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Conization pathologic features as a predictor of intermediate and high risk features on radical hysterectomy specimens in early stage cervical cancer

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HIGHLIGHTS

- Conization lymphovascular space invasion is associated with high risk final pathology.
- Absence of conization lymphovascular space invasion may be predictive of favorable final pathology.
- Positive conization margins for invasive cancer have a high incidence of intermediate and high risk final pathology.

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ABSTRACT

Objective. The impact of pathologic features of a cone biopsy on the management of women with early stage cervical cancer is understudied. Our objective was to evaluate the additive value of pathologic features of a cone biopsy toward identifying patients with high risk tumors for which adjuvant therapy may be indicated.

Methods. Patients with early stage cervical cancer undergoing a conization followed by radical hysterectomy from 1995 to 2016 were retrospectively identified. Clinical and pathologic data were abstracted from patient medical records.

Results. A total of 115 patients were identified. Based on final pathology, 70.5% were low risk, 10.4% intermediate risk, and 19.1% were high risk. The additive pathologic features of the conization specimen would have reclassified five patients from low into the intermediate risk group. Though depth of invasion did not correlate with final pathology results, when lymphovascular space invasion (LVSI) was present in the conization specimen, 51.2% of patients were noted to meet intermediate/high risk; compared to only 9.5% without LVSI.

Conclusions. In women with early stage cervical cancer, additive pathology of the conization and hysterectomy specimen did not significantly impact risk stratification, only affecting 4.3% of patients. However, presence of LVSI in the conization was associated with intermediate risk criteria in 60% of cases and high risk criteria in 37% of cases. As patients with intermediate/high risk criteria would meet recommendations for adjuvant therapy, the evaluation of LVSI in conization specimens may influence the selection of primary treatment for women with cervical cancer.

1. Introduction

Despite improvements in prevention, screening, and treatment, cervical cancer continues to significantly impact the United States. In 2018, it is estimated there will be 13,240 women with new diagnoses and 4170 deaths from cervical cancer [1]. Survival outcomes are impacted by stage of disease and nodal status, as well as other clinical and pathologic factors [2–6]. In the setting of early stage disease, patients may be candidates for either surgical intervention with radical hysterectomy/trachelectomy and lymphadenectomy or pelvic radiation with concurrent chemotherapy [7–9]. If radical hysterectomy is selected, the need for adjuvant radiation therapy is based on the assessment of surgical

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pathology findings [10–12]. When evaluating the primary tumor, certain levels of tumor size, depth of invasion (DOI), and presence of lymphovascular space invasion (LVSI) can place women in an intermediate risk group, where the risk of cancer recurrence increases to approximately 30%. [2,9–11]. The presence of tumor involvement of the parametria, positive margins, or lymph node metastases increase the risk of recurrence to 50–70% and are known as high risk criteria for recurrence [9,12]. When intermediate or high risk criteria are present, adjuvant therapy, radiation with or without chemotherapy, is advised [2,10–12].

For diagnosis, patients with suspected early stage disease may undergo a cervical conization to identify the presence and extent of invasive disease. The conization may influence the radicality of the definitive surgical intervention. In the setting of the radical hysterectomy/trachelectomy, evaluation for intermediate and high risk pathologic criteria is routine, but the pathology of the conization may not be considered. In the current staging system, information from the conization specimen is not included but may be important both prognostically and in assigning risk groups for adjuvant therapy. Therefore, the objective of this study was to evaluate the tumor characteristics of a conization specimen in addition to the radical hysterectomy pathology for women with early stage cervical cancer.

2. Methods

Approval to conduct this study was obtained from the Institutional Review Board from The Ohio State University Wexner Medical Center. All patients who underwent conization followed by a radical hysterectomy or trachelectomy and lymph node dissection with IA2 to IB2 cervical cancer from 1995 to 2016 were retrospectively identified from electronic medical record databases. Conization was defined as either cold knife conization or loop electrosurgical excision procedure. Patients must have had conization within six months of the radical hysterectomy, had squamous, adenosquamous, or adenocarcinoma of the cervix, and must have been over 18 years of age. Patients missing measurements for some pathology features were included, as long as the measurements that were missing would not have changed the risk group given the known data. All patients were treated at a single institution and all pathology was reviewed by a gynecologic pathologist.

Clinical information abstracted from the medical records included the following: demographic data (age at time of diagnosis and race), surgical procedures performed, disease stage, histology, presence of residual tumor in the hysterectomy specimen, presence of any of the intermediate risk criteria (depth of invasion, lymphovascular space invasion, and tumor size) on conization or hysterectomy specimen and high risk criteria on final pathology. Depth of invasion was based on the summation of the tumor from the two pathology specimens as a percentage of the entire cervical stroma.

Additional data were obtained including follow-up time, receipt of adjuvant treatment, date of recurrence, and survival outcomes. The date of last contact and disease status were recorded as well. Recurrence free survival was defined as date from radical hysterectomy to date of recurrence or death from disease or date of last contact without evidence of disease.

Recurrence risk was analyzed using univariate and multivariate analysis based on intermediate risk criteria from either the radical hysterectomy alone or the conization and radical hysterectomy, or high risk criteria from the radical hysterectomy and lymphadenectomy specimen. A fourth group was designed to evaluate inclusion of the conization specimen on decision for adjuvant therapy with the radical hysterectomy specimen. This group of patients had low risk features on the radical hysterectomy specimen, but would have met intermediate risk criteria when the conization pathologic features were added to the radical hysterectomy specimen (Fig. 1). Kaplan-Meier curves were used to evaluate progression free survival. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

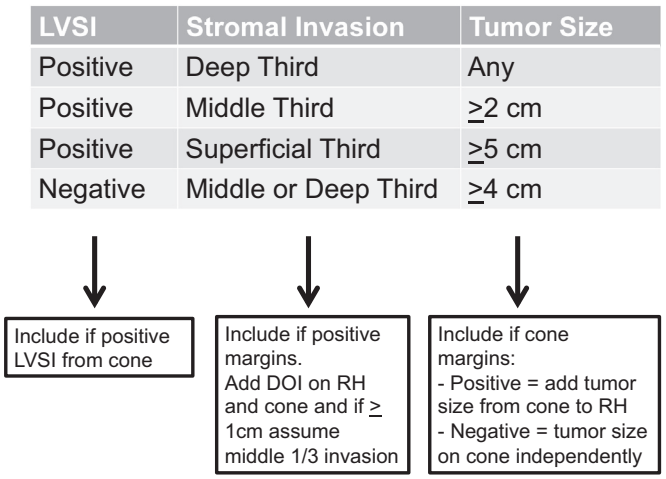

Fig. 1. Criteria for low risk subjects to meet intermediate risk criteria with addition of conization pathologic features. Abbreviations: LVSI = lymphovascular space invasion, DOI = depth of invasion, RH = radical hysterectomy.

3. Results

During the study period, 152 women had a conization followed by radical hysterectomy or trachelectomy. Patients were excluded for incomplete pathologic records (n = 34) and stage IA1 disease (n = 3); the remaining 115 patients met study inclusion criteria. The mean age of patients was 41.8 years and a majority of patients had squamous cell carcinoma (67.8%). Median follow up for the entire cohort was 27.1 months (4.8–43.2 months). Complete demographic and pathologic data are listed in Table 1.

Based on radical hysterectomy pathology, there were 81 (70.5%) low risk, 12 (10.4%) intermediate risk, and 22 (19.1%) high risk patients. When the conization specimen features were added to the hysterectomy specimen results, five (6.2%) patients in the low risk group would have met intermediate risk criteria. Two patients met this criterion with presence of LVSI on conization specimen that was not present on hysterectomy specimen. A third patient met this criterion with presence of conization LVSI and depth of stromal invasion. The last patient met this criterion with both the presence of conization LVSI and conization tumor size alone. Positive conization margins were noted in 48% of patients with low risk criteria, 100% of intermediate risk patients, and 94.7% of high risk patients. All five of the low risk patients who would have met intermediate risk with addition of conization pathology had positive conization margins.

Conization pathologic features were compared with final radical hysterectomy and lymphadenectomy specimens and are reported in Table 2. The median depth of invasion in the conization specimen was similar for subjects with low/intermediate risk and high risk factors, 0.4 cm and 0.5 cm, respectively. Interestingly, 37% of patients with high risk factors on radical hysterectomy specimen had presence of LVSI on conization. In contrast, only 2% of high risk patients did not have LVSI on conization.

Three of the five patients in the low risk group who would have met intermediate risk criteria with addition of conization pathologic features received adjuvant therapy. There were no known recurrences or disease related deaths among these five patients. One patient in the intermediate risk group declined adjuvant therapy and had no evidence of recurrent disease at her last follow up visit. In the intermediate risk group, there were three recurrences and two disease related deaths. In the high risk group, there were five recurrences, five disease related deaths, and two unrelated deaths. At the time of last contact, 98% of the low risk patients were alive without recurrence, 66.7% of the intermediate risk patients were alive without recurrence, and 61.1% of high risk patients were alive without recurrence (Fig. 2).

Table 1
Patient demographic and pathologic data based on final pathology.

Variable (%)	Low (n = 81)	Intermediate (n = 12)	High (n = 22)	Total (n = 115)
Age (years) ± SD	40.3 ± 8.5	50.9 ± 14.2	42.4 ± 11.3	41.8 ± 10.2
Race				
White	61 (75.3)	10 (83.3)	16 (72.7)	87 (75.7)
Non-white	8 (9.9)	1 (8.3)	1 (4.6)	10 (8.7)
Not specified	12 (14.8)	1 (8.3)	5 (22.7)	18 (15.7)
Stage				
IA2	22 (27.2)	0 (0)	1 (4.6)	23 (20.0)
IB1	59 (72.8)	11 (91.7)	18 (81.8)	88 (76.5)
IB2	0 (0)	1 (8.3)	3 (13.6)	4 (3.5)
Histology				
SCC	51 (63.0)	9 (75.0)	18 (81.8)	78 (67.8)
AC	24 (29.6)	3 (25.0)	4 (18.2)	31 (27.0)
AS	6 (7.4)	0 (0)	0 (0)	6 (5.2)
Grade (n = 74)[a]				
Low (1)	11 (24.4)	0 (0)	1 (5.0)	12 (16.2)
High (2 or 3)	34 (75.6)	9 (100)	19 (95.0)	62 (83.8)
Adjuvant therapy				
Yes	3 (3.7)	4 (33.3)	17 (77.3)	24 (20.9)
No	72 (88.9)	7 (58.3)	1 (4.6)	80 (69.6)
Unknown	6 (7.4)	1 (8.3)	4 (18.2)	11 (9.6)
RH residual tumor				
No	54 (66.7)	0 (0)	0 (0)	54 (47.0)
Yes	18 (22.2)	12 (100)	22 (100)	52 (45.2)
Dysplasia	9 (11.7)	0 (0)	0 (0)	0 (0)
Cone tumor size (cm) (n = 84)[a]	0.86 (0.50–1.20)	1.70 (1.40–1.80)	1.50 (1.10–2.20)	1.00 (0.60–1.50)
Cone LVSI (n = 104)[a]				
Positive	20 (26.0)	6 (60.0)	15 (88.2)	41 (39.4)
Negative	57 (74.0)	4 (40.0)	2 (11.8)	63 (60.6)
Cone positive margins (n = 110)[a]				
Positive	38 (48.1)	12 (100)	18 (94.7)	68 (61.8)
Negative	25 (31.7)	0 (0)	0 (0)	25 (22.7)
Dysplasia	16 (20.3)	0 (0)	1 (5.3)	17 (15.5)
Follow-up time (months)	22.4 (4.3–41.9)	36.7 (23.5–38.3)	31.1 (8.6–60.9)	27.1 (4.8–43.2)

Abbreviations: SCC = squamous cell carcinoma, AC = adenocarcinoma, AS = adenosquamous carcinoma.
[a] Missing data.

4. Discussion

Risk of recurrence in early stage cervical cancer varies depending on stage of disease, nodal status (added to the FIGO 2018 staging system), and certain pathologic risk factors [2–6]. Identifying patients who are most likely to benefit from surgery alone may help reduce morbidity from surgery and adjuvant radiation therapy. When occult tumors are present, conization may be performed prior to radical surgery. As recurrence risk is affected by tumor size, LVSI, and depth of stromal invasion, it is unclear if the conization pathologic features influence the final hysterectomy pathology, which may potentially affect the recommendations for adjuvant therapy.

There are few studies that have evaluated several pathologic factors in patients who underwent conization followed by radical hysterectomy with lymphadenectomy for cervical cancer. In regards to margin status, a series of 297 patients, negative conization margins were associated with no residual disease in the hysterectomy in ~98% of cases [13]. Diaz et al. evaluated the predictive value of positive conization margin status, which was associated with residual disease in the final pathology specimen [14]. Similarly, our results noted that 100% of patients with intermediate risk final pathology had positive margin status on conization as did 94.7% of high risk cases. This is in contrast to only 48% of patients with low risk disease. Not surprisingly, patients who had no residual disease had negative margins in 100% of cases.

Table 2
Impact of lymphovascular space invasion on conization specimen with final pathology.

	High risk	+ Margins	+ Lymph nodes	+ Parametria
+ LVSI on cone	15 (37%)	1 (2.5%)	12 (29%)	9 (22%)
− LVSI on cone	2 (3%)	0 (0%)	2 (3%)	1 (2%)

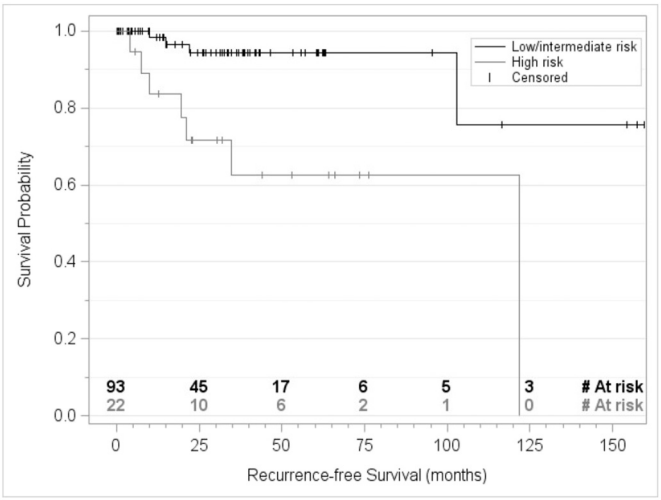

Fig. 2. Recurrence-free survival of patients in the low and intermediate risk groups and the high risk group.

In patients with IB1 disease (FIGO 1995 staging), Kim and colleagues noted that a depth of invasion (>5 mm) correlated with parametrial involvement in 15.3% and lymph node metastases in 23% [5]. Depth of stromal invasion was similar across patients with low, intermediate, or high risk disease. Our study did report the finding of larger conization tumor size was associated with intermediate risk (median 1.7 cm) and high risk (median 1.5 cm) compared to low risk (median 0.9 cm) criteria.

While there was no correlation with depth of invasion or additive tumor size to final pathology high risk features, our study did indicate an association of LVSI on conization and lymph node metastases. In this study, 41 (39.4)% of patients were noted to have positive LVSI in the conization specimen. Strikingly, when LVSI was noted in the conization specimen, the presence of positive lymph node metastases was detected in 29% of the cases. On the contrary, when conization LVSI was not present, only 2% of patients were noted to have any one of the high risk criteria. However, it should be noted that 26% of low risk patients also had LVSI on the conization specimen. Bidus and colleagues evaluated cervical biopsy or conization specimens prior to definitive surgery and noted that the pre-hysterectomy sampling had poor sensitivity and low negative predictive value for the presence of LVSI in the final specimen [15]. In another series, it was reported that the sensitivity of conization margin status to predict LVSI in the final hysterectomy specimen was only 70%; however, they did not directly comment on LVSI in the conization specimen [13]. Though the lymph node metastases rate was not reported, Kim and colleagues noted that depth of invasion, which was associated with the high risk criteria of parametrial involvement, also correlated with the presence of LVSI (55.3%) in the conization specimen [5]. In addition to a correlation with lymph node positivity, a prior study from our institution also reported that presence of LVSI in the conization specimen was significantly associated with positive parametrial involvement [16]. Therefore, the presence of LVSI in the conization specimen may represent the presence of high risk criteria (parametrial or lymph node involvement) in final pathology and may influence the treatment approach.

As a retrospective study, there are inherent limitations that should be recognized. Though every effort was made to include all eligible patients and review all records, selection and sample bias may be present. The exclusion of patients with incomplete data may also affect the results of the study. Testing for statistical significance was not performed due to small counts in some groups and only rare instances of death or

disease recurrence in our cohort. The patient cohort was evaluated from a single institution and data obtained from multiple institutions or in a prospective fashion may provide more definitive conclusions. Lastly, we selected patients based on conization which limits the population to those with small or not readily visible tumors, which accounts for the small numbers of cases. Despite these potential limitations, this study adds to the existing literature regarding the potential prognostic implications of conization in conjunction with radical hysterectomy specimens.

In conclusion, this study is unable to determine if pathology findings of tumor size and depth of invasion on conization impact the final pathology characteristics of a radical hysterectomy. However, when LVSI is present in the conization specimen, patients are more likely to meet intermediate or high risk criteria for risk of recurrence. These findings may help provide guidance on the selection of primary therapy in patients with presumed early stage cervical cancer undergoing conization.

Conflict of interest statement

All of the authors have completed the disclosure form and all authors have no conflict of interest with the content of the manuscript.

Author contributions

Megan L Hutchcraft conceived project, collected data, analyzed data, prepared manuscript and figures. Blair Smith conceived project and collected data. Eric M McLaughlin and Erinn M Hade analyzed data and prepared figures and reviewed the manuscript. Floor J Backes, David M O'Malley, David E Cohn, Jeffrey M Fowler, and Larry J Copeland reviewed and edited manuscript. Ritu Salani conceived project and prepared manuscript. All authors approved the final manuscript.

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