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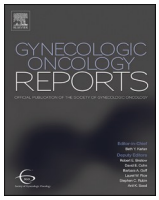

Presence of low volume metastases does not alter management in node-negative, early-stage cervical cancer patients who underwent postoperative adjuvant therapy: A retrospective cohort study

Annalyn M. Welp [a,*], Mick Crawford [b], Rachel O'Brien [a], Stephanie A. Sullivan [c], Linda R. Duska [a]

[a] Department of Obstetrics and Gynecology, University of Virginia, Charlottesville, VA, United States
[b] Department of Pathology, University of Virginia, Charlottesville, VA, United States
[c] Department of Obstetrics and Gynecology, Virginia Commonwealth University, Richmond, VA, United States

A B S T R A C T

Objective: This study sought to determine if patients with early stage cervical cancer who possessed intermediate-high risk factors (defined by Peters or Sedlis criteria) and had pathologically negative lymph nodes at the time of surgery had higher rates of low volume metastases (LVM) on retrospective ultrastaging.
Methods: This IRB-approved retrospective cohort study collected data via chart review on early stage, surgically-treated node-negative cervical cancer patients who underwent postoperative adjuvant therapy, treated at a single institution from January 2011 through June 2021. Nodal blocks were retrospectively ultrastaged per standard protocol. Descriptive statistics were performed for analysis.
Results: Over the 10-year study period, n = 20 patients met study inclusion criteria. Most patients were white with squamous cell histology, with a mean number of 25.15 (SD = 12) nodes examined on initial pathologic evaluation. 85 % (n = 17) patients were pathologic stage IB. 85 % of the cohort were recommended for adjuvant radiation, with the remaining 15 % for cisplatin-based chemoradiation. LVM in the form of micrometastasis was retrospectively identified in one patient (5 %) who had received whole pelvic radiation and recurred locally within the irradiated field.
Conclusions: This small retrospective series of surgically managed cervical cancer with intermediate-high risk tumor factors identified only 1 patient with LVM, representing 5% of the total population. The biologic importance of ITC and LVM remains unclear in cervical cancer, however this investigation highlights the low incidence even when all nodes are evaluated in a higher risk cohort. The presence of LVM would not have changed management decisions based on this retrospective analysis.

1. Introduction

Cervical cancer is a human papillomavirus (HPV)-related gynecologic malignancy that has decreased in incidence with the increased uptake of the HPV vaccine. However, during 2022 in the United States alone, there were approximately 13,000 new cases diagnosed and approximately 4,000 deaths (CDC, 2022). Patients with early stage disease including International Federation of Gynecology and Obstetrics (FIGO) stage IA1 to IB2 are treated via radical hysterectomy with bilateral pelvic lymph node dissection (NCCN, 2022).

Lymph node metastasis are classified by size into three categories based on breast cancer literature: (1) macrometastases, disease larger than 2 mm; (2) micrometastases (MM), disease measuring between 0.2 and 2 mm; and (3) isolated tumor cells (ITC), disease measuring < 0.2 mm(3). MM and ITCs together are categorized as low volume metastasis (LVM). Routine sectioning of nodes will identify macrometastases, while LVM is detected through ultrastaging of sentinel lymph node (SLN) biopsies. LVM has been identified in an estimated 5.1–8.1 % of sentinel nodes in reported literature (Silva et al., 2005; Juretzka et al., 2004). The use of SLN mapping and biopsy is still being actively studied in cervical cancer, with ongoing prospective trials comparing this technique to the current standard of care (ClinicalTrials.gov., 2017).

Nodal positivity has long been an important prognostic factor, and is one of several high-risk factors that directs receipt of adjuvant postoperative therapy. The high-risk factors for early stage cervical cancer, colloquially termed "Peters Criteria" include nodal positivity, parametrial invasion, or positive margins as indications for adjuvant cisplatin-based chemoradiation (Peters et al., 2000). Additional high-risk factors detailed for node-negative patients by Gynecologic Oncology Group (GOG)-92, better known as the "Sedlis criteria," included greater than one-third stromal invasion, lymphovascular space involvement, and tumor size greater than 4 cm as indications for postoperative radiation (Sedlis et al., 1999).

Given that the presence of positive nodes dictates the indication for

* Corresponding author at: 1215 Lee St. Department of Obstetrics and Gynecology, University of Virginia, Charlottesville, Virginia, United States.
E-mail address: amw2cn@uvahealth.org (A.M. Welp).

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Table 1
Demographic, clinical and pathologic characteristics of the study cohort.

Characteristics		N (%)/mean +/- SD
Race/Ethnicity		
	White	13 (65)
	Black	5 (25)
	Hispanic/Latino	2 (10)
Mean age[1]		51 y.o. (SD = 12)
Tobacco use[1]		
	Yes	16 (80)
	No	4 (20)
Type of Hysterectomy		
	Minimally-invasive[2] radical hysterectomy	6 (30)
	Radical[3] hysterectomy	14 (70)
Type of Nodal Dissection		
	Bilateral pelvic	19 (95)
	Bilateral pelvic and *para*-aortic	1 (5)
Tumor histology		
	Squamous cell carcinoma	16 (80)
	Adenocarcinoma	2 (10)
	Adenosquamous carcinoma	2 (10)
Tumor Grade		
	Grade 1	2 (10)
	Grade 2	13 (65)
	Grade 3	5 (25)
Tumor Size		
	<2 cm	5 (25)
	≥ 2 cm, <3 cm	7 (35)
	≥ 3 cm, <4 cm	6 (30)
	≥ 4 cm	2 (10)
LVSI		
	Present	15 (75)
	Not present	5 (25)
Stromal invasion		
	Superficial one-third	1 (5)
	Middle one-third	6 (30)
	Deep one-third	13 (65)
Parametrial Invasion		
	Present	1 (5)
	Not present	19 (95)
Positive Margins		
	Present	1 (5)
	Not present	19 (95)
Pathologic Tumor Stage[4]		
	IB	17 (85)
	IIA	2 (10)
	IIB[5]	1 (5)
Type of post-operative adjuvant therapy[6]		
	Chemoradiation	3 (15)
	Radiation alone	17 (85)

[1]At time of diagnosis; [2]Minimally-invasive includes both laparoscopic and robotic; [3]includes radical and modified radical hysterectomies; [4]tumor size categorized by 2018 FIGO staging system for uterine cervix cancer; [5]This patient was pathologically staged IIB due to an unexpected finding of parametrial invasion on surgical pathology; [6]Includes patients who were indicated for post-operative adjuvant therapy based on pathologic factors, but declined to pursue further treatment.

Abbreviations: FIGO- International Federation of Gynecology and Obstetrics; LVSI- lymphovascular space invasion

postoperative adjuvant therapy, with "positive nodes" defined as > 2 mm of disease, the treatment implications for the finding of LVM remain in question. Different studies have come to conflicting conclusions regarding the prognostic and clinical value of LVM; consequently, this question is being studied in the ongoing prospective SENTICOL-III trial. Studies to date have generally focused on determining the incidence of macrometastases compared to LVM in node positive and node negative patients, and attempting to clarify any associations that may impact prognostication. No study to date has examined specifically the presence of LVM in node-negative patients who were treated with adjuvant therapy for indications other than nodal positivity.

We sought to determine if patients with early stage cervical cancer who possessed intermediate-high risk factors and had pathologically negative lymph nodes at the time of surgery had higher rates of LVM on retrospective ultrastaging.

2. Methods

This retrospective cohort study collected clinicopathologic data via chart review on early stage, surgically-treated cervical cancer patients, treated at a single institution from January 2011 through June 2021. This study was approved by the human subject research institutional review board (HSR-IRB protocol #23486). Data regarding treatment of all cervical cancer patients during this time frame was pulled by the institution's cancer center certified tumor registrar after IRB approval and were reviewed by the study team (A.W.).

Patients were included in the study based on the following inclusion criteria: (i) patients > 18 years old at time of diagnosis, treated at the study team's institution between January 1, 2011 and June 30, 2021 who underwent a radical hysterectomy (open, laparoscopic, or robotic) or radical trachelectomy with any form of lymph node assessment (full dissection versus sentinel nodes) for biopsy-proven cervical cancer; (ii) Patients with pathology-proven negative nodes from time of surgery; and (iii) patients who met criteria for any post-operative adjuvant therapy. Exclusion criteria included patients who had rare, high-risk, or incorrect histologic diagnoses (i.e., neuroendocrine, clear cell, rhabdomyosarcoma), those who were lost to follow up with no outcomes data available, or with node-positive macrometases on surgical pathology were excluded. Demographic, clinical, pathologic, and outcome data was collected from the medical record on each patient by the study team (A.W., R.O.B.) to determine eligibility.

Given the study period included an interval where the FIGO staging was updated, the study team re-staged the entire cohort based on FIGO 2018 staging in an effort to ensure uniformity.

Resected nodes were ultrastaged per standard protocol and read by one gynecologic pathologist (M.C.). Ultrastaging was performed via four re-cuts at 20 μm on each lymph node section. The sections were stained with hematoxylin and eosin and one level with CK AE1/AE3 to identify MM and ITCs.

This cohort represents a convenience sample and no de novo power calculation was performed. Descriptive statistics were used for analysis utilizing Microsoft Excel (2019).

3. Results

197 patients were surgically-treated for cervical cancer between January 2011 and June 2021. 101 patients underwent a radical hysterectomy or trachelectomy, 31 of these patients underwent post-operative adjuvant therapy or were candidates for radiation therapy. Of the 31, eleven (n = 11) patients had positive nodes on final surgical pathology, leaving 20 eligible patients. Overall, the most common reason for exclusion from the study was failing to receive specifically a radical hysterectomy or trachelectomy with nodal assessment, as outlined by the inclusion criteria.

Table 1 details the demographic, clinical and pathologic characteristics of the study cohort. Of the patients in the cohort, a majority of the patients were white with squamous cell carcinoma histology. The mean number of nodes examined on initial surgical pathologic evaluation was 25.15 (SD = 12).

Most patients (n = 14, 70 %) underwent an open radical hysterectomy, the rest (n = 6,30 %) underwent a minimally-invasive- radical hysterectomy (5 robotic and 1 laparoscopic). There were no patients in the cohort who had a radical trachelectomy. 95 % of the cohort (n = 19) underwent bilateral pelvic lymph node dissection; the remaining 5 % underwent both bilateral pelvic and *peri*-aortic nodal dissection. No patients underwent sentinel node mapping and dissection.

85 % of the patients (n = 17) were pathologically staged as FIGO IB. The remaining patients were FIGO Stage II. Of the cohort, all of whom were node-negative and recommended to receive adjuvant treatment, 85 % received adjuvant radiation, and the remaining 15 % received

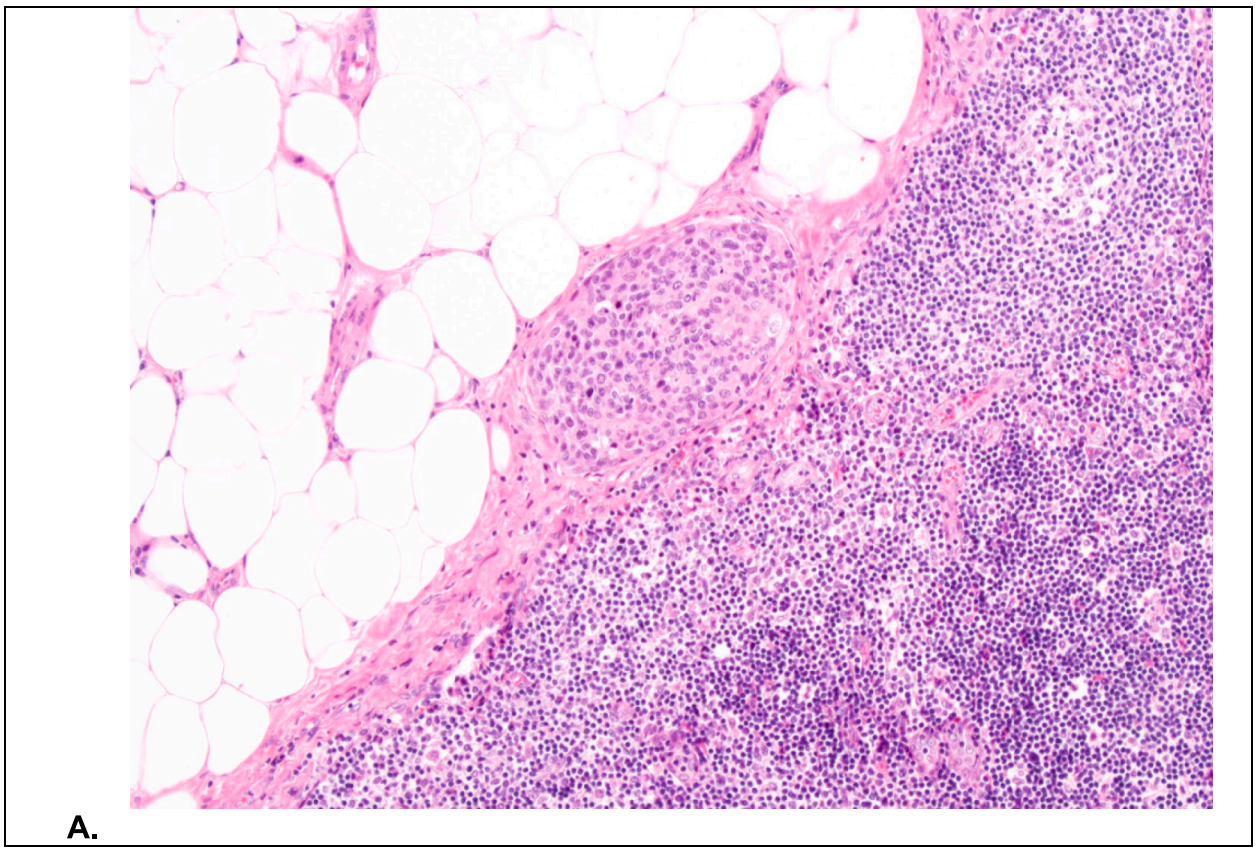

Fig. 1. Histology of micrometastasis on retrospective evaluation.

cisplatin-based chemoradiation (Table 1).

LVM in the form of MM was retrospectively identified in one patient (5 %) (Fig. 1); this patient post-operatively received whole pelvis radiation therapy, completed in 37 days. She went on to experience disease recurrence regionally at the pelvic brim within the irradiated field approximately 11 months after her initial surgery and passed away 12 months after the diagnosis of recurrence. A macrometastases was identified as missed in the initial pathologic evaluation of one other. This was not visualized on the initial tissue cut, however with ultrastaging, the presence of disease meeting size criteria for macrometastasis was appreciated (Fig. 2). The presence of this macrometastasis was not included in calculating the final incidence of LVM. This patient is currently still undergoing treatment for recurrent disease.

4. Discussion

This small retrospective series of surgically managed cervical cancer with intermediate-high risk tumor factors identified only 1 patient with LVM, representing 5 % of the total population. This finding is similar to other studies, which have identified LVM in 5.1–8.1 % of ultrastaged negative nodes (Silva et al., 2005; Juretzka et al., 2004). In intermediate-high risk tumors, in a higher risk patient population who went on to receive adjuvant therapy, there was not significant identification of LVM on ultrastaging. The biologic importance of ITC and LVM remains unclear in cervical cancer, however this investigation highlights the low incidence even when all nodes are evaluated in a higher risk cohort.

The technique of sentinel node sampling in cervical cancer staging is gaining traction, supported by data from SENTICOL-I and SENTICOL-II trials. These two prospective trials supported the diagnostic validity of sentinel node dissection and biopsy with less postoperative morbidity when compared to full lymphadenectomy (Lécuru et al., 2011; Mathevet et al., 2021). Post-hoc analyses have not identified an increased recurrence risk in patients who undergo sentinel node mapping and dissection (Balaya et al., 2022). Ultrastaging nodes detected additional LVM in 10 % of patients as compared to standard pathologic analysis in the secondary analysis of the SENTICOL-1 patients (Guani et al., 2019). In this trial, of the 13 recurrences observed, one patient with micrometastasis developed recurrent disease, one patient with macrometastasis recurred, and the other 11 were all node-negative at time of initial pathologic analysis (Guani et al., 2019). No patients with ITCs present on nodes developed recurrence, and the only statistically significant prognostic factor for recurrence in this cohort was age (Guani et al., 2019). An earlier study by Cibula and colleagues came to similar conclusions regarding ITCs, noting a similar prevalence of ITCs demonstrated across FIGO stages consequently did not result in statistical difference in relapse-free or overall survival, suggesting little clinical utility (Cibula et al., 2012). However, the Cibula study differed notably in that a statistically significant difference in overall survival was observed with micrometastatic disease (Cibula et al., 2012). Micrometastasis as a prognostic factor was found to have a multivariable-adjusted RR of 4.06 ($p = 0.015$), which they note was found to be of greater significance than the FIGO stage in their results (Cibula et al., 2012). This association is likely overstated given the limited power, as addressed by the authors (Cibula et al., 2012). As more providers increasingly utilize sentinel node sampling and ultrastaging, findings of LVM will continue to be identified. The current standard of care does not attach clinical or prognostic significance to findings of LVM, specifically ITC, on surgical pathology (Dostálek et al., 2023; Cervical, 2022; Guani et al., 2020). An improved understanding of this association warrants future investigation. A recently published study in the melanoma literature identified higher risk of disease progression in patients with LVM in sentinel nodes, specifically suggesting these patients may benefit from adjuvant therapy or clinical trial enrollment (Moncrieff et al., 2022).

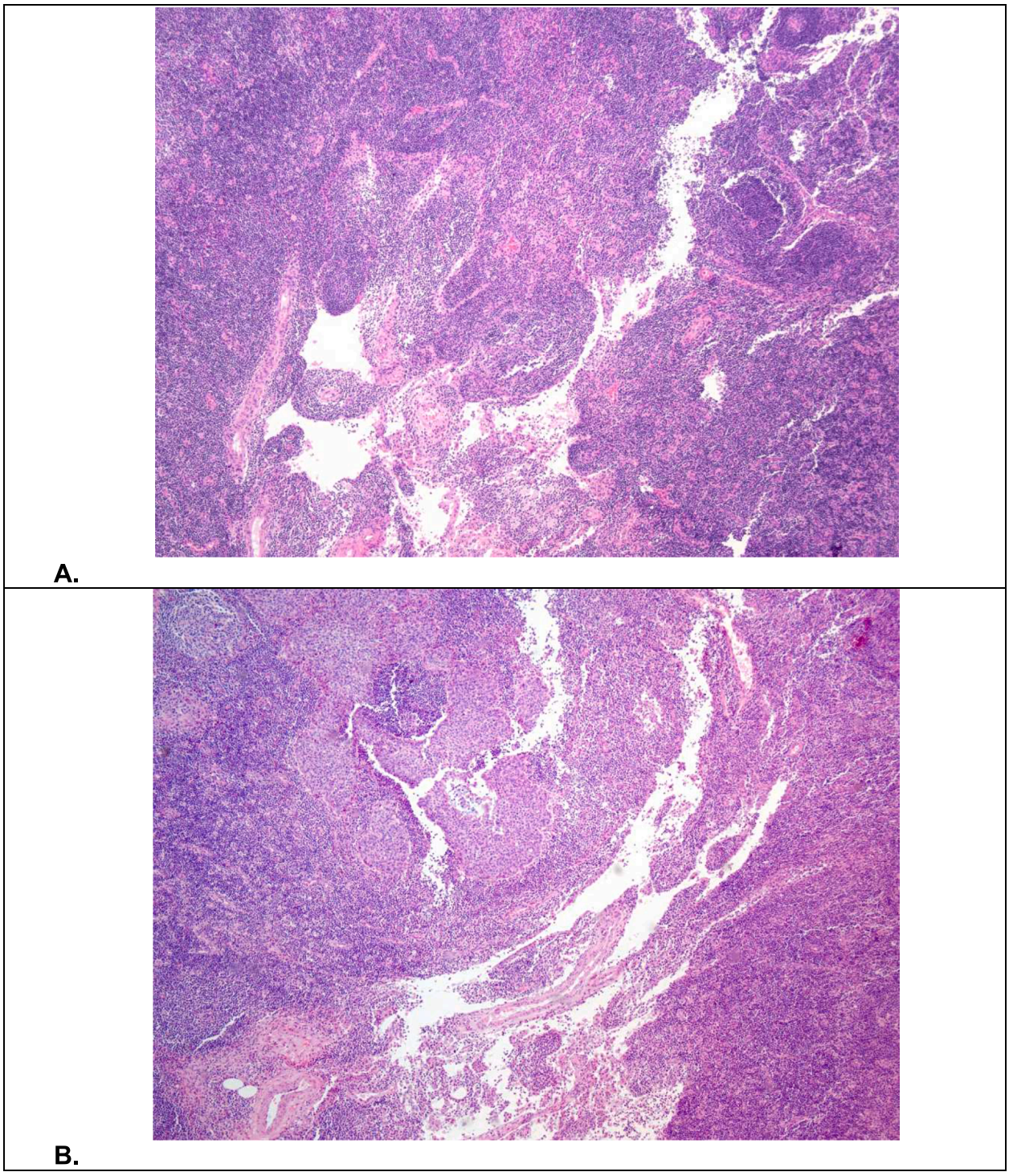

Fig. 2. Histology of macrometastasis on retrospective evaluation.

This current study is the first to retrospectively query the clinical significance of LVM in a subset of node-negative patients that possess intermediate-high risk tumor factors that would meet Sedlis/Peters criteria for adjuvant treatment. Given the 5 % detection rate of LVM in our higher-risk cohort is similar to previous studies with broader inclusion criteria and less of a focus on high-risk features, our findings suggest that ITC may not have clinical significance in a higher-risk cohort. These patients would have been indicated for adjuvant treatment by other high-risk characteristics and treated regardless, and consequently the presence of LVM would not have changed management decisions based on our retrospective analysis.

Our findings suggest that LVM in a higher-risk cohort would not have clinical significance. This study is underpowered to come to any conclusions regarding the prognostic significance of LVM. This shortcoming is not unique to this study, and has been cited as a notable limitation in other reports (Delomenie et al., 2019). In addition, an acknowledged limitation in this study is the inconsistent follow-up time; patients treated towards the end of our included dates (June 2021) will not have

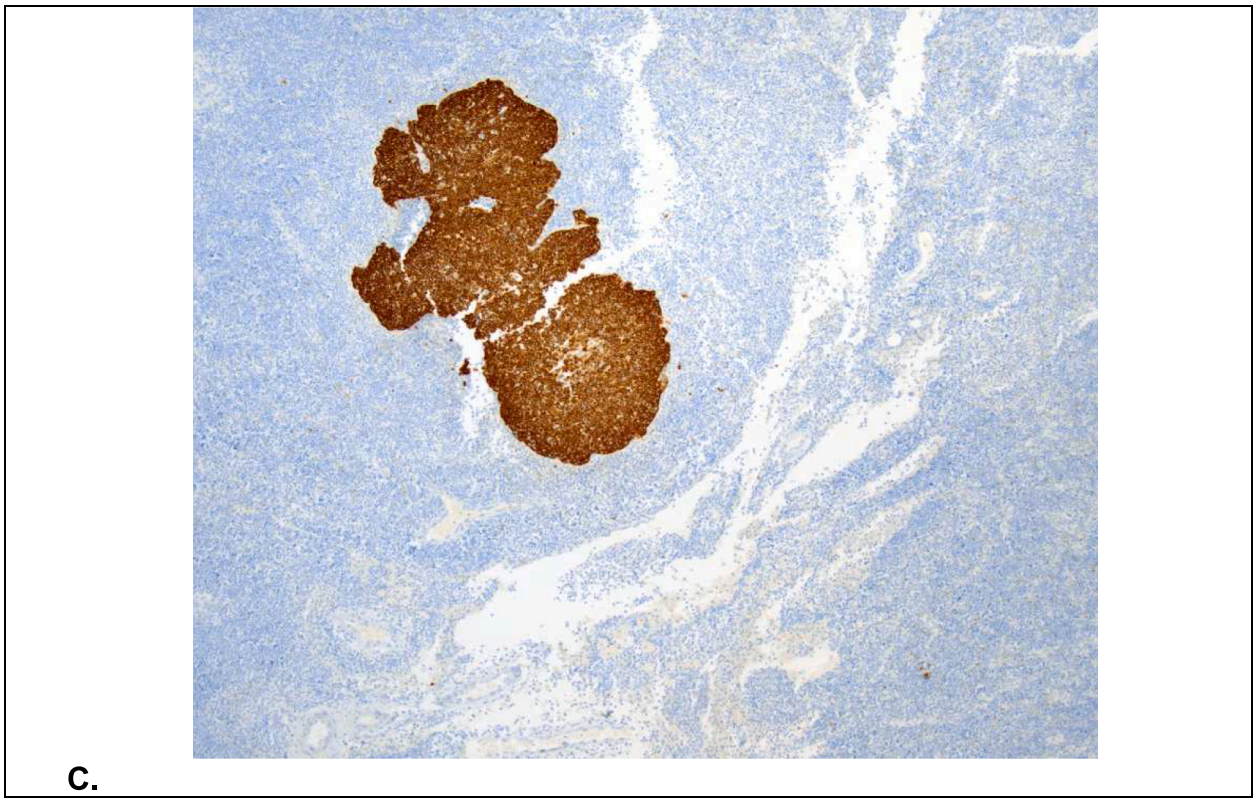

Fig. 2. (*continued*).

as complete follow up and vital status information as those treated earlier in the time frame.

Future opportunities for inquiry include re-defining the size cut-offs for LVM in cervical cancer. These size categorizations were extrapolated from breast cancer literature, and recent studies have suggested disease-free survival may be negatively impacted by micrometastatic nodal disease measuring greater than > 0.4 mm, instead of the currently accepted 0.2 mm cut-off (Dostálek et al., 2023).

5. Conclusion

As ongoing prospective non-inferiority trials continue to evaluate sentinel node mapping and dissection as an alternate standard-of-care to full pelvic lymphadenectomy, the significance of LVM will continue to be a topic of interest. The findings from this retrospective cohort study suggest that in a cohort with traditional intermediate-high risk tumor factors, sentinel nodes in surgical staging will accurately identify patients who meet criteria for post-operative adjuvant therapy, and there is little clinical significance to finding LVM in this population. The prognostic implication remains to be seen and is an area of active interest.

Uncited reference

CRediT authorship contribution statement

Annalyn M. Welp: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Project administration, Writing – original draft, Writing – review & editing. **Mick Crawford:** Data curation, Formal analysis, Investigation. **Rachel O'Brien:** Data curation, Investigation, Project administration. **Stephanie A. Sullivan:** Conceptualization, Supervision, Writing – review & editing. **Linda R. Duska:** Conceptualization, Project administration, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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