

## Original Article



# Surgical or imaging lymph node assessment in locally advanced cervical cancer: a systematic review and meta-analysis

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### Conflict of Interest

No potential conflict of interest relevant to this article was reported.

## ABSTRACT

**Objective:** To evaluate the survival impact of imaging vs surgical nodal assessment in patients with cervical cancer stage IB2–IVA prior to definitive chemoradiotherapy (CRT).

**Methods:** PubMed, MEDLINE, Cochrane Library, and ClinicalTrials.gov were used to search for publications in English and Chinese over a 50-year period. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols was used to conduct this review.

Inclusion criteria were studies that compared survival outcomes in International Federation of Gynecology and Obstetrics 2009 stage IB2–IVA cervical cancer patients with pre-therapy pelvic and/or aortic lymphadenectomy (LND) or imaging. One or more of the following modalities were used for nodal assessment: computed tomography (CT), magnetic resonance imaging, or positron emission tomography-CT. The National Institutes of Health Quality Assessment Tool was utilized to assess study quality.

**Results:** The initial search identified 65 studies, and five met the inclusion criteria. There were a total of 1,112 patients. Seven hundred and fifty-four underwent pelvic and/or aortic LND and 358 had imaging. When compared to LND, imaging had a sensitivity and specificity of 88.9% and 22.2% for pelvic lymph node (LN), and 33%–62.5% and 92%–95.5% for para-aortic LN. There were no differences in progression-free survival (PFS) (hazard ratio [HR]=1.13; 95% confidence interval [CI]=0.73–1.74; I<sup>2</sup>=75%; p<0.01) and overall survival (OS) (HR=1.06; 95% CI=0.66–1.69; I<sup>2</sup>=75%; p<0.01) between surgical and imaging nodal assessment.

**Conclusions:** Imaging and surgical nodal assessment has comparable PFS and OS in patients with cervical cancer stage IB2–IVA.

**Trial Registration:** PROSPERO Identifier: [CRD42020155486](https://www.crd42020155486)

**Keywords:** Uterine Cervical Neoplasms; Lymph Nodes; Lymphadenectomy; Diagnostic Imaging; Survival Analysis; Radiation Therapy

## INTRODUCTION

Cervical cancer ranks fourth highest in incidence and mortality amongst women worldwide [1,2]. The International Federation of Gynecology and Obstetrics (FIGO) revised cervical

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cancer staging in 2018 to improve treatment allocation and inform prognosis [3]. In the FIGO 2018 staging system, patients with pelvic and/or aortic nodal metastases are assigned stage IIIC [1,3]. Lymph node (LN) metastases can be assessed using imaging with or without pathologic confirmation, and nodal status largely dictates radiotherapy (RT) dose and field [3,4]. However, approach to pre-therapy LN assessment in patients with locally advanced cervical cancer is debatable [5-8].

Aortic lymphadenectomy (LND) with or without pelvic LND was gold standard in earlier practices and used as criterium for enrollment into clinical trials [9]. Some literature suggests LND has therapeutic benefit and impacts survival in advanced-stage cervical cancer patients [7]. However, LND requires advanced surgical skills and increases risk for complications, potentially delaying initiation of chemoradiation.

Advanced imaging modalities such as positron emission tomography (PET) can be used to determine disease extent and eliminate need for invasive diagnostics, but detection of nodal involvement remains unsatisfactory. PET-computed tomography (CT) demonstrates a sensitivity of 83% and 50% in detecting pelvic LN aortic LN metastases respectively [10]. Magnetic resonance imaging (MRI) and CT are comparable with a reported false-negative rate of 20%–50% for macroscopic nodal metastases [11].

Additionally, there are no standard recommendations for staging LND in the setting of locally advanced cervical cancer, and the survival benefit of staging LND is uncertain [12]. Some patients undergo aortic LND only, however enlarged pelvic LN (>2 cm) portends RT failure, cancer persistence or recurrence [13]. The primary objective of this systematic review and meta-analysis was to evaluate survival outcomes of imaging versus surgical nodal assessment in patients with cervical cancer stage IB2–IVA.

## MATERIALS AND METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) was used to conduct this systematic review [14,15]. This systematic review was submitted for registration on PROSPERO International Prospective Register of Systematic Review (ID No. CRD42020155486) and can be accessed at [www.crd.york.ac.uk/PROSPERO](http://www.crd.york.ac.uk/PROSPERO).

### 1. Search strategy

A literature search was performed using PubMed, MEDLINE, Cochrane Library, and ClinicalTrials.gov on December 13, 2019. A combination of MeSH terms and keywords were included: cervical cancer, para-aortic, lymph node excision, lymphadenectomy, surgical staging, and imaging staging. The complete search strategy can be found in Appendix 1.

### 2. Study selection

The eligibility of retrieved articles was independently determined by 2 reviewers (JY and RD). Disagreements were resolved by discussion between the two reviewers or by appeal to 2 senior reviewers (KB and PM) when necessary. Institutions, journals or authors were not concealed from the reviewers.

### 3. Selection criteria

All studies available in English and Chinese that reported survival outcomes for patients with FIGO 2009 stage IB2–IVA cervical cancer were included. Studies were initially screened by title and abstract to include pertinent comparative studies. The references of the included studies were cross-referenced to find additional publications.

LND or CT, MRI, or PET-CT imaging were used to determine pelvic and aortic LN status. LND was performed either minimally-invasive (laparoscopy or robotic-assisted) or open, then categorized by approach (retroperitoneal or transperitoneal). Aortic LND was performed either to the level of the infrarenal vein or the inferior mesenteric artery (IMA).

Review articles, animal studies, abstract- or protocol-only publications, case reports, and video reports were excluded. Studies of patients with non-cervical malignancies, or studies where radiologic-assisted biopsies were used to assess nodal status were also excluded.

### 4. Data extraction

Data from each study was independently abstracted by two reviewers (JY and RD). The manuscript title, journal name, country, research methodology, number of patients, patient age, tumor characteristics (histology, stage, grade, tumor size), and pelvic and aortic nodal involvement were collected. Operative details including surgical approach (laparoscopy, robotic assisted laparoscopy, laparotomy), LND approach (transperitoneal, retroperitoneal), cephalad border of aortic LND (infrarenal vein, IMA), operative time, estimated blood loss, and perioperative complications were abstracted.

Oncologic treatments including RT dose and duration, extended field radiotherapy (EFRT), brachytherapy, concurrent chemoradiotherapy (CCRT), and follow-up time (months) were also collected. Progression-free survival (PFS) was defined as the time (months) from diagnosis to disease recurrence. Overall survival (OS) was defined as the time (months) from initial diagnosis to death from all causes.

### 5. Risk of bias and statistical analysis

Quality assessment was performed by two reviewers (JY and RD) for included studies. The Study Quality Assessment Tool was utilized to assess the quality of observational cohort and controlled intervention studies (<https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools>). The included studies were critically appraised for potential bias involving treatment allocation and other confounding factors. Studies with a low risk of bias were rated as good or fair quality, and those with a high risk of bias were rated as poor quality. Conflicts regarding study quality were resolved by 2 senior reviewers (KB and PM) when necessary.

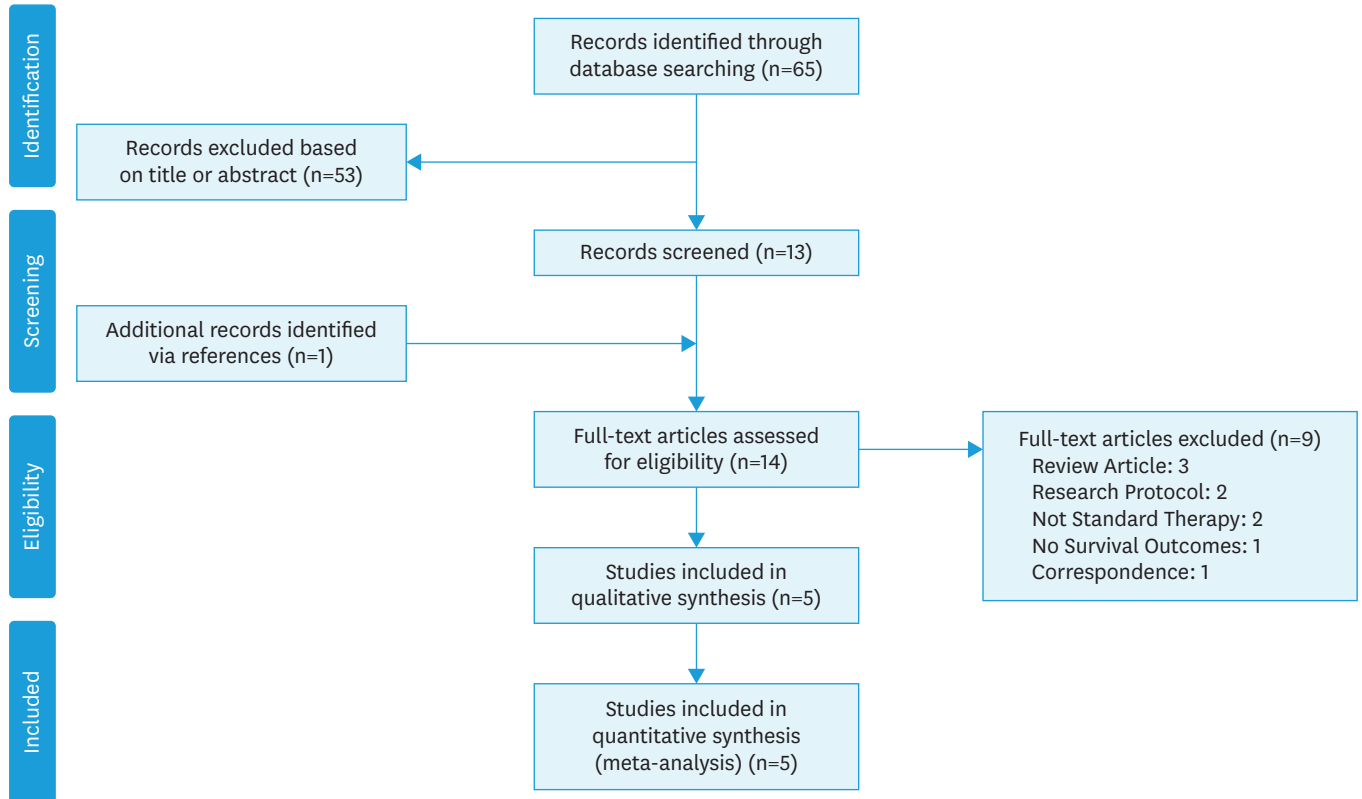
Abstracted data were presented as means with or without standard deviation, medians, and absolute or relative frequencies as was appropriate to the data characteristics or distribution. Hazard ratios (HR) were used as the principal summary measure for PFS and OS. Pooled estimates of the HR's and confidence intervals were computed using the DerSimonian and Laird method of inverse-variance weighting [16]. The fraction of between-study variance that is due to heterogeneity ( $I^2$ ) was also estimated. All analyses were completed using R version 3.6 (R Foundation for Statistical Computing, Vienna, Austria) [17].

## RESULTS

The search yielded 65 records (**Fig. 1**). After review of titles and abstracts, and identification of publications from cross references, 14 full-text articles were assessed for eligibility. Nine articles were excluded, of which three were review articles, 2 were study protocols with no reported data, 2 used unconventional oncologic therapies, 1 reported no survival outcomes, and 1 was a correspondence.

Five studies, with a cumulative total of 1,112 patients, met inclusion criteria (**Table 1**). The research methodologies included three retrospective cohorts with one utilizing a propensity-score matched analysis. In addition, there was one post hoc analysis and one randomized controlled trial (RCT). Seven hundred fifty-four patients underwent pelvic and/or aortic LND, and 358 had imaging for nodal assessment. The most common stage was IIB (n=653, 58.7%) followed by IIIB (n=358, 32.2%). Additional data on stage and tumor histology can be found in **Table 2**.

Surgical data was available for 199 patients (26.4%). Laparoscopic LND was performed in 161 patients (21.4%) with 16 completed with robotic-assistance (2.1%), and laparotomy performed in 22 patients (**Table 1**). A transperitoneal (n=65) or retroperitoneal (n=45) approach was used. The cephalad border for aortic LND was either the infrarenal vein (n=63) or the IMA (n=44). In the remaining 555 patients (73.6%), the approach to LND and the cephalad border for aortic LND were not described.



**Fig. 1.** PRISMA-P diagram [15].  
PRISMA-P, Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols.

**Table 1.** Summary of study methodologies and comparison group characteristics

First author	Year	Country	Methodology	Surgery			Imaging			Quality assessment*		
				No.	Age (yr)	Approach	No.	Age (yr)	Approach			
									CT		MRI	PET
Yang et al. [18]	2002	USA	Retrospective matched cohort	35	54.4±12.9	Laparoscopy (retroperitoneal, transperitoneal), laparotomy	70	52.6±12.4	21 (20)	16 (15.2)	15 (14.3)	Fair
Gonzalez-Benitez et al. [5]	2019	Spain	Retrospective cohort	43	48.4±9.5	Laparoscopy (retroperitoneal, transperitoneal), laparotomy	31	60.1±15.1	52 (70.3)	55 (74.3)	30 (40.5)	Poor
Pomel et al. [7]	2016	France	Retrospective cohort	89	49.9±11.7	Laparoscopy	98	56.8±12.9	11 (5.8)		176 (94.1)	Poor
Gold et al. [8]	2008	USA	Post hoc	555	49.1±12.0	NR	130	49.6±11.4	NR	NR	NR	Poor
Lai et al. [6]	2003	Taiwan	RCT	32	56±39	Laparoscopy, laparotomy (extraperitoneal)	29	53±70	NR	NR	NR	Fair

Values are reported as count (%) or mean ± standard deviation.

NR, data not reported; CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; RCT, randomized controlled trial.

\*Study Quality Assessment Tool was utilized to assess the quality of observational cohort studies and controlled intervention studies (<https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools>).

In three studies, 132 patients underwent aortic LND, and metastases were present in 44 patients (33%) [5-7,18]. Two studies reported percentages of pelvic LN metastasis while one study reported neither pelvic nor aortic LN status (**Table 3**) [6,8,18]. Two studies evaluated for concordance between surgical and imaging LN assessment, with radiography demonstrating a sensitivity of 33.3%–62.5% and specificity of 92%–95.5% for aortic LN metastases [5,18]. However, only one study presented a sensitivity and specificity for pelvic LN metastases, 88.9% and 22.2% respectively.

Brachytherapy was more commonly performed in patients who received pelvic or aortic nodal assessment with surgery (n=138, 38.5%) than imaging (n=187, 24.8%). Conversely, EFRT was more commonly performed in patients who received imaging (n=40, 15.5%) than those who received LND (n=47, 6.2%). One study did not report details on either chemotherapy or RT [8].

Hazard ratios for survival were reported in four of the five studies (**Table 4, Fig. 2**) [6-8,18]. After compilation of data, meta-analysis determined comparable PFS (HR=1.13; 95% CI=0.73–1.74; I<sup>2</sup>=75%; p<0.01) and OS (HR=1.06; 95% CI=0.66–1.69; I<sup>2</sup>=75%; p<0.01) between surgical and imaging nodal assessment (**Fig. 2**).

## DISCUSSION

This systematic review and meta-analysis found no difference in PFS and OS in patients who underwent pelvic or aortic LND versus imaging nodal assessment. There is no high-quality evidence to recommend LND for therapeutic or prognostic indications, however there is some evidence to recommend LND in patients with advanced stage.

Prospective data comparing surgical to imaging nodal assessment are limited, and to our knowledge there are two RCTs that compared these two diagnostic approaches in patients with locally advanced cervical cancer assigned to receive definitive RT [6,19,20]. One RCT terminated prematurely after an interim analysis showed LND had worse PFS (HR=1.71; 95% CI=1.17–2.49; p=0.005) [6]. However, patients who received LND had more unfavorable prognosticators and few received concurrent chemotherapy, allocating these patients to a survival disadvantage. Next, preliminary results of the Uterus-11 multicenter RCT in Germany

**Table 2.** Tumor stage and histology

First author	Year	FIGO stage												Histology															
		I			IIA			IIB			IIIA			IIIB			IVA			IVB			Squamous		Adenosquamous				
		Surgery	Imaging	%	Surgery	Imaging	%	Surgery	Imaging	%	Surgery	Imaging	%	Surgery	Imaging	%	Surgery	Imaging	%	Surgery	Imaging	%	Surgery	Imaging	%	Surgery	Imaging	%	Surgery
Yang et al. [18]	2020	26 (37.1)	26 (23.0)	8 (11.4)	13 (11.5)	24 (34.3)	41 (36.3)	0	1 (0.9)	12 (17.1)	32 (28.3)	0	0	0	0	0	0	0	0	0	0	0	0	0	48 (68.6)	86 (76.1)	6 (8.6)	7 (6.2)	
Gonzalez-Benitez et al. [5]	2019	0	0	1 (2.3)	0	11 (25.5)	23 (74.1)	0	0	10 (23.2)	7 (22.5)	0	1 (3.2)	21 (48.8)	0	0	0	0	0	0	0	0	0	0	32 (44)	52 (72)	NR	NR	
Pomet et al. [7]	2016	17 (19.1)	13 (13.3)	0	0	53 (59.6)	72 (73.5)	0	0	10 (11.2)	7 (7.1)	4 (4.5)	6 (6.1)	0	0	0	0	0	0	0	0	0	0	79 (88.8)	69 (70.4)	7 (7.9)	27 (27.5)		
Gold et al. [8]	2008	0	0	0	0	310 (55.9)	86 (66.2)	13 (2.3)	0	217 (39.1)	38 (29.2)	15 (2.7)	6 (4.6)	0	0	0	0	0	0	0	0	0	0	488 (97.9)	112 (86.2)	23 (4.1)	8 (6.2)		
Lai et al. [6]	2003	0	0	0	0	15 (47)	18 (62)	2 (6)	1 (3)	15 (47)	10 (35)	0	0	0	0	0	0	0	0	0	0	0	0	27 (75)	27 (93)	5 (16)	2 (7)		

Values are reported as count (%).

FIGO, International Federation of Gynecology and Obstetrics; NR, data not reported.

**Table 3.** Distribution of lymph node metastasis, and radiotherapy treatment characteristics

First author	Year	Pelvic LN metastasis			Para-aortic LN metastasis			Dose of external RT (Gy)			Duration of external RT (days)			Dose of brachytherapy (Gy)			Extended field RT											
		Surgery	Imaging	%	Surgery	Imaging	%	Surgery	Imaging	Mean±SD	Surgery	Imaging	Mean±SD	Surgery	Imaging	Mean±SD	Surgery	Imaging	Mean±SD	Surgery	Imaging	Mean±SD	Surgery	Imaging	Mean±SD	Surgery	Imaging	Mean±SD
		No.	%	SE	No.	%	SE	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.
Yang et al. [18]	2020	61.4	88.9	22.2	57.5	11.1	62.5	92	17.7	35	51.1±5.2	70	51.8±5.5	35	NR	70	NR	100	NR	100	NR	100	NR	8	(22.9)	12	(17.1)	
Gonzalez-Benitez et al. [5]	2019	NR	NR	NR	NR	48.8	33.3	95.5	NR	41	50.5±NR	30	45.5±NR	NR	NR	NR	NR	38	26.1±NR	24	(77.4)	25.9±NR	19	(44.2)	6	(19.4)		
Pomet et al. [7]	2016	NR	NR	NR	NR	25.8	NR	NR	14.2	NR	NR	NR	NR	NR	NR	NR	NR	65	NR	93	NR	93	NR	20	(22.5)	22	(22.4)	
Gold et al. [8]	2008	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Lai et al. [6]	2003	19	NR	NR	31	NR	NR	NR	NR	NR	NR	NR	NR	32	59±83	29	56±83	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

LN, lymph node; NR, data not reported; RT, radiotherapy; SD, standard deviation; SE, sensitivity; SP, specificity.

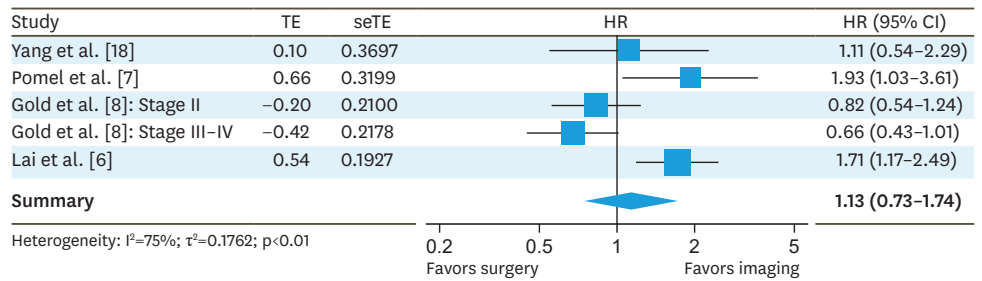
**Table 4.** Follow-up time and survival outcomes

First author	Year	Follow-up time (mo)						PFS (mo)						OS (mo)					
		Surgery			Imaging			Surgery			Imaging			Surgery			Imaging		
		No.	Mean±SD	HR (95% CI)	No.	Mean±SD	HR (95% CI)	No.	Median±QD	No.	Median±QD	No.	Median±QD	No.	Median±QD	No.	Median±QD	No.	Median±QD
Yang et al. [18]	2020	35	41 (7-218)*	70	51.5 (7-198)*	35	NR	70	NR	1.11 (0.54-2.30)	35	NR	70	NR	1.02 (0.46-2.29)				
Gonzalez-Benitez et al. [5]	2019	43	19.1±13	31	24.2±16.6	43	14.4±12.6	31	17.4±17.4	NR	NR	NR	NR	NR	NR				
Pomet et al. [7]	2016	NR	43.4±NR	NR	35.6±NR	NR	NR	NR	NR	1.93 (1.03-3.61)	NR	NR	NR	NR	2.55 (1.09-5.99)				
Gold et al. [8]	2008	NR	NR	NR	NR	NR	NR	NR	NR	0.82 (0.54-1.23)	NR	NR	NR	NR	0.72 (0.47-1.11)				
Stage II	NR	NR	NR	NR	NR	NR	NR	NR	NR	0.66 (0.43-1.01)	NR	NR	NR	NR	0.63 (0.40-0.97)				
Stage III-IV	NR	NR	NR	NR	NR	NR	NR	NR	NR	1.71 (1.17-2.49)	NR	NR	NR	NR	1.5 (1.04-2.17)				
Lai et al. [6]	2003	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR				

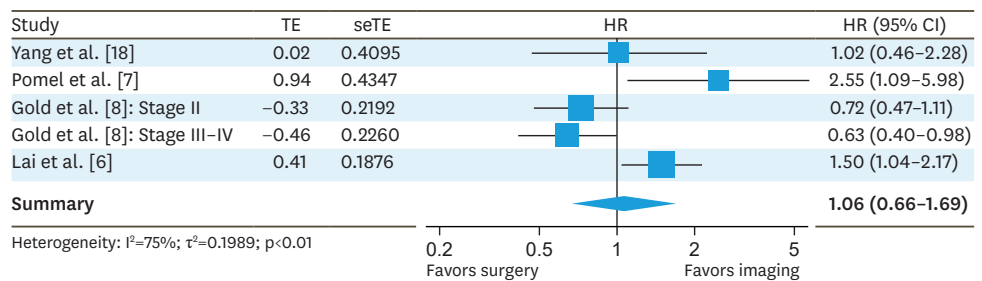
HR, hazard ratio; NR, data not reported; OS, overall survival; PFS, progression-free survival; QD, quartile deviation; SD, standard deviation.

\*Data shown as median (range).

**PFS**



**OS**



**Fig. 2.** Forest plots demonstrating PFS and OS for patients who underwent imaging versus surgical nodal assessment. Pooled summary estimates were computed using inverse-variance weighting. TE, treatment effect; seTE, standard error of treatment effect; HR, hazard ratio; CI, confidence interval; PFS, progression-free survival; OS, overall survival.

demonstrated that LND led to upstaging in >30% of patients, had acceptable morbidity, and did not delay initiation of CRT [19]. Investigators found similar PFS and OS between patients who received imaging versus surgical staging, however found cancer specific survival ( $p=0.028$ ) in favor of LND. The Uterus-11 was excluded from our systematic review because complete survival data was unavailable at the time of this publication. Lastly, the Lymphadenectomy in Locally Advanced Cervical Cancer Study (LiLACS), an international multicenter randomized phase 3 clinical trial (ClinicalTrials.gov identifier [NCT02848716](https://clinicaltrials.gov/ct2/show/study/NCT02848716)), compared survival outcomes between patients who underwent surgical versus imaging nodal assessment [20]. LiLACS required enrollment of 600 patients with an estimated 8 years to study completion [20]. However, this trial closed for enrollment due to poor accrual and had no survival data available for inclusion into our systematic review [20].

Retrospective studies present conflicting survival outcomes. A post hoc analysis of Gynecologic Oncology Group (GOG) 85, 120, and 165 found stage III–IV cervical cancer patients who received imaging nodal assessment had worse PFS (HR=0.66; 95% CI=0.43–1.01) and OS (HR=0.63; 95% CI=0.40–0.97) [8]. Patients with stage III–IV disease who underwent LND demonstrated OS but no PFS benefit, but those with stage II demonstrated neither PFS nor OS benefit. The 3 GOG studies introduced patient selection bias with their variable chemotherapy and RT protocols. In contrast, Pomel et al. [7] found PFS (HR=1.93; 95% CI=1.03–3.61) and OS (HR=2.55; 95% CI=1.09–5.99) benefit for imaging nodal assessment. Authors of this retrospective cohort noted less aortic LN involvement on imaging, and correspondingly less patients underwent completion surgery and more received brachytherapy. In concordance, Gonzalez-Benitez et al. [5] showed LND had higher diagnostic accuracy but no survival benefit. However, their patients received variable therapies with higher rates of EFRT and chemotherapy administration and larger RT doses in those patients who received LND. In addition, almost half of the patients (48.8%) who

received LND were advanced staged (stage IVA) and a greater percentage had non-squamous tumors (52.7%). We suspect that more aggressive treatments were pursued for these patients due to their already poor prognosis. Lastly, Yang et al. [18] also confirmed no survival benefit for LND. However, authors found surgical staging resulted in a change in the radiation treatment plan in as high as 31.4% of patients, suggesting that LND may play a role in tailoring CRT in cases of enlarged PLN or positive common iliac involvement [18].

The role of LND in local control and distant metastasis for locally advanced cervical cancer remains uncertain. There are reports that LND improves local control and decreases extra-pelvic failures in patients with metastases [21,22]. We hypothesize that the survival benefit for LND is limited due to the natural history of cervical cancer and the treatment effect of RT. If there is pelvic nodal involvement, RT with pelvic boost can be used to achieve local control. If there is aortic nodal involvement, there may already be distant metastasis beyond the aortic LN, and neither EFRT nor consolidation chemotherapy will improve the already poor survival associated with more advanced stages.

While this review had a reasonable sample size of 1,112 patients, 94.5% of the patients (n=1,051) were from retrospective cohort analyses, so our review was limited by the high risk of bias inherent to retrospective methodologies. There was also significant heterogeneity with respect to the chemo- and radiotherapy protocols, and some data points were not reported. The clinical and methodologic heterogeneity of included literature likely contributed to our inability to find significant survival differences. Our systematic review and meta-analysis emphasize the need for prospective trials to determine if LND has therapeutic or prognostic benefits in cervical cancer patients.

A strength of our study is that it synthesized available literature comparing survival outcomes in patients with locally advanced cervical cancer who received either surgical versus imaging nodal assessment. While the post hoc analysis of GOG 85, 120, and 165 remains the largest study to date to answer this clinical question, there only appeared to be OS benefit for stage III–IV cervical cancer patients but no survival benefit for patients with early stage disease. The GOG demonstrated a high risk of bias due to its post hoc methodology.

Our systematic review found no difference in PFS or OS for locally advanced cervical cancer patients who received pelvic or aortic LND versus imaging nodal assessment prior to CRT. We recognize that an international multicenter RCT would provide the most robust data to answer this clinical question, but as with the LiLACS trial, patient accrual remains a challenge. In cervical cancer patients, the radiologic literature suggests PET or PET-CT has a higher sensitivity and specificity to detect nodal metastases as compared to CT or MRI [23]. We suggest PET-CT for nodal assessment in patients with locally advanced cervical cancer because it is less invasive and does not negatively impact survival outcomes. In conclusion, imaging and surgical nodal assessment showed no difference in PFS and OS in patients with cervical cancer stage IB2–IVA prior to definitive CRT.

## REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;68:394-424.  
[PUBMED](#) | [CROSSREF](#)



2. Cohen PA, Jhingran A, Oaknin A, Denny L. Cervical cancer. *Lancet* 2019;393:169-82.  
[PUBMED](#) | [CROSSREF](#)
3. Bhatla N, Berek JS, Cuello Fredes M, Denny LA, Grenman S, Karunaratne K, et al. Revised FIGO staging for carcinoma of the cervix uteri. *Int J Gynaecol Obstet* 2019;145:129-35.  
[PUBMED](#) | [CROSSREF](#)
4. Leath CA 3rd, Monk BJ. Twenty-first century cervical cancer management: a historical perspective of the gynecologic oncology group/NRG oncology over the past twenty years. *Gynecol Oncol* 2018;150:391-7.  
[PUBMED](#) | [CROSSREF](#)
5. Gonzalez-Benitez C, Salas P, Grabowski JP, Hernandez A, De Santiago J, Zapardiel I. Lack of survival benefit of para-aortic lymphadenectomy in advanced cervical cancer. *Gynecol Obstet Invest* 2019;84:407-11.  
[PUBMED](#) | [CROSSREF](#)
6. Lai CH, Huang KG, Hong JH, Lee CL, Chou HH, Chang TC, et al. Randomized trial of surgical staging (extraperitoneal or laparoscopic) versus clinical staging in locally advanced cervical cancer. *Gynecol Oncol* 2003;89:160-7.  
[PUBMED](#) | [CROSSREF](#)
7. Pomel C, Martinez A, Bourgin C, Beguinot M, Benoit C, Naik R, et al. Survival effect of laparoscopic para-aortic staging in locally advanced cervical cancer: a retrospective cohort analysis. *BJOG* 2017;124:1089-94.  
[PUBMED](#) | [CROSSREF](#)
8. Gold MA, Tian C, Whitney CW, Rose PG, Lanciano R. Surgical versus radiographic determination of para-aortic lymph node metastases before chemoradiation for locally advanced cervical carcinoma: a Gynecologic Oncology Group Study. *Cancer* 2008;112:1954-63.  
[PUBMED](#) | [CROSSREF](#)
9. Monk BJ, Tian C, Rose PG, Lanciano R. Which clinical/pathologic factors matter in the era of chemoradiation as treatment for locally advanced cervical carcinoma? Analysis of two Gynecologic Oncology Group (GOG) trials. *Gynecol Oncol* 2007;105:427-33.  
[PUBMED](#) | [CROSSREF](#)
10. Atri M, Zhang Z, Dehdashti F, Lee SI, Ali S, Marques H, et al. Utility of PET-CT to evaluate retroperitoneal lymph node metastasis in advanced cervical cancer: Results of ACRIN6671/GOG0233 trial. *Gynecol Oncol* 2016;142:413-9.  
[PUBMED](#) | [CROSSREF](#)
11. Choi HJ, Roh JW, Seo SS, Lee S, Kim JY, Kim SK, et al. Comparison of the accuracy of magnetic resonance imaging and positron emission tomography/computed tomography in the presurgical detection of lymph node metastases in patients with uterine cervical carcinoma: a prospective study. *Cancer* 2006;106:914-22.  
[PUBMED](#) | [CROSSREF](#)
12. Smits RM, Zusterzeel PL, Bekkers RL. Pretreatment retroperitoneal para-aortic lymph node staging in advanced cervical cancer: a review. *Int J Gynecol Cancer* 2014;24:973-83.  
[PUBMED](#) | [CROSSREF](#)
13. Wang W, Liu X, Meng Q, Zhang F, Hu K. Nomograms predicting survival and patterns of failure in patients with cervical cancer treated with concurrent chemoradiotherapy: a special focus on lymph nodes metastases. *PLoS One* 2019;14:e0214498.  
[PUBMED](#) | [CROSSREF](#)
14. Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. *BMJ* 2015;350:g7647.  
[PUBMED](#) | [CROSSREF](#)
15. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.  
[PUBMED](#) | [CROSSREF](#)
16. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177-88.  
[PUBMED](#) | [CROSSREF](#)
17. R Development Core Team. R: A language and environment for statistical computing. Vienna: R Foundation for Statistical Computing; 2010.
18. Yang J, Delara R, Magrina J, Magtibay P, Yi J, Langstraat C, et al. Comparing survival outcomes between surgical and radiographic lymph node assessment in locally advanced cervical cancer: a propensity score-matched analysis. *Gynecol Oncol* 2020;156:320-7.  
[PUBMED](#) | [CROSSREF](#)
19. Marnitz S, Martus P, Köhler C, Stromberger C, Asse E, Mallmann P, et al. Role of surgical versus clinical staging in chemoradiated FIGO stage IIB-IVA cervical cancer patients-acute toxicity and treatment quality

of the Uterus-11 Multicenter Phase III Intergroup Trial of the German Radiation Oncology Group and the Gynecologic Cancer Group. *Int J Radiat Oncol Biol Phys* 2016;94:243-53.

[PUBMED](#) | [CROSSREF](#)

20. Frumovitz M, Querleu D, Gil-Moreno A, Morice P, Jhingran A, Munsell MF, et al. Lymphadenectomy in locally advanced cervical cancer study (LiLACS): Phase III clinical trial comparing surgical with radiologic staging in patients with stages IB2–IVA cervical cancer. *J Minim Invasive Gynecol* 2014;21:3-8.

[PUBMED](#) | [CROSSREF](#)

21. Kupets R, Thomas GM, Covens A. Is there a role for pelvic lymph node debulking in advanced cervical cancer? *Gynecol Oncol* 2002;87:163-70.

[PUBMED](#) | [CROSSREF](#)

22. Mezquita G, Muruzabal JC, Perez B, Aguirre S, Villafranca E, Jurado M. Para-aortic plus pelvic lymphadenectomy in locally advanced cervical cancer: a single institutional experience. *Eur J Obstet Gynecol Reprod Biol* 2019;236:79-83.

[PUBMED](#) | [CROSSREF](#)

23. Khiewvan B, Torigian DA, Emamzadehfard S, Paydary K, Salavati A, Houshmand S, et al. Update of the role of PET/CT and PET/MRI in the management of patients with cervical cancer. *Hell J Nucl Med* 2016;19:254-68.

[PUBMED](#) | [CROSSREF](#)

**Appendix 1.** Search strategy: National Center for Biotechnology Information (NCBI)

```
(((((((para-aortic) AND ((“Lymph Node Excision”[Mesh] OR Lymphadenectomy))) OR “para-aortic lymph node dissection”)) AND ((“Uterine Cervical Neoplasms”[Mesh] OR “cervical cancer”))) AND (((“surgical staging”) OR “imaging staging”) OR “Neoplasm Staging/methods”[Mesh]) Filters: English, Chinese
```