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RESEARCH ARTICLE

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Utilization of lymph node evaluation at hysterectomy for cervical carcinoma in situ

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Abstract

Background and Objectives: This study examined the utilization and characteristics of lymph node evaluation at hysterectomy for carcinoma in situ of the uterine cervix.

Methods: This retrospective cohort study queried the Healthcare Cost and Utilization Project's National Inpatient Sample, evaluating 7395 patients with cervical carcinoma in situ who underwent hysterectomy from 2016 to 2019. A multivariable binary logistic regression model was fitted to identify independent characteristics related to lymph node evaluation. A classification-tree was constructed with recursive partitioning analysis to examine utilization patterns of lymph node evaluation.

Results: Lymph node evaluation at hysterectomy was performed in 4.6%. In amultivariable analysis, older age, higher income, use of robotic-assisted hysterectomy, and surgery at large bed capacity or urban teaching centers in the northeast US region were associated with increased likelihood of lymph node evaluation (all, $p < 0.05$). Of those independent factors, robotic-assisted surgery exhibited the largest effect size (adjusted odds ratio 3.23, 95% confidence interval 2.54–4.10). Utilization pattern analysis identified nine unique characteristics, of which robotic-assisted surgery was the primary indicator for cohort allocation (12.4% vs. 3.2%, $p < 0.001$). The difference between the lowest–highest patterns was 33.3% (range, 0%–33.3%).

Conclusion: Lymph node evaluation was rarely performed for cervical carcinoma in situ overall and robotic surgery was associated with increased utilization of lymph node evaluation.

KEYWORDS

adenocarcinoma in situ, cervical carcinoma in situ, cervical intraepithelial neoplasm III, hysterectomy, lymph node evaluation

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1 | INTRODUCTION

Cervical carcinoma in situ is a high-grade, preinvasive lesion of the uterine cervix.[1,2] Treatment typically consists of either cervical excision or hysterectomy.[1,2] A dilemma is that although rare, occult invasive cervical cancer can be identified in the hysterectomy specimen.[1–4] Invasive cervical cancer can be seen in 5%–19% of cases of cervical carcinoma in situ when the cervical excision margin/endocervical curettage is both positive.[2–5]

Cervical carcinoma in situ is the most frequent preoperative diagnosis associated with occult invasive cervical cancer (72%), and the majority of occult cervical cancers are stage I tumors (IA1 33% and IB1 58%) with a mean tumor size of 1.1 cm.[6] In cases of invasive cervical cancer, nodal status confers important information to guide anticancer treatment and predict prognosis. In stage IA disease, lymph node metastasis is seen in 0.7%–2.2% of those who undergo lymph node evaluation.[7–9] The rate is higher in stage IB with tumors (7.4% for ≤2 cm, and 22.2% for >2 cm).[10] In low-risk, early-stage cervical cancer, the incidence rate of lymph node metastasis is 5%.[11]

Owing to this concern for occult invasive cervical cancer with possible nodal involvement in the setting of preoperative cervical carcinoma in situ, the 2020 Society of Gynecologic Oncology (SGO) Evidence-Based Review and Recommendations endorsed by the American Society for Colposcopy and Cervical Pathology (ASCCP) stated that lymph node evaluation at the time of hysterectomy for adenocarcinoma in situ is acceptable but not required and should be tailored per risk factors.[2] Given the paucity of national-level data on surgical practice, the current study examined the utilization and characteristics of lymph node evaluation at hysterectomy for carcinoma in situ of the uterine cervix in the United States.

2 | MATERIALS AND METHODS

2.1 | Data source

The National Inpatient Sample (NIS) was queried for this study. The NIS program is a publicly available and deidentified program that was developed as a part of the Healthcare Cost and Utilization Project, supported by the Agency for Healthcare Research and Quality.[12] The NIS program is a population-based all-payer database for inpatient records that randomly selects 20% of admissions in each hospital, and the weighted data for national estimates represents more than 90% of the US population.[13] The University of Southern California Institutional Review Board deemed this study exempt due to the use of publicly available deidentified data.

2.2 | Study eligibility

This is a retrospective cohort study examining the NIS program from January 2016 to December 2019. This starting point was chosen due to the introduction of International Classification of Disease 10th revision (ICD-10) codes into the NIS program. Patients with carcinoma in situ of the uterine cervix who had hysterectomy were eligible for the study. The patient identification was based on the ICD-10 diagnosis code of D06 that was consistent throughout the study period. The code includes cervical adenocarcinoma in situ and cervical intraepithelial neoplasia III.

Patients with invasive cervical cancer, endometrial cancer, and ovarian cancer were excluded. Patients were also excluded if they did not have a hysterectomy or had no information for surgery. These exclusions were to ensure that lymph node evaluation at hysterectomy was most likely performed for carcinoma in situ of the uterine cervix.

2.3 | Main outcome measure

Performance of lymph node evaluation at hysterectomy was the primary outcome in this study. The ICD-10 codes for lymph node evaluation were based on prior analyses.[14]

2.4 | Study covariates

Among the eligible patients for analysis, patient demographic, hospital characteristics, and treatment information were abstracted from the NIS program. The current study utilized the same ICD-10 codes for the extraction of information that was unchanged during the study period.[14]

(i) Abstracted patient characteristics included age at surgery (continuous), year of surgery (2016, 2017, 2018, and 2019), race and ethnicity (White, Black, Hispanic, Asian, or others) determined per the NIS program, primary expected payer (private including HMO, Medicaid, Medicare, and others), census-level median household income (per quartile), Charlson Comorbidity Index (0 or ≥1) calculated according to prior analysis,[14,15] and obesity (yes or no).
(ii) Treatment information included hysterectomy modality (abdominal, laparoscopic, laparoscopy-assisted vaginal, and vaginal) and use of robotic-assisted surgery (yes or no).
(iii) Hospital characteristics included hospital bed capacity (small, mid, and large), location/teaching status (rural, urban nonteaching, and urban teaching), and regional area (Northeast, Midwest, South, and West).

2.5 | Analytic approach

The performance rate of lymph node evaluation at hysterectomy was determined based on demographic factors. Differences in continuous, ordinal, and categorical variables were assessed with the Mann–Whitney U test, Fisher exact test, or χ^2 test, as appropriate,

in univariable analysis. Temporal trends in lymph node evaluation over time were assessed with multinomial regression model and compared to 2016.

In a multivariable analysis, a binary logistic regression model was fitted to determine independent characteristics associated with lymph node evaluation at hysterectomy. Initial covariate selection was set at a $p < 0.05$ in the univariable analysis. Conditional backward selection was then performed with the stopping rule of $p < 0.05$ in the final model.[16] Effect size for lymph node evaluation was expressed with an adjusted odds ratio with a corresponding 95% confidence interval. Multicollinearity was assessed among the covariates in the model.

Utilization patterns of lymph node evaluation at hysterectomy for cervical carcinoma in situ were assessed by constructing a classification tree with recursive partitioning analysis.[17] All the independent factors for lymph node evaluation in multivariable analysis were entered in the modeling. The chi-square automatic interaction detector method was used with a stopping rule of a maximum of three layers. In the determined terminal nodes, the frequency rate per the study population and the performance rate of lymph node evaluation at hysterectomy were computed.

The weighted values for national estimates provided by the NIS program were used for analysis. Statistical interpretation was based on a two-tailed hypothesis. A $p < 0.05$ was considered statistically significant. IBM SPSS Statistics (version 28.0) was used for all analyses. The Strengthening The Reporting of OBservational Studies in Epidemiology reporting guidelines were consulted to summarize the performance of the cohort study.[18]

3 | RESULTS

3.1 | Cohort characteristics

A total of 7395 patients met the study criteria. The cohort level characteristics are shown in Table 1. The median age was 44 (interquartile range, 37–54) years. The patients were most frequently White (54.8%), privately insured (48.1%), resided in census-level lower household income (61.6%), nonobese (85.7%), and had no comorbidity (69.2%). Abdominal hysterectomy was the most common surgical modality (52.9%), and robotic-assisted hysterectomy was performed in 14.7%. The majority of patients had hysterectomy at centers with large bed capacity (54.6%) and urban teaching settings (65.9%).

3.2 | Factors for nodal evaluation

Overall, 340 (4.6%, 95% confidence interval 4.1–5.1) patients had surgical lymph node evaluation. The utilization of lymph node evaluation at hysterectomy in 2019 was higher compared to 2016 albeit statistically nonsignificant (5.5% vs. 4.2%, odds ratio 1.32, 95% confidence interval 0.99–1.77, $p = 0.060$; Figure 1).

TABLE 1 Patient demographics of lymph node evaluation at hysterectomy

Characteristic	N (%)[a]	Nodal evaluation	p value
No.	7395 (100)	4.6%	
Age (years)	44 (37–54)	48 (39–59)	<0.001
Year			0.118[b]
2016	2380 (32.2)	4.2%	
2017	1950 (26.4)	4.9%	
2018	1425 (19.3)	3.9%	
2019	1640 (22.2)	5.5%	
Race/ethnicity			<0.001
White	4055 (54.8)	5.1%	
Black	1195 (16.2)	5.0%	
Hispanic	1320 (17.8)	2.3%	
Asian	330 (4.5)	6.1%	
Others	495 (6.7)	5.1%	
Primary expected payer			<0.001
Private including HMO	3555 (48.1)	5.1%	
Medicaid	2395 (32.4)	3.5%	
Medicare	885 (12.0)	6.8%	
Others	560 (7.6)	2.7%	
Median household income			<0.001
QT1–2	4555 (61.6)	3.4%	
QT3–4	2725 (36.8)	6.6%	
Unknown	115 (1.6)	[b]	
Charlson comorbidity index			0.016
0	5120 (69.2)	4.2%	
≥1	2275 (30.8)	5.5%	
Obesity			0.204
No	6340 (12.2)	4.7%	
Yes	1055 (14.3)	3.8%	
Hysterectomy type			<0.001
TAH	3915 (52.9)	4.5%	
TLH	1305 (17.6)	7.7%	
LAVH	1330 (18.0)	4.9%	
TVH	845 (11.4)	0	
Robotic-assisted			<0.001
No	6310 (85.3)	3.2%	
Yes	1085 (14.7)	12.4%	

(Continues)

TABLE 1 (Continued)

Characteristic	*N* (%)[a]	Nodal evaluation	*p* value
Hospital bed capacity			<0.001
Small/mid	3360 (45.4)	3.0%	
Large	4035 (54.6)	5.9%	
Hospital setting			<0.001
Rural/urban nonteaching	2525 (34.1)	1.8%	
Urban teaching	4870 (65.9)	6.1%	
Hospital region			<0.001
Northeast	1110 (15.0)	7.2%	
Midwest	1365 (18.5)	5.9%	
South	2960 (40.0)	3.0%	
West	1960 (26.5)	4.6%	

Note: A total of 340 (4.6%) patients underwent lymph node evaluation at hysterectomy.

Abbreviations: HCUP, Healthcare Cost and Utilization Project; LAVH, laparoscopy-assisted vaginal hysterectomy including robotic-assisted; QT, quartile; TAH, total abdominal hysterectomy; TLH, total laparoscopic hysterectomy including robotic-assisted; TVH, total vaginal hysterectomy.

[a]Percentage per row is shown.

[b]Small number suppressed per the HCUP instruction.

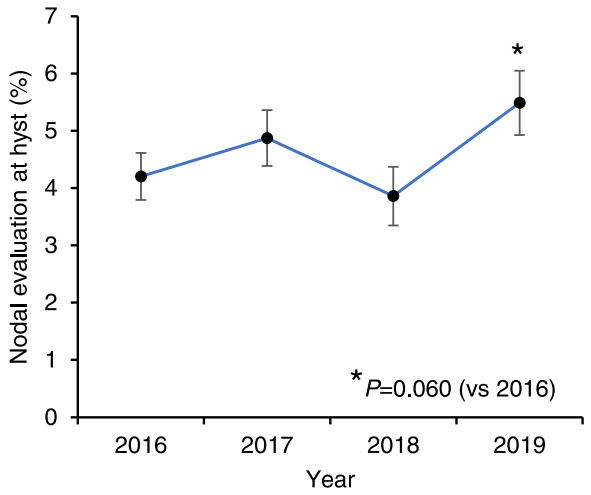

FIGURE 1 Temporal trend of lymph node evaluation at hysterectomy. *$p = 0.060$ for 2019 versus 2016 with a multinomial regression model.

In univariable analysis (Table 1), all the measured covariates except for year and obesity were statistically significantly associated with lymph node evaluation at hysterectomy (all, $p < 0.05$). In a multivariable analysis (Table 2), seven factors were independently associated with lymph node evaluation at hysterectomy. These included age, race/ethnicity, household income, robotic-assisted surgery, hospital bed capacity, hospital teaching/location setting, and hospital regions.

TABLE 2 Independent characteristics related to lymph node evaluation at hysterectomy

Characteristic	aOR (95% CI)[a]	*p* value[a]
Age (years)	1.01 (1.01–1.02)	0.004
Race/ethnicity		0.002*
White	1	
Black	0.95 (0.70–1.30)	0.759
Hispanic	0.43 (0.28–0.64)	<0.001
Asian	0.75 (0.46–1.25)	0.273
Others	0.87 (0.56–1.35)	0.528
Median household income		0.003*
QT1–2	1	
QT3–4	1.53 (1.20–1.94)	<0.001
Unknown	1.37 (0.54–3.47)	0.503
Robotic-assisted		
No	1	
Yes	3.23 (2.54–4.10)	<0.001
Hospital bed capacity		
Small/mid	1	
Large	1.87 (1.46–2.39)	<0.001
Hospital setting		
Rural/urban nonteaching	1	
Urban teaching	2.96 (2.13–4.10)	<0.001
Hospital region		0.003*
Northeast	1.40 (1.01–1.95)	0.045
Midwest	1.14 (0.81–1.60)	0.446
South	0.76 (0.55–1.07)	0.108
West	1	

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; QT, quartile.

[a]Multivariable binary logistic regression model (conditional backward selection with stopping rule of $p < 0.05$).

*Overall *p* value.

Specifically, older age, higher census-level household income, use of robotic-assisted hysterectomy, and surgery at large bed capacity or urban teaching centers in the northeast US region were associated with increased likelihood of lymph node evaluation, while Hispanic patients were less likely to undergo nodal assessment (all, $p < 0.05$; Table 2).

Of those seven independent factors, robotic-assisted surgery exhibited the largest effect size for the performance of lymph node evaluation at hysterectomy for cervical carcinoma in situ (adjusted

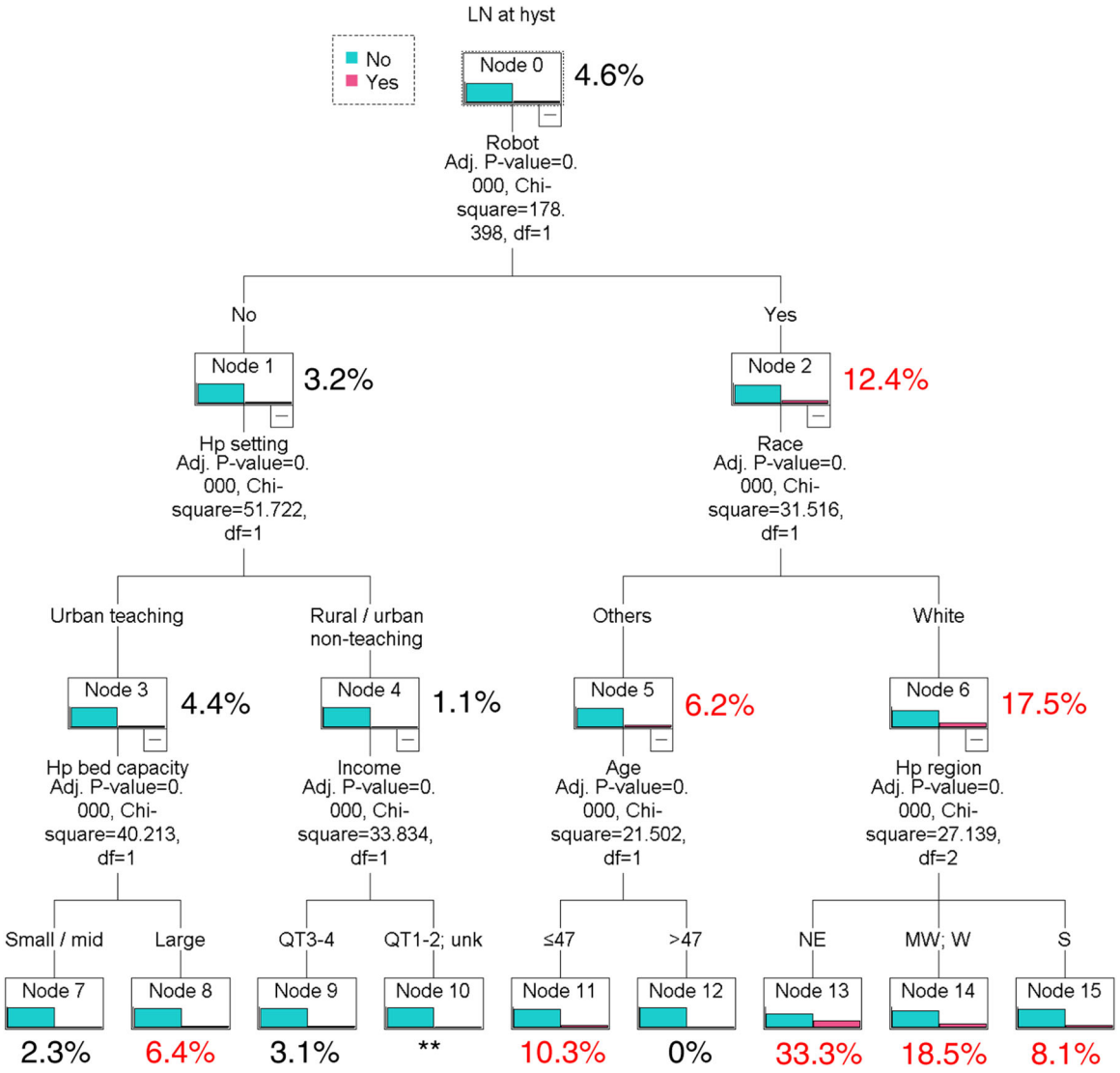

FIGURE 2 Utilization patterns of lymph node evaluation at hysterectomy. A classification-tree was constructed with recursive partitioning analysis (stopping rule of three layers). All the independent characteristics related to nodal evaluation shown in Table 2 were entered in the modeling. Red letters indicate the rate of nodal evaluation, higher than the cohort-level rate of 4.6%. Metadata is shown in Table 3. **Suppressed per the HCUP instruction. Hp, hospital; hyst, hysterectomy; LN, lymph node evaluation; MW, Midwest; NE, Northeast; QT, quartile; S, South; W, West.

odds ratio 3.23, 95% confidence interval 2.54–4.10). This was followed by urban teaching hospital (adjusted-odds ratio 2.96, 95% confidence interval 2.13–4.10; Table 2).

3.3 | Utilization pattern of lymph node evaluation

A classification-tree analysis identified nine unique characteristics of lymph node evaluation at hysterectomy for cervical carcinoma in situ (Figure 2). Of the patterns, robotic-assisted surgery was the primary indicator for cohort allocation (12.4% vs. 3.2%; Figure 2).

Among the nine patterns, three patterns had the lymph nodal evaluation rates exceeding 10% and all were associated with robotic-assisted surgery (10.3%, 18.5%, and 33.3%; Table 3). The rate difference between the highest and lowest groups for lymph node evaluation was 33.3% (range, 0%–33.3%).

4 | DISCUSSION

4.1 | Principal findings

Overall, one in 22 patients with carcinoma in situ of the uterine cervix underwent lymph node evaluation at the time of inpatient hysterectomy from 2016 to 2019. In addition, there was a marked association between robotic-assisted surgery and lymph node evaluation at hysterectomy for cervical carcinoma in situ.

TABLE 3 Classification-tree model for lymph node evaluation at hysterectomy

Tree node	Robotic	Hp teaching	Race	Hp size	Income	Age[a]	Hp region	Tree node (%)	LN (%)
13	Yes		White				NE	1.2	33.3
14	Yes		White				MW, W	4.4	18.5
11	Yes		Non-White			≤47		3.9	10.3
15	Yes		White				S	2.5	8.1
8	No	Urban teaching		Large				28.4	6.4
9	No	Other[b]			QT3–4			8.6	3.1
7	No	Urban teaching		Small, mid				26.3	2.3
10	No	Other[b]			QT1–2, unk			22.0	[c]
12	Yes		Non-White			>47		2.6	0

Note: A classification-tree model for utilization patterns of nodal evaluation at hysterectomy is shown with the descending order of nine discrete patterns (33.0%–0%). In each determined terminal node (Nodes 7–15), the rate of the nodal evaluation was computed. The corresponding model figure is shown in Figure 2.

Abbreviations: HCUP, Healthcare Cost and Utilization Project; Hp, hospital; Income, household income; LN, surgical lymph node evaluation at hysterectomy; MW, Midwest; NE, Northeast; QT, quartile; Robotic, robotic-assisted hysterectomy; S, South; unk, unknown; W, West.

[a]The cutpoint was automated based on the analysis.

[b]Rural area and urban nonteaching.

[c]Small number suppressed per HCUP requirement.

4.2 | Strengths and limitations

Large sample size, national-level analysis, rigorous inclusion/exclusion criteria, and contemporaneous study period relevant to current practice enhanced the interpretation of study findings.

Limitations of the study include lack of information on the indication of lymph node evaluation including shared decision-making between surgeon and patient, lymph node evaluation type (sentinel lymph node biopsy or lymphadenectomy), preoperative information (cervical excision and its surgical margin status, histology subtypes for adenocarcinoma in situ vs. cervical intraepithelial neoplasm III, and endocervical cytology results), hysterectomy type (simple or modified radical), intraoperative findings of nodal appearance (grossly abnormal or normal), histopathology information of sampled lymph nodes, surgeon specialty (gynecologic oncologist or gynecologist), surgical and long-term complications, and quality-of-life measures.

There is also a possibility that a small number of patients with invasive cervical cancer on final pathology and a preoperative diagnosis of preinvasive disease may have been excluded. When invasive cervical cancer cases were included in a post-hoc analysis, patients with invasive cervical cancer were 28 times more likely to undergo lymph node evaluation compared to those without (adjusted odds ratio 28.0, 95% confidence interval 17.6–44.6), implying that the diagnosis of invasive cervical cancer recorded in the database was most likely made preoperatively.

The accuracy of data was not assessable as the actual medical record review was not performed in this study. Trends in outpatient surgery and generalizability in other populations were also unknown. Ascertainment bias due to the data capturing schema is another limitation.

4.3 | Results

Despite these limitations, there are several important findings in the current study. The first key finding was the utilization rate of lymph node evaluation at hysterectomy. In microinvasive cervical cancer, a 2010 meta-analysis reported the utilization of lymph node evaluation of 0%–100% for stage IA1 disease and 38%–100% in stage IA2 disease, respectively.[8] While the rate for in situ disease in the current study was much lower than the invasive disease (overall, 4.6%), as there is a paucity in data on performing lymph node evaluation at hysterectomy for cervical carcinoma in situ,[19] the observed results in this study were somewhat higher than expected, adding new information to the literature.

In addition, this study found that patients who had a robotic-assisted hysterectomy for cervical carcinoma in situ were nearly three times more likely to have lymph node evaluation at surgery. This factor indeed exhibited the largest association for lymph node evaluation among the measured factors in the current study. It is possible that those who underwent lymph node evaluation were via sentinel lymph node biopsy. Performance of nodal evaluation for carcinoma in situ is in line with recent practice trends for invasive cervical cancer.[20,21]

In 2015, the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines for cervical cancer incorporated the use of sentinel lymph node biopsy at invasive cervical cancer surgery for selected patients with the early-stage disease based on mounting data supporting this surgical procedure.[21,22] Since then, the utilization of sentinel lymph node biopsy in stage I cervical cancer has been gradually increasing in recent years in the United States.[20]

It may be possible that, in selected patients with preinvasive cervical cancer with a high suspicion of occult invasive diseases such as adenocarcinoma in situ involving cervical excisional margins and the endocervix, the surgeon and patient may have discussed the risks and benefits of lymph node evaluation at hysterectomy. Decreased early morbidity for lymphatic complications and neurological symptoms with sentinel lymph node biopsy compared to comprehensive lymphadenectomy seen in the invasive cervical cancer trial may have influenced surgeons to offer this surgical procedure in preinvasive cervical cancer with high suspicion of invasive disease.[23]

For some preinvasive gynecological conditions, such as atypical endometrial hyperplasia, there has been a trend towards increasing utilization of surgical nodal evaluation with sentinel lymph node biopsy at the time of hysterectomy.[24] Collectively, these recent trends are likely driven by the increased availability of sentinel lymph node mapping which decreases the morbidity of nodal evaluation.

This study also found that older patients were more likely to undergo lymph node evaluation at the time of hysterectomy. It is speculated that, as older patients were more likely to have positive endocervical cytology at cervical excision and occult invasive cancer in the subsequent hysterectomy,[5] older patients were more likely to have lymph node evaluation at hysterectomy.

Hospital factors appear to have a role in the management of patients with preinvasive cervical cancer. Specifically, patients who had hysterectomy at hospitals with large bed capacity or urban-teaching centers in the northeast region were more likely to have lymph node evaluation at hysterectomy. Adoption of recent SGO guidelines,[2] patient characteristics, access to robotic-assisted surgery, and gynecologic oncologist availability may be likely different across these hospitals, resulting in variability of surgical practice.

4.4 | Clinical implications

There are several areas of clinical relevance and implications based on the current study. First, the results of this study need to be validated in different populations, particularly, the outpatient hysterectomy population. Second, it is necessary to examine if the lymph node evaluation at hysterectomy for preinvasive cervical cancer is performed via sentinel lymph node biopsy.

Third, examining the incidence and risk factors for occult invasive cervical cancer with lymph node metastasis in the setting of preinvasive cervical cancer, similar to prior analyses for preinvasive endometrial cancer,[25] would be of value clinically. Such analysis will triage the patients who ultimately may benefit from lymph nodal evaluation at hysterectomy for preinvasive cervical cancer to avoid the overuse of this surgical procedure.

Last, the use of lymph node evaluation for cervical carcinoma in situ clearly requires further study to examine the long-term risks and benefits of the procedure. Until further data are available, this surgical procedure needs to be used with caution including careful assessment of the possible candidate and patient counseling.

AUTHOR CONTRIBUTIONS

Conceptualization: Koji Matsuo and Jason D. Wright; *Data curation*: Rachel S. Mandelbaum; *Formal analysis*: Koji Matsuo; *Funding acquisition*: Koji Matsuo and Lynda D. Roman; *Investigation*: all authors; *Methodology*: Koji Matsuo and Jason D. Wright; *Project administration*: Koji Matsuo; *Resources*: Koji Matsuo; *Software*: Koji Matsuo and Rachel S. Mandelbaum; *Supervision*: Maximilian Klar, Lynda D. Roman, and Jason D. Wright; *Validation*: Koji Matsuo; *Visualization*: Koji Matsuo; *Writing—original draft*: Koji Matsuo; *Writing—review & editing*: all authors.

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CONFLICTS OF INTEREST

Lynda D. Roman: consultant, Quantgene; Maximilian Klar, consultant, CooperSurgical, KLS Martin, and GlaxosmithKline; Jason D. Wright: research grant, Merck; royalties, UpToDate; all were unrelated to the study. The remaining authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data on which this study is based are publicly available upon request at Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality (https://www.hcup-us.ahrq.gov/nisoverview.jsp).

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