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

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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; I2=75%; p<0.01) and overall survival (OS) (HR=1.06; 95% CI=0.66–1.69; I2=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.

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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
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 criterion 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.

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, MRJ, 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.
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; I²=75%; p<0.01) and OS (HR=1.06; 95% CI=0.66–1.69; I²=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

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>FIGO stage</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yang et al. [18]</td>
<td>2020</td>
<td>I</td>
<td>Squamous</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IIA</td>
<td>Adenosquamous</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IIB</td>
<td></td>
</tr>
<tr>
<td>Gonzalez-Benitez et al. [5]</td>
<td>2019</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Godet et al. [8]</td>
<td>2008</td>
<td></td>
<td></td>
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</tbody>
</table>

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

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Pelvic LN metastasis</th>
<th>Para-aortic LN metastasis</th>
<th>Dose of external RT (Gy)</th>
<th>Duration of external RT (days)</th>
<th>Dose of brachytherapy (Gy)</th>
<th>Extended field RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yang et al. [18]</td>
<td>2020</td>
<td>61.4±NR</td>
<td>22.2±NR</td>
<td>35.1±5.2</td>
<td>70</td>
<td>NR</td>
<td>100 (88.3)</td>
</tr>
<tr>
<td>Gonzalez-Benitez et al. [5]</td>
<td>2019</td>
<td>NR NR NR</td>
<td>NR NR NR NR</td>
<td>NR NR NR NR</td>
<td>NR</td>
<td>NR</td>
<td>100 (94.2)</td>
</tr>
<tr>
<td>Pomel et al. [7]</td>
<td>2016</td>
<td>NR NR NR</td>
<td>NR NR NR NR</td>
<td>25.8±NR</td>
<td>65</td>
<td>NR</td>
<td>65 (94.9)</td>
</tr>
<tr>
<td>Godet et al. [8]</td>
<td>2008</td>
<td>NR NR NR</td>
<td>NR NR NR NR</td>
<td>NR NR NR NR</td>
<td>NR</td>
<td>NR</td>
<td>NR NR NR NR NR</td>
</tr>
<tr>
<td>Lai et al. [6]</td>
<td>2003</td>
<td>19 NR NR</td>
<td>31 NR NR NR</td>
<td>22.2±NR</td>
<td>22 (22.2)</td>
<td>NR</td>
<td>NR NR</td>
</tr>
</tbody>
</table>

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

Table 4. Follow-up time and survival outcomes

<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
<th>Follow-up time (mo)</th>
<th>PFS (mo)</th>
<th>HR (95% CI)</th>
<th>OS (mo)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yang et al. [18]</td>
<td>2020</td>
<td>35 (7-21.8)*</td>
<td>35 NR</td>
<td>1.11 (0.54-2.30)</td>
<td>35 NR</td>
<td>1.02 (0.46-2.29)</td>
</tr>
<tr>
<td>Gonzalez-Benitez et al. [5]</td>
<td>2019</td>
<td>43 (19.1±13)</td>
<td>43 NR</td>
<td>1.93 (1.03-3.61)</td>
<td>NR NR</td>
<td>2.55 (1.09-5.99)</td>
</tr>
<tr>
<td>Pomel et al. [7]</td>
<td>2016</td>
<td>NR 43.4±NR NR NR NR</td>
<td>NR NR</td>
<td>0.82 (0.54-1.23)</td>
<td>NR NR</td>
<td>0.72 (0.47-1.11)</td>
</tr>
<tr>
<td>Godet et al. [8]</td>
<td>2008</td>
<td>Stage II</td>
<td>NR NR</td>
<td>0.66 (0.43-1.01)</td>
<td>NR NR</td>
<td>0.63 (0.40-0.97)</td>
</tr>
<tr>
<td>Lai et al. [6]</td>
<td>2003</td>
<td>Stage II-IV</td>
<td>NR NR</td>
<td>1.71 (1.17-2.49)</td>
<td>NR NR</td>
<td>1.5 (0.4-2.17)</td>
</tr>
</tbody>
</table>

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).
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), 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=0.40–0.98) [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

<table>
<thead>
<tr>
<th>Study</th>
<th>TE</th>
<th>seTE</th>
<th>HR</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yang et al. [18]</td>
<td>0.10</td>
<td>0.3697</td>
<td></td>
<td>1.11 (0.54–2.29)</td>
</tr>
<tr>
<td>Pomel et al. [7]</td>
<td>0.66</td>
<td>0.3199</td>
<td></td>
<td>1.93 (1.03–3.61)</td>
</tr>
<tr>
<td>Gold et al. [8]: Stage II</td>
<td>−0.20</td>
<td>0.2100</td>
<td></td>
<td>0.82 (0.54–1.24)</td>
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<tr>
<td>Gold et al. [8]: Stage III–IV</td>
<td>−0.42</td>
<td>0.2178</td>
<td></td>
<td>0.66 (0.43–1.01)</td>
</tr>
<tr>
<td>Lai et al. [6]</td>
<td>0.54</td>
<td>0.1927</td>
<td></td>
<td>1.71 (1.17–2.49)</td>
</tr>
</tbody>
</table>

**Summary**

Heterogeneity: $I^2=75%$; $\tau^2=0.1762$; $p<0.01$

**OS**

<table>
<thead>
<tr>
<th>Study</th>
<th>TE</th>
<th>seTE</th>
<th>HR</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yang et al. [18]</td>
<td>0.02</td>
<td>0.4095</td>
<td></td>
<td>1.02 (0.46–2.28)</td>
</tr>
<tr>
<td>Pomel et al. [7]</td>
<td>0.94</td>
<td>0.4347</td>
<td></td>
<td>2.55 (1.09–5.98)</td>
</tr>
<tr>
<td>Gold et al. [8]: Stage II</td>
<td>−0.33</td>
<td>0.2192</td>
<td></td>
<td>0.72 (0.47–1.11)</td>
</tr>
<tr>
<td>Gold et al. [8]: Stage III–IV</td>
<td>−0.46</td>
<td>0.2260</td>
<td></td>
<td>0.63 (0.40–0.98)</td>
</tr>
<tr>
<td>Lai et al. [6]</td>
<td>0.41</td>
<td>0.1876</td>
<td></td>
<td>1.50 (1.04–2.37)</td>
</tr>
</tbody>
</table>

**Summary**

Heterogeneity: $I^2=75%$; $\tau^2=0.1989$; $p<0.01$

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.
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


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