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Diagnostic performance of conventional and advanced imaging modalities for assessing newly diagnosed cervical cancer: systematic review and meta-analysis

Sungmin Woo^{1,*}, Rifat Atun², Zachary J. Ward³, Andrew M. Scott⁴, Hedvig Hricak¹, Hebert Alberto Vargas¹

¹Department of Radiology, Memorial Sloan Kettering Cancer Center, NY, USA

²Department of Global Health and Population, Department of Health Policy and Management, Harvard TH Chan School of Public Health, Harvard University, Boston, MA, USA

³Center for Health Decision Science, Harvard TH Chan School of Public Health, Harvard University, Boston, MA, USA

⁴Department of Molecular Imaging and Therapy, Austin Health and University of Melbourne, and Olivia Newton-John Cancer Research Institute, and La Trobe University, Melbourne, Australia

Abstract

OBJECTIVES: To review the diagnostic performance of contemporary imaging modalities for determining local disease extent and nodal metastasis in patients with newly-diagnosed cervical cancer.

METHODS: Pubmed and Embase databases were searched for studies published from 2000 to 2019 that used ultrasound (US), CT, MRI, and/or PET for evaluating various aspects of

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*Address correspondence to: Sungmin Woo, MD, PhD, Department of Radiology, Memorial Sloan Kettering Cancer Center, 1275 York Ave, New York, NY 10065, Tel: 646-888-4573, Fax: 212-717-3234, woos@mskcc.org.

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The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article.

Compliance with Ethical Standards

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No complex statistical methods were necessary for this paper.

Informed Consent:

Written informed consent was not required for this study because this was a systematic review and meta-analysis using published studies in the literature but not analysing specific human subjects.

Ethical Approval:

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Methodology

- retrospective
- multicenter study

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local extent and nodal metastasis in patients with newly-diagnosed cervical cancer. Sensitivities and specificities from the studies were meta-analytically pooled using bivariate and hierarchical modelling.

RESULTS: Of 1,311 studies identified in the search, 115 studies with 13,999 patients were included. MRI was the most extensively studied modality (MRI, CT, US, and PET were evaluated in 78, 12, 9 and 43 studies, respectively). Pooled sensitivities and specificities of MRI for assessing all aspects of local extent ranged between 0.71–0.88 and 0.86–0.95, respectively. In assessing parametrial invasion (PMI), US demonstrated pooled sensitivity and specificity of 0.67 and 0.94, respectively—performance levels comparable to those found for MRI. MRI, CT and PET performed comparably for assessing nodal metastasis, with low sensitivity (0.29–0.69) but high specificity (0.88–0.98), even when stratified to anatomical location (pelvic or paraaortic) and level of analysis (per patient vs. per site).

CONCLUSIONS: MRI is the method of choice for assessing any aspect of local extent, but where not available, US could be of value, particularly for assessing PMI. CT, MRI and PET all have high specificity but poor sensitivity for detection of lymph node metastases.

Keywords

Uterine cervical neoplasms; Neoplasm staging; Ultrasonography; Magnetic resonance imaging; Positron-emission tomography

Introduction

Cervical cancer is the fourth most common cancer worldwide, with an estimated 570,000 new cases having occurred in 2018 [1]. That year, cervical cancer was linked to 311,000 deaths, most of them in low- and middle-income countries, where the disease is most prevalent and more often diagnosed at advanced stages [1–4]. The anatomic extent of disease at diagnosis significantly affects prognosis and is used to tailor the initial treatment strategy. Small (<4-cm) tumors confined to the cervix are treated surgically, while “advanced” disease (e.g., extending to the parametrial tissues and beyond) is treated with concurrent chemoradiation [5].

The staging system most commonly used for cervical cancer is that of the International Federation of Gynecology and Obstetrics (FIGO). In the updated 2018 guidelines, FIGO for the first time recommended using “any available” imaging modality for staging cervical cancer, reflecting increasing recognition of the value of imaging for disease management [6].

State-of-the-art imaging technologies, such as magnetic resonance imaging (MRI) and positron emission tomography (PET), have repeatedly been shown to aid in cervical cancer staging but have historically had limited availability, especially in low-income countries. Though many studies have reported on the roles of these technologies [7–9], a lesser number have reported on ultrasound (US) and computed tomography (CT)-modalities that are more widely available in low-income countries [10]. While a direct comparison of the four imaging modalities in a single patient population is not feasible, the purpose of this study was to systematically review the diagnostic performance of all four of them for determining

local disease extent and nodal metastasis in patients with treatment-naïve cervical cancer of any clinical stage.

Materials and methods

Literature search

This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [11]. Pubmed and Embase databases were systematically searched for original articles published from January 1, 2000 to December 5, 2019 assessing the diagnostic performance of US, CT, MRI, and PET in determining local extent and nodal metastasis in patients with treatment-naïve cervical cancer using a search query shown in supplementary data. The references in the eligible studies found were then screened for additional potentially eligible studies. The search was limited to studies published in English.

Inclusion criteria

Inclusion was based on the PICOS criteria [11]: (1) patients (P), newly-diagnosed cervical cancer; (2) index test (I), US, CT, MRI, or PET; (3) comparator (C), surgico-pathological findings as reference standard, with the exception of bladder or rectal invasion, for which cystoscopy and proctoscopy with or without biopsy could be used; (4) outcomes (O), 2×2 contingency table regarding sensitivity and specificity of each imaging modality could be reconstructed for various endpoints of local extent and nodal metastases; and (5) study design (S), randomized controlled trials (RCT), quasi-RCTs, and prospectively or retrospectively performed observational studies.

Exclusion criteria

Studies meeting any of the following criteria were excluded: (1) published before 1 January 2000; (2) <10 patients; (3) publication type other than original research article (i.e., conference abstract, case report, etc.); (4) patients with recurrent tumors or who received neoadjuvant treatment; (5) “investigational” techniques, including texture analysis, radiomics, intravoxel incoherent motion (IVIM) MRI, or others not representative of current daily practice; (6) insufficient data for reconstructing 2×2 contingency tables; and (7) substantial overlap in patient population. When publications’ patient populations overlapped substantially, only the study with the largest population was used.

One investigator (S.W.) performed the initial systematic search, which was double-checked by another investigator (H.A.V.).

Data extraction and quality assessment

We extracted the following information from the studies using a standardized form: first author, publication year, institution, duration of patient enrollment; study design (whether prospective, multicenter, consecutive enrollment or not); number of patients; FIGO stages; imaging modality used (US, CT, MRI, or PET); evaluated endpoint (e.g., parametrial invasion [PMI], vaginal invasion, bladder invasion, pelvic nodal metastasis); level of analysis (e.g., per patient vs. per site [stratified to side/region/node]). Methodological quality was

evaluated based on the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool at the study level [12]. One reviewer (S.W.) extracted these data and performed quality assessment, and the results were double checked by another (H.A.V.).

Data synthesis and analysis

Reconstructed raw data in the form of 2×2 contingency tables were used to calculate sensitivity and specificity values from each study. When diagnostic performance values of multiple imaging criteria/techniques were reported within a single study, for each imaging modality and endpoint, the one most widely available and clinically feasible was used to represent that study. For example, if a study compared MRI with pelvic phased-array coils to MRI with endovaginal coils for determining PMI, the former was used; if a study reported mean apparent diffusion coefficient (ADC) and minimum ADC values for detecting metastatic lymph nodes, we used the former. Furthermore, when multiple readers' diagnostic performance values were given, we used the average value across all readers.

Pooled sensitivity and specificity were calculated using hierarchical logistic regression modelling including bivariate modelling and hierarchical summary receiver operating characteristic (HSROC) modelling [13]. We only meta-analytically pooled endpoints that had at least four available studies, as pooling small numbers of studies has been recognized as misleading [14]. HSROC curves with 95% confidence and prediction regions were plotted. Publication bias was tested for analyses including more than 10 studies and was considered present if visually present on Deeks' funnel plot or when p-values for Deeks' asymmetry test were <0.1 [15].

Heterogeneity between the studies was assessed using Cochran's Q-test and Higgins I^2 test and was considered present if p-value for the Q-test was <0.05 . The degree of heterogeneity was categorized using the inconsistency index (I^2) as follows: 0–40%, might not be important; 30–60%, moderate heterogeneity; 50–90%, substantial heterogeneity; and 75–100%, considerable heterogeneity [16]. For PMI and nodal metastasis, we additionally reported diagnostic performance for each combination of (1) level of analysis and (2) anatomical location (e.g., PMI per patient and PMI per side [right vs left], pelvic lymph node metastasis per patient, paraaortic lymph node metastasis per region, etc.).

For statistical analysis, the 'midas' and 'metandi' modules in Stata 13.0 were used (StataCorp LP) and the 'mada' package in R software version 3.2.1 (R Foundation for Statistical Computing).

Results

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Figure 1 presents a flowchart of the study selection process. Ultimately, 115 articles reporting on a total of 13,999 patients were included (Supplementary material). US was assessed in 9 studies, CT in 12, MRI in 78, and PET in 43.

Study characteristics

Table 1 summarizes the characteristics of the individual studies. In short, 44 studies were prospective and 71 were retrospective. Thirteen were multi-center and 102 were single-institution studies; 81, 29 and 5 studies were performed in high-, upper middle-, and lower middle-income countries, respectively, as defined by the World Bank. The numbers of patients ranged from 14 to 1,347. The distribution of patients' FIGO stages was heterogeneous: 46 studies only included early stages (IIA), 2 only included advanced stages (IIB), while 67 included patients with both early (IIA) and advanced (stage IIB) disease. Evaluated endpoints were PMI, deep stromal invasion, internal cervical os invasion, vaginal invasion, bladder invasion, rectal invasion, and lymph node metastases, which were categorized as pelvic, paraaortic, or both.

Methodological quality

In general, the quality of the studies was considered at least moderate, with 86% (99/115) showing low risk of bias and low concern for applicability in five or more of the seven domains (Figure 2). Regarding the patient selection domain, the risk of bias was high in three studies due to issues with the exclusion criteria and unclear in three others in which it was not specified whether the study population was consecutive. Concern for applicability was high in one study that only included patients with neuroendocrine cancers. Regarding the index test domain, risk of bias was considered high in 25 studies because radiologists were not blinded to the pathological results (n=2) or criteria for determining positive index test results were not pre-specified (n=10) or were derived from receiver operating characteristic curve analysis (n=13), and it was considered unclear in 27 studies because blinding was uncertain (n=18) or it was uncertain whether the criteria were pre-specified (n=9). The concern for applicability was high in 5 studies because MRI was performed using endovaginal coils (n=3) or only lymph nodes >5mm were assessed (n=2), and concern for applicability was unclear in 16 studies because the criteria for determining positive index test results were not provided. Regarding the reference standard domain, 5 studies had a high risk of bias because some patients did not have a pathological reference standard. Regarding the flow and timing domain, these same 5 studies were considered to have a high risk of bias because not all patients received the same reference standard. Furthermore, 40 studies had an unclear risk of bias because the interval between index test and reference standard was not provided.

Diagnostic performance of imaging modalities in determining local disease extent

The diagnostic performance of PMI was assessed in 8, 1, 42, and 4 studies using US, CT, MRI, and PET, respectively. For US, the pooled sensitivities and specificities were 0.67 (95% CI 0.54–0.78) and 0.94 (95% CI 0.87–0.98), respectively). For CT, they were 0.43 and 0.71, respectively. For MRI, the pooled estimates were 0.71 (0.62–0.79) and 0.91 (95% CI 0.88–0.93), respectively. With regard to PET, the sensitivity and specificity were 0.73 (95% CI 0.56–0.85) and 0.91 (95% CI 0.83–0.96), respectively. Details of the sensitivity and specificity estimates for other endpoints regarding local extent along with the heterogeneity indices are summarized in Table 2. The HSROC curves and coupled forest plots of sensitivities and specificities for US, MRI, and PET for determining PMI are

provided in Figures 3 and 4, while those for other combinations of imaging modalities and endpoints are provided in Supplementary Figures 1 and 2.

Diagnostic performance of imaging modalities in detecting nodal metastases

Our review included 1, 8, 38, and 42 studies assessing the diagnostic performance of US, CT, MRI, and PET, respectively, in the evaluation of any metastatic nodes, regardless of anatomical location (pelvic and/or paraaortic) and level of analysis (per patient or per site). The study using US demonstrated sensitivity of 0.43 and specificity of 0.96. The pooled sensitivities and specificities were 0.51 (95% CI 0.36–0.67) and 0.87 (95% CI 0.81–0.92), respectively, for CT, 0.57 (95% CI 0.49–0.64) and 0.93 (95% CI 0.89–0.95), respectively, for MRI, and 0.57 (95% CI 0.48–0.65) and 0.95 (95% CI 0.93–0.97), respectively for PET. Table 3 shows the breakdown of the diagnostic performance levels with their heterogeneity indices. The HSROC curves and coupled forest plots of sensitivities and specificities for the overall analysis are provided in Figures 3 and 4.

Publication bias

Publication bias was suggested for studies using MRI for PMI ($p=0.05$) but not for any of the other endpoints that included more than 10 patients (MRI for vaginal invasion, MRI for nodal metastasis, and PET for nodal metastasis; Figure 5).

Discussion

Our systematic review and meta-analysis comprehensively evaluated data published over the last two decades on the diagnostic performance of US, CT, MRI, and PET in assessing local extent and lymph node metastasis of patients with newly diagnosed cervical cancer. Our findings indicate that MRI has been extensively evaluated for assessing all aspects of local extent, demonstrating moderate sensitivity and good specificity; CT has been much less well studied and generally shows slightly lower performance levels than MRI in the assessment of local extent, while there is a paucity of data for US except with respect to assessment of PMI, where it performs comparably to MRI. For analysis of nodal metastasis, MRI and PET were the most extensively studied of the cross-sectional modalities, all of which performed comparably, with low and varied sensitivity but high specificity.

Our findings support the recommendation in the FIGO 2018 guidelines for utilization of “any imaging modality,” as they confirmed that all four modalities assessed have the potential to contribute clinically meaningful information. Because our review examined state-of-the-art and standard imaging modalities currently used to evaluate local extent and nodal metastasis of cervical cancer, it is relevant to diverse health-care settings, including low- and middle-income countries where ultrasound and CT are more widely available than MRI and PET. Furthermore, it focused on treatment-naïve disease, whereas earlier published studies mostly did not differentiate between newly diagnosed, neoadjuvant treated, and recurrent disease. In addition, it included a large number of studies ($n=115$) and patients ($n=13,999$) to provide a robust overview of the role of imaging in pretreatment evaluation of cervical cancer. In our review, the diagnostic performance levels of MRI for assessing PMI and vaginal invasion—important determinants of treatment selection—were assessed in 42 and

13 studies, respectively. Regardless of the individual endpoint regarding local extent, MRI consistently demonstrated high pooled specificities (0.86–0.95), likely due to its excellent soft-tissue resolution, which enables differentiation of tumor from adjacent structures [17]. The high specificity of MRI may explain why it was recommended (although not required) in earlier FIGO guidelines [18]. Guidelines of the National Comprehensive Cancer Network and European Society of Urogenital Radiology have also recommended MRI as the imaging modality of choice in this setting [19; 20].

Our review included only 5 studies in which CT was evaluated for assessment of local extent in treatment-naïve cervical cancer. The literature is sparse relative to MRI even when taking into account an earlier systematic review by Bipat et al [21] in 2003 that included studies performed between 1985 and 2002, which only found 2, 3, and 9 studies assessing rectal, bladder and PMI, respectively. Although direct comparison is not possible, in our meta-analysis, CT demonstrated inferior performance compared to MRI for several endpoints regarding assessment of local extent which are consistent with results showing inferior performance for the assessment of PMI and invasion of bladder and rectum in studies published in 1985–2002 [21]. Because CT has poorer soft-tissue resolution than MRI as well as lower spatial resolution than ultrasound, it is generally not considered to be a modality of choice for evaluating local extent, as it cannot differentiate the anatomical details of the uterus and adjacent structures. Nevertheless, as shown in our pooled analysis of endpoints related to local extent, CT can provide clinically useful information, as its specificity, though lower than that of MRI, is moderate to good.

The performance of US is more difficult to interpret for several reasons. Ultrasound has excellent soft-tissue resolution, especially when performed transvaginally [22]. However, of the four modalities we assessed, it is also the most operator dependent. Furthermore, if applied to a patient population with more advanced stages of disease, it could artificially inflate performance estimates, as patients with markedly evident extension beyond the cervix are grouped together with those with microscopic involvement. Notwithstanding these considerations, when limited to PMI, the sensitivity and specificity estimates of US appear comparable to those of MRI: 0.67 (95% CI 0.54–0.78) and 0.94 (95% CI 0.87–0.98), respectively, for US vs. 0.71 (95% CI 0.62–0.79) and 0.91 (95% CI 0.88–0.93), respectively, for MRI. Nevertheless, it should be cautioned that these similar values cannot be directly compared, as they were not acquired only from studies that were head-to-head comparisons. Taking into account all above mentioned factors, our findings suggest there may be a potential role for US in the assessment of cervical cancer, especially in certain clinical settings—for example, patients in resource-constrained areas, where access to MRI is very limited, US in addition to clinical examination would be superior to clinical examination alone for local staging. Although implementation of screening programs is one of the most important factors in facilitating detection of cervical cancer at earlier stages and in turn improve survival, potentially better evaluation of local extent by using US in certain settings will be of incremental value in this regard [23].

Regarding the detection of lymph node metastases, CT, MRI and PET were evaluated in 8, 38, and 42 studies included in our meta-analysis, respectively. Though pooled sensitivities and specificities differed slightly when stratified by level of analysis (per patient, side,

station, and node) and anatomical location (pelvic and/or para-aortic), as noted above, these modalities consistently showed poor sensitivity (0.29–0.69) and high specificity (0.88–0.98). This is mainly because metastatic nodes are evaluated based on size on CT and MRI or elevated radiotracer uptake on PET—criteria that are well known to have limitations for detecting micro-metastases across various types of pelvic malignancies [24–26]. Our search yielded only 1 study since 2000 that used US to evaluate nodal metastasis, almost certainly because the field of view of US is inherently limited (especially in terms of depth) for assessing pelvic or paraaortic nodes.

Our study had several limitations. First, we could not directly compare the diagnostic performance levels of the modalities examined due to a paucity of studies providing such information. However, theoretically, network meta-analyses based on indirect comparisons could be performed, despite their inherent limitations [27]. An earlier meta-analysis that used such a methodology and included a small number of studies showed a possible, though not statistically significant, trend for PET to outperform other modalities in detecting nodal metastasis [28]. Second, the pooled sensitivities and specificities for each diagnostic modality should be used to gain a general idea of their performance for each endpoint but not compared directly, partly because they could have been influenced by the characteristics of their respective patient populations. Furthermore, in our review, we purposefully avoided incorporating cutting-edge, non-standard techniques, which include analytical methods (e.g., radiomics, histogram analysis), acquisition techniques (e.g., IVIM, integrated PET/MRI), and investigational contrast media (e.g., USPIO). There are early data supporting the incremental value of some of these techniques, but they need validation, and furthermore, they are unlikely to be available in the regions where cervical cancer is most prevalent [29–31]. It should also be noted that we focused on the diagnostic performance of imaging modalities but not on outcomes or cost. However, some studies have reported that using certain imaging modalities (e.g., MRI) for triage before treatment is cost effective [32] and that pretreatment imaging has prognostic value regarding recurrence and survival [33; 34].

In conclusion, multiple imaging modalities can contribute to the assessment of local extent of newly diagnosed cervical cancer. MRI is the method of choice for assessing any aspect of local extent, but where it is not available, US could be of value, particularly for assessing PMI. CT, MRI and PET all have high specificity but poor sensitivity for the detection of lymph node metastases and cannot obviate the need for node sampling or dissection in high-risk patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

ADC	apparent diffusion coefficient
CT	computed tomography
FIGO	International Federation of Gynecology and Obstetrics
HSROC	hierarchical summary receiver operating characteristic
IVIM	intravoxel incoherent motion
MRI	magnetic resonance imaging
PET	positron emission tomography
PICOS	patient, index test, comparator, outcome, and study design
PMI	parametrial invasion
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
US	ultrasound

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Key points

- Magnetic resonance imaging is the method of choice for assessing local extent.
- Ultrasound may be helpful in determining parametrial invasion, especially in lower-resourced countries.
- Computed tomography, magnetic resonance imaging, and positron emission tomography perform similarly for assessing lymph node metastasis, with high specificity but low sensitivity.

Figure 1.
Flowchart showing study selection process.

Figure 2.
QUADAS-2 plots summarizing risk of bias and concern for applicability in the 115 studies included.

Figure 3.

Hierarchic summary ROC curves of diagnostic performance for assessment of parametrial invasion (PMI) using (A) ultrasound (US), (B) magnetic resonance imaging (MRI), (C) positron emission tomography (PET) and nodal metastasis using (D) computed tomography (CT), (E) MRI, and (F) PET in patients with newly diagnosed cervical cancer.

Figure 4.

Coupled forest plots of sensitivity and specificity for studies assessing parametrial invasion (PMI) using (A) ultrasound (US), (B) magnetic resonance imaging (MRI), (C) positron emission tomography (PET) and nodal metastasis using (D) computed tomography (CT), (E) MRI, and (F) PET in patients with newly diagnosed cervical cancer. Numbers are Dashed vertical lines and diamonds represent meta-analytically pooled estimates with their corresponding 95% confidence intervals (CI). Heterogeneity statistics are provided on lower right corners.

Figure 5.

Deek's funnel plots for endpoints including more than 10 studies. Publication bias ($p = 0.05$) was only suggested in (A) studies using MRI for assessment of parametrial invasion (PMI) but not in those assessing vaginal invasion using MRI (B) and lymph node metastasis using MRI (C) and PET (D). Circles represent each study while line indicates the regression line. ESS = effective sample size

Table 1.

Study Characteristics

Author, year [*]	Institution	Period	Country	Prospective	No. of patients	FIGO stages	Imaging modality	Endpoint
Anner P et al, 2018	Medical University of Vienna	January 2008 - July 2011	Austria	No	27	NR	MRI, PET	PLN
Atri M et al, 2016	Multicenter	September 2007 - June 2013	US, Canada	Yes	153	IB2 - IVA	CT, PET	PLN, PALN, PLN+PALN
Atri M et al, 2015	Multicenter	September 2007 - June 2013	US, Canada	Yes	33	IB2 - IVA	MRI	PLN, PALN, PLN+PALN
Bhosale PR et al, 2016	The University of Texas MD Anderson Cancer Center	NR	US, Canada	No	79	IA - IB2	MRI	Internal os, PLN
Bipat et al, 2011	Academic Medical Centre, University of Amsterdam	January 2003 - December 2007	The Netherlands	No	27	IB1	MRI	Internal os, PLN
Bleker SM et al, 2013	Academic Medical Centre, University of Amsterdam	January 2003 - January 2011	The Netherlands	No	203	IB - IIA	MRI	PMI
Bourgioti C et al, 2014	Aretaieion Hospital	September 2008 - June 2013	Greece	Yes	21	IA - IB1	MRI	Internal os, deep stromal invasion
Brocker KA et al, 2014	University of Heidelberg Medical School	February 2007 - September 2010	Germany	Yes	44	IA1 - IV	MRI	PMI
Byun JM et al, 2013	Busan Paik Hospital	January 2009 - December 2009	Korea	Yes	24	IA - IIB	US, MRI	PMI, vagina
Canaz E et al, 2017	Istanbul Kanuni Sultan Suleyman Training and Research Hospital	2001 - 2015	Turkey	No	76	IB1 - IIA2	US, MRI	PMI
Chen YB et al, 2011 (1)	Fujian Medical University Teaching Hospital	September 2006 - March 2009	China	Yes	26	NR	MRI	PLN-r
Chen YB et al, 2011 (2)	Fujian Medical University Teaching Hospital	September 2006 - March 2009	China	Yes	61	IB - IIB	MRI	PLN-n
Choi HJ et al, 2006	National Cancer Center, Korea	October 2001 - October 2004	Korea	No	55	IB - IVA	MRI	PLN+PALN-r, PLN+PALN-n
Choi SH et al, 2004	Seoul National University College of Medicine	January 2000 - June 2003	Korea	Yes	115	NR	MRI	PMI-s, vagina, PLN
Chou HH et al, 2010	Chang Gung Memorial Hospital	April 2002 - March 2008	Taiwan	No	83	IB1 - IIB	MRI, PET	PLN+PALN-r, PLN-r, PALN-r
Chung HH et al, 2009	Seoul National University	January 2003 - July 2007	Korea	No	34	IA2 - IIB	PET	PLN-r

Author, year*	Institution	Period	Country	Prospective	No. of patients	FIGO stages	Imaging modality	Endpoint
	College of Medicine							
Chung HH et al, 2010	Seoul National University College of Medicine	January 2004 - December 2008	Korea	No	83	IB1 - IIB	MRI, PET	PLN
Chung HH et al, 2007	Seoul National University College of Medicine	January 2004 - May 2006	Korea	No	119	IA1 - IIB	MRI	PMI, PLN+PALN, PLN+PALN-r
Crivellaro C et al, 2012	University of Milano Bicocca	January 2005 - December 2010	Italy	Yes	69	IB1 - IIA	PET	PLN
De Cuypere M et al, 2019	Multicenter	March 2010 - December 2016	Belgium, Spain	No	168	IB2 - IVA	PET	PALN
deSouza NM et al, 2006	Hammersmith Hospital	February 1993 - January 2002	UK	No	119	IA - IIB	MRI	PMI
Dong Y et al, 2014	Shanghai First People's Hospital Affiliated to Shanghai Jiaotong University	September 2009 - November 2012	China	No	63	IA - IIA	PET	Vagina, PLN
Downey K et al, 2016	The Institute of Cancer Research and Royal Marsden NHS Foundation Trust	May 2013 - August 2014	United Kingdom	Yes	25	IA/IB	MRI	PMI-s
Driscoll DO et al, 2015	St. James Hospital, Ireland	January 2009 - September 2011	Ireland	No	47	IA - IB1	PET	PLN+PALN
Duan X et al, 2016	Sun Yat-Sen Memorial Hospital	February 2006 - July 2014	China	No	20	NR	MRI	PMI
Epstein E et al, 2013	Multicenter	September 2007 - April 2010	Sweden, Italy, Lithuania, Belgium, Czech Republic	Yes	182	IA2 - IIA	US, MRI	PMI, deep stromal invasion
Fischerova D et al, 2008	General Teaching Hospital, Charles University	January 2004 - February 2006	Czech Republic	Yes	95	IA1 - IIA	US, MRI	PMI
Fujiwara K et al, 2000	Kawasaki Medical School	August 1997 - December 1998	Japan	Yes	75	IA - IB	MRI	Deep stromal invasion
Ghi T et al, 2007	Universit'a degli Studi di Bologna	January 2005 - May 2006	Italy	Yes	14	NR	US	PMI-s, rectum, bladder
Goyal BK et al, 2010	Army Hospital (Research & Referral), New Delhi	May 2007 - November 2009	India	No	80	IB1 - IIA	PET	PLN+PALN
Grueneisen J et al, 2015	University Hospital Essen	NR	Germany	Yes	27	NR	PET	PMI, vagina, bladder/rectum, PLN+PALN

Author, year*	Institution	Period	Country	Prospective	No. of patients	FIGO stages	Imaging modality	Endpoint
Hancke K et al, 2008	University of Ulm	1992 - 2003	Germany	No	109	NR	CT, MRI	PMI
Hansen MA et al, 2000	Copenhagen University Hospital	June 1993 - June 1996	Denmark	No	61	IB - IIB	MRI	PMI
He F et al, 2018	The First Affiliated Hospital of Nanchang University	2005 - 2012	China	No	1347	IB1 - IIA2	MRI	PMI
Hertel H et al, 2002	Friedrich-Schiller-University of Jena	April 1995 - March 2001	Germany	No	109	IB2 - IVB	CT, MRI	Bladder, rectum, PLN, PALN
Hori M et al, 2009	Osaka University Graduate School of Medicine	November 2006 - October 2007	Japan	No	31	IA1 - IIB	MRI	PMI, vagina, PLN
Hricak H et al, 2005	Multicenter	March 2000 - November 2002	US	Yes	172	IA - IVA	CT, MRI	PLN+PALN
Jena A et al, 2005	Rajiv Gandhi Cancer Institute & Research Centre	1999 - 2002	India	No	105	NR	MRI	PMI
Jeong BK et al, 2012	Samsung Medical Center	January 1997 - December 2010	Korea	No	769	IA - IVB	MRI, CT	Bladder, rectum
Jung DC et al, 2010	Seoul National University Hospital	2006 - 2009	Korea	No	167	IA2 - IIA	MRI	PMI
Jung W et al, 2017	Ewha Womans University Mokdong Hospital	January 2009 - March 2015	Korea	No	114	IA1 - IIB	CT, MRI, PET	PLN-s
Kan Y et al, 2019	Dalian Medical University, Cancer Hospital of China Medical University, Liaoning Cancer Hospital & Institute	March 2014 - October 2017	China	No	143	IA2 - IIB	MRI	PLN
Kang S et al, 2013	Asan Medical Center	January 2001 - January 2010	Korea	No	699	IB1 - IIA	MRI	PLN+PALN-r
Kido A et al, 2014	Graduate School of Medicine, Kyoto University	1998 - 2012	Japan	No	67	IA - IVA	MRI	PMI, vagina
Kim M et al, 2017	Seoul National University Bundang Hospital	2003 - 2014	Korea	No	215	IB1 - IIA2	MRI	PMI
Kim MH et al, 2011	Asan Medical Center	January 2005 - March 2009	Korea	No	143	NR	MRI	PLN-n
Kim SH et al, 2012	Keimyung University, Dongsan Hospital	January 2005 - January 2010	Korea	No	200	IB - IIA	MRI	PLN+PALN, PLN+PALN-r
Kim SK et al, 2009	Asan Medical Center	October 2001 -	Korea	No	79	IB - IVA	PET	PLN+PALN, PLN+PALN-r

Author, year*	Institution	Period	Country	Prospective	No. of patients	FIGO stages	Imaging modality	Endpoint
		December 2007						
Kim WY et al, 2011	Myongji Hospital, Kwandong University School of Medicine	January 2005 - December 2009	Korea	No	257	NR	MRI	Bladder/rectum
Kitajima K et al, 2014	Kobe University Graduate School of Medicine	December 2011 - February 2013	Japan	No	30	IB1 - IV	MR, PET	PMI, vagina, bladder, PLN
Klerkx WM et al, 2012	Multicenter	2006 - 2009	The Netherlands	Yes	68	IA2 - IIB	MRI	PLN-r
Kong TW et al, 2016	Ajou University Hospital	February 2000 - March 2015	Korea	No	298	IB	MRI	PMI
Lakhman Y et al, 2013	MSKCC	November 2001 - January 2011	US	No	62	IB1	MRI	Deep stromal invasion
Lam WW et al, 2000	Chinese University of Hong Kong, Prince of Wales Hospital, Shatin	December 1995 - January 1998	Hong Kong	Yes	38	I	MRI	PMI-s
Leblanc E et al, 2011	Multicenter	2004 - 2008	France	No	125	IB2 - IVA	PET	PALN
Li K et al, 2019	Shengjing Hospital of China Medical University	January 2013 - June 2017	China	No	394	IA - IIA	PET	PLN
Lin AJ et al, 2019	Washington University School of Medicine	March 1999 - February 2018	US	Yes	212	IB1 - IB2	PET	PLN, PALN
Lin WC et al, 2003	China Medical College Hospital	NR	China	Yes	50	IIB - IVA	PET	PALN
Liu Y et al, 2011	Tianjin Medical University Cancer Institute and Hospital	October 2006 - January 2010	China	Yes	42	IB - IIB	MRI	PLN
Loft A et al, 2007	Copenhagen University Hospital	November 2002 - October 2005	Denmark	Yes	27	IB1 - IVA	PET	PLN, PALN
Lv K et al, 2014	Shandong Provincial Hospital affiliated to Shandong University	October 2009 - November 2011	China	No	87	IA1 - IIB	MRI, PET	PLN+PALN, PLN+PALN-n
Ma X et al, 2017	Kunshan Hospital Affiliated to Jiangsu University	May 2014 - June 2016	China	Yes	39	IB1 - IV	US, MRI	PMI
Manfredi R et al, 2009	University of Verona	NR	Italy	Yes	53	<IIB	MRI	Vagina, internal os, PLN+PALN
Mansour SM et al, 2017	Kasr Al Ainy Hospital	March 2015 - September 2016	Egypt	No	50	IB - IVB	MRI	PMI, PLN+PALN

Author, year*	Institution	Period	Country	Prospective	No. of patients	FIGO stages	Imaging modality	Endpoint
Massad LS et al, 2000	Cook County Hospital	July 1994 - July 1999	US	No	96	IB2 - IVB	CT	Bladder
Mayoral et al, 2017	Hospital Clinic, Barcelona	June 2011 - January 2013	Spain	Yes	17	IA2 - IB1	PET	PLN, PALN
Moloney F et al, 2016	Cork University Hospital	January 2011 - December 2013	Ireland	Yes	33	IB - IIA	US, MRI	PMI, deep stromal invasion
Monteil J et al, 2011	University Hospital, Limoges	September 2004 - December 2007	France	Yes	40	IA - IB1	MRI, PET	PLN, PALN
Narayan K et al, 2001	Peter MacCallum Cancer Institute	November 1998 - August 2000	Australia	No	27	IB - IVB	MRI, PET	PLN, PALN
Nogami et al, 2015	School of Medicine, Keio University	September 2012 - March 2014	Japan	No	70	IA1 - IIB	PET	PLN+PALN, PLN+PALN-r
Palsdottir K et al, 2015	Multicenter	December 2007 - October 2012	Sweden	Yes	104	IA2 - IIB	US	PLN, deep stromal invasion
Papadia A et al, 2017	University Hospital of Bern and University of Bern	December 2008- November 2016	Switzerland	No	60	IA1 - IIA	PET	PLN+PALN
Park JJ et al, 2014	Samsung Medical Center	January 2010 - December 2012	Korea	No	152	IA - IIA	MRI	PMI
Park W et al, 2005	Samsung Medical Center	1997 - 2003	Korea	No	36	IB1 - IIA	MRI, PET	PMI, PLN, PLN-s
Perez-Medina T et al, 2013	Multicenter	January 2009 - June 2012	Spain	Yes	52	IB2 - IVA	PET	PALN
Postema S et al, 2000	Leiden University Medical Center	NR	The Netherlands	No	82	IA - IV	MRI	PMI-s, bladder
Qu JR et al, 2018	The Affiliated Cancer Hospital of Zhengzhou University	January 2010 - October 2014	China	No	192	IB1 - IIA	MRI	PMI
Ramirez PT et al, 2011	Multicenter	April 2004 - May 2009	US	Yes	60	IB2 - IVA	PET	PALN
Reinhardt MJ et al, 2001	University Hospital of Freiburg	1995 - 1998	Germany	Yes	35	IB - IIA	MRI, PET	PLN+PALN, PLN+PALN-r
Rizzo S et al, 2014	European Institute of Oncology	2006 - 2012	Italy	No	217	IA1 - IIB	MRI	Deep stromal invasion, PLN
Roh HJ et al, 2018	Asan Medical Center	January 2007 - December 2016	Korea	No	260	IA2 - IIA	MRI	PMI
Roh JW et al, 2005	National Cancer Center, Korea	May 2002 - August 2003	Korea	Yes	54	IB - IVA	PET	PLN+PALN-r
Sahdev A et al, 2007	St. Bartholomew's Hospital	1995 - 2005	UK	No	150	IB	MRI	PMI, internal os, PLN, PLN-n

Author, year*	Institution	Period	Country	Prospective	No. of patients	FIGO stages	Imaging modality	Endpoint
Sandvik RM et al, 2011	Glostrup Hospital	May 2006 - November 2007	Denmark	No	41	IA - IVB	PET	PLN+PALN
Sarabhai T et al, 2018	University Hospital Essen	NR	Germany	Yes	53	IB - IV	MRI, PET	PMI, vagina, bladder/rectum, PLN, PALN, PLN+PALN
Sharma DN et al, 2010	All India Institute of Medical Sciences	2003 - 2005	India	No	305	IB - IVB	CT	Bladder
Sheu MH et al, 2001	Veterans General Hospital-Taipei and School of Medicine	April 1996 - June 1999	Taiwan	Yes	41	IA - IVA	MRI	PMI, vagina, PLN
Shin YR et al, 2013	Seoul St. Mary's Hospital	August 2009 - November 2010	Korea	No	45	IB	MRI	PMI, vagina, PLN
Shweel MA et al, 2012	Minia University	February 2009 - August 2010	Egypt	Yes	30	IB - IVA	MRI	PMI, vagina, bladder, rectum
Signorelli M et al, 2011	Multicenter	January 2004 - December 2010	Italy	Yes	159	IB1 - IIA	PET	PLN+PALN, PLN+PALN-r
Sironi S et al, 2006	University of Milano Bicocca	January 2003 - August 2004	Italy	Yes	47	IA1 - IB2	PET	PLN, PLN-n
Song J et al, 2019	The First Affiliated Hospital of Nanjing Medical University	January 2011 - December 2016	China	No	92	IB - III	MRI	PLN-n
Song J et al, 2019	The First Affiliated Hospital of Nanjing Medical University	January 2011 - December 2017	China	No	81	IB - IIA	MRI	PMI
Sozzi G et al, 2019	Multicenter	January 2013 - December 2018	Italy	No	79	IA1 - IIB	US, MRI	PMI, vagina
Tanaka T et al, 2018	Osaka Medical College	September 2013 - January 2016	Japan	No	48	IA2 - IIA	PET	PLN-s
Vazquez-Vicente D et al, 2018	Jiménez Díaz Foundation Hospital	2009 - 2015	Argentina, Spain	No	59	IB2 - IVA	CT	PALN
Vural GU et al, 2014	Ankara Oncology Education and Research Hospital	NR	Turkey	No	74	IB - IVB	PET	PLN+PALN
Wagenaar HC et al, 2001	Leiden University Medical Center	January 1994 - July 1997	The Netherlands, Belgium	Yes	90	IA - IVA	MRI	Deep stromal invasion
Wang T et al, 2019	Shengjing Hospital of China Medical University	December 2016 - October 2018	China	No	79	IB - IIB	MRI, PET	PMI
Woo S et al, 2018	Seoul National University	2010 - 2013	Korea	No	87	IA2 - IIB	MRI	PMI

Author, year*	Institution	Period	Country	Prospective	No. of patients	FIGO stages	Imaging modality	Endpoint
Wright JD et al, 2005	Barnes-Jewish Hospital	January 1999 - September 2004	US	No	59	IA - IIA	PET	PLN, PLN-s, PALN, PALN-s
Wu Q et al, 2017	Henan Provincial People's Hospital	May 2015 - August 2016	China	Yes	50	NR	MRI	PLN-n
Xu D et al, 2017	Cancer Hospital of China Medical University	March - December 2016	China	Yes	159	IB1 - IA1	CT	PLN+PALN
Xu X et al, 2016	The First Affiliated Hospital of Anhui Medical University	January 2011 - October 2015	China	No	51	IB - IVA	PET	PLN+PALN
Xue HD et al, 2008	Peking Union Medical College Hospital	December 2006 - March 2008	China	No	24	IB1 - IIB	MRI	PLN-n
Yang K et al, 2017	Samsung Medical Center	2001 - 2011	Korea	No	303	IB1 - IIA2	MRI	PMI
Yang WT et al, 2000	Chinese University of Hong Kong, Prince of Wales Hospital, Shatin	NR	Hong Kong	Yes	43	IA - IIB	CT, MRI	PLN-s
Yang Z et al, 2016	Shengjing Hospital of China Medical University	January 2006 - June 2013	China	No	113	IB - IIA	PET	PLN+PALN, deep stromal invasion
Yildirim Y et al, 2008	Aegean Obstetrics and Gynecology Training and Research Hospital	March 2006 - November 2006	Turkey	Yes	16	IIB - IVA	PET	PALN
Yu L et al, 2011	The Affiliated Tumor Hospital of Harbin Medical University	NR	China	Yes	16	IB1 - IIA	PET	PLN
Yu X et al, 2015	Peking Union Medical College Hospital	April 2009 - September 2010	China	No	71	IB1 - IIB	MRI	PMI, vagina
Yu YY et al, 2019	Cancer Hospital of China Medical University	January 2015 - October 2017	a,ma	No	153	IB - IIA	MRI	PLN
Zade AA et al, 2019	Tata Memorial Hospital	NR	India	Yes	44	IA2 - IIB	CT,PET	PLN, PALN
Zhang W et al, 2019	Multicenter	January 2009 - December 2015	China	No	1016	IB1 - IIA2	MRI	PMI, vagina
Zhang W et al, 2014	Peking Union Medical College Hospital	September 2009 - December 2013	China	No	125	IA2 - IIA	MRI	PLN+PALN

CT = computed tomography; MRI = magnetic resonance imaging; NR = not reported; PALN = paraaortic lymph node (per patient); PET = positron emission tomography; PMI = parametrial invasion; PLN = pelvic lymph node (per patient); PLN+PALN = pelvic and/or paraaortic lymph node; US = ultrasonography; -n = per node; -r = per nodal region; -s = per-side

* Full bibliographical details provided in electronic supplementary data

Table 2.

Diagnostic performance of various imaging modalities in determining local extent of cervical cancer.

Endpoint	Modality	No. of studies	Publication years	Sensitivity			Specificity			Cochran's Q	P-value
				Summary estimate	95% CI*	I ² (%)	Summary estimate	95% CI*	I ² (%)		
PMI	US	8	2007–2019	0.67	0.54–0.78	59.8	0.94	0.87–0.98	82.3	2.994	0.112
	per patient	7	2008–2019	0.63	0.50–0.73	45.7	0.94	0.85–0.98	83.2	4.924	0.043
	per side	1	2007	N/A	1.00		N/A	0.95			
	CT	1	2008	N/A	0.43		N/A	0.71			
	MRI	42	2000–2019	0.71	0.62–0.79	78.0	0.91	0.88–0.93	88.5	105.480	<0.001
Deep stromal invasion	per patient	38	2000–2019	0.72	0.62–0.79	78.7	0.90	0.87–0.93	88.2	93.953	<0.001
	per side	4	2000–2016	0.60	0.28–0.85	65.6	0.95	0.87–0.98	91.8	7.095	0.014
	PET	4	2014–2019	0.73	0.56–0.85	54.4	0.91	0.83–0.96	0.0	0.178	0.457
Deep stromal invasion	US	3	2013–2016	N/A	0.80–0.91		N/A	0.50–0.97			
	MRI	7	2000–2016	0.82	0.71–0.90	79.6	0.91	0.73–0.97	88.0	12.892	<0.001
	PET	1	2016	N/A	0.98		N/A	0.59			
Internal os invasion	MRI	5	2007–2016	0.84	0.70–0.92	0.0	0.96	0.93–0.98	0.0	0.004	0.499
Vaginal invasion	US	2	2013, 2019	N/A	0.00–0.44		N/A	0.99–1.00			
	MRI	13	2001–2019	0.71	0.54–0.84	76.3	0.86	0.81–0.89	68.4	28.651	<0.001
	PET	4	2014–2017	0.88	0.53–0.98	68.1	0.93	0.72–0.99	85.3	9.960	0.003
Bladder invasion	US	1	2007	N/A	1.00		N/A	1.00			
	CT	4	2000–2012	0.41	0.01–0.98	91.4	0.92	0.82–0.96	93.8	23.103	<0.001
	MRI	5	2002–2014	0.84	0.57–0.95	18.8	0.95	0.87–0.98	75.2	0.011	0.497
	PET	1	2014	N/A	0.00		N/A	1.00			
Rectum invasion	US	1	2007	N/A	1.00		N/A	0.92			
	CT	2	2002, 2012	N/A	0.00–0.86		N/A	0.85–0.99			
	MRI	3	2002–2012	N/A	0.50–1.00		N/A	0.86–1.00			
Bladder or rectum invasion	MRI	2	2011, 2018	N/A	1.00 (both)		N/A	0.96–0.98			

Endpoint	Modality	No. of studies	Publication years	Sensitivity			Specificity			I ² (%)	Cochran's Q	P-value
				Summary estimate	95% CI*	I ² (%)	Summary estimate	95% CI*	I ² (%)			
	PET	2	2015, 2017	N/A			N/A			0.98–1.00		

CI = confidence interval; N/A = none available

* ranges for endpoints with 3 included studies

Table 3.

Diagnostic performance of various imaging modalities in detecting nodal metastases.

Anatomic Location	Analysis level	Modality	No. of studies	Sensitivity			Specificity			Cochran's Q	P-value
				Publication Years	Summary estimate	95% CI*	I ² (%)	Summary estimate	95% CI*	I ² (%)	
All	Any	US	1	2015	N/A	0.43	N/A	N/A	0.96		
		CT	8	2000–2019	0.51	0.36–0.67	81.5	0.87	0.81–0.92	74.8	<0.001
		MRI	37 [#]	2000–2019	0.57	0.49–0.64	85.5	0.93	0.89–0.95	96.5	<0.001
		PET	42	2001–2019	0.57	0.48–0.65	80.3	0.95	0.93–0.97	91.0	<0.001
Pelvic	Patient	US	1	2015	N/A	0.43	N/A	N/A	0.96		
		CT	3	2002–2019	N/A	0.15–0.79		N/A	0.63–0.97		
		MRI	19	2001–2019	0.61	0.51–0.70	72.6	0.88	0.82–0.92	91.0	<0.001
		PET	18	2001–2019	0.60	0.48–0.70	73.8	0.93	0.87–0.96	82.9	<0.001
Pelvic	Site	CT (per side)	2	2000, 2017	N/A	0.51–0.65		N/A	0.86–0.97		
		MRI	12	2000–2019	0.59	0.43–0.74	90.4	0.94	0.88–0.97	97.3	<0.001
		per side	3	2000–2017	N/A	0.24–0.71		N/A	0.80–0.96		
		per region	3	2010–2012	N/A	0.25–0.83		N/A	0.93–0.98		
	per node		6	2007–2019	0.66	0.44–0.82	93.8	0.92	0.80–0.97	98.4	<0.001
		PET	7	2005–2018	0.44	0.35–0.54	56.1	0.98	0.93–0.99	92.1	<0.001
		per side	4	2005–2018	0.38	0.24–0.54	53.6	0.95	0.88–0.98	70.5	0.027
		per region	2	2009, 2010	N/A	0.36–0.46		N/A	0.94–0.99		
	Per node		1	2006	N/A	0.72		N/A	1.00		
Paraaortic	Patient	CT	4	2002–2019	0.29	0.06–0.71	64.8	0.91	0.83–0.96	49.1	2.403
		MRI	4	2002–2018	0.40	0.17–0.68	60.1	0.91	0.79–0.97	76.9	8.431
		PET	15	2001–2019	0.59	0.37–0.77	78.8	0.96	0.92–0.98	83.5	26.834
Paraaortic	Site	MRI (per region)	1	2010	N/A	0.25		N/A	0.94		
		PET	2	2005, 2010	N/A	0.40–0.67		N/A	0.99–1.00		
	per side		1	2005	N/A	0.40		N/A	0.99		
		per region	1	2010	N/A	0.67		N/A	1.00		

Anatomic Location	Analysis level	Modality	No. of studies	Publication Years	Sensitivity			Specificity			Cochran's Q	P-value
					Summary estimate	I ² (%)	95% CI*	Summary estimate	I ² (%)	95% CI*		
Pelvic or paraaortic	Patient	CT	3	2005–2017	N/A		0.31–0.76	N/A		0.62–0.88		
		MRI	10	2001–2018	0.55		0.41–0.69	0.90		0.81–0.95	48.196	<0.001
		PET	15	2007–2017	0.69		0.53–0.81	0.90		0.84–0.94	49.770	<0.001
Pelvic or paraaortic	Site	MRI	8	2001–2014	0.39		0.29–0.50	0.96		0.94–0.98	213.842	<0.001
		per region	6	2001–2012	0.37		0.26–0.49	0.97		0.94–0.98	100.231	<0.001
		per node	2	2006, 2014	N/A		0.37–0.58	N/A		0.88–0.99		
		PET	7	2001–2015	0.53		0.33–0.73	0.98		0.96–0.99	45.766	<0.001
		per region	6	2001–2015	0.44		0.30–0.58	0.98		0.96–0.99	30.214	<0.001
		per node	1	2014	N/A		0.91	N/A		0.98		

CI = confidence interval; N/A = none available

* ranges for endpoints with 3 included studies

1 of 38 studies (Kang S et al. 2013) assessing nodal metastasis using MRI was excluded due to instability of hierarchical modeling