systematic review - Sources of funding: none mentioned - Search date: January 2007 - Searched databases: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, PsycINFO AMED, CINAHL National Health Service Research Register - Included study designs: RCT - Number of included studies: 1	- Eligibility criteria Patiënts undergoing interventions for sexual dysfunction following treatments for cancer	Psychoeducational support for the use of dilation Other non randomised studies	Sexual functional score after 3 months mean difference (IV, fixed, 95% CI) 0.04 [–0.03, 0.11] Sexual functional score after one year mean difference (IV, fixed, 95% CI) –0.01 [–0.07, 0.05] One comparative unmatched trial showed no advantage from inserting mitomycin C One retrospective report implied that dilation lowered stenosis rates, but the control group was not comparable	Case reports described vaginal fistulas or psychological morbidity A report of five women implied that stenosis can be treated by dilation many years after radiotherapy. One uncontrolled observational report involving 89 women showed that the median vaginal length 6–10 weeks after therapy was measured at 6 cm, but women tolerated a 9 cm measurer after 4 months of dilation experience	Level of evidence: C No RCT with a direct comparison was identified, only one small trial involving support identified Authors concluded that there was insufficient evidence supporting dilation