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Substantial lymph-vascular space invasion (LVSI) is a significant risk factor for recurrence in endometrial cancer – A pooled analysis of PORTEC 1 and 2 trials

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Abstract ***Background:*** Lymph-vascular space invasion (LVSI) is an important adverse prognostic factor in endometrial cancer (EC). However, its role in relation to type of recurrence and adjuvant treatment is not well defined, and there is significant interobserver variation. This study aimed to quantify LVSI and correlate this to risk and type of recurrence.
Methods: In the post operative radiation therapy in endometrial carcinoma (PORTEC)-trials stage I EC patients were randomised to receive external beam radiotherapy (EBRT) versus no additional treatment after surgery (PORTEC-1, $n = 714$), or to EBRT versus vaginal brachytherapy (PORTEC-2, $n = 427$). In tumour samples of 926 (81.2%) patients with endometrioid tumours LVSI was quantified using 2-, 3- and 4-tiered scoring systems. Cox proportional hazard models were used for time-to-event analysis.

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Results: Any degree of LVSI was identified in 129 cases (13.9%). Substantial LVSI ($n = 44$, 4.8%) using the 3-tiered approach had the strongest impact on the risk of distant metastasis (hazard ratio (HR) 4.5 confidence interval (CI) 2.4–8.5). In multivariate analysis (including: age, depth of myometrial invasion, grade, treatment) substantial LVSI remained the strongest independent prognostic factor for pelvic regional recurrence (HR 6.2 CI 2.4–16), distant metastasis (HR 3.6 CI 1.9–6.8) and overall survival (HR 2.0 CI 1.3–3.1). Only EBRT (HR 0.3 CI 0.1–0.8) reduced the risk of pelvic regional recurrence.

Conclusions: Substantial LVSI, in contrast to focal or no LVSI, was the strongest independent prognostic factor for pelvic regional recurrence, distant metastasis and overall survival. Therapeutic decisions should be based on the presence of substantial, not 'any' LVSI. Adjuvant EBRT and/or chemotherapy should be considered for stage I EC with substantial LVSI.

1. Introduction

Lymph-vascular space invasion (LVSI) is found in about 8–10% of patients with International Federation of Gynaecology and Obstetrics (FIGO) stage I endometrial carcinoma (EC), and is increasingly found with higher tumour grade, deeper invasion and older age [1–3]. LVSI has been reported as a risk factor for recurrence and for both lymph node and distant metastasis [4–10]. Presence of LVSI has been related with a 5-fold risk of microscopic pelvic lymph node metastases [11], but LVSI is also an important risk factor for distant metastases in the absence of nodal involvement [5]. This has led to the question if LVSI can be used as a surrogate marker of nodal involvement in the absence of surgical nodal staging [4].

A clinical dilemma arises when LVSI is found in a patient with otherwise intermediate risk features with regard to the recommendation for adjuvant radiotherapy. While LVSI was included as a risk factor in the definition of high-intermediate risk in the GOG#99 trial [12], it was not included in the post operative radiation therapy in endometrial carcinoma 1 (PORTEC-1) definition [13]. In the PORTEC-1 trial LVSI was mainly found in the registered group with grade 3 and >50% myometrial invasion [1]. Apart from retrospective studies in which treatment was not controlled, the randomised trials of radiotherapy did not report separately on the outcome of patients with LVSI, making it difficult to draw firm conclusions [12–16].

Lack of uniform histological criteria to establish LVSI in EC specimens; the possibility that a quantification factor is important and the considerable interobserver variability in the assessment of LVSI might explain part of these conflicting findings. In most studies no definition for assessment of LVSI has been reported. Often a comment is made that there should be a clear presence of LVSI, in contrast to cases presenting with focal or questionable LVSI that can be difficult to distinguish from retraction artifacts or a so-called 'microcystic, elongated and fragmented' (MELF-like) pattern of invasion [17]. Two-, three- and four-tiered scoring systems of LVSI have been proposed, with increasing degrees of LVSI and the question is whether or not this semi-quantification is clinically relevant (Fig. 1) [18,19].

The hypothesis of the current study was that more prominent LVSI would result in higher risk of disease recurrence and stronger prognostic significance. The aim of this study was to analyse the prognostic value of two-, three- and four-tiered scoring systems in relation to adjuvant radiotherapy within the PORTEC trials.

2. Methods

2.1. Study population

For this study patients and follow-up data from the PORTEC-1 and -2 studies were used. PORTEC-1 included 714 patients with FIGO (1988) stage IB grade 2 or 3 and stage IC grade 1 or 2 EC between 1990 and 1997 [13]. The PORTEC-2 study included 427 patients between 2002 and 2006 who had stage I EC with high-intermediate risk features (FIGO 1988 stage 1B grade 3, IC grade 1 or 2 or stage 2A) [15]. All patients underwent total hysterectomy and bilateral salpingo-oophorectomy without lymphadenectomy and were randomly allocated to receive external beam radiation therapy (EBRT) versus no additional treatment (NAT, PORTEC-1) or EBRT versus vaginal brachytherapy (VBT, PORTEC-2). In both studies central pathology review was performed to assess histological type, stage, grade and LVSI. Representative histological slides and/or tumour samples were available from 926 (81.2%) patients with endometrioid type tumours, of the in total 1141 randomised patients.

2.2. LVSI definition

LVSI was defined as the presence of tumour cells in a space lined by endothelial cells outside the immediate invasive border. In case of possible mimics such as

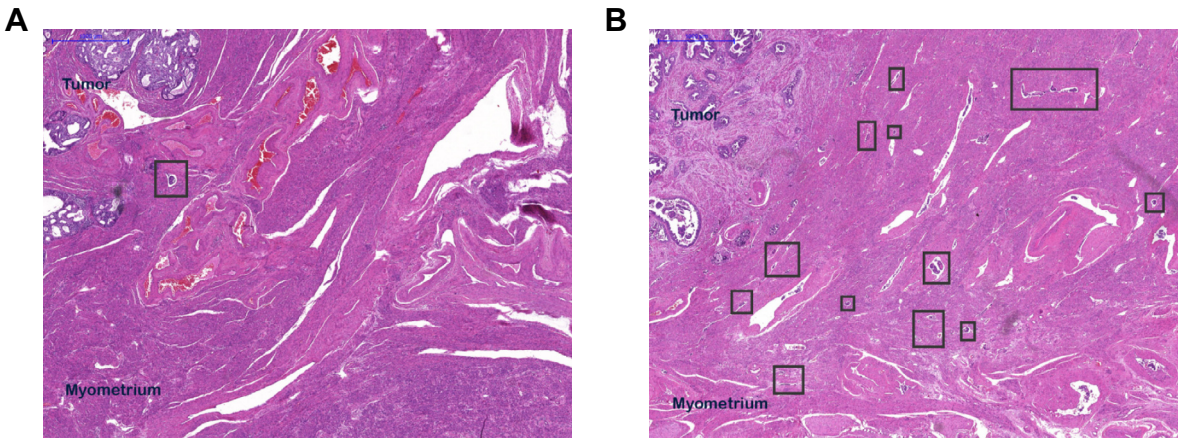

Fig. 1. Representative pictures of haematoxylin & eosin (H&E) stained slides (magnification 2.5×) illustrating how the 3-tiered scoring was applied. Representative examples of focal (A) and substantial (B) Lymph-vascular space invasion (LVSI). Black boxes indicate foci of LVSI.

retraction/shear artefacts, smear artefacts and MELF-type invasion there was restraint to designate involved foci as LVSI. Intratumoural LVSI foci were not considered. Supportive criteria used to define LVSI presence were: foci near other vessels and presence of a lymphocytic infiltrate around the involved vessel.

2.3. Scoring systems for LVSI in endometrial cancer

In order to semi quantify the above-described LVSI definition; we searched the endometrial cancer literature for LVSI scoring methods. The majority of publications describe LVSI as present or not present mostly without any further detail '*two-tiered system*'). Two publications were identified with a more detailed description of LVSI and a semi-quantitative scoring method, including a *three-* and *four-tiered* scoring system [18,19]. These scoring systems are outlined in Table 1.

All available haematoxylin & eosin (H&E) slides were systematically screened at 10×10 magnification and scored by the first observer (EP) for the presence of LVSI. Additionally, to further substantiate the semi-quantitative scoring systems, the number of involved vessels was counted. Finally, the presence of a perivascular infiltrate was noted, which has been reported to be indicative for the presence of LVSI. To make our findings comparable to previous publications, a perivascular infiltrate was present if there were aggregates of >20 lymphocytes around a vessel per section [20].

All cases in which LVSI was reported at least once (original pathology report, central pathology review and/or first observer) or in which the presence of LVSI was uncertain, were scored by two additional observers (TB, VS). All reviews were performed blinded from previous reports and scores. Consensus was reached if the first and second observer agreed. If there was no consensus the case was discussed at a multi-headed microscope with all observers present until consensus was reached.

2.4. Statistical analyses

Patient, tumour and treatment characteristics were analysed using Chi-square statistics or Fishers exact test in case of categorical and *t* test or analysis of variance (ANOVA) for continuous variables.

Time to event analysis were calculated from the date of randomisation as starting point and patients who were alive and without recurrence were censored at the date of last follow-up. Data for survival curves were calculated using the Kaplan–Meier method with log-rank test. For the following endpoints events between brackets were considered as events: vaginal recurrence rate (all vaginal recurrences); pelvic regional recurrence (all pelvic nodal or non-vaginal recurrences); distant metastasis (all distant metastasis) and overall survival (all deaths). Cox proportional hazards models included established prognostic factors: age, grade, depth of myometrial invasion and treatment received. All statistical analyses were done with IBM SPSS (version 20.0).

3. Results

3.1. Study population

Patient characteristics are detailed in Table 2 and Supplementary Tables S1A–C. Since the PORTEC-2 trial include high-intermediate risk patients while the PORTEC-1 trial also included (low-)intermediate risk cases, patients in the VBT group were on average older and had more grade 3 tumours. Median follow-up for patients alive was 160 months for PORTEC-1 and 89 months for PORTEC-2.

3.2. Lymph-vascular space invasion

In the original pathology reports, LVSI had been found in 64 (6.9%) tumours. While in the current analysis any degree of LVSI was found in 129 (13.9%) tumours, LVSI was more frequently observed in

Table 1
Scoring methods for lymph vascular space invasion (LVSI).*

A	*Two-tiered approach*	
	No LVSI	Definition not met
	LVSI present	Definition met
B [18]	*Three-tiered approach*	
	No LVSI	Definition not met
	Focal	A single focus of LVSI was recognised around a tumour
	Substantial	Diffuse or multifocal LVSI was recognised around the tumour
C [19]	*Four-tiered approach*	
	No LVSI	Definition not met
	Minimal	Only a few lymph vascular vessels were involved on the border of the invasive front of the tumour
	Moderate	More vessels were involved in a wider area surrounding the tumour
	Prominent	Many vessels were diffusely involved in the deeper part of the myometrium

* See methods section for definition of LVSI.

tumours with deep (>50%) myometrial invasion (15.9%) than in those with superficial invasion (9.4%, $p = 0.008$, Table S1C). The agreement between the original reports and the current analysis was low (Kappa 0.30). Results using the different LVSI scoring systems are shown in Table 3. Both the three- and four-tiered approaches showed an increase in the number of involved vessels.

Perivascular lymphocytic infiltrates were found in 305 (32.7%) tumours. Although these changes were found more frequently in tumours with LVSI, only 26.4% of patients with perivascular lymphocytic infiltrates had LVSI (Table S1C).

3.3. Prognostic value

Hazard ratios (HR) for the risk of distant metastases in relation to LVSI using the different approaches, both unadjusted and adjusted for age, depth of myometrial invasion, grade and treatment received are shown in Table 3. There was no prognostic difference between minimal and moderate LVSI in the four-tiered approach, and therefore this scoring system had no added value over the three-tiered approach (Table 3, Fig. 2A and B). In the three-tiered scoring system there was a stepwise increase in the prognostic impact of focal LVSI and substantial LVSI, with a markedly increased HR of substantial LVSI compared to LVSI in the two-tiered approach (4.5 versus 3.1). For these reasons, the three-tiered method was included in a multivariate Cox regression analysis (Table 4). Substantial LVSI was an independent prognostic factor for pelvic regional recurrence, distant metastasis (DM) and overall survival (OS). Substantial LVSI was the strongest independent prognostic factor for an increased risk of pelvic regional recurrence (at 5 years, the regional risk with no LVSI was 1.7%, for focal LVSI 2.5% and for substantial LVSI 15.3%), while EBRT (but not VBT) independently decreased the risk of pelvic regional recurrence (Table 4 and Fig. 2C). In the subgroup of patients with substantial LVSI, the risk of pelvic regional recurrence at 5 years after EBRT was 4.3% compared to VBT 27.1% and NAT 30.7% (Fig. 2D). In addition to substantial LVSI, grade 3 was an independent risk factor for pelvic regional recurrence. Both focal and substantial LVSI and grade 3 were independent prognostic factors for DM. Age >60 years, grade 3 and substantial LVSI were independent prognostic factors for a decreased OS. For the risk of vaginal recurrence, both EBRT and VBT were the strongest independent predictive factors for a decreased risk, both age >60 years and grade 3 increased the risk while the presence of LVSI was no independent prognostic factor.

Finally, the presence of a perivascular lymphocytic infiltrate was not associated with endometrioid EC recurrence (HR 1.0, CI 0.74–1.44).

4. Discussion

In this large cohort of 926 intermediate to high-intermediate risk Stage I endometrioid type EC patients randomised in the PORTEC-1 and -2 trials, 4.8% were found to have substantial LVSI in a three-tiered semi-quantitative scoring system, which was the strongest independent prognostic factor for pelvic regional recurrence, distant metastasis and overall survival. LVSI was not predictive for the risk of local vaginal recurrence when adjusted for treatment received, showing the large risk reduction with both EBRT and VBT. Importantly, EBRT was associated with a decrease in the risk of pelvic regional recurrence, in contrast to VBT. EBRT and VBT did not impact on the risk of distant metastasis and overall survival.

The assessment of LVSI in hysterectomy specimens is not easy due to frequently found artifacts such as tumour spill due to bad fixation or retraction artifacts. Also, a MELF like growth pattern can mimic LVSI [17]. Additionally, there is no uniformity in the definitions used to describe LVSI. This is possibly one of the explanations for the broad variation in reported prevalence of LVSI in stage I EC, and for the low inter-observer agreement. In this study all available H&E slides were systematically screened for the presence of

Table 2
Patient characteristics by treatment received and after central review of pathology.

	Total ($n = 926$)	NAT ($n = 287$)		EBRT ($n = 450$)		VBT ($n = 189$)		
	N	*N*	%	*N*	%	*N*	%	*p*-Value
Age								
Mean (range)	67.8 (41–90)	66.3 (46–90)		67.7 (41–88)		70.2 (52–86)		<0.001
<60 years	158	77	48.7	74	46.8	7	4.4	
>60 years	768	210	27.3	376	49.0	182	23.7	
Myometrial invasion								
<50%	278	125	45.0	120	43.2	33	11.9	<0.001
>50%	648	162	25.0	330	50.9	156	24.1	
Differentiation grade								
1	673	186	27.6	337	50.1	150	22.3	0.001
2	137	48	35.0	67	48.9	22	16.1	
3	116	53	45.7	46	39.7	17	14.7	
LVSI								
Absent	856	274	32.0	410	47.9	172	20.1	0.065
Present	70	13	18.6	40	57.1	17	24.3	

LVSI: lymph vascular space invasion; NAT: no additional treatment; EBRT: external beam radiotherapy; VBT: vaginal brachytherapy.

Table 3
Different approaches for scoring of LVSI by number of involved vessels and the prognostic efficacy for distant metastasis.

	Total		Involved vessels		Distant metastasis			
	N	%	Mean (95% CI)	*p*-Value	HR (95% CI) unadjusted	*p*-Value	HR (95% CI) adjusted*	*p*-Value
Original reports								
No LVSI	862	93.1						
No LVSI	862	93.1						
LVSI present	64	6.9			3.3 (1.9–5.9)	<0.001	3.1 (1.8–5.7)	<0.001
Central review								
No LVSI	856	92.4			1		1	
LVSI present	70	7.6			2.6 (1.4–4.8)	0.001	2.2 (1.2–4.1)	0.012
Two-tiered								
No LVSI	797	86.1	0	<0.001	1		1	
LVSI present	129	13.9	2.5 (2.1–2.9)		3.1 (2.0–5.0)	<0.001	2.9 (1.8–4.6)	<0.001
Three-tiered								
No LVSI	797	86.1	0	<0.001	1		1	
Focal	85	9.2	1.8 (1.5–2.1)		2.4 (1.3–4.9)	0.004	2.4 (1.3–4.5)	0.005
Substantial	44	4.8	3.9 (3.1–4.7)		4.5 (2.4–8.5)	<0.001	3.6 (1.9–6.8)	<0.001
Four-tiered								
No LVSI	797	86.1	0	<0.001	1		1	
Minimal	46	5.0	1.2 (1.0–1.3)		2.8 (1.3–5.8)	0.007	3.0 (1.4–6.3)	0.004
Moderate	55	5.9	2.4 (2.0–2.9)		2.6 (1.3–5.3)	0.008	2.3 (1.1–4.7)	0.023
Prominent	28	3.0	4.9 (3.9–6.0)		4.9 (2.3–10.3)	<0.001	3.8 (1.8–8.1)	0.001

CI: confidence interval; HR: hazard ratio; LVSI: lymph vascular space invasion.
* Adjusted for age, review grade, review depth of myometrial invasion and treatment.

any degree of LVSI. This was done at high magnification, adequate to identify tumour cells along with sufficient view of its surroundings, and doubled the amount of LVSI positive cases compared to initial pathology reports. However, most cases had focal LVSI and the number of cases with more clinical relevant substantial LVSI was reduced compared to the initial pathology reports. Low magnification was sufficient to recognise cases with substantial LVSI. Despite the stepwise increase of number of involved vessels in the largest embolus within both the three- and four-tiered scoring system, the four-tiered approach had no stronger prognostic significance than the three-tiered approach, due to the lack of difference between minimal and moderate LVSI. Identification of perivascular infiltrates, did not contribute to the prognostic significance of LVSI.

The three-tiered approach confirmed our hypothesis that more LVSI would result in a higher risk of disease recurrence. Substantial LVSI in the three-tiered method had a markedly increased HR compared to

the two-tiered approach and to the original pathology reports, and its prognostic significance was strongest and most clinically relevant in the multivariate Cox regression analysis. In this scoring system focal LVSI was defined as a single focus of LVSI. However, analyses of number of involved vessels shows that on average two involved vessels were found, indicating that the interpretation of this definition is not absolute. An interobserver study has been initiated to determine if the use of the three-tiered system will lead to more reproducible reporting of substantial LVSI with clinical consequences.

While the obvious strengths of this analysis are the inclusion of a large cohort of randomised, uniformly treated patients with complete follow-up data, and the central review of pathology, there are limitations. Although an effort was made to include as many H&E slides per case as possible, for a proportion of the patients there was only one tumour-containing slide available, which might have led to underreporting of LVSI. However, based on the prevalence of LVSI in the original pathology reports and during initial central pathology review and the low agreement with the current analysis including more of the focal LVSI cases, this is most likely minor underreporting. In addition, despite the inclusion of more than 900 cases, the proportion of patients with substantial LVSI ($n = 44$) was small, with corresponding wide confidence intervals.

Well-known risk factors in endometrial cancer are age, FIGO stage, histological subtype, tumour grade and depth of myometrial invasion. In stage I-II disease, most studies reported LVSI (and grade 3) as a significant risk factor for distant metastasis, and showed that the presence of LVSI was associated with microscopic lymph node metastases in lymphadenectomy specimens [4,7,8,10,11]. Most studies that investigated prognostic factors in EC patients were cohort studies in which adjuvant treatment was not controlled, hampering conclusions with regard to pelvic recurrence. The randomised trials reporting on the role of radiotherapy in EC have

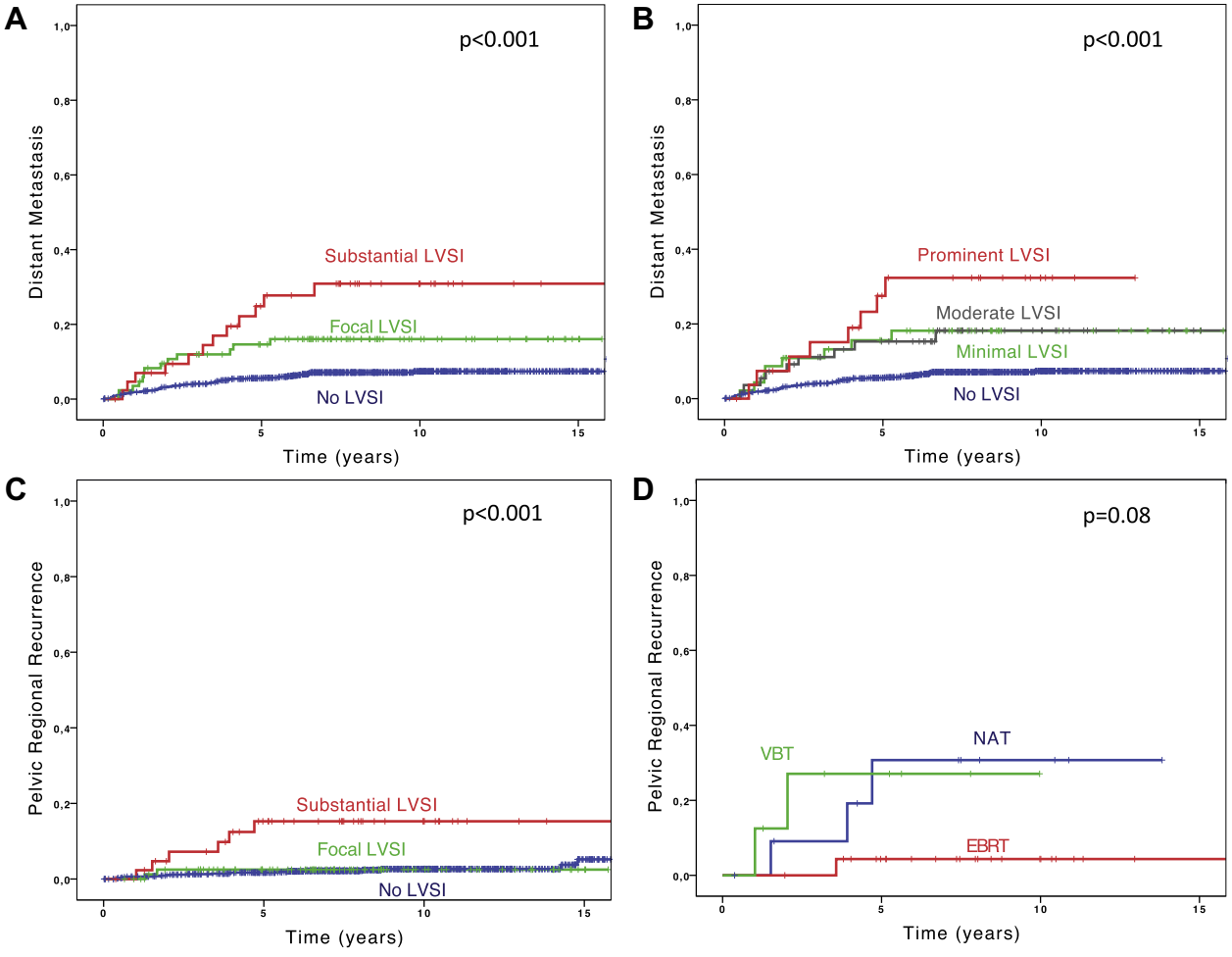

Fig. 2. Kaplan Meier curves for the risk of distant metastasis for the three-tiered (A) and four-tiered definition (B) of lymph-vascular space invasion (LVSI). Kaplan Meier curves of the risk of pelvic regional recurrence using a three-tiered definition of LVSI (C) and for treatment received in the subgroup of 44 patients with substantial LVSI (D).

Table 4
Multivariate Cox proportional hazard regression models for the three-tiered scoring system for LVSI.

	Vaginal Recurrence			Pelvic Regional Recurrence			Distant Recurrence			Overall Survival		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
Age												
<60	1			1			1			1		
>60	3.15	1.10–9.01	0.032	2.00	0.58–6.89	0.275	1.29	0.68–2.45	0.437	3.19	2.15–4.74	<0.001
Differentiation grade												
1	1			1			1			1		
2	1.68	0.75–3.76	0.212	2.13	0.82–5.55	0.120	1.89	1.05–3.42	0.035	1.19	0.87–1.62	0.285
3	2.31	1.01–5.26	0.046	2.75	1.02–7.43	0.045	3.72	2.12–6.53	<0.001	1.79	1.30–2.48	<0.001
Myometrial invasion												
<50%	1			1			1			1		
>50%	1.47	0.71–3.03	0.301	1.89	0.72–4.97	0.195	1.25	0.74–2.12	0.409	1.08	0.83–1.41	0.546
LVSI												
No LVSI	1			1			1			1		
Focal	1.86	0.65–5.35	0.251	1.10	0.26–4.74	0.900	2.42	1.31–4.45	0.005	1.36	0.93–2.00	0.111
Substantial	1.69	0.51–5.66	0.393	6.19	2.35–16.3	<0.001	3.61	1.90–6.84	<0.001	2.02	1.30–3.12	0.002
Treatment received												
NAT	1			1			1			1		
EBRT	0.17	0.08–0.37	<0.001	0.30	0.11–0.80	0.016	1.14	0.67–1.93	0.640	1.04	0.81–1.34	0.734
VBT	0.13	0.04–0.43	0.001	1.16	0.47–2.87	0.745	1.21	0.63–2.33	0.568	0.82	0.56–1.21	0.319

HR: hazard ratio; CI: confidence interval; LVSI: lymph vascular space invasion; NAT: no additional treatment; EBRT: external beam radiotherapy; VBT: vaginal brachytherapy.

not specifically reported on the outcomes of patient with and without LVSI [12–16]. Based on previous results in GOG studies LVSI was included in GOG#99 as a risk factor for defining high-intermediate risk [12], while in PORTEC-1 the high-intermediate risk factors (age >60 years, grade 3, >50% myometrial invasion) were based on multivariate regression analysis of prognostic factors within the trial population. LVSI was found in 5% of 714 randomised patients, but was mainly found in 17% of the cohort of 99 patients with deep invasive grade 3 tumours that were registered but not randomised [1,13]. For these reasons LVSI was not included in the PORTEC definition of high-intermediate risk. Currently VBT is preferred in high-intermediate risk patients based on its capability of ensuring vaginal control with only minimal toxicity and without any negative impact on quality of life [15,21]. Vaginal brachytherapy is a local treatment of the vaginal vault region (where 75% of the local recurrences in the NAT arm of the PORTEC-1 trial were located), leaving regional pelvic nodes untreated. Clinical pelvic regional recurrence only occurred in 3.4% of the NAT patients in PORTEC-1 and in 3.8% of the VBT patients in PORTEC-2 at 5 years and most had synchronous distant metastases for which systemic therapy was needed. However, the optimal adjuvant treatment of patients whose tumours have substantial LVSI can be debated.

In both PORTEC trials routine staging lymphadenectomy was not performed, in contrast to GOG#99. However, even after routine lymphadenectomy in GOG#99 recurrence was reduced with pelvic radiotherapy [12]. With two large randomised trials showing no survival benefit but increased morbidity, it is currently widely accepted that a staging lymphadenectomy is not indicated in low- and intermediate-risk EC [22,23]. Available evidence points in the direction that (substantial) LVSI in the primary tumour serves as a surrogate marker for both (microscopically) involved lymph nodes and more distant disease spread. Pelvic EBRT offers a significant reduction in the risk of both pelvic nodal recurrence and vaginal recurrence in patients with risk factors, both with and without lymphadectomy. Patients with substantial LVSI who received NAT or VBT had a 5-year risk of pelvic regional recurrence of 25–30% that was reduced to 5% with EBRT. These patients were only 5% of all PORTEC-1 and -2 trial patients, and these may well be the small subgroup of patients with increased risk of pelvic and distant relapse justifying the use of EBRT as for them the benefits outweigh the risks [24,25].

Given the increased risk of distant metastasis in cases with substantial LVSI, it seems logical to explore adjuvant systemic treatment in these patients. However, despite that adjuvant chemotherapy is increasingly employed in high-risk EC, there is no data showing a benefit of chemotherapy specifically for patients with (substantial) LVSI. Recently the results of the GOG#249 trial in stage I–II, high-intermediate and high-risk EC patients have been presented and showed no benefit of the combination of VBT and three adjuvant cycles of carboplatin/paclitaxel compared to EBRT alone [26]. The results of the PORTEC-3 and GOG#258 trials comparing EBRT plus chemotherapy

versus EBRT alone and versus chemotherapy alone, respectively, are therefore eagerly awaited.

It will be essential to determine which specific patients benefit from adjuvant therapy. In the near future, molecular factors may be used for selecting specific tumours that are sensitive for systemic therapies.

In conclusion, substantial LVSI using a three-tiered scoring system (see Table 1 for detailed description) is the strongest independent prognostic factor for pelvic regional recurrence, distant metastasis and overall survival. Adjuvant EBRT should be considered for the small subgroup of stage I EC patients who have substantial LVSI, especially those with grade 3 tumours, and the role of systemic therapy should be determined.

Conflict of interest statement

None declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ejca.2015.05.015.

References

[1] Creutzberg CL, van Putten WL, Warlam-Rodenhuis CC, et al. Outcome of high-risk stage IC, grade 3, compared with stage I endometrial carcinoma patients: the postoperative radiation therapy in endometrial carcinoma trial. J Clin Oncol 2004;22(7):1234–41. http://dx.doi.org/10.1200/JCO.2004.08.159 [published Online First: Epub Date].

[2] Chi DS, Barakat RR, Palayekar MJ, et al. The incidence of pelvic lymph node metastasis by FIGO staging for patients with adequately surgically staged endometrial adenocarcinoma of endometrioid histology. Int J Gynecol Cancer 2008;18(2):269–73. http://dx.doi.org/10.1111/j.1525-1438.2007.00996.x [published Online First: Epub Date].

[3] Creasman WT, Morrow CP, Bundy BN, et al. Surgical pathologic spread patterns of endometrial cancer. A gynecologic oncology group study. Cancer 1987;60(8 Suppl.):2035–41.

[4] Cohn DE, Horowitz NS, Mutch DG, et al. Should the presence of lymphvascular space involvement be used to assign patients to adjuvant therapy following hysterectomy for unstaged endometrial cancer? Gynecol Oncol 2002;87(3):243–6.

[5] Gadducci A, Cavazzana A, Cosio S, et al. Lymph-vascular space involvement and outer one-third myometrial invasion are strong predictors of distant haematogeneous failures in patients with stage I–II endometrioid-type endometrial cancer. Anticancer Res 2009;29(5):1715–20.

[6] Gemer O, Arie AB, Levy T, et al. Lymphvascular space involvement compromises the survival of patients with stage I endometrial cancer: results of a multicenter study. Eur J Surg Oncol 2007;33(5):644–7. http://dx.doi.org/10.1016/j.ejso.2007.01.009 [published Online First: Epub Date].

[7] Guntupalli SR, Zighelboim I, Kizer NT, et al. Lymphovascular space invasion is an independent risk factor for nodal disease and poor outcomes in endometrioid endometrial cancer. Gynecol Oncol 2012;124(1):31–5. http://dx.doi.org/10.1016/j.ygyno.2011.09.017 [published Online First: Epub Date].

[8] Hahn HS, Lee IH, Kim TJ, et al. Lymphovascular space invasion is highly associated with lymph node metastasis and recurrence in endometrial cancer. Aust N Z J Obstet Gynaecol 2013;53(3):293–7. http://dx.doi.org/10.1111/ajo.12089 [published Online First: Epub Date].

[9] O'Brien DJ, Flannelly G, Mooney EE, et al. Lymphovascular space involvement in early stage well-differentiated endometrial cancer is associated with increased mortality. BJOG 2009;116(7):991–4. http://dx.doi.org/10.1111/j.1471-0528.2009.02162.x [published Online First: Epub Date].

[10] Vaizoglu F, Yuce K, Salman MC, et al. Lymphovascular space involvement is the sole independent predictor of lymph node metastasis in clinical early stage endometrial cancer. Arch Gynecol Obstet 2013;288(6):1391–7. http://dx.doi.org/10.1007/s00404-013-2913-x [published Online First: Epub Date].

[11] Briet JM, Hollema H, Reesink N, et al. Lymphvascular space involvement: an independent prognostic factor in endometrial cancer. Gynecol Oncol 2005;96(3):799–804. http://dx.doi.org/10.1016/j.ygyno.2004.11.033 [published Online First: Epub Date].

[12] Keys HM, Roberts JA, Brunetto VL, et al. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study. Gynecol Oncol 2004;92(3):744–51. http://dx.doi.org/10.1016/j.ygyno.2003.11.048 [published Online First: Epub Date].

[13] Creutzberg CL, van Putten WL, Koper PC, et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. Lancet 2000;355(9213):1404–11.

[14] ASTEC Group, Blake P, Swart AM, et al. Adjuvant external beam radiotherapy in the treatment of endometrial cancer (MRC ASTEC and NCIC CTG EN.5 randomised trials): pooled trial results, systematic review, and meta-analysis. Lancet 2009;373(9658):137–46. http://dx.doi.org/10.1016/S0140-6736(08)61767-5 [published Online First: Epub Date].

[15] Nout RA, Smit VT, Putter H, et al. Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial. Lancet 2010;375(9717):816–23. http://dx.doi.org/10.1016/S0140-6736(09)62163-2 [published Online First: Epub Date].

[16] Aalders J, Abeler V, Kolstad P, et al. Postoperative external irradiation and prognostic parameters in stage I endometrial carcinoma: clinical and histopathologic study of 540 patients. Obstet Gynecol 1980;56(4):419–27.

[17] Murray SK, Young RH, Scully RE. Unusual epithelial and stromal changes in myoinvasive endometrioid adenocarcinoma: a study of their frequency, associated diagnostic problems, and prognostic significance. Int J Gynecol Pathol 2003;22(4):324–33. http://dx.doi.org/10.1097/01.pgp.0000092161.33490.a9 [published Online First: Epub Date].

[18] Fujimoto T, Nanjyo H, Fukuda J, et al. Endometrioid uterine cancer: histopathological risk factors of local and distant recurrence. Gynecol Oncol 2009;112(2):342–7. http://dx.doi.org/10.1016/j.ygyno.2008.10.019 [published Online First: Epub Date].

[19] Hachisuga T, Kaku T, Fukuda K, et al. The grading of lymphovascular space invasion in endometrial carcinoma. Cancer 1999;86(10):2090–7.

[20] Ambros RA, Kurman RJ. Combined assessment of vascular and myometrial invasion as a model to predict prognosis in stage I endometrioid adenocarcinoma of the uterine corpus. Cancer 1992;69(6):1424–31.

[21] Nout RA, Putter H, Jurgenliemk-Schulz IM, et al. Quality of life after pelvic radiotherapy or vaginal brachytherapy for endometrial cancer: first results of the randomized PORTEC-2 trial. J Clin Oncol 2009;27(21):3547–56. http://dx.doi.org/10.1200/JCO.2008.20.2424 [published Online First: Epub Date].

[22] Aalders JG, Thomas G. Endometrial cancer–revisiting the importance of pelvic and para aortic lymph nodes. Gynecol Oncol 2007;104(1):222–31. http://dx.doi.org/10.1016/j.ygyno.2006.10.013 [published Online First: Epub Date].

[23] Mariani A, Dowdy SC, Cliby WA, et al. Prospective assessment of lymphatic dissemination in endometrial cancer: a paradigm shift in surgical staging. Gynecol Oncol 2008;109(1):11–8. http://dx.doi.org/10.1016/j.ygyno.2008.01.023 [published Online First: Epub Date].

[24] Nout RA, Putter H, Jurgenliemk-Schulz IM, et al. Five-year quality of life of endometrial cancer patients treated in the randomised Post Operative Radiation Therapy in Endometrial Cancer (PORTEC-2) trial and comparison with norm data. Eur J Cancer 2012;48(11):1638–48. http://dx.doi.org/10.1016/j.ejca.2011.11.014 [published Online First: Epub Date].

[25] Nout RA, van de Poll-Franse LV, Lybeert ML, et al. Long-term outcome and quality of life of patients with endometrial carcinoma treated with or without pelvic radiotherapy in the post operative radiation therapy in endometrial carcinoma 1 (PORTEC-1) trial. J Clin Oncol 2011;29(13):1692–700. http://dx.doi.org/10.1200/JCO.2010.32.4590 [published Online First: Epub Date].

[26] McMeekin DS, Filiaci VL, Aghajanian C. A randomized phase III trial of pelvic radiation therapy (PXRT) versus vaginal cuff brachytherapy followed by paclitaxel/carboplatin chemotherapy (VCB/C) in patients with high risk (HR), early stage endometrial cancer (EC): a Gynecologic Oncology Group trial. Late-breaking Abstract 1, Society of Gynecological Oncology Meeting 2014 2014.