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Impact of Depth and Extent of Lymphovascular Space Invasion on Lymph Node Metastasis and Recurrence Patterns in Endometrial Cancer

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Abstract

Background and Objectives—To determine the significance of depth and extent of lymphovascular space invasion (LVSI) on lymph node metastasis and recurrence in endometrial cancer.

Methods—A case-control study was conducted to examine LVSI-positive (n=70) and LVSI-negative (n=641) stage I–III endometrial cancer cases that underwent hysterectomy-based surgical staging. The risk of lymph node metastasis and distant recurrence was estimated based on LVSI patterns.

Results—In multivariate analysis, deep (>50% invasion), and extensive (≥7 foci/slide) LVSI patterns had a significantly increased risk of lymph node metastasis (incidence 57.6% and 72.7%, odds ratio 33.8 and 49.9, respectively, $P<0.001$) as compared to other traditional uterine factors (>50% myometrial tumor invasion, cervical stromal invasion, and adnexal involvement: incidence range 30.4–37.9%, odds ratio range 3.80–7.03). Deep and extensive of LVSI patterns were both significantly correlated to distant recurrence ($P<0.001$). Among women who received postoperative chemotherapy, deep and extensive LVSI patterns did not have increased risks for distant recurrence compared to no LVSI ($P=0.47$ and 0.32, respectively). Among women who received postoperative radiotherapy, the depth of LVSI was significantly associated with recurrence outside the radiated field ($P=0.02$).

Conclusions—Depth and extent of LVSI are important predictors for lymph node metastasis and distant recurrence in endometrial cancer.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web-site.

Keywords

endometrial cancer; lymphovascular space invasion; lymph node metastasis; recurrence; chemotherapy; radiotherapy

INTRODUCTION

In 2015, endometrial cancer continues to be the most common gynecologic malignancy in the United States with over 54,000 newly diagnosed cases projected to occur this year [1]. Surgery plays an important role in the management of endometrial cancer with regard to determination of extent of disease and to determine the need for adjuvant treatment [2]. The standard surgical procedure for endometrial cancer includes total hysterectomy and bilateral salpingo-oophorectomy with additional lymphadenectomy in selected cases [2]. Surgical specimens obtained from the hysterectomy-based surgical staging are valuable to identify histological factors that determine the patient's prognosis such as lymphovascular space invasion (LVSI).

LVSI is known to be associated with an increased risk of lymph node metastasis and decreased survival outcome of women with various types of gynecological cancers including cervical [3–9], endometrial [10–14], and ovarian cancers [15–18]. In endometrial cancer, presence of LVSI in the uterine myometrial layer is a key finding that has implications for therapy and women with LVSI-positive endometrial cancers in a particular setting such as older age, higher tumor grade, and deeper myometrial tumor invasion benefit from radiotherapy after surgical staging to reduce the risk of disease recurrence [19]. However, interpretation of LVSI is generally done in a qualitative fashion as dichotomized into presence or absence, and the significance of quantitative measurement for extent of LVSI or anatomical location of LVSI within the myometrial layer of the uterus has not been completely elucidated. The aim of the study was to examine the impact of (i) the extent of LVSI foci and (ii) depth of LVSI within the myometrium on lymph node metastasis and recurrence patterns of women with endometrial cancer.

MATERIALS AND METHODS

Eligibility

After Institutional Review Board approval was obtained at University of Southern California, the institutional database for endometrial cancer was utilized to identify eligible cases. The database consists of consecutive patients with all histology type endometrial cancer who underwent hysterectomy-based surgical staging at Los Angeles County/ University of Southern California Medical Center (January 2000 and December 2013) and the University of Southern California Keck Medical Center (December 2008 and December 2013). The case group consists of endometrial cancer patients with histopathologically confirmed LVSI in the hysterectomy specimen (LVSI-positive group). The control group consists of endometrial cancer with no LVSI in the hysterectomy specimen (LVSI-negative group). Cases receiving neoadjuvant chemotherapy or radiation, those with sarcoma, metastatic tumors to the endometrium, and endometrial hyperplasia were not included. Stage

IV disease were also excluded. Among eligible patients for the case and control groups, the following information was abstracted from the medical records: (i) patient demographics, (ii) pathology results for hysterectomy-based surgical staging, (iii) treatment pattern for adjuvant therapy, and (iv) survival outcome. The STROBE guidelines were consulted for reporting in a case-control study [4]. Some of the patients in this study were within the context of our previous studies [20–24].

Clinical Information

Archived medical records were utilized to obtain the following information: (i) patient demographics included age at surgery, ethnicity, and body mass index (BMI, kg/m^2); (ii) histopathology results included histologic subtypes, grade, stage, depth of myometrial tumor invasion (%), LVSI, cervical stromal invasion, adnexal tumor involvement, and pelvic/para-aortic nodal metastasis (number of nodal metastasis, and total lymph node number sampled); (iii) treatment pattern included use of neoadjuvant therapy (chemotherapy or radiotherapy), details of surgical staging (hysterectomy, salpingo-oophorectomy, and lymphadenectomy), postoperative radiotherapy (whole pelvic radiotherapy [WPRT], intracavitary brachytherapy [ICBT], and WPRT with extended field to para-aortic lymph node chain [WPRT+ext]), and postoperative chemotherapy (type and cycle); and (iv) survival outcomes including time to recurrence and its anatomical location that was grouped into vaginal cuff-recurrence, pelvic-recurrence (other than vaginal cuff), and distant-recurrence (abdomen including liver, spleen, para-aortic lymph nodes, and carcinomatosis; chest including lung, pleura, and mediastinum lymph nodes; osseous structure; and brain).

Evaluation of LVSI

Archived hematoxylin and eosin stained slides for the hysterectomy specimen were retrieved and examined by a gynecologic pathologist who was completely blind for clinical information. LVSI was defined as the presence of tumor cells within lymphatic or vascular spaces within the myometrial layer of the uterus but not the endometrial stromal layer [25]. The foci had to be considered unequivocal and potential artifacts or tumor cell contamination were not counted as LVSI. The distance between the serosa of the myometrium and the deepest focus of LVSI within the myometrial layer of the uterus was measured, and the depth of LVSI was expressed as percent distribution in the full thickness of the myometrial layer in the same histological section. For the extent of LVSI, all histopathology slides containing myometrium were examined, and the crude number of LVSI foci was manually counted in each case. In each case, the number of sections with LVSI, tumor and myometrial tumoral invasion was recorded and the number of LVSI foci was then adjusted for the number of slides representing myometrium and tumor.

Study Definition

Endometrial cancer grading was based on the International Federation of Gynecology and Obstetrics (FIGO) system, and cancer stage was re-classified based on the 2009 system [26]. In our study, deep LVSI was defined as the presence of LVSI in the outer half of the myometrial layer (>50%) as opposed to superficial LVSI (located in the inner half, ≤50%). Various cutoffs for LVSI foci adjusted for slide number were tested by correlating to endometrial cancer recurrence (Table S1). Based on the results, LVSI foci of ≥7 per slide

was found to be the optimal cutoff to predict the risk of recurrence and was defined as extensive LVSI. LVSI foci<7 per slide was then defined as focal LVSI. Lymph node ratio (LNR) was defined as the percent proportion of positive lymph node count among total sampled lymph node counts [27]. Among patients who received postoperative radiotherapy, the recurrence sites were further categorized into the following two: recurrence within the radiation field (infield-recurrence) versus recurrence outside the radiation field (outfield-recurrence).

Statistical Analysis

The primary interest of analysis was to determine the significance of depth and extent of LVSI on lymph node metastasis risk. The secondary interest of analysis was to examine the pattern of recurrence based on LVSI patterns. Continuous variables were assessed for the normality by Kormogrov-Sminorov test and expressed as mean (± SD) or median (range) as appropriate. Statistical significance of continuous variables was assessed with Student *t*-test or Mann–Whitney U-test as appropriate. Categorical and ordinal variables were described as number (%), and statistical significance was assessed with chi-square test or Fisher's exact test as appropriate, expressed with odds ratio (OR) and 95% confidence interval (CI). Spearman's correlation coefficient was used to examine the correlation between depth of LVSI, number of LVSI foci per slide, depth of myometrial tumor invasion, and LNR.

In order to determine the independent risk factor for lymph node metastasis (no versus yes), a binary logistic regression model was used for the multivariate analysis. In this study, 3 models were examined to evaluate the significance of LVSI: (i) depth of LVSI (none vs. superficial versus deep); (ii) extent of LVSI (none vs. focal versus extensive); and (iii) combination of depth and extent (none, superficial/focal, superficial/extensive, deep/focal, and deep/extensive). Covariates entered in to the final model include age (≥60 vs. <60), ethnicity (Hispanic vs. non-Hispanic), BMI (≥30 vs. <30 kg/m^2), histology (endometrioid vs. non-endometrioid), grade (1–2 vs. 3), depth of myometrial tumor invasion (≤50 vs. >50%), cervical stromal invasion (no vs. yes), adnexal involvement (no vs. yes), and LVSI patterns. Statistical significance was expressed with OR and 95%CI. Cumulative risks for time to develop recurrence were analyzed by Log-rank test. Kaplan–Meier method was used to construct survival and cumulative risk curves. All statistical analyses were two-tailed and $P<0.05$ was considered significant. Statistical Package for the Social Science (SPSS Inc, version 12.0, Chicago, IL) was used for the analysis.

RESULTS

There were 70 cases in the LVSI-positive group and 641 cases in the LVSI-negative group examined for statistical analysis (Table S2). Demographics of the two groups are shown in Table I. Patients in the LVSI-positive group were significantly older, less likely to be Hispanic, and had lower BMIs compared to patients in the LVSI-negative group (all, $P<0.01$). Tumor characteristics for the LVSI-positive group were significantly associated with non-endometrioid histology, grade 3 tumor, stage III disease, deep myometrial tumor invasion, cervical stromal invasion, adnexal tumor involvement, and lymph node metastasis

(all, $P<0.01$). Patients in the LVSI-positive group were significantly more likely to receive postoperative radiotherapy and/or chemotherapy (both, $P<0.001$).

Detailed patterns of LVSI are shown in Table S3. Median number of examined slides for myometrium with endometrial tumor was 6 (range, 2–22). All cases with LVSI had myometrial tumor invasion, and there were no cases with LVSI without myometrial invasion. Median of depth of LVSI within the myometrium was 66.7% (range, 3.9–99.8), and deep LVSI was seen in 60.0% of LVSI-positive cases. Median number of LVSI foci per slide was 2.4 (range, 0.1–148.8). Extensive LVSI was seen in 24.3% of LVSI-positive cases. When depth and extent of LVSI were combined, deep and extensive LVSI was seen in 25.3% of LVSI-positive cases. There was no case exhibiting superficial and extensive LVSI. Among 70 LVSI positive cases, depth of LVSI was significantly correlated with extent of LVSI (r=0.65, $P<0.001$), depth of myometrial tumor invasion (r=0.55, $P<0.001$), and LNR (pelvic and/or para-aortic, r=0.37, $P=0.006$). Similarly, extent of LVSI was significantly correlated with depth of myometrial tumor invasion (r=0.30, $P=0.012$).

To determine the independent risk factors for deep LVSI and extensive LVSI, multivariate analysis was performed (Table II). After controlling for patient demographics and tumor factors, grade 3 tumors (OR 10.3), myometrial tumor invasion >50% (OR 9.35), and stage III disease (OR 5.78) remained independent risk factors associated with increased risk of deep LVSI while obesity (OR 0.40) was independently associated with decreased risk of deep LVSI (all, $P<0.05$). In the same multivariate model, grade 3 tumors (OR 4.51), stage III disease (OR 6.42), and myometrial tumor invasion >50% (OR 17.6) remained independent risk factors for increased risk of extensive LVSI (all, $P<0.05$).

The association between LVSI patterns and lymph node metastasis was examined. Median numbers of pelvic and para-aortic lymph nodes sampled were 17.5 (n=298) and 7 (n=93), respectively. Depth of LVSI was significantly associated with an increased risk of multiple pelvic (deep, superficial, and no LVSI: 39.4%, 13.6%, 2.1%, $P<0.001$) and para-aortic nodal metastasis (37.5%,10%, and 4.5%, $P=0.003$). The risk of multiple lymph node metastases was similar between extensive and focal LVSI for both pelvic (27.3%, 29.5%, and 2.1%, $P<0.001$) and para-aortic (16.7%, 30%, and 4.5%, $P=0.005$) lymph nodes.

On multivariate analysis, controlling for patient demographics and tumor factors, all of the three tested models of LVSI pattern (depth of LVSI, extent of LVSI, and combination of depth and extent of LVSI) were independently associated with an increased risk of pelvic and/or para-aortic lymph node metastasis (Table III). In each model, there was a sequential increase of lymph node metastasis for (i) depth of LVSI (prevalence of lymph node metastasis, no LVSI 4.1%, superficial LVSI 22.7% [OR 6.48], and deep LVSI 57.6% [OR 33.8]), (ii) extent of LVSI (no LVSI 4.1%, focal LVSI 36.4% [OR 11.4], and extensive LVSI 72.7% [OR 49.9]), and (iii) combination of depth and extent of LVSI (no LVSI 4.1%, superficial/focal 22.7% [OR 6.43], deep/focal 50.0% [OR 26.3], and deep/extensive 72.7% [OR 63.9]). Among tested covariates, myometrial tumor invasion >50%, cervical stromal invasion, adnexal involvement, and LVSI were all significant for increased risk of lymph node metastasis with deep and extensive LVSI holding substantially higher risks compared to the other factors (nodal metastasis 30.4–37.9% versus 57.6–72.7%; and OR 3.80–7.03

versus 33.8–49.9). The combination of deep and extensive LVSI had the highest OR for risk of lymph node metastasis (OR 63.9).

Median follow-up time of the study population was 31.2 months. There were 50 (7.0%) cases of recurrence reported (any distant-recurrence 31, pelvic-recurrence 14, and vaginal cuff-recurrence 13). Patterns for distant-recurrence were shown in Table S4. The depth of LVSI was significantly associated with distant-recurrence (5-year cumulative risks for deep, superficial, and no LVSI: 30.8%, 0%, and 5.2%, $P<0.001$, Fig. 1A), and deep LVSI had a significantly increased risk of distant-recurrence compared to no LVSI (hazard ratio [HR] 6.97, 95%CI 3.20–15.2, $P<0.001$). The extent of LVSI was also significantly associated with distant-recurrence (5-year cumulative risks for extensive, focal, and no LVSI: 39.7%, 10.1%, and 5.2%, $P<0.001$, Fig. 1B), and, extensive LVSI had a significantly increased risk of distant-recurrence compared to no LVSI (HR 8.55, 95%CI 2.95–24.8, $P<0.001$).

The risks of pelvic-recurrence were examined. The depth of LVSI was significantly associated with pelvic-recurrence (5-year cumulative risks for deep, superficial, and no LVSI: 10.9%, 0%, and 2.7%, $P=0.021$, Fig. 1C). Deep LVSI had a significantly increased risk of pelvic-recurrence compared to no LVSI (HR 4.65, 95%CI 1.29–16.7, $P=0.019$). Extent of LVSI was significantly associated with pelvic-recurrence (5-year cumulative risks for extensive, focal, and no LVSI: 22.2%, 2.0%, and 3.6%, $P=0.003$, Fig. 1D). Extensive LVSI had a significantly increased risk of pelvic-recurrence compared to no LVSI (HR 8.72, 95%CI 1.93–39.4, $P=0.005$). Depth and extent of LVSI were not associated with vaginal cuff-recurrence ($P=0.79$ and 0.32, respectively, Fig. 1E–F).

The effects of chemotherapy on distant-recurrences were examined (Table IV). While the depth of LVSI was significantly associated with distant-recurrence in patients who did not receive chemotherapy ($P<0.001$, Fig. 2A) with deep LVSI holding the highest risk compared to no LVSI (HR 21.2, $P<0.001$), the rate of distant-recurrence was similar across the LVSI groups in patients receiving chemotherapy ($P=0.22$, Fig. 2B), and deep LVSI had a non-significant risk of distant-recurrence compared to no LVSI (HR 1.43, $P=0.47$). The extent of LVSI was significantly associated with distant-recurrence in patients who did not receive chemotherapy ($P<0.001$) with extensive LVSI holding the highest risk compared to no LVSI (HR 22.1, $P=0.004$); however, the rates of distant-recurrence were not significantly different across the LVSI groups in patients who received chemotherapy ($P=0.38$), and extensive LVSI had a non-significant risk of distant-recurrence compared to no LVSI (HR 1.89, $P=0.32$). Effects of radiotherapy on outfield-recurrence were examined among patients who received radiotherapy. The depth of LVSI was significantly associated with outfield-recurrence (5-year cumulative risks for deep, superficial, and no LVSI: 36.4%, 0%, and 16.3%, $P=0.02$, Fig. 2C) but not associated with infield-recurrence ($P=0.72$, Fig. 2D). In-post hoc analysis, cases of endometrioid histology were analyzed (Table S5–8). The similar results were re-demonstrated and deep and extensive LVSI patterns were associated with the strongest risk factors for lymph node metastasis and with increased risk of distant-recurrence.

DISCUSSION

Our study showed that depth and extent of LVSI are important considerations in the management of endometrial cancer. The presence of both deep and extensive LVSI patterns was significantly associated with an increased risk of lymph node metastasis. This is particularly significant in that the magnitudes of significance of the deep and extensive LVSI patterns for lymph node metastasis were substantially larger than the other traditional prognostic tumor factors for endometrial cancer. This implies that determining the location and quantification of LVSI can be a useful tool to identify the patient at risk of lymph node metastasis during surgical staging for endometrial cancer in the era of selective lymph node dissection to avoid complication from lymphadenectomy in low risk patients [28].

Currently, widely accepted tumor factors that indicate additional lymphadenectomy is not required include grade 1–2 tumor, <50% myometrial tumor invasion, and <2 cm tumor size. LVSI is not considered as one of the criteria [29]. This is likely due to the difficulty and challenge in the evaluation of LVSI on frozen section. In fact, previous reports in the literature described that the accuracy for LVSI on frozen section varies across studies (68.3–92.4%) [30,31]. However, some institutions successfully integrated frozen section to evaluate LVSI as the standard algorithm for selective lymphadenectomy during surgical staging [32]. Because our study showed that deep and extensive LVSI patterns are the strongest predictors associated with lymph node metastasis, developing a technique and approach to improve the accuracy of LVSI in frozen section will be of utmost benefit to guide clinicians to identify women for lymphadenectomy during surgical staging. Possible clinical implication based on our results may be that additional lymphadenectomy is indicated if the evaluation of frozen section shows deep or extensive LVSI pattern even absence of other classic tumor factors for lymphadenectomy.

Therapeutic implication for depth and extent of LVSI merits further discussion. Our results showed that both deep and extensive LVSI patterns were associated with markedly high risk of distant-recurrence. Notably, the increased risks of distant-recurrence in such particular LVSI patterns were diminished in a group of patients who received postoperative chemotherapy. In addition, among patients who received radiotherapy, deep LVSI remained the highest risk factor for outfield-recurrence compared to focal and no LVSI. This implies that deep and extensive LVSI patterns may be associated with increased risk of metastasis to distant organs that can benefit from systemic chemotherapy to eliminate these metastatic implants but not from radiotherapy that cannot sterilize such microscopic metastasis outside the radiation field [9]. Indeed, LVSI is known to be associated with increased risk of distant-recurrence in other types of gynecologic malignancy [17], and systemic chemotherapy is suggested for LVSI-positive cases to reduce the risk of recurrence [17,18]. In support of this rationale, another study reported that additional chemotherapy reduces the risk of para-aortic lymph node recurrence among patients with pelvic lymph node metastasis, a surrogate marker for deep and extensive LVSI patterns found in our study [33].

Radiotherapy remains the mainstay of postoperative therapy in endometrial cancer and the role of adjuvant chemotherapy in early stage disease has not been completely elucidated [34]. LVSI is one of 3 components for high-intermediate risk stratification in early stage

endometrial cancer that benefits from radiotherapy to reduce the risk of local recurrence [19]. Whether chemotherapy plays a role in controlling disease recurrence is currently being examined in multiple phase III clinical trials including PORTEC3 and GOG249 [35]. Both trials have a treatment arm for additional chemotherapy with carboplatin and paclitaxel after radiotherapy. In a preliminary result from GOG249, a randomized controlled trial for high-risk early-stage endometrial cancer comparing WPRT (n=287) versus ICBT followed by chemotherapy (carboplatin + paclitaxel 3 cycles, n=291), distant-recurrence rates were similar between the two arms (11.1% vs. 8.2%). It may be a future interest to analyze the data by stratifying depth and extent of LVSI based on our results to see if the study validates an impact of LVSI patterns on distant-recurrence and if chemotherapy reduces the risk of distant-recurrence in deep and extensive LVSI cases.

A strength of the study is that this study provides quantitative measurement of LVSI correlating to outcome in endometrial cancer. Potential weakness of the study is that this is a retrospective study that may have missed potential confounding factors. For instance, not all cases underwent systematic lymphadenectomy during surgical staging. In addition, sample size for the case group is relatively small. A limitation of the study is that additional immunohistochemistry study was not able to perform to distinguish lymphatic and vascular tumor involvements for LVSI.

CONCLUSION

Characterizing LVSI patterns by depth and quantification is a useful approach to identify a subgroup of endometrial cancer patients at high risk of distant-recurrence, suggesting that routine evaluation of LVSI patterns may be an important consideration in practice. Adaptation of LVSI patterns into surgical strategy for lymphadenectomy or indication for postoperative chemotherapy may potentially change patient outcome of endometrial cancer and thus further development will be warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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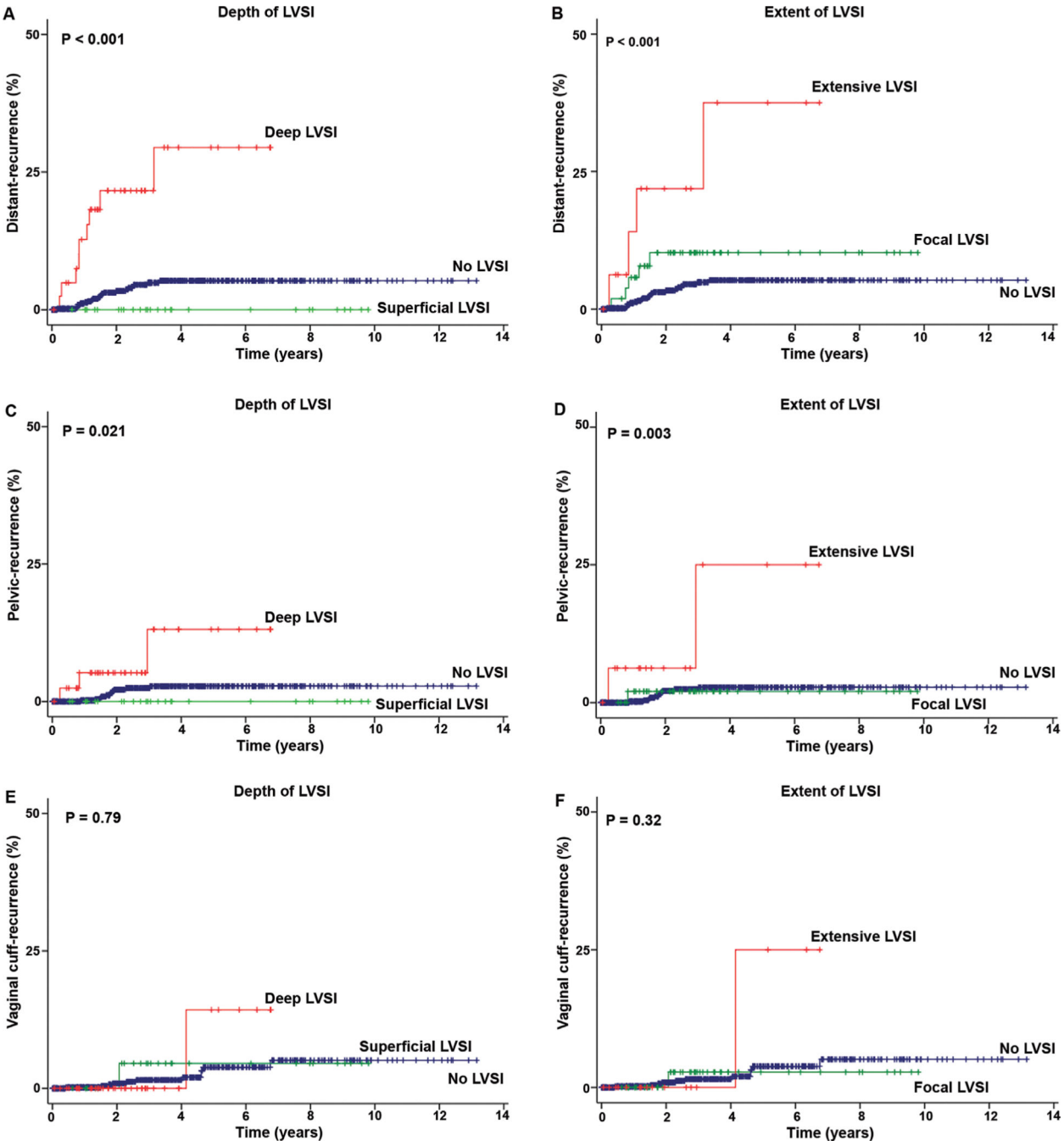

Fig. 1.

Depth and extent of LVSI and recurrence patterns in endometrial cancer. Kaplan–Meier methods for survival curves for (**A**) depth and (**B**) extent of LVSI for distant-recurrence, (**C**) depth, and (**D**) extent of LVSI for pelvic-recurrence, and (**E**) depth and (**F**) extent of LVSI for vaginal cuff-recurrence. Log-rank test for *P*-values.

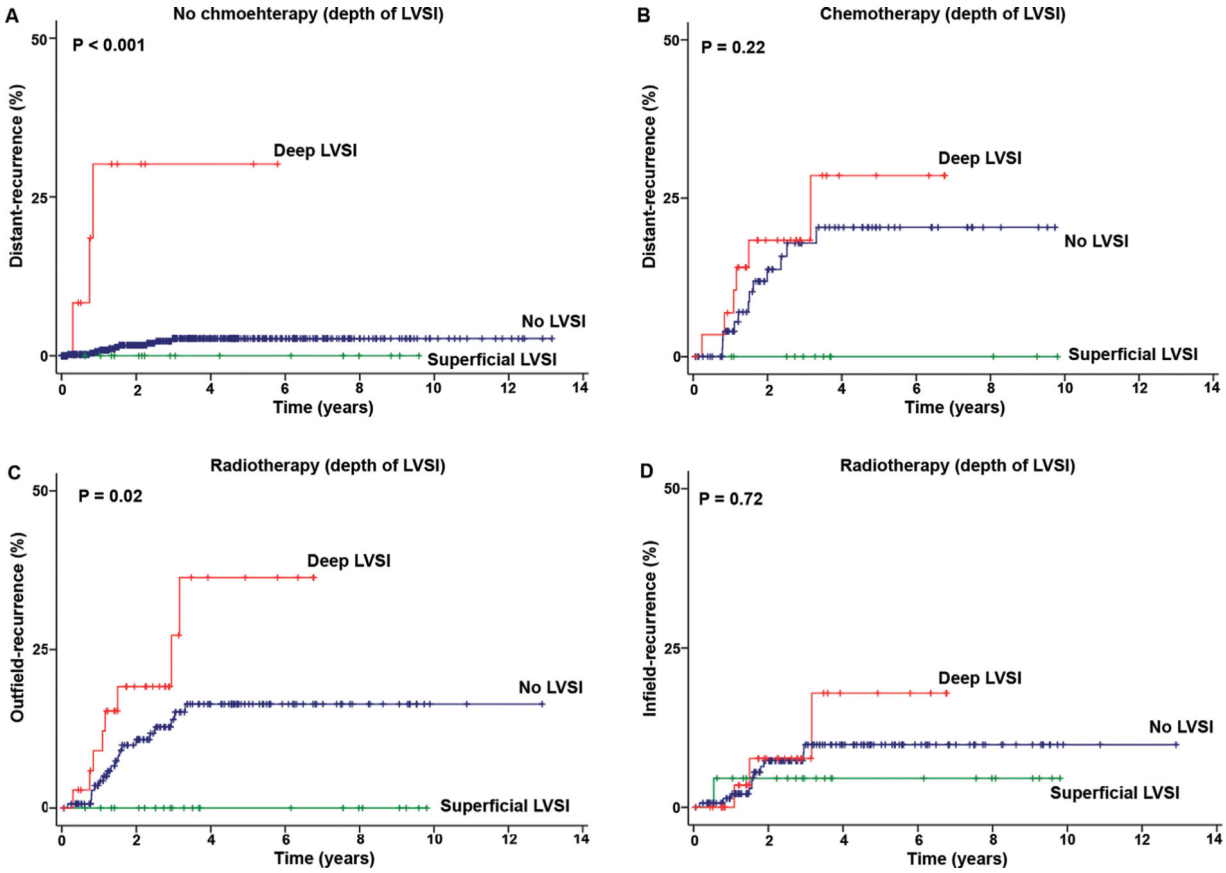

Fig. 2.

Postoperative therapy and distant-recurrence per LVSI patterns in endometrial cancer. Kaplan–Meier methods for survival curves for risk of distant-recurrence based on depth of LVSI for (**A**) no chemotherapy and (**B**) chemotherapy. Risks of recurrence in (**C**) outside the radiation field and (**D**) inside the radiation field are shown based on depth of LVSI. Log-rank test for *P*-values.

TABLE I.

Demographics of Endometrial Cancer

No.	LVSI-positive n=70	LVSI-negative n=641	*P*-value
Age	57.8 (± 9.4)	52.8 (± 11.0)	<0.001
<60	38 (54.3%)	475 (74.1%)	
≥60	32 (45.7%)	166 (25.9%)	
Ethnicity			0.005
Caucasian	14 (20.0%)	118 (18.4%)	
African American	0	26 (4.1%)	
Hispanic	38 (54.3%)	419 (65.4%)	
Asian	18 (25.7%)	78 (12.2%)	
BMI (kg/m^2)	31.7 (± 7.9)	36.3 (± 10.1)	<0.001
<30	33 (47.1%)	179 (28.2%)	
≥30	37 (52.9%)	456 (71.8%)	
Histology			0.001
Endometrioid	53 (75.7%)	582 (909.8%)	
Serous	8 (11.4%)	33 (5.1%)	
Clear	5 (7.1%)	13 (2.0%)	
Others	4 (5.7%)	13 (2.0%)	
Grade			<0.001
1	11 (15.7%)	428 (66.8%)	
2	22 (31.4%)	138 (21.5%)	
3	37 (42.9%)	75 (11.7%)	
Stage			<0.001
I	35 (50.0%)	551 (86.0%)	
II	4 (5.7%)	47 (7.3%)	
III	31 (44.3%)	43 (6.7%)	
Myometrial invasion (%)	70 (1–100)	13 (0–100)	<0.001
≤50%	25 (35.7%)	554 (87.5%)	
>50%	45 (64.3%)	79 (12.5%)	
Cervical stromal invasion			<0.001
No	54 (77.1%)	598 (93.4%)	
Yes	16 (22.9%)	42 (6.6%)	
Adnexal involvement			<0.001
No	58 (82.9%)	615 (93.6%)	
Yes	12 (17.1%)	42 (6.4%)	
Pelvic node metastasis			<0.001
No	33 (60.0%)	236 (97.1%)	
Yes	22 (40.0%)	7 (2.9%)	
Para-aortic node metastasis			0.007
No	18 (69.2%)	62 (92.5%)	

No.	LVSI-positive n=70	LVSI-negative n=641	*P*-value
Yes	8 (30.8%)	5 (7.5%)	
Radiotherapy type			<0.001
None	12 (17.1%)	486 (76.2%)	
ICBT alone	24 (34.3%)	77 (12.1%)	
WPRT alone	21 (30.0%)	41 (6.4%)	
WPRT + ext	4 (5.7%)	1 (0.2%)	
WPRT + ICBT	9 (12.9%)	31 (4.9%)	
WPRT + ext + ICBT	0	2 (0.3%)	
Chemotherapy type *			<0.001
None	28 (40.0%)	554 (86.6%)	
Carboplatin + paclitaxel	37 (52.9%)	77 (12.0%)	
Other	5 (7.1%)	9 (1.4%)	

Number (%), mean (± SD), or median (range) are shown. Student *t* test, Mann–Whitney U test, chi-square test, or Fisher exact test for *P*-values. Significant *P*-values are in bold.

* median 6 cycles (range 3–10) for chemotherapy recipients. 6 missing for BMI, 8 missing for myometrial tumor invasion, 2 missing for cervical stromal invasion, 1 missing for adnexal involvement. 3 missing for radiotherapy, 3 missing for chemotherapy. Pelvic and para-aortic lymphadenectomy were performed in 308 and 99 cases, respectively.

BMI, body mass index; LVSI, lymphovascular space invasion; ICBT, intracavitary brachytherapy; WPRT, whole pelvis radiotherapy; and ext, extended filed to cover aortic nodal chain.

TABLE II.

Independent Risk Factors for Deep and Extensive Lymphovascular Space Invasion

	Deep LVSI		Extensive LVSI	
	OR (95%CI)	***P*-value**	**OR (95%CI)**	***P*-value**
Age		0.23		0.29
<60	1		1	
≥60	1.67 (0.72–3.86)		0.50 (0.14–1.79)	
Ethnicity		0.73		**0.023**
Non-hispanic	1		1	
Hispanic	0.86 (0.37–1.99)		0.22 (0.06–0.81)	
BMI (kg/m^2)		**0.031**		0.28
<30	1		1	
≥30	0.40 (0.18–0.92)		0.49 (0.14–1.75)	
Histology		0.29		0.52
Endometrioid	1		1	
Non-endometrioid	0.57 (0.20–1.64)		1.59 (0.39–6.46)	
Grade		**<0.001**		**0.038**
1–2	1		1	
3	10.3 (4.03–26.6)		4.51 (1.09–18.7)	
Stage		**0.001**		**0.014**
I–II	1		1	
III	5.78 (1.97–16.9)		6.42 (1.46–28.3)	
Myometrial invasion (%)		**<0.001**		**<0.001**
≤50%	1		1	
>50%	9.35 (3.93–22.2)		17.6 (3.53–87.7)	
Cervical stromal invasion		0.92		0.75
No	1		1	
Yes	1.06 (0.37–2.06)		0.79 (0.18–3.40)	
Adnexal involvement		0.52		0.51
No	1		1	
Yes	0.63 (0.16–2.55)		0.55 (0.09–3.36)	

Multivariate analysis with binary logistic regression test for *P*-values. Covariates listed in table are entered in the final model. Significant *P*-values are in bold. BMI, body mass index; and LVSI, lymphovascular space invasion.

TABLE III

Independent Risk Factor for Pelvic and/or Para-Aortic Lymph Node Metastasis

			Depth of LVSI		Extent of LVSI		Depth/extent of LVSI	
	No.	**Mets (%)**	**OR (95%CI)**	***P*-value**	**OR (95%CI)**	***P*-value**	**OR (95%CI)**	***P*-value**
Age				0.16		0.28		0.21
<60	212	11.3%	1		1		1	
≥60	88	11.4%	0.42 (0.13–1.41)		0.52 (0.16–1.71)		0.45 (0.13–1.56)	
Race				0.19		0.12		0.15
Non-hispanic	120	9.2%	1		1		1	
Hispanic	180	12.8%	2.09 (0.69–6.34)		2.58 (0.79–8.39)		2.41 (0.74–7.91)	
BMI (kg/m^2)				**0.03**		**0.017**		**0.032**
<30	110	18.2%	1		1		1	
≥30	188	7.4%	0.30 (0.10–0.89)		0.26 (0.09–0.79)		0.30 (0.10–0.90)	
Histology				0.98		0.73		0.8
Endometrioid	248	10.5%	1		1		1	
Non-endometrioid	52	15.4%	0.98 (0.24–3.93)		0.77 (0.18–3.37)		0.83 (0.19–3.64)	
Grade				0.11		0.27		0.13
1–2	216	7.9%	1		1		1	
3	84	20.2%	0.31 (0.07–1.32)		0.46 (0.12–1.81)		0.32 (0.07–1.42)	
Myometrial invasion (%)				**0.001**		**0.002**		**0.002**
≤50%	207	2.9%	1		1		1	
>50%	92	30.4%	7.03 (2.21–22.4)		6.26 (1.92–20.4)		6.33 (1.93–20.8)	
Cervical stromal invasion				**0.019**		**0.017**		**0.017**
No	257	7.0%	1		1		1	
Yes	43	37.2%	3.80 (1.24–11.6)		3.95 (1.28–12.1)		3.97 (1.28–12.3)	
Adnexal involvement				**0.012**		**0.015**		**0.012**
No	271	8.5%	1		1		1	
Yes	29	37.9%	5.92 (1.48–23.7)		5.48 (1.39–21.6)		6.00 (1.49–24.1)	
Depth of LVSI								
None	245	4.1%	1					
Superficial	22	22.7%	6.48 (1.52–27.6)	**0.011**				

			Depth of LVSI		Extent of LVSI		Depth/extent of LVSI	
	No.	**Mets (%)**	**OR (95%CI)**	***P*-value**	**OR (95%CI)**	***P*-value**	**OR (95%CI)**	***P*-value**
Deep	33	57.6%	33.8 (7.36–155)	**<0.001**				
Extent of LVSI								
None	245	4.1%			1			
Focal	44	36.4%			11.4 (3.32–38.9)	**<0.001**		
Extensive	11	72.7%			49.9 (5.81–428)	**<0.001**		
Combination LVSI								
None	245	4.1%					1	
Superficial/focal	22	22.7%					6.43 (1.51–27.4)	**<0.001**
Deep/focal	22	50.0%					26.3 (5.17–134)	**<0.001**
Deep/extensive	11	72.7%					63.9 (7.14–571)	**<0.001**

Multivariate analysis with binary logistic regression test for *P*-values. Three hundered cases of pelvic and/or para-aortic lymphadenectomy were examined. Three different patterns of LVSI are tested in the analysis. Covariates listed in table are entered in the final model. Significant *P*-values are in bold.

BMI, body mass index; and LVSI, lymphovascular space invasion.

TABLE IV.

Effects of Chemotherapy on Distant-Recurrence in Endometrial Cancer

	No.	5-yr (%)	HR (95%CI)	*P*-value
Depth of LVSI				
Chemotherapy (−)				
None	554	2.7%	1	
Superficial	16	0%	n.a.	0.98
Deep	12	28.6%	21.2 (5.73–78.3)	<0.001
Chemotherapy (+)				
None	86	20.5%	1	
Superficial	12	0%	n.a.	0.98
Deep	30	30.8%	1.43 (0.54–3.84)	0.47
Extent of LVSI				
Chemotherapy (−)				
None	554	2.7%	1	
Focal	23	8.9%	4.71 (1.03–21.5)	0.046
Extensive	5	28.6%	22.1 (2.770176)	0.004
Chemotherapy (+)				
None	86	20.5%	1	
Focal	30	11.1%	0.63 (0.18–2.24)	0.48
Extensive	12	42.5%	1.89 (0.53–6.71)	0.32

Five-year cumulative distant-recurrence rates are shown. Cox proportional hazard regression test for *P*-values. Significant *P*-values are emboldened. 5-yr, 5 year: LVSI, lymphovascular space invasion; n.a., not available; HR, hazard ratio; and CI, confidence interval.