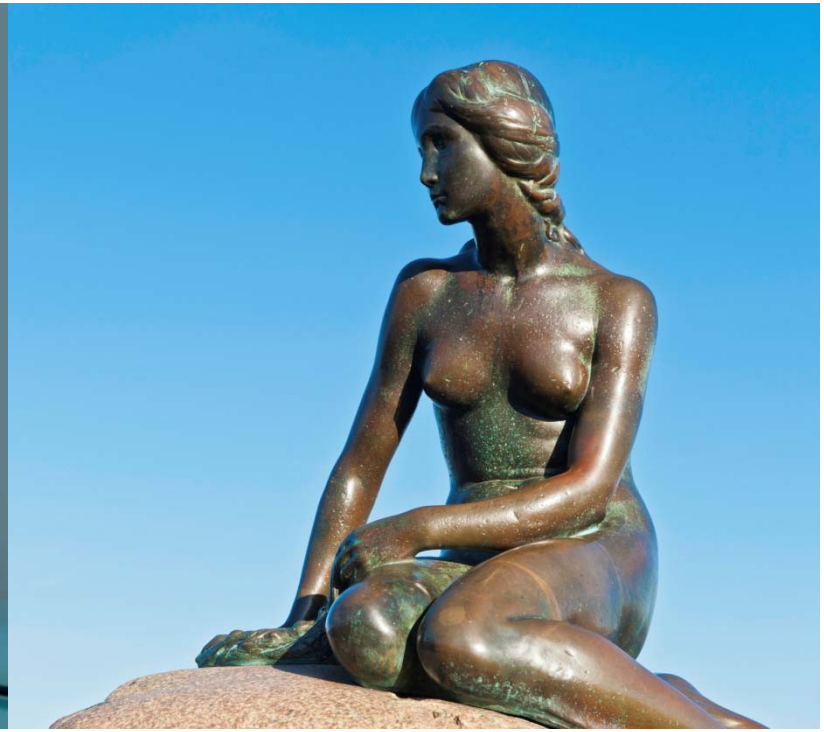
KCE REPORTS 168A

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Center

EEN NATIONALE PRAKTIJKRICHTLIJN VOOR DE AANPAK VAN CERVIXKANKER



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KCE REPORTS 168A
GOOD CLINICAL PRACTICE

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EEN NATIONALE PRAKTIJKRICHTLIJN VOOR DE AANPAK VAN CERVIXKANKER

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Titel: Een nationale praktijkrichtlijn voor de aanpak van cervixkanker

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Belangenconflict: Sigrid Stroobants heeft verklaard een samenwerkingsovereenkomst met Janssen Pharmaceutica te hebben gehad voor geneesmiddelontwikkeling op het vlak van neurowetenschappen (PET-tracers, preklinische beeldvorming). Philippe Simon heeft verklaard te hebben deelgenomen aan een Fase I en II studie over topische behandelingen voor cervixdysplasie.

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Disclaimer	• **De externe experten werden geraadpleegd over een (preliminaire) versie van het wetenschappelijke rapport. Hun opmerkingen werden tijdens vergaderingen besproken. Zij zijn geen coauteur van het wetenschappelijke rapport en gingen niet noodzakelijk akkoord met de inhoud ervan.** • **Vervolgens werd een (finale) versie aan de validatoren voorgelegd. De validatie van het rapport volgt uit een consensus of een meerderheidsstem tussen de validatoren. Zij zijn geen coauteur van het wetenschappelijke rapport en gingen niet noodzakelijk alle drie akkoord met de inhoud ervan.** • **Tot slot werd dit rapport unaniem goedgekeurd door de Raad van Bestuur.** • **Alleen het KCE is verantwoordelijk voor de eventuele resterende vergissingen of onvolledigheden alsook voor de aanbevelingen aan de overheid.**

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VOORWOORD

Baarmoederhalskanker is de eerste kanker waartegen een routine-vaccinatie mogelijk is, wat de hoop doet rijzen dat – op lange termijn – het probleem quasi 'uitgeroeid' zal zijn. Jammer genoeg zijn er vele redenen waarom dit nog lang geen realiteit zal zijn. En tot zolang moeten de vrouwen die door cervixkanker getroffen zijn behandeld en opgevolgd worden. Cervixkanker is niet zo heel frequent, maar toch zullen jaarlijks een paar honderd vrouwen overlijden ten gevolge van deze kanker.

Een ziekte die de baarmoeder treft, raakt ook aan de kern van het vrouw-zijn. Goed klinisch handelen moet dus ook aandacht hebben voor het seksueel functioneren, voor fertiliteit en zwangerschap, en dus komen ook deze aspecten in de richtlijn aan bod.

Zoals de vorige kankerrichtlijnen van het KCE kwam ook deze tot stand in samenwerking met het College voor Oncologie. Wat bijzonder is aan deze richtlijn, is dat de concrete productie ervan gebeurde in partnership met het Integraal Kankercentrum Nederland (IKNL). Deze samenwerking verliep niet alleen zeer vlot en aangenaam, maar bovendien zorgde de intense wisselwerking tussen onze beide organisaties voor een kwaliteitswinst, zowel op het vlak van de gehanteerde methodieken, als voor het eindprodukt. Een win-win situatie die zeker voor herhaling vatbaar is. Maar hopelijk is de grootste winnaar van deze oefening de patiënte die een meer optimale behandeling zal hebben gekregen

Jean-Pierre CLOSON
Adjunct Algemeen Directeur

Raf MERTENS
Algemeen Directeur

SAMENVATTING

INLEIDING

Deze studie wil een praktijkrichtlijn (CPG) voor cervixkanker opstellen. De onderzoekskwesties gaan over een brede waaier van onderwerpen: diagnose, stadiëring, behandeling, ondersteunende therapie en follow-up. Ook de behandeling van cervicale intra-epitheliale neoplasie (CIN) komt aan bod. Deze CPG gaat niet over de screening van cervixkanker.

Deze richtlijn werd opgesteld in samenwerking met het Integraal Kankercentrum Nederland. Deze richtlijn is bedoeld voor alle zorgverleners die bij de zorg voor deze patiënten betrokken zijn.

METHODOLOGIE

Voor de ontwikkeling van deze richtlijn werd de ADAPTE-methodologie gebruikt, waarbij (inter)nationale praktijkrichtlijnen aan de Belgische context werden aangepast. Bestaande (inter)nationale richtlijnen werden gezocht in Medline, National Guideline Clearinghouse en websites van richtlijnorganisaties en oncologische organisaties. De 25 gevonden richtlijnen werden door middel van het AGREE-instrument beoordeeld op hun kwaliteit door twee onafhankelijke reviewers en al dan niet geselecteerd op basis van een algemeen kwaliteitsoordeel. Vervolgens werden de 5 geselecteerde richtlijnen voor elke klinische vraag geüpdatet, door bijkomend bewijsmateriaal te zoeken in Medline, EMBASE en de Cochrane Database of Systematic Reviews. De meest recente zoekstrategieën werden in mei 2011 uitgevoerd. Een niveau van bewijskracht werd toegekend aan elke originele aanbeveling en bijkomende studie door gebruik te maken van het GRADE-systeem (tabel 1).

Op basis van het gevonden bewijsmateriaal stelde de multidisciplinaire richtlijnontwikkelingsgroep (i.e. auteurs van deze richtlijn) de aanbevelingen op. Een review van deze aanbevelingen werd uitgevoerd door externe experts door middel van een formele procedure. Belangenconflicten werden genoteerd.

Tabel 1. GRADE niveaus van bewijskracht en graden van aanbeveling.

Graad	Beschrijving
1A	Sterke aanbeveling op basis van een hoog niveau van bewijskracht
1B	Sterke aanbeveling op basis van een matig niveau van bewijskracht
1C	Sterke aanbeveling op basis van een laag of zeer laag niveau van bewijskracht
2A	Zwakke aanbeveling op basis van een hoog niveau van bewijskracht
2B	Zwakke aanbeveling op basis van een matig niveau van bewijskracht
2C	Zwakke aanbeveling op basis van een laag of zeer laag niveau van bewijskracht

DEFINITIEVE AANBEVELINGEN

De details van de richtlijn bevinden zich in het wetenschappelijk rapport na deze samenvatting. De tabel bevat alle aanbevelingen geordend per hoofdstuk.

Behandeling van hooggradige CIN

Aanbevelingen	Graad
Cytologische cervicale afwijkingen worden ingedeeld als laaggradige of hooggradige squameuze intra-epitheliale laesies. De resultaten van een cervixbiopsie worden gerapporteerd volgens de CIN-classificatie.	1C
Vrouwen met door biopsie bewezen, hooggradige CIN (CIN2, CIN3, cervicale glandulaire intra-epitheliale neoplasie) vereisen behandeling, oplettend afwachten kan niet overwogen worden.	1C
De behandeling van zwangere vrouwen met hooggradige CIN kan worden uitgesteld tot na de bevalling.	1C
Zowel ablatieve therapie (bv. laserablatie, cryotherapie, koude coagulatie, radicale diathermie) als excisionele therapie (bv. lisexcisie van de transformatiezone, chirurgische conisatie (cold knife)) zijn aanbevolen behandelingsopties voor hooggradige CIN.	1B
In de meeste gevallen verdienen excisionele technieken de voorkeur boven ablatie omdat ze histologische evaluatie van de transformatiezone mogelijk maken.	1C
De omvang en vorm van het excisiespecimen moet bepaald worden door aflijning van de laesie door middel van colposcopie.	1C
Het risico op ongewenste obstetrische uitkomsten bij excisionele therapie moet afgewogen worden tegen een hoger risico op recidief en de moeilijkheden om te evalueren of de laesie volledig werd verwijderd wanneer ablatieve therapieën worden gebruikt. Bij vrouwen die vruchtbaar willen blijven, kan ablatie overwogen worden als de laesie duidelijk afgebakend is door middel van colposcopie, niet alle 4 kwadranten betrokken zijn en de ingreep therapeutisch is.	2B
Ablatieve therapie kan enkel overwogen worden als aan een aantal bijkomende voorwaarden is voldaan: • De volledige transformatiezone moet zichtbaar zijn; • Er moeten één of meerdere biopsieën genomen worden van de zone(s) die bij colposcopisch onderzoek de meest ernstige verandering toont/tonen; • Het resultaat van de biopsie(ën) moet beschikbaar zijn voordat de destructieve therapie plaatsvindt; • Cryotherapie mag niet worden voorgesteld aan vrouwen met grote laesies die meer dan 75% van de ectocervix in beslag nemen, zich naar de vaginawand uitstrekken of zich tot meer dan 2 mm buiten de cryoprobe uitstrekken. Dit geldt ook voor koude coagulatie, maar niet voor radicale diathermie; • Bij de cytologie, colposcopie of biopsie mogen geen aanwijzingen voor invasieve ziekte gevonden worden; • Het pap uitstrijkje mag geen glandulaire atypische cellen bevatten; • De destructieve therapie moet door een ervaren colposcopist worden uitgevoerd onder colposcopische controle; • Adequate follow-up is noodzakelijk (zie infra).	1C
Vrouwen moeten ingelicht worden over de mogelijke ongewenste obstetrische uitkomsten van excisionele therapie.	1B

Aanbevelingen	Graad
Aan vrouwen die behandeld werden voor hooggradige ziekte kan follow-up cytologie en een test op humaan papillomavirus (HPV) 6 maanden na de therapeutische ingreep worden voorgesteld. Als de resultaten negatief zijn, kan een bijkomende bevestigende cytologie na 1 jaar worden voorgesteld alvorens terug te keren naar een routinescreening volgens het gebruikelijke interval.	1C

Aanpak van invasieve cervixkanker

Diagnose en stadiëring van invasieve cervixkanker

De klinische stadiëring van cervixkanker is gebaseerd op het FIGO-stadiëringssysteem. Klinisch onderzoek en beeldvorming worden gebruikt om de categorieën T(umour), N(odes) en M(etastasis) te beoordelen. De details van het FIGO-stadiëringssysteem staan in het wetenschappelijk rapport.

Aanbevelingen	**Graad**
Alle patiënten met een zichtbaar, door biopsie bewezen cervixcarcinoom moeten een MRI-scan (Magnetic Resonance Imaging) van minstens het bekken ondergaan.	1C
Een CT-scan (Computed Tomography) met gebruikmaking van een contrastmiddel moet als alternatief voor MRI overwogen worden bij patiënten met een medische contra-indicatie voor MRI.	1C
Een PET/CT-scan (Positron Emission Tomography/Computed Tomography) wordt aanbevolen bij tumoren van FIGO-stadium IB1 met verdachte bekkenlymfeklieren en bij grote tumoren van het FIGO-stadium IB2 en hoger.	1C
Schildwachtklierbiopsie zonder lymfadenectomie wordt niet aanbevolen bij patiënten met cervixkanker in de gewone klinische praktijk.	1C
Tumormarkers kunnen niet gebruikt worden voor de diagnose en stadiëring van cervixkanker. Ze (CA-125, Squamous Cell Carcinoma Antigen) kunnen echter gebruikt worden voor de monitoring van de respons op de behandeling. Daarom kan overwogen worden om de aanvangswaarde vóór de behandeling te meten.	2C
De behandelingsopties voor patiënten met invasieve cervixkanker moeten tijdens de meeting van het multidisciplinaire team besproken worden.	1C

Behandeling van cervixkanker FIGO-stadium IA

Aanbevelingen	**Graad**
Bi patiënten met cervixkanker FIGO-stadium IA1 en vrije randen van het conisatiespecimen is geen verdere behandeling noodzakelijk.	1C
Bij patiënten met een preliminaire diagnose van cervixkanker FIGO-stadium IA1 en positieve randen van het conisatiespecimen zijn reconisatie, totale hysterectomie of uterovaginale brachytherapie opties als het FIGO-stadium IA1 histologisch bevestigd is.	2C
Op basis van het beschikbare bewijsmateriaal blijkt parametriale aantasting zelden voor te komen bij patiënten met cervixkanker FIGO-stadium IA2. Derhalve wordt een eenvoudige hysterectomie met systematische lymfadenectomie van minstens 20 lymfeklieren als voldoende beschouwd.	2C
Bij patiënten met cervixkanker FIGO-stadium IA2 die medisch niet-opereerbaar zijn en geen kinderen wensen, kunnen radicale externe radiotherapie en brachytherapie overwogen worden.	2C

Aanbevelingen	Graad
Wanneer de preoperatieve stadiëring uitwijst dat postoperatieve behandeling noodzakelijk zal zijn, wordt gelijktijdige cisplatine-gebaseerde chemoradiotherapie aanbevolen in plaats van een chirurgische ingreep.	1C

Behandeling van niet-metastatische cervixkanker

Stadium IB1 en IIA1

Aanbevelingen	Graad
Bij patiënten met een cervixcarcinoom klinisch stadium IA2, IB, of IIA en risicofactoren voor een recidief (positieve bekkenlymfeklieren en/of positieve randen en/of microscopische aantasting van het parametrium) die radicale hysterectomie en bekkenlymfadenectomie hebben ondergaan, moet adjuvante behandeling met gelijktijdige platinum-gebaseerde chemoradiotherapie overwogen worden.	1B
Wanneer de preoperatieve stadiëring uitwijst dat postoperatieve behandeling noodzakelijk zal zijn, wordt gelijktijdige cisplatine-gebaseerde chemoradiotherapie aanbevolen in plaats van een chirurgische ingreep.	1C

Stadium IB2, IIA2, IIB, IIIA, IIIB en IVA

Aanbevelingen	Graad
Bij patiënten met cervixkanker FIGO-stadium IB-IVA die geschikt worden bevonden voor behandeling met radicale radiotherapie wordt gelijktijdige platinum-gebaseerde chemoradiotherapie aanbevolen, indien de patiënt gezond genoeg is.	1B
De balans van risico's (acute hematologische en gastro-intestinale toxiciteit) en voordelen (verbeterde progressievrije en totale overleving) moet met de patiënt besproken worden voordat chemoradiotherapie wordt toegediend ter behandeling van cervixkanker.	1C
Bij patiënten met cervixkanker FIGO-stadium IB-IIIB moet brachytherapie overwogen worden als een onderdeel van radicale radiotherapie of chemoradiotherapie.	1C
Men wacht op bewijsmateriaal van het EORTC 55994 onderzoek om de plaats van neoadjuvante chemotherapie gevolgd door een chirurgische ingreep in vergelijking met gelijktijdige chemoradiotherapie opnieuw te evalueren voor de behandeling van vrouwen met cervixkanker FIGO-stadium IB2, IIA>4 cm of IIB.	-
Als neoadjuvante chemotherapie voorafgaand aan een chirurgische ingreep wordt gekozen voor de behandeling van patiënten met cervixkanker FIGO-stadium IB2, IIA of IIB, dan worden dosisintensieve (cisplatine ≥ 25 mg/m2) behandelingsschema's met een korte cyclus (≤ 14 dagen) aanbevolen.	1B

Behandeling van metastatische en recidiverende ziekte

Aanbevelingen	Graad
Alle recidieven moeten tijdens de multidisciplinaire oncologische meeting besproken worden.	1C
Bij patiënten met een locoregionaal recidief in het bekken dat beperkt is in omvang en de omliggende structuren niet invadeert, en die geen bekkenradiotherapie als onderdeel van hun initiële behandeling kregen, kan resectie of (chemo)radiotherapie overwogen worden.	2C
Bij patiënten met een recidiverend cervixcarcinoom dat beperkt is tot het centrale bekken na eerdere (chemo)radiotherapie, kan bekkenexenteratie overwogen worden. De selectie van opereerbare patiënten kan geoptimaliseerd worden met een preoperatieve PET- of PET/CT-scan van het hele lichaam, als aanvulling op de MRI- en CT-scan die de recidiverende of persisterende ziekte bevestigde.	1C
Aan patiënten met cervixkanker FIGO-stadium IVB of een recidiverend cervixcarcinoom die niet in aanmerking komen voor curatieve (chemo)radiotherapie of chirurgie, zou, na bespreking van de relatieve voordelen en risico's, palliatieve chemotherapie moeten worden gegeven met: • cisplatine 50 mg/m^2 op dag 1 plus paclitaxel 135 mg/m^2 om de 3 weken, of • cisplatine 50 mg/m^2 op dag 1 plus topotecan 0,75 mg/m^2 op de dagen 1 tot 3 om de 3 weken	1B
Tripletcombinaties en gerichte therapieën moeten geëvalueerd worden in grootschalige fase III gerandomiseerde klinische studies.	1C

Fertiliteitssparende behandeling

Aanbevelingen	Graad
Bij vrouwen die vruchtbaar willen blijven, kunnen radicale trachelectomie en pelviene lymfeklierdissectie overwogen worden op voorwaarde dat de diameter van de tumor kleiner is dan 2 cm.	1C
Een alternatieve experimentele behandeling zou kunnen bestaan uit neoadjuvante chemotherapie, pelviene lymfeklierdissectie en conisatie.	2C
Chirurgische conisatie (cold knife) of lisexcisie van de transformatiezone is een geschikte behandeling voor vrouwen met IA1 ziekte die vruchtbaar willen blijven. In geval van invasie van de lymfovasculaire ruimte moet pelviene lymfeklierdissectie overwogen worden.	2C
Chirurgische conisatie (cold knife) of lisexcisie van de transformatiezone in combinatie met pelviene lymfeklierdissectie kan een geschikte behandeling zijn voor vrouwen met ziekte in een vroeg stadium en geen invasie van de lymfovasculaire ruimte (FIGO-stadium IA2 en microscopisch IB1) die vruchtbaar willen blijven.	2C
Vrouwen die vruchtbaar willen blijven, moeten ingelicht worden over de mogelijke bijkomende risico's op recidief en over het experimentele karakter van trachelectomie.	1C

Behandeling van invasieve kanker tijdens de zwangerschap

Aanbevelingen	Graad
Wanneer cervixkanker tijdens het eerste trimester van een gewenste zwangerschap wordt gediagnosticeerd, wordt een conserverende aanpak voorgesteld om het tweede trimester te bereiken.	1C
De behandeling van cervixkanker tijdens het tweede trimester hangt af van het stadium: • Ziekte in stadium IA1 wordt behandeld met een platte exconisatie; • Voor stadium IA2-1B1 kleiner dan 2 cm kan neoadjuvante chemotherapie gevolgd door conserverende chirurgie (bv. trachelectomie) overwogen worden als er geen lymfekliermetastasen aanwezig zijn; • Voor stadium IB1 2-4 cm is lymfadenectomie verplicht, maar kan na neoadjuvante chemotherapie worden uitgevoerd. De mogelijkheid om de zwangerschap te behouden hangt voornamelijk af van de nodale status en de respons op de neoadjuvante chemotherapie; • Voor hogere stadia wordt fertiliteitssparende behandeling niet aanbevolen.	1C
Tijdens het derde trimester wordt gewacht tot de foetus rijp is en wordt een keizersnede, gevolgd door een standaardbehandeling, voorgesteld.	1C

Seksuele morbiditeit na behandeling voor cervixkanker

Aanbevelingen	Graad
Een gezondheidswerker die hiervoor werd opgeleid moet aan de patiënten informatie geven over de vrouwelijke seksuele functie na de behandeling.	2C
Patiënten kunnen, zo snel mogelijk na de behandeling, hulpsessies aangeboden krijgen door een aangewezen lid van hun verzorgingsteam.	2C
Topische oestrogenen kunnen overwogen worden om vaginale complicaties van de (chemo)radiotherapie te verlichten.	2C
Vaginale dilatatie kan overwogen worden bij patiënten die met (chemo)radiotherapie werden behandeld.	2C

Follow-up na behandeling voor cervixkanker

Aanbevelingen	Graad
Een redelijke follow-upstrategie omvat follow-upbezoeken om de drie tot vier maanden in de eerste twee jaar, en om de zes tot twaalf maanden van jaar 3 tot jaar 5.	2C
De anamnese moet worden afgenomen en een klinisch onderzoek (inclusief een speculumonderzoek met een bimanueel en bekken/rectaal onderzoek) moet plaatsvinden tijdens de follow-up van patiënten met cervixkanker om symptomatische en asymptomatische recidieven op te sporen.	1C
Cervixcytologie of uitstrijkjes van de fornix kunnen overwogen worden om een asymptomatisch recidief van cervixkanker op te sporen in gevallen waarin curatieve behandeling van een centraal recidief een optie is en niet eerder behandeld werd met radiotherapie.	2C
Beeldvormingsonderzoeken (CT, MRI, PET, PET/CT-scan) als onderdeel van routine follow-up bij asymptomatische patiënten worden niet aanbevolen.	1C
Bepaling van het Squamous Cell Carcinoma Antigen (SCCA) kan tijdens de follow-up overwogen worden.	1C
MRI-scan van minstens het bekken moet in eerste instantie overwogen worden om bij symptomatische patiënten een potentieel klinisch recidief ter hoogte van het bekken te evalueren.	2C
Een PET/CT-scan moet overwogen worden bij alle patiënten bij wie recidiverende of persisterende ziekte werd aangetoond tijdens een klinisch onderzoek of MRI-scan en bij wie reddingstherapie overwogen wordt.	1C

AANBEVELINGEN[a]

IMPLEMENTATIE

- **De implementatie van deze richtlijn zal worden gestuurd door het College voor Oncologie. Er zal een online implementatietool worden ontwikkeld die vergelijkbaar is met de tools die bij de vorige richtlijnen werden uitgewerkt.**

KWALITEITSCONTROLE

- **Op basis van deze richtlijn zullen, in samenwerking met de Stichting Kankerregister, kwaliteitsindicatoren ontwikkeld moeten worden om de implementatie ervan te evalueren en feedback aan de betrokken gezondheidszorgverleners te geven. Deze kwaliteitsindicatoren zullen in een integratief kwaliteitssysteem moeten worden ingebed, zoals in het KCE rapport 152 wordt aanbevolen.**

UPDATE VAN DE RICHTLIJN

- **Gelet op het veranderend bewijsmateriaal en op basis van een pre-evaluatie van de literatuur zou deze richtlijn volledig geüpdatet moeten zijn in 5 jaar. Ondertussen zal op de website van het College voor Oncologie vermeld worden wanneer er belangrijk bewijsmateriaal beschikbaar wordt.**

[a] Alleen het KCE is verantwoordelijk voor de aanbevelingen aan de overheid

SCIENTIFIC REPORT

INHOUDSTAFEL

ABBREVIATIONS

ABBREVIATION	DEFINITION
95%CI	95% confidence interval
CCO	Cancer Care Ontario
CEA	Carcinoembryonic antigen
CG	Control group
CGIN	Cervical glandular intraepithelial neoplasia
CIN	Cervical intraepithelial neoplasia
CPG	Clinical practice guideline
CRT	Chemoradiotherapy
CT	Computed Tomography
EBRT	External Beam Radiotherapy
ECOG	The Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
FIGO	International Federation of Gynaecology and Obstetrics
Gy	Gray
HDR	High dose rate
HPV	Human papillomavirus
HR	Hazard Ratio
IG	Intervention group
IKNL	Integrale Kankercentra Nederland
ICBT	Intracavitary brachytherapy
ICER	Incremental cost-effectiveness ratio
IPD	Individual patient data
ITT	Intention-to-treat
LACC	Locally advanced cervical cancer
LARVH	Laparoscopic-assisted radical vaginal hysterectomy
LARVT	Laparoscopic-assisted radical vaginal trachelectomy
LDR	Low dose rate

LEEP	Loop electrosurgical excision procedure
LND	Lymph node dissection
LLETZ	Large Loop Excision of the Transformation Zone
LVSI	Lymphovascular space invasion
MA	Meta-analysis
MD	Mean Difference
MRI	Magnetic Resonance Imaging
NACCCMA	Neoadjuvant Chemotherapy for Cervical Cancer Metaanalysis Collaboration
NACT	Neoadjuvant chemotherapy
NPV	Negative Predictive Value
OR	Odds ratio
OS	Overall survival
PET	Positron Emission Tomography
PFS	Progression-free survival
PLND	Pelvic Lymph node dissection
PPV	Positive Predictive Value
QoL	Quality of Life
RCT	Randomised Controlled Trial
RHT	Radiotherapy and hyperthermia
RR	Relative Risk
RT	Radiotherapy
RVT	Radical vaginal trachelectomy
SCCA	Squamous Cell Carcinoma Antigen
SIGN	Scottish Intercollegiate Guidelines Network
SR	Systematic review
WHO	World Health Organization

1. INTRODUCTION

1.1. Scope

This study aims to develop a clinical practice guideline (CPG) on cervical cancer. The CPG will cover a broad range of topics: diagnosis, staging, treatment, supportive therapy, and follow-up. Treatment of Cervical Intraepithelial Neoplasia (CIN) will also be addressed. The CPG is intended to be used by all care providers involved in the care for these patients. Importantly, the CPG will not address screening for cervical cancer.

1.2. Epidemiology

In Belgium, cervical cancer is the 8th most frequent tumour in females (N=643 in 2008), with an age-standardised rate of 8.2/100 000 person years [1]. The mean age at diagnosis is 54 years. In 2008, 186 women died of cervical cancer, translating in an age-standardised rate of 1.8/100 000 person years. In comparison, the age standardised mortality rate in the Netherlands was 1.6/100 000 person years in 2008 (www.ikcnet.nl, accessed on August 2nd 2011).

National 5-year survival data are not yet available for Belgium. For the period 1997-2001, the Flemish Cancer Registry Network reported a 5-year observed survival of 65% and a relative survival of 68% for the Flemish Region [2]. Table 1 provides an overview of the 5-year relative survival in other countries.

Table 1. Cervical cancer 5-year relative survival in selected countries.

Country	Period	5-year relative survival
Denmark	1999-2003	64%
Finland	1999-2003	68%
France	1994-1999	66%
Norway	1999-2003	70%
Sweden	1999-2003	66%
The Netherlands	2002-2004	67%
US	2001-2007	69%

2. METHODOLOGY

2.1. General approach

The present CPG was developed by adapting (inter)national CPGs to the Belgian context (www.kce.fgov.be). This approach was recently structured in a formal methodology by the ADAPTE group, an international group of guideline developers and researchers [3]. The ADAPTE methodology generally consists of three major phases (www.adapte.org):

1. Set-up Phase: Outlines the necessary tasks to be completed prior to beginning the adaptation process (e.g., identifying necessary skills and resources).
2. Adaptation Phase: Assists guideline developers in moving from selection of a topic to identification of specific clinical questions; searching for and retrieving guidelines; assessing the consistency of the evidence therein, their quality, currency, content and applicability; decision making around adaptation; and preparing the draft adapted guideline.
3. Finalization Phase: Guides guideline developers through getting feedback on the document from stakeholders who will be impacted by the guideline, consulting with the source developers of guidelines used in the adaptation process, establishing a process for review and updating of the adapted guideline and the process of creating a final document.

If necessary, included guidelines were updated with more recent evidence.

2.2. Clinical questions

The CPG will address the following clinical topics for cervical cancer: diagnosis, staging, neoadjuvant treatment, surgery, adjuvant treatment, follow-up, palliative treatment, supportive care and recurrent disease. More specifically, the following research questions will be answered:

1. Which diagnostic and staging techniques (tumour markers, CT, MRI, PET, sentinel lymph node mapping, histopathology) are needed for patients with invasive cervical cancer?
2. What are the best treatment options for patients with CIN?

3. What are the best treatment options (conisation, surgery, chemotherapy, radiotherapy, brachytherapy) for early stages of invasive cervical cancer (stage IA)?
4. Should postoperative radiotherapy rather than chemoradiotherapy be considered in patients with invasive cervical cancer and all FIGO stages?
5. What is the place of neoadjuvant chemotherapy versus primary chemoradiation?
6. A. What are the treatment options for invasive cervical cancer during pregnancy? B. What is the place of fertility-sparing treatment for cervical cancer?
7. How should sexual morbidity be handled after treatment for cervical cancer?
8. How should the follow-up of patients treated for cervical cancer be organised?
9. What are the treatment options for metastatic or recurrent cervical cancer?

In general, technical aspects of interventions were not addressed, e.g. mode of surgery (e.g. open surgery vs. laparoscopy vs. robot surgery) or radiotherapy schedules. The question about fertility-sparing treatment is an exception to this general rule.

Volume-outcome associations were not addressed in this guideline.

2.3. International collaboration

IKNL updated its 2004 guideline on cervical cancer, which was not entirely evidence-based. The update focused on 4 research questions, while KCE developed a full guideline. The 4 research questions of IKNL were fully in common with those of KCE (question 1, 4, 6B and 8), and were divided between the 2 organisations.

Aspects of the collaboration between IKNL and KCE were:

1. Scope: the mutual development of a clinical practice guideline for cervical cancer only concerned the search for evidence (search strategy + selection), quality appraisal, evidence tables and the writing of the evidence report. The formulation of recommendations was the responsibility of the two organisations separately.
2. Form of cooperation: Two research questions were elaborated by IKNL (question 1 and 8), while the two other common research questions (4 and 6B) were elaborated by KCE (in addition to the research questions that are not in common).

Cross-validation was done after each of the following steps:

- Development of the search strategy
- Selection of the literature
- Quality appraisal + evidence tables
- Evidence report

2.4. Literature searches

2.4.1. Search strategy

To identify published CPGs on cervical cancer, OVID Medline, the National Guideline Clearinghouse and specific websites (Table 2) were searched. Both national and international CPGs were searched. A language (English, Dutch, French) and date restriction (2000 – 2010) were used. CPGs without references were excluded, as were CPGs without clear recommendations.

Table 2. Searched guideline websites and websites of oncologic organisations.

Alberta Heritage Foundation For Medical Research (AHFMR)	**http://www.ahfmr.ab.ca/**
American Society of Clinical Oncology (ASCO)	**http://www.asco.org/**
American Society of Clinical Oncology (ASCO)	**http://www.asco.org/**
American College of Surgeons (ACS)	**http://www.facs.org/cancer/coc/**
Cancer Care Ontario	**http://www.cancercare.on.ca/english/home/**
CMA Infobase	**http://mdm.ca/cpgsnew/cpgs/index.asp**

Guidelines International Network (GIN)	http://www.g-i-n.net/
National Comprehensive Cancer Network (NCCN)	http://www.nccn.org/
National Cancer Institute	http://www.cancer.gov/
Haute Autorité de Santé (HAS)	http://bfes.has-sante.fr/HTML/indexBFES_HAS.html
BC Cancer Agency	http://www.bccancer.bc.ca/default.htm
Institute for Clinical Systems Improvement (ICSI)	http://www.icsi.org/index.asp
National Health and Medical Research Council (NHMRC)	http://www.nhmrc.gov.au/
Scottish Intercollegiate Guidelines Network (SIGN)	http://www.sign.ac.uk/
New Zealand Guidelines Group (NZGG)	http://www.nzgg.org.nz/
Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC)	http://www.fnclcc.fr/sor/structure/index-sorspecialistes.html
National Institute for Health and Clinical Excellence (NICE)	http://www.nice.org.uk/

The search for peer-reviewed articles included a search in OVID Medline, EMBASE and the Cochrane Database of Systematic Reviews (see appendix for search strings). As for the CPGs, the search was limited to articles published in English, French and Dutch. For most questions, the search was focused on systematic reviews and randomized controlled trials (RCT). However, when these study designs were unavailable, the search was expanded to observational studies. For diagnostic questions, the search also included diagnostic accuracy studies. In general, systematic reviews not reporting the search strategy and/or the quality appraisal of the included studies were excluded.

All searches were run between December 2010 and May 2011.

The identified studies were selected based on title and abstract. For all eligible studies, the full-text was retrieved. In case no full-text was available, the study was not taken into account for the final recommendations.

2.4.2. Quality appraisal

2.4.2.1. Clinical practice guidelines

The AGREE instrument [4] was used to evaluate the methodological quality of the identified CPGs. Each of the 25 identified CPGs was scored by two independent researchers (JV and JR) and discussed in case of disagreement (see appendix for an overview of the scores). Based on an overall assessment – taking into account the AGREE scores – 5 high-quality CPGs were finally selected. In general, CPGs with an aggregated domain score of 66% or less on the domain 'Rigour of development' were not included (see appendix 3).

It should be noted that, in the absence of good CPGs on CIN, the guidelines of the NHMRC [5] and IARC [6] were used as a basis despite their poor methodological quality.

2.4.2.2. Peer-reviewed articles

The quality of the retrieved systematic reviews, RCTs and observational studies was assessed using the checklists of the Dutch Cochrane Centre (www.cochrane.nl). All critical appraisals were done by a single KCE expert.

The studies selected for the 4 research questions being subject of the collaboration between IKNL and KCE were appraised with critical appraisal

checklists developed during the CoCanCPG project, a European project involving several oncology institutions and guideline-developing organisations (www.cocancpg.eu) (see appendix 4).

2.5. Data extraction and summary

For each included CPG the following data were extracted: search date and publication year, searched databases, availability of evidence tables, recommendations and referenced evidence.

For each systematic review, the search date, publication year, included studies and main results were extracted. For primary studies, the following data were extracted: publication year, study population, study intervention, and outcomes.

For each clinical question, the recommendations from the identified CPGs and the additional evidence were summarized in evidence tables. A level of evidence was assigned to each recommendation and additional study using the GRADE system (see appendix 1).

Evidence tables are provided in appendix 6.

2.6. Formulation of recommendations

Based on the retrieved evidence, a first draft of recommendations was prepared by a KCE expert (JV, JR, SS). This draft together with the evidence tables were circulated to the guideline development group (Table 3) prior to each face-to-face meeting. The guideline development group met on four occasions (January 31st, March 28th, May 9th and June 27th 2011) to discuss the first draft. Recommendations were changed if important evidence supported this change. Based on the discussion meetings a second draft of recommendations was prepared.

A grade of recommendation was assigned to each recommendation using the GRADE system (see appendix 1). The second draft was once more circulated to the guideline development group for final approval.

Table 3. Composition of guideline development group.

Expert	Field of expertise
Claire Bourgain	Pathology
Jacques De Grève	Medical Oncology
Frédéric Kridelka	Gynaecology
Pierre Scalliet	Radiotherapy
Philippe Simon	Gynaecology
Sigrid Stroobants	Nuclear Medicine
Peter Van Dam	Gynaecology
Erik Van Limbergen	Radiotherapy
Ignace Vergote (president)	Gynaecology
Geert Villeirs	Radiology

2.7. External expert meeting

Several professional associations were asked by the College of Oncology to appoint two representatives to act as an external reviewer of the draft guideline. The consulted associations are provided in Table 4. Not all associations appointed a representative.

External experts received the recommendations 3 weeks prior to the expert meeting. As a preparation of the meeting all invited experts were asked to score each recommendation on a 5-point Likert-scale to indicate their agreement with the recommendation, with a score of '1' indicating 'completely disagree', '2' indicating 'somewhat disagree', '3' indicating 'unsure', '4' indicating 'somewhat agree', and '5' indicating 'completely agree' (the experts were also able to answer 'not applicable' in case they were not familiar with the underlying evidence). In case an expert disagreed with the recommendation (score '1' or '2'), (s)he was asked to provide appropriate evidence. All scores were then anonymized and summarized into a median score, minimum score, maximum score and % of 'agree'-scores (score '4' and '5') to allow a targeted discussion (see appendix 5). The recommendations were then discussed during a face-to-face meeting on September 5th 2011. Based on this discussion a final draft of the recommendations was prepared. In appendix 5, an overview is

provided of how the comments of the external experts were taken into account.

Table 4. Consulted professional associations for peer review.

- Belgian Society of Pathology
- Belgian Society of Medical Oncology
- Belgische Vereniging voor Radiotherapie-Oncologie - Association Belge de Radiothérapie-Oncologie
- Royal Belgian Radiological Society
- Belgian Association of Clinical Cytology
- Domus Medica
- Société Scientifique de Médecine Générale
- Vlaamse Vereniging voor Obstetrie en Gynaecologie
- Groupement des Gynécologues Obstétriciens de Langue Française de Belgique

3. FINAL RECOMMENDATIONS

3.1. Treatment of high-grade cin

3.1.1. Treatment of CIN2/3

Cytological cervical abnormalities are classified into low-grade (LSIL) and high-grade squamous intraepithelial lesions (HSIL). The results of cervical biopsies are reported according to the CIN classification. A histological diagnosis of cervical intraepithelial neoplasia (CIN) indicates the presence of a lesion which, if untreated, may progress to invasive cancer.

The lowest grade is CIN1 (low-grade CIN) which may represent no more than changes due to human papillomavirus (HPV). On the other hand CIN2-3 (high-grade CIN) definitely has the potential to progress to invasive cancer.

3.1.1.1. Existing guidelines

According to the European guideline [6], women with high-grade CIN require treatment, while observational follow-up is not an option. The natural history of histologically confirmed high-grade CIN is only documented by a few small case series conducted in the fifties and sixties, since these lesions are almost always treated and contemporary studies on this issue would be unethical. The pooled progression rate to carcinoma in situ or cancer was 20%, but varied widely (from 0% to 53%).

Excisional therapy is preferred in most circumstances, but local ablation or destruction, using laser ablation, cryotherapy, cold coagulation or radical diathermy are acceptable management strategies if colposcopy is satisfactory. For CGIN, therapy should be excisional [6].

In case of recurrence or when colposcopy is unsatisfactory, excision using large loop excision of the transformation zone (LLETZ) or cold knife conisation should be chosen. Of these two approaches, excision is preferred. In pregnant women treatment can be delayed until after delivery [6].

The Australian guideline [5] essentially draws the same conclusions, but add that local ablative or excisional treatments should destroy or remove tissue to a depth of at least 7 mm and that it is advisable that women with CIN3 are not treated with cryotherapy.

There is no obviously superior conservative surgical technique for treating and eradicating CIN according the review of Martin-Hirsch of 2000, which was updated in 2010 [7]. The European guideline [6] states that excisional techniques are preferred in the majority of cases because of their clear superiority over ablation in terms of histological evaluation of the transformation zone.

The European guideline [6] contains a number of recommendations on excisional therapy, both based on expert opinion and a Cochrane systematic review conducted by Martin-Hirsh et al. in 2000 [7] (Table 5).

Table 5. European guideline recommendations on excisional therapy [6].

- The procedure should be carried out under colposcopic control;
- The lesion together with the entire transformation zone should be removed;
- It is helpful to mark the excised specimen with a thread at 12 o'clock, thereby facilitating the histopathologist to orient the specimen;

- Surgeons should avoid damage of the ecto-cervical epithelium or of the endo-cervical canal;
- A cervical dilator for orientation of the excision specimen is unhelpful;
- The size and shape of the excised specimen will be determined by the colposcopic delineation of the lesion;
- Excision should be mandatory if the lesion involves the endo-cervical canal;
- If the lesion involves the endo-cervical canal, endo-cervical sampling should be considered after the excision;
- Thorough histological assessment by a pathologist skilled in gynaecological pathology is essential;
- The histopathologist should be informed of the cytology and colposcopic findings;
- Cold knife conisation gives excision margins that are not affected by thermal artefact, whereas the margins of laser excisional cone or diathermy loop excision cone may be damaged. In skilled hands, the thermal artefact is generally minimal. In the meta-analysis of Martin-Hirsch et al. there was a clear advantage of cold knife cone biopsy over laser or LLETZ;
- Excision of the transformation zone in multiple fragments can complicate histopathological assessment. Furthermore, if microinvasive disease is present, it may be impossible to allocate a substage or define completeness of excision in fragmented excisional specimens.

The European guideline [6] only recommends ablative therapy if a number of selection criteria is fulfilled (Table 6).

Table 6. Conditions that need to be fulfilled before ablative therapy can be recommended [6].

- The entire transformation zone must be visible;
- One or more biopsies should be taken from the area or areas that colposcopically show the most severe change;
- The result of the biopsy or biopsies should be available prior to the destructive therapy;
- Cryotherapy should not be offered to women with large lesions, occupying more than 75% of the ectocervix, extending to the vaginal wall or extending more than 2 mm beyond the cryoprobe. This applies also to cold coagulation but not to radical diathermy;
- There should be no evidence of invasive disease on cytology, colposcopy, or biopsy;
- The Pap smear should not contain glandular atypical cells;
- The destructive therapy should be carried out under colposcopic control by an experienced colposcopist;
- There must be adequate follow-up.

The Australian guideline contains similar recommendations [5].

3.1.1.2. Update review and meta-analyses

The Cochrane systematic review of Martin-Hirsh et al., on which part of the above recommendations are based, was updated in 2010 [7], identifying 29 RCTs comparing (1) pooled risk ratios for residual disease after follow up examination and (2) adverse events in women who received one of either laser ablation, laser conisation, LLETZ, knife conisation or cryotherapy. The additionally collected evidence in this update did not alter the previous conclusions. The vast majority of RCTs evaluating the differences in treatment success are grossly underpowered to demonstrate a significant difference between treatment techniques and no real conclusions can be drawn on differences of treatment effect. Many analyses included only one or two randomised trials due to the different outcome measures chosen and reported in the trials. This limits the conclusions that can be drawn from these analyses. Furthermore, the randomisation method was not optimal in many trials, inducing a possible selection bias. Therefore, the

authors call for a large RCT tackling the question if excisional or ablative therapy has better outcomes in general.

A second Cochrane review was conducted by Martin-Hirsh et al. [8] specifically focussing on methods for the prevention of blood loss during the intervention. Conclusions were that tranexamic acid significantly reduced the risk of secondary haemorrhage (RR = 0.23, 95%CI 0.11-0.50), but not primary haemorrhage (RR = 1.24, 95%CI 0.04-38.23) after cold knife conisation and laser cone biopsy, compared with placebo. There was also a statistically significant reduction in postoperative blood loss compared with placebo (MD = -55.60, 95%CI -94.91 to -16.29). Packing with Monsel's solution resulted in less perioperative blood loss (MD = -22.00, 95%CI -23.09 to -20.91) and decreased the risk of dysmenorrhoea (RR = 0.37, 95%CI 0.16-0.84), unsatisfactory colposcopy (RR = 0.43, 95%CI 0.30- 0.63) and cervical stenosis (RR = 0.35, 95%CI 0.25-0.49) compared to routine suturing, but was not statistically different to sutures for risk of primary and secondary haemorrhages. Amino-Cerv antibiotic gel failed to make a difference on secondary haemorrhage, but was associated with significantly less vaginal discharge at 2 weeks compared with routine care (RR = 0.27, 95%CI 0.09-0.86).

There was no significant difference in blood loss between women who received ball electrode diathermy and those who received Monsel's paste (MD = 4.82, 95%CI -3.45 to 13.09).

An additional search for primary studies was performed to update both Cochrane reviews. One high-quality pilot study [9] comparing the efficacy of a CIN excisor with LLETZ showed a difference in the proportion of histopathological specimens with clear resection margins in favour of the CIN excisor group (95.7% vs. 85.7%; p < 0.001). Subanalysis of the proportion of histopathological specimens with clear resection margins in relation to CIN grades revealed a statistically significant difference in favour of the CIN excisor group for CIN1 (96.1% vs. 86.3%; p = 0.01), and CIN2 (94.8% vs. 85%; p = 0.04). There is a numerical difference in the proportion of clear resection margins in favour of the CIN excisor for CIN3 (96.7% vs. 85.7%), but this difference was not statistically significant (p = 0.21). Perioperative complications were similar between the two groups. However, further studies are needed for CIN2 and CIN 3 before firm conclusions can be drawn.

Ghaem-Maghami et al. [10] performed a meta-analysis of observational studies examining the effect of incomplete excision on the risk of treatment failure. They found that, after incomplete excision, the RR of post-treatment disease of any grade was 5.47 (95%CI 4.37-6.83) and the RR of high-grade disease (i.e. CIN2 or 3, or high-grade squamous intraepithelial lesion) was 6.09 (3.87-9.60) compared with the reference group who had complete excision. High-grade post-treatment disease occurred in 597 of 3 335 (18%) women who had incomplete excision vs. 318 of 12 493 (3%) women who had complete excision. The authors concluded that incomplete excision of CIN exposes women to a substantial risk of high-grade post-treatment disease. Some of these women would be safer with a second treatment, especially if deep margins are involved, but most will need close follow-up for at least 10 years.

In an update of Kyrgiou et al., Arbyn et al. [11, 12] did a meta-analysis of observational studies and concluded that cold knife conisation and probably both laser conisation and radical diathermy are associated with an increased risk of subsequent perinatal mortality and other serious pregnancy outcomes, unlike laser ablation and cryotherapy. LLETZ was associated with obstetric morbidity, but an association with mortality and other serious obstetric outcomes could not be demonstrated but not excluded either. Due to selection bias in the observational studies, differences cannot be completely attributed to the different techniques used and conclusions should be treated with caution. However, it is unlikely that an RCT sufficiently powered to deal with these obstetric outcomes will be conducted in the future due to the rareness of severe obstetric events and infant mortality. However, the potential increase in adverse obstetric outcomes seen with excisional therapy has to be weighed against the potential increase in residual disease following ablative therapy. As noted by Martin-Hirsh et al.[7], at least one adequately powered study is needed to settle this question. Women, however, should be informed about the potential risks for adverse obstetric outcomes and fertility.

3.1.2. Follow up of CIN2/3

The European guideline [6] recommends that women treated for high-grade disease (CIN2, CIN3, CGIN) require a 6, 12 and 24-month follow-up cytology and thereafter an annual follow-up cytology for a further 5 years before returning to screening at routine interval, based on observational studies. Colposcopy is performed in addition to cytology at the 6-month follow-up visit. Most persistent/recurrent disease is detected within the first 24 months. However, there is clear evidence for a persistent long-term risk of invasive cancer for ten years after treatment [6]. There is conflicting evidence concerning the added value of colposcopy in addition to cytology for follow up [6]. The Australian guideline provide similar recommendations, but recommend returning to screening at routine interval if follow up tests are negative for two consecutive years [5].

3.1.3. Role of HPV testing in the follow up after treatment

According to the European guideline [6] DNA detection predicted residual/recurrent CIN with significantly higher sensitivity (ratio of sensitivities: 1.27; 95%CI 1.06-1.51) and not-significantly lower specificity (ratio of specificities: 0.94; 95%CI 0.87-1.01) than follow-up cytology. HPV DNA testing was also more sensitive than histology of the section margins (ratio of sensitivities: 1.30; 95%CI 1.05-1.62). HPV testing was even more specific, but this difference was statistically not significant. These data are based on a meta-analysis of observational studies done in the framework of the development of the guideline. The Australian guideline recommends HPV testing in addition at 12 and 24 months, based on its high negative predictive value in order to identify women at high risk [5]. However, no treatment based on HPV results is recommended.

Chan et al. [13] did a meta-analysis on post-treatment HPV testing for recurrent CIN. They found that the pooled sensitivity for Hybrid Capture 2 (HC2) was 90.7% (95%CI 75.4-96.9%), and the pooled specificity 74.6% (95%CI 60.4-85.0%). Pooled sensitivity for cervical cytologic testing was 76.6% (95%CI 62.0-86.8%), and the pooled specificity was 89.7% (95%CI 22.7-99.6%), based on 6 studies. Pooled sensitivity for the HC2 or cytologic combination was 93.1% (95%CI 16.7-99.9%), and the pooled specificity was 75.7% (95%CI 57.2-87.9%), based on 3 studies (not all studies could be used for this estimate). They concluded that, although HC2 testing can identify approximately 91% of women with residual or recurrent CIN2, approximately 30% of women would undergo colposcopy during follow-up evaluation. The authors call for a RCT comparing HPV-testing with cytologic testing and perhaps to colposcopy, with a follow-up of at least 5 years to clarify the best approach and to permit an evaluation of the impact of both false-positive and false-negative findings as current evidence is insufficient to base recommendations on.

3.1.4. Conclusions

- **The pooled progression rate to carcinoma in situ or cancer is estimated to be 20%, but estimations in case series varied widely (from 0% to 53%) (European guideline; very low level of evidence).**
- **There are indications that delaying treatment of pregnant women with high-grade CIN is safe (European guideline; low level of evidence).**
- **There are no indications of one clearly superior method of fertility-sparing treatment for CIN2 and 3. There is a need for sufficiently powered studies comparing the therapeutic outcomes of ablative and excisional therapy (Martin-Hirsch 2010; low level of evidence).**
- **There are indications that cold knife conisation and probably both laser conisation and radical diathermy are associated with an increased risk of subsequent perinatal mortality and other serious pregnancy outcomes, unlike laser ablation and cryotherapy. There are also indications that large loop excision of the transformation zone was associated with obstetric morbidity, but an association with mortality and other serious obstetric outcomes could not be demonstrated but not excluded either (Arbyn 2008; low level of evidence).**
- **There are indications that incomplete excision of CIN exposes women to a substantial risk of high-grade post-treatment disease (Ghaem-Maghami 2007; low level of evidence).**
- **It is plausible that retinoids are not helpful in the management of CIN (Helm 2007; moderate level of evidence).**

- **There are indications that most persistent/recurrent disease is detected within the first 24 months. However, there is clear evidence that there is a persistent long-term risk of invasive cancer for ten years after treatment based on observational studies (European guideline; moderate level of evidence).**
- **There is conflicting evidence concerning the added value of colposcopy in addition to cytology for follow up after treatment for CIN (European guideline; very low level of evidence).**
- **There are indications that HPV testing is more sensitive than cytology in the follow up after treatment, but it tends to be less specific. Implications for management of patients remain unclear (Chan 2009; low level of evidence).**

Other considerations

- Two old case series reported poor clearance rates of CIN3 with cryosurgery [14, 15].
- In young women (aged < 25 years), high regression rates are reported for CIN2 and CIN3 [16, 17]. Therefore, close observation for CIN2 in young women can be considered an acceptable and safe option if any invasive lesion has been excluded, colposcopy is satisfactory, and patient compliance is not a limitation for follow-up.
- In a narrative review Kietperakool et al. reported preliminary results and identified promising candidates for medical treatment of CIN2 and 3, including COX-2 inhibitors, novel immunotherapies, including ZYC101a, MVA E2, and HspE7, efflornithine and indole-3-carbinol [18]. These enouraging results provide data for the future direction of clinical research, but treatments need to be considered experimental at best for the moment. Finally, a Cochrane review by Helm et al. on the effect of retinoids in the management of CIN lesions did not show a benefit [19].

3.1.5. Recommendations

- **Cytological cervical abnormalities are classified into low-grade (LSIL) and high-grade squamous intraepithelial lesions (HSIL). The results of cervical biopsies are reported according to the CIN classification (1C).**
- **Women with biopsy-proven high-grade CIN (CIN2, CIN3, CGIN) require treatment, watchful waiting cannot be considered (1C).**
- **Treatment of pregnant women with high-grade CIN can be delayed until after the delivery (1C).**
- **Ablative and excisional therapies are both recommended treatment options for high-grade CIN (1B).**
- **Excisional techniques can be preferred over ablation in the majority of cases because they permit histological evaluation of the transformation zone (1C).**
- **The size and shape of the excised specimen should be determined by the colposcopic delineation of the lesion (expert opinion).**
- **The risk for adverse obstetric outcomes with excisional therapy should be weighed against a higher risk of recurrence and difficulties in evaluating complete removal of the lesion when applying ablative therapies (2B). In women requesting fertility conservation, ablation can be considered if the lesion is well-defined on colposcopy, not all 4 quadrants are involved, and if the intervention is therapeutic.**
- **Ablative therapy can only be considered if a number of additional conditions are fulfilled (1C):**
  - **The entire transformation zone must be visible;**
  - **One or more biopsies should be taken from the area or areas that colposcopically show the most severe change;**
  - **The result of the biopsy or biopsies should be available prior to the destructive therapy;**
  - **Cryotherapy should not be offered to women with large lesions, occupying more than 75% of the ectocervix, extending to the vaginal wall or extending more than 2 mm beyond the cryoprobe. This applies also to cold coagulation but not to radical diathermy;**

- **There should be no evidence of invasive disease on cytology, colposcopy, or biopsy;**
- **The Pap smear should not contain glandular atypical cells;**
- **The destructive therapy should be carried out under colposcopic control by an experienced colposcopist;**
- **There must be adequate follow-up.**

- **Women should be informed about the possible adverse obstetric outcomes of excisional therapy (1B).**
- **Women treated for high-grade disease can be proposed a follow-up cytology and HPV testing 6 months after the therapeutic intervention. In case of negative results, an additional confirmative cytology can be proposed after 1 year before returning to screening at routine interval (1C).**

3.2. DIAGNOSIS AND STAGING OF INVASIVE CERVICAL CANCER

Table 7 provides an overview of the SIGN recommendations [20] on diagnosis and staging of cervical cancer. These recommendations mainly relate to radiological staging.

The literature search to update the SIGN recommendations mainly focused on CT, MRI, PET and PET/CT.

Table 7. SIGN recommendations on diagnosis and staging of cervical cancer [20].

- All patients with visible, biopsy proven cervical carcinoma (except those with FIGO IV disease) should have an MRI scan;
- The MRI scan should include:
  - thin section T2 weighted images perpendicular to the cervix, and
  - sequences to include urinary tract and para-aortic nodal areas;
- Post contrast spiral CT should be considered as an alternative to MRI in patients who cannot have MRI;
- Women who have clinically apparent FIGO stage IV disease should have post contrast spiral or multislice CT scans of chest abdomen and pelvis;
- Patients not suitable for surgery should be considered for a PET scan;
- Cystoscopy and sigmoidoscopy should not be routinely performed for staging purposes;
- If imaging cannot exclude bladder or bowel involvement, cystoscopy and sigmoidoscopy should be used for staging;
- Ultrasound, IVU and lymphangiography are not recommended for staging.

3.2.1. FIGO staging

Clinical staging of cervical cancer is based on the FIGO staging system [21]. Clinical examination and imaging are used for assessing T, N and M categories. In contrast with the TNM staging, FIGO no longer includes stage 0 (Tis). A comparison between the FIGO and TNM staging systems is provided in Table 8.

Table 8. Comparison between FIGO and TNM staging systems for the staging of cervical cancer [21].

TNM	Description	FIGO
Tis	In situ	-
T1	Confined to cervix	I
T1a	Diagnosed only by microscopy	IA
T1a1	Stromal invasion: depth ≤ 3 mm, horizontal spread ≤ 7 mm	IA1
T1a2	Stromal invasion: depth > 3 and ≤ 5 mm, horizontal spread ≤ 7 mm	IA2
T1b	Clinically visible or microscopic lesion greater than T1a2	IB
T1b1	≤ 4 cm	IB1
T1b2	> 4 cm	IB2
T2	Beyond uterus but not pelvic wall or lower third vagina	II

TNM	Description	FIGO
T2a	No parametrial invasion	IIA
T2a1	≤ 4 cm	IIA1
T2a2	> 4 cm	IIA2
T2b	Parametrial invasion	IIB
T3	Lower third vagina/ pelvic wall/ hydronephrosis	III
T3a	Lower third vagina	IIIA
T3b	Pelvic wall/hydronephrosis	IIIB
T4	Mucosa of bladder/rectum; beyond true pelvis	IVA
N1	Regional lymph node metastasis	
M1	Distant metastasis	IVB

3.2.2. Tumour characteristics

3.2.2.1. Systematic review

One systematic review with meta-analysis evaluated CT and MRI for the detection of parametrial, bladder and rectal invasion with histopathology as the reference standard [22]. Fifty-seven studies were included in this review of which the majority had methodological limitations. The sensitivity for detecting invasion of the parametrium was significantly higher in MRI than in CT (MRI sensitivity: 74% [95%CI 68-79], N=52 studies vs. CT 55% (95%CI 44-66), N=9 studies; p=0.0027). The differences between CT and MRI were not significant for the results of bladder invasion and rectal invasion. The sensitivity for detecting bladder invasion of MRI was 75% (95%CI 66-83) with a specificity of 91% (95%CI 83-95; N=16 studies) vs. a sensitivity of 64% ((95%CI 39-82) and a specificity of 73% (95%CI 52-87); N=3 studies) for CT. The sensitivity of MRI for detecting rectal invasion was 71% (95%CI 53-83; N=9 studies) vs. a sensitivity for CT of 45% (95%CI 20-73; N=2 studies).

3.2.2.2. Primary studies

After the search date of this systematic review, another 19 primary studies were identified that evaluated CT and/or MRI for the detection of different tumour characteristics.

CT

Four primary studies described different outcomes for CT [23-26]. Two studies reported divergent results for the accuracy of CT for the detection of bladder invasion: sensitivity 100% (specificity 92%; NPV 100%; PPV 40%; N=305) vs. 9% (specificity 73%; PPV 4%; NPV 85%; N=109) [24, 26]. For the detection of urinary tract invasion a third study reported a sensitivity of 100% (specificity 99.7%; NPV 100%; PPV 75%) [25]. In the same study a sensitivity of 50% (specificity 99.7%; NPV 99.7%; PPV 50%) was reported for gastrointestinal tract invasion, while a sensitivity of 0% (specificity 85%; PPV 0%; NPV 92%) was reported for the detection of rectal invasion in the study of Hertel et al. [26]. Differences in patient characteristics, definitions of outcomes and research methods probably can explain these divergent results. Finally, Mitchell et al. reported that the area under the curve was 0.66 for the detection of uterine involvement [23].

MRI

Seventeen primary studies evaluated the value of MRI for the description of different tumour characteristics. The results of the studies are given below per characteristic.

1. Tumour size

Few studies specifically evaluated the diagnostic accuracy of MRI for measuring the tumour size. Mitchell et al. found a higher correlation between pathology and MRI (r=0.54) than with CT (r=0.45) and clinical examination (r=0.37; p<0.0001 for all) [27]. However, insufficient data were available to calculate the sensitivity and specificity.

2. Parametrial invasion

Parametrial invasion was evaluated in one good study and eight studies of lower quality (Table 9). The nine primary studies in general reported a median prevalence of parametrial invasion of 15% (range 6.3-22%), a median sensitivity of 75% (range 40-100%) and a median specificity of 91% (range 70-100%) [28-36].

The study that reported a contradictory low specificity of 70% was a study that only included 31 patients [33]. The main objective of this study was the comparison between 1.5T and 3.0T MRI.

Table 9. Sensitivity and specificity of MRI for parametrial invasion.

Reference	Number of studies/ patients in the analysis	Years of inclusion	T2-weighted	Contrast	Cervical angulation	Sensitivity	Specificity
Systematic reviews							
Bipat 2003 [22]	52	1985-2002*	No*	No	No	74%	85%#
Primary studies							
Chung 2007 [35]	119	2004-2006	Yes	No	No	100%	89%
deSouza 2006 [30]	119	1993-2002	Yes	No	No	80%	91%
Fischerova 2008 [31]	95	2994-2006	Yes	No	No	50%	98%
Hori 2009 [33]	31	2006-2007	Yes	Yes	Yes	75%	70%
Jung 2010 [28]	251	2006-2009	Yes	Yes	No	43%	93%
Matsushita 2001 [34]	23	1991-2000	Yes	Yes	No	60%	100%
Oberoi 2002 [36]	105	1997-2001	Yes	No	No	87%	93%
Sironi 2002 [37]	73	Not reported	Yes	Yes	No	79%	81%
Testa 2009 [32]	68	2002-2005	Yes	No	Yes	40%	89%
Median sensitivity of 9 primary studies (range)						75% (40-100%)	
Median specificity of 9 primary studies (range)						91% (70-100%)	
Median sensitivity of 4 primary studies with contrast (range)						68% (43-79%)	
Median specificity of 5 primary studies without contrast (range)						80% (40-100%)	

**No difference was found in the accuracy of the subgroup analyses in which older studies were compared to newer studies, or for T2-weighted vs. T1-weighted studies. # Read from the forest plot.*

3. Invasion of bladder and rectum

Four primary studies described the value of MRI for the detection of bladder and/or rectal invasion, with divergent results for both outcomes [26, 36, 38, 39]. The small sample sizes and the resulting very low number of patients with the evaluated outcomes are probably the reason for this. However, a difference in the definitions of the outcomes may also play a role. The median sensitivity of MRI for the detection of bladder invasion was 97% (range 64-100%). The median specificity was 88% (range 63-100%). The three studies that reported on rectal invasion, reported a sensitivity of MRI of 100%, 100% and 50% respectively, and a specificity of 100%, 91% and 86% respectively [26, 36, 39].

4. Vaginal invasion

Six primary studies described the value of MRI for detecting vaginal invasion [32, 33, 36, 40-42]. The median sensitivity was 75% (range 67-87%) and the median specificity was 80% (range 72-92%) in four comparable studies [33, 40-42]. Testa et al. reported a sensitivity of 0% and a specificity of 95% [32]. The estimated values are probably divergent because of the small sample sizes and the even smaller number of outcomes (median number of patients: 47; range: 31-115 patients). Oberoi et al. reported the sensitivity separately for invasion of the upper 2/3 part of the vagina (sensitivity 83%; specificity 94%) and the lower 1/3 section (sensitivity 78%; specificity 100%) [36]. Testa et al. reported a sensitivity of 100% (specificity 97%; NPV 100%; PPV 33%) for the detection of invasion of the vesicovaginal septum, and a specificity of 97% (PPV 33%) for the detection of invasion of the rectovaginal septum [32]. Because there were respectively one and zero patients with these outcomes, these data do not appear very reliable.

5. Invasion of os interna

Two primary studies were found that evaluated the ability of MRI to detect invasion of the os interna [29, 41]. Both had a high specificity. In one study (N=53) MRI detected invasion of the os interna with a sensitivity of 86% (specificity 93%; PPV 67%; NPV 98%) [41]. In a larger study (N=150) the sensitivity of MRI for the invasion of the os interna was 90% (specificity 98%; NPV 98%; PPV 86%) [29].

6. Myometrial invasion

Two primary studies evaluated the ability of MRI to detect invasion of the myometrium. One study evaluated myometrial invasion with a sensitivity of 100% (specificity 99%; NPV 100%; PPV 88%) [29]. The second study (N=208) found an area under the curve of 0.80 [23].

Conclusions of tumour characteristics CT.

- **There are indications that CT has a low sensitivity (55%, 9 studies) to detect parametrial invasion (Bipat 2003; low level of evidence).**
- **Diagnostic accuracy studies indicate diverging sensitivities (9-100%) and specificities (67-100%) for CT to detect tumour invasion of the bladder and the urinary tract (Sharma 2010, Kokka 2003, Bipat 2003, Hertel 2002; low level of evidence).**
- **There are indications that CT has a low sensitivity (0-50%) for the detection of invasion of the rectum or the gastrointestinal tract. The reported specificities are moderate to high (85-100%) (Kokka 2003, Bipat 2003, Hertel 2002; low level of evidence).**

Conclusions of tumour characteristics MRI.

- **It is plausible that MRI has a low sensitivity (~75%) for the detection of parametrial invasion. Its specificity appears to be moderate to high (Sironi 2002, deSouza 2006, Fischerova 2008, Bipat 2003, Jung 2010, Matsushita 2001, Hori, 2009, Testa 2009, Oberoi 2002, Chung 2007, Sahdev 2007; low level of evidence).**
- **Diagnostic accuracy studies indicate diverging sensitivities and moderate to high specificities for MRI to detect bladder and rectal invasion (Bipat 2003, Oberoi 2002, Hertel 2002, Nam 2010, Rockall 2006; low level of evidence).**
- **There are indications that MRI has a low sensitivity (range 0-87%) and a low-moderate specificity (range 72-95%) to detect vaginal invasion, although the results are divergent (Testa 2009, Manfredi 2009, Hori 2009, Choi 2004, Oberoi 2002, Sheu 2001; low level of evidence).**
- **The reported sensitivities of MRI to detect invasion of the os interna are moderate (86%) to high (90%). However, the specificity is consistently high (93-98%) (Sahdev 2007, Manfredi 2009; low level of evidence).**

- **One diagnostic accuracy study found a high sensitivity and specificity of MRI to detect invasion of the myometrium (Sahdev 2007; low level of evidence).**

Other considerations

According to the American College of Radiology, MRI is superior to clinical evaluation in assessing tumour size, and MRI measurements are within 0.5 cm of the surgical size in 70%-94% of cases [43]. The clinical experts involved in the development of the present guideline suggested some studies to support this statement [40, 44, 45], but in fact no study was identified that evaluated the diagnostic accuracy of MRI to differentiate tumours of < 4 cm from those of > 4 cm diameter.

3.2.3. Lymph node metastases

Both CT and MRI rely on size criteria for assessing lymph nodes, which are considered positive when the minimal nodal diameter exceeds 10 mm. Small metastatic deposits and microscopic disease will therefore be missed, yielding a relatively low sensitivity [46, 47].

Diffusion-weighted MRI has the ability to identify metastatic lymph nodes without necessarily taking tumour size into account [48]. Further investigation is needed to evaluate its role in the staging of patients with cervical cancer.

3.2.3.1. Systematic reviews

Four systematic reviews evaluated imaging techniques for the detection of lymph node metastases [22, 49-51] (Table 10 and Table 11).

One systematic review has already been discussed above [22]. The sensitivity for detecting lymph node metastases (unspecified location) for MRI was 60% (95%CI 52-68; N=25 studies), being significantly higher than for CT (43%; 95%CI 37-57; N=17 studies; p=0.047).

The second review by Havrilesky et al. included 15 small studies, of which none reported blinded evaluation of the imaging [49]. In a meta-analysis of two studies the sensitivity of CT to detect pelvic lymph node metastases was 47% (95%CI 21–73) (reference standard: histology or follow-up). For MRI the sensitivity was 72% (95%CI 53–87) with a specificity of 96% (95%CI 92–98) (meta-analysis of two studies with histology or follow-up as reference standard). For PET the sensitivity was 79% (95%CI 65–90) with a specificity of 99% (95%CI 96–99) (meta-analysis of four studies with histology or follow-up as reference standard). One of the studies reported a sensitivity of 67% (95%CI 9-99) and a specificity of 100% (95%CI 66-100) for the detection of para-aortal lymph node metastases by means of MRI (reference standard histology). In a meta-analysis of four studies the sensitivity of PET for the detection of para-aortal lymph node metastases was 84% (95%CI 68-94%) and the specificity was 95% (95%CI 89-98) (reference standard histology).

Kang et al. included ten studies that evaluated the detection of para-aortal lymph node metastases using PET or PET/CT, of which eight were prospective and six evaluated the imaging in a blind way [50]. A meta-analysis of these ten studies (five studies of PET and five studies of PET/CT, always with histology as the reference standard) showed a sensitivity of 34% (95%CI 10-72), a specificity of 97% (95%CI 93-99%), a negative likelihood ratio of 0.68 (95%CI 0.40-1.15), and a positive likelihood ratio of 12.49 (95%CI 4.64-33.62). The sensitivity and specificity for PET were 66% (95%CI 33-89) and 97% (95%CI 90-99), and for PET/CT 13% (95%CI 2-56) and 98% (95%CI 78-100). The meta-analysed sensitivity was extremely heterogeneous: the authors concluded that bias in studies with a lower prevalence of lymph node metastases must have played a major role. In the five studies with a high prevalence (>15%) the sensitivity was 73% (95%CI 53-87%) and the specificity 93% (95%CI 86-97%).

In the fourth and last review Selman et al. reported 95 test results of 72 included studies with histology as the reference standard, in which both studies that considered pelvic lymph nodes and studies that considered para-aortal lymph nodes were included [51]. All primary studies had methodological limitations. A meta-analysis of 32 studies that evaluated CT showed a sensitivity of 58% (95%CI 54-61) with a specificity of 92% (95%CI 92-94). A meta-analysis of 24 studies of MRI showed a sensitivity of 56% (95%CI 49-62) with a specificity of 93% (95%CI 91-94). A meta-analysis of 8 studies of PET showed a sensitivity of 75% (95%CI 63-84) with a specificity of 98% (95%CI 95-99). PET was more accurate than MRI (odds ratio 3.84; 95%CI 1.22-12.12). CT and MRI were equally accurate (odds ratio 0.63; 95%CI 0.36-1.12).

3.2.3.2. Primary studies

After the search date of the systematic reviews [22, 49-51] one primary study was found with information about CT, nine primary studies evaluated MRI, 3 studies evaluated PET, and 13 studies evaluated PET/CT.

CT

In a multi-centre study (N=208) the low sensitivity of CT was confirmed (31%) but the specificity was slightly lower than previously reported, i.e. 86% [27].

MRI

The nine primary studies that considered MRI confirmed its low sensitivity for the detection of lymph node metastases reported in the systematic reviews (median sensitivity [including the primary study reported in Havrilesky 2005]: 61%; range 0-77%) [27, 29, 32, 33, 35, 36, 52-54] (Table 10). However, the specificity was reported as low to moderate (<90%) in four studies [33, 35, 53, 54] and as high in the other five studies [27, 29, 32, 36, 52]. The median specificity of all nine primary studies (and the one primary study reported in Havrilesky 2005) was 95% (range 56-100%).

Table 10. Sensitivity and specificity of MRI for the detection of lymph node metastases.

Reference	Number of studies/ patients in the analysis	Years of inclusion	Contrast	Location	Sensitivity	Specificity
Systematic reviews						
Bipat 2003 [22]	25	1985-2002	Not reported	Not reported	60%*	93%*#
Havrilesky 2005 [49]	2	1966-2003	Not reported	Pelvic	72%	96%
	1			PALN	67%	100%
Selman 2008 [51]	24	1966-2006	Not reported	Pelvic and PALN	56%	93%
Primary studies						
Choi 2006 [53]	22	2003-2005	Yes	Pelvic and PALN	77%	56%
Chung 2007 [35]	119	2004-2006	No	Pelvic and PALN	71%	69%
Chung 2010 [54]	83	2004-2008	Yes	Pelvic	64%	69%
Hoon Chung 2005 [52]	44	2001-2004	Not reported	PALN	0%	100%
Hori 2009 [33]	31	2006-2007	Yes	Pelvic	57%	83%
Mitchell 2009 [27]	161	2000-2002	Not reported	Pelvic and PALN	37%	94%
Oberoi 2002 [36]	105	1997-2001	Not reported	Pelvic	67%	96%
Sahdev 2007 [29]	150	1995-2005	Not reported	Pelvic	37%	95%
Testa 2009 [32]	68	2002-2005	Not reported	Pelvic	27%	96%
Median sensitivity 10 primary studies (range)†					61% (0-77%)	
Median specificity 10 primary studies (range)†					95% (56-100%)	
Median sensitivity 5 primary pelvic studies (range)					57% (27-67%)	
Median sensitivity 5 primary pelvic studies (range)					95% (69-96%)	
Median sensitivity 2 primary PALN studies (range)†					34% (0-67%)	
Median sensitivity 2 primary PALN studies (range)†					100% (100%)	

** No difference was found in the accuracy of the subgroup analyses in which older studies were compared with newer studies. # Read from the forest plot. † Including the primary study reported in Havrilesky 2005. Abbreviations: PALN: para-aortic lymph nodes.*

PET

Two primary studies evaluated PET. The first study concerned patients (N=60) who did not have lymph node metastases on MRI [55]. In this population the sensitivity of PET for detecting pelvic lymph node metastases was 10% (specificity 94%, NPV 84%, PPV 25%). In the second study (N=47) all patients had a suspected para-aortic, inguinal and/or supraclavicular lymph node metastasis [56]. Nine patients were evaluated with PET/CT, but these results were not reported separately. In all patient groups the sensitivity of PET or PET/CT for the detection of para-aortic lymph nodes was 97% (specificity 90%; NPV 90%; PPV 97%), for the detection of inguinal lymph nodes 80% (specificity 86%; NPV 97%; PPV 40%), and for the detection of supraclavicular lymph nodes 85% (specificity 100%; NPV 94%; PPV 100%).

PET/CT

Thirteen primary studies evaluated PET/CT. All studies had methodological shortcomings. The median sensitivity for twelve more or less comparable studies was 39% (range 0-100%) and the median specificity was 94% (range 56-100%) [53, 54, 57-66] (Table 11). There were no clear indications why some studies reported contradictory results, such as the study of Loft et al. which was the only study to report a sensitivity above 90%, and the studies of Kim et al. and Choi et al, which were the only ones to report a specificity below 90% [53, 58, 63]. One small study (N=16) reported a sensitivity of 0% for the detection of bilateral lymph node metastases in a selective subgroup that underwent both MRI and PET/CT before surgery (NPV 88%) [67].

Table 11. Sensitivity and specificity of PET/CT for the detection of lymph node metastases.

Reference	Number of studies/ patients in the analysis	Years of inclusion	Location	Sensitivity	Specificity
Systematic reviews					
Kang 2010 [50]	5	1980-2009	PALN	13%	98%
Primary studies					
Amit 2006 [61]	16	Not reported	Not reported	0%	Not reported
Choi 2006 [53]	22	2003-2005	Pelvic and PALN	77%	56%
Chung 2009 [60]	34	2003-2007	Pelvic	41%	94%
Chung 2010 [54]	83	2004-2008	Pelvic	29%	84%
Goyal 2010 [59]	80	2007-2009	Pelvic	58%	93%
Kim 2009 [63]	79	2001-2007	Pelvic and PALN	47%	71%
Leblanc 2011 [57]	125	2004-2008	PALN	33%	94%
Loft 2007 [58]	119	2002-2005	PALN	100%	99%
Ramirez 2010 [62]	60	2004-2009	PALN	36%	96%
Sandvik 2011 [66]	36	2006-2007	Pelvic	20%	90%
Sironi 2006 [64]	47	2003-2004	Pelvic	73%	97%
Yu 2011 [65]	16	Not reported	Not reported	0%	100%
Median sensitivity 12 primary studies (range)				39% (0-100%)	
Median specificity 11 primary studies (range)				94% (56-100%)	
Median sensitivity 5 primary pelvic studies (range)				41% (20-73%)	
Median sensitivity 5 primary pelvic studies (range)				93% (84-97%)	
Median sensitivity 3 primary PALN studies (range)				36% (33-100%)	
Median sensitivity 3 primary PALN studies (range)				96% (94-99%)	

Abbreviations: PALN: para-aortic lymph nodes.

Conclusions

- **There are indications that CT and MRI have a low sensitivity but a high specificity to detect lymph node metastases (Bipat 2003, Selman 2008, Mitchell 2009, Choi 2006, Hori 2009, Sahdev 2007, Testa 2009; low level of evidence). These findings also specifically apply to pelvic lymph node metastases for CT and MRI (Havrilesky 2005, Chung 2010, Chung 2007, Oberoi 2002; low level of evidence), and to para-aortic lymph nodes for MRI (Havrilesky 2005, Hoon Chung 2005, Chung 2007; low level of evidence).**
- **There are indications that PET has a low sensitivity and a high specificity for the detection of lymph node metastases (Selman 2008; low level of evidence). These findings also specifically apply to pelvic (Havrilesky 20056; low level of evidence) and para-aortic lymph node metastases (Havrilesky 2005, Kang 2010; low level of evidence). One diagnostic accuracy study found a low sensitivity and a high specificity for the detection of pelvic lymph nodes that were not detected by MRI (Chou 2006; low level of evidence).**
- **There are indications that PET/CT has a low sensitivity and a high specificity for the detection of lymph node metastases, although the evidence is heterogeneous (Choi 2006, Kim 2009, Yu 2011; low level of evidence). A low sensitivity and high specificity were specifically found for pelvic (Chung 2009, Chung 2010, Goyal 2010, Sironi 2006; low level of evidence) and para-aortic lymph node metastases (Kang 2010, Leblanc 2011, Loft 2007; low level of evidence). One diagnostic accuracy study found a low sensitivity and a high specificity for the detection of para-aortic lymph nodes that were not detected by MRI or CT (Ramirez 2010; low level of evidence).**

3.2.4. Surgical lymph node staging

3.2.4.1. Systematic reviews

Two systematic reviews and five primary studies evaluated the value of a sentinel lymph node biopsy in the staging of cervical cancer. One systematic review also included information about CT, MRI and PET and was previously discussed [51]. This review showed in a meta-analysis of 31 studies that in 96% of patients a sentinel lymph node was found if both technetium and blue dye were used. The sensitivity of sentinel lymph node biopsy was 91% (95%CI 87-95) with a specificity of 100% (95%CI 99.6-100). A sentinel lymph node biopsy was more accurate than an MRI (odds ratio 18.49; 95%CI 3.59-95.17; p<0.01).

The second systematic review carried out a meta-analysis of 22 studies with histology as the reference standard [68]. The reference standard was not evaluated in a blind way in any of the studies. The sensitivity of sentinel lymph node biopsy was 89% (95%CI 83-94). In 95% of patients a sentinel lymph node was found if both technetium and blue dye were used.

3.2.4.2. Primary studies

After the search date of the systematic reviews three studies with over 100 patients were found and two studies that considered an intra-operative evaluation of the sentinel lymph node. In 84-90% of patients at least one sentinel lymph node was found if both technetium and blue dye were used [69-71]. In 59-66% of patients a sentinel lymph node was found on both sides [70, 71]. In the three larger patient series the sensitivity of a sentinel lymph node biopsy was between 77% and 94% (range NPV 94-96%). The sensitivity was the highest in the patient subgroup with a tumour of 2 cm or smaller (91%), and when a sentinel lymph node was found on both sides in patients (87%) [69]

If the sentinel lymph node was evaluated during the operation the sensitivity varied greatly in the two studies that considered this. In the first study (N=38) the sensitivity was significantly lower (33% intra-operative vs. 83% postoperative; NPV 89% vs. 97%) [72], while it was high in the second study (N=58%) (100% intra-operative; NPV 100%) [73].

Conclusion

- **The available evidence indicates a moderate sensitivity of sentinel lymph node biopsy for the detection of lymph node metastases, although the results are conflicting (Selman 2008, van de Lande 2007, Altgassen 2008, Wydra 2006, Darlin 2010, Fader 2008, Yamashita 2009; low level of evidence).**

Other considerations

- Since the search date for the present report, several new studies on sentinel lymph node biopsy for cervical cancer were published [74-76]. These will need to be taken into account when the present guideline is updated.
- In a recent Cochrane review, the effectiveness of pre-treatment surgical para-aortic lymph node (PALN) assessment in locally-advanced cervical cancer was evaluated [77]. Brockbank et al. identified only 1 small RCT of moderate quality including 61 women. This trial reported data on surgical versus clinical staging and an assessment of the two surgical staging techniques, i.e. laparoscopic versus extraperitoneal surgical staging. The clinical staging was either a contrast-enhanced CT scan or MRI scan of the abdomen and pelvis to determine nodal status. In this trial, clinical staging appeared to significantly prolong overall (HR 1.50, 95%CI 1.04-2.17) and progression-free survival (HR 1.71, 95%CI 1.17-2.49) compared to surgical staging. There was no statistically significant difference in the number of women who experienced severe (grade 3 or 4) toxicity. There was no statistically significant difference in the risk of death, disease recurrence or progression, blood loss, severe toxicity and the duration of the operational procedure between laparoscopic and extraperitoneal surgical staging techniques.

3.2.5. Distant metastases

Four primary studies evaluated the value of various diagnostic techniques for detecting distant metastases. In the first study (N=165) Liu et al. evaluated the value of CT, MRI and PET for the detection of haematogenous bone metastases in patients with FIGO stage III or IV [78]. PET was the most accurate in diagnosing haematogenous bone metastases with a sensitivity of 100% (specificity 99%; NPV 100%; PPV 91%). MRI and CT performed less (sensitivity 80%; specificity 99%; NPV 99%; PPV 80% vs. sensitivity 25%; specificity 100%; NPV 92%; PPV 100%). The accuracy of PET or PET/CT was confirmed in a second series (N=47) of patients, all with suspected distal lymph node metastases (sensitivity of detection of bone metastases 100%; specificity 98%; NPV 100%; PPV 50%) [56]. In the same study the sensitivity of PET or PET/CT for detecting other, non-skeletal distant metastases was 100% (specificity 91%; NPV 100%; PPV 33%). In the third, smaller (N=17) series of patients who underwent routine preoperative examinations, including CT and MRI, new metastases were discovered with PET in 5 patients (29%) (sensitivity 83%; specificity 100%; NPV 92%; PPV 100%) [79]. The fourth study (N=119) evaluated PET/CT [58]. The sensitivity for detecting distant metastases was 100% (specificity 94%; PPV 53%; NPV 100%).

Conclusions

- **The dedicated literature about imaging techniques to detect distant metastases in patients with cervical cancer is limited.**
- **One diagnostic accuracy study indicated a low sensitivity but high specificity of CT and MRI for the detection of haematogenous bone metastases (Liu 2009; low level of evidence).**
- **There are indications that PET and PET/CT have a high sensitivity and specificity to detect distant metastases (Loft 2007, Chao 2008; low level of evidence).**
- **There are indications that PET and PET/CT have a high sensitivity and specificity to detect bone metastases (Liu 2009, Chao 2008; low level of evidence).**

3.2.6. Global staging accuracy

Four primary studies were found that evaluated the global staging accuracy of imaging techniques. One well-executed multi-centre study (N=208) evaluated the ability of CT to detect stage IIB or higher (reference standard: surgical resection specimen) [80]. CT had a sensitivity of 42% (95%CI 26-59) and a specificity of 82% (95%CI 75-88). In the three studies that investigated the same outcome for MRI the median sensitivity was 85% (range 53-100%) and the median specificity 84% (range 75-

93%)[36,42,80]. In a fourth smaller study (N=28) MRI detected stage I with a sensitivity of 54% (specificity 60%; PPV 54%; NPV 60%). No data were available to calculate these outcomes for higher stages [81].

Conclusions

- **There are indications that CT has a low sensitivity and a moderate specificity to detect stage IIB or higher (Hricak 2005; low level of evidence).**
- **The evidence on the ability of MRI to detect stage IIB or higher indicates a moderate sensitivity and specificity, but is conflicting (Hricak 2005, Oberoi 2002, Sheu 2001; low level of evidence).**

3.2.7. Tumour markers

3.2.7.1. CA-125 and SCCA for defining a high-risk group

High-risk groups were defined in five fairly good-quality studies on the basis of different cut-off points of SCCA and CA125.

CA-125

Two studies evaluated CA-125 for the detection of lymph node metastases. Using a cut-off point of ≥30 U/mL the sensitivity of CA-125 for the detection of lymph node metastases was 67% (specificity 84%; NPV 92%; PPV 46%) compared to the histological specimen [82]. At a cut-off point of ≥5,0 ng/ml the sensitivity of CA-125 for the detection of lymph node metastases was 18% (specificity 60%; NPV 66%; PPV 15%), when compared to the histological specimen or CT [83].

SCCA

Four studies evaluated different cut-off points for SCCA (one of the studies that evaluated CA-125 also studied SCCA). One study evaluated whether SCCA could detect a tumour size of 4 cm or more. In a study in which SCCA was compared to CT or clinical examination, the sensitivity at a cut-off point of ≥2.0 ng/ml was 64% (specificity 31%; NPV 8%; PPV 91%) [84]. Four studies evaluated whether SCCA could detect lymph node metastases. In the first study, which compared SCCA with CT, the sensitivity of SCCA ≥2.0 ng/ml was 77% (specificity 38%; NPV 91%; PPV 18%) [84]. In the second study, which compared with histology or CT, the sensitivity of SCCA ≥1.5 ng/ml was 67% (specificity 84%; NPV 92%; PPV 46%) [83]. The third study compared SCCA ≥1.5 ng/ml with histology and found a sensitivity of 79% (specificity 56%; NPV 88%; PPV 40%) [85]. The fourth study also compared SCCA with histology, but in two different subgroups [86]. In patients with stage IB1 the sensitivity of SCCA ≥1.65 ng/ml was 53% (specificity 84%; NPV 85%; PPV 50%). In patients with stage IIB2 or IIA the sensitivity was 63% (specificity 46%; NPV 63%; PPV 40%).

Conclusions

- **There are no indications that a high-risk group can be defined for lymph node metastases using a CA-125 determination (Bender 2003, Kotowicz 2008; low level of evidence).**
- **There are no indications that a high-risk group for a tumour size of more than 4 cm can be defined using a SCCA determination (Chen 2008, low level of evidence).**
- **There are no indications that a high-risk group for lymph node metastases can be defined using a SCCA determination (Chen 2008, Kotowicz 2008, Takeda 2002, van de Lande 2009; low level of evidence).**

3.2.8. Histopathology

A diagnosis of cervical cancer is made by the histopathological examination of cervical biopsies [20]. As a rule, a LEEP/cone biopsy should be submitted entirely for histopathological evaluation.

Several histological features can be used to stratify women to higher risk or lower risk of metastatic disease, recurrence or death [87, 88]. These histological features should be included in the pathology report:

- Tumour type [89-93]: squamous carcinoma, adenocarcinoma or other, according to the WHO classification [94];
- Tumour size [88, 89, 91, 92, 95, 96];
- Extent of tumour, e.g. parametrial involvement [89, 90, 93, 97-100];
- Depth of invasion [100, 101]: this is to be measured from the base of the epithelium;
- Lymphovascular space invasion [96, 97, 99, 102, 103];

- Status of resection margins [97, 104]: margin invasion by invasive or in-situ carcinoma should be specified;
- Status of lymph nodes [88, 90-93, 96, 97, 100, 104-108]: the region and number of resected lymph nodes and the number of involved lymph nodes should be mentioned. Importantly, there is no current guidance on how isolated tumour cells (ITC) should be coded. Until further studies become available, patients with ITC should be coded N1 with a comment on how the cells were identified;
- Tumour grade [91, 96, 109].

In addition, the pathology report should include the procedure (LEEP/cone biopsy, radical trachelectomy, radical hysterectomy, pelvic exenteration) and the tumour site.

3.2.9. Recommendations

- **All patients with visible, biopsy proven cervical carcinoma should have an MRI scan of at least the pelvis (1C).**
- **Contrast-enhanced CT should be considered as an alternative to MRI in patients who have a medical contraindication for MRI (1C).**
- **PET/CT is recommended in tumours FIGO stage IB1 with suspicious pelvic lymph nodes and in large tumours FIGO stage IB2 and above (1C).**
- **Sentinel lymph node biopsy without lymphadenectomy is not recommended in patients with cervical cancer in routine clinical practice (1C).**
- **Tumour markers cannot be used for the diagnosis and staging of cervical cancer. However, they can be used for the monitoring of treatment response. Therefore, a pre-treatment baseline measurement can be considered (2C).**
- **Treatment options for patients with invasive cervical cancer should be discussed at the multidisciplinary team meeting (1C).**

3.3. Treatment of FIGO stage Ia cervical cancer

In this chapter, the treatment of microscopically invasive disease (i.e. stromal invasion ≤ 5 mm) is discussed.

According to the 2008 SIGN guideline, standard treatment for IA1 disease is simple hysterectomy if fertility is not an issue [20]. Removal of pelvic lymph nodes is not recommended during treatment for FIGO IA1 disease. However, in women with FIGO IA1 disease with lymphovascular space invasion (LVSI), the decision to carry out pelvic lymphadenectomy must be individualised taking account of the pattern and extent of invasion. For IA2 disease standard treatment is simple hysterectomy and pelvic lymph node dissection (PLND). Women with FIGO IA2 (and microscopic IB1) disease and no LVSI requesting fertility conservation may be offered cold knife conisation or LLETZ combined with pelvic lymph node dissection. Women with FIGO IA2 (and microscopic IB1) disease and LVSI requesting fertility conservation may be at risk of local recurrence and treatment should be individualised [20].

After the search date of the SIGN guideline (i.e. 2005), few systematic reviews were published including trials with cervical cancer patients and FIGO stage IA, but these trials never included stage IA patients exclusively. Furthermore, no RCTs were published since these systematic reviews. Therefore, the search was extended to comparative observational trials, published since 2005.

Five retrospective cohort studies were identified. These studies mainly included patients with FIGO stage IA1 disease (N=393 in total) [110-114]. Bisseling et al. also included 9 patients with stage IA2 disease [110], while Reynolds et al. included 14 patients with stage IA2 disease [113]. The mean follow-up ranged from 34 to 80 months.

Four of these studies reported an absence of recurrences during follow-up, both in patients undergoing primary conization or hysterectomy [110, 112-114]. Kim et al. reported a recurrence rate of 10% (N=7) in the conization only group, all occurring in patients with positive resection margins at primary conization [111]. Six of these patients were successfully treated with repeat conization or simple hysterectomy. One patient that was lost to follow-up for 6 years was treated with chemoradiotherapy for advanced disease. In the study of Bisseling et al. 10 patients with FIGO stage IA1 and 7 patients with FIGO stage IA2 also received PLND, but the resected pelvic lymph

nodes were all free from disease [110]. Reynolds et al. reported one patient with positive lymph nodes among 46 patients undergoing PLND (2.2%) [113].

Several (narrative) reviews discussed the parametrial and nodal involvement in patients with FIGO stage IA2 cervical cancer [110, 113, 115]. When these 3 reviews were considered together, a total of 12 observational studies including 179 patients with stage IA2 cervical cancer reported on parametrial involvement. Of these, 151 patients (84%) underwent radical hysterectomy. No parametrial involvement was found. A total of 25 observational studies including 1 241 patients with stage IA2 cervical cancer reported on nodal involvement. Of these, 945 patients (76%) underwent PLND. Positive pelvic lymph nodes were found in 39 patients (4.1%). Pelvic lymph node involvement was more pronounced in squamous cell cancer compared to adenocarcinomas (3.3% [95%CI 1.2-5.2%] vs. 0.3% [95%CI 0-0.9%]) [115]. More patients with LVSI had positive pelvic lymph nodes compared to patients without LVSI (12.0% [95%CI 6.9-17%] vs. 1.3% [95%CI 0.2-2.4%]) [115].

No good evidence is available on the number of lymph nodes to be removed during a PLND. However, it is good clinical practice to remove as many lymph nodes as possible.

Conclusions from the literature update

- **The recurrence rate in patients with cervical cancer FIGO stage IA1 treated with primary conization is low and seems to be limited to patients with positive resection margins (Bisseling 2007, Kim 2010, Lee 2009, Yahata 2010, Reynolds 2010; very low level of evidence).**
- **Based on the available observational studies and case series, parametrial involvement seems to be very limited in patients with cervical cancer FIGO stage IA2. Lymph node involvement varies between 0% and 9.7%; adenocarcinomas and tumours without LVSI have a low risk of lymph node metastases (Reynolds 2010, van Meurs 2009, Bisseling 2007; very low level of evidence).**

Other considerations

One ongoing RCT (SHAPE trial) is evaluating whether treatment with radical hysterectomy and PLND is non-inferior to treatment with simple hysterectomy and PLND in terms of pelvic-relapse free survival in patients with low-risk cervical cancer defined as lesions measuring < 2 cm with < 50% stromal invasion. Recruitment is currently ongoing.

Few old observational studies evaluated the role of definite utero-vaginal brachytherapy in patients with FIGO IA disease [116, 117]. The recurrence rates were very low (0-3%), and utero-vaginal brachytherapy alone was associated with a low risk for severe complications.

Several systematic reviews that are discussed in the chapters on more advanced stages provide indirect evidence for patients with FIGO IA2 disease:

- The Chemoradiotherapy for Cervical Cancer Meta-analysis Collaboration (CCCMAC) performed an individual patient data (IPD) meta-analysis of 15 trials comparing concomitant chemotherapy and radical radiotherapy to radical radiotherapy alone in patients with locally-advanced cervical cancer [118]. Twenty-four percent of the included women had stage IA-IIA disease. When all stages were considered, chemoradiotherapy was associated with an improved 5-year survival (HR 0.81, p<0.0001). Although no separate results were provided by stage, a trend in relative effect by tumour stage was found (p=0.017), with a more pronounced effect on overall survival in patients with stage IA-IIA.
- In a recent Cochrane review, Baalbergen et al. compared primary surgery to primary radiotherapy in women with early adenocarcinoma of the uterine cervix [119]. Only one RCT was identified, comparing class III radical hysterectomy (and adjuvant radiotherapy in case of risk factors, 64%) with external pelvic irradiation plus brachytherapy in 337 women with stage IB and IIA cervical carcinoma [120]. The majority of these patients had stage IB disease (88%), while 83% had squamous cell cancer. After a median follow-up of 87 months, 5-year overall survival (83%) and disease-free survival (74%) were identical in both groups. However, for the subgroup of patients with adenocarcinoma, a significant survival advantage was found with surgery (5-year survival: 70% vs. 59%, OR 0.67). Overall, in the surgery group, more patients

showed severe (grade 2-3) morbidity that required medical or surgical treatment (28% vs. 12%, p=0.0004).

- Another recent Cochrane review identified 3 RCTs comparing adjuvant platinum-based chemotherapy (in addition to radical hysterectomy, radiotherapy or both) to no such adjuvant chemotherapy [121]. All trials included patients with FIGO stage IB and IIA disease. Two trials enrolling 325 women compared radiotherapy and chemotherapy with radiotherapy alone and found that adjuvant chemotherapy significantly reduced the risk of death (HR 0.56; 95%CI 0.36-0.87) and disease progression (HR 0.47; 95%CI 0.30-0.74). One trial assessing 71 women compared chemotherapy followed by radiotherapy with radiotherapy alone and found no significant difference between the two groups in terms of disease progression (HR 1.34; 95%CI 0.24-7.66).

3.3.1. Recommendations

- **In patients with cervical cancer FIGO stage IA1 and free margins of the conization specimen, no further treatment is needed (1C).**
- **In patients with a preliminary diagnosis of cervical cancer FIGO stage IA1 and positive margins of the conization specimen, repeat conization, total hysterectomy or utero-vaginal brachytherapy are options if the FIGO stage IA1 is confirmed histologically (2C).**
- **Based on the available evidence, parametrial involvement seems to be rare in patients with cervical cancer FIGO stage IA2, and hence a simple hysterectomy with systematic lymphadenectomy with the goal of at least 20 nodes is considered to be sufficient (2C).**
- **In patients with cervical cancer FIGO stage IA2 who are medically inoperable and without fertility wish, radical external radiotherapy and brachytherapy can be considered (2C).**
- **In case the preoperative staging indicates that postoperative treatment will be needed, concomitant cisplatin-based chemoradiotherapy is recommended instead of surgery (1C).**

3.4. Treatment of non-metastatic cervical cancer

In the past, the treatment of early-stage and locally-advanced cervical cancer consisted of radical surgery or radical radiotherapy. Lower stages were more often treated with radical surgery, while the more advanced stages more often received radical radiotherapy. Late nineties, Landoni et al. compared radical surgery with radiotherapy in patients with stage IB and IIA cervical cancer [120]. After a median follow-up of 87 months, 5-year overall and disease-free survival were identical in the surgery and radiotherapy groups (83% and 74%, respectively, for both groups). However, radical surgery was associated with significantly more severe morbidity, mainly in the subgroup of patients who received adjuvant radiotherapy.

More recently, several trials compared radiotherapy with newer treatment options such as primary chemoradiation or neoadjuvant chemotherapy (see below). This lead to new treatment standards for patients with FIGO stage IB2, IIA2, III and IVA disease. However, for patients with IB1 [20] and IIA1 disease (i.e. tumours < 4 cm), radical surgery remains the standard of care.

In this chapter, radical surgery refers to radical hysterectomy, involving the en-bloc removal of the uterus, cervix, parametrial tissues and upper vagina. The extent of parametrial and vaginal tissue removed determines whether a class II or III radical hysterectomy has been done. Historically, radical hysterectomy involves open surgery. However, since radical surgery is associated with important morbidity, surgical techniques were developed to decrease the morbidity, e.g. laparoscopy, nerve-sparing surgery, robot-assisted surgery, etc. However, it is beyond the scope of this guideline to evaluate and compare these different techniques.

3.4.1. Stage IB1 and IIA1

Women with early-stage cervical cancer and risk factors such as large tumour size, deep stromal invasion, involvement of the lymphovascular space positive nodes, parametrial invasion, or positive surgical margins have higher risk of recurrence compared to women with early-stage cervical cancer but no such risk factors [122]. According to the 2008 SIGN guideline [20], patients who have undergone surgery for cervical carcinoma and have positive nodes should be considered for adjuvant treatment with concurrent chemoradiotherapy with cisplatin based chemotherapy.

Patients having negative nodes and any two of the following risk factors should be considered for adjuvant treatment with radiotherapy, if fit enough: 1) greater than a third stromal invasion; 2) lymphovascular space invasion; 3) tumour diameter of >4 cm. According to SIGN, concurrent chemoradiation should be considered in preference to radiation alone [20].

After the search date of the SIGN guideline (i.e. 2005), one Cochrane systematic review [121] of trials including early-stage cervical cancer patients (FIGO stages IA2-IIA) with risk factors for recurrence was published. Rosa et al. included three trials (N=368) [123-125] comparing adjuvant radiotherapy alone with adjuvant radiotherapy and cisplatin-based chemotherapy after radical surgery for early-stage cervical cancer (stages IA2, IB1 or IIA). Two of these trials (N=297) [123, 124] compared concomitant chemoradiotherapy with radiotherapy alone. In the largest trial [124], which was already included in the SIGN guideline, women had one or more risk factors (positive pelvic lymph nodes and/or positive margins and/or microscopic involvement of the parametrium). Meta-analysis of these two RCTs showed that chemoradiotherapy significantly reduced the risk of death (HR=0.56, 95%CI 0.36-0.87) and disease progression (HR=0.47, 95%CI 0.30-0.74), with no between-study heterogeneity (I2=0% for both meta-analyses). The pooled RR comparing grade 4 toxicities in both arms was 5.7 (95%CI 2.1-14.5), with no between-study heterogeneity (I2=0%), indicating a significantly higher risk of severe adverse events in the chemoradiotherapy arm than in radiotherapy alone. The median follow-up varied from 29 to 42 months.

For one of the trials [123], only unpublished individual patient data were available. However, since there was no between-study heterogeneity, the results in both studies were in the same direction, and the risk of bias was limited according to Rosa et al., the study of Peters et al. [124], being already included in the SIGN guideline, was not evaluated separately here.

The third trial (N=71) [125] compared chemotherapy followed by radiotherapy with radiotherapy alone in women with clinical stage IB and IIA carcinoma of the cervix, initially treated with radical hysterectomy and pelvic lymphadenectomy, and who had positive pelvic lymph nodes (1 to >5). Results reported no significant difference in disease progression (HR=1.34; 95%CI 0.24-7.66). This trial did not report data on treatment toxicity. The median follow-up was 30 months.

The highest potential bias in the Cochrane review was that the report of Peters et al. was based on an interim analysis which rejected the null hypothesis of no benefit of chemotherapy. The benefit of the combination of radiotherapy and chemotherapy may have been overestimated [121]. In 2005, Monk et al. [126] retrospectively analyzed the data from Peters' trial investigating histopathologic and clinical factors which might be predictive of recurrence. This study was also included in the SIGN guideline. Their exploratory, hypothesis-generating analysis reported a higher 5-year survival in the chemoradiotherapy group (80%) than in the radiotherapy group (66%), confirming previous results. Patient age, histological type or tumour grade were not strongly associated with a beneficial effect of adjuvant chemotherapy. The absolute improvement in 5-year survival for adjuvant chemotherapy in patients with tumours >2 cm was 19% (58% vs. 77%), whereas for those with tumours ≤2 cm it was only 5% (77% vs. 82%). Similarly, the absolute 5-year survival benefit was more clear when at least two nodes were positive (55% versus 75%) than for patients with one nodal metastasis (79% versus 83%). As this study is retrospective, a definitive conclusion cannot be drawn, and a randomized study investigating the expanded role of chemotherapy after radical hysterectomy in women with ≥2 positive nodes is required. In the same way, the benefit of adjuvant chemotherapy in women with only one positive node, especially if tumour size is less than 2 cm needs a prospective trial [126].

No additional randomised trials were identified.

Conclusions

- **It is plausible that, compared to adjuvant radiotherapy alone, adjuvant cisplatin-based chemoradiotherapy significantly improves progression-free and overall survival at 3 years in women with early-stage cervical cancer and risk factors for recurrence (positive pelvic lymph nodes and/or positive margins and/or microscopic involvement of the parametrium) who undergo radical hysterectomy and pelvic lymphadenectomy (Rosa 2009; moderate level of evidence) (1B).**

- **There are indications that adjuvant cisplatin-based chemoradiotherapy is associated with a higher risk of severe adverse events than adjuvant radiotherapy alone (Rosa 2009; moderate level of evidence) (1B).**

3.4.2. Recommendations

- **Patients with a clinical stage IA2, IB, or IIA carcinoma of the cervix and risk factors for recurrence (positive pelvic lymph nodes and/or positive margins and/or microscopic involvement of the parametrium) who have undergone radical hysterectomy and pelvic lymphadenectomy should be considered for adjuvant treatment with concurrent platinum-based chemoradiotherapy (1B).**
- **In case the preoperative staging indicates that postoperative treatment will be needed, concomitant cisplatin-based chemoradiotherapy is recommended instead of surgery (1C).**

3.4.3. Stage IB2, IIA2, IIB, IIIA, IIIB and IVA

3.4.3.1. Primary chemoradiotherapy

According to the SIGN guideline [20], any patient with cervical cancer considered suitable for radical radiotherapy treatment should have concurrent chemoradiotherapy with a platinum-based chemotherapy. This recommendation is based on RCTs showing that improvements in progression-free and overall survival are more pronounced with chemoradiotherapy than with radiation alone in patients with locally-advanced stage IIB-IVA disease. These results were confirmed by a Cochrane review [127] reporting a HR for platinum-based chemotherapy of 0.70 (95%CI 0.61-0.80; p<0.0001) compared to 0.81 (95%CI 0.56-1.16; p=0.20) for non-platinum-based chemotherapy. In a meta-analysis of Lukka et al. [128], chemoradiation with cisplatin alone resulted in a RR of death of 0.74 (95%CI 0.59-0.93) compared to 0.70 (95%CI 0.56-0.86) for chemoradiation with cisplatin/5-fluorouracil (5FU). However, chemoradiation is associated with increased acute haematological and gastrointestinal toxicity, requiring considering the balance of risks and benefits before offering such aggressive treatment [20].

Wang et al. [129] published a meta-analysis including 18 RCTs and based on 3 517 patients comparing the effectiveness and safety of chemoradiotherapy with RT alone in locally advanced cervical cancer (FIGO stages IB-IVA). The response rate (81.8% vs. 69.8%; RR 1.17 95%CI 1.11-1.23; N = 1 928), 3-year survival rate (76.9% vs. 67.9%; RR 1.13 95%CI 1.04-1.24; N=709) and 5-year survival rate (73.0% vs. 60.1%; RR 1.22; 95%CI 1.13-1.31; N = 1 563) were significantly better in patients in chemoradiotherapy group than in RT group. However, chemoradiotherapy group has higher incidence rates than RT group in gastrointestinal, myelosuppression and leucopenia.

The CCCMAC performed an IPD meta-analysis of 15 trials comparing chemoradiotherapy to radical radiotherapy alone in patients with locally-advanced cervical cancer (IA-IIA: 24%; IIB: 36%; III-IVA: 38%) [118]. When all stages were considered, chemoradiotherapy was associated with an improved 5-year survival (HR 0.81, p<0.0001). A decreasing relative effect of chemoradiotherapy on survival with increasing tumour stage was suggested, with estimated absolute survival benefit of 10% (stage IA to IIA), 7% (stage IIB) and 3% (stage III to IVA) at 5 years. Although the size of the benefit may vary, chemoradiotherapy benefits were confirmed for all stages of cervical cancer.

Tzioras et al. [130] combined 65 heterogeneous trials (22 comparisons; N = 3 837 patients) covering large periods and enrolling IIB-IV stage cancers. This meta-analysis reported higher benefits for chemoradiotherapy compared to radiotherapy alone in terms of mortality (HR 0.95; 95%CI 0.83–1.08; I2 = 38%). The between-study heterogeneity seemed to be due to contradictory results in early trials. Restricting the analysis to trials published between 1997 and 2006 (11 comparisons) confirmed these results, since benefits were found with short-length cycles of cisplatin-based regimens (≤14 days; HR 0.80, 95%CI 0.66-0.99) and concurrent chemoradiotherapy (HR 0.89, 95%CI 0.78-1.02, I2 = 0%).

A RCT of moderate quality [131] including 369 patients with stage IB cervical cancer confirmed the results of these systematic reviews, both in terms of progression (RR 0.61, 95%CI 0.43-0.85) and 10-year overall survival (73.8% vs. 63.4%; adjusted death HR 0.63, 95%CI 0.43-0.91). Another RCT of moderate quality [132] including 160 patients with stage IIB - IVA cervical cancer reported results that followed the same trends, without reaching statistical significance. In 158 stage IIB - IVA patients without

para-aortic lymph nodes, Kim et al. [133] reported 4-year survival rates superior than 65% with cisplatin-based chemoradiation.

Surgery versus primary chemoradiation

No studies comparing primary surgery with primary chemoradiation were identified. This is confirmed by Baalbergen et al., who did not identify studies for this comparison in their Cochrane review [119]. Our search identified one recently published observational study [134] and one cost-effectiveness study [135] for FIGO stages other than IB1. In a retrospective study, Yin et al. compared the long-term survival of patients with FIGO stage IB2-IIB cervical cancer treated with neoadjuvant cisplatin-based chemotherapy followed by radical hysterectomy (plus PLND) (N=187), radical surgery alone (including PLND) (N=195) or primary concurrent cisplatin-based chemoradiotherapy (N=94) [134]. Median follow-up was 82.8 months. Five-year disease-free survival was 85%, 77% (HR 1.87) and 53%, respectively (HR 3.53) (p<0.001). Five-year overall survival was 89%, 80% (HR 1.81) and 64%, respectively (HR 3.16) (p<0.001). Hazard ratios or p-values for chemoradiotherapy compared to surgery alone were not provided.

Using a Markov model, Jewell et al. compared the cost-effectiveness of primary chemoradiotherapy and primary radical hysterectomy with tailored adjuvant therapy in patients with FIGO stage IB2 cervical cancer [135]. For the calculation of the clinical estimates, results from case series and studies comparing surgery with primary radiotherapy or comparing chemoradiotherapy with radiotherapy were used. The model predicted a 5-year overall survival of 79.6% in the surgery arm vs. 78.9% in the chemoradiotherapy arm. With a mean cost at 5 years of $ 27 840 for surgery compared to $ 21 403 for chemoradiotherapy, the incremental cost-effectiveness ratio (ICER) was estimated to be $ 63 689 per additional life year saved. However, when assuming a constant mortality over a 5-year period, the predicted difference in 5-year survival translates in a difference in life years of 0.019. Considering a cost difference of about $6 400, the reported ICER seems to be largely underestimated.

A well-conducted RCT comparing primary radical surgery with primary chemoradiotherapy, in particular in patients with stage IB1 cervical cancer for whom the standard treatment still is primary surgery (see above), is needed before definite recommendations can be formulated.

3.4.3.2. Thermoradiotherapy

Hyperthermia is a type of cancer treatment in which body tissue is exposed to high temperatures (i.e. around 42 to 43 degrees Celsius during one hour) to damage and kill cancer cells. This temperature is in itself able to kill tumour cells under certain conditions and also increases the cytotoxic effect of irradiation on tumour cells [136].

The comparison between RT alone and the combined use of hyperthermia and radiotherapy (RHT) was not a research issue in the SIGN guideline [20]. In 2010, a Cochrane systematic review [136] was published including 6 (phase II and phase III) trials published between 1987 and 2009 and, recruiting patients of any age with histologically proven locally advanced cervical cancer (central diameter ≥ 4 cm and/or FIGO stage IIB - IVA). Two additional RCTs (including one follow-up study) were further identified.

The Cochrane review [136] aimed to assess whether adding hyperthermia to standard radiotherapy for locally-advanced cervical cancer has an impact on local tumour control, survival and treatment related morbidity. Radiotherapy regimens included EBRT with or without brachytherapy. A minimum temperature of 40° Celsius was required for hyperthermia. The total number of patients included in the analysis varied between 264 and 310 according to outcomes; 74% of patients had FIGO stage IIIB locally-advanced cervical cancer. The pooled data analysis yielded a significantly higher complete response rate (RR 0.56; 95%CI 0.39-0.79; p<0.001; N=267), a significantly reduced local recurrence rate (HR 0.48; 95%CI 0.37-0.63; p<0.001; N=264) and a significantly better overall survival following the combined treatment with RHT (HR 0.67; 95%CI 0.45-0.99; p=0.05; N=264). No significant difference was observed in treatment-related acute (RR 0.99; 95%CI 0.30-3.31; p=0.99; N=310) or late grade 3 to 4 toxicity (RR 1.01; CI 95% 0.44-2.30; p=0.96; N=264) between both treatments. Importantly, the small number of patients available for analysis, methodological flaws and a significant over-representation of patients with FIGO stage IIIB hamper drawing definite conclusions regarding the impact of adding hyperthermia to standard radiotherapy.

A small RCT published since the Cochrane review [137] conducted in 40 patients with FIGO Stage IIIB cervical cancer also reported higher complete response rates in the RHT group (N=20; 80%) than in the RT group (N=20; 50%) (p=0.048) without significant differences in overall (58.2% vs. 63.6%) and disease-free survival (48.1% vs. 45%).

3.4.3.3. Brachytherapy

Brachytherapy is a form of very localised radiotherapy delivered by the insertion of applicators into the uterus via the vagina (intracavitary brachytherapy), and in advanced disease with additional interstitial needle implants. The SIGN guideline [20] referred to guidelines published by the American Brachytherapy Society, indicating that brachytherapy should be considered an essential component of definitive radiotherapy treatment.

A recent Cochrane review [138] aimed to assess the efficacy and safety of high dose rate (HDR) versus low dose rate (LDR) intracavitary brachytherapy (ICBT) in women having uterine cervical cancer. It included 4 low quality level RCTs (N = 1 265 patients), recruiting patients with FIGO stages I-III (146 stage I, 500 stage II and 619 stage III) and conducted between 1993 and 2004. In the meta-analysis performed to compare HDR and LDR-ICBT, the pooled RRs were respectively 0.95 (95%CI 0.79-1.15), 0.93 (95%CI 0.84-1.04) and 0.79 (95%CI 0.52-1.20) for 3-, 5- and 10-year overall survival rates; and 0.95 (95%CI 0.84-1.07) and 1.02 (95%CI 0.88-1.19) for 5- and 10-year disease-specific survival rates. Restricting analyses to stage II and III patients did not change results. No difference was found between treatment arms for relapse-free survival, local control rates, locoregional recurrence, for local and distance recurrence, for para-aortic lymph node metastasis and for distance metastasis. Results indicated no significant differences for bladder and rectosigmoid complications, but increased small bowel complications with HDR (RR 3.37; 95%CI 1.06-10.72; p=0.04). Authors underlined some potential advantages of HDR-ICBT which include outpatient treatment, patient convenience, accuracy of treatment and individualized treatment with complete radiation protection for personnel.

Conclusion from the literature update

- **It is demonstrated that concomitant platinum-based chemoradiotherapy is associated with an improved progression-free and overall survival compared to adjuvant radiotherapy alone in patients with stage IA-IVA cervical cancer (Green 2005, Wang 2011, CCCMAC 2010, Tzioras 2007, Kim 2008; moderate level of evidence).**
- **It is demonstrated that chemoradiation increases acute haematological and gastrointestinal toxicity compared to radiation alone, requiring to consider the balance of risks and benefits before offering such aggressive treatment (Wang 2011, Stehman 2007; moderate level of evidence).**
- **It is plausible that the addition of hyperthermia to radiotherapy improves local tumour control and overall survival in patients with IIB-IVA cervix carcinoma without increasing acute or late toxicity (Lutgens 2010, Harima 2009; moderate level of evidence).**
- **There are indications of benefits obtained with brachytherapy in terms of tumour control rate and survival in patients having I-III cervical cancer (Wang 2010; low level of evidence).**

Other considerations

Recent data on 3D MRI-guided brachytherapy have shown an increase of 25 to 30% in centropelvic tumour control and a reduction of up to 50% in severe complications compared to classical 2D image-guided brachytherapy [139].

Recommendations

- **In patients with cervical cancer FIGO stage IB-IVA considered suitable for radical radiotherapy treatment, concurrent chemoradiotherapy with a platinum-based chemotherapy is recommended, if fit enough (1B).**
- **The balance of risks and benefits should be discussed with the patient before offering chemoradiation for treatment of cervical cancer (1C).**
- **In patients with cervical cancer FIGO stage IB-IIIB, brachytherapy should be considered as a component of radical radiotherapy or chemoradiotherapy (1C).**

3.4.3.4. *Neoadjuvant treatment*

Neoadjuvant chemotherapy (NACT) can be proposed to reduce tumour size, facilitating subsequent therapy (radiotherapy or surgery). Inoperable tumours can be transformed into radically resectable ones. NACT also increases radiosensitivity and treats micrometastatic disease, preventing a significant proportion of relapses [140]. However, NACT can also delay curative treatment in patients who do not respond to chemotherapy or induce a cross-resistance with radiotherapy [140].

SIGN did not identify RCTs describing the value of using neoadjuvant chemotherapy to make large inoperable tumours surgically resectable [20].

Neoadjuvant chemotherapy versus radical surgery alone

Although it was not a formal research question for this guideline, we did identify a recent Cochrane review comparing neoadjuvant chemotherapy plus surgery versus radical surgery alone [141]. Rydzewska et al. included 6 RCTs involving 1072 women with cervical cancer. Whilst progression-free survival was significantly improved with neoadjuvant chemotherapy (HR 0.76, 95%CI 0.62-0.94), overall survival did not differ (HR 0.85, 95%CI 0.67-1.07). Furthermore, estimates for both local (OR 0.76, 95%CI 0.49-1.17) and distant (OR 0.68, 95%CI 0.41-1.13) recurrence and rates of resection (OR 1.55, 95%CI 0.96-2.50) only tended to be in favour of neoadjuvant chemotherapy, and heterogeneity was observed.

Neoadjuvant chemotherapy versus primary radiotherapy alone

In 2003, Tierney et al. [142] published an individual patient data meta-analysis carried out by the Neoadjuvant Chemotherapy for Cervical Cancer Metaanalysis Collaboration (NACCCMA Collaboration). This meta-analysis included all relevant trials published up to December 2002. Two distinct treatment comparisons were included:

1. Comparison 1: NACT followed by local treatment versus the same local treatment (mainly radiotherapy) alone
2. Comparison 2: NACT followed by surgery (± radiotherapy) versus radical radiotherapy.

Comparison 1 was based on 18 trials including 2 074 patients [142]. Almost 70% of patients had advanced disease (stage II or III). Most had moderately or poorly differentiated tumours of squamous histology. Five-year survival data were available for all 18 trials, involving 1 084 deaths. The median follow-up across all trials was 5.7 years for surviving patients. The addition of NACT to radiotherapy (comparison 1) did not have an impact on overall survival (HR 1.05; 95%CI 0.94–1.19), disease-free survival (HR 1.00; 95%CI 0.88–1.14), or locoregional disease-free survival (HR 1.03; 95%CI 0.9–1.17). However, the heterogeneity between trials was significant for each of the outcomes measured. Indeed, included trials compared different chemotherapy cycles and cisplatin dose intensities. Further analyses were conducted stratifying trials according to these factors (Table 12).

Table 12. Five-year overall survival by length of chemotherapy regimen and cisplatin dose intensity.

Trial groups	Number of trials	HR (95%CI)	p value	Hetero-geneity p value	5-year overall survival
Chemotherapy cycle frequency					
> 14 days	11	1.25 (1.07-1.46)	0.005	0.23	Decrease 8%
≤ 14 days	6	0.76 (0.62-0.92)	0.005	0.19	Increase 7%
Cisplatin dose intensity					
< 25 mg/m^2	7	1.35 (1.11-1.64)	0.002	0.74	Decrease 11%
≥ 25 mg/m^2	11	0.91 (0.78-1.05)	0.2	0.001	Increase 3%

For trials with treatment cycles longer than 14 days, the pooled HR was 1.25, translating into an absolute reduction in 5-year survival of 8% (from 45 to 37%), whereas trials using shorter cycle lengths had a pooled HR of 0.76, equivalent to a 7% absolute improvement in 5-year survival (from 45 to 52%). A comparable but less clear result was observed when grouping trials according to the planned cisplatin dose intensity. Trials using a dose intensity of less than 25 mg/m2 per week had an HR of 1.35, which translated into an 11% reduction in 5-year overall survival. Higher dose intensity was associated with a 3% improvement in 5-year overall survival, without reaching a statistically significant level (p=0.2).

Comparison 2 was based on 5 RCTs including 872 patients [142]. Almost 90% of the included patients had locally advanced disease (FIGO stage IB bulky, IIB-IIIB), all with good performance status. Most tumours were moderately or poorly differentiated. Median age was 49 years (range 42–58 across trials). Cisplatin was the main drug in all chemotherapy regimens with a planned total dose between 100 and 300 mg/m2 in 10–21-day cycles. In one trial, chemotherapy was delivered intra-arterially. External beam radiotherapy (EBRT) and intracavitary radiotherapy (RT) doses were very similar across trials (45–60 and 25–40 Gy, respectively). However, in many patients included in the 'NACT plus surgery' arm, pelvic RT was also used. These confounding factors were impossible to take into account in the analysis. The median follow-up across all trials was 5 years for surviving patients (range 3.9 to 9.0 years). NACT was associated with an HR of 0.65 (95%CI 0.53-0.80; p=0.00004), translating into an absolute gain in 5-year overall survival of 14% (from 50% to 64%). Hazard ratios for both overall disease-free survival and locoregional disease-free survival were 0.68 (95%CI 0.56-0.82; p=0.0001), translating into a 13% absolute improvement in both endpoints from 45 to 58%. For metastases-free survival, the HR was 0.63 (95%CI 0.52-0.78; p=0.00001), corresponding to an absolute benefit of 15% at 5 years (from 45 to 60%). Tierney et al. reported a low proportion of deaths for this comparison (368/872) and, in some cases, missing baseline data, reducing the power to detect a difference in effect of NACT for predefined patient subgroups.

Despite these encouraging results, this meta-analysis generally has not been considered definitive evidence for NACT for the following reasons [140]:

- Twenty-five percent of patients in the largest Italian trial [143] did not complete the planned therapy;
- A benefit in survival was only observed for disease stages IB to IIB;
- The radiotherapy in the control arm was inferior to today's standard of care of chemoradiation (in terms of median total dose of radiotherapy and use of para-aortic irradiation in advanced disease);
- The heterogeneity of the stages included in the trials was too large; and
- The chemotherapy regimens (cisplatin monotherapy) did not include modern, more active drugs (cisplatin doublets including ifosfamide, paclitaxel or topotecan).

In 2010, Mossa et al. [144] reported the results of a RCT of NACT in stage IB-III cervical cancer. In total, 288 patients with squamous cell carcinoma, FIGO Stage IB-IIIB were randomized to one of the following treatments: three courses of NACT with cisplatin, vincristine, bleomycin (NACT arm; N=159) followed by radical hysterectomy and systematic LND of the lumbar-aortic area; radical hysterectomy or exclusive radiotherapy (CONV arm; N=129). Only non-operable stage III patients in control group (N=24) or in the intervention group (N=6) underwent exclusive radiotherapy (EBRT on the whole pelvis plus intracavitary LDR brachytherapy). Follow-up extended for seven years. Only for overall survival an ITT analysis was done but no significant differences were found for all stages (70.4% vs. 65.9%; p=0.17). For disease-free survival, some patients with stages IIIA-IIIB were excluded from the statistical analyses in the conventional arm. Disease-free survival did not differ for stages IB-IIA (76.2% vs. 64.3%; p=0.07) or for stages IIB (58.3% vs. 57.1%; p=0.93) NACT enabled a surgical approach in 80% of inoperable patients (24/30 in NACT arm).

Neoadjuvant chemotherapy versus primary chemoradiotherapy

The most important limitation and criticism of the meta-analysis discussed above is that the radiotherapy in the control arm is inferior to chemoradiotherapy, which is considered the standard of care now. However, no published RCTs were found comparing NACT with primary chemoradiotherapy.

One trial launched by the European Organization for Research and Treatment of Cancer (EORTC) is investigating the role of NACT followed by radical hysterectomy and lymph node dissection versus concomitant chemoradiation in early/intermediate cervical cancer. The EORTC 55994 trial is recruiting patients with FIGO stage IB2, IIA, or IIB cervical cancer, with adequate performance status (0–2), an age of 18–75 years, and any histology (squamous carcinoma, adenocarcinoma, or adenosquamous carcinoma). Patients are randomized to neoadjuvant cisplatin-based chemotherapy followed by hysterectomy or to chemoradiotherapy. The neoadjuvant cisplatin-based chemotherapy must include a minimum total dose of 225 mg/ m2, with a dose intensity of at least 25 mg/m2 per week, and the final dose should be administered no later than the eighth week. The chemoradiotherapy arm consists of the standard dosage cisplatin at 40 mg/m2 per week for 6 weeks concomitantly with external beam radiotherapy (45–50 Gy). The main objectives of this trial are to compare

the overall and progression-free survival, the toxicity and the quality of life of patients in both groups [145]. This trial started in 2002 with a planned accrual of 686 patients (343 per treatment arm). So far, around half of the patients have been recruited, and the study is still ongoing [140].

Conclusion from the literature update

- **It is plausible that short cycle, dose-intensive neoadjuvant chemotherapy (NACT) before radiotherapy improves survival, whereas longer, less intensive schedules tended to show a detrimental effect of NACT (NACCCMA Collaboration 2003; moderate level of evidence).**
- **It is plausible that neoadjuvant chemotherapy before surgery improves 5-year overall survival in patients with localised disease (FIGO stage IB-IIA) and in patients with locally advanced disease (FIGO stage IB bulky, IIB-IIIB) (NACCCMA Collaboration 2003; moderate level of evidence).**
- **It is plausible that the following two alternative neoadjuvant strategies improve long-term outcomes (NACCCMA Collaboration 2003; moderate level of evidence): 1) A short cycle, dose intensive course of cisplatin-based chemotherapy prior to radiotherapy. 2) A similar chemotherapy regimen given prior to surgery (with or without radiotherapy).**
- **Due to important limitations (problem of heterogeneity in comparison 1 and potential confounding factors; small quantity of data available for comparison 2), the NACCCMA meta-analysis is not considered definitive evidence for NACT. At present the gold standard of treatment remains concomitant chemo/radiation (expert opinion).**
- **Results of EORTC 55994 trial are awaited to reconsider the place of NACT in the management of cervical cancer (expert opinion).**

Other considerations

In small stage IB1 tumours (< 2 cm) without LVSI and lymph node involvement, the incidence of parametrial involvement is low [146]. In these patients, conservative surgery could become the standard of care. As already mentioned above, the SHAPE trial is currently evaluating whether treatment with radical hysterectomy and PLND is non-inferior to treatment with simple hysterectomy and PLND in terms of pelvic-relapse free survival in patients with low-risk cervical cancer defined as lesions measuring < 2 cm with < 50% stromal invasion.

Recommendations

- **Evidence from EORTC 55994 trial is awaited to reconsider the place of NACT followed by surgery compared to concomitant chemoradiotherapy in the management of women with FIGO IB2, IIA>4cm or IIB cervical cancer.**
- **If NACT prior to surgery is chosen to treat patients with FIGO stage IB2, IIA, or IIB cervical cancer, then short cycle (≤ 14 days) and dose-intensive regimens (cisplatin ≥ 25 mg/m2) are recommended (1B).**

3.5. Management of metastatic and recurrent disease

The recurrence rate of cervical cancer is between 10% and 20% for FIGO stages IB–IIA and 50–70% in locally advanced cases (stages IIB–IVA) [147]. The prognosis for patients with recurrent disease is six months to two years; improvement in survival has to be aimed. However, palliation of symptoms due to clinical regression of metastases at a cost of minimal levels of toxicity is an acceptable goal of treatment in patients with such incurable cancer [147]. The SIGN guideline identified three therapeutic options for women whose first line treatment failed to control the tumour: salvage surgery, chemotherapy or palliative treatment only [20]. In 2006, Cancer Care Ontario (CCO) recommended the combination of cisplatin and topotecan above cisplatin alone for the treatment of women with metastatic, recurrent, or persistent cervical cancer for whom first-line treatment with chemotherapy is indicated [148].

3.5.1. Surgery

Since most women who develop recurrent disease will have previously received pelvic radiotherapy, the only potentially curative option is pelvic exenteration. This salvage surgery should be reserved for women with recurrent cervical cancer confined to the central pelvis, whose chemotherapy has failed [20].

3.5.2. Chemotherapy for recurrent and stage IVB

Metastatic disease or recurrent lesions not amenable to radical local excision or regional radiation are currently treated with palliative chemotherapy [122, 149]. The Gynecologic Oncology Group (GOG) conducts phase II and phase III trials on combinations of chemotherapy products in order to increase overall survival and progression-free survival, taking into account quality of life. In phase III trials testing different doublets, progression-free survival advantages have been demonstrated for ifosfamide plus cisplatin, paclitaxel plus cisplatin, and topotecan plus cisplatin; overall survival advantage has been demonstrated only for topotecan plus cisplatin [147].

In its 2008 guideline, SIGN recommended to offer palliative chemotherapy to women with FIGO stage IVB or recurrent cervical carcinoma, with either cisplatin and topotecan or cisplatin and paclitaxel.

After the search date of SIGN guidelines, randomized clinical trials were recently published testing multiple combination chemotherapies based on cisplatin for stage IVB and/or recurrent disease.

A four arm RCT [149] aimed to assess toxicity and efficacy of cisplatin doublet combinations in stage IV advanced and recurrent cervical carcinoma. The reference treatment combined paclitaxel and cisplatin (PC) whereas the interventional arms combined respectively vinorelbine and cisplatin (VC), gemcitabine and cisplatin (GC) and topotecan and cisplatin (TC). A total of 513 patients were enrolled when a planned interim analysis recommended early closure for futility.

The median overall survival was respectively 12.9 months (95%CI 10.02-16.76 months) for PC, 9.99 months (95%CI 8.25-12.25 months) for VC, 10.3 months (95%CI 7.62-11.60 months) for GC and 10.2 months (95%CI 8.61-11.66 months) for TC. The experimental-to-PC hazard ratios of death were 1.15 (95%CI, 0.79 to 1.67) for VC, 1.32 (95%CI, 0.91 to 1.92) for GC, and 1.26 (95%CI, 0.86 to 1.82) for TC. The hazard ratios for progression-free survival (PFS) were 1.36 (95%CI, 0.97 to 1.90) for VC, 1.39 (95%CI, 0.99 to 1.96) for GC, and 1.27 (95%CI, 0.90 to 1.78) for TC. Response rates for PC, VC, GC, and TC were 29.1%, 25.9%, 22.3%, and 23.4%, respectively. The arms were comparable with respect to toxicity except for leucopenia, neutropenia, infection, and alopecia. No significant differences were reported for quality of life, neuropathy or pain between arms [150]. Experimental arms were not superior to reference arm in terms of overall survival. However, the trend in response rate, progression free and overall survival tends to favor paclitaxel based combination.

Mountzios (2009) [151] undertook a randomized phase II trial in 153 patients with recurrent or metastatic cancer of the uterine cervix to test whether the addition of paclitaxel (ITP) to the cisplatin and ifosfamide combination could improve objective response rate, progression-free survival (PFS) and overall survival (OS). Objective response rate was significantly higher in the ITP group (59% vs. 33%, p=0.002). Median PFS was 7.9 and 6.3 months for patients in the ITP and IP arms, respectively (p=0.023). Median OS was 15.4 months and 13.2 months in the ITP and IP arms, respectively (p=0.048). In multivariate analysis, the triplet yielded a hazard ratio of 0.70 for relapse or progression (p=0.046) and 0.75 for death (p=0.124) compared with the doublet. An increase in neurotoxicity was observed with the triplet combination (43% vs. 11%, p<0.001).

Conclusion from the literature update

- **The only potentially curative option for recurrent disease is pelvic exenteration provided relapsed disease is confined to the central pelvis. The selection of operable patients can be optimized with a preoperative whole body PET or PET-CT scan, in addition to MRI and CT having confirmed the recurrent or persistent disease (SIGN 2008; low level of evidence).**
- **It is plausible that combination therapy improves response rate, progression-free and overall survival in stage IVB metastatic or recurrent cervical cancer compared to monochemotherapy based on cisplatin. Combination therapy induces higher toxicity, although it did not significantly reduce quality of life (Monk 2009, Mountzios 2009, Cella 2010; moderate level of evidence).**
- **There are indications that paclitaxel plus cisplatin has superior results in median overall survival and response rate than topotecan plus cisplatin without higher toxicity (Monk 2009, Cella 2010; moderate level of evidence).**
- **Triplet combinations need to be evaluated in large phase III RCTs (expert opinion).**

Other considerations

In women with advanced disease and median expected survival of 10 months, a relative hazard of 0.9 would translate approximately to 1 month prolongation of median survival. This slight survival improvement has to be weighed against the considerable haematological and gastrointestinal toxicity induced by the current combined chemotherapy regimens.

All RCTs testing chemotherapy regimens restricted their eligibility criteria to patients having a performance status 0-2. Considering the high toxicity of the products and the need to frequently reduce the planned doses during the treatment due to induced acute grade 3 adverse events, treatment with cisplatin and topotecan combination should be reserved to patients having a performance status 0-2.

In all studies combining cisplatin with another agent, patients with no prior treatment reported higher response rates than those with prior radiation therapy or chemotherapy. Consequently, large variations of response are obtained in the various trials according to patient selection. Due to a high refractoriness among patients who have failed any prior chemotherapy [147, 152], cisplatin and topotecan combination should be restricted to cisplatin naïve patients.

Ongoing trials are testing new combinations as first-line chemotherapy (GOG 0076-DD, cetuximab plus cisplatin), or second-line therapy for patients who relapse after primary platin-based chemotherapy for advanced, persistent, and recurrent cervix cancer (GOG 0227-C, bevacizumab and GOG 0227-D, erlotinib) [152]. Phase II trials with targeted therapy (monoclonal antibodies or small molecules) alone or in combination with chemotherapy are currently under way and the results are awaited [147, 152].

Locoregional pelvic recurrence (e.g. vaginal vault or isolated iliacal lymph node), when limited in size and not invading neighbouring structures, in women not previously treated with radiotherapy, does not necessarily require an exenteration. Limited surgery might be sufficient in these cases. However, it might prove difficult to remove the recurrence with clear margins, unless reverting to a more mutilating operation. On the other hand, the radiosensitivity of cervical cancer is proven. Therefore, local radical radiotherapy (with a curative dose) remains an alternative in patients that did not receive pelvic radiotherapy as part of their initial treatment. Current radiotherapy techniques (IMRT) can easily achieve high-dose irradiation in limited volumes, even in patients with a history of previous pelvic surgery. This should be discussed on a case per case basis during the multidisciplinary oncological meeting.

Recommendations

- **All recurrences should be discussed at the multidisciplinary oncological meeting (1C).**
- **Patients with a locoregional pelvic recurrence that is limited in size and not invading neighbouring structures, and who did not receive pelvic radiotherapy as part of their initial treatment, can be considered for resection or (chemo)radiotherapy (2C).**
- **In patients with recurrent cervical carcinoma confined to the central pelvis after earlier (chemo)radiotherapy, pelvic exenteration can be considered (1C). The selection of operable patients can be optimized with a preoperative whole body PET or PET/CT scan, in addition to MRI and CT having confirmed the recurrent or persistent disease (1C).**
- **In patients with cervical cancer FIGO stage IVB or recurrent cervical carcinoma and who are no candidate for curative (chemo)radiotherapy or surgery, palliative chemotherapy should be offered, after discussion of the relative benefits and risks, with either (1B):**
  - **cisplatin 50 mg/m^2 on day 1 plus paclitaxel 135 mg/m^2 every 3 weeks, or**
  - **cisplatin 50 mg/m^2 on day 1 plus topotecan 0.75 mg/m^2 on days 1 to 3 every 3 weeks**
- **Triplet combinations and targeted therapies need to be evaluated in large phase III RCTs (1C).**

3.6. Fertility-sparing treatment

SIGN recommended that women requesting fertility conservation should be offered radical trachelectomy and pelvic lymph node dissection, providing the tumour diameter is less than 2 cm and no LVSI is present. Surgeons wishing to offer laparoscopic-vaginal radical hysterectomy should have appropriate training. This is based on case series that show a low recurrence rate in patients in this group. Cold knife conization or LLETZ is adequate treatment for women with IA1 disease where fertility conservation is requested. If LVSI is present, PLND needs to be considered. Women with early-stage disease and no LVSI (FIGO IA2 and microscopic IB1) requesting fertility conservation may be offered cold knife conization or LLETZ combined with pelvic lymph node dissection. Women with FIGO IA2 (and microscopic IB1) disease and LVSI requesting fertility conservation may be at risk of local recurrence and treatment should be individualised [20].

Three narrative reviews including case series and retrospective comparative studies [153-155] were used for reference tracking. No RCTs were identified comparing fertility-sparing surgery with radical hysterectomy. However, such an RCT is considered not feasible because of the ethical issues involved in recruiting women who wish to remain fertile and because of the large sample sizes that would be needed [153]. No RCTs comparing different forms of fertility-sparing surgery were identified either. One review [155] combined case series dividing the number of recurrences and deaths by the number of participants involved. However, the validity of this procedure is questionable, because of large differences in follow-up time between participants and average follow-up times across studies. Therefore, the search was extended to comparative observational trials, and case series larger than 50 cases, published since 2005.

3.6.1. Conization

For the comparison of conization with hysterectomy, 5 retrospective cohort studies were identified. These studies mainly included patients with FIGO stage IA1 disease (N=393 in total, of whom 123 underwent conization, 209 simple and 61 radical hysterectomy) [110-114, 156]. Bisseling et al. also included 9 patients with stage IA2 disease (2 conizations, no recurrences) [110], while Reynolds et al. included 14 patients with stage IA2 disease (1 conization, no recurrences) [113]. All studies suffered from methodological drawbacks, especially in the comparability of the control group and the statistical power. The mean follow-up ranged from 34 to 80 months. These cohort studies are therefore not more valid than case series.

None of the studies diagnosed recurrences in the control group. Four of these studies reported an absence of recurrences during follow-up, both in patients undergoing primary conization or hysterectomy [110, 112-114]. Only Kim et al. reported a recurrence rate of 10% (N=7) in the conization only group, all occurring in patients with positive resection margins at primary conization [111]. Six of these patients were successfully treated with repeat conization or simple hysterectomy. One patient that was lost to follow-up for 6 years was treated with chemoradiotherapy for advanced disease.

3.6.2. Radical vaginal trachelectomy

Two controlled studies comparing laparoscopic-assisted radical vaginal trachelectomy (LARVT) with laparoscopic-assisted radical vaginal hysterectomy (LARVH) were identified. Marchiole et al. [157] published a study comparing LARVT (N=118) with LARVH (N=139) in FIGO stage I–IIA cervical carcinoma. Median follow-up was 95 months (range 31–234). Recurrence was identified in 7 cases (5.2%) treated with LAVRT and 9 cases (6.5%) treated with LAVRH. The rate of intraoperative complications (2.5% for LAVRT and 5.8% for LAVRH, p=NS) and postoperative complications (21.2% for LAVRT and 19.4% for LAVRH, p=NS) were similar in both groups. In terms of recurrence-free survival statistical adjustment was done with Cox regression for the following risk factors: tumour size, nodal status, LVSI, histology, age and type of operation. Adjustment did not alter the conclusions, but details of the adjustment were not reported.

In a retrospective cohort study, Beiner et al. [158] matched 90 patients undergoing LARVT with 90 patients undergoing LARVH for age (± 5 years), tumour size (± 1 mm), histology, grade, depth of invasion (± 1 mm), presence of capillary lymphatic space invasion, pelvic lymph node metastasis, and adjuvant radiotherapy. Eligibility criteria were: patients who sought preservation of fertility with cervical cancer, tumour size ≤2 cm, and not meeting the Society of Gynecologic Oncologists' definition of microinvasive cancer (squamous cell carcinoma, less than 3 mm invasion, and no capillary lymphatic space invasion). Five and 1 recurrences were diagnosed in the LARVT and LARVH group, respectively. Five-year recurrence-free survival rates were 95% and 100%, respectively (p=0.17).

In addition, 3 and 1 deaths occurred, resulting in 5-year survival rates of 99% and 100%, respectively (p=0.55).

The absence of differences in both studies needs to be interpreted with caution because of a lack of power and no reporting of confidence intervals.

In addition to these controlled studies, several case series were identified. The largest case series of Plante et al. [159] reported on 125 patients with early-stage cervical cancer (stages IA, IB, and IIA) and a desire to preserve fertility. All patients underwent. Mean follow-up was 93 months (range 4-225). There were 6 recurrences (4.8%) and 2 deaths (1.6%). The actuarial 5-year recurrence-free survival was 95.8% (95%CI 0.90-0.98) for the entire series, and 79% (95%CI 0.49-0.93) in the group in which RVT was abandoned (p=0.001). Tumour size >2 cm was associated with a higher risk of recurrence (p=0.002) (3 recurrences in 13 women). Fifty-eight women conceived a total of 106 pregnancies: 77 pregnancies (73%) reached the third trimester of which 58 (75%) delivered at term. The number of women attempting pregnancy was not reported.

Hertel et al. [160] published a case series of 108 patients undergoing RVT with lymphadenectomy (TNM stage IA1, L1 N=18, IA2 N=21, IB1 N=69). Eight patients were excluded as the study criteria were not met after RVT (tumour size >2 cm, neuroendocrine tumour type, tumour-involved resection margins, or positive pelvic lymph nodes). Three recurrences were found in the 100 patients (3%) treated according to the protocol. The projected 5-year recurrence-free and overall survival rates were 97% and 98%. The median follow-up time was 29 (1-128) months.

Shepherd et al. [161] reported a case series (N=123) of patients undergoing RVT with pelvic lymphadenectomy for early-stage cervical cancer. Eleven women (8.9%) had completion treatment (meaning that the fertility-sparing aspect was abandoned and more invasive treatment was given). Two had completion surgery and nine had chemoradiotherapy. Mean follow-up period was 45 months (SD 32 months, range 1-120 months). There were 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 women. There were 6 perioperative and 26 postoperative complications.

A smaller case series by Nam et al. [162] (N=59) reported 2 recurrences and 1 death by cervical cancer during a median follow-up of 31 months (range 7-70). Sixteen patients attempted to conceive resulting in 8 pregnancies and 3 healthy babies.

3.6.3. *Abdominal radical trachelectomy*

Compared to RVT, fewer studies are available on abdominal radical trachelectomy.

Nishio et al. [163] reported a case series (N=61) of Japanese women with FIGO stage IA1 and LVSI, FIGO stage IA2 or stage IB1, and a desire for fertility preservation. Median follow-up time was 27 months (range 1-79). There were six recurrences (9.8%). None of the recurrences occurred in patients with a tumour diameter of <20 mm, except in one case with adenocarcinoma. Twenty-nine women attempted to conceive, of which four were successful. All four women had live births: two preterm deliveries and two full-term deliveries. Li et al. reported no recurrences in a series of 64 women with cervical cancer (stage IA1 27%, IA2 12%, IB1 61%) treated with abdominal radical trachelectomy. Median follow-up was 22.8 months (range 1-78). Fourteen women had tumour sizes > 2 cm.

Kim et al. [164, 165] reported on a case series of 105 women with cervical cancer undergoing radical trachelectomy by either an abdominal (RAT; N=49), vaginal (RVT; N=52) or robotic approach (RRT; N=4). Twelve patients had FIGO stage IA1 disease (12%), 12 FIGO stage IA2 (12%), and 81 FIGO stage IB2 (77%). One patient recurred and died of cervical cancer 24 months after surgery. Two patients expired from non-oncologic causes during a median follow-up of 29 months (range 0.1-99.8).

3.6.4. *Fertility-sparing treatment according to tumour size*

Some of the above-mentioned studies excluded patients with a tumour size > 2 cm [158, 160], while other studies did not differentiate results by tumour size [161, 162, 164, 165]. Marchiole et al. reported 6 recurrences in 21 patients with a tumour size > 2 cm [157], Plante et al. 3/13 [159], Nishio et al. 5/13 [163] and Li et al. [166] reported no recurrences in 14 patients. Pooling of these data would not be valid due to the differences in follow-up time. However, these results give additional support to the recommendations of SIGN that patients with tumours > 2 cm should not be offered fertility-sparing treatment.

3.6.5. Experimental protocols

Two small observational studies were identified on experimental treatment strategies.

3.6.5.1. Simple trachelectomy.

In a small pilot study, Rob et al. [167] describe a surgical protocol involving simple trachelectomy in 40 patients (10 IA2 patients [40% with LVSI], and 27 IB1 patients [38.5% with LVSI]), which was preceded by neoadjuvant chemotherapy in 9 patients. The median follow-up was 47 months (range 12-102 months). One central recurrence occurred (in the isthmic part of the uterus) 14 months after surgery.

3.6.5.2. Neoadjuvant therapy

Maneo et al. [168] described a chemo-surgical conservative therapy for stage IB1 cervical cancer in 21 patients desiring to preserve fertility. There were no recurrences after a median follow up of 69 months.

Conclusions

- **The recurrence rate in patients with cervical cancer FIGO stage IA1 treated with primary conization seems to be low (range: 0-10%) and might be limited to patients with positive resection margins (Bisseling 2007, Kim 2010, Lee 2009, Yahata 2010, Reynolds 2010; very low level of evidence).**
- **There is no evidence that women with cervical cancer stage IA1, IA2 or IB1 and a tumour < 2 cm undergoing radical trachelectomy have increased recurrence rates compared with standard therapy (radical hysterectomy), but this cannot be excluded either (SIGN 2008, Hertel 2006, Beiner 2008, Shepperd 2006, Kim 2011, Nam 2011, Machiole 2007, Plante 2011, Nishio 2009, Li 2011; very low level of evidence).**
- **There are indications of higher recurrence rates in patients with a tumour size > 2 cm, although the absolute numbers are limited (SIGN 2008, Marchiole 2007, Plante 2011, Nishio 2009, Li 2011; very low level of evidence).**
- **No evidence is available on the differences in outcome between radical vaginal trachelectomy and radical abdominal trachelectomy.**

Other considerations

In a small case series of 9 women with stage IB1 cervical cancer treated with neoadjuvant chemotherapy [169], Berger et al. found similar results as Maneo et al. [168]. These results were presented as an abstract.

Recommendations

- **In women requesting fertility conservation, radical trachelectomy and pelvic lymph node dissection can be considered, providing the tumour diameter is less than 2 cm (1C).**
- **An alternative experimental treatment might be neoadjuvant chemotherapy, pelvic lymph node dissection and conisation (2C).**
- **Cold knife conisation or large loop excision of the transformation zone (LLETZ) is adequate treatment for women with IA1 disease where fertility conservation is requested. If LVSI is present PLND needs to be considered (2C).**
- **Cold knife conisation or LLETZ combined with pelvic lymph node dissection may be adequate treatment in women with early stage disease and no LVSI (FIGO IA2 and microscopic IB1) requesting fertility conservation (2C).**
- **Women requesting fertility conservation should be informed of the potential additional risk of recurrence and of the experimental nature of trachelectomy (1C).**

3.7. Treatment of invasive cancer during pregnancy

SIGN recommended that the choice of a therapeutic modality for pregnant women with cervical cancer should be decided in the same manner as for non-pregnant patients, as there was no evidence identified to suggest that pregnancy accelerates the natural history of cervical cancer. The prognosis of a pregnant patient with cervical cancer is similar to that of a non-pregnant patient when matched for stage, tumour type and tumour volume. Disease-specific survival is independent of the trimester of pregnancy in which the diagnosis is made [20].

SIGN also stated that the evidence supports immediate treatment for patients diagnosed with cervical cancer at or before 16 weeks of gestation, irrespective of stage [20]. After 16 weeks of gestation, in patients with early stage disease (FIGO 1A1, 1A2, 1B), delivery may be delayed until foetal maturity. For women with more advanced disease, there is no good evidence to support delaying treatment to allow foetal maturity, as very few cases are described in the literature. No evidence was identified that compared maternal survival after diagnosis at different periods of gestation. If gestational age is less than 20 weeks at diagnosis of advanced cervical cancer (FIGO IB2 or higher), evidence supports immediate delivery and treatment of the disease. If gestational age is more than 20 weeks, delivery and treatment should be initiated within four weeks of diagnosis.

SIGN did not identify RCTs describing outcomes after delivery by caesarean section compared to vaginal delivery and retrospective studies found no statistically different survival between both methods [20].

After the search date of the SIGN guideline (i.e. 2005), no relevant systematic reviews, RCTs or observational studies were identified.

Conclusions

- **There is no evidence to suggest that pregnancy accelerates the natural history of cervical cancer. The prognosis of a pregnant patient with cervical cancer seems to be similar to that of a non-pregnant patient (SIGN 2008; very low level of evidence).**
- **The evidence seems to be favourable of immediate treatment for patients diagnosed with cervical cancer at or before 16 weeks of gestation, irrespective of stage (SIGN 2008; very low level of evidence).**
- **If gestational age is less than 20 weeks at diagnosis of advanced cervical cancer (FIGO IB2 or higher), evidence seems to be favourable of immediate delivery and treatment of the disease (SIGN 2008; very low level of evidence).**

Other considerations

Amant et al. published a consensus-based guideline on the treatment of gynaecologic cancers during pregnancy [170]. Treatment of cervical cancer during pregnancy primarily depends on the gestational age at which the diagnosis was made:

- When cervical cancer is diagnosed during the first trimester of a wanted pregnancy, a conservative approach is proposed to reach the second trimester;
- Treatment of cervical cancer during the second trimester is determined by the stage:
  - Stage IA1 disease is treated by a flat cone biopsy;
  - For stage IA2-1B1 less than 2 cm, NACT followed by conservative surgery (e.g. trachelectomy) can be considered in the absence of nodal metastasis;
  - For stage IB1 2-4 cm, lymphadenectomy is mandatory but can be performed after NACT. The potential to preserve the pregnancy depends mainly on the nodal status and the response to NACT;
  - For higher stages fertility-sparing treatment is not recommended;
- During the third trimester, foetal maturity is awaited and a caesarean delivery (to prevent recurrences in the episiotomy scar) followed by standard treatment is proposed. However, when the cervix is cleared from tumour, a vaginal delivery can be proposed.

Since these recommendations reflect the opinion of the Belgian experts and in view of the absence of sound evidence, the guidelines of Amant et al. are adopted.

Recommendations

- **When cervical cancer is diagnosed during the first trimester of a wanted pregnancy, a conservative approach is proposed to reach the second trimester (1C).**
- **Treatment of cervical cancer during the second trimester is determined by the stage (1C):**
  - **Stage IA1 disease is treated by a flat cone biopsy;**
  - **For stage IA2-1B1 less than 2 cm, NACT followed by conservative surgery (e.g. trachelectomy) can be considered in the absence of nodal metastasis;**
  - **For stage IB1 2-4 cm, lymphadenectomy is mandatory but can be performed after NACT. The potential to preserve the pregnancy depends mainly on the nodal status and the response to NACT;**
  - **For higher stages fertility-sparing treatment is not recommended.**
- **During the third trimester, foetal maturity is awaited and a caesarean delivery followed by standard treatment is proposed (1C).**

3.8. Sexual morbidity after treatment for cervical cancer

Concerning physical interventions, SIGN 2008 [20] recommends that women should be offered a vaginal stent or dilator to prevent post-radiotherapy vaginal complications, and that topical oestrogens or benzydamine douches may be considered to alleviate post-radiotherapy vaginal complications. Both recommendations are based on the Cochrane review of Denton et al. [171], although no significant results were reported. Concerning psycho-educational interventions, SIGN recommends that information about female sexual function should be offered to patients by a relevantly trained healthcare professional using a model of care that involves addressing motivational issues and teaching behavioural skills. This recommendation is based on one small RCT of poor quality evaluating psycho-educational therapy (consisting of two 90-minute group counselling sessions based on the Intervention-Motivation-Behavioural Skills model) (Robinson 1999), which reported a significantly reduced fear about sexuality, an increased knowledge, and increased vaginal dilation compliance rates. SIGN also recommends that patients should be offered support sessions by a designated member of their care team, as soon as possible after treatment, which may include one or more of the following: relaxation, personalised information about their disease and treatment, and emotional support and care. This recommendation is also based on one RCT (Peterson 2002) [20]. However, this study does not report on sexual functioning.

An update of the literature was done starting from the search date of the SIGN guideline, i.e. 2005. Three systematic reviews were identified (one review was published twice, as a Cochrane review and in a peer-reviewed journal).

A Cochrane review of Flynn et al.[172], focusing on interventions for psychosexual dysfunction in women treated for gynaecological malignancy, included data from 5 studies, comprising a total of 413 patients and examining 5 different interventions. One trial suggested a short-term benefit of vaginal dienoestrol in women after pelvic radiotherapy. A smaller proportion of women in the intervention group reported dyspareunia (6/44) than in the placebo group (16/49). However, although the authors of the primary study reported that this did not reach statistical significance with chi-square testing (p=0.09), Flynn et al. reanalyzed the data and their analysis suggested that there was a significant difference with an OR of 0.33 (95%CI 0.11-0.93). Among the 26 patients in the intervention group who were sexually active, the majority (N=20) reported no dyspareunia and the remainder reported mild dyspareunia only. Of the 30 women in the control arm who reported to be sexually active, 14 denied dyspareunia, 16 reported dyspareunia, of whom 6 graded it as severe. When the sexually active participants were analysed separately with dyspareunia as an outcome measure, a more pronounced treatment effect was demonstrated (OR 0.26, 95%CI 0.08-0.84). Another trial suggested a short-term benefit for one regimen of low dose-rate brachytherapy over another. Overall prevalence of dyspareunia was significantly lower in the 0.4 Gy/hr group compared to the 0.8 Gy/hr group (OR 0.37, 95%CI 0.15-0.93). The authors also stated that dyspareunia had resolved in the majority of both groups by 25 months after treatment and by this stage the differences were no longer significant (OR 0.39, 95%CI

0.07-2.05). However, low-dose-rate brachytherapy is not in widespread use for this indication.

A study of a clinical nurse specialist intervention, consisting of a pre-surgery consultation with a psychosexually-trained gynaecological oncology specialist nurse followed by home visits on an average of three further occasions after surgery, found no significant improvement in any of the sexual functioning scales examined, and although the rates of resumption of intercourse in those previously sexually active showed a trend towards benefit, this was not statistically significant (OR 0.63, 95%CI 0.17-2.36).

Significantly less women in the intervention group (2/10 versus 9/10) had diminished satisfaction with intercourse six months after their surgery (OR 0.03, 95%CI 0.00-0.37). A poor-quality study on psycho-educational group therapy, which was already included in the SIGN guideline (Robinson 1999), did not show any significant effect on sexual dysfunction. Another RCT on a couple-coping intervention, consisting of counselling sessions for the patient and the partner (Scott 2004), also showed no effect on sexual dysfunction. All 5 studies included by Flynn et al. were of poor methodological quality.

A Cochrane review of Miles et al [173], focusing on interventions for sexual dysfunction following treatments for cancer in general, identified the same study on the use of vaginal dienoestrol in women after pelvic radiotherapy as Flynn et al.

A Cochrane review of Miles et al. [174, 175] focusing on vaginal dilator therapy for women receiving pelvic radiotherapy, identified two low-quality randomized trials showing that psycho-educational interventions encouraging dilation increased compliance. However, one of these (Jeffries 2006) did not measure sexual function, while the other trial (Robinson 1999) found no difference in sexual function scores. Miles et al. also included observational studies in their review, but none of these provided evidence that vaginal dilation has an effect on sexual function. They also identified case reports describing vaginal fistulas or psychological morbidity. Miles et al. concluded that dilation during or immediately after radiotherapy can cause damage, that there is no evidence that it prevents stenosis, and that routine dilation during treatment is not supported by good evidence. They suggest that it may be useful for late vaginal complications when inflammation is settled. However, these findings are against the recommendations of SIGN and most other guidelines [174].

A search for primary studies from 2008 (i.e. the search date of the two most recent Cochrane reviews) until now only yielded 2 small low-quality studies that did not alter the conclusions, but we describe them briefly. One small pilot study on psycho-educational intervention for sexual dysfunction in women with gynaecologic cancer demonstrated a significant positive effect on sexual desire, arousal, orgasm, satisfaction, sexual distress, depression, and overall well-being, and a trend towards significantly improved physiological genital arousal and perceived genital arousal. Qualitative feedback indicated that the psycho-educational materials were very user-friendly, clear, and helpful. However, this was a before-after study without a comparison group and was therefore not retained [176]. A longitudinal study of sexual functioning and quality of life amongst 88 women with newly diagnosed stage IB1+ cervical cancer was excluded due to poor quality [177].

Conclusions

- **There is limited evidence in favour of psycho-educational interventions to alleviate psychosexual morbidity (SIGN 2008, Flynn 2009; very low level of evidence).**
- **There is limited evidence in favour of topical oestrogens or benzydamine douches for the alleviation of post-radiotherapy vaginal complications (SIGN 2008, Flynn 2009, Miles 2007; very low level of evidence).**
- **There is no evidence supporting the systematic use of vaginal dilation after radiotherapy (Miles 2010; very low level of evidence).**

Recommendations

- **Information about post-treatment female sexual function should be offered to patients by a relevantly trained healthcare professional using a model of care that involves addressing motivational issues and teaching behavioural skills (2C).**

- **Patients can be offered support sessions by a designated member of their care team, as soon as possible after treatment (2C).**
- **Topical oestrogens can be considered to alleviate post-(chemo)radiotherapy vaginal complications (2C).**
- **Vaginal dilation can be considered in patients treated with (chemo)radiotherapy (2C).**

3.9. Follow-up after treatment for cervical cancer

According to the SIGN guideline [20], history taking and clinical examination should be carried out during follow-up of patients with cervical cancer to detect symptomatic and asymptomatic recurrence. Cervical cytology or vault smears are not indicated to detect asymptomatic recurrence of cervical cancer. According to SIGN, MRI or CT should be considered initially to assess potential clinical recurrence in symptomatic patients. A whole body PET scan or PET-CT should be performed on all patients 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 [20].

3.9.1. Follow-up after primary treatment

No controlled studies that reported on survival or quality of life were found. One systematic review evaluated the type and frequency of follow-up following primary treatment [178]. This review also failed to find randomised or controlled studies and included 17 uncontrolled retrospective observational studies with widely differing patient populations. The frequency of follow-up was generally every 3-4 months during the first two years, every half year up to five years and annually up to 10 years after primary treatment. The median time to recurrence varied from 7 to 36 months. Of all recurrences, 62-89% was found in the first two years, 75-85% in the first three years and 89-99% in the first five years. Furthermore, 14-57% of the recurrences were found in the pelvis and 15-61% of the recurrences were remote metastases or metastases in several locations. Finally, 29-71% of the recurrences were detected by physical examination, 20-47% by chest X-ray, 0-34% by CT scan, 0-17% by vaginal smear, 0-2% by ultrasound, 0% by intravenous pyelogram, 0-26% based on tumour markers and 11-33% based on other tests. Symptomatic patients showed a median survival of 8-38 months after recurrence. For asymptomatic patients, survival varied between 8 months and a median survival that had not been achieved yet after 53 months of follow-up.

Based on this systematic review of retrospective studies, Cancer Care Ontario issued recommendations for the follow-up of women who are clinically disease free after receiving potentially curative primary treatment for cervical cancer [179] (see appendices 4.6.1.8).

Conclusion

- **There are indications that 89-99% of cervical carcinoma recurrences are detected within 5 years after primary treatment (Elit 2009; low level of evidence).**

3.9.2. PET for the detection of (local or distant) cervical carcinoma recurrence

One systematic review evaluated PET for the detection of cervical carcinoma recurrence [49]. Six retrospective studies were included. The sensitivity of PET was 96% (95%CI 87-99%) with a specificity of 81% (95%CI 58-94%) in a meta-analysis of three studies that evaluated the detection of recurrence in patients with a clinical suspicion. When there was no clinical suspicion, the sensitivity of PET was 92% (95%CI 77-98%) with a specificity of 75% (95%CI 69-80%) (meta-analysis of 2 studies). For one of the six included studies, no distinction was made between patients with or without a clinical suspicion. In this study, the sensitivity of PET was 100% (specificity 77%).

After this systematic review, five studies with more than 50 patients were published on PET or PET/CT.

In a retrospective series of 121 patients with a minimum follow-up of 6 months following successful treatment for cervical carcinoma, the sensitivity for detection of a recurrence with PET was 96% (specificity 84%; NPV 93%; PPV 91%) [180]. For patients without symptoms but in whom other tests did indicate a recurrence, the sensitivity of PET was 85%. When an increased tumour marker (SCCA or CEA) was detected in addition, the sensitivity was higher (100%). However, when patients did not

have symptoms and no other abnormal tests, the specificity was 80% (NPV 100%, PPV 0%).

A second prospective study examined a series of 52 patients with a suspicion of recurrence [181], and evaluated both PET and PET/CT. For PET, this study found a lower sensitivity of 80% (95%CI 64-96%) for the detection of a recurrence (specificity 78% [95%CI 62-94%]; NPV 81%; PPV 77%). Why the sensitivity in this study was lower than in other studies is not clear. It is possible that the different study design (prospective, with blind evaluation of PET and PET/CT images) provides a more realistic evaluation, although patient characteristics or selection criteria may also play a role. In that same study, the sensitivity of PET/CT was again higher (sensitivity 92% [95%CI 81-100%]; specificity 93% [95%CI 83-100%]; NPV 93%; PPV 92%).

The third retrospective study evaluated PET/CT in a series of 52 patients with a suspicion of recurrence [182]. The sensitivity of PET/CT for the detection of a recurrence was 90% (specificity 81%; NPV 88%; PPV 85%).

The fourth study was a retrospective evaluation of 103 patients in whom a PET or PET/CT was performed during follow-up [183]. In all patients, both symptomatic and asymptomatic, who had a recurrence based on PET or PET/CT, a recurrence was confirmed by biopsy or progression on follow-up imaging studies.

The fifth and last study evaluated PET for the detection of haematogenous bone metastases [78]. In a retrospective series of 226 patients with a suspicion of recurrence, PET had a sensitivity of 91% (specificity 100%; NPV 100%; PPV 91%) for the detection of haematogenous bone metastases.

Conclusions

- **There are indications that PET has a moderate to high sensitivity to detect a cervical carcinoma recurrence, but the evidence is conflicting. The specificity is low (Chung 2006, Kitajima 2008, Havrilesky 2005, Brooks 2009; low level of evidence).**
- **There are indications that PET/CT has a high sensitivity to detect a cervical carcinoma recurrence in asymptomatic and symptomatic patients. The specificity is moderate to high, but the evidence is conflicting (Kitajima 2008, Brooks 2009, Chung 2007; low level of evidence).**
- **There are indications that PET has a high sensitivity and specificity to detect haematogenous bone metastases in patients with a suspicion of recurrence (Liu 2009; low level of evidence).**

3.9.3. SCCA for the detection of cervical carcinoma recurrence

Four studies evaluated the accuracy of SCCA determination during the follow-up of patients with treated cervical carcinoma.

In a prospective study of 135 patients, the sensitivity of SCCA (cut-off value 1.4 ng/ml) for the detection of a recurrence before symptoms occurred was 79% (specificity 96%; NPV 91%; PPV 90%). In combination with a gynaecological exam, the sensitivity was 95% (specificity 96%; NPV 98%; PPV 91%) [184].

A retrospective study evaluated the SCCA value in 112 patients treated with chemoradiation [185]. The sensitivity of persistently increased SCCA levels (cutoff value 2.0 ng/ml) for the detection of a recurrence was 61% (specificity 98%; NPV 93%; PPV 85%).

A third retrospective study evaluated the SCCA in a group of patients (N=384) with squamous cell carcinoma [186]. The sensitivity of persistently increased SCCA levels (cutoff value 1.5 ng/ml) for the detection of a recurrence was 71% (specificity 98%; NPV 95%; PPV 85%).

Finally, the fourth retrospective study evaluated the SCCA in a group of patients (N=225) with stage IB or IIA squamous cell carcinoma [187]. The sensitivity of persistently increased SCCA levels (cutoff value 1.9 ng/ml) for the detection of a recurrence was 74% (specificity 96%; NPV 95%; PPV 79%). In 7-8% of the patients, a transient increase of SCCA levels was found that normalised after 6 to 8 weeks [186, 187].

Conclusions

- **There are indications that SCCA has a low sensitivity but a high specificity for the detection of a cervical carcinoma recurrence (Forni 2007, Yoon 2010, Chan 2002, Esajas 2001; low level of evidence).**
- **There are indications that SCCA in combination with a gynaecological exam has a high sensitivity and specificity for the detection of a cervical carcinoma recurrence (Forni 2007; low level of evidence).**

3.9.4. Vaginal smear for the detection of cervical carcinoma recurrence

Two studies that evaluated the value of smears during the follow-up of cervical carcinoma patients were found. One retrospective study evaluated the value of isthmic-vaginal smears during the follow-up of 94 patients following radical trachelectomy [188]. All central recurrences (N=2) were detected by smears. However, in 75% of the women, at least one abnormal smear was found (atypical cells, low- or high-grade intraepithelial lesions or malignant cells). In 46% of women, abnormalities found at the start of follow-up later disappeared. The second retrospective study evaluated smears in patients who had undergone radiation therapy with curative intent [189]. The sensitivity of a positive result for malignancy of a smear for the detection of a central recurrence was 66% (specificity 100%). The sensitivity of a positive result for a malignant or high-grade squamous intraepithelial lesion for the detection of a central recurrence was 83% (specificity 95%). In this series of patients, the majority of the smears were not abnormal: 66% of the smears were normal, reactive changes or atrophy with inflammation were observed in 25%, while atypical cells were present in 3%.

Conclusion

- **There are indications that post-trachelectomy smears have a high specificity for the detection of a central recurring cervical carcinoma (Chien 2005; very low level of evidence).**

3.9.5. Recommendations

- **A reasonable follow-up strategy involves follow-up visits every three to four months within the first two years, and every six to 12 months from years 3 to 5 (2C).**
- **History taking and clinical examination (including speculum exam with bimanual and pelvic/rectal examination) should be carried out during follow up of patients with cervical cancer to detect symptomatic and asymptomatic recurrence (1C).**
- **Cervical cytology or vault smears can be considered to detect asymptomatic recurrence of cervical cancer in cases where curative treatment of a central recurrence is an option and not previously treated with radiotherapy (2C).**
- **Imaging examinations (CT, MRI, PET, PET/CT) as part of routine follow-up in asymptomatic patients are not recommended (1C).**
- **SCCA can be considered during follow-up (1C).**
- **MRI of at least the pelvis should be considered initially to assess potential clinical pelvic recurrence in symptomatic patients (expert opinion).**
- **A PET/CT should be considered in all patients in whom recurrent or persistent disease has been demonstrated on clinical exam or MRI and in whom salvage therapy is being considered (1C).**

4. APPENDICES

4.1. Appendix 1: Grade system

4.1.1. Levels of evidence [190]

Quality level	Definition	Methodological Quality of Supporting Evidence
High (A)	We are very confident that the true effect lies close to that of the estimate of the effect	**RCTs without important limitations or overwhelming evidence from observational studies**
Moderate (B)	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different	**RCTs with important limitations (inconsistent results, methodological flaws, indirect, or imprecise) or exceptionally strong evidence from observational studies**
Low (C)	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect	**RCTs with very important limitations or observational studies or case series**
Very low (C)	**We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect**	

4.1.2. Down- or upgrading the evidence [191]

Study Design	Quality of Evidence	Lower if	Higher if
Randomized trial →	High	Risk of bias -1 Serious -2 Very serious	Large effect +1 Large +2 Very large
	Moderate	Inconsistency -1 Serious -2 Very serious	Dose response +1 Evidence of a gradient
Observational study →	Low	Indirectness -1 Serious -2 Very serious	All plausible confounding +1 Would reduce a demonstrated effect or +1 Would suggest a spurious effect when results show no effect
	Very low	Imprecision -1 Serious -2 Very serious Publication bias -1 Likely -2 Very likely	

4.1.3. Strength of recommendations

4.1.3.1. Definitions [192]

Grade	Definition
Strong	**The desirable effects of an intervention clearly outweigh the undesirable effects, or clearly do not**
Weak	**The desirable effects of an intervention probably outweigh the undesirable effects, or probably do not**

4.1.3.2. Factors that influence the strength of a recommendation [192]

Factor	Comment
Balance between desirable and undesirable effects	**The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. The narrower the gradient, the higher the likelihood that a weak recommendation is warranted**
Quality of evidence	**The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted**
Values and preferences	**The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted**
Costs (resource allocation)	**The higher the costs of an intervention—that is, the greater the resources consumed—the lower the likelihood that a strong recommendation is warranted**

4.2. Appendix 2: search strategy

4.2.1. OVID Medline

4.2.1.1. CIN

1. exp Cervical Intraepithelial Neoplasia/
2. CIN.mp or CIN1.mb or CIN2.mb or CIN3.mb.
3. (cervi* and (intraepithel* or epithel*)).mp.
4. (cervi* and dysplasia).mp.
5. (cervi* and carcinoma in situ).mp.
6. (cervi* and cancer in situ).mp.
7. (cervi* and (precancer* or pre-cancer*)).mp.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7

4.2.1.2. Early-stage cervical cancer

1. ((cervix or cervical) adj5 (neoplas$ or cancer$ or tumo$ or metasta$ or malign$ or $carcin$)).mp.
2. exp Uterine Cervical Neoplasms/
3. 1 or 2
4. (stage adj5 (IA$ or 1A$ or early)).mp.
5. 3 and 4
6. animals/ not humans/
7. 5 not 6

4.2.1.3. Neoadjuvant treatment

1. exp Uterine Cervical Neoplasms/
2. exp Cervix Uteri/ or cervi*.mp.
3. exp Adenocarcinoma/
4. adenocarcinoma*.mp.
5. exp Carcinoma, Adenosquamous/
6. adenosquamous carcinoma*.mp.
7. or/3-6
8. 2 and 7
9. (cervi$ adj5 neoplas$).tw.

10.(cervi$ adj5 cancer$).tw.
11.(cervi$ adj5 carcin$).tw.
12. (cervi$ adj5 tumo$).tw.
13. (cervi$ adj5 metasta$).tw.
14. (cervi$ adj5 malig$).tw.
15.or/9-14
16.1 or 8 or 15
17.exp Neoadjuvant therapy/
18.concomitant chemoradiotherapy.tw.
19.exp Combined Modality Therapy/
20.neo adjuvant therap$.tw.
21.neoadjuvant therap$.tw.
22.exp Chemotherapy, Adjuvant/
23.exp radiotherapy/
24.chemoradiotherapy.tw.
25.or/17-24
26.16 and 25
27.meta-analysis.mp,pt. or review.pt. or search:.tw.
28.randomized controlled trial.pt.
29.controlled clinical trial.pt.
30.randomized.ab.
31.placebo.ab.
32.clinical trials as topic.sh.
33.randomly.ab.
34.trial.ti.
35.27 or 28 or 29 or 30 or 31 or 32 or 33 or 34
36.exp animals/ not humans.sh.
37.35 not 36
38.26 and 37

4.2.1.4. Surgery vs. primary chemoradiation

1. (cervi$ adj5 neoplas$).tw.
2. (cervi$ adj5 cancer$).tw.
3. cervi$ adj5 carcin$).tw.
4. (cervi$ adj5 tumo$).tw.
5. (cervi$ adj5 metasta$).tw.
6. (cervi$ adj5 malig$).tw.
7. exp Uterine Cervical Neoplasms/
8. or/1-7
9. Uterine Cervical Neoplasms/su [Surgery]
10. Hysterectomy, Vaginal/ or Hysterectomy/
11. hysterectomy.mp.
12. lymphadenectomy.mp. or Lymph Node Excision/ or PLND.mp.
13. SLN$.mp.
14. Sentinel Lymph Node Biopsy/
15. Lymph Nodes/su [Surgery]
16. Cervix Uteri/su [Surgery]
17. trachelectomy.mp.
18. Pelvic Exenteration/
19. LLETZ.mp.
20. conisation.mp. or Conization/
21. large loop excision.mp.
22. exenterative surgery.mp.
23. or/9-22
24. Antineoplastic Combined Chemotherapy Protocols/
25. chemothera$.mp.
26. Drug Therapy/
27. radiothera$.tw.
28. Radiotherapy/
29. antineoplastic agents combined/

30.drug therapy combination/
31.combined modality therapy/
32.chemoradi$.mp.
33.Uterine Cervical Neoplasms/dt, rt [Drug Therapy, Radiotherapy]
34.or/24-33
35.8 and 23 and 34

4.2.1.5. Adjuvant treatment

1. exp Uterine Cervical Neoplasms/
2. exp Cervix Uteri/ or cervi*.mp.
3. exp Adenocarcinoma/
4. adenocarcinoma*.mp.
5. exp Carcinoma, Adenosquamous/
6. adenosquamous carcinoma*.mp.
7. or/3-6
8. 2 and 7
9. (cervi$ adj5 neoplas$).tw.
10. (cervi$ adj5 cancer$).tw.
11. (cervi$ adj5 carcin$).tw.
12. (cervi$ adj5 tumo$).tw.
13. (cervi$ adj5 metasta$).tw.
14. (cervi$ adj5 malig$).tw.
15.or/9-14
16.1 or 8 or 15
17.Radiotherapy/
18.concurrent chemoradiotherapy.tw.
19.exp Combined Modality Therapy/
20.exp radiotherapy/
21.chemoradiotherapy.tw.
22.or/17-21
23.16 and 22
24.meta-analysis.mp,pt. or review.pt. or search:.tw.
25.randomized controlled trial.pt.
26.controlled clinical trial.pt.
27.randomized.ab.
28.placebo.ab.
29.clinical trials as topic.sh.
30.randomly.ab.
31.trial.ti.
32.24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
33.exp animals/ not humans.sh.
34.32 not 33
35.23 and 34

4.2.1.6. Metastatic or recurrent cervical cancer

1. exp Uterine Cervical Neoplasms/
2. (cervi$ adj5 neoplas$).tw.
3. (cervi$ adj5 cancer$).tw.
4. (cervi$ adj5 carcin$).tw.
5. (cervi$ adj5 tumo$).tw.
6. (cervi$ adj5 metasta$).tw.
7. (cervi$ adj5 malig$).tw.
8. or/1-7
9. exp Neoplasm Metastasis/
10.metastas$.tw.
11.stage iv$.tw.
12.exp Neoplasm Recurrence, Local/
13.exp Recurrence/
14.(recurr$ and (distan$ or local$ or metasta$)).tw.
15.9 or 10 or 11 or 12 or 13 or 14
16.8 and 15
17.meta-analysis.mp,pt. or review.pt. or search:.tw.

18.randomized controlled trial.pt.
19.controlled clinical trial.pt.
20.randomized.ab.
21.placebo.ab.
22.clinical trials as topic.sh.
23.randomly.ab.
24.trial.ti.
25.17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26.exp animals/ not humans.sh.
27.25 not 26
28.16 and 27

4.2.1.7. Fertility-sparing treatment

1. ((cervix or cervical) adj5 (neoplas$ or cancer$ or tumo$ or metasta$ or malign$ or $carcin$)).mp.
2. exp Uterine Cervical Neoplasms/
3. 1 or 2
4. animals/ not humans/
5. 3 not 4
6. Infertility, Female/pc [Prevention & Control]
7. (fertility adj5 (preserv* or sparing or saving)).mp.
8. (preserv* adj5 reproduc*).mp.
9. exp Fertility/
10. exp Pregnancy/
11. trachelectomy.mp.
12. cervicectomy.mp.
13. exp Conization/
14. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. 5 and 14

4.2.1.8. Treatment during pregnancy

1. ((cervix or cervical) adj5 (neoplas$ or cancer$ or tumo$ or metasta$ or malign$ or $carcin$)).mp.
2. exp Uterine Cervical Neoplasms/
3. 1 or 2
4. animals/ not humans/
5. 3 not 4
6. exp Pregnancy/
7. 5 and 6

4.2.1.9. Sexual morbidity

1. ((cervix or cervical) adj5 (neoplas$ or cancer$ or tumo$ or metasta$ or malign$ or $carcin$)).mp.
2. exp Uterine Cervical Neoplasms/
3. 1 or 2
4. animals/ not humans/
5. 3 not 4
6. exp Sexual Dysfunctions, Psychological/
7. exp Sexual Behavior/
8. vaginal stenosis.tw.
9. vaginal fibrosis.tw.
10. vaginal shortening.tw.
11. sex$ aid$.tw.
12. dilator$.tw.
13. vibrator$.tw.
14. doughnut$.tw.
15. lubrication.tw.
16. exp Dyspareunia/
17. exp Sexual Dysfunctions, Psychological/ or exp Sexual Dysfunction, Physiological/
18. exp Coitus/ or exp Vagina/

19.exp Copulation/
20.exp Sexuality/
21.exp Vulvovaginitis/
22.stent*.mp.
23.exp Libido/
24.6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
25.5 and 24
26.limit 25 to yr="2005 -Current"
27.meta-analysis.mp,pt. or review.pt. or search:.tw.
28.26 and 27

4.2.2. PubMed

4.2.2.1. Diagnosis and staging

Filters used for systematic reviews: [population] AND [outcome] AND [study type] AND [time]

4.2.2.2. Follow-up

Population

Population Cancer topic searches, National Cancer Institute; gynaecologic cancers: cervical cancer. Adapted to include Dutch language and key words in abstract http://www.cancer.gov/cancertopics/litsearch	(((cervix neoplasms[majr] AND human[mh] AND (english[la] OR dutch[la])) OR ((cervix[Title/Abstract] OR cervical[Title/Abstract] OR exocervix[Title/Abstract] OR exocervical[Title/Abstract]) AND (cancer*[Title/Abstract] OR carcinoma*[Title/Abstract] OR adenocarcinoma*[Title/Abstract] OR malignan*[Title/Abstract] OR tumor*[Title/Abstract]] OR tumour*[Title/Abstract] OR neoplasm*[Title/Abstract]))))
Intervention	No filters used for intervention
Control	No filters used for control
Outcome	("Sensitivity and Specificity"[Majr] AND human[mh] AND (english[la] OR dutch[la])) OR (Sensitivity OR specificity OR ((pre-test or pretest) AND probability) OR "post-test probability" OR "predictive value*" OR "likelihood ratio*")
Study type: systematic reviews Hunt D, et al. Ann Intern Med 1997;126:532-538 Adapted to English and Dutch languages	(("meta-analysis"[pt] AND (english[la] OR dutch[la])) OR "meta-anal*"[tw] OR "metaanal*"[tw] OR ("quantitativ* review*"[tw] OR "quantitative* overview*"[tw]) OR ("systematic* review*"[tw] OR "systematic* overview*"[tw]) OR ("methodologic* review*"[tw] OR "methodologic* overview*"[tw]) OR ("review"[pt] AND "medline"[tw] AND (english[la] OR dutch[la]))
Time	Publication date from 2001

Filters used for randomised controlled trials: [population] AND [outcome] AND [study type] AND [time]

Population	(((cervix neoplasms[majr] AND human[mh] AND (english[la] OR dutch[la])) OR ((cervix[Title/Abstract] OR cervical[Title/Abstract] OR exocervix[Title/Abstract] OR exocervical[Title/Abstract]) AND (cancer*[Title/Abstract] OR carcinoma*[Title/Abstract] OR adenocarcinoma*[Title/Abstract] OR malignan*[Title/Abstract] OR tumor*[Title/Abstract]] OR tumour*[Title/Abstract] OR neoplasm*[Title/Abstract]))))
Intervention	No filters used for intervention
Control	No filters used for control
Outcome	("Sensitivity and Specificity"[Majr] AND human[mh] AND (english[la] OR dutch[la])) OR (Sensitivity OR specificity OR ((pre-test or pretest) AND probability) OR "post-test probability" OR "predictive value*" OR "likelihood ratio*")
Study type: randomised controlled trials Cochrane highly sensitive search strategy adapted to include non-indexed records and non-therapeutic studies	(randomized controlled trial[pt] OR controlled clinical trial[pt] NOT (animals[mh] NOT (animals[mh] AND humans [mh]))) OR (random*[tiab] OR trial[tiab] OR groups[tiab])
Time	Publication date from 2001

Filters used for observational studies: ([population] AND [outcome]) NOT ([SR] OR [RCT] OR [NOT]) AND [time]

Population	(((cervix neoplasms[majr] AND human[mh] AND (english[la] OR dutch[la])) OR ((cervix[Title/Abstract] OR cervical[Title/Abstract] OR exocervix[Title/Abstract] OR exocervical[Title/Abstract]) AND (cancer*[Title/Abstract] OR carcinoma*[Title/Abstract] OR adenocarcinoma*[Title/Abstract] OR malignan*[Title/Abstract] OR tumor*[Title/Abstract]] OR tumour*[Title/Abstract] OR neoplasm*[Title/Abstract]))))
Control	No filters used for control
Outcome	("Sensitivity and Specificity"[Majr] AND human[mh] AND (english[la] OR dutch[la])) OR (Sensitivity OR specificity OR ((pre-test or pretest) AND probability) OR "post-test probability" OR "predictive value*" OR "likelihood ratio*")
Study type: observational studies	NOT (SR OR RCTs)
NOT	"Head and Neck Neoplasms"[Majr] OR "Mass Screening"[Majr] OR "Papillomavirus Infections"[Majr] OR

	HPV[ti]
Time	Publication date from 2001

Pubmed SCC and CA125: (([population] and ([SCC] OR [CA-125])) NOT [NOT]) AND [time]

4.2.2.3. Follow-up

Population Cancer topic searches, National Cancer Institute; gynaecologic cancers: cervical cancer. Adapted to include Dutch language, abstract text words and to exclude head and neck cancer http://www.cancer.gov/cancertopics/litsearch	(((cervix neoplasms[majr] AND human[mh] AND (english[la] OR dutch[la])) OR ((cervix[Title/Abstract] OR cervical[Title/Abstract] OR exocervix[Title/Abstract] OR exocervical[Title/Abstract]) AND (cancer*[Title/Abstract] OR carcinoma*[Title/Abstract] OR adenocarcinoma*[Title/Abstract] OR malignan*[Title/Abstract] OR tumor*[Title/Abstract]] OR tumour*[Title/Abstract] OR neoplasm*[Title/Abstract])))) NOT "Head and Neck Neoplasms"[Majr]
Intervention	(("Case Management"[Mesh] OR "Office Visits"[Mesh] OR "Recurrence"[Mesh] OR "Neoplasm Recurrence, Local"[Mesh]) AND human[mh] AND (english[la] OR dutch[la])) OR (follow-up[Title/Abstract] OR followup[Title/Abstract] OR follow up[Title/Abstract] OR follow$[Title/Abstract] OR monitor$[Title/Abstract] OR surveillance[Title/Abstract] OR recur[Title/Abstract])
Control	No filters used for control
Outcome	No filters used for outcome
Study type: systematic reviews Hunt D, et al. Ann Intern Med 1997;126:532-538 Adapted to English and Dutch languages	(("meta-analysis"[pt] AND (english[la] OR dutch[la])) OR "meta-anal*"[tw] OR "metaanal*"[tw] OR ("quantitativ* review*"[tw] OR "quantitative* overview*"[tw]) OR ("systematic* review*"[tw] OR "systematic* overview*"[tw]) OR ("methodologic* review*"[tw] OR "methodologic* overview*"[tw]) OR ("review"[pt] AND "medline"[tw] AND (english[la] OR dutch[la]))
Time limit systematic reviews	Publication date from 2001
Time limit observational studies	Publication date from 2007

4.2.3. Embase

4.2.3.1. Diagnosis and staging (through OVID)

Population	((cervix or cervical) adj5 (neoplas$ or cancer$ or tumo$ or metasta$ or malign$ or $carcin$)).mp. exp Uterine Cervical Neoplasms/ 1 or 2
Outcome	exp "Sensitivity and Specificity"/ sensitivity.tw. specificity.tw. ((pre-test or pretest) adj probability).tw. post-test probability.tw. predictive value$.tw. likelihood ratio$.tw. or/1-7
Study type: systematic reviews	exp Meta Analysis/ ((meta adj analy$) or metaanalys$).tw. (systematic adj (review$1 or overview$1)).tw. or/1-3 cancerlit.ab. cochrane.ab. embase.ab. (psychlit or psyclit).ab. (psychinfo or psycinfo).ab. (cinahl or cinhal).ab. science citation index.ab. bids.ab. or/5-12 reference lists.ab. bibliograph$.ab. hand-search$.ab.

	manual search$.ab. relevant journals.ab. or/14-18 data extraction.ab. selection criteria.ab. 20 or 21 review.pt. 22 and 23 letter.pt. editorial.pt. animal/ human/ 27 not (27 and 28) or/25-26,29 4 or 13 or 19 or 24 31 not 30
Study type: randomised controlled trials	Randomized controlled trials/ Randomized controlled trial.pt. Random allocation/ Double blind method/ Single blind method/ Clinical trial.pt. exp clinical trials/ or/1-7 (clinic$ adj trial$1).tw. ((singl$ or doubl$ or treb$ or tripl$) adj blind$3 or mask$3)).tw. Placebos/ Placebo$.tw.

	Randomly allocated.tw. (allocated adj2 random).tw. or/9-14 8 or 15 Case report.tw. Letter.pt. Historical article.pt. Review of reported cases.pt. Review, multicase.pt. or/17-21 16 not 23
Study type: observational studies	mass screening/ papilloma virus/ hpv.ti. or/1-3
Time and language	limit [search] to ((dutch or english) and yr="2001 -Current")

Population	((cervix or cervical) adj5 (neoplas$ or cancer$ or tumo$ or metasta$ or malign$ or $carcin$)).mp. exp Uterine Cervical Neoplasms/ 1 or 2
Intervention: SCC	exp squamous cell carcinoma antigen/ scc$.ti,ab. 1 or 2
Intervention: CA-125	exp CA 125 antigen/ CA125.ti,ab. Ca 125.ti,ab. Ca-125.ti,ab. or/1-4

Time and language	limit [search] to (human and (dutch or english) and yr="2001 -Current")

4.2.3.2. Early-stage cervical cancer

'uterine cervix cancer'/de OR 'uterine cervix carcinoma'/exp OR (cervi* NEAR/5 neoplas*):ab,ti OR (cervi* NEAR/5 cancer*):ab,ti OR (cervi* NEAR/5 carcin*):ab,ti OR (cervi* NEAR/5 tumo*):ab,ti OR (cervi* NEAR/5 metasta*):ab,ti OR (cervi* NEAR/5 malig*):ab,ti AND ('hysterectomy'/exp OR 'lymphadenectomy'/exp OR 'sentinel lymph node biopsy'/exp OR 'pelvis exenteration'/exp OR 'uterine cervix conization'/exp OR lletz OR trachelectomy OR conisation) AND [randomized controlled trial]/lim AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND ([dutch]/lim OR [english]/lim OR [french]/lim) AND [embase]/lim AND [2005-2011]/py

4.2.3.3. Neoadjuvant treatment

#1.	'uterine cervix cancer'/exp OR 'uterine cervix carcinoma'/exp OR (cervi* NEAR/5 neoplas*):ab,ti OR (cervi* NEAR/5 cancer*):ab,ti OR (cervi* NEAR/5 carcin*):ab,ti OR (cervi* NEAR/5 tumo*):ab,ti OR (cervi* NEAR/5 metasta*):ab,ti OR (cervi* NEAR/5 malig*):ab,ti
#2.	neoadjuvant AND ('therapy'/exp OR therapy)
#3.	neo AND ('adjuvant'/exp OR adjuvant) AND ('therapy'/exp OR therapy)
#4.	'preoperative therapy'
#5.	'concomitant chemoradiotherapy'
#6.	'multimodality cancer therapy'/exp OR 'multimodality cancer therapy'
#7.	'adjuvant chemotherapy'/exp OR 'adjuvant chemotherapy'
#8.	'radiotherapy'/exp OR 'radiotherapy'
#9.	'surgery'/exp OR 'surgery'
#10.	#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8
#11.	#1 AND #10
#12.	#9 AND #11
#13.	#12 AND ([cochrane review]/lim OR [meta analysis]/lim OR [randomized controlled trial]/lim OR [systematic review]/lim) AND ([article]/lim OR [article in press]/lim) AND ([dutch]/lim OR [english]/lim OR [french]/lim) AND [2005-2011]/py

4.2.3.4. Surgery vs. primary chemoradiation

'uterine cervix cancer'/de OR 'uterine cervix carcinoma'/exp OR (cervi* NEAR/5 neoplas*):ab,ti OR (cervi* NEAR/5 cancer*):ab,ti OR (cervi* NEAR/5 carcin*):ab,ti OR (cervi* NEAR/5 tumo*):ab,ti OR (cervi* NEAR/5 metasta*):ab,ti OR (cervi* NEAR/5 malig*):ab,ti AND ('hysterectomy'/exp OR 'lymphadenectomy'/exp OR 'sentinel lymph node biopsy'/exp OR 'pelvis exenteration'/exp OR 'uterine cervix conization'/exp OR lletz OR trachelectomy OR conisation OR (large AND loop AND excision) OR (exenterative AND surgery)) AND ('antineoplastic agent'/exp OR 'cancer chemotherapy'/exp OR 'cancer

combination chemotherapy'/exp OR 'combination chemotherapy'/exp OR 'radiotherapy'/exp OR chemoradiotherapy OR chemoradiation OR radiochemotherapy OR crt) AND ([cochrane review]/lim OR [meta analysis]/lim OR [randomized controlled trial]/lim OR [systematic review]/lim) AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND ([dutch]/lim OR [english]/lim OR [french]/lim) AND [embase]/lim

4.2.3.5. Adjuvant treatment

#1.	'uterine cervix cancer'/exp OR 'uterine cervix carcinoma'/exp OR (cervi* NEAR/5 neoplas*):ab,ti OR (cervi* NEAR/5 cancer*):ab,ti OR (cervi* NEAR/5 carcin*):ab,ti OR (cervi* NEAR/5 tumo*):ab,ti OR (cervi* NEAR/5 metasta*):ab,ti OR (cervi* NEAR/5 malig*):ab,ti
#2.	'concomitant chemoradiotherapy'
#3.	'multimodality cancer therapy'/exp OR 'multimodality cancer therapy'
#4.	'adjuvant chemotherapy'/exp OR 'adjuvant chemotherapy'
#5.	'radiotherapy'/exp OR 'radiotherapy'
#6.	‘'adjuvant'/exp AND 'radiotherapy'/exp
#7.	#2 OR #3 OR #4 OR #5 OR #6
#8.	#1 AND #7
#9.	#8 AND ([cochrane review]/lim OR [meta analysis]/lim OR [randomized controlled trial]/lim OR [systematic review]/lim) AND ([article]/lim OR [article in press]/lim) AND ([dutch]/lim OR [english]/lim OR [french]/lim) AND [2005-2011]/py

4.2.3.6. Metastatic cancer

#1.	'uterine cervix cancer'/exp OR 'uterine cervix carcinoma'/exp OR (cervi* NEAR/5 neoplas*):ab,ti OR (cervi* NEAR/5 cancer*):ab,ti OR (cervi* NEAR/5 carcin*):ab,ti OR (cervi* NEAR/5 tumo*):ab,ti OR (cervi* NEAR/5 metasta*):ab,ti OR (cervi* NEAR/5 malig*):ab,ti AND ([cochrane review]/lim OR [meta analysis]/lim OR [randomized controlled trial]/lim OR [systematic review]/lim) AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND ([dutch]/lim OR [english]/lim OR [french]/lim) AND [2005-2011]/py

4.2.3.7. Recurrent cancer

#1	'uterine cervix cancer'/exp OR 'uterine cervix carcinoma'/exp OR (cervi* NEAR/5 neoplas*):ab,ti OR (cervi* NEAR/5 cancer*):ab,ti OR (cervi* NEAR/5 carcin*):ab,ti OR (cervi* NEAR/5 tumo*):ab,ti OR (cervi* NEAR/5 metasta*):ab,ti OR (cervi* NEAR/5 malig*):ab,ti
#2.	'tumor recurrence'/exp
#3.	'recurrence':ab,ti
#4.	#2 OR #3
#5.	#1 AND #4

#6.	#1 AND #4 AND ([cochrane review]/lim OR [meta analysis]/lim OR [randomized controlled trial]/lim OR [systematic review]/lim) AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND ([dutch]/lim OR [english]/lim OR [french]/lim) AND [2005-2011]/py

4.2.3.8. Fertility-sparing treatment

#1	'uterine cervix cancer'/exp OR 'uterine cervix carcinoma'/exp OR (cervi* NEAR/5 neoplas*):ab,ti OR (cervi* NEAR/5 cancer*):ab,ti OR (cervi* NEAR/5 carcin*):ab,ti OR (cervi* NEAR/5 tumo*):ab,ti OR (cervi* NEAR/5 metasta*):ab,ti OR (cervi* NEAR/5 malig*):ab,ti
#2	'fertility'/de AND (preserv* OR sparing OR saving)
#3	preserv* AND reproduc*
#4	'pregnancy'/exp
#5	'fertility'/exp
#6	trachelectomy
#7	cervicectomy
#8	'conization'/exp
#9	#5 OR #6 OR #2 OR #3 OR #4 OR #7 OR #8
#10	#1 AND #9
#11	#10 AND (2005:py OR 2006:py OR 2007:py OR 2008:py OR 2009:py OR 2010:py OR 2011:py)

4.2.3.9. Treatment during pregnancy

#1	'uterine cervix cancer'/exp OR 'uterine cervix carcinoma'/exp OR (cervi* NEAR/5 neoplas*):ab,ti OR (cervi* NEAR/5 cancer*):ab,ti OR (cervi* NEAR/5 carcin*):ab,ti OR (cervi* NEAR/5 tumo*):ab,ti OR (cervi* NEAR/5 metasta*):ab,ti OR (cervi* NEAR/5 malig*):ab,ti
#2	'pregnancy'/exp
#3	#1 AND #2
#4	#3 AND (2005:py OR 2006:py OR 2007:py OR 2008:py OR 2009:py OR 2010:py OR 2011:py)

4.2.3.10. Sexual morbidity

#1	'uterine cervix cancer'/exp OR 'uterine cervix cancer' OR 'uterine cervix carcinoma'/exp OR 'uterine cervix carcinoma' OR (cervi* NEAR/5 neoplas*):ab,ti OR (cervi* NEAR/5 cancer*):ab,ti OR (cervi* NEAR/5 carcin*):ab,ti OR (cervi* NEAR/5 tumo*):ab,ti OR (cervi* NEAR/5 metasta*):ab,ti OR (cervi* NEAR/5 malig*):ab,ti
#2	sexual AND dysfunctions
#3	sexual AND ('behavior'/exp OR 'behavior')
#4	vaginal AND ('stenosis'/exp OR stenosis)
#5	vaginal AND ('fibrosis'/exp OR fibrosis)
#6	vaginal AND shortening
#7	'sex' OR 'sex'/exp OR sex AND aid
#8	dilator
#9	vibrator
#10	doughnut
#11	'lubrication'/de OR lubrication
#12	'dyspareunia'/exp OR dyspareunia
#13	'coitus'/exp OR coitus
#14	vagina
#15	copulation
#16	'sexuality'/exp OR sexuality
#17	vulvovaginitis
#18	stent*
#19	#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18
#20	#1 AND #19
#21	#20 AND (2005:py OR 2006:py OR 2007:py OR 2008:py OR 2009:py OR 2010:py OR 2011:py)

#22	#20 AND (2005:py OR 2006:py OR 2007:py OR 2008:py OR 2009:py OR 2010:py OR 2011:py) AND 'review'/it

4.2.3.11. Follow-up (through OVID)

Population systematic reviews	((cervix or cervical) adj5 (neoplas$ or cancer$ or tumo$ or metasta$ or malign$ or $carcin$)).mp. exp Uterine Cervical Neoplasms/ 1 or 2
Population observational studies	((cervix or cervical) adj5 (neoplas$ or cancer$ or tumo$ or metasta$ or malign$ or $carcin$)).mp. exp Uterine Cervical Neoplasms/ 1 or 2 exp "head and neck tumor"/ or exp "head and neck carcinoma"/ or exp "head and neck cancer"/ 3 not 4
Intervention	Follow-Up Studies/ follow-up.ti,ab. followup.ti,ab. follow up.ti,ab. Follow$.ti,ab. Monitor$.ti,ab. surveillance.ti,ab. Recur$.ti,ab. exp tumor recurrence/ exp recurrent disease/ or/1-10 letter.pt. editorial.pt Case report.tw. or/12-14 11 not 15
Control	No filters used for outcome

Study type: systematic reviews	exp Meta Analysis/ ((meta adj analy$) or metaanalys$).tw. (systematic adj (review$1 or overview$1)).tw. or/1-3 cancerlit.ab. cochrane.ab. embase.ab. (psychlit or psyclit).ab. (psychinfo or psycinfo).ab. (cinahl or cinhal).ab. science citation index.ab. bids.ab. or/5-12 reference lists.ab. bibliograph$.ab. hand-search$.ab. manual search$.ab. relevant journals.ab. or/14-18 data extraction.ab. selection criteria.ab. 20 or 21 review.pt. 22 and 23 letter.pt. editorial.pt. animal/ human/ 27 not (27 and 28) or/25-26,29

	4 or 13 or 19 or 24 31 not 30
Time and language limit systematic reviews	limit [search] to (human and (dutch or english) and yr="2001 -Current")
Time and language limit observational studies	limit [search] to (human and (dutch or english) and yr="2007 -Current")

4.3. Appendix 3: quality appraisal of guidelines

Source	Title	Standardised Methodology Score	Final Appraisal
Cancer Care Ontario	Follow-up for Women after Treatment for Cervical Cancer: Guideline Recommendations (Evidence-Based Series #4-16)	96%	**Recommended**
Cancer Care Ontario	Chemotherapy for Recurrent, Metastatic, or Persistent Cervical Cancer: A Clinical Practice Guideline (Evidence-Based Series #4-20)	95%	**Recommended**
Cancer Care Ontario	Primary Treatment for Locally Advanced Cervical Cancer: Concurrent Platinum-based Chemotherapy and Radiation (Practice Guideline Report #4-5)	92%	**Recommended**
Scottish Intercollegiate Guidelines Network	Management of cervical cancer. A national clinical guideline.	83%	**Recommended**
Haie-Meder C et al.	SOR guidelines for concomitant chemoradiotherapy for patients with uterine cervical cancers: evidence update bulletin 2004	80%	**Recommended**
Cancer Care Ontario	PET Imaging in Cervical Cancer: Recommendations	63%	**Not recommended**
National Comprehensive Cancer Network	Cervical cancer V.I. 2010	52%	**Not recommended**
Sturgeon CM et al.	National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines for Use of Tumor Markers in Liver, Bladder, Cervical, and Gastric Cancers	52%	**Not recommended**
American College of Radiology	ACR Appropriateness Criteria®: Staging of Invasive Cancer of the Cervix	50%	**Not recommended**
Society of American Gastrointestinal and Endoscopic Surgeons	SAGES Guidelines for the Use of Laparoscopic Ultrasound	48%	**Not recommended**
National Health and Medical Research	Screening to Prevent Cervical Cancer: Guidelines for the Management of Asymptomatic Women with Screen Detected	42%	**Not recommended**

Source	Title	Standardised Methodology Score	Final Appraisal
Council	Abnormalities		
Resbeut M et al.	Standards, Options and Recommandations pour la prise en charge de patients atteintes de cancer invasif du col utérin (stade non métastatique)	32%	**Not recommended**
International Agency for Research on Cancer	European guidelines for quality assurance in cervical cancer screening	32%	**Not recommended**
Nag S et al.	The American Brachytherapy Society recommendations for low-dose-rate brachytherapy for carcinoma of the cervix	30%	**Not recommended**
Nag S et al.	The American Brachytherapy Society recommendations for high-dose-rate brachytherapy for carcinoma of the cervix	30%	**Not recommended**
Amant F et al.	Gynecologic cancers in pregnancy: guidelines of an international consensus meeting	29%	**Not recommended**
Institut National du Cancer	Cancer invasif du col utérin	29%	**Not recommended**
Haie-Meder C et al.	Cervical cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up	28%	**Not recommended**
Morice P et al.	French recommendations for invasive cervix cancer management during pregnancy on the behalf of the Société française d'oncologie gynécologique, the Société française de chirurgie pelvienne and the Collège national des gynécologues et obstétriciens français	25%	**Not recommended**
Vereniging van Integrale Kankercentra	Cervixcarcinoom	20%	**Not recommended**
Nagase S et al.	Evidence-based guidelines for treatment of cervical cancer in Japan: Japan Society of Gynecologic Oncology (JSGO) 2007 edition	13%	**Not recommended**
Toita T et al.	A consenus-based guideline defining the clinical target volume for pelvic lymph nodes in external beam radiotherapy for uterine	6%	**Not recommended**

Source	Title	Standardised Methodology Score	Final Appraisal
	cervical cancer		
Small W et al.	Consensus guidelines for delineation of clinicaltarget volume for intensity-modulated pelvic radiotherapy in postoperative treatment of endometrial and cervical cancer	4%	**Not recommended**
Association of Directors of Anatomic and Surgical Pathology	Recommendations for the Reporting of Surgical Specimens Containing Uterine Cervical Neoplasms	3%	**Not recommended**
Benedet JL et al.	**FIGO staging classifications and clinical practice guidelines in the management of gynecologic cancers**	**0%**	**Not recommended**

4.4. Appendix 4: quality appraisal checklists CocanCPG

4.4.1. Systematic reviews

- Internal validity
- The study addresses an appropriate and clearly focused question
- A description of the methodology used is included
- The literature search is sufficiently rigorous to identify all the relevant studies
- Study quality is assessed
- Data extraction is clearly described
- The most important characteristics from the original research are described
- There are enough similarities between the selected studies to make combining them reasonable
- Statistical pooling is correctly performed
- Statistical heterogeneity is adequately taken into account
- Study quality is taken into account
- Overall assessment of the study
- Are the results of the systematic review:
  - valid?
  - applicable to the patient group targeted in the search question?

4.4.2. Randomised controlled trials

- Internal validity
- The study addresses an appropriate and clearly focused question
- The assignment of subjects to treatment groups is randomized
- An adequate concealment method is used
- Subjects are kept blind about treatment allocation
- Outcome assessors are kept blind about treatment allocation
- The treatment and control groups are similar at the start of the trial
- The only difference between groups is the treatment under investigation
- All relevant outcomes are measured in a standard, valid and reliable way
- All the subjects are analyzed in the groups to which they were randomly allocated (intention to treat)
- Overall assessment of the study
- Are the results of the study:
  - valid?
  - applicable to the patient group targeted in the search question?

4.4.3. Cohort studies

- Internal validity
- The study addresses an appropriate and clearly focused question
- The cohort being studied is selected from source populations that are comparable in all respects other than the factor under investigation
- The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis
- Comparison by exposure status is made between full participants and those lost to follow up
- The outcomes are clearly defined
- The assessment of outcome is made blind to exposure status
- The measure of assessment of exposure is reliable
- The main potential confounders are identified and taken into account in the design and analysis
- Overall assessment of the study
- Are the results of the study:
  - valid?
  - applicable to the patient group targeted in the search question?

4.4.4. Case-control studies

- Internal validity
- The study addresses an appropriate and clearly focused question

- The cases and controls are taken from comparable populations
- The same exclusion criteria are used for both cases and controls
- Cases are clearly defined and differentiated from controls
- Case ascertainment is performed blind from the exposure status
- Exposure status is measured in a standard, valid and reliable way
- The main potential confounders are identified and taken into account in the design and analysis
- Overall assessment of the study
- Are the results of the study:
  - valid?
  - applicable to the patient group targeted in the search question?

4.4.5. Diagnostic accuracy studies

- Internal validity
- The index test being studied is clearly specified
- The index test is compared with a reference standard
- The reference standard is likely to correctly classify the target condition
- The spectrum of the included patients is representative of the patients who will receive the test in practice
- Selection criteria are clearly described
- The time period between reference standard and index test is short enough to be reasonably sure that the target condition did not change between the two tests
- The whole sample or a random selection of the sample received verification using the reference standard of diagnosis
- Patients received the same reference standard regardless of the index test result
- The reference standard is independent of the index test (i.e. the index test did not form part of the reference standard)
-
- The execution of the index test is described in sufficient detail to permit replication of the test
- The execution of the reference standard is described in sufficient detail to permit its replication
- The index test results were interpreted without knowledge of the results of the reference standard
- The reference standard results were interpreted without knowledge of the results of the index test
- The same clinical data were available when test results were interpreted as would be available when the test is used in practice
- Uninterpretable/ intermediate test results are reported
- Withdrawals from the study are explained
- Overall assessment of the study
- Are the results of the study:
  - valid?
  - applicable to the patient group targeted in the search question?

4.5. Appendix 5: external expert review

N°	Item	Recommendation(s)	GOR	LoE	Comments	Min	Max	Mean	Median	% 4 or 5	Decision
1	Treatment of high-grade CIN	It is considered common sense that histological confirmation of a high-grade CIN is required before definitive treatment is undertaken	Expert opinion		EE4: No see & treat if high grade smear and high grade aspect on colposcopy?	4	5	4,8	5	100%	Replaced by new recommendation
2		Women with high-grade CIN require treatment, watchful waiting cannot be considered	1	C	EE3: what about verry yong patient EE4: how about very young patients? < 25y?	3	5	4,3	4	88%	Added as other consideration
3		Treatment of pregnant women can be delayed until after the delivery	1	C	EE4: if colposcopy reassuring	4	5	4,8	5	100%	Comment withdrawn by expert; 'with high-grade CIN' added to recommendation
4		Ablative and excisional therapies are both recommended treatment options for high-grade CIN	1	B	EE4: cryotherapy for high grade lesions?	3	5	4,5	5	88%	Added as other consideration
5		Excisional techniques can be preferred over ablation in the majority of cases because they permit histological evaluation of the transformation zone	Expert opinion			4	5	4,8	5	100%	
6		The size and shape of the excised specimen should be determined by the colposcopic delineation of the lesion	Expert opinion			4	5	4,8	5	100%	
7		The risk for adverse obstetric outcomes with excisional therapy should be weighted against a higher risk of recurrence and difficulties in evaluating complete removal of the lesion when applying ablational therapies	2	B	EE4: but rather vague recommendation, no clear advise	3	5	4,5	5	75%	Criteria added
8		Women should be informed about the possible adverse obstetric outcomes of excisional therapy	1	B		3	5	4,6	5	88%	
9		Women treated for high-grade disease (CIN2, CIN3, CGIN) can be proposed a 6, 12 and 24-month follow-up cytology and thereafter annual follow-up cytology for a further 5 years before returning to screening at routine interval	1	C	EE2: depending whether the lesion was completely removed and HPV status at 6 months postconisation EE5: What about HPV testing? See Belgian and international guidelines and Belgian reimbursment criteria for HPV testing EE6: IF HPV NEGATIVE	3	5	4,5	5	88%	Merged with recommendation 11 + rephrased
10		Colposcopy can be added at 6 months in the follow up of women treated with CIN	2	C	EE1: Only in case of positive margins EE2: HPV testing much more sensitive - colposcopy never been a screening tool EE4: zoals vermeld in IARC: low evidence, marginal increased sensitivity, no data on specificity. IARC guidelines verwijzen naar NHS guidelines 2004. In de updated NHS guidelines 2010 http://www.cancerscreening.nhs.uk/cervical/publications/nhscsp20.pdf (pg 39) wordt de colposcopie na 6 maanden niet langer vermeld.	1	5	3,8	4	75%	Removed
11		A woman already undergoing annual cytological review for follow-up of a previously treated high-grade CIN, may be offered HPV testing. In case of negative cytology and HPV testing on two consecutive occasions, screening within the general screening programme can be considered	Expert opinion		EE4: with two extra HPV-tests, you save one PAP-smear? Definition of general screening program in Belgium? EE5: Same remark then before EE6: TWO CONSECUTIVE ONLY	3	5	4,3	4	88%	Merged with recommendation 9 + rephrased
12		If the margins of the treatment biopsy are involved with CIN or are uncertain, close follow-up with cytology and colposcopy is warranted	2	C	EE4: colposcopy?? Zie http://www.cancerscreening.nhs.uk/cervical/publications/nhscsp20.pdf. Endocervical margin can not be assessed by colposcopy. Define close FU? Verschil met negative margins??	1	5	4,0	5	75%	Removed

N°	Item	Recommendation(s)	GOR	LoE	Comments	Min	Max	Mean	Median	% 4 or 5	Decision
13		Ablational therapy can only be considered if a number of conditions are fulfilled: - The entire transformation zone must be visible; - One or more biopsies should be taken from the area or areas that colposcopically show the most severe change; - The result of the biopsy or biopsies should be available prior to the destructive therapy; - Cryotherapy should not be offered to women with large lesions, occupying more than 75% of the ectocervix, extending to the vaginal wall or extending more then 2 mm beyond the cryoprobe. This applies also to cold coagulation but not to radical diathermy; - There should be no evidence of invasive disease on cytology, colposcopy, or biopsy; - The Pap smear should not contain glandular atypical cells; - The destructive therapy should be carried out under colposcopic control by an experienced colposcopist; - There must be adequate follow-up.	Expert opinion			3	5	4,1	4	88%	Moved up (after recommendation 8)
14	Diagnosis and staging	All patients with visible, biopsy proven cervical carcinoma should have an MRI scan of at least the pelvis	1	C		5	5	5,0	5	100%	
15		Contrast-enhanced CT should be considered as an alternative to MRI in patients who have a medical contraindication for MRI	1	C	EE4: (PET/CT??)	4	5	4,9	5	100%	Comment withdrawn by expert
16		PET/CT is recommended in tumours FIGO stage IB1 with suspicious pelvic lymph nodes and in large tumours FIGO stage IB2 and above	1	C	EE4: low sensitivity for para-aortic lymph nodes, low level of evidence for distant metastases	3	5	4,3	4	89%	Comment withdrawn by expert
17		Sentinel lymph node biopsy is not recommended in patients with cervical cancer in routine clinical practice	1	C	EE3: what abaout Senticol study ref jco vol 29 n 131686-1691 interest in small lesion <2cm when bilat nodes are present : no false neg result	2	5	4,1	5	78%	New studies referenced in 'Other considerations' 'without lymphadenectomy' added
18		Tumour markers cannot be used for the diagnosis and staging of cervical cancer. However, they can be used for the monitoring of treatment response. Therefore, a pre-treatment baseline measurement can be considered	Expert opinion		EE4: evidence for usefulness in monitoring response???	3	5	4,2	4	78%	It is expert opinion
19	Stage IA cervical cancer	In patients with cervical cancer FIGO stage IA1 and free margins of the conization specimen, no further treatment is needed	1	C	EE4: even if no wish to preserve fertility!	4	5	4,8	5	100%	Comment withdrawn by expert
20		In patients with cervical cancer FIGO stage IA1 and positive margins of the conization specimen, repeat conization, total hysterectomy or utero-vaginal brachytherapy are options	2	C		4	5	4,9	5	100%	
21		The treatment choice should take into account the child wish and the operability of the patient	Expert opinion		EE4: also patient preerences and side effects of hysterectomy	3	5	4,4	5	75%	Removed
22		Based on the available evidence, parametrial involvement seems to be rare in patients with cervical cancer FIGO stage IA2, and hence a simple hysterectomy with systematic lymphadenectomy with the goal of at least 20 nodes is probably sufficient	2	C	EE2: all guidelines recommend wide local excision with parametrectomy either biy Wertheim or radical trachelectomy. Nevertheless I follow the reasoning EE4: waarom 20?	3	5	4,3	4,5	75%	Explanation added to text
23		In patients with cervical cancer FIGO stage IA2 who are medically inoperable and without fertility wish, radical external radiotherapy and brachytherapy can be considered	2	C	EE4: EBRT in case of LVSI negative?	3	5	4,8	5	88%	
24		In case the preoperative staging indicates that postoperative treatment will be needed, concomitant cisplatin-based chemoradiotherapy can be considered instead of surgery	2	C	EE4: Triple therapy to be avoided in view of morbidity. Randomized trial (Landoni F., ref 103) radical surgery versus radiotherapy, in which 64% of surgery patients recieved adjuvant radiotherapy, showed identical survival but significantly more severe morbidity in the surgery group. In case of pre-operative indications for adjuvant treatment, chemoradiation without surgery should be given!	2	5	4,0	4,5	63%	1C evidence 'is recommended' instead of 'can be considered' Also applies to more advanced stages: will be repeated there

N°	Item	Recommendation(s)	GOR	LoE	Comments	Min	Max	Mean	Median	% 4 or 5	Decision
25	Advanced non-metastatic cervical cancer	Short cycle, dose-intensive neo-adjuvant chemotherapy before surgery is recommended in patients with FIGO stage IB2, IIA, or IIB cervical cancer	1	B	EE4: add important note: "if considered for surgery". As length of cycles and dose-intensity are so important: define maximum length and minimal intensity in the recommendation!	2	5	4,0	4,5	67%	If considered for surgery' added Criteria added to recommendation
26		Evidence from EORTC 55994 trial is awaited to reconsider the place of NACT followed by surgery compared to concomitant chemo-radiotherapy in the management of women with FIGO IB2, IIA>4cm or IIB cervical cancer	Expert opinion			4	5	4,6	5	100%	Moved up (before recommendation 25)
27		A well-conducted RCT comparing primary radical surgery with primary chemoradiotherapy is needed before definite recommendations can be formulated	Expert opinion		EE4: Do you mean for stage Ib1?? If you mean Ib2-IIB, you repeat the recommendation re:EORTC 55994, as that is exactly what that trial is investigating. In view of the NACCCMA meta-analysis, comparing radical surgery without neo-adjuvant chemotherapy with chemoradiation is not appropriate.	1	5	4,1	5	86%	in patients with stage IB1 cervical cancer' added Explanation in text rephrased
28		Patients with a clinical stage IA2, IB, or IIA carcinoma of the cervix and risk factors for recurrence (positive pelvic lymph nodes and/or positive margins and/or microscopic involvement of the parametrium) who have undergone radical hysterectomy and pelvic lymphadenectomy should be considered for adjuvant treatment with concurrent platinum-based chemoradiotherapy	1	B		4	5	4,9	5	100%	
29		In patients with cervical cancer FIGO stage IB-IVA considered suitable for radical radiotherapy treatment, concurrent chemoradiotherapy with a platinum based chemotherapy is recommended, if fit enough	1	A	EE4: (IB2?)	5	5	5,0	5	100%	Comment withdrawn by expert
30		The balance of risks and benefits should be discussed with the patient before offering chemoradiation for treatment of cervical cancer	1	A		5	5	5,0	5	100%	
31		In patients with cervical cancer FIGO stage IIB-IVA, thermoradiotherapy can be considered as an alternative in case chemotherapy is contra-indicated, especially in higher tumour stages	1	B		2	5	4,0	4	86%	
32		In patients with cervical cancer FIGO stage IB-IIB, brachytherapy can be considered as a component of radical radiotherapy or chemoradiotherapy (1C). In patients with higher stages (IIIA-IIIB) cervical cancer, brachytherapy can be considered as a component of the main therapy	1	C	EE4: te zwak geformuleerd; brachytherapy is essential part of radical chemoradiation!!! Verschil tussen twee zinnen is mij niet volledig duidelijk	4	5	4,6	5	100%	should' instead of 'can be considered' One recommendation instead of two
33	Metastatic and recurrent disease	All recurrences should be discussed in the multidisciplinary oncological meeting	Expert opinion			4	5	4,9	5	100%	
34		Patients with a locoregional pelvic recurrence that is limited in size and not invading neighbouring structures, and who did not receive pelvic radiotherapy as part of their initial treatment, can be considered for resection or (chemo)radiotherapy	Expert opinion		EE4: how about resection followed by radiotherapy?	4	5	4,9	5	100%	Comment withdrawn by expert
35		In patients with recurrent cervical carcinoma confined to the pelvis after earlier (chemo)radiotherapy, pelvic exenteration can be considered (1C). The selection of operable patients can be optimized with a preoperative whole body PET or PET-CT scan, in addition to MRI and CT having confirmed the recurrent or persistent disease	1	C	EE4: confined to the central pelvis	4	5	4,9	5	100%	central' added
36		In patients with cervical cancer FIGO stage IVB or recurrent cervical carcinoma and who are no candidate for curative (chemo)radiotherapy or surgery, palliative chemotherapy should be offered, after discussion of the relative benefits and risks, with either: o cisplatin 50 mg/m2 on day 1 plus paclitaxel 135 mg/m2 every 3 weeks, or o cisplatin 50 mg/m2 on day 1 plus topotecan 0.75 mg/m2 on days 1 to 3 every 3 weeks	1	B	EE2: carboplatin Saito et al Jpn J Clin Oncol 2010;40:90 EE4: not familiar with precise schedules	3	5	4,3	4	88%	Saito et al. is ongoing trial
37		Triplet combinations and targeted therapies need to be evaluated in large phase III RCTs	Expert opinion			3	5	4,6	5	86%	

N°	Item	Recommendation(s)	GOR	LoE	Comments	Min	Max	Mean	Median	% 4 or 5	Decision
38	Fertility-sparing treatment	In women requesting fertility conservation, radical trachelectomy and pelvic lymph node dissection can be considered, providing the tumour diameter is less than 2 cm and no lymphatic-vascular space invasion is present	1	C	EE2: LVSI + irrelevant as a LND is performed EE4: the limitation of "no LVSI" is not mentioned in the studies and conclusions of full text. Why keep it?	3	5	4,6	5	86%	and no LVSI is present' removed from recommendation
39		An alternative experimental treatment might be neoadjuvant chemotherapy, pelvic lymph node dissection and conisation	Expert opinion		EE2: to be discussed as a guideline !! EE4: agree, would broaden it up	3	5	4,0	4	67%	Is an option (expert opinion), so not changed
40		Cold knife conisation or large loop excision of the transformation zone (LLETZ) is adequate treatment for women with IA1 disease where fertility conservation is requested. If LVSI is present PLND needs to be considered	2	C	EE4: Add comment re: negative resection margins as essential?	4	5	4,6	5	100%	
41		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	2	C	EE2: requires parametrectomy for local control EE4: Add comment re: negative resection margins as essential?	1	5	3,9	4	71%	Reformulated
42		Women requesting fertility conservation should be informed of the potential additional risk of recurrence and of the experimental nature of trachelectomy	1	C		4	5	4,9	5	100%	
43	Treatment during pregnancy	When cervical cancer is diagnosed during the first trimester of a wanted pregnancy, a conservative approach is proposed to reach the second trimester	Expert opinion		EE4: for early-stage only?	4	5	4,4	4	100%	Not only for early-stage
44		Treatment of cervical cancer during the second trimester is determined by the stage: o Stage IA1 disease is treated by a flat cone biopsy; o For stage IA2-1B1 less than 2 cm, NACT followed by conservative surgery (e.g. trachelectomy) can be considered in the absence of nodal metastasis; o For stage IB1 2-4 cm, lymphadenectomy is mandatory but can be performed after NACT. The potential to preserve the pregnancy depends mainly on the nodal status and the response to NACT; o For higher stages fertility-sparing treatment is not recommended	Expert opinion			4	4	4,0	4	100%	
45		During the third trimester, fetal maturity is awaited and a cesarean delivery followed by standard treatment is proposed	Expert opinion		EE2: cesarean section only when radical surgery at the same time is planned EE4: is it necessaty to await the second trimester to perform a flat cone biopsy?	3	5	4,3	4,5	83%	Explanation added to text
46	Sexual morbidity	Information about female sexual function should be offered to patients by a relevantly trained healthcare professional using a model of care that involves addressing motivational issues and teaching behavioural skills	2	C		4	5	4,4	4	100%	
47		Patients can be offered support sessions by a designated member of their care team, as soon as possible after treatment	2	C		4	5	4,4	4	100%	
48		Topical oestrogens can be considered to alleviate post-radiotherapy vaginal complications	2	C		4	5	4,6	5	100%	chemoradiotherapy
49		Vaginal dilation can be considered in patients treated with radiotherapy	2	C		3	5	4,0	4	63%	2C recommendation chemoradiotherapy
50	Follow-up	A reasonable follow-up strategy involves follow-up visits every three to four months within the first two years, and every six to 12 months from years 3 to 5	Expert opinion			4	5	4,8	5	100%	
51		History taking and clinical examination (including speculum exam with bimanual and pelvic/rectal examination) should be carried out during follow up of patients with cervical cancer to detect symptomatic and asymptomatic recurrence	Expert opinion			3	5	4,7	5	89%	
52		Cervical cytology or vault smears can be considered to detect asymptomatic recurrence of cervical cancer in cases where curative treatment of a central recurrence is an option	Expert opinion		EE2: cytology of no value EE4: for post-trachelectomy patients only??	2	5	3,9	4	67%	and not previously treated with radiotherapy' added
53		Imaging examinations (CT, MRI, PET, PET/CT) as part of routine follow-up in asymptomatic patients are not recommended	1	C		3	5	4,6	5	89%	
54		SCCA can be considered during follow-up	1	C	EE2: if elevated at diagnosis	3	5	4,3	4,5	75%	
55		MRI of at least the pelvis should be considered initially to assess potential clinical pelvic recurrence in symptomatic patients	Expert opinion		EE2: biopsies rather	3	5	4,3	4,5	75%	
56		A PET/CT should be considered in all patients in whom recurrent or persistent disease has been demonstrated on clinical exam or MRI and in whom salvage therapy is being considered	1	C		4	5	4,9	5	100%	
57		After five years of recurrence-free follow-up, the patient can return to annual assessment with a history, physical, and pelvic examination with cervical/vaginal cytology	Expert opinion		EE4: 99% of recurrences is found in the five first years after primary treatment (see full text). FU can thus be stopped after 5 years if still disease-free.	2	5	4,6	5	89%	Removed

After the validation meeting of October 4th 2011, the following changes were made to the scientific report and recommendations:

- To correctly apply the GRADE methodology, expert opinion was removed as level of evidence;
- In chapter 3.1.5 it was stressed that close observation can be an option for young women with CIN2;
- In chapter 3.1.5 medical treatment options voor high-grade CIN were briefly mentioned;
- In chapter 3.2.4 – other considerations, surgical para-ortic lymph node assessment was mentioned;
- In chapter 3.2.9, a general recommendation on multidisciplinary discussion was added;
- In chapter 3.3.1, the second recommendation was reformulated;
- Chapter 3.4 was restructured: a general introduction highlighting the historical standard treatments was added, the discussion on adjuvant treatment was moved to chapter 3.4.1 on stage IB1 and IIA1 disease, the discussion on primary chemoradiotherapy and neoadjuvant treatment was moved to chapter 3.4.2 on stage IB2, IIA2, IIB, III and IVA disease. In addition, the recommendation on the need for a trial comparing surgery with primary chemoradiation in stage IB1 patients was removed;
- In chapter 3.4.2.4, the second recommendation was reformulated.

4.6. Appendix 6: evidence tables

4.6.1. Guidelines

4.6.1.1. CIN

Treatment of high-grade lesions CIN 2, CIN 3 and CGIN

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
IARC 2008[6]	2006	Women with high-grade CIN require treatment; observational follow-up is not an option	Observational studies	No grading RCT no option for ethical reasons
		Local ablation or destruction, using laser ablation, cryotherapy, cold coagulation or radical diathermy is acceptable management strategies if colposcopy is satisfactory	RCTs	Low (downgraded for imprecision and risk of bias
		All women over the age of 50 years who have CIN3 at the endo-cervical margin and in whom satisfactory cytology and colposcopy cannot be guaranteed should have a repeat excision to try to obtain clear margins	Observational	Low
NHMRC 2006[5]	2005	Women with a histological diagnosis of CIN 2 or CIN 3 should be treated in order to reduce the risk of developing invasive cervical carcinoma	Observational studies	No grading RCT no option for ethical reasons
		Local ablative or excisional treatments should destroy or remove tissue to a depth of at least 7 mm	Case series	Very low
		There is no clearly superior method of fertility-sparing treatment for CIN 2 and 3	Meta analysis of RCT	Low (downgraded for imprecision and risk of bias)
		It is advisable that women with CIN 3 are not treated with cryotherapy	Expert opinion	No evidence

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
		The management of women diagnosed with AIS on cone biopsy will be dependent upon the age and fertility requirements of the women and the status of excision margins. Hysterectomy is recommended for women who have completed childbearing because of the difficulties of reliable cytological follow-up, a high recurrence rate and the reported multifocality of the disease	Case series	Very low

Follow up of CIN 2&3 after treatment

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
IARC 2008[6]	2006	Women treated for high-grade disease (CIN2, CIN3, CGIN) require 6, 12 and 24-month follow-up cytology and thereafter annual cytology for a further 5 years before returning to screening at routine interval. Colposcopy should be performed in addition to cytology at the 6-month follow-up visit	Observational studies	Low
		The role of HPV testing in follow-up after treatment HPV DNA detection predicted residual/recurrent CIN with significantly higher sensitivity (ratio: 1.27; 95%CI:1.06-1.51) and not-significantly lower specificity (ratio: 0.94; 95%CI: 0.87-1.01) than follow-up cytology. HPV DNA testing was also more sensitive than histology of the section margins (ratio:1.30; 95%CI: 1.05-1.62). HPV testing was even more specific but this difference in specificity was statistically insignificant	Meta-analysis of observational studies	Low
NHMRC 2006[5]	2005	A woman previously treated for HSIL requires a colposcopy and cervical cytology at 4–6 months after treatment. Cervical cytology and HPV typing should then be carried out at 12 months after treatment and annually thereafter until the woman has tested negative by both tests on two consecutive occasions. The woman should then be screened according to the recommendation for the average population	Observational studies	Low

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
		A woman already undergoing annual cytological review for follow-up of a previously treated HSIL may be offered HPV testing. Once she has tested negative by both cytology and HPV typing on two consecutive occasions, she should be screened according to the recommendation for the average population	Observational studies	Low

Specific recommendations on excisional therapy for CIN

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
IARC 2008[6]	2006	The procedure should be carried out under colposcopic control	Expert opinion	No grading
		The lesion together with the entire transformation zone should be removed		
		It is helpful to mark the excised specimen with a thread at 12 o'clock, thereby facilitating the histopathologist to orient the specimen.		
		Surgeons should avoid damage of the ecto-cervical epithelium or of the endo-cervical canal		
		A cervical dilator for orientation of the excision specimen is unhelpful		
		The size and shape of the excised specimen will be determined by the colposcopic delineation of the lesion		
		Excision should be mandatory if the lesion involves the endo-cervical canal		
		If the lesion involves the endo-cervical canal, endo-cervical sampling should be considered after the excision		
		Thorough histological assessment by a pathologist skilled in gynaecological pathology is essential		
		The histopathologist should be informed of the cytology and colposcopic findings		

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
		Cold knife conisation gives excision margins that are not affected by thermal artefact, whereas the margins of laser excisional cone or diathermy loop excision cone may be damaged. In skilled hands, the thermal artefact is generally minimal. In the meta-analysis of Martin-Hirsch et al., (2000) there was a clear advantage of cold knife cone biopsy over laser or LLETZ	Meta-analysis of RCT	
		Excision of the transformation zone in multiple fragments can complicate histopathological assessment. Furthermore, if microinvasive disease is present, it may be impossible to allocate a substage or define completeness of excision in fragmented excisional specimens. When using LLETZ, the external os and lower canal should be removed in a single sample. Disease lateral to the central area can be removed separately	Expert opinion	
		If cold knife conisation is performed great care must be taken to minimise side effects such as haemorrhage and cervical stenosis. Haemorrhage can be minimised by injecting the cervix pre-operatively with adrenalin 1 in 200,000. If haemorrhage is controlled with diathermy and the use of Monsel's solution cervical stenosis is much less likely to occur than if cervical sutures are used to control bleeding at the time of conisation	Expert opinion	
NHMRC 2006[5]	2005	Excess diathermy artefact should be avoided when using LEEPs in order to allow comprehensive pathological examination, including margin status.	Expert opinion	
		Cone biopsy may be necessary to treat women with high-grade squamous lesions and absolute indications that include: • failure to visualise the upper limit of the cervical transformation zone in a woman with a high-grade squamous abnormality on her referral cervical smear (i.e. unsatisfactory colposcopy); • suspicion of an early invasive cancer on cytology, biopsy or colposcopic assessment; • the suspected presence of an additional significant glandular abnormality (i.e. adenocarcinoma in situ) on cytology or biopsy (i.e. a mixed lesion)	Expert opinion	

Specific recommendations on ablative therapy for CIN

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
IARC 2008[6]	2006	Ablative therapy is only recommended if a number of selection criteria are fulfilled: • The entire transformation zone must be visible; • One or more biopsies should be taken from the area or areas that colposcopically show the most severe change; • The result of the biopsy or biopsies should be available prior to the destructive therapy; • Cryotherapy should not be offered to women with large lesions, occupying more than 75% of the ectocervix, extending to the vaginal wall or extending more then 2 mm beyond the cryoprobe. This applies also to cold coagulation but not to radical diathermy; • There should be no evidence of invasive disease on cytology, colposcopy, or biopsy; • The Pap smear should not contain glandular atypical cells; • The destructive therapy should be carried out under colposcopic control by an experienced colposcopist; • There must be adequate follow-up;	Expert opinion	
NHMRC 2006[5]	2005	Ablative therapy may be considered, provided: • The cervix has been assessed by an experienced colposcopist; • A targeted biopsy has confirmed the diagnosis; • There is no evidence of an invasive cancer on cytology, colposcopic assessment or biopsy; • The entire cervical transformation zone has been visualised; • There is no evidence of a glandular lesion on cytology or biopsy;	Expert opinion	

Treatment of residual and recurrent lesions of CIN

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
IARC 2008[6]	2006	The presence of residual disease warrants excision of the transformation zone although in skilled hands, destruction may be considered provided that the conditions relating to preoperative assessment are met. However, post-treatment recurrence frequently occurs in the endo-cervical canal where it is not colposcopically detectable and therefore not suitable for ablative therapy	Observational studies	Low
		In the case of recurrence or when colposcopy is unsatisfactory, excision using LLETZ or cold knife must be chosen.	Observational studies	Low

Treatment of a high-grade lesion during pregnancy

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
IARC 2008[6]	2006	The safety of delaying treatment of pregnant women has been shown in a number of cohort and retrospective uncontrolled studies	Observational studies	Low
NHMRC 2006[5]	2005	Definitive treatment of a high-grade lesion, with the exception of invasive cancer, may be deferred safely until after the pregnancy	Observational studies	Low

4.6.1.2. Diagnosis and staging of invasive cervical cancer

Reference	Search date	Recommendations	Evidence base	Level of evidence
SIGN 2008 [20]	2005	Pathology reports of cervical tumours should include the following histological features: • Tumour type • Tumour size • Extent of tumour • Depth of invasion • Patterns of invasion • Lymphovascular space invasion • Status of resection margins • Status of lymph nodes • Presence of pre-invasive disease	Prognostic studies (conflicting results)	Very low
		All patients with visible, biopsy proven cervical carcinoma (except those with FIGO IV disease) should have an MRI scan	SR of diagnostic accuracy studies	Moderate
		The MRI scan should include: • Thin section T2 weighted images perpendicular to the cervix • Sequences to include urinary tract and para-aortic nodal areas	Diagnostic accuracy studies	Low
		Post-contrast spiral CT should be considered as an alternative to MRI in patients who cannot have MRI	Diagnostic accuracy studies	Low
		Women who have clinically apparent FIGO stage IV disease should have post-contrast spiral or multislice CT scans of chest, abdomen and pelvis	Diagnostic accuracy studies	Low
		Patients not suitable for surgery should be considered for a PET scan	Diagnostic accuracy studies	Low
		Cystoscopy and sigmoidoscopy should not be routinely performed for staging purposes	Diagnostic accuracy studies	Low
		If imaging cannot exclude bladder or bowel involvement, cystoscopy and sigmoidoscopy should be used for staging	Diagnostic accuracy studies	Low
		Ultrasound, IVU and lymphangiography are not recommended for staging	Diagnostic accuracy studies	Low

4.6.1.3. Surgery for invasive cervical cancer

Reference	Search date	Recommendations	Evidence base	Level of evidence
SIGN 2008[20]	2005	Removal of pelvic lymph nodes is not recommended during treatment for FIGO IA1 disease	No evidence	Expert opinion
		Pelvic lymph nodes should be removed if FIGO IA2 disease is present	Observational studies: Raspagliesi F 2003, Delgado G 1990	Low
		In women with FIGO IA1 disease with LVSI the decision to carry out pelvic lymphadenectomy must be individualised taking account of the pattern and extent of invasion	No evidence	Expert opinion
		Radical surgery is recommended for FIGO IB1 disease if there are no contraindications to surgery	Unclear	
		Radical hysterectomy is not recommended if the tumour measures more than 4 cm to reduce the likelihood of using chemoradiotherapy post-surgery	Prognostic study	Low
		Cancer of the cervical stump should be managed in the same way as cervical cancer arising in an intact uterus	Observational studies	Low
		Laparoscopic-vaginal radical hysterectomy should not be offered to patients with tumour diameter greater than 2 cm	Observational studies	Low
		Surgeons wishing to offer laparoscopic-vaginal radical hysterectomy should have appropriate training	Observational studies	Low

4.6.1.4. Chemoradiotherapy vs. radiotherapy alone

Reference	Search date	Recommendations	Evidence base	Level of evidence
SIGN 2008[20]	2005	Any patient with cervical cancer considered suitable for radical radiotherapy treatment should have concurrent chemoradiotherapy with a platinum based chemotherapy, if fit enough	SR: Green J 2005, Lukka H 2002	Moderate
		The balance of risks and benefits must be addressed before offering chemoradiation for treatment of cervical cancer	No evidence	Expert opinion

Reference	Search date	Recommendations	Evidence base	Level of evidence
CCO 2004[193]	June 2004	Women with cervical cancer for whom treatment with radiotherapy is being considered (locally advanced cervical cancer; bulky clinical stage IB [>4 cm] cervical cancer, treated with radiotherapy; high-risk early-stage cervical cancer [node-positive or margin-positive] who will be treated with radiotherapy following hysterectomy) should be offered concurrent cisplatin with their course of radiotherapy	RCT: Wong 1989, Tseng 1997, Morris 1999, Pearcey 2000, Rose 1999, Whitney 1999, Keys 1999, Peters 2000	Low-Moderate
		There are no direct comparisons of different cisplatin regimens. Based on the review of the available toxicity data from the randomized controlled trials, the Disease Site Group felt that cisplatinum should be given weekly (40 mg/m²)	RCT: Wong 1989, Tseng 1997, Morris 1999, Pearcey 2000, Rose 1999, Whitney 1999, Keys 1999, Peters 2000	Low-Moderate
FNCLCC 2004 [194]		Therapeutic indications for patients with stage IB, IIA and proximal IIB tumours with poor prognosis (4 cm or larger and/or pelvic lymph node involvement) without para-aortic lymph node involvement include combination chemoradiotherapy including cisplatin (standard; level of evidence A)	RCTs	Low-Moderate
		The chemotherapy regimen can be (option; level of evidence B1): • Cisplatin at 40 mg/m² weekly • Cisplatin and 5-fluorouracil: 50–75 mg/m² every 3 to 4 weeks for cisplatin and 4 g/m² over 4 days for 5-fluorouracil	RCTs	Low-Moderate
		When response is poor, particularly in patients with tumours larger than 4 cm, hysterectomy is recommended (recommendation; level of evidence C)	Unclear	
		Patients that cannot be treated with chemoradiotherapy because of their general status may be treated with radiotherapy alone (recommendation; level of evidence expert opinion)	Expert opinion	
		It is recommended that patients should be included in randomised clinical trials to identify the optimal chemotherapy regimens for combination with	Expert opinion	

Reference	Search date	Recommendations	Evidence base	Level of evidence
		external-beam radiotherapy and brachytherapy. In addition, patients should be included in randomised trials to determine if the benefit for patients with later stage disease (III and IV) is less than that for patients with earlier stage disease (recommendation)		

4.6.1.5. Adjuvant chemoradiotherapy/radiotherapy

Reference	Search date	Recommendations	Evidence base	Level of evidence
SIGN 2008 [20]	2005	Patients who have undergone surgery for cervical carcinoma and have positive nodes should be considered for adjuvant treatment with concurrent chemoradiotherapy with platinum based chemotherapy	RCTs	Moderate
		Patients 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	RCTs	Moderate
		Concurrent chemoradiation should be considered in preference to radiation alone	RCTs	Moderate

4.6.1.6. Brachytherapy

Reference	Search date	Recommendations	Evidence base	Level of evidence
SIGN 2008 [20]	2005	Brachytherapy should be considered an essential component of radical radiotherapy or chemoradiotherapy	Expert opinion	

4.6.1.7. Treatment of recurrent, metastatic or persistent cervical cancer

Reference	Search date	Recommendations	Evidence base	Level of evidence
SIGN 2008 [20]	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	Low
		MRI or CT should be considered initially to assess potential clinical recurrence in symptomatic patients	Observational studies	Low
		A whole body PET scan or PET-CT should be performed on all patients 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	Low
		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	RCTs	Moderate
CCO 2006 [148]	February 2006	It is recommended that all patients, 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	
		Until further evidence becomes available, it is recommended that cisplatin in combination with topotecan should be offered to patients 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)	RCTs	Moderate

4.6.1.8. Follow-up

Reference	Search date	Recommendations	Evidence base	Level of evidence
SIGN 2008 [20]	2005	History taking and clinical examination should be carried out during follow up of patients with cervical cancer to detect symptomatic and asymptomatic recurrence	Observational studies	Low
		Cervical cytology or vault smears are not indicated to detect asymptomatic recurrence of cervical cancer	Observational studies	Low
		MRI or CT should be considered initially to assess potential clinical recurrence in symptomatic patients	Observational studies	Low
		A whole body PET scan or PET-CT should be performed on all patients 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	Low
CCO 2009 [179]	November 2007	Patients need to be informed about symptoms of recurrence, because the majority of women have signs or symptoms of recurrence that occur outside of scheduled follow-up visits	Expert opinion	
		Follow-up care after primary treatment should be conducted and coordinated by a physician experienced in the surveillance of cancer patients. Continuity of care and dialogue between the health care professional and patient may well enhance and facilitate early cancer recurrence detection and help avoid duplication of surveillance testing and effort	Expert opinion	
		A reasonable follow-up strategy involves follow-up visits every three to four months within the first two years, and every six to 12 months from years 3 to 5	Expert opinion	
		After five years of recurrence-free follow-up, the patient should return to annual assessment with a history, general physical, and pelvic examination with cervical/vaginal cytology performed by the primary care physician	Expert opinion	
		At a minimum, follow-up visits should include a patient history and complete physical examination • Symptoms elicited during the patient history should include general performance status, lower back pain especially if it radiates down one	Expert opinion	

Reference	Search date	Recommendations	Evidence base	Level of evidence
		leg, vaginal bleeding, or unexplained weight loss • A physical examination should attempt to identify abnormal findings related to general health and/or those that suggest vaginal, pelvic sidewall, or distant recurrence. Since central pelvic recurrences are potentially curable, the physical examination should include a speculum exam with bimanual and pelvic/rectal examination		
		The routine use of other investigations in asymptomatic patients is not advocated as their role has yet to be evaluated in a definitive manner: • There is little evidence to suggest that vaginal vault cytology adds significantly to the clinical exam in detecting early disease recurrence. If cytology is performed as part of routine follow-up after surgery for cervical cancer, its role would be to detect new precancerous conditions of the vagina and should be no more frequent than once a year. An abnormal cytology result that suggests the possibility of neoplasia warrants colposcopic evaluation and directed biopsy for histologic confirmation • The role of abdominal or pelvic computed tomography, magnetic resonance imaging scans, positron emission tomography, or ultrasound as part of routine follow-up has not been fully evaluated in prospective studies • Use of serum markers such as squamous cell carcinoma antigen or cancer antigen 125 have shown promise in predicting surgical findings, or in the post-radiotherapy course when disease is present; however, their role in following patients post-treatment has yet to be determined	Observational studies	Low

4.6.1.9. *Fertility sparing treatment*

Reference	Search date	Recommendations	Evidence base	Level of evidence
SIGN 2008 [20]	2005	Women requesting fertility conservation should be offered radical trachelectomy and pelvic lymph node dissection, providing the tumour diameter is less than 2 cm and no lymphatic-vascular space invasion is present.	Case series	Low
		Women with early stage disease and no LV SI (FIGO IA2 and microscopic IB1) requesting fertility conservation may be offered cold knife conisation or LLETZ combined with pelvic lymph node dissection.	Case series	Low
		Laparoscopic-vaginal radical hysterectomy should not be offered to patients with tumour diameter greater than 2 cm.	Case series	Low
		Surgeons wishing to offer laparoscopic-vaginal radical hysterectomy should have appropriate training.	Expert opinion	

4.6.1.10. *Treatment during pregnancy*

Reference	Search date	Recommendations	Evidence base	Level of evidence
SIGN 2008 [20]	2005	For pregnant women with cervical cancer, the choice of therapeutic modality should be decided in the same manner as for non-pregnant patients	Observational studies	Very low
		For pregnant women diagnosed with cervical cancer before 16 weeks of gestation, immediate treatment is recommended	Observational studies	Very low
		For pregnant women with early stage disease (FIGO IA1, IA2, IB) diagnosed after 16 weeks of gestation, treatment may be delayed to allow foetal maturity to occur	Observational studies	Very low
		For pregnant women with advanced disease (FIGO IB2 or greater) diagnosed after 16 weeks of gestation, consideration for delay must be based on gestational age at time of diagnosis	Observational studies	Very low

4.6.1.11. Sexual morbidity

Reference	Search date	Recommendations	Evidence base	Level of evidence
SIGN 2008 [20]	2005	Women should be offered a vaginal stent or dilator to prevent post-radiotherapy vaginal complications	SR of retrospective studies	Low
		Information about female sexual function should be offered to patients by a relevantly trained healthcare professional using a model of care that involves addressing motivational issues and teaching behavioural skills	RCT	Moderate
		Patients should be offered support sessions by a designated member of their care team, as soon as possible after treatment, which may include one or more of the following: • Relaxation • Personalised information about their disease and treatment • Emotional support and care	Observational studies	Low

4.6.2. Additional evidence

4.6.2.1. CIN

Surgery for CIN

Systematic reviews

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
Martin-Hirsch 2010 [7]	• SR • Funding: none • Search date: April 2009 • Databases: Cochrane Gynaecological Cancer Group Trials Register, Cochrane Central Register	Women with CIN confirmed by biopsy and undergoing surgical treatment. Not included are treatments for glandular intraepithelial neoplasia	Single freeze cryotherapy versus double freeze cryotherapy	Residual Disease within 12 months (1 study): Risk Ratio 2.66 [0.96, 7.37]		The vast majority of RCTs evaluating the differences in treatment success are grossly underpowered to demonstrate a significant difference between treatment techniques and no

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
	of Controlled Trials (CENTRAL) The Cochrane Library), MEDLINE and EMBASE clinical trials, abstracts of scientific meetings and reference lists of included studies • Study designs: RCT, • 29 RCT included					real conclusions can be drawn on differences of treatment effect.
			Laser ablation versus cryotherapy	Residual Disease (All Grades of CIN) (N=6): Risk Ratio (95%CI) 1.13 [0.73, 1.76] Residual Disease (CIN1, CIN2, CIN3) (N=4):Risk Ratio (95%CI) 1.51 [0.91, 2.51] • CIN1 (N=4): 2.75 [0.68, 11.11] • CIN2 (N=4): 1.37 [0.65, 2.88] • CIN3 (N=4): 1.38 [0.62, 3.09]	Peri-operative Severe Pain (N=3): Risk Ratio (IV, Random, 95%CI) 2.00 [0.64, 6.27] Peri-operative Severe Bleeding (N=2): Risk Ratio 5.83 [0.71, 47.96] Malodorous Discharge (N=2): Risk Ratio 0.30 [0.12, 0.77] Inadequate Colposcopy at Follow-up (N=2): Risk Ratio 0.38 [0.26, 0.56] Cervical Stenosis at Follow-up (N=2): Risk Ratio 1.45 [0.45, 4.73]	Many analyses included only one or two randomised trials due to the different outcome measures chosen and reported in the trials. This limits the conclusions which may be drawn from some of the analyses. Furthermore, the method of randomisation in many of the trials was not optimised so that the results might be prone to bias due to inherent methodological flaws in these trials.
			Laser conisation versus knife conisation	Residual Disease (All Grades of CIN) (N=2): Risk Ratio (95%CI) 0.64 [0.22, 1.90]	Primary Haemorrhage (N=2): Risk Ratio (IV, Random, 95%CI) 0.53 [0.18, 1.54]	

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
					Secondary Haemorrhage (N=3): Risk Ratio 0.91 [0.34, 2.40] Inadequate Colposcopy at Follow-up (N=2): Risk Ratio 0.57 [0.39, 0.81] Cervical Stenosis at Follow-up (N=4): Risk Ratio 0.38 [0.19, 0.76]	
			Laser conisation versus loop excision	Residual Disease (N=3) Risk Ratio (95%CI) 1.24 [0.77, 1.99]	Duration of Procedure (N=3): Mean Difference (IV, Random, 95%CI) 11.66 [1.37, 21.95] Peri-operative Severe Pain (N=2): Risk Ratio 4.34 [0.25, 75.67] Secondary Haemorrhage (N=4): Risk Ratio (1.41 [0.72, 2.76] Significant Thermal Artefact on Biopsy (N=2): Risk Ratio 2.38 [0.61, 9.34] Inadequate Colposcopy (N=2): Risk Ratio 1.38 [0.48, 3.97] Cervical Stenosis (N=3): Risk	

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
					Ratio 1.21 [0.57, 2.57]	
			Laser ablation versus loop excision	Residual Disease (N=3): Risk Ratio (95%CI) 1.15 [0.59, 2.25]	Peri-operative Severe Pain (N=1): Risk Ratio (IV, Random, 95%CI) 0.38 [0.02, 7.91] Primary Haemorrhage (N=2): Risk Ratio 0.35 [0.04, 3.14] Secondary Haemorrhage (N=2): Risk Ratio (0.54 [0.14, 2.10]	
			Knife conisation versus loop excision	Residual Disease (N=3): Risk Ratio (95%CI) 0.47 [0.20, 1.08]	Primary Haemorrhage (N=2): Risk Ratio (IV, Random, 95%CI) 1.04 [0.45, 2.37] Inadequate Colposcopy at Follow-up (N=3): Risk Ratio 1.63 [0.85, 3.15] Cervical Stenosis (N=3): Risk Ratio 1.12 [0.44, 2.84]	
			Knife cone biopsy: haemostatic sutures versus none	Primary Haemorrhage (N=2): Risk Ratio (95%CI) 0.42 [0.06, 3.23]	Secondary Haemorrhage (N=2): Risk Ratio (IV, Random, 95%CI) 2.68 [1.27, 5.66] Cervical Stenosis (N=2): Risk Ratio 1.75 [0.65, 4.72] Dysmenorrhoea (N=2): Risk Ratio 2.50 [1.41, 4.45]	

Primary studies

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of study quality
Sanu 2010 [9]	• RCT • Source of funding not mentioned • Setting: London NHS hospital • Sample size: N=381 • Duration: January 2006 to April 2008	Women with confirmed cervical dysplasia (CIN 1–3) following colposcopy directed punch biopsy Comparable groups	Cervical intraepithelial neoplasia excisor vs. Loop electrosurgical excision procedure	Proportion of histopathological specimens with clear resection margins: 95.7% (201/210) vs., 85.7% (180/210) (p < 0.001)	• CIN 1: 96.1% (99/103) vs. 86.3% (82/95) (p = 0.01) • CIN 2 94.8% (73/77) vs. 85% (68/80) (p = 0.04) • CIN 3 96.7% (29/30) vs. 85.7% (30/35) (p = 0.21)	Level of evidence: Moderate • 10 patients excluded because of uninterpretable resection margins • Low risk of bias, but imprecise estimates for the target group CIN2 and CIN 3

Interventions to prevent blood loss during surgery for CIN

Systematic reviews

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
Martin-Hirsch 2010 [8]	• SR • Funding: none • Search date: April 2009 • Databases: Cochrane Gynaecological Cancer Group Trials Register, Cochrane Central Register of Controlled Trials (CENTRAL) The Cochrane	Women with CIN confirmed by biopsy and undergoing surgical treatment. Not included are treatments for glandular intraepithelial neoplasia	Vasopressin versus placebo	Measured blood loss (N=1): MD = -100.80 (95%CI -129.48 to - 72.12)	Subjective troublesome bleeding: RR = 0.40 (95%CI 0.09 to 1.87) Bleeding requiring haemostatic sutures (N=1): RR = 0.39 (95%CI 0.27 to 0.56) Cervical stenosis (N=1): RR = 0.32 (95%CI 0.06 to 1.67)	Level of evidence: low "Due to the heterogeneity of the outcomes and treatments considered, there are many single trial analyses and limited consistent data available to compare between trials. The majority of the included trials were underpowered to demonstrate a significant effect and most did not include a power calculation

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
	Library), MEDLINE and EMBASE clinical trials, abstracts of scientific meetings and reference lists of included studies • Study designs: RCT, • 29 RCT included					in their methodologies. As the majority of comparisons relied on single trials that were underpowered, the treatment effects should ideally be examined by conducting further studies Downgraded RCTs, small or no effect, wide CI, most RCTs high risk of bias
			Tranexamic acid versus control	Postoperative blood loss (N=1): MD= -55.60 (95%CI -94.91 to -16.29) Primary hemorrhage (N=2): RR = 1.24 (95%CI 0.04 to 38.10; I2 = 62%)	Secondary hemorrhage (N=4): RR = 0.23 (95%CI 0.11 to 0.50; I2 = 0%)	
			Vaginal pack with Monsel's solution versus haemostatic suture	Perioperative blood loss (N=1): MD = -22.00 (95%CI -23.09 to -20.91) Primary haemorrhage (N=1): RR = 1.00 (95%CI 0.36 to 2.75)	Secondary haemorrhage (N=1): RR = 0.44 (95%CI 0.19 to 1.02) Amenorrhoea (N=1): RR = 0.20 (95%CI 0.01 to 4.11) Dysmenorrhoea (N=1): RR = 0.37 (95%CI 0.16 to 0.84) Transformation zone	

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
					not visible at colposcopy (N=1): RR = 0.43 (95%CI 0.30 to 0.63) Cervical stenosis (N=1): RR = 0.35 (95%CI 0.25 to 0.49)	
			Cerclage suture versus electrical coagulation	Duration of procedure (N=1): MD = -9.50 (95%CI -11.57 to -7.43) Primary haemorrhage (N=1): RR = 0.86 (95%CI 0.06 to 13.22)	Secondary haemorrhage (N=1): RR = 0.14 (95%CI 0.02 to 1.13) Dysmenorrhoea (N=1): RR = 0.48 (95%CI 0.18 to 1.29) Unsatisfactory colposcopy (N=1): RR = 0.61 (95%CI 0.39 to 0.94) Inadequate Colposcopy (N=2): Risk Ratio (IV, Random, 95%CI) 1.38 [0.48, 3.97] Cervical Stenosis (N=3): Risk Ratio 1.21 [0.57, 2.57]	

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
			Vaginal Amino-Cerv versus routine treatment	Secondary haemorrhage (N=1): No women experienced secondary haemorrhage in either the Amino-Cerv or the routine care group	Vaginal discharge at 2 weeks (N=1): RR = 0.27 (95%CI 0.09 to 0.86) Vaginal discharge at 4 weeks (N=1): RR = 0.33 (95%CI 0.04 to 2.98)	
			Prilocaine with felypressin versus lignocaine with adrenaline in Large Loop Excision of the Transformation Zone (LLETZ)	Duration of procedure (N=1): MD = 0.40 (95%CI -0.19 to 0.99)		
			Ball electrode versus Monsel's paste for haemostasis after Loop Electrosurgical Excision Procedure (LEEP)	Blood loss (N=1): MD = 4.82 (95%CI -3.45 to 13.09)		

Retinoids for the treatment of CIN2/3

Systematic reviews

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
Helm 2011 [19]	• Cochrane SR • Funding: none • Search date: July 2009 • Databases Register of Controlled Trials (CENTRAL) (Issue 3,2010), MEDLINE and EMBASE • Study designs: RCT and non RCTs • 5 RCTs included	Women with CIN confirmed by biopsy and undergoing surgical treatment Not CIN in women of all ages	Retinoid vs. control	Complete or partial regression of CIN2/3 at 3-12 months (N=3): Odds Ratio (95%CI) 0.99 [0.57, 1.72] Complete regression of CIN2/3 at 9-27 months (N=2): Odds Ratio 0.79 [0.51, 1.23] Complete regression of CIN2 at 9-27 months (N=2): Odds Ratio [0.43, 1.29]		Level of evidence: moderate No evidence for an effect of retinoids RCT downgraded for imprecision

Incomplete excision of cervical intraepithelial neoplasia and risk of treatment failure

Systematic reviews

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
Ghaem-Maghami 2007 [10]	• SR • Funding: ? • Search date: Jan2007 • Databases MEDLINE • Study designs: observational studies • 66 studies included	Women with CIN confirmed by biopsy and undergoing surgical treatment	All treatment methods	Low or high grade disease: Pooled RR: 5.47 (4.37–6.83) Absolute risk: 20% High grade disease: Pooled RR: 6.09 (3.87–9.60) Absolute risk: 18%		Level of evidence: moderate Observational studies, RCT no option for this question Upgraded observational studies: large effect, few reasons why confounding would play a role
			Loop diathermy	Low or high grade disease: Pooled RR: 8.08 (4.60–14.18) Absolute risk: 22%		
			Laser-cone biopsy	Low or high grade disease: Pooled RR: 3.34 (2.66–4.19) Absolute risk: 11%		
			Knife-cone biopsy	Low or high grade disease Pooled RR: 7.37 (4.41–12.32) Absolute risk: 27%		

Use of HPV testing

Systematic reviews

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
Chan 2009 [13]	• SR • Funding: National cancer Institute • Search date: Sept 2007 • Databases: MEDLINE • 20 studies included	Women followed up after treatment for CIN	HC 2 testing	Recurrence rate 6.6 (95%CI 3.9-10.9) Pooled sensitivity 90.7% (95%CI 75.4-96.9%), Pooled specificity 74.6 (95%CI 60.4-85.0)	Clinical outcomes: Cytology: 147 positive test results per 1000 women or 14.7% referred to colposcopy HPV testing: 297 positive test results per 1000 women or 29.7% referred to colposcopy	Level of evidence: low
			Cytology	Pooled sensitivity 76.6 (95%CI 62.0-86.8) Pooled specificity 89.7 (95%CI 22.7-99.6)		
			Combined cytology HC2 testing	Pooled sensitivity 93.1 (95%CI 16.7-99.9) Pooled specificity 75.7 (95%CI 57.2-87.9)		

Obstetric outcomes after excisional or ablative therapy

Systematic reviews

Reference	Methodology	Patient characteristics	Intervention(s)	Results pooled RR (heterogeinity I2, p Qtest) (CI)		Critical appraisal of review quality
Arbyn 2008 (update of Kyrgiou 2006)[11, 12]	• SR • Funding: European commission • Search date: July 2007 • Databases: Register of Controlled Trials (CENTRAL) (Issue 3,2010), MEDLINE and EMBASE • Study designs: prospective and retrospective cohort studies • 1 prospective and 19 retrospective studies retrieved	Women with CIN confirmed by biopsy and undergoing excisional or ablative treatment		*Perinatal mortality*		Level of evidence: low Pooling of observational studies were (residual) confounding in particular cannot be excluded
			Cold knife conisation	pooled RR (I2=17.0%, p=0.300)	2.87 (1.42 to 5.81)	
			Laser conisation	No pooling		
			Large loop excision of transformation zone	pooled RR (I2=0.0%, p=0.862)	1.17 (0.74 to 1.87)	
			Excision	pooled RR (I2=0.0%, p=0.892	2.70 (1.89 to 3.85)	
			Ablative treatment	pooled RR (I2=22.5%, p=0.271)	0.87 (0.53 to 1.45)	
				Severe preterm delivery (<32/34 weeks)		
			Cold knife conisation	pooled RR (I2=0.0%,p=0.911)	2.78 (1.72 to 4.51)	
			Laser conisation	pooled RR (I2=42.7%, p=0.156)	1.20 (0.50 to 2.89)	
			Excision	pooled RR (I2=50.7%,p=0.154)	2.63 (1.41 to 4.89)	
			Ablative treatment	pooled RR (I2=0.0%,p=0.492)	0.88 (0.49 to 1.56)	
				Severe low-birth weight (<2000 g)		
			Excisional treatment	Pooled RR (I2=0.0%, p=0.418)	2.47 (1.43 to 4.28)	
			Ablative treatment	Pooled RR (I2=0.0%, p=0.980)	1.01 (0.71 to 1.45)	

4.6.2.2. Diagnosis and staging

Systematic reviews

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
Bipat 2003 [22]	• 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 patients; histopathology as reference standard; sufficient data to construct a 2x2 contingency table • Exclusion criteria: data reported elsewhere in more detail • Patient 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)	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	Level of evidence: low 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

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
				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) 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 metastasis: Se 60% (95%CI 52-68); Sp 93% (visual inspection forest plot)	of publication or sample size did not reveal differences in accuracy. No data on cervical angulation technique	heterogeneity partially taken into account 53 studies published before 2001

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
Havrilesky [49]	• 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 patients • Patient 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:	No data on T1 vs. T2 weighted or contrast enhanced MRI	Level of evidence: low Included studies were small (none included over 50 patients) and none reported blinded assessment Three studies were in selected subgroups, e.g. patients 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 11 studies published before 2001

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
				histology): Se 67% (95%CI: 9-99), Sp 100% (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)		
Kang 2010 [50]	• 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 patients included; with histology as a reference standard • Patient characteristics: • Boughanim: IB2 or II • Choi: IB-IVA • Lin: IIB-IVA or IB/ IIA with a tumor	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)	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	Level of evidence: low 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

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
		diameter ≥5 cm or involvement of pelvic lymph nodes; negative abdominal CT finding • Narayan: all operable patients without definitive CT evidence of para-aortic lymph node metastasis • Reinhardt: cervical cancer patients • 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 patients across all studies had para-aortic lymph node		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)	(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)	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 patients with negative results for para-aortic lymph nodes on prior CT, MRI, or PET 11 studies published before 2001

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
		metastases				
van de Lande 2007 [68]	• 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 patients with early stage cervical cancer (FIGO I-IIA); English language studies; ≥ 10 patients included; sufficient data to reconstruct 2x2 tables • Patient 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: low Study quality: none of the studies used masked assessment of the reference standard; 19/22 studies were prospective; 17/22 studies used consecutive patients Meagre description of patient characteristics 2 studies published before 2001
Selman 2008 [51]	• Design: systematic review with meta-analysis • Funding: A Medical Research Council training fellowship • Conflict of interest: none declared	• Eligibility criteria: accuracy of index test compared with histological examination of lymph nodes in women with a primary presentation of cervical cancer of	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);	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)	Level of evidence: low 29/95 test results reported blinded assessment of index test; 2/95 test results

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
	• 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	any histological type or stage; data could be used to create 2x2 tables. • Exclusion criteria: fewer than 10 participants • Patient characteristics: primary presentation of cervical cancer		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-	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	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 36 studies published before 2001

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
				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)		

Primary studies

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
Akata 2005 [81]	• 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 • Patient 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 discriminate stage I from other stages: 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 73%		Level of evidence: low Dropouts: none reported Consecutive patients Exclusion of 20 patients who did not undergo surgery: partial verification bias exclusion of 2 patients who could not receive vaginal contrast medium Blinded assessment of index test; blinded assessment of reference test not reported on
Altgassen 2008 [69]	• Design: prospective multicenter cohort study • Source of funding: in part by the Deutsche Krebshilfe (German	• Eligibility criteria: invasive cervical cancer of all stages, intention of surgical staging, complete pelvic lymphadenectomy in	Index test: SNB (Technetium: 9%; patent blue: 31%; both: 60%) Reference standard: histopathology from	Accuracy of SNB to detect lymph node metastasis (N=507): Se 77% Technetium 71% Patent blue 73%	One-sided sentinel node detection rate (N=590): 89% Technetium: 82% Patent blue: 82% Combined: 94%	Level of evidence: low Dropouts: reported on. In 7 patients the reference

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
	Cancer Aid) • Conflict of interest: no potential conflicts of interest • Setting: 18 centres in Germany • Sample size: N=590 • Duration: 1998-2006	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 • Patient 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	pelvic lymphadenectomy (507 patients) and para-aortic lymphadenectomy (190 patients)	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%	Two-sided sentinel node detection rate: not reported An anaphylactic reaction was seen in two patients which necessitated abandoning surgery. Surgery was performed 2 days later without any labelling	standard was inconclusive or unknown; in 3 patients the index test was inconclusive Non-blinded study Consecutive patients
Amit 2006 [61]	• Design: not reported • Source of funding: not reported on • Conflict of interest: not reported on • Setting: Israel	• Eligibility criteria: patients with proven cervical cancer referred for hysterectomy and pelvic lymphadenectomy	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	-	Level of evidence: low Dropouts: not reported on Risk of selection

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
	• Sample size: N=16 • Duration: not reported	with a follow-up of >6 months (group 1) • Patient characteristics: mean age: 45 y; all stage I patients • Disease prevalence: 25% lymph node metastases		patients with positive lymph nodes		bias through eligibility criteria Unclear whether patients were consecutive Blinded assessment not reported
Bentivegna 2010 [67]	• 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 • Patient characteristics: median age 43 y; 61% SCC; 17% AC; 17% ASC; 14 patients underwent preoperative utero-vaginal brachytherapy; 2 patients 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: low Consecutive patients Blinded assessment not reported on Long interval between index and reference test in which 14/16 patients had brachytherapy Selection bias through eligibility criteria

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
Bjurberg 2007 [79]	• 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) • Patient 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% (5/6); Sp 100% (11/11); NPV 92% (11/12); PPV 100% (5/5)	-	Level of evidence: low Dropouts: none Consecutive patients Blinded assessment not reported The one false negative finding was detected by CT 5 weeks after PET (and then confirmed by histology)
Chao 2008 [56]	• Design: prospective cohort study • Source of funding: research grants from Chang Gung Memorial Hospital • Conflict of interest: no conflicts of interest to declare • Setting: Chang	• Eligibility criteria: newly diagnosed SCC cervical cancer patients with a suspicion of para-aortic lymph node metastasis based on CT/MRI, or inguinal or supraclavicular lymph node metastasis	Index test: PET (N=38) or PET/CT (N=9) Reference standard: CT/MRI, biopsy or follow-up through imaging including PET	Accuracy of PET or PET/CT to detect para-aortal lymph node metastasis (N=47): Se 97%; Sp 90%; NPV 90%; PPV 97% Accuracy of PET or PET/CT to detect inguinal	PET or PET/CT had positive clinical impact in 21 of the 47 study patients, in 23 it had no impact, and in three it had negative impact. Positive impact included disclosing additional curable	Level of evidence: low Dropouts: not reported Unclear whether patients were consecutive Only patients with

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
	Gung Memorial Hospital, Taiwan • Sample size: N=47 • Duration: 2001-2007	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 • Patient 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%;		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%	sites (N=8), down-staging (N=6), offering metabolic biopsy (N=4) or change to palliation (N=3)	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

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
		supraclavicular lymph node metastasis: 26%; bone metastasis: 2%; other distant non skeletal sites: 4%				remission of the lesion after definitive treatment´
Choi 2004 [40]	• Design: prospective cohort 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	• Eligibility criteria: • cervical carcinoma with proven histopathological staging and operable state • Patient characteristics: mean age 52.3 y • Prevalence of disease: 20.2% vaginal invasion	Index test: MRI Reference standard: histopathology	Accuracy of MRI to detect vaginal invasion (N=114): Se 87%; Sp79%; PPV 51%; NPV 96%	Region-based analysis of parametria and pelvic lymph node metastasis	Level of evidence: low Dropouts: 1 patient didn't undergo surgery due to confirmation of bladder invasion by cystoscopy Consecutive patients Exclusion of patients that did not have histopathological confirmation: partial verification bias Blinded assessment of index test; blinded assessment of reference test not reported on

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
Choi 2006 [53]	• 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 patients with histo-pathologically 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; ECOG performance status of 0-1 • Exclusion criteria: patients who did not want to undergo PET/CT or laparoscopic lymphadenectomy (N=63) and tumours other than SCC (N=10) • Patient characteristics: mean age 50 y; 100% SCC • Prevalence of disease: 59% lymph nodes metastasis	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% (5/13); 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: low Dropouts: none reported Consecutive patients Selective subgroup: high prevalence of lymph node metastasis Blinded assessment of index and reference test

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
Chou 2006 [55]	• 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 patients 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 • Patient characteristics: median age: 48 y; 60% SCC; 33% AC; 7% ASC. FIGO staging: IA2: 2%; IB1: 90%; IB2: 5%; IIA:3% • Disease prevalence:	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: low No dropouts Unclear if patients were consecutive Blinded assessment not reported Selective subgroup of MRI negative patients

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
		18% lymph node metastases				
Chung 2007 [35]	• Design: retrospective cohort study • Source of funding: Korea Health 21 R&D Project, Ministry of Health & Welfare, Republic of Korea • Conflict of interest: none declared • Setting: Seoul National University College of Medicine, Seoul, Korea • Sample size: N=119 • Duration: 2004-2006	• 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 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;	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% Accuracy of MRI to detect pelvic &/ para-aortic lymph node metastasis (N=119): Se 71%; Sp 69%; PPV 48%; NPV 86%; accuracy 70%	Cervical angulation not reported	Level of evidence: low Consecutive patients Blinded assessment of index test; blinded assessment of reference test not reported on Retrospective selection of patients who underwent MRI and surgery: risk of selection bias

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
		contra-indication to MRI; previous diagnosis of cancer other than non-melanoma skin cancer; pregnancy • Patient 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				
Chung 2010 [54]	• Design: retrospective cohort study • Source of funding: none stated • Conflict of interest: not reported on • Setting: not stated • Sample size: N=83 • Duration: 2004-	• Eligibility criteria: histopathologically confirmed FIGO stages IB-II invasive cervical cancer with no distant metastasis who underwent radical surgery and had undergone both preoperative MRI and	Index test: MRI (T2 weighted, contrast enhanced) and PET/CT Reference standard: histopathology	Accuracy of MRI to detect pelvic lymph node metastasis (N=83): Se 64.3%; Sp 69.1%; PPV 51.4%; NPV 79.2%; Area under the ROC curve 0.667 (95%CI 0.542-0.792) Accuracy of PET/CT to	-	Level of evidence: low Consecutive patients Exclusion of 21 patients whom didn't meet inclusion criteria:

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
	2008	PET/CT before radical surgery • Patient 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		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)		risk of selection bias Blinded assessment of index test; blinded assessment of reference test not reported on
Chung 2009 [60]	• 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 • Patient 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 LN 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: low Consecutive patients Exclusion of 12 patients 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

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
						assessment not reported on
Darlin 2010 [71]	• Design: cohort study • Source of funding: not reported on • Conflict of interest: none stated • Setting: Lund University Hospital, Sweden. • Sample size: N=105 • Duration: 2005-2009	• Eligibility criteria: early stage (IA1-IIA) cervical cancer with SNB procedure and pelvic lymphadenectomy • Patient 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	Index test: SNB (Tc99 human-albumin nanocolloid injection, lymphoscintigram and gamma probe) Reference standard: histopathology	Accuracy of SNB to detect lymph node metastasis (N=94): Se 94% (95%CI 73-10); NPV 99% (95%CI 93-100)	One-sided sentinel node detection rate: 90% ≤ 20 mm 94% > 20 mm 83% Two-sided sentinel node detection rate: 59% ≤ 20 mm 65% > 20 mm 50%	Level of evidence: low Dropouts: not reported on Consecutive patients Unclear if the design was prospective Blinded assessment not reported on
deSouza 2006 [30]	• Design: retrospective cohort study • Source of funding: not reported on • Conflict of interest: not reported on • Setting: Hammersmith Hospital, UK • Sample size: N=119 • Duration: 1993-	• Eligibility criteria: cervical cancer on biopsy referred for MRI prior to radical hysterectomy and pelvic lymphadenectomy • Patient characteristics: average age 43.5 y; 68% SC; 24% AC; 5% ASC;3% neuroendocrine. FIGO stage IA:3%; IB1:71%;	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: low Consecutive patients Risk of selection bias through retrospective application of eligibility criteria Blinded assessment of index test; blinded

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
	2002	IB2:21%; IIA:3%; IIB:3% • Prevalence of disease: 13% parametrial invasion				assessment of reference test not reported on
Fader 2008 [72]	• 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 patients, undergoing radical hysterectomy and pelvic/para-aortic lymphadenectomy • Exclusion: prior history of chemotherapy, radiation therapy or retroperitoneal surgery • Patient 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: low Dropouts: none Consecutive patients: not reported Blinded assessment not reported
Fischerova 2008 [31]	• Design: prospective cohort study • Source of funding: not reported on • Conflict of interest: not reported on	• Eligibility criteria: early-stage cervical cancer (T1a1-T2a) examined by both TRUS and MRI and undergoing surgical	Index tests: MRI Reference standard: histopathology	Accuracy of MRI to 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-	-	Level of evidence: low Dropouts: 1 patient refused to

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
	• Setting: General Teaching hospital, Charles University, Prague • Sample size: N=95 • Duration: 2004-2006	treatment • Patient 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		94.73); NPV 97% (95%CI 90.57-99.31); Accuracy 95% (95%CI 88.14-98.27)		undergo surgery Consecutive patients Only patients examined by both MRI and TRUS were included (selection bias) Exclusion of 22 patients due to more advanced disease on imaging and 2 patients due to contraindication for surgery: partial verification bias Blinded assessment not reported on
Goyal 2010 [59]	• 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 • Patient characteristics: mean age 48.5 y; FIGO stage IB1:64%;	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 patients (in 32 patients because of suspicious pelvic lymph nodes; in 14 patients routinely) and the one suspicious para-aortic lymph node on PET/CT was	Level of evidence: low Dropouts: none Consecutive patients, unclear if the design was prospective Exclusion of 2 patients due to distant

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
		IB2:21%; IIA:15%; 81% SCC; 16% AC; 1% ASC; 1% Signet cell type • Prevalence of disease: 30% pelvic lymph node metastasis			confirmed histologically	metastasis. Selection of operable patients only: risk of selection bias Blinded assessment of index test; blinded assessment of reference test not reported on
Hertel 2002 [26]	• 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 • Patient 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	Data of lymph node metastasis included in [51]	Level of evidence: low Dropouts: none Consecutive patients Subgroup of IB2 patients Differential verification Blinded assessment not reported on

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
				(N=67): Se 50%; Sp 86% (95%CI 77-95); PPV 18%; NPV 96% (95%CI 91-98)		
Hoon Chung 2005 [52]	• 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 evidence of distant metastasis; Eastern Cooperative Oncology Group performance status 0 or 1; informed consent • Patient 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	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: low Dropouts: none reported Consecutive patients, unclear if the design was prospective Exclusion of two patients due to severe intra-abdominal adhesion related to previous surgery No blinded assessment of index and reference test
Hori 2009 [33]	• Design: prospective cohort study • Source of funding: not reported on • Conflict of interest:	• Eligibility criteria: biopsy-proved untreated cervical carcinoma • Patient characteristics:	Index tests: 3.0-T MRI and 1.5-T MRI (T2 weighted, contrast enhanced with cervical	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%	There were no significant differences between 3.0- and 1.5-T MR imaging	Level of evidence: low Consecutive

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
	no financial relationship disclosed • Setting: Osaka University Hospital • Sample size: N=31 • Duration: 2006-2007	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	angulation) Reference standard: Histopathology or follow-up CT	(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); 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	in terms of the areas under the ROC curve, sensitivity or specificity (p>0.5 for all comparisons)	patients Dropouts:16 patients did not agree to be included in the study: risk of selection bias 12 patients were excluded due to radiation therapy Differential verification: 1 patient 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 reader 2 also shown in article

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
				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% (95%CI 67-95); area under ROC curve 0.78		
Hricak 2005 [80]	• Design: prospective multicenter cohort study • Source of funding: National Cancer Institute	• Eligibility criteria: untreated biopsy-confirmed cervical cancer of all cell types, scheduled for hysterectomy	Index test: CT, MRI Reference standard: surgicopathologic findings (data from	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	Four cases of rectal involvement (surgicopathological finding) were not detected by CT nor MRI	Level of evidence: low Dropouts: 36 patients were

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
	• Conflict of interest: no potential conflicts of interest declared • Setting: 25 centers, United States • Sample size: N=208 • Duration: 2000-2002	• Patient 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	the surgical report and pathologic analysis of specimens)	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)	There were 6 cases of bladder involvement, of whom none were detected by CT and two were detected by MRI See also [23] and [27]	excluded because of enrolment disqualification or missing data; including 13 patients who did not have surgery (risk of partial verification bias) Consecutive patients 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 2010 [28]	• Design: retrospective cohort study • Source of funding: National Cancer Center, Korea • Conflict of interest: none declared • Setting: Seoul National University	• 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	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: low Consecutive patients Risk of selection bias through retrospective application of

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
	Hospital and the National Cancer Center , Republic of Korea • Sample size: N=251 • Duration: 2006-2009	chemotherapy before surgery • Patient characteristics: FIGO stage IA2:3%; IB1:75%; IB2:6%; IIA:15%; 72% SCC; 28% AC/ASC. • Prevalence of disease: 18% parametrial invasion				selection criteria Blinded assessment of index test; blinded assessment of reference test not reported on A 2x2 table could not be constructed
Kim 2009 [63]	• 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 patients who did not undergo laparoscopic lymph node dissection • Patient characteristics:	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: low Consecutive patients Retrospective selection of patients 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

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
		not reported on • Prevalence of disease: 38% metastatic lymph nodes				
Kokka 2003 [25]	• 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 patients who completed pre-treatment evaluation at the institution • Exclusion criteria: neoadjuvant treatment and/or radiotherapy • Patient characteristics:mean age: 48 y; SCC: 86%; AC: 11%; ASC: 2%. FIGO surgicopathological staging IB: 65%; IIA: 34%; IV: 1% • Disease prevalence: urinary tract invasion: 1%; gastrointestinal tract invasion: 0.3%	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 [51]	Level of evidence: low Consecutive patients Risk of selection bias through selection criteria Blinded assessment not reported Differential verification, and partial verification (307/309) for gastrointestinal tract invasion
Leblanc 2011 [57]	• Design: retrospective multicenter study • Source of funding: not reported on • Conflict of interest: not reported on	• Eligibility criteria: primary stage IB2-IVA locally advanced cervical cancer or a centropelvic recurrence after chemoradiation for locally advanced	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%;	Level of evidence: low Unclear if patients were consecutive Blinded

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
	• Setting: 5 French tertiary-care centers • Sample size: N=125 • Duration: 2004-2008	cervical cancer, without evidence of distant metastasis and enlarged para-aortic nodes (>10mm) at abdominopelvic MRI with or without CT scan • Patient 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			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%	assessment of index test; blinded assessment of reference test not reported on Selection bias through retrospective application of selection criteria 2/125 patients had centropelvic recurrence
Liu 2009 [195]	• 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 patients (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	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 (N=40): Se 100%; Sp 100%; NPV	-	Level of evidence: low Not reported whether patients were consecutive Risk of selection bias through retrospective application of selection criteria Blinded index test

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
		those who died of disease within 180 days) • Patient 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	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%		assessment Differential verification Incorporation bias
Loft 2007 [58]	• 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-	• 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 • Patient	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	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: low Dropouts: none reported Consecutive patients 1 patient who had had a hysterectomy prior to PET/CT was excluded Differential verification: histology, other imaging

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
	2005	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 metastasis: 13%; distant metastasis: 8%	follow-up (N=108)			modalities and follow-up Partial verification: 14 patients who had positive pelvic lymph nodes on PET and were not examined histologically were excluded for calculations concerning pelvic lymph node status Incorporation bias in some patients Blinded assessment not reported on
Manfredi 2009 [41]	• 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 • Patient characteristics: mean age 47.3 y; 73% SCC; 18% AC; 9% ASC. Grade I:9%; Grade II:32%; Grade III:59%. • Prevalence of	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: low Consecutive patients Dropouts: 2 patients who refused MRI were not included in analysis: risk of selection bias Exclusion of 5

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
		disease: 6% vaginal invasion; 13% tumour extension to the internal os				patients due to locally advanced disease on MRI (partial verification) No blinded assessment of index and reference test
Matsushita 2001 [34]	• 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 • Patient 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% serous AC; 6 patients received neoadjuvant chemotherapy • Prevalence of disease: 22% parametrial invasion	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: low Consecutive patients Risk of selection bias through retrospective design where MRI is needed to be included Blinded assessment of index test; blinded assessment of reference test not reported on
Mitchell 2006 [23]	• Design: prospective	• Eligibility criteria: untreated biopsy-confirmed cervical	Index tests: CT, MRI	Accuracy of CT to detect uterine involvement	Agreement between CT and	Level of evidence: low

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
	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	cancer of all cell types, scheduled for hysterectomy • Patient 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	Reference standard: histology	(N=na): AUC 0.66 Accuracy of MRI to detect uterine involvement (N=na): AUC 0.80	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:	Dropouts: 36 patients were excluded because of enrolment disqualification or missing data including 13 patients who did not have surgery (risk of partial verification bias) Consecutive patients 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

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
					54-74); Sp 43% (95%CI: 23-66); NPV 23% (95%CI: 12-39); PPV 82% (95%CI: 72-90) 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 [80] and [27]	
Mitchell 2009 [27]	• Design: prospective	• Eligibility criteria: untreated biopsy-confirmed cervical	Index tests: CT, MRI (T2 weighted)	Accuracy of CT to detect pelvic &/ para-aortic	See also [80] and [23]	Level of evidence: low

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
	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	cancer of all cell types, scheduled for hysterectomy • Patient 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 metastases; 9% para-aortic nodal metastases	Reference standard: histology (pelvic lymph node dissection, para-aortic dissection was performed at the discretion of the surgeon)	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%		Dropouts: 47 patients were excluded because of enrolment disqualification or missing data (risk of partial verification bias) Consecutive patients 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
Nam 2010 [38]	• Design: retrospective cohort study • Source of funding: not reported on • Conflict of interest: not reported on • Setting: Samsung Medical Centre, Seoul, South	• Eligibility criteria: uterine cervical cancer patients (FIGO stage IIB-IVA), treated with radiotherapy with a curative intent, with or without chemotherapy, who had a pre-treatment	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	-	Level of evidence: low Dropouts: 4 patients were excluded because of missing follow-up data and 1 patient because

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
	Korea • Sample size: N=92 • Duration: 1997-2007	MRI • Patient characteristics: 37% > 60 y of age; 95% SCC; 5% AC. All patients were FIGO stage IIB-IVA • Disease prevalence: 15% mucosal bladder invasion		as mucosal invasion) (N=92): Se 93%; Sp 94%; NPV 99%; PPV 72%		of hysterectomy after radiotherapy Consecutive patients Risk of selection bias through selection criteria Blinded assessment not reported
Oberoi 2002 [36]	• 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 • Patient 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 1/3 rd: 7%;	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 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%;	Accuracy of MRI to detect surgico-pathological staging: stage IB: 90%; IIA: 57%; IIB: 84%; IIIA: 83%; IVA: 100%	Level of evidence: low Consecutive patients Risk of selection bias through retrospective selection of patients with available index test Blinded assessment of index and reference test not reported on

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
		bladder invasion: 2%; rectum invasion: 1%; pelvic lymph node metastasis: 13%		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 2010 [62]	• Design: prospective study • Source of funding: supported in part by a Cancer Center Support Grant • Conflict of interest: not reported on • Setting: University of Texas M. D. Anderson Cancer	• 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 <2 cm in diameter) on preoperative CT or	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 patients (N=60): Se 36%; Sp 96%; NPV 83%; PPV 71%	There was one conversion from laparoscopy to laparotomy because of uncontrolled bleeding The median length of hospital stay was 1 day (range: 0-4	Level of evidence: low Dropouts: 1; another 4 patients were excluded because of too high blood glucose levels or supraclavicular metastasis on

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
	Center and Lyndon Baines Johnson General Hospital, Houston, United States • Sample size: N=60 • Duration: 2004-2009	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 • Patient 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			days). Five procedures were performed as an outpatient procedure Seven patients developed a lymphocyst postoperatively requiring drain placement 1/14 lymph node metastasis was found through ultrastaging	PET/CT (N=2, partial verification) Unclear whether patients were consecutive Selected subgroup with negative para-aortic lymph nodes on CT or MRI Blinded assessment not reported
Rockall 2006 [39]	• Design: retrospective study • Source of funding:	• Eligibility criteria: confirmed cervical cancer, clinical staging	Index test: MRI Reference standard:	Accuracy of MRI to detect bladder invasion (N=112): Se 100%; Sp 88%; NPV	-	Level of evidence: low

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
	not reported on • Conflict of interest: not reported on • Setting: St. Bartholomew's Hospital, London, United Kingdom • Sample size: N=112 • Duration: 1996-2004	and MRI performed on-site and availability of clinical notes and MRI for review • Patient characteristics: not described • Disease prevalence: bladder invasion: 1%; rectal invasion: 2%	cystoscopy and endoscopic examination of the rectum	100%; PPV 7% Accuracy of MRI to detect rectal invasion (N=112): Se 100%; Sp 91%; NPV 100%; PPV 17%		Consecutive patients Risk of selection bias through exclusion criteria Blinded assessment of index test
Sahdev 2007 [29]	• 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 patients 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 • Patient 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;	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%;	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: low Consecutive patients Risk of selection bias through exclusion criteria (81 patients were excluded) leaves a selective subgroup Blinded assessment of index test

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
		2% parametrial invasion; 13% lymph node metastases		PPV 39%		
Sandvik 2011 [66]	• Design: retrospective cohort study • Source of funding: not reported on • Conflict of interest: none stated • Setting: Herlev Hospital, Denmark • Sample size: N=117 • Duration: 2006-2007	• Eligibility criteria: • Patient 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: low Consecutive patients 34 patients with early stage disease did not have PET because of limited capacity and were excluded (selection bias) 41 patients did not have the PET/CT findings verified (partial verification bias) Blinded assessment not reported
Sharma 2010 [24]	• Design: cohort study • Source of funding: not reported on • Conflict of interest: not reported on • Setting: All India Institute of	• Eligibility criteria: cervical cancer to be treated by radiotherapy with or without concurrent chemotherapy • Patient characteristics:	Index test: CT Reference standard: cystoscopy with biopsy or vesicovaginal fistula on clinical	Accuracy of CT to detect bladder invasion (N=305): Se 100%; Sp 92%; NPV 100%; PPV 40%	-	Level of evidence: low Dropouts: not reported on Consecutive patients, unclear if

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
	• Medical Sciences, New Delhi, India • Sample size: N=305 • Duration: 2003-2005	mean age 50 y; 93% SCC; 54% FIGO stage IIIB or higher • Disease prevalence:5.5% bladder invasion	examination			the design was prospective Double-blind assessment Differential verification (not reported how many patients had vesicovaginal fistulas and consequently did not undergo cystoscopy with biopsy)
Sheu 2001 [42]	• 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 • Sample size: N=41 • Duration: 1996-1999	• Eligibility criteria: primary untreated cervix carcinoma; MRI-imaging and surgical treatment • Patient 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 patients after preoperative chemotherapy and in 4 patients after preoperative radiation therapy • Prevalence of disease:	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 86-100) Accuracy of MRI to detect tumor size >	Level of evidence: low Dropouts: none Exclusion of 38 women who did not undergo surgical treatment because of high surgical risk, clinically advanced disease status, refusal of surgical intervention (preferred radiotherapy) or did not undergo

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
		27% vaginal invasion			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 [22]	MRI due to pacemaker implantation, intracranial vascular clips or claustrophobia (partial verification bias) Consecutive patients Blinded assessment of index test; blinded assessment of reference test not reported on
Sironi 2002 [37]	• 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: low Dropouts: 8 patients were excluded because they refused surgery Subgroup of IB1 patients Consecutive patients 2x2 tables could not be constructed: the

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review 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)		reported outcomes are presented Double-blind assessment
Sironi 2006 [64]	• 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 • Patient characteristics: mean age 45.3 y; FIGO stage IA1: 9%; IB1: 74%; IB2: 17%; 79% SCC; 21% AC; 6 patients 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: low Dropouts: none Consecutive patients Double-blind assessment
Testa	• Design: prospective	• Eligibility criteria: patients with early	Index test: MRI (T2	Accuracy of MRI to detect	Mean difference	Level of evidence:

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
2009[32]	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 • Sample size: N=75 • Duration: 2002-2005	cervical cancer planned for primary surgery and patients with locally advanced cervical cancer planned for surgery after neoadjuvant treatment • Exclusion: patients who underwent a cervical cone biopsy; patients who underwent surgery >7 days after MRI • Patient characteristics: 78% SCC. FIGO stage IA2: 3%; IB1: 33%; IB2: 12%; IIA: 3%; IIB: 32%; IIIA: 3%; IIIB: 6%; IV: 5%. 33 patients 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%;	weighted) Reference standard: histopathology	parametrial invasion (N=68): Se 40%; Sp 89%; NPV 95%; PPV 22% Accuracy of MRI to detect vaginal invasion (N=68): Se 0%; Sp 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%	between histopathological measurements and MRI measurements of the craniocaudal diameter of the tumor: 1.49 mm (95% CI: −1.41 to 4.40 mm, 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%	low Dropouts: seven patients were not operated on because of no response to neoadjuvant treatment (partial verification bias) Consecutive patients MRI assessor was blinded to FIGO staging, but not to patient history

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
		rectovaginal septum invasion: 0%; lymph node metastases: 14.1%				
Wydra 2006 [70]	• 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 • Patient 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: low Dropouts: none Consecutive patients Blinded assessment not reported Unclear which patients got a para-aortic lymphadenectomy and why Small discrepancy in number of patients with a one-sided sentinel node detected (84 vs. 88) in text vs. table
Yamashita 2009 [73]	• Design: prospective study • Source of funding: not reported on • Conflict of interest: not reported on	• Eligibility criteria: FIGO stages Ia to IIIb uterine cervical cancer • Patient characteristics: mean age: 47 y; 88% SCC. FIGO stage: IA:	Index test: SNB (blue dye and radioactive material) with intraoperative frozen section assessment	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:	Level of evidence: low Dropouts: none Unclear if patients

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
	• Setting: Asahikawa Medical College, Asahikawa, Japan • Sample size: N=58 • Duration: 2001-2007	5%; IA1: 14%; Ia2: 3%; Ib1: 45%; IIA: 5%; IIB: 14%; IIIA: 2%; IIIB: 12% • Disease prevalence: 8.6% lymph node metastases	Reference standard: histopathology from pelvic lymphadenectomy		48%	were consecutive Blinded assessment not reported Unclear if patients got a para-aortic lymphadenectomy
Yu 2011 [65]	• 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 • Patient 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: low Dropouts: not reported on Study design was not described; nor was blinding. Unclear if patients were consecutive

4.6.2.3. SCCA and CA-125 for identification of high-risk patients

Primary studies

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
Bender 2003 [82]	• 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 patients treated) • Patient characteristics:mean age 45 y; 93% AC; 86% with low (I- IIA) FIGO stage; 52 patients 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: low Consecutive patients; risk of selection bias through eligibility criteria Partial verification: only patients 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 2008 [84]	• Design: prospective study • Source of funding: not reported on • Conflicts of interest: not reported on • Setting: China Medical University Hospital, China	• Eligibility criteria: untreated stage IB2–IVA squamous cell cancer of the uterine cervix, without evidence of enlarged para-aortic lymph nodes • Patient characteristics: not	Index tests: SCCA Reference standard: CT (lymph node positivity) and CT or pelvic examination (tumour size)	Accuracy of SCCA ≥2.0 ng/ml to predict a tumour size ≥4cm (N=148): Se 64%; Sp 31%; NPV 8%; PPV 91% Accuracy of SCCA ≥2.0 ng/ml to predict	-	Level of evidence: low Dropouts: not reported Unclear if patients were consecutive Differential verification for the outcome tumour size

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
	• Sample size: N=148 • Duration: 2001-2006	specified. All patients went for concurrent chemoradiation • Disease prevalence: tumor size >4 cm: 91 %; 15% lymph node metastases		positive lymph nodes (N=148): Se 77%; Sp 38%; NPV 91%; PPV 18%		The reference standard for parametrial invasion was not stated: not included as an outcome Concerns a subgroup of patients who did not receive surgery
Kotowicz 2008 [83]	• 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 • Patient 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 SCCA ≥1.5 ng/ml to predict positive lymph nodes (N=182): Se 67%; Sp 84%; NPV 92%; PPV 46%	-	Level of evidence: low Dropouts: not reported Design is not reported on, nor is blinding Differential verification
Takeda 2002 [85]	• 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 • Patient	Index tests: either SCCA or CA 125, or both combined Reference standard: histology	Accuracy of SCCA ≥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: low Dropouts: not reported Unclear if patients were consecutive Design is not reported on, nor is blinding. Likely a retrospective study because preoperative tumour

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
		characteristics: median age 52 y; 55% FIGO stage IB; 43% stage IIB • Disease prevalence:27% lymph node metastases				markers had to be available for inclusion Risk of selection bias through selection of hysterectomy patients with preoperative tumor markers available
van de Lande 2009 [86]	• 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 • Patient 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 SCCA ≥1.65 ng/ml to predict positive lymph nodes in patients with stage IB1 (N=72): Se 53%; Sp 84%; NPV 85%; PPV 50% Accuracy of SCCA ≥1.65 ng/ml to predict positive lymph nodes in patients with stage IB2 or IIA (N=19): Se 63%; Sp 46%; NPV 63%; PPV 40%	-	Level of evidence: low No dropouts Unclear if patients were consecutive Design is not reported on, nor is blinding The cut off level for SCCA was not predefined Insufficient data to construct a 2x2 table; the accuracy data from the study are reported here

4.6.2.4. Treatment of stage IA cervical cancer

Systematic reviews

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
CCCMAC 2010 [196]	• SR • Funding: UK Medical Research Council, UK • Search date: October 2009 • Databases: Medline, LILACS, CancerLit, trial registers, conference proceedings • Study designs: RCT • N included studies: N=15 (3452 patients) (Chen 1997a; Chen1997b; Cikaric 2005; GaripaÄŸaoÄŸlu 2004; Kantardzic 2004; Keys 1999; Lal 2004; Lanciano 2005a; Lanciano 2005b; Leborgne 1995; Lorvidhaya 2003a; Lorvidhaya 2003b; Onishi 2000; Pearcey 2002; Peters 2000; Pras 1995; Roberts 2000; Thomas 1998a; Thomas 1998b)	• Eligibility criteria: • Women with locally advanced cancer of the uterine cervix who had not received any previous treatments likely to interfere with protocol treatments or comparisons • Patient characteristics: • Median age: 47 years • Stage: IA-IIA 24% • Histology: squamous cell 89%	Concomitant chemotherapy and radical RT (with or without surgery) vs. Radical RT (with or without surgery)	Overall survival (N=16): HR 0.81 (95%CI 0.71-0.91; p<0.001; I² 0%) Trend in relative effect of CRT by tumour stage: p=0.017 Disease-free survival: Trend in relative effect of CRT by tumour stage: p=0.073		Level of evidence: moderate IPD analysis Adequate allocation concealment: N=14 No blinding Detailed results by stage are not provided
Viani 2009 [197]	• SR • Funding: not reported • Search date: May 2007 • Databases: Medline, CancerLit, Cochrane Library, trial registers, conference proceedings	• Eligibility criteria: • Patients with histologically confirmed cervical cancer and at least 18 years of age	HDR brachytherapy following pelvic RT vs. LDR brachytherapy	Overall mortality: LDR 34.1% vs. HDR 35.1%, OR 0.94 (95%CI -0.78, 1.13; p=0.52; I² 0%) Stage I: OR 0.68	Local recurrence: OR 1.05 (0.85-1.29; p=0.68; I² 0%) Stage I: OR 2.31 (0.61-8.71)	Level of evidence: low (for stage I outcomes)

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
	• Study designs: RCT • N included studies: N=5 (2145 patients) (Lertsanguansinchai 2004, Hareyama 2002, Teshima 1993, Patel 1994, Shrivastava 2006)		following pelvic RT	(0.36-1.29)	Grade 3-4 complications: Rectal: OR 0.9 (0.52-1.56) Bladder: OR 0.98 (0.49-1.96) Small intestine: OR 3.15 (0.9-10.37; p=0.06)	Presented using GRADE system
NICE 2006 [198]	• SR • Funding: not reported • Search date: May 2005 • Databases: Medline, PreMedline, EMBASE, Cochrane Library, Science Citation Index, trial registers, internet • Study designs: clinical studies • N included studies: N=7 (4 RCTs, 3 case series) (RCTs: El-Baradie 1997, Patel 1993, Lertsanguansinchai 2004, Hareyama 2002)	• Eligibility criteria: • Patients with carcinoma of the cervix	HDR brachytherapy	HDR vs. LDR: Overall mortality (all stages): HDR 54% at 5 years, LDR 55% Disease-free survival (stage II): HDR 69% vs. LDR 87% at 5 years HDR vs. MDR: Overall mortality (all stages): 61% vs. 63% at 5 years	Serious complications that required subsequent surgery: between 2% and 6% of cases (2 case series) In a large case series with a median 8 year follow up period the overall complication rate was 35% and radiation therapy oncology group grade 3 or 4 complications occurred in 7% of cases In a RCT comparing HDR and MDR brachytherapy the	Level of evidence: ? Information on methodological quality not completely given for all studies

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
					grade 2 complication rate among HDR treated patients was 13% Where reported separately, rectal complications (all grades) were reported in between 4% and 20% of cases, and bladder complications between 4% and 24% of cases	

Primary studies

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
Bisseling 2007 [110]	• 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: • Patients with stage IA1 and IA2 cervical cancer • Patient 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	No recurrence Excised parametria (N=8) and pelvic lymph nodes (N=17) were all free from disease	18 fertility preserving treatment: 11 patients with 18 pregnancies resulting in 13 live births, 2 terminations and 3 spontaneous abortions	Level of evidence: very low Average follow-up: 72 months
Kim 2010 [111]	• Retrospective cohort	• Eligibility criteria:	Hysterectomy (N=40)	No recurrence in	6 patients with	Level of evidence:

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
	study • Funding: not stated • Setting: university hospital, Korea • Sample size: N=108 • Duration: Jan 1999 – Feb 2008	• Patients with stage IA1 cervical cancer undergoing conization • Patient characteristics: • Median age: 41 vs. 38 years	vs. Conservative management (N=68)	hysterectomy group 7 recurrences in conization only group, all in patients with positive resection margins (N=40)	recurrence were treated successfully with repeat conization or simple hysterectomy; pathology was primarily CIN 3 or microinvasive disease at most	very low Median follow-up: 67 months No correction for confounders 1 patients with recurrence lost to follow up for 6 years and subsequently treated with CRT for advanced disease
Lee 2009 [112]	• Retrospective cohort study • Funding: not stated • Setting: 3 tertiary hospitals, Korea • Sample size: N=75 • Duration: Jan 1997 – Dec 2006	• Eligibility criteria: • Patients with stage IA1 cervical cancer undergoing conization • Patient characteristics: • Mean age: 48 vs. 35 years (p<0.05)	Hysterectomy (N=53) vs. Conservative management (N=22)	No recurrence in the hysterectomy group In the conservative group, 10 patients underwent repeat conization; 2 patients underwent hysterectomy for abnormalities at second follow-up	2 pregnancies and live births in conservative group	Level of evidence: very low Mean follow-up: 34 vs. 37 months Selection bias is possible, given the difference in mean age between the 2 groups
Yahata 2010 [114]	• Retrospective cohort study • Funding: not stated • Setting: 2 hospitals, Japan • Sample size: N=27 • Duration: 1990-2004	• Eligibility criteria: • Patients with stage IA1 cervical cancer • More than 5 years follow-up • Patient characteristics:	Hysterectomy (N=17) vs. Conservative management (N=10)	No recurrence in both groups 2 second conizations for positive margins in conservative group 2 patients with positive margins underwent	3 pregnancies and live births in conservative group	Level of evidence: very low Mean follow-up: 75 months for conization group vs. 133 months for hysterectomy group

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
		• Mean age: 43 years		hysterectomy (are included in hysterectomy group)		
Reynolds 2010 [113]	• 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: • Patients with stage IA1 (N=52) or IA2 (N=14) cervical cancer • Patient characteristics: • Median age: 39 years	Conization (N=7 and N=1) Simple hysterectomy (N=16 and N=2) Radical hysterectomy (N=29 and N=9) Radical vaginal trachelectomy (N=0 and N=2) 34 and 12 patients respectively also underwent PLND	No recurrences No parametrial involvement in any of the 40 patients who underwent radical surgery One patient with positive lymph nodes in the group that underwent PLND (1/46, 2.2%)		Level of evidence: very low Mean follow-up: 71 months for IA1 group vs. 80 months for IA2 group

4.6.2.5. Neoadjuvant treatment

Neoadjuvant treatment vs. primary radiotherapy

Systematic reviews

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
Tierney et al. 2003 [142]	• SR of individual patient data and MA • Sources of funding: The British Medical Research Council • Search date: January 1998 (updated until December 2002)	a) IIB-N1, III, M0 (N=182) b) IIIB (N=103) c) IIB-IVA (N=71) d) IIB-IVA, IIA inoperable (N=177) e) IB bulky	Comparison 1: *NACT + Local treatment* Cisplatin was the main drug in all CT regimens, with a planned total dose of between 100	5 years overall survival HR=1.05 (95%CI 0.94-1.19); p=0.393; heterogeneity: p=0.0003	Overall disease-free survival HR = 1.00 (95%CI 0.88-1.14); p=1.000; heterogeneity: p=0.001	Level of evidence: moderate No description about papers selection nor quality appraisal

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
	• Databases: Medline, CancerLit, handsearching (published and non-published trials) • Included study designs: RCTs • 18 trials (N=2074 patients) a) Chauvergne 1993 b) Souhami 1991 c) Tattersall 1992 d) Herod 2000 e) Sardi 1997 f) Cardenas 1993 g) Sardi 1998 h) Cardenas 1991 i) Chiara 1994 j) Sardi 1996 k) PMB Group unpublished l) Sundfor 1996 m) CCSG AOCOA n) Kumar 1998 o) Symonds 2000 p) Leborgne 1997 q) MRC CeCa unpublished r) LGOG unpublished	(N=210) f) IIIB (N=30) g) IIB (N=147) h) IIB N=31) i) IIB-III (N=64) j) IIIB (N=108) k) IIB, III IVA, bulky IB, IIA (N=35) l) IIIB-IVA (N=96) m) IIB-IVA (N=260) n) IIB-IVA (N=173) o) IIB bulky, III, IVA (N=215) p) IB-IVA (IB >4cm) (N=97) q) IB-IVA (N=48) r) IIB, III, IVA, bulky IB, IIA (N=27) Most had moderately or poorly differentiated, stage II-III tumours of squamous histology; the largest proportion had stage III (44%) tumours. Median age of 48 years (range 40–59 across trials) Good performance status	and 320 mg/m^2 in 10–28-day cycles. vs. *Local treatment* (mainly RT) Both the EBRT and intracavitary radiotherapy dose varied (40–60.8 and 18–80 Gy, respectively), with a total dose in the range 55–80 Gy.		Loco-regional disease-free survival HR = 1.03 (95%CI 0.90-1.17); p=1.000; heterogeneity: p=0.0002 Metastases-free survival HR = 1.00 (95%CI 0.88-1.14); p=1.000; heterogeneity: p=0.002	Analyses based on ITT Analyses of all endpoints were stratified by trial Trials were grouped according to frequency of chemotherapy cycles, cisplatin dose intensity, total dose of cisplatin, local treatment used and whether adjuvant chemotherapy was also given

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
Tierney et al. 2003 [142]	• SR of individual patient data and MA • Sources of funding: The British Medical Research Council • Search date: January 1998 (updated until December 2002) • Databases: Medline, CancerLit, handsearching (published and non-published trials) • Included study designs: RCTs • 5 usable trials for 'NACT+RT vs. Primary RT'(N=872 patients) a) Sardi 1996 b) Sardi 1998 c) Kigawa 1996 d) Benedetti-Panici 2002 e) Chang 2000	a) IIIB (N=107) b) IIB (N=154) c) IIB-IIIB (N=50) d) IB2-IIA ≥ 4 cm, IIB-III (N=441) e) Bulky IB, IIA (N=124) Moderately or poorly differentiated Median age of 49 years (range 42–58 across trials) Good performance status	Comparison 2: *(NACT + surgery) ± RT* Cisplatin was the main drug in all CT regimens with a planned total of dose between 100 and 300 mg/m^2 in 10–21-day cycles vs. *Primary RT* EBRT and Intra-cavitary RT doses were very similar across trials (45–60 and 25–40 Gy, respectively) The median follow-up across all trials is 5 years for surviving patients (3.9 to 9.0 years in the individual trials)	5 years overall survival HR=0.65 (95%CI 0.53-0.80); p=0.00004; heterogeneity: p=0.06	Overall and locoregional disease-free survival HR = 0.68 (95%CI 0.56-0.82); p=0.0001; heterogeneity: p=0.02 and 0.005 respectively Metastases-free survival HR = 0.63 (95%CI 0.52-0.78); p=0.00001 heterogeneity: p=0.217	Level of evidence: moderate No description about papers selection and quality appraisal Analyses based on ITT Analyses of all endpoints were stratified by trial Trials were grouped according to frequency of chemotherapy cycles, cisplatin dose intensity, total dose of cisplatin, local treatment used and whether adjuvant chemotherapy was also given

Primary studies

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of study quality
Mossa 2010 [144]	• Design: RCT 2 arms • Research funding: not reported • Setting: one hospital (Italy) • Sample size: • 304 patients enrolled in RCT • 288 eligible patients: Comparator group (elective surgery or exclusive RT, N=129) or intervention group (NACT+surgery, N=159). • Last follow-up : 84 months	• Eligibility criteria: < 65 years, FIGO Stage IB-IIIB squamous cell cancer, absence of severe systemic or other neoplastic pathologies, adequate bone marrow, renal and hepatic function. • Median age: 48.5 (range 32-65 years) • No statistical differences in patients age, stage, tumour size and lymph nodes between groups	Intervention NACT (vincristine-cisplatin chemotherapy at 21-days interval for 3 cycles) Type III-IV radical hysterectomy and systematic LND of the lumbar-aortic area (pelvic lympha-denectomy) Control Type III-IV radical hysterectomy and systematic LND of the lumbar-aortic area (pelvic lympha-denectomy) For non operable stage III patients in control group (N=24) or in the intervention group (N=6): EBRT on the whole pelvis (50Gy) + intracavitary LDR brachytherapy (30Gy)	Response to NACT Complete response: 22.6% Stage IB-IIA: 24.8% Stage IIB: 25% Stage IIIA-IIIB: 13.3% < 5 cm: 28.1% ≥ 5 cm: 14.3% LN - : 24.3% LN + : 18.2% Partial response: 56.6% No response: 20.8% Overall survival 70.4% vs. 64.9% (p=0.17) Stages IIIA-IIIB: 40.0% vs. 37.5% (p= 0.70)	Disease-free survival 65.4% vs. 53.5% (p=0.39) Stages IIIA-IIIB: 33.3% vs. 25% (p not reported)	Level of evidence: moderate Phase III trial Randomisation by a computer generated algorithm Repartition of patients: 55% (intervention group) vs. 45% (control group) No blinding reported ITT analysis only for overall survival For disease-free survival, some patients were excluded from the analyses

4.6.2.6. Adjuvant treatment

Systematic reviews

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
Rosa 2009 [121]	• 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 patients) • Tattersall 1992 (N=71)[125] • Peters 2000 (N=268 enrolled; 243 assessed)[124] • Protocol CE3005 - UK Clinical Trials Register 2001 (N=57 enrolled;	• Eligibility criteria: • Peters 2000 • Patients 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: • Patients 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	CRT vs. RT (N=2)		Level of evidence: moderate 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 patients): HR 0.56 (95%CI 0.36-0.87; p=0.0096; I^2 0%) in favour of chemotherapy	Disease progression (243 patients): HR 0.47 (0.30-0.74; p=0.0012; I^2 0%) in favour of chemotherapy Grade 4 toxicity (288 patients): HR 5.66 (2.14-14.98; p=0.00048; I^2 0%) in favour of no chemotherapy	
		Tattersall 1992	3 cycles of CT	Chemotherapy followed by RT vs. RT (N=1)		

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
	54 assessed)[123]	Patients 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	with cisplatin, vinblastine and bleomycin followed by pelvic RT Vs. RT only		Disease progression (71 patients): HR 1.34 (0.24-7.66)	

Primary studies

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of study quality
Monk 2005 [126] **retrospective analysis of Peters 2000 data**	• Design: RCT 2 arms • Research funding: National Cancer Institute grants • Setting: multicenter study • Sample size: 268 patients enrolled in RCT • 243 eligible patients • Median follow-up: 5.2 years	• Eligibility criteria: Patients 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]; CRT group 40 [19–74] • No statistical differences in patients age, stage, tumour size and	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% (CRT) vs. 66% (RT) 5-year survival (%) by prognostic factor (RT, CRT, p value) *Tumor size* *RT* *CRT* *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* *CRT* *p* Squamous 0.69 0.80 0.019 Nonsquam. 0.55 0.82 0.014 P value 0.17 0.76 *Grade* *RT* *CRT* *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* *CRT* *p* Neg 0.78 0.84 0.052 Pos 0.49 0.73 0.009 p value 0.007 0.19		Level of evidence: low exploratory, hypothesis-generating analysis survival was estimated with Kaplan–Meier method with differences analyzed using a log-rank test

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of study quality
		lymph nodes between groups		*Nodes* *RT* *CRT* *p* 1 node 0.79 0.83 0.438 ≥2 nodes 0.55 0.75 0.006 p value 0.01 0.37		

4.6.2.7. Management of advanced stages disease

Radiotherapy

Systematic reviews

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
Lutgens 2010 [136]	• SR • Sources of funding: none • Search date: January 2009 • Searched databases: Cochrane Central Register of Controlled Trials, Cochrane Gynaecological Cancer Groups Specialised Register, MEDLINE, EMBASE, CINAHL, metaRegister of Controlled Trials, Cancer Research UK,	• Eligibility criteria: Patients of any age with histologically proven LACC (central diameter ≥ 4 cm and/or FIGO stage IIB to IVA) and with a WHO performance status 0 to 2. • Patient characteristics: 74% had FIGO stage IIIB	Intervention: external beam radiotherapy (EBRT) with or w/o brachytherapy (BCT) + hyperthermia (min T° 40°C) Comparator(s): EBRT with or w/o BCT	Overall survival (N=264) HR 0.67; 95%CI 0.45-0.99; p = 0.05 Complete tumour response (N=267) RR 0.56 ; 95%CI 0.39-0.79; p < 0.001 Local recurrence (N=264)		Level of evidence: moderate Studies with less than 20 patients were excluded. No blinding Patients with concomitant chemo were excluded No info about the adequacy of RT dose delivery (no standardization) Hyperthermia:

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
	Cancer.gov, The Eastern Cooperative Oncology Group Trials Database • Included study designs: RCTs (phase II or III) • Number of included studies: 6 a) Datta 1987 b) Sharma 1991 c) Chen 1997 d) Harima 2001 e) Van der Zee 2000 f) Vasanthan 2005			HR0.48 ; 95%CI 0.37-0.63; p < 0.001 Acute toxicity < 3 months (N=310) RR 0.99 ; 95% CI 0.30-3.31; p = 0.99 Late toxicity (N=264) RR 1.01 ; 95%CI 0.44-2.30); p = 0.98		variability in T°, energy distribution systems, frequency of administration, trt duration
Wang 2010 [138]	• SR • Funding: Radio-oncology Clinical Medicine Certra, Gansu Province and the science technology renovation team of tumour treatment using heavy ion of Lanzhou, China • Search date: November 2009 • Databases: Medline, Embase, Cochrane Gynaecological	• Eligibility criteria: Patients with histologically confirmed cervical cancer and at least 18 years of age • Patients characteristics: patients with FIGO stages I to III, with most having stages II and III	HDR brachytherapy following pelvic RT vs. LDR brachytherapy following pelvic RT	Three-year survival stage IIB (N=125) RR 0.87 ; 95%CI 0.69-1.10) stage IIIB (N=81) RR 1.10; 95%CI 0.81-1.50 Five-year survival stage II (N=324) RR 0.95; 95%CI 0.81-1.11 stage III (N=454) RR 0.94; 95%CI 0.76-	Five-year local control rate stage II (N=183) RR 0.96; 95%CI 0.82-1.13 stage III (N=225) RR 0.93; 95%CI 0.80-1.09 Recurrence and metastasis no result per subgroup no heterogeneity	Level of evidence: low Selection bias for older patients (referred to HDR) Allocation concealment and blinding were often unclear

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
	Cancer Group Specialised Register, Cochrane Library, Chinese Biomedical Literature Database, LILACS • Study designs: RCT • N included studies: N=4 (1 265 patients) a) Lertsanguansinchai 2004 b) Hareyama 2002 c) Teshima 1993 d) Patel 1994			1.15 Ten-year survival stage II (N=141) RR 0.94; 95%CI 0.69-1.28 stage III (N=229) RR 1.01; 95%CI 0.73-1.41 Five-year disease specific survival stage II (N=189) RR 0.88; 95%CI 0.75-1.03 stage III (N=313) RR 1.03; 95%CI 0.82-1.29 Ten-year disease specific survival stage II (N=141) RR 0.96; 95%CI 0.77-1.20 stage III (N=229) RR 1.16; 95%CI 0.87-1.56	between groups RTOG grade 3-5 complications (N=1265) bladder RR 1.33 ; 95%CI 0.53-3.34; P = 0.54 rectosigmoid RR1.00 ; 95%CI 0.52- 1.91; P = .00 small bowel RR 3.37 95%CI 1.06-10.72; P = 0.04	

Primary studies

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of study quality
Harima 2009 [137]	• Design: RCT • Source of funding: not reported • Setting: hospital • Sample size: 40 patients (20 RT/ 20 TRT) • Duration: 3 years	• Eligibility criteria: o histologically proven cervical (FIGO) Stage IIIB o performance status of 0–2 o no prior chemo, RT or surgery o adequate bone marrow, liver and renal function o no concomitant malignancies o informed consent • Group comparability o Mean FU: 25 months (RT) vs. 36.3 (TRT) o Mean age: 61-65 years o Majority: squamous cell carcinoma	Intervention(s): RT + brachytherapy + hyperthermia Comparator(s) RT + brachytherapy	Complete response TRT = 80% RT = 50% P = 0.048 Partial response TRT = 15% RT = 25% P = 0.3 No response TRT = 5% RT = 25% P = 0.09 3-year OS TRT = 58.2% RT = 48.1% KM – log-rank; p=0.3 3-year DFS TRT = 63.6% RT = 45% KM – log-rank; p=0.2	3-year local relapse-free survival TRT = 79.7% RT = 48.5% P = 0.048 Toxicity TRT = 25% acute (grade 1: subcutaneous fatty tissue necrosis, colitis) and/or late toxicities (grade 3: diarrhoea+ sigmoid-ileum fistula, obstructive ileus of the colon) RT = 0%	Level of evidence: moderate Dropouts: no Results critical appraisal No blinding

Radiochemotherapy

Systematic reviews

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
Wang 2011 [129]	• Design: SR and MA • Sources of funding: not reported • Search date: not reported (most recent included papers in 2009) • Searched databases • Cochrane library, • Medline, • EMBASE, • Chinese biomedicine literature database, • Chinese scientific full-text database • Chinese journal full-text database • Included study designs: RCT • Number of included studies: 18 RCT (3517 patients) a) Ma 2009 b) Herod 2000 c) Fu H. 2007	• Eligibility criteria: patients having primary, previously untreated; histologically or cytologically confirmed carcinoma of the cervix; no evidence of extrahepatic metastases • Patients characteristics: most patients were in IB-IVA stage groups	*Intervention(s):* radiochemotherapy (RTCT) *Comparator(s):* radiotherapy (RT)	Response rate (N=1928) RTCT: 81.8% RT: 69.8% I2 = 13% RR 1.17; 95%CI 1.11-1.23) Three-year survival (N=709) RTCT: 76.9% RT: 67.9% I2 = 0% RR 1.13; 95%CI 1.04-1.24) Five year survival (N=1563) RTCT: 73.0% RT: 60.1% I2 = 0% RR 1.22; 95%CI 1.13-1.31)	Adverse events Mention of higher incidence rates for RTCT group in gastrointestinal, myelosuppression and leucopenia, but no results were reported	Level of evidence: moderate No details about blinding in original studies Potential problems in allocation concealment in some studies Papers published by Lu, Stehman and Peters did not appeared in the analyses for the three primary outcomes Some studies included patients who underwent a hysterectomy

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
	d) Keys 1999 e) Monk 2005 f) Morris 1999 g) Nagy 2009 h) Pearcy 2002 i) Peters 2000 j) Stehman 2007 k) Yang 2003 l) Fu W. 2008 m) Wang 2007 n) Chen 2007 o) Chen 2008 p) Yazigi 2003 q) Gao 2009 r) Lu 2004					
CCCMAC 2010 [196]	• SR • Funding: UK Medical Research Council, UK • Search date: October 2009 • Databases: Medline, LILACS, CancerLit, trial registers, conference proceedings • Study designs: RCT • N included studies: N=15 (3452 patients) (Chen 1997a; Chen 1997b; Cikaric	• Eligibility criteria: Women with locally advanced cancer of the uterine cervix who had not received any previous treatments likely to interfere with protocol treatments or comparisons • Patient characteristics: Median age: 47 years ; Stage: IA-IIA 24%; IIB 36%; III-IVA 38% ; Histology: squamous cell	Concomitant chemotherapy and radical RT (with or without surgery) vs. Radical RT (with or without surgery)	*Overall survival (N=16):* HR 0.81 (95%CI 0.71-0.91; p<0.001; I^2 0%) *Trend in relative effect of CRT by tumour stage:* p=0.017 The HRs obtained for each stage translate to 5-year survival benefits of 10% for women with stages IB to IIA cervical cancer, 7% for women with stage IIB cervical cancer, and 3% for women with stage III to IVA cancer. *Disease-free survival:* Trend in relative effect of		Level of evidence: moderate IPD analysis Adequate allocation concealment: N=14 No blinding

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
	2005; GaripaÄŸaoÄŸlu 2004; Kantardzic 2004; Keys 1999; Lal 2004; Lanciano 2005a; Lanciano 2005b; Leborgne 1995; Lorvidhaya 2003a; Lorvidhaya 2003b; Onishi 2000; Pearcey 2002; Peters 2000; Pras 1995; Roberts 2000; Thomas 1998a; Thomas 1998b)	89%		CRT by tumour stage: p=0.073		
Tzioras 2007 [130]	• Design: SR and MA • Sources of funding: none • Search date: January 2006 • Searched databases • Cochrane library • Medline • EMBASE • Included study designs: RCT • Number of included studies: 65 RCT (11180 patients)	• Eligibility criteria: Advanced disease: FIGO stages IIB, III, IV, unresectable or recurrent	Comparison between neo-adjuvant or concurrent chemotherapy plus radiotherapy versus radiotherapy alone Comparison between different chemotherapy regimens among themselves (with or without previous radiotherapy in both arms)	Mortality CRT vs. RT 22 comparisons on 3837 patients First analysis: HR 0.95, 95%CI 0.83–1.08; I2 = 38% due to contradictory results in early trials Second analysis on trials published between 1997-2006 (11 comparisons) HR 0.89; 95%CI 0.78–1.02; I2 = 0%		Level of evidence: low Considerable between study heterogeneity Contradictions between early trials In some trials, enrolment of early stages of cancer → more benefit from treatment

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
				Platinum +RT vs. RT (3 trials), HR 1.10, 95%CI 0.75–1.60, I2 = 25% Platinum + non-platinum agents +RT vs. RT (12 trials), HR 1.03, 95%CI 0.86–1.23, I2 = 46% Different chemotherapy regimens: subgroup analysis Cisplatin or cisplatin-based combinations: short-length cycles (≤14 days) HR 0.80, 95%CI 0.66–0.99 longer cycles HR 1.18, 95%CI 1.02–1.38 Neoadjuvant vs. concurrent chemotherapy Neoadjuvant: HR 1.02, 95%CI 0.84–1.24) Concurrent: HR 0.85 (95%CI 0.73–1.00)		

Primary studies

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of study quality
Kim 2008 [133]	• Design: RCT • Setting: one hospital • Sample size: 158 (RT+Cis/FU=79 / RT+Cis=79) • Duration: median follow-up=39 months	• Eligibility criteria: pathologically FIGO stage IIB to IVA, uterine cervical cancer, ≥18 years old, ECOG ≤2, adequate hepatic, renal, and bone marrow function, negative para-aortic lymph node status, no history of prior chemotherapy, radiotherapy, or abdominopelvic surgery	Intervention: RT + 3 monthly cycles of FU (1000 mg/m2/ day i.v.) plus cisplatin (20 mg/m2/day i.v.) for 5 days Comparator: RT + 6 cycles of weekly cisplatin (30 mg/m2 i.v.) RT = external irradiation + HDR intracavitary brachytherapy	Complications grade 2 hematologic toxicity IG=31% CG=53% grade 3/4 hematologic toxicity IG=43% CG=26% p=0.037 Complete response rate IG=91% CG=91%	Four-year overall survival IG=70% CG=67% Four-year progression-free survival IG=67% CG=66% Non significant differences (p not reported)	Level of evidence: moderate Dropouts: 3 patients were ineligible; 40% of the IG and 17% of the CG patients received less than 80% of their full doses of scheduled chemoRT Results critical appraisal No information about blinding
Stehman 2007 [131]	• Design: RCT • Source of funding: grants from the National Cancer Institute (CA 27469, to the Gynecologic Oncology Group Administrative Office, and CA 37517, to the Gynecologic Oncology Group Statistical Office).	• Eligibility criteria: patients having primary, previously untreated; histologically or cytologically confirmed carcinoma of the cervix (stage IB); adequate renal, hepatic, and bone marrow function; entry within 8 weeks of diagnosis	Intervention(s): RT: 45 Gy in 20 fractions+ LDR intracavitary application(s) of 30 Gy to point A CT: cisplatin 40 mg/m2 every week for up to 6 weekly cycles Comparator(s):	Progression RR 0.61; 95%CI 0.43- 0.85 p<.004 10 year survival RTCT= 73.8% RT= 63.4% Adjusted death hazard ratio = 0.63; 95%CI	Adverse events Increased rate of early hematologic and gastrointestinal toxicity in RTCT No detectable difference in the frequency of late adverse events.	Level of evidence: moderate Dropouts: 5 patients were ineligible Results critical appraisal No information about blinding

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of study quality
	• Setting: multicenter hospitals • Sample size 369 (RTCT=183 / RT=186) • Duration : median follow-up=101 months	• Group comparability: risk factors including cell type, tumor grade, age, performance status, and tumor size were balanced between the 2 randomization arms; 96% had hysterectomy in RTCT group vs. 90% in RT group	RT: 45 Gy in 20 fractions+ LDR intracavitary application(s) of 30 Gy to point A Total extrafascial hysterectomy followed the completion of RT by 6-8 w	0.43-0.91, p<.015		
Mitra 2006 [132]	• Design: RCT • Setting: one hospital • Sample size: 160 (RTCT=80 / RT=80) • Duration: median follow-up=54 months	• Eligibility criteria: pathologically FIGO stage IIB to IVA, uterine cervical cancer, WHO performance score 0-1, adequate hepatic, renal, and bone marrow function, no history of prior chemotherapy, radiotherapy, or surgery, presence of metastatic disease or uncontrolled systemic illness • Characteristics: Mean age=45 years; Majority of patients had squamous cell carcinoma; 58% had Stage IIIB	Interventions: Weekly cisplatin 30 mg/m2 for 5 cycles RT 5000cGy in 25 fractions (single fraction daily, 5 fractions per week) + LDR brachytherapy 2500 cGy at point A Comparator RT 5000cGy in 25 fractions (single fraction daily, 5 fractions per week) + LDR brachytherapy 2500 cGy at point A	Complete response rate IG=83% CG=73% p>0.1 Toxicity Grade 3 neutropenia IG=12% CG=0% Grade 2 anaemia IG=20% CG=0% Grade 3 nausea-vomiting IG=20% CG=0%	Overall survival (54 months) IG=56% CG=47% p>0.1 Disease-free survival (54 months) IG=51% CG=37% p>0.05	Level of evidence: moderate Dropouts: 5 patients refused to continue due to personal reasons (included in ITT analysis) Results critical appraisal No information about blinding

Chemotherapy for recurrent and stage IVB

Primary studies

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of study quality
Monk 2009 [149] **Cella 2010** [150]	• Design: RCT 4 arms • Research funding: none • Setting: one hospital • Sample size: • 513 patients enrolled in RCT with 2 arms → early closure for futility • 472 patients enrolled in RCT with 4 arms → 434 patients 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	Intervention(s) VC (N=108): vinorelbine 30mg/m2 on days 1 and 8 plus cisplatin 50 mg/m2 on day 1 every 3 weeks; GC (N=112): gemcitabine 1,000 mg/m2 on days 1 and 8 plus cisplatin 50 mg/m2 on day 1 every 3 weeks; TC (N=111): topotecan 0.75 mg/m2 on days 1, 2, and 3 plus cisplatin 50 mg/m2 on day 1 every 3 weeks. Comparator(s) PC (N=103): paclitaxel 135mg/m2 over 24 hours plus cisplatin 50mg/m2 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)	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: moderate Results critical appraisal No information about blinding No information about comparability of treatments

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of study quality
				Median progression-free survival PC: 5.82 months (95%CI 4.53-7.59 months, unadjusted 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 [151]	• Design: RCT 2 arms • Setting: outpatient administration • Sample size: • 153 patients enrolled	Eligibility criteria: • histologically documented primary metastatic or recurrent carcinoma of the	Intervention ITP : ifosfamide 1.5 g/m2, daily, on days 1–3 + cisplatin 70 mg/m2	Complete response ITP: 25%; 95%CI 16%-36% IP: 11%; 95%CI 5%-	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 =	Level of evidence: moderate Results critical

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of study quality
	in RCT → 149 eligible patients • Median follow-up : 57.3 months (range 4–96 months)	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 marrow function Exclusion criteria: brain metastases, active infection, serious concurrent medical illnesses and preexisting peripheral neuropathy Characteristics of patients • Median age: 50-55 (range (28-75) • Majority: squamous cancer • FIGO Stage at diagnosis: I-IV	on day 2 + paclitaxel 175 mg/m2 on day 1 Comparator IP : ifosfamide 1.5 g/m2, daily, on days 1–3 + cisplatin 70 mg/m2 on day 2	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% (95%CI 47%-70%) vs. 33% (95%CI 29%-45%) P = 0.002	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 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	appraisal No information about technique for randomisation Blinding of outcome evaluation ITT analysis Phase II trial No loss to follow-up

4.6.2.8. Fertility-sparing treatment

Conization

Primary studies

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
Bisseling 2007 [110]	• 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: Patients with stage IA1 and IA2 cervical cancer Patient 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	18 fertility preserving treatment: 11 patients with 18 pregnancies resulting in 13 live births, 2 terminations and 3 spontaneous abortions	Level of evidence: very low Average follow-up: 72 months No correction for confounders
Bull-Phelps 2007 [199]	• Case series • Funding: not stated • Setting: multicentre USA • Sample size: N=101 • Duration: 1993 - 2001	Eligibility criteria: Patients with cervical adenocarcinoma in situ (AIS) Patient characteristics: Median age 29 years Fifty-seven percent were nulliparous and 23% primiparous	Primary fertility-sparing surgery with either loop excision or cold knife conization	Thirty-six patients had a repeat cone biopsy. Five ultimately underwent hysterectomy. No invasive cervical adenocarcinomas were observed during the study interval Thirty-five women had a total of 49 pregnancies. Thirty-five gestations were delivered at term	There were two preterm births, eight spontaneous miscarriages, three elective terminations, and one ectopic pregnancy	Level of evidence: low Mean follow-up of 51 months

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
Kim 2010 [111]	• Retrospective cohort study • Funding: not stated • Setting: university hospital, Korea • Sample size: N=108 • Duration: Jan 1999 – Feb 2008	Eligibility criteria: Patients with stage IA1 cervical cancer undergoing conization Patient 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 patients with positive resection margins (N=40)	6 patients 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 Median follow-up: 67 months No correction for confounders 1 patients with recurrence lost to follow up for 6 years and subsequently treated with CRT for advanced disease
Lee 2009 [112]	• Retrospective cohort study • Funding: not stated • Setting: 3 tertiary hospitals, Korea • Sample size: N=75 • Duration: Jan 1997 – Dec 2006	Eligibility criteria: Patients with stage IA1 cervical cancer undergoing conization Patient 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 patients underwent repeat conization; 2 patients underwent hysterectomy for abnormalities at second follow-up	2 pregnancies and live births in conservative group	Level of evidence: very low Mean follow-up: 34 vs. 37 months No correction for confounders Selection bias is possible, given the difference in mean age

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
						between the 2 groups
Reynolds 2010 [113]	•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: Patients with stage IA1 (N=52) or IA2 (N=14) cervical cancer Patient 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 patients respectively also underwent PLND	No recurrences No parametrial involvement in any of the 40 patients who underwent radical surgery One patient with positive lymph nodes in the group that underwent PLND (1/46, 2.2%)		Level of evidence: very low No correction for confounders Mean follow-up: 71 months for IA1 group vs. 80 months for IA2 group
Yahata 2010 [114]	•Retrospective cohort study •Funding: not stated •Setting: 2 hospitals, Japan •Sample size: N=27 •Duration: 1990 – 2004	Eligibility criteria: Patients with stage IA1 cervical cancer More than 5 years follow-up Patient 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 patients with positive margins underwent hysterectomy (are included in hysterectomy group)	3 pregnancies and live births in conservative group	Level of evidence: very low No correction for confounders Mean follow-up: 75 months for conization group vs. 133 months for hysterectomy group

Radical trachelectomy

Primary studies

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
Beiner 2008 [158]	• Retrospective cohort study (matched) • Funding: not stated • Setting: Gynecologic Oncology at the University of Toronto • Sample size: N=180 • Duration: 1994 - 2007	Eligibility criteria: Patients 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) Patients were matched with controls who underwent radical vaginal hysterectomy Patient 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 patients 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 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 [160]	• Case series • Funding: not stated • Setting: multicentre Germany	Eligibility criteria: Patients with cervical cancer Exclusion criteria: Tumor	Radical vaginal trachelectomy (RVT) and pelvic lymphadenectomy	Three (3%) recurrences in 100 patients treated with RVT according to protocol	Average duration of surgery: 253 min (115–402) Perioperative	Level of evidence: very low Median follow-up

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
	• Sample size: N=108 • Duration: March 1995 - November 2005	size >2 cm, neuroendocrine tumor type, tumor-involved resection margins, or positive pelvic lymph nodes Patient characteristics: TNM stage 1A1, L1 N=18, 1A2 N=21, 1B1 N=69		Projected 5-year recurrence-free and overall survival rates: 97% and 98%	complications: postoperative bleeding, embolism of the external iliac artery, retroperitoneal lymphocele, and paralytic ileus in one patient, respectively	time: 29 months (1-128) 8 patients excluded as the study criteria were not met after RVT
Kim 2011 [164]	• Case series • Funding: not stated • Setting: Memorial Sloan–Kettering Cancer Center, New York • Sample size: N=105 • Duration: November 2001 - September 2010	Eligibility criteria: Patients who attempted fertility-sparing surgery Patient characteristics: Preoperative stages: 12 stage IA1 (12%), 12 stage IA2 (12%), and 81 stage IB2 (77%)	Radical trachelectomy by either an abdominal (RAT), vaginal (RVT) or robotic approach (RRT) (49 RAT, 52 RVT, and 4 RRT)	One patient recurred and died of disease 24 months after surgery. Two patients expired from non-oncologic causes 35 were actively attempting conception 6-12 months after surgery 22 patients (63%) successfully conceived	9% required an intervention for perioperative complications	Level of evidence: very low Heterogeneous intervention in a specialised centre Median follow-up: 29 months (range 0.1–99.8)
Li 2011 [166]	• 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	Abdominal radical trachelectomy	No recurrences 14 patients tumor > 2 cm 10 patients 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	Level of evidence: very low Median follow-up: 22.8 months (range 1–78 months)

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
		cervicovaginal anatomy after conization; or stage IA2 or IB1 disease Desire to preserve fertility Patient characteristics: Median age: 29.5 years (range 11-41) Stage IA1 27%, IA2 12%, IB1 61% SCC 81%			cervical stenosis: 4/64 (6.25%)	
Marchiole 2007 [157]	• 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 Patient 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 patients treated with LAVRT and 9 cases (6.5%) in patients 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 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	Patient 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 [200]	• Case series • Funding: not stated • Setting: four institutions in Korea • Sample size: N=59 • Duration: not mentioned	Eligibility criteria: Patients with early-stage cervical cancer who wanted to preserve fertility Patient characteristics: Median age: 29 years (range 22-44) Median tumour size: 1.8 cm	Laparoscopic radical trachelectomy	59 enrolled for LRT In 5 patients, LRT was abandoned because of lymph node metastasis or parametrial involvement 2 recurrences and 1 death from disease 16 patients attempted to conceive: 8 pregnancies, 3 healthy babies	Median estimated blood loss: 300 mL (range 50–1000) Perioperative transfusion in 15 patients 6 received adjuvant treatment 1 vesicovaginal fistula	Level of evidence: very low Median follow-up was 31 months (range 7–70)
Nishio 2009 [163]	• 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 Patient characteristics: Median age: 33 years	Abdominal radical trachelectomy	Six recurrences (9.8%); none of the recurrences occurred in patients with a tumor diameter of <20 mm except in one case with adenocarcinoma among the 13 patients 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,	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 Median follow-up: 27 months (range 1-79 months)

Reference	Methodology	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
		(range 26-44) FIGO IA1 6.6%, IA2 13.1%, IB1 80.3% SCC 95.1%		and two full-term deliveries		
Plante 2011 [159]	• Case series • Funding: not stated • Setting: one centre in Quebec • Sample size: N=140 • Duration: not mentioned	Eligibility criteria: Patients with early-stage cervical cancer (stages IA, IB, and IIA) Desire to preserve fertility Patient characteristics: Median age: 31 years Stage IA2 21%, IB1 69% SCC 56%	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 associated with a higher risk of recurrence (p=0.002) 3 recurrences in 13 tumors > 2 cm	58 women conceived a total of 106 pregnancies The first- and second-trimester miscarriage rates were 20 and 3% 77 (73%) pregnancies reached the third trimester 58 (75%) delivered at term	Level of evidence: very low Mean follow-up was 93 months (range 4–225) RVT was abandoned in 15 patients (reasons not stated) Correction for confounders unclear
Shepherd 2006 [161]	• Case series • Funding: not stated • Setting: multicentre UK • Sample size: N=123 • Duration: August 1994 - 2005	Eligibility criteria: Patients with early-stage cervical cancer Patient 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 Mean follow-up period: 45 months (SD 32 months, range 1–120 months)

4.6.2.9. Sexual morbidity

Systematic reviews

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
Flynn 2009 [172]	• 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: N=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	Dyspareunia in all patients (N=93): Odds Ratio (95%CI) 0.33 [0.11, 0.93] Dyspareunia in sexually active (N=56): Odds Ratio 0.26 [0.08, 0.84]		Level of evidence: very low 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 over. Studies of a Clinical Nurse Specialist intervention, Psychoeducational Group Therapy and a Couple-Coping intervention, did not show any significant benefit. All the studies were of poor methodological quality. There is no convincing evidence to support the use of any intervention.
			Brachytherapy 0.4Gy/Hr versus 0.8Gy/hr	Dyspareunia in all patients (N=204): Odds Ratio 0.37 [0.15, 0.93] Dyspareunia at 25 months post-treatment (N=204): Odds Ratio 0.39 [0.07, 2.05]		
			Clinical Nurse Specialist versus Standard Care	Not sexually active (N=36): Odds Ratio 0.63 [0.17, 2.36] Previously active, unsatisfactory now (N=20): Odds Ratio 0.03 [0.00, 0.37]		

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
Miles 2007 [173]	• Design : systematic review • Sources of funding:none mentioned • Search date januari 2007 • Searched databases: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and PsycINFO AMED, CINAHL National Health Service Research Register • Included study designs: RCT • Number of included studies 1	Eligibility criteria Patients undergoing interventions for sexual dysfunction following treatments for cancer For this report only interventions for women were retained	Vaginal oestrogen versus placebo	Sexual vaginal intercourse (self report): Odds Ratio (95%CI) 0.91 [0.40, 2.10] Dyspareunia (self report): Odds Ratio 3.81 [1.19, 12.16] Severe dyspareunia (self report): Odds Ratio 0.07 [0.00, 1.33]		Level of evidence: very low 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.
Miles 2010 [174] **Johnson 2010** [175] **(two reports of the same systematic review)**	• Design : systematic review • Sources of funding: none mentioned • Search date januari 2007 • Searched databases: Cochrane Central Register of Controlled Trials	Eligibility criteria Patients undergoing interventions for sexual dysfunction following treatments for cancer For this report only interventions voor women were retained.	Psycheducational support for the use of Dilation	Sexual functional score after 3 months: Mean difference (95%CI) 0.04 [–0.03, 0.11] Sexual functional score after one year: Mean difference (95%) –0.01 [–0.07, 0.05]	Case reports describe 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	Level of evidence: very low No RCT with a direct comparison were identified, only one small trial involving support identified Authors conclude that there is insufficient

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
	(CENTRAL), MEDLINE, , and PsycINFO AMED, CINAHL National Health Service Research Register • Included study designs: RCT • Number of included studies 1				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	evidence supporting dilation
			Other non randomised studies	One comparative unmatched trial showed no advantage from inserting mitomycin C One retrospective report implied that dilation lowered stenosis rates, but the control group is not comparable		

4.6.2.10. Follow-up

Systematic reviews

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
Elit 2009 [178]	• 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 patient quality of life; >25 patients included and English language Patient characteristics: 15/17 studies included patients with surgical stage IB or IIA; 6/17 studies included patients with all stages. The majority of included patients 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 patients who were symptomatic at the time of recurrence detection, median overall survival after recurrence ranged from 8- 38 months, and for asymptomatic	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 patients 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: very low All studies were retrospective, uncontrolled observational studies Very heterogeneous patient populations

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
				patients the range was 8 months to a median survival that was not reached after 53 months of follow-up		
Havrilesky 2005 [49]	• 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 patients Patient 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: low All studies were retrospective and none of them reported blinded assessment

Primary studies

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of study quality
Brooks 2009 [183]	• Design: retrospective cohort study • Source of funding: not reported on • Conflicts of interest: one author received honoraria from various manufacturers • Setting: Washington University School of Medicine, St. Louis, United States • Sample size: N=103 • Duration: 2000-2006	Eligibility criteria: patients treated with definitive chemoradiation for advanced-stage (IB1–IIIB) cervical cancer; a post-therapy PET showing complete response; subsequent PET scan for follow-up Patient characteristics: 90% SCC; 7% AD. Stage IB1–IIIB (discordant figures provided per stage). 24% of patients were symptomatic Disease prevalence: 29% recurrence. In symptomatic patients: 84% recurrence; in asymptomatic patients 12% recurrence	Index test: PET or PET/CT (from 2002 onwards) Reference standard: histology, radiologic progression (unspecified), follow-up	All recurrences detected by PET or PET/CT were confirmed by biopsy or radiologic progression (N=103; PPV 100%)	Of the 21 PET detected recurrences in symptomatic patients 4 were locoregional and 17 distant recurrences. Of the 9 PET detected recurrences in asymptomatic patients 8 were locoregional and 1 was a distant recurrence	Level of evidence: low Data were collected prospectively in a tumour registry Consecutive patients. Only patients with a PET/CT during follow-up were selected: risk of selection bias Blinded assessment not reported Differential verification False-negative and true negative rates not reported Risk of incorporation bias as radiologic follow-up may have included PET
Chan 2002 [186]	• Design: retrospective cohort study • Source of funding: not reported on • Conflicts of interest: not reported on • Setting: Queen Mary Hospital, Hong Kong	Eligibility criteria: all patients with SCC and SCCA measurement Patient characteristics: mean age 55 y; FIGO stage I: 49%; II: 30%; III:17%; IV:3%; 21 patients had	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 98%; NPV: 95%; PPV 85%	7/10 patients with locoregional disease had elevated SCCA levels (not reported for the patients with a distant recurrence)	Level of evidence: low Consecutive patients Risk of selection bias through selection criteria Blinded assessment

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of study quality
	SAR, China • Sample size: N=384 • Duration: 1994-1999	persistent/progressive disease Disease prevalence: 14% recurrence (3% locoregional and 12% distant)		Mean lead time: 9.8 months; median lead time: 7.8 months (range: 1-21 months)	8% of patients 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 patients with SCCA>2.5 ng/mL had recurrent disease	not reported Differential verification
Chien 2005 [189]	• 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: patients with cervical cancer (primary or recurrent) treated with curative radiotherapy in 1996 and available follow-up Pap smears Patient 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%	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: low Consecutive patients 4 patients 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 patients were followed

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of study quality
		central recurrence; 57% recurrence				with Pap smears
Chung 2006 [180]	• Design: retrospective cohort study • Source of funding: not reported on • Conflicts of interest: not reported on • Setting: Research Institute and Hospital, National Cancer Center, Gyeonggi, South Korea • Sample size: N=121 • Duration: 2001-2004	Eligibility criteria: women who had reached complete response after primary treatment (absence of detectable disease on physical and gynaecological examination, cytologic/histologic evaluation, imaging studies and normal SCCA and CEA) and a follow-up of ≥ 6 months Exclusion criteria: unable to undergo PET imaging; had previous malignant disease other than non-melanoma skin malignancy; diagnosed as unsuited for treatment with curative intent at the time of disease recurrence; had skin or pulmonary lesions or impaired renal functions contributable to the elevation of serum SCCA level or other hepatic or colonic pathology	Index test: whole-body PET, performed when patients had symptoms suspecting recurrence; had new lesions on surveillance imaging studies; had elevated serum tumor markers; had abnormal results on physical or cytologic examination on routine surveillance; wanted surveillance PET scan for fear of recurrence without evidence of disease. PET was not performed when patients had had microscopic lesions cured by definitive treatment; had multiple sites of recurrence on other imaging studies disabling therapy with curative intent; rejected PET scan for financial reasons Reference standard:	The accuracy of PET to detect recurrence(N=121): Se 96%; Sp 84%; NPV 93%; PPV 91% The accuracy of PET to detect recurrence in asymptomatic patients (N=65): Se 85% With elevated tumor markers (N=8): Se 100% Normal tumor markers: Se 82% The accuracy of PET to detect recurrence during surveillance (absence of symptoms and no indications from tests) (N=30): Sp 80%; NPV: 100%, PPV: 0	Of the 20 patients with asymptomatic recurrence 8 had locoregional recurrence, 7 had distant recurrence and 5 had both locoregional and distant recurrence (not reported for symptomatic patients, nor for PET positive patients)	Level of evidence: low 121 of the 517 patients treated for cervical carcinoma had had PET: risk of selection bias Consecutive patients Blinded assessment not stated Differential verification Serial imaging may have included PET: risk of incorporation bias

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of study quality
		contributable to the elevation of serum CEA level Patient characteristics: median age: 52 y; SCC: 80%; AD: 11%; ASC: 3%; other: 6%; FIGO stage IB1: 34%; IB2: 7%; IIA: 8%; IIB: 38%; IIA: 2%; IIIB: 8%; IVB: 2% Disease prevalence: 63% had recurrence (72% of recurrences were in symptomatic patients)	histology or the demonstration of progressive disease by serial imaging studies			
Chung 2007 [182]	• Design: retrospective cohort study • Source of funding: grant of the Ministry of Health and Welfare, Korea • Conflicts of interest: not reported on • Setting: Seoul National University College of Medicine, Seoul, South Korea • Sample size: N=52 • Duration: 2003-2005	Eligibility criteria: cervical cancer with complete remission after primary treatment and subsequent suspected recurrence Exclusion criteria: previous malignant disease other than non-melanoma skin cancer; diagnosed as unsuited for treatment with curative intent at the time of disease recurrence; had skin or pulmonary lesions or impaired renal functions contributable to	Index test: PET/CT Reference standard: biopsy or by clinical decision. Exclusion of recurrence was based on histologic findings or on a clinical and radiological follow-up period of ≥ 6 months with no evidence of active malignancy	The accuracy of PET to detect recurrence in patients suspected of recurrence (N=52): Se 90%; Sp 81%; NPV 88%; PPV 85%	Locoregional or distant recurrence not reported separately	Level of evidence: low Consecutive patients Risk of selection bias Blinded assessment not reported Differential verification

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of study quality
		the elevation of serum SCC-Ag level or other hepatic or colonic pathology contributable to the elevation of serum CEA level Patient characteristics: mean age: 53 y; 87% SCC; 10% AD; 4% neuroendocrine carcinoma. FIGO staging IA1: 8%; IA2: 6%; IB1: 37%; IIA: 21%; IIB: 19%; IIIB: 2%; IVA: 8% Disease prevalence: 60% recurrence				
Esajas 2001 [187]	• Design: retrospective cohort study • Source of funding: not reported on • Conflicts of interest: not reported on • Setting: University Hospital Groningen, the Netherlands • Sample size: N=225 • Duration: 1987-1998	Eligibility criteria: FIGO stage IB and IIA patients with SCC Exclusion: primary radiotherapy with or without chemotherapy, and not primary surgery Patient characteristics: see eligibility Disease prevalence: 16% recurrence (10% locoregional, 4% distant and 1% both)	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 patients with elevated SCCA with a recurrence 16 patients recurred locoregional, 8 distal and 2 both. Of the nine patients without elevated SCCA with a recurrence 6 patients had a locoregional recurrence, 2 patients had a distal recurrence and 1 a mixed recurrence	Level of evidence: low Consecutive patients with no loss to follow-up Blinded assessment not reported Differential follow-up

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of study quality
					7% of patients 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 2009	
Forni 2007 [184]	• 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 patients treated by the same team Patient 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	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 patients with both locoregional and distant recurrence had elevated SCCA In all patients, the elevation of SCCA	Level of evidence: low Dropouts: none Consecutive patients Blinded assessment not reported Differential verification

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of study quality
		distant)			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 patient. The projected cost of the approach using only SCCA and gynaecologic examination was 298.5 Euros per patient	
Ghorab 2009 [188]	• Design: retrospective cohort study • Source of funding: not reported on • Conflicts of interest: not reported on • Setting: Odette-Sunnybrook Cancer Center, Toronto,	Eligibility criteria: patients with available postradical trachelectomy cytology Patient characteristics: median age: 31 y; 37% SCC; 54% AD; 5% ASC; 3% other. Median follow-up: 51 months (range: 1-149 months)	Index test: isthmic-vaginal Pap smear or liquid-based cytology Reference standard: histology or follow-up (including physical and pelvic examination, smears, colposcopy	All central recurrence patients (N=2) were detected by isthmic-vaginal smears before final diagnosis (N=94)	75% of patients had at least one abnormal smear with atypical cells, low or high grade squamous intraepithelial lesions or malignant cells 46% of patients	Level of evidence: low Consecutive patients 38 patients with follow-up in other centres were excluded Blinded assessment not reported

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of study quality
	Canada • Sample size: N=94 • Duration: 1994-2007	Disease prevalence: 2% central recurrence; 5% recurrence	and further examinations (e.g. CT) if required)		initially had positive smears which converted later to negative	Differential verification 2x2 tables could not be constructed
Kitajima 2008 [181]	• Design: prospective cohort study • Source of funding: Source of funding: not reported on • Conflicts of interest: not reported on • Setting: not reported, Japan • Sample size: N=52 • Duration: 2005-2006	Eligibility criteria: patients with suspected recurrence Patient characteristics: median age: 58 y; SCC: 81%; AD: 15%; ASC: 4%; FIGO stage I: 23%; II: 29%; III: 40%; IV: 8%; time since last treatment to PET/CT: median 14 months Disease prevalence: 48% had recurrence (25/52 patients, 21 histology proven)	Index test: PET, PET/CT Reference standard: histology or follow-up ≥ 1 year with tumor markers and/or CT or PET/CT	The accuracy of PET to detect recurrence (N=52): Se 80% (95%CI: 64-96); Sp 78% (95%CI: 62-94); NPV 81%; PPV 77% The accuracy of PET/CT to detect recurrence (N=52): Se 92%; (95%CI: 81-100); Sp 93% (95%CI: 83-100); NPV 93%; PPV 92%	Locoregional or distant recurrence not reported separately per patient	Level of evidence: low Dropouts: none Study design unclear. All patients had to give consent for PET/CT so enrolment seems prospective Consecutive patients Blinded index test assessment Differential verification Risk of incorporation bias as 12 patients were followed-up through PET
Liu 2009 [78]	• Design: retrospective study • Source of funding: not reported on • Conflict of interest: no conflicts of interest to declare • Setting: Chang Gung Memorial Hospital,	Eligibility criteria: cervical cancer patients with suspected recurrent disease who had had PET and either CT or MRI performed within 30 days Exclusion: history of other malignancy; follow-	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,	CT and PET group: accuracy of CT to detect hematogenous bone metastases (N=233): Se 36%; Sp 99%; NPV 96%; PPV 67% CT and PET group:	-	Level of evidence: low Not reported whether patients were consecutive Blinded assessment of the index test Risk of selection bias

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of study quality
	Taiwan • Sample size: N=226 • Duration: not reported	up <180 days after PET (except those who died of disease within 180 days) Patient characteristics: not described Disease prevalence: 7.5% had hematogenous bone metastasis	with or without a transient response to palliative treatment. In case of 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	accuracy of PET to detect hematogenous bone metastases (N=233): Se 91%; Sp 100%; NPV 100%; PPV 91% MRI and PET group: accuracy of MRI to detect hematogenous bone metastases (N=245): Se 57%; Sp 92%; NPV 97%; PPV 36% MRI and PET group: accuracy of PET to detect hematogenous bone metastases (N=245): Se 86%; Sp 99%; NPV 99%; PPV 86%		Differential verification Risk of selection bias as follow-up by PET may have been used in follow-up Selective outcome reporting
Yoon 2010 [185]	• Design: retrospective cohort study • Source of funding: not reported on • Conflict of interest: no conflicts of interest to declare	Eligibility criteria: cervical cancer stage IB-IV treated by concurrent chemoradiotherapy Exclusion criteria: no SCCA determined in the follow-up period Patient characteristics:	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: low Consecutive patients Risk of selection bias Blinded assessment not reported Differential verification

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of study quality
	• Setting: National Cancer Center Goyang, Gyeonggi, Republic of Korea • Sample size: N=112 • Duration: 2001-2004	median age 55 y. SCC: 91%; AD: 6%; ASC: 3%. FIGO stage IB: 10%; IIA: 12%; IIB: 59%; II/IV: 20%. 96% of patients had normalized SCCA levels at one month after treatment completion Disease prevalence: 16% recurrent disease				

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