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Extent of Lymphovascular Space Invasion May Predict Lymph Node Metastasis in Uterine Serous Carcinoma

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Abstract

Objectives—Emerging evidence suggests that extent of lymphovascular space invasion (LVSI) predicts for risk of lymph node metastasis in endometrioid uterine cancers. However, this correlation remains unknown in the setting of uterine serous carcinoma (USC). We sought to examine the association between extent of LVSI and other histopathologic characteristics with risk of nodal metastasis for women with USC.

Materials/Methods—Pathological data from all cases of uterine serous carcinoma between July 1998 to July 2015 at our institution were reviewed. Descriptive, univariate, and multivariate logistic regression analysis of selected pathologic features were performed.

Results—88 patients with USC underwent total abdominal or laparoscopic hysterectomy, bilateral salpingo-oophorectomy, and selective lymphadenectomy. Surgical staging revealed the following FIGO stage distributions: I (41%), II (8%), III (32%), IV (19%). LVSI was present in 44 (50%) patients. 36 patients (41%) had LN metastases with median number of total nodes removed of 17 (range, 1–49). On univariate analysis, depth of myometrial invasion, LVSI, tumor size, and cervical stromal involvement were significantly associated with nodal involvement. In a multivariate model, LVSI (OR 6.25, 95% CI 2.2–18.0, $p < 0.01$) and cervical stromal involvement (OR 3.33, 95% CI 1.10–10.0, $p = 0.03$) were the only factors that remained significant. Among patients with LVSI-positive disease, extensive LVSI was associated with increased risk of nodal involvement compared to focal LVSI (90% vs 29%, $p = 0.04$).

Conclusions—Presence and extent of LVSI, and cervical stromal invasion are important predictors for lymph node metastasis in uterine serous carcinoma.

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Introduction

Uterine cancer is the most common gynecologic malignancy of women from developed countries and the second most common in developing countries, with an estimated incidence of over 61,300 new cases in the United States in 2017 (1). While endometrioid carcinoma is the most common histology in endometrial cancers, uterine serous carcinoma (USC) is a rare and aggressive histology associated with poor outcomes (2). Integrated genomic characterization shows that USC exhibits extensive somatic copy number alterations, few DNA methylation changes, low estrogen/progesterone receptor levels, and high frequency of TP53 mutations, thus sharing similar molecular features with high grade serous ovarian carcinoma and basal-like breast cancer (3). Multiple groups have reported on the propensity of early nodal metastasis in USC, with significantly higher rates of pelvic and para-aortic lymph node (LN) metastasis compared with endometrioid carcinomas (4,5). Given its aggressive nature and distinct profile, USC presents unique challenges in determining optimal treatment, even for early stage patients.

Typically, primary treatment for uterine cancer patients eligible for surgery includes total hysterectomy with bilateral salpingo-oophorectomy (TH/BSO), pelvic and para-aortic lymph node (LN) assessment, and omental biopsy or omentectomy, and given the aggressive nature of USC most patients also receive chemotherapy and many also receive radiotherapy (RT) (6). Histopathologic factors obtained from the hysterectomy specimen provide critical information that allows clinicians to risk stratify and determine appropriate adjuvant treatment for patients. One such factor is lymphovascular space invasion (LVSI), which has been shown to be associated with increased risk of nodal metastases and worsened survival outcomes in women with endometrial cancer (7–11). However for women with USC, evidence suggests that traditional clinicopathologic risk factors, such as depth of myometrial invasion (12–14), may be much less helpful for risk stratification, and that alternative prognostic markers based on novel techniques are needed to better identify patients who could benefit from adjuvant therapy (15).

In the majority of studies in the literature, LVSI is typically classified in a qualitative (present vs. absent) rather than quantitative manner (extensive vs. focal). Limited but emerging evidence suggests that extent of LVSI predicts for risk of lymph node metastasis in endometrial cancers with endometrioid or other favorable histologies (9,16,17). In a pooled analysis of the PORTEC-1 and 2 trials, Bosse et al. determined that a 3-tiered quantification system for LVSI (none, focal, substantial) was most predictive for risk of distant metastases (18). Notably the proportion of patients with USC in PORTEC-1 was < 1%, and such patients were excluded from PORTEC-2 (19,20). Overall, the association between extent of LVSI and lymph node metastases remains unknown in the setting of USC. We undertook this study to examine how the extent of LVSI and other histopathologic characteristics of hysterectomy specimens predict for lymph nodes metastasis for women with serous endometrial carcinoma of the uterus.

Methods

Patient Population

With institutional review board approval, we retrospectively examined pathological data from consecutive cases of uterine serous carcinoma (July 1998 to July 2015) reviewed at our institution. Patients were included if they underwent at least a total abdominal or laparoscopic hysterectomy, bilateral salpingo-oophorectomy, and lymph node sampling or dissection. At our institution, the extent of lymph node dissection was at the surgeon's discretion. For mixed tumors, diagnosis of USC was made when there was at least 10% serous component found in the hysterectomy specimen.

Pathology Data Abstraction

Pathologic data were abstracted from the pathology reports and included tumor size and histology; stage; myometrium invasion; presence and extent of lymphovascular space invasion; involvement of the cervical stroma, adnexa, vagina, parametrium, serosa, bladder, bowel or omentum; peritoneal cytology; and number of lymph nodes sampled and involved. There is no standard pathologic reporting format for the extent of LVSI. At our institution, the presence of LVSI in the pathology report is sometimes accompanied by a modifier describing it as "focal" or "extensive". These terms do not have set definitions. However, "focal" generally describes 1–2 small foci of LVSI on a single slide, while "extensive" generally describes multiple foci (≥ 3) on more than one slide. Figure 1 shows representative histologic images illustrating what would be considered extensive LVSI. Many reports mention that LVSI is present but do not offer a quantitative description; for the purposes of this analysis, these were referred to as "intermediate," with the understanding that the extent of LVSI is unknown. Staging was assigned according to the FIGO 2009 staging system for endometrial cancer (21).

Statistical Analysis

Univariate and multivariate logistic regression analysis was performed to test the association between pathologic features and risk of lymph node involvement in our cohort of women with USC. Fisher's exact test was used to assess association between extent of LVSI and nodal involvement. A reverse stepwise selection process was used to construct our multivariate model, retaining only variables deemed clinically relevant with $p < 0.1$.

Given controversies in the number of lymph nodes removed for adequate lymph node dissection (22,23), we conducted a sensitivity analysis whereby we included only patients with 10 or more dissected nodes in our models. All statistical tests were two-sided, and a p -value of < 0.05 was considered significant. Statistical analysis was performed using SAS software (SAS Institute, Cary, NC, version 9.4).

Results

Patient and Pathological Characteristics

We identified 88 patients who fulfilled criteria for this study, with detailed pathologic features at the time of surgical staging listed in Table 1. Median age was 69 years (range 50–

84) at time of surgical staging. No patient had prior treatment for endometrial cancer. In terms of histology, 77 patients (87.5%) had pure uterine serous tumors, 5 patients (5.7%) had mixed serous and endometrioid carcinoma, 5 patients (5.7%) had mixed serous and clear cell carcinoma, and 1 patient (1.1%) had mixed serous, clear cell, and endometrioid carcinoma.

While pelvic nodes were sampled in all cases, paraaortic nodes were sampled in 61 (69%) cases. The median number of total lymph nodes removed was 17 (range, 1–49). Of 36 (41%) patients with metastasis to lymph nodes, 31 patients (35%) had pelvic lymph node metastases, 11 patients (13%) had both pelvic and paraaortic lymph node metastases, and 5 patients (6%) had isolated paraaortic metastases. Seventeen patients (19%) had stage IV disease, with all patients having either bowel, bladder and/or omental involvement. One patient had distant disease involving lymph nodes in the neck and thorax.

LVSI was present in 44 (50%) patients, with 7 (8%) cases of focal LVSI, 27 (31%) cases of intermediate LVSI, and 10 (11%) cases of extensive LVSI. Notably, 90% of patients with extensive LVSI had LN involvement, compared to 59% for intermediate LVSI, and 29% for focal LVSI (Table 2) ($p = 0.04$). Of the nine patients with extensive LVSI and lymph node involvement, two (22%) had depth of myometrial invasion limited to the inner half; eight (89%) patients, including the above two with superficially invasive disease, had cervical stromal involvement. Rate of nodal metastasis was 61% in patients with LVSI, compared to 17% in those without LVSI. When limited to only patients with Stage IV disease, LVSI was present in 12 (71%) of patients.

Univariate and multivariate predictors for lymph node involvement

Univariate analysis revealed that LVSI, cervical stromal involvement, tumor size (> 2 cm vs. ≤ 2 cm), and $\geq 1/2$ myometrial invasion predicted for lymph node involvement. Age (at surgical staging) did not predict for lymph node involvement. In a multivariate model, LVSI (OR 6.25, 95% CI 2.2–18.0, $p < 0.01$) and cervical stromal involvement (OR 3.33, 95% CI 1.10–10.0, $p = 0.03$) again remained significant predictors of lymph node involvement, and tumor size and myometrial invasion were no longer significant, when considered together with other factors in the multivariate model (Table 3). Notably, all eight women with extensive LVSI and cervical stromal invasion had lymph node involvement compared to one of five women with focal LVSI without cervical stromal involvement (Table 4).

Sensitivity analysis

When we limited our analysis to only those patients who had 10 or more lymph nodes removed ($n = 69$, 78.4%), LVSI (OR 11.14, 95% CI 2.1–58.6, $p < 0.01$) remained significantly associated with lymph node involvement, while cervical stromal involvement (OR 3.82, 95% CI 0.9–16.7, $p = 0.07$) showed a trend towards significance, likely due to decreased power (Supplementary Table 1).

Discussion

Our study shows that both LVSI and cervical stromal involvement are important predictors of lymph node metastasis in women with USC. Beyond presence of LVSI, the quantitative

extent of LVSI provides further prognostic information about risk of nodal involvement. Furthermore, risk of nodal involvement may be significant despite absence of myometrial invasion. These findings are particularly significant because identification of women diagnosed with USC at high risk of lymph node metastasis can assist clinicians in risk stratification and ultimately help guide adjuvant therapy.

Given its rarity and limited data, significant uncertainty exists about the most appropriate management for uterine serous cancer. The NCCN lists a variety of adjuvant treatment options for Stage IA patients with USC, including observation, chemotherapy alone, chemotherapy with vaginal brachytherapy, external beam radiation therapy (EBRT) alone or EBRT plus vaginal brachytherapy. For stages IB-IV, NCCN suggests treatment can include chemotherapy +/- EBRT +/- brachytherapy (6). Meanwhile, the Society of Gynecologic Oncology (SGO) recommends a more aggressive approach with chemotherapy +/- vaginal brachytherapy for stage IA disease, with consideration of additional pelvic EBRT for stage IB-II disease (24).

Although whole abdominal radiotherapy (WART) has been used in the past for early stage patients such as in GOG 94 (25), the current trend is a move towards adjuvant chemotherapy coupled with tumor-directed RT. A multi-institutional consortium study of 206 women with stage I-II USC patients showed that chemotherapy improves progression-free and overall survival (24). The Rare Cancer Network reported outcomes on 138 women with USC. In their study, a subset of patients underwent combined modality therapy, with platinum based-chemotherapy and varying field sizes of adjuvant RT (23% WART, 51% pelvic field). The study demonstrated that chemotherapy improves disease specific survival, RT reduces pelvic recurrences, and that combined modality chemotherapy with pelvic RT can be an appropriate adjuvant treatment approach (26). Given the widespread use of adjuvant chemotherapy even for early stage patients, the value of direct assessment or prediction of nodal status may potentially lie in guiding adjuvant radiotherapy treatment. A pooled analysis of endometrioid endometrial cancer patients enrolled in the PORTEC-1 and 2 trials demonstrated that women with substantial LVSI who received vaginal brachytherapy alone or no adjuvant therapy had a 25–30% risk of 5-year pelvic recurrence, which was reduced to 5% with external beam radiotherapy (18). It may be possible that a similar benefit in pelvic control may exist with use of pelvic radiotherapy in USC patients with extensive LVSI.

Our study has several strengths and limitations. Given the rarity of USC, we present a large series of consecutive patients treated at our institution over time. To our knowledge, there has been no other dedicated series evaluating extent of LVSI with LN involvement risk in a cohort of predominately USC patients. Our study is consistent with limited but emerging reports on similar associations between extent of LVSI and LN risk in the setting of endometrioid endometrial cancer (9,16–18). Bosse et al. evaluated quantification by 2-, 3-, and 4-tiered scoring systems and determined that a 3-tiered system (none, focal, substantial) provided the optimal prognostic utility, and confirmed that increased extent of LVSI resulted in higher risk of disease recurrence in patients with endometrioid endometrial cancer enrolled in the PORTEC-1 and 2 trials (18). Our results are also in accord with multiple studies showing that nodal metastasis risk may be significant despite absence of myometrial invasion (12–14).

It should be noted that in our study, the majority of LVSI cases (27 of 44) were designated with the “intermediate” modifier, which refers to present but unspecified extent of LVSI, as exact quantification or grading was not mentioned in the pathology report. Furthermore, heterogeneity across different pathologists’ assessment of the extent of LVSI could potentially contribute more variability in the unspecified category versus the extremes of focal or extensive. It is not currently the practice in pathology to quantify LVSI according to standardized criteria; however, the findings from this and other studies suggest that this would be useful. This could be as simple as using a modifier for extent of LVSI in the synoptic table of focal (1–2 foci on one slide), moderate (> 3 foci on one slide), or extensive (multiple foci on more than one slide). It should be noted that these are only proposed cut-offs, and will require further validation and study.

Proper pathological classification is essential for diagnosis and treatment. We used standard criteria, taking into account morphologic features, immunophenotype, and pattern of involvement to identify the primary site and prevent misclassification of ovarian cancer as endometrial cancer. In cases where tumor involves both the ovaries and the endometrium, extensive uterine involvement (deeply invasive) with LVSI with superficial involvement of the ovary favors endometrial origin. Conversely, extensive peritoneal and ovarian involvement with only superficial tumor in the endometrium favors an ovarian origin. In other cases with ovarian involvement, tumor found in the medulla while sparing the cortex, or tumor limited only to the vascular spaces of the ovary, also favors a metastatic process as opposed to a primary ovarian malignancy.

It should also be noted that frequent mimics of LVSI include smear artifacts, retraction artifacts, and microcystic, elongated and fragmented (MELF)-type invasion (27). In brief, true LVSI involves smooth bordered and cohesive clusters of tumor cells that conform to the contours of the vascular space. These cells often have more eosinophilic cytoplasm and are often present in lymphatic spaces adjacent to larger vessels. In contrast, disaggregated tumor cells intermixed with inflammation, floating freely or in fragments in the vascular space, with similar morphology to the main tumor mass, and present in spaces adjacent to the invasive tumor bulk, likely reflect artefactual vascular space involvement (28). Prior to adoption of a novel quantification method for characterizing the extent of LVSI, the gynecologic pathology community should adopt a consensus approach to address these aspects in order to reduce false positive reporting of LVSI.

In our study, 19 (21.6%) patients had < 10 lymph nodes removed. Given the controversy regarding the required number of dissected LNs in an adequate lymphadenectomy (22,23), we conducted another sensitivity analysis in endometrial cancer patients by excluding that subset of patients and thus including only those with ≥ 10 LN removed. LVSI remained a significant predictor of LN involvement, while cervical stromal involvement trended toward significance, likely due to decreased power.

Ultimately, our study shows that extent of LVSI and cervical stromal invasion are important predictors for nodal metastasis in USC. Additional studies incorporating clinical outcomes, including rates of local recurrence, could further strengthen the importance of these histopathologic factors for women with USC. With further validating studies demonstrating

its predictive utility, extent of LVSI could be used to guide potential adjuvant treatment options. Given the widespread use of adjuvant chemotherapy regardless of stage in the management of USC (24), the value of extent of LVSI as a predictor for nodal status may ultimately be in identifying women at particularly high risk who may benefit from pelvic radiotherapy.

Conclusion

Emerging evidence suggests that quantitative extent of LVSI predicts for risk of lymph node metastasis in endometrioid uterine cancers. Given the low incidence of USC, this and other correlations between pathologic features and clinical aggressiveness remains incompletely understood. We found that USC has a high propensity for lymph node metastases even in the absence of myometrial invasion, with LVSI and cervical stromal involvement as the most significant pathologic factors predicting for nodal metastases. Furthermore, the extent of LVSI provides additional prognostic information with 90% of patients with extensive LVSI having nodal metastases versus 29% with focal LVSI ($p = 0.04$). Given this difference, we propose that pathologists begin systematically and consistently commenting on the extent of LVSI in endometrial cancer in order to gather more data on its prognostic significance. Patients with USC found to have extensive LVSI and/or cervical stromal involvement in the hysterectomy specimen, who are unable to or undergo only minimal lymph node sampling, may be at high risk of nodal involvement, and may benefit from consideration of additional treatment such as pelvic radiotherapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- USC has a high propensity for nodal spread even in absence of myometrial invasion
- LVSI and cervical stromal involvement predict for lymph node metastases in USC
- Extent of LVSI provides further prognostic information on risk of nodal involvement

Figure 1. Representative histologic images from cases with extent of LVSI reported as “extensive” (10x objective). All four cases (A–D) showed outer half or full thickness invasion of the uterine wall and positive lymph node involvement. All pictures show at least 6 foci of LVSI (arrows) in one 10x field; these cases have multiple areas with this appearance.

Table 1

Pathologic Features of Tumor from Patients with Uterine Serous Carcinoma

Pathologic Features	Serous N (%)
All patients	88
FIGO Stage (2009)	
I	36 (41%)
IA	29 (33%)
IB	7 (8%)
II	7 (8%)
III	28 (32.2%)
IIIA	4 (5%)
IIIB	0 (0%)
IIIC1	15 (17%)
IIIC2	9 (10.2%)
IV	17 (19.3%)
IVA	2 (2.2%)
IVB	15 (17.1%)
LVSI	
Present	44 (50%)
Focal	7 (8%)
Intermediate	27 (30.7%)
Extensive	10 (11.3%)
Not reported	3 (3%)
Depth of Myometrial Invasion	
None	1 (0.3%)
< 50%	48 (54.6%)
50%	39 (44.3%)
Tumor Size (median, range)	3.4 (0.3–18.6)
Tumor Size Categories	
Tumor size > 2 cm	59 (67.1%)
Tumor size ≤ 2 cm	15 (17.1%)
Not reported	14 (15.9%)
Cervical Stromal Involvement	
Present	26 (29.6%)
Adnexal Involvement	26 (29.6%)
Serosal Involvement	11 (12.5%)
Vaginal Involvement	3 (3.4%)
Parametrial Involvement	5 (1.3%)
Involvement of GI/GU Structures	
Bladder Involvement	11 (12.5%)
Bowel Involvement	2 (2.3%)
Omental Involvement	15 (17.1%)

Pathologic Features	Serous N (%)
Peritoneal Cytology	
Positive	20 (22.7%)
Atypical	1 (1.1%)
Not performed	19 (21.6%)
Lymph Nodes	
Lymph Node Involvement	36 (41%)
Total Number Removed (median, interquartile range)	17 (10.5–26)
10 Lymph Nodes Removed	69 (78.4%)

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; LVSI, lymphovascular space involvement; GI, gastrointestinal; GU, genitourinary

Table 2

Risk of Lymph Node Involvement by Extent of Lymphovascular Space Invasion in Uterine Serous Carcinoma Patients with LVSI-Positive Disease (44 patients).

	Extent of LVSI			p-value *
	Focal	Intermediate	Extensive	
Patients with nodal involvement (#/total patients) (%)	2/7 (29%)	16/27 (59%)	9/10 (90%)	p = 0.04

* p – Fisher's Exact Test

Univariate and multivariate analysis for lymph node involvement in patients with Uterine Serous Carcinomas. A reverse stepwise selection process was used to construct our multivariate model, retaining only variables with $p < 0.1$.

Table 3

Features	Univariate			Multivariate		
	OR	95% CI	p	OR	95% CI	p
Age at Surgical Staging	0.99*	0.93–1.05	0.76	–	–	–
Myometrium Invasion < 50% (vs 50%)	0.258	0.11–0.64	<0.01	–	–	–
LVS1 Present	7.71	2.80–21.3	<0.01	6.25	2.2–18.0	<0.01
Tumor Size > 2 cm vs 2 cm)	0.18	0.04–0.88	0.03	–	–	–
Cervical Stromal Involvement	5.5	2.03–14.91	<0.01	3.33	1.10–10.0	0.03

Abbreviation: LVS1, lymphovascular space involvement

* Per one year increase in age

Table 4

Risk of Lymph Node Involvement by Lymphovascular Space Invasion and Cervical Stromal Involvement in Uterine Serous Carcinoma (85 patients).

Patients with nodal involvement (#/total patients)(%)	LVSI			
	Absent	Focal	Intermediate	Extensive
Cervical Stromal Invasion				
Absent	7/35 (20%)	1/5 (20%)	9/19 (47%)	1/2 (50%)
Present	0/6 (0%)	1/2 (50%)	7/8 (88%)	8/8 (100%)

* 3 patients for whom LVSI was not reported were excluded from this Table