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Original Article

Substantial Lymphovascular Space Invasion Is an Adverse Prognostic Factor in High-Risk Endometrial Cancer

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Summary: Approximately 15% of patients with endometrial cancer present with high-risk disease (HREC). Moreover, assessing the extent of lymphovascular space invasion (LVSI) may provide prognostic insight among patients with HREC. The aim of this study was to determine whether the extent of LVSI can serve as a prognostic factor in HREC. All cases of ESMO-ESGO-ESTRO 2016 classified HREC in the Danish Gynecological Cancer Database (DGCD) diagnosed from 2005 to 2012 were reviewed for the presence and extent of LVSI (categorized using a 3-tiered definition). We used the Kaplan-Meier analysis to calculate actuarial survival rates, both adjusted and unadjusted Cox regression analyses were used to calculate the proportional hazard ratio (HR). A total of 376 patients were included in our analysis. Among 305 patients with stage I/II HREC, 8.2% and 6.2% had focal or substantial LVSI, respectively, compared with 12.7% and 38.0% of 71 patients with stage III/IV HREC, respectively. Moreover, the estimated 5-yr recurrence-free survival rate was significantly lower among patients with substantial LVSI compared with patients with no LVSI for both stage I/II (HR: 2.8; $P = 0.011$) and stage III/IV (HR: 2.9; $P = 0.003$) patients. Similarly, overall survival was significantly lower among patients with substantial LVSI for both stage I/II (HR: 3.1; $P < 0.001$) and stage III/IV (HR: 3.2; $P = 0.020$) patients. In patients with HREC, substantial LVSI is an independent adverse prognostic factor for lymph node and distant metastases, leading to reduced survival. Thus, the extent of LVSI should be incorporated into routine pathology reports in order to guide the appropriate choice of adjuvant treatment. **Key Words:** Lymphovascular space invasion—LVSI—Endometrial carcinoma—Prognostic biomarker.

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The majority of women with endometrial cancer present with either low-risk or intermediate-risk disease according to ESMO-ESGO-ESTRO 2016 risk classification. However, ~15% of patients present with high-risk disease (HREC), including stage IB grade 3 endometrioid endometrial cancer (EEC), stage II-III EEC, and stage I-IVA nonendometrioid endometrial cancer tumor types (1,2), and these patients generally have a higher risk of disease recurrence and reduced overall survival (3–6).

Lymphovascular space invasion (LVSI) is a well-known adverse prognostic factor in endometrial cancer and is associated with an increased risk of lymph node (LN) involvement, as well as distant metastases (7–11). In patients with high-intermediate-risk EEC, assessing the extent of LVSI using a 3-tiered scoring system revealed that substantial LVSI was the strongest independent factor for predicting pelvic LN recurrence (12). In addition, retrospective and case-control studies have confirmed the prognostic effect of assessing the extent of LVSI on both recurrence and survival (13,14); thus, LVSI assessment is currently being incorporated into international guidelines for reporting diagnostic pathology and is used in risk stratification models (1). Nevertheless, whether substantial LVSI is an independent risk factor in HREC is currently unknown, particularly among stage IIIC patients with LN metastases at diagnosis, as these patients are already at a higher risk of developing recurrent disease (6).

The aim of this study was to determine the prognostic value of assessing the extent of LVSI in a large population-based cohort of patients with HREC.

MATERIALS AND METHODS

The Danish Gynecological Cancer Database (DGCD) includes nearly all patients with endometrial cancer diagnosed in Denmark from January 1, 2005 through December 31, 2012. The DGCD contains prospectively registered information regarding the initial surgical and adjuvant treatment, pathology-based diagnosis, and follow-up data. Any missing data and histology-confirmed recurrences were retrieved from the pathology reports in Patobank, the Danish National Pathology Database. Nonhistology verified recurrences were retrieved from medical records based on gynecologic or radiologic examination. The Danish National Patient Register (*Landspatientregistret*) and the patients' individual medical records were used to retrieve information regarding adjuvant treatment, recurrence, and missing data. Information regarding patient death was retrieved from The (Danish) Central Person Registry.

A total of 376 hysterectomy specimens of ESMO-ESGO-ESTRO 2016 classified HREC (1) were available for assessment of LVSI (Supplementary Fig. S1, Supplemental Digital Content 1, http://links.lww.com/IJGP/A125). The patients' clinical data were originally collected by Ørtoft et al. (3,15) in order to evaluate the introduction of systematic lymphadenectomy in Denmark. All pathology slides were obtained from local hospitals for a central pathology review with respect to tumor type, tumor grade (EEC only), and disease stage (3). Carcinosarcomas were excluded.

LVSI was assessed by 4 trained pathologists (authors E.E.M.P., A.L.-C., V.T.H.B.M.S., and T.B.) using hematoxylin and eosin (H&E)–stained slides, without immunohistochemistry. Ethical approval to perform revision, denied access of the study pathologists to the original pathology reports. The presence of LVSI was defined as the unequivocal presence of non-necrotic tumor cells or tumor cell clusters in an endothelial lined space within the uninvolved myometrium (i.e. beyond the invasive border of the tumor). In tumors that were determined to be positive for LVSI, the extent of LVSI was further specified as either focal or substantial using a qualitative approach as described previously (12). In brief, focal LVSI was defined as a "single focus" of LVSI, and substantial LVSI was defined as the "multifocal/diffuse" presence of LVSI (12). Intratumoral LVSI was not considered. In case of artefacts like smear, retraction or mimics like microcystic, elongated and fragmented-type invasion, there was reticence to diagnose LVSI. Consensus among the four pathologists was required in order to classify a case as having substantial LVSI. In addition, the following quantitative features were also recorded for each case: (1) the total number of H&E-stained slides from the uterus available for review, (2) the number of tumor-containing H&E-stained slides, (3) the number for H&E-stained slides showing the presence of LVSI, and (4) the number of involved vessels in each H&E-stained slide showing LVSI. In case of any doubt about (artificial) LVSI, tumor type, tumor grade or disease stage, cases were discussed with all study pathologists present at a multiheaded microscope where also all cases with substantial LVSI were discussed until consensus was reached.

Calculations on the number of slides was done using *t* test. Recurrences were defined as local, pelvic/para-aortic LN, distant LN, and/or distant metastases. Recurrence-free survival (RFS) was calculated as either the interval between the date of surgery and the date of first recurrence or—in event-free patients—until death or the date of last follow-up, censoring

patients who died from a cause other than endometrial cancer. Cancer-specific survival (CSS) was calculated as the interval between the date of surgery and death due to endometrial cancer, censoring patients who died from a cause other than endometrial cancer. Overall survival (OS) was calculated as the interval between the date of surgery and the date of death due to any cause. The Kaplan-Meier method was used to calculate the actuarial survival rate. Adjusted and unadjusted Cox regression analyses were used to calculate the proportional hazard ratio; adjustments were made for the following clinically relevant but potentially confounding prognostic factors: age, comorbidity using the American Society of Anesthesiologists (ASA) score, lymphadenectomy, and/or adjuvant treatment (radiotherapy and/or chemotherapy). Since only HREC were included, no correction for grade and depth of myometrial invasion was performed. Data were analyzed using Stata 11 (StataCorp LLC, College Station, TX), and differences with a 2-sided *P*-value ≤ 0.05 were considered statistically significant.

RESULTS

Study Population

A total of 4707 patients with endometrial cancer were diagnosed from 2005 through 2012 and registered in the DGCD. After central pathology review of 623 cases and excluding patients with low-risk or intermediate-risk endometrial cancer, a total of 376 HREC cases were included in our LVSI analysis (Supplementary Fig. S1, Supplemental Digital Content 1, http://links.lww.com/IJGP/A125). During the initial central review, 68 of the 376 HREC cases (18%) were downgraded from high-risk to high-intermediate risk due to changes in the histologic type; however, these cases were still included in our analysis. The median number of H&E-stained slides available for assessing LVSI was 9 (range: 1–70) and the mean was 6 (SD = 3.1), respectively. For 15 (4.0%) cases only 1 H&E was available for LVSI assessment.

The patient characteristics are summarized in Table 1. Systematic pelvic lymphadenectomy was performed in 266 patients (71%), including 195 stage I/II patients. In 172 of the 195 stage I/II patients (88%), lymphadenectomy was limited to pelvic LN regions; the remaining 23 patients also underwent a para-aortic lymphadenectomy. A total of 267 patients did not receive adjuvant treatment; 255 of these patients (96%) had stage I/II disease. Of 71 LN-positive patients, 59 (83%) received adjuvant treatment; 47 of these 59 patients (80%) received chemotherapy alone, 7 (12%) received external beam radiotherapy (EBRT) alone, and 5 (8.5%) received both chemotherapy and EBRT.

LVSI

Among the 376 patients who were evaluated for LVSI, 80 (21%) had evidence of LVSI visible in at least one H&E-stained slide. Among the 305 patients with stage I/II disease, 44 (14%) had either focal (25 cases; 57%) or substantial (19 cases; 43%) LVSI. Among the 71 patients with stage III/IV disease, 36 (51%) had either focal (9 cases; 25%) or substantial (27 cases; 75%) LVSI.

Recurrence

An analysis of the 5-yr recurrence rate revealed that substantial LVSI was a significant risk factor for overall recurrence, pelvic/para-aortic LN recurrence, and distant LN recurrence—but not local recurrence and distant metastases—among patients with stage I/II disease (Table 2). The adjusted hazard ratio (HR) between substantial LVSI compared with no LVSI was the strongest for pelvic and para-aortic LN recurrence [HR: 4.8; 95% confidence interval (CI): 1.76–13.3]. In contrast, focal LVSI was not a significant risk factor for any site of recurrence, and neither focal nor substantial LVSI was a significant risk factor for any site of recurrence among patients with stage III/IV disease.

Prognosis

The estimated 5-yr OS rate for all patients with stage I/II disease was 68% (95% CI: 62%–72%). When these patients were stratified based on LVSI status, 5-yr OS was 42% among patients with substantial LVSI compared with 70% among patients with no LVSI (HR: 3.1, 95% CI: 1.6–5.9, $P < 0.001$). Among the patients with stage III/IV disease, the estimated 5-yr OS was 44% (95% CI: 32%–55%); when stratified for LVSI status, OS was 22% among patients with LVSI compared with 57% among patients with no LVSI (HR: 3.2; 95% CI: 1.5–6.5, $P < 0.05$). Similarly, substantial LVSI was a major risk factor for reduced 5-yr CSS and RFS among both patients with stage I/II disease and patients with stage III/IV disease. In contrast, focal LVSI was not a significant risk factor for OS, CSS, or RFS. The 5-yr OS, CSS, and RFS rates stratified by LVSI status and disease stage are summarized in Table 3 and Kaplan-Meier curves are shown in Figure 1 (for OS) and Figure 2 (for RFS).

Subgroup Analyses

Among the 305 patients with stage I/II disease, 195 underwent a lymphadenectomy and were histologically

TABLE 1. *Summary of patient characteristics, stratified by disease stage and LVSI status*

		Stage I and II				Lymph node metastases			
	All patients, n	All, n	No LVSI, n (%)	Focal LVSI, n (%)	Substantial LVSI, n (%)	All, n	No LVSI, %	Focal LVSI, %	Substantial LVSI, %
	376	305	261 (85.6)	25 (8.2)	19 (6.2)	71	35 (42.3)	9 (12.7)	27 (38.0)
Follow-up (yr ± SD)	8.55 (2.1)	8.6 (2.2)	8.6 (2.1)	8.3 (2.5)	9.0 (2.4)	8.5 (1.9)	8.5 (1.9)	8.7 (2.1)	8.4 (2.0)
Age at diagnosis (yr ± SD)	69 (9.7)	70 (9.8)	70 (9.8)	70 (11.4)	69 (8.5)	67 (9.0)	66 (10.1)	68 (4.7)	67 (8.6)
ASA (score ± SD)	1.8 (0.6)	1.8 (0.6)	1.8 (0.6)	1.7 (0.7)	1.9 (0.6)	1.8 (0.5)	1.8 (0.5)	1.8 (0.7)	1.7 (0.5)
Stage	n (%)	n	n (%)	n (%)	n (%)	n	n	n	n
Stage I-II	305 (81.1)	305	261 (85.6)	25 (8.2)	19 (6.2)	NA			
Stage IIIc and IV	71 (18.9)	NA	—	—	—	71	35	9	27
Histology, n (%)									
EEC grade 3	143 (38.0)	120 (39.3)	104 (39.9)	6 (24.0)	10 (52.6)	23 (32.4)	11 (31.4)	4 (44.4)	8 (29.6)
Non-EEC	233 (62.0)	185 (60.7)	157 (60.1)	19 (76.0)	9 (47.4)	48 (67.6)	24 (68.6)	5 (55.6)	19 (70.4)
Risk group, n (%)									
High-Intermediate-risk	68 (18.1)	68 (22.3)	60 (22.9)	4 (16.0)	4 (21.1)				
Stage I	208 (55.3)	208 (68.2)	176 (67.4)	19 (76.0)	13 (68.4)				
Stage II	29 (7.7)	29 (9.5)	25 (8.2)	2 (8.0)	2 (10.5)				
Stage IIIc and IV	71 (18.9)					71	35 (49.3)	9 (12.7)	27 (38.0)
Lymphadenectomy, n (%)									
No	110 (29.3)	110 (36.9)	95 (36.4)	10 (40.0)	5 (26.3)	0			
Pelvic	216 (57.5)	172 (54.6)	146 (55.9)	13 (52.0)	13 (68.4)	44 (62.0)	24 (68.6)	5 (55.6)	15 (55.6)
Para-aortic	1 (0.3)	0				1 (1.4)	1 (2.9)		
Pelvic and para-aortic	49 (13.0)	23 (7.5)	20 (7.7)	2 (8.0)	1 (5.3)	26 (36.6)	10 (28.6)	4 (44.4)	12 (44.4)
Adjuvant therapy, n (%)									
No	267 (71.0)	255 (83.6)	218 (83.5)	23 (92.0)	14 (73.7)	12 (16.9)	5 (14.3)	2 (22.2)	5 (18.5)
EBRT (incl. chemo + EBRT)	33 (8.8)	21 (6.9)	17 (6.5)	1 (4.0)	3 (15.8)	12 (16.9)	8 (22.9)	2 (22.2)	2 (7.4)
Chemo	82 (21.8)	30 (9.8)	27 (10.3)	1 (4.0)	2 (10.5)	52 (73.2)	25 (71.4)	5 (66.6)	21 (77.8)

ASA indicates American Society of Anesthesiologists physical status classification system; EBRT, external beam radio therapy; EEC, endometrioid endometrial cancer; LN, lymph node; LVSI, lymphovascular space invasion; NA, not available.

confirmed to have no LN metastases (pN0), and the remaining 110 patients were determined to have no LN metastases based on clinical findings. Patients who had stage I/II disease and substantial LVSI had significantly higher rates of overall recurrence, pelvic/para-aortic LN, and distant metastasis. However, similar 5-yr recurrence rates were obtained from a subgroup analysis of the 195 patients with stage I/II pN0 disease. Patients who had stage I/II disease and focal LVSI did not have higher rates of recurrence; in the subgroup of stage I/II pN0, patients had a significantly higher rate of local recurrence rate in cases with focal LVSI compared with cases with no LVSI (HR: 3.7, 95% CI: 1.18–11.50). These results are summarized in Supplementary Table S1 (Supplemental Digital Content 2, http://links.lww.com/IJGP/A126).

We also performed a subgroup analysis of patients with stage I/II disease stratified by histological tumor type (EEC vs. NEEC) and found that substantial LVSI was a significant risk factor for local recurrence only among patients with EEC; however, it should be noted that this analysis was based on only 9 patients with focal LVSI and 10 patients with substantial LVSI. In contrast, substantial LVSI was a significant risk factor for pelvic/para-aortic LN recurrence (HR: 4.1), distant LN recurrence (HR: 9.7), distant metastases (HR: 3.2), reduced OS (HR: 5.0) and CSS (HR: 3.7), among patients with NEEC (Supplementary Table S2, Supplemental Digital Content 3, http://links.lww.com/IJGP/A127 and Supplementary Fig. S1, Supplemental Digital Content 1, http://links.lww.com/IJGP/A125).

DISCUSSION

By analyzing a relatively large, well-documented patient cohort, we found that the presence of substantial LVSI is an independent adverse prognostic

TABLE 2. *Summary of the 5-yr recurrence rate relative to date time of surgery, stratified by disease stage and LVSI status*

		Overall recurrence rate			Local			Pelvic/para-aortic LN			Distant LN			Distant metastases		
	n	5-yr recurrence rate (%)	HR (95% CI)	*P*	5-yr recurrence rate (%)	HR (95% CI)	*P*	5-yr recurrence rate (%)	HR (95% CI)	*P*	5-yr recurrence rate (%)	HR (95% CI)	*P*	5-yr recurrence rate (%)	HR (95% CI)	*P*
Stage I/II	305															
No LVSI	261	21.6			12.0			8			4.0			18.5		
Focal LVSI	25	23.0	1.1 (0.43–2.78)	0.849	23.0	2.0 (0.74–5.22)	0.177	15.1	2.1 (0.60–7.45)	0.242	5.3	1.7 (0.21–13.47)	0.632	17.9	1.1 (0.39–3.13)	0.848
Substantial LVSI	19	44.3	2.8 (1.26–6.24)	0.011	25.5	2.7 (0.94–7.96)	0.065	34.3	4.8 (1.76–13.3)	0.002	15.2	4.6 (0.95–21.92)	0.058	40.6	2.8 (1.18–6.64)	0.019
Stage III/IV, pN1	54															
No LVSI	32	40.8			17.1			17.1			17.1			40.8		
Focal LVSI	6	33.3	0.5 (0.10–3.10)	0.496	0.0	—	1.000	20.0	1.2 (0.09–14.28)	0.911	0.0	—	1.0	33.3	0.7 (0.12–4.17)	0.692
Substantial LVSI	16	65.1	2.1 (0.81–5.31)	0.130	37.0	3.5 (0.76–16.20)	0.109	46.7	3.7 (0.92–14.68)	0.065	26.7	2.0 (0.40–10.32)	0.395	58.1	1.7 (0.62–4.39)	0.314

Stage I/II includes patients with and without lymphadenectomy at time of primary surgery. Stage III/IV, lymph node-positive patients with progressive disease early after primary surgery were excluded from the analysis (n = 17 patients). Overall recurrence refers to any recurrence regardless of site. Local refers to non-nodal recurrence in the vagina, bladder, and/or rectum. Distant LN refers to lymph node recurrence in a site other than the pelvic or para-aortic lymph nodes. Distant metastasis refers to non-nodal recurrence in the abdomen or extra-abdominal site.
95% CI indicates 95% confidence interval; HR, hazard ratio adjusted for significant and/or potential confounders by multivariate analysis, including age, ASA score, lymph node resection, adjuvant radiotherapy, and/or chemotherapy; LVSI, lymphovascular space invasion.

factor in patients with high-risk endometrial cancer. Specifically, we found that substantial LVSI was more prevalent among patients with stage III/IV disease. Moreover, substantial LVSI was associated with significantly lower rates of recurrence-free survival, cancer-specific survival, and overall survival compared with patients with no LVSI; in contrast, focal LVSI was not associated with the risk profile among these patients, confirming that the extent of LVSI plays an important role in determining outcome. Together with our novel finding that substantial LVSI was an independent adverse prognostic factor for survival in patients with stage III/IV disease, our results indicate that substantial LVSI is a strong predictor of recurrence and survival among patients with HREC regardless of disease stage, even in patients with documented lymph node metastases.

The presence of LVSI in endometrial cancer is a well-known risk factor repeatedly reported to be associated with poor outcome, including reduced OS, CSS, and RFS (8–10,16–18). Moreover, a recent nationwide Swedish population–based study by Stålberg et al. (18) found that LVSI was the strongest prognostic factor for LN metastases and was independently associated with decreased survival among patients with EEC. Nevertheless, assessing the extent of LVSI, rather than simply reporting the presence or absence of LVSI, is a relatively new concept. Using a 3-tiered qualitative approach (i.e. no LVSI, focal LVSI, or substantial LVSI), we previously reported that substantial LVSI was the strongest independent predictor of locoregional recurrence, distant metastases, and OS in patients with intermediate-risk endometrial cancer (12). We also recently reported that this 3-tiered classification is reproducible in an interobserver study addressing diagnosis and assessment of LVSI extent in patients with endometrial cancer, reaching a considerable level of agreement (19). Using this same method in the current study confirms that the presence of substantial LVSI is an independent risk factor among women with HREC, who otherwise already have a relatively poor prognosis. Importantly, the HRs associated with substantial LVSI among patients with high-risk endometrial cancer are consistent with our previous results on intermediate-risk patients (12). Moreover, our results add to the results obtained in a retrospective study by Winer et al. (20), who found that extensive LVSI (defined by the authors as the involvement of ≥ 3 vessels) was an independent prognostic factor for overall survival among patients with stage I/II serous type endometrial cancer.

TABLE 3. *Summary of the 5-yr survival rate expressed relative to the date of surgery, stratified by disease stage and LVSI status*

		All	No LVSI	Focal LVSI	Substantial LVSI	Focal vs. no LVSI		Substantial vs. no LVSI	
Stage I/II (n)		305	261	25	19				
		% 5-yr survival (95% CI)	% 5-yr survival (95% CI)	% 5-yr survival (95% CI)	% 5-yr survival (95% CI)	HR (95% CI)	*P*	HR (95% CI)	*P*
	OS	68 (62–72)	70 (64–75)	60 (38–76)	42 (20–62)	1.7 (0.9–3.3)	0.128	3.1 (1.6–5.9)	<0.001
	CSS	81 (76–86)	82 (77–87)	86 (63–95)	61 (33–80)	0.9 (0.3–3.1)	0.907	2.8 (1.2–6.8)	0.020
	RFS	77 (72–81)	78 (73–83)	77 (53–90)	54 (27–75)	1.1 (0.4–2.8)	0.849	2.8 (1.3–6.2)	0.011
Stage III/ IV, pN1 (n)		71	35	9	27				
		% 5-yr survival (95% CI)	% 5-yr survival (95% CI)	% 5-yr survival (95% CI)	% 5-yr survival (95% CI)	HR (95% CI)	*P*	HR (95% CI)	*P*
	OS	44 (32–55)	57 (39–72)	56 (20–80)	22 (9–39)	1.0 (0.3–3.7)	0.070	3.2 (1.5–6.5)	0.020
	CSS	46 (34–57)	60 (42–74)	56 (20–80)	23 (10–41)	1.2 (0.3–4.2)	0.817	3.2 (1.6–7.0)	0.002
	RFS	40 (29–51)	54 (37–69)	44 (14–72)	20 (7–37)	1.3 (0.4–4.1)	0.649	2.9 (1.4–6.0)	0.003

95% CI indicates 95% confidence interval; CSS, cancer-specific survival; HR, hazard ratio adjusted for significant and/or potential confounders by multivariate analysis, including age, ASA score, lymph node resection, adjuvant radiotherapy, and/or chemotherapy; LVSI, lymphovascular space invasion; OS, overall survival; RFS, recurrence-free survival.

The latest update of the guideline for EC management by ESGO-ESTRO-ESP (21) has made changes to the prognostic risk groups by incorporating molecular classification and extent of LVSI. As a consequence, a part of the cases in the current study would be assigned to the high-intermediate risk group according to the new classification. Nevertheless, substantial LVSI is acknowledged as a risk factor for pelvic and para-aortal LN recurrence and as a consequence EBRT should be considered. The benefit of added chemotherapy was established for patients with serous endometrial cancer or stage III endometrial cancer to increase both failure-free survival and overall survival (22). However, little is known how this relates to LVSI status, let alone extent of LVSI. Although the guidelines are based on clinical trials in which LVSI status is often known, the extent of LVSI has not been reported, and the effect of adjuvant chemotherapy on the risk of distant metastases among patients with endometrial cancer and substantial LVSI remains unknown. By incorporating substantial LVSI in the latest ESGO-ESTRO-ESP guideline, the reporting of the extent of LVSI is being encouraged which offers possibilities to study the effect of adjuvant chemotherapy on recurrence in patients with substantial LVSI in the future.

Between 2005 and 2012, systematic lymphadenectomy was introduced in Denmark as part of the standard management and serves primarily as a diagnostic procedure. Here, we found that both LVSI

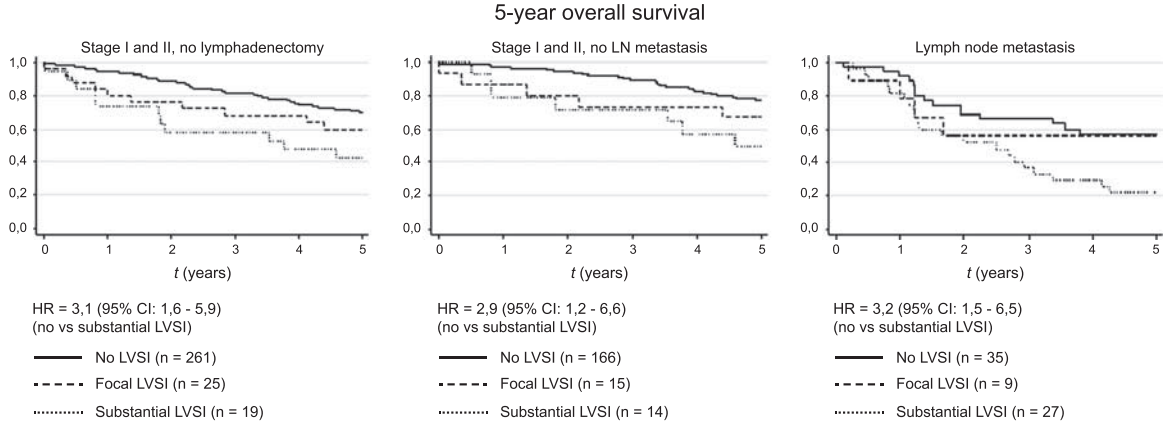

FIG. 1. Kaplan-Meier curves of 5-yr overall survival for patients in the indicated patient groups. CI indicates confidence interval; HR, hazard ratio; LN, lymph node; LVSI, lymphovascular space invasion.

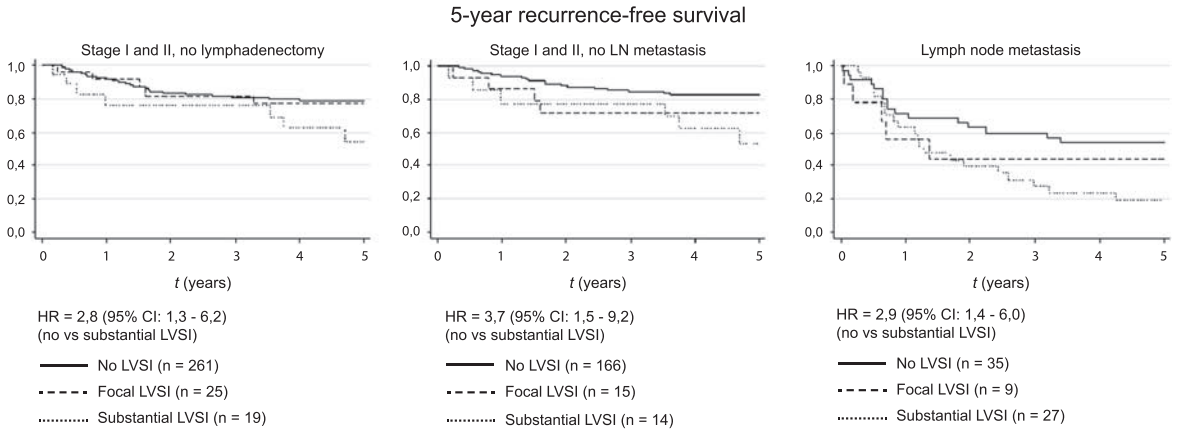

FIG. 2. Kaplan-Meier curves of 5-yr recurrence-free survival for patients in the indicated patient groups. CI indicates confidence interval; HR, hazard ratio; LN, lymph node; LVSI, lymphovascular space invasion.

status and recurrence rate were largely similar among patients with stage I/II disease regardless of whether surgical lymph node staging was performed. The similarity in recurrence rates suggests that clinical staging is relatively accurate, consistent with the results of 2 large randomized trials involving patients who underwent systematic pelvic lymphadenectomy (23,24). We did find a significant risk for local recurrence for patients with focal LVSI in stage I/II pN0. However, this finding is based on small numbers of events and patients and therefore deserves caution.

This study has several strengths. First, the data were retrieved from a national population-based registry, resulting in a relatively large, well-documented cohort for which extensive follow-up data were available, thus ensuring reliable data regarding recurrence and survival, as well as detailed information regarding LN status. Second, LVSI status was reviewed independently by 4 trained pathologists using a large number of slides prepared from the hysterectomy specimens. Finally, the majority of patients (71%) with stage I/II disease did not receive adjuvant therapy, allowing us examine the putative effects of LVSI independent of adjuvant treatment.

Despite these strengths, this study also has several limitations that warrant discussion. First, the patients with HREC were originally selected (using local pathology reports) from the DGCD in order to evaluate the introduction of systematic lymphadenectomy in Denmark, which may have led to a relative underrepresentation of patients with stage II, IIIa, and/or IIIb disease. Second, the central pathology review resulted in the reclassification of 18% of patients with stage I disease from high-risk to high-intermediate risk due to changes in the histologic type. Finally, although the majority of cases had a relatively high number of H&E-stained hysterectomy slides, only one slide was available for 15 patients which may have resulted in an underestimation of LVSI positive cases. Although there is no evidence providing guidance on the minimum number of H&Es to be assessed to avoid under-reporting, we recommend to include at least 1 block per centimeter of tumor.

One caveat to the qualitative nature in which LVSI assessment was performed in our study is that this to some extent limits clinical implementation due to interobserver variability. This interobserver variability may partly explain the differences in the reported prevalence of substantial LVSI (12,25,26), although some of these differences can also be explained by study cohort composition. However, we acknowledge that borderline cases exist in which the qualitative nature of this approach will result in variability in the interpretation of focal versus substantial LVSI. Furthermore, correct interpretation of true LVSI versus artifactual displacement remains another challenge and may also impact reported prevalence. Intriguingly, despite all of this, the prognostic power of substantial LVSI is generally found across many independent cohorts (12,18,20,25). We foresee that the increased attention on this topic will eventually result into international consensus, which through training will lead to improved agreement among pathologists. To further support progress in this field a quantitative definition for what is clinically relevant LVSI extent is much needed. In our companion paper by Peters and colleagues (27), we used the cohorts available to us to address this specific point.

In conclusion, we report that substantial LVSI, but not focal LVSI, is an independent significant risk factor for survival in patients with high-risk endometrial

cancer. These results both support and validate previous findings and underscore the clinical value of assessing the extent of LVSI in routine pathologic testing. Finally, since extent of LVSI has recently been incorporated in (European) clinical guidelines for EC management, we recommend reporting of extent of LVSI in EC pathology reports (21).

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