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Prognostic factors for and pattern of lymph-node involvement in patients with operable cervical cancer

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Abstract

Purpose Lymph node metastases significantly worsen the prognosis in cervical carcinoma. Risk factors—pathological and patient related—could select patients at high risk for lymph node involvement.

Methods This retrospective analysis was performed by analyzing data from patients with cervical carcinoma treated between 2000 and 2017 at the Department of Obstetrics and Gynecology of the University Hospital Ulm.

Results In total, 261 patients with cervical carcinoma (International Federation of Gynecology and Obstetrics (FIGO) stage IA–IIB) and lymphadenectomy with at least 10 removed lymph nodes were available for analysis. Overall, 86 (33.0%) patients had lymph node metastases; 73 patients had pelvic lymph node metastases only and 13 patients had both pelvic and paraaortic lymph node metastases. Lymph node metastases were found most often in the region of the external iliac artery and obturator fossa, with 57.0% and 54.7% of all 86 node-positive patients, respectively. Univariable analyses showed that presence of lymph node metastases was significantly associated with both preoperative FIGO stage ($p=0.001$) and final pathological tumor stage ($p<0.001$), status of resection margin ($p=0.002$), lymphovascular space invasion (LVSI), ($p<0.001$) and vascular space invasion, ($p<0.001$). In a multivariable logistic regression model with presence of lymph node metastases (yes/no) as binary response variable, only LVSI ($p<0.001$) and body mass index (BMI), ($p=0.035$) remained as significant independent predictors of lymph node involvement. Subgroup analyses showed that LVSI was a significant predictive factor for lymph node involvement in patients with a preoperatively assessed FIGO stage < IIB ($p<0.001$), but not for patients with a preoperatively assessed FIGO stage ≥ IIB ($p=0.122$).

Conclusions The risk factor LVSI should play an important role in deciding whether an individualized therapy concept is based on escalating or deescalating treatment. In future, the sentinel concept could reduce morbidity and at the same time provide an important prognostic assessment for a subset of cervical cancer patients.

Keywords Cervical cancer · Lymph node · Prognostic factor · Pattern · LVSI

Introduction

Lymph node metastases significantly worsen the prognosis in cervical carcinoma [1, 2] and assessment of lymph node involvement is therefore important for preoperative therapy planning. Nevertheless, preoperative lymph node staging has now been included in the International Federation of Gynecology and Obstetrics (FIGO) staging guidelines for the first time [3]. However, it should be considered that the predictive value of lymph node metastases is inferior to surgical staging in imaging techniques [4, 5]. The lack of preoperatively available information has implications for further adjuvant treatment, as patients with initially unknown lymph node metastases usually need additional postoperative therapies such as chemotherapy or chemoradiation. However, the combination of different treatment modalities results in elevated patients morbidities and therefore should be avoided [6]. In contrast to preoperative staging procedures, systematic lymph node staging is an integral component of surgical therapy in early cervical carcinoma [7, 8]. According to current German treatment guideline, patients with suspected pelvic lymph node metastases should be staged with pelvic lymphadenectomy (LNE) [9]. In case of involved pelvic lymph nodes, a paraaortic LNE is recommended for the determination of field extension for chemoradiation. On the

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other hand, increasing acceptance and feasibility of sentinel lymph node biopsy (SNB) in clinically node-negative cervical cancer could lead to a reduction of the extensive lymph node assessment, but so far has not reached clinical routine [10].

Several factors like large clinical tumor size, deep cervical stroma invasion and LVSI are associated with an increased risk of recurrence and poor overall survival [11–13] in early and advanced stages of cervical cancer. The presence of lymph node metastases has also negative prognostic impact [14], while parametrial infiltration alone without lymph node involvement does not always worsen the prognosis [15]. In addition to information regarding the presence of lymph node metastases, knowledge of the (suspected) localization of the lymph node metastases is important in order to find metastases as precisely as possible, but also to be able to operate in regions with low probability for the presence of positive lymph nodes and high morbidity with restraint. As treatment in oncology should avoid unnecessary toxicity, assessment of individual patient risk is essential to perform any surgical procedure in a risk-adapted manner. We therefore investigated which clinicopathological patient and tumor characteristics are associated with an increased risk for presence of lymph node metastases in cervical cancer and provide a more detailed analysis of the localizations of positive lymph nodes.

Methods

Study design and patients

Records from all patients with cervical cancer treated with radical hysterectomy, pelvic and—if necessary—paraaortic lymphadenectomy at the Department of Gynecology and Obstetrics, University Hospital Ulm, Germany between 2000 and 2017 were retrospectively analyzed. In total, 261 patients with complete data set (surgery report, clinical FIGO stage, final histology report and information on adjuvant therapy) and at least 10 removed lymph nodes could be included for this analysis. All patients had a complete bilateral pelvic lymphadenectomy along the common, the external and the internal iliac vessels and the obturator fossae. In the majority of patients with total mesometrial resection (TMMR) and independently of pelvic lymph node status, a lower paraaortic LNE (up to the inferior mesenteric artery) was performed. This approach is in line with the published concept of TMMR by Michael Höckel [16]. Bilateral salpingoophorectomy was performed depending on age or risk constellation.

All patient records were extracted from our clinical documentation system SAP GUI (Systeme, Anwendungen und Produkte in der Datenverarbeitung; Graphical User Interface) and SAP ISH (Industry Solution Hospital; version 6.17 SP 18).

Local ethics committee approval was given prior to the retrospective data assessment (Number 133/16). Because of the retrospective nature of this analysis patient consent was not required for ethical approval.

Data analysis

All categorical data are described with absolute and relative frequencies. As the metric variables age (years) and body mass index (BMI, kg/m^2) did not meet the assumptions of a normal distribution (Shapiro–Wilk test, both $p < 0.001$), they were described using median and range. Between-group comparisons regarding age or BMI were accordingly performed using the non-parametric Mann–Whitney U test, while between-group comparisons of categorical data were performed using the Chi square test. To analyze which factors independently predict lymph node involvement, we used a multivariable logistic regression (generalized linear model) with presence of positive nodes (yes/no) as a binary response variable. Age at diagnosis (years), BMI (kg/m^2), preoperative FIGO stage (IA, IB, IIA, IIB), histopathological grading ($G1$, $G2$, $G3/G4$), histological type (squamous, adenocarcinoma, other), lymphovascular space invasion (LVSI, no, yes), vascular space invasion (VSI, no, yes), resection status ($R0$, $R1$) and total number of lymph nodes removed were included as factors. As the result of the preoperatively obtained FIGO stage in terms of a FIGO stage < IIB versus ≥ IIB has important implications for the subsequent treatment, we performed a subgroup analysis by running the multivariable logistic regression separately for patients with a preoperative FIGO stage < IIB and for patients with a preoperative FIGO stage ≥ IIB. Furthermore, we performed a similar multivariable logistic regression analysis with presence of positive paraaortic lymph nodes (yes/no) as a binary response variable and the same variables included as factors for the subset of patients that received a paraaortic lymphadenectomy in addition to pelvic lymphadenectomy. As there was a quasi-complete separation by LVSI in the data (see results), Wald statistics and maximum likelihood estimates could not be calculated, and likelihood ratio tests were used to assess significance of parameters instead.

Statistical analyses were performed using the statistical software package SPSS® version 24 (IBM Corp. Armonk, NY, USA). All statistical tests were two-sided, and p values of less than 0.05 were considered significant.

Results

Patient and tumor characteristics

Details on patient and tumor characteristics are shown in Table 1. The median age was 46 (26–84) and median BMI was 24.8 (15.1–50.8). 221 (84.7%) patients underwent open radical hysterectomy, while 40 (15.3%) underwent minimal invasive surgery (conventional laparoscopy or robotic). Overall, paraaortal LNE was performed in 82 (31.4%) patients (80 patients in the open surgery group, 2 patients in the minimal invasive surgery group). In the open surgery group, 33 (14.9%) patients received a TMMR, and a lower paraaortic (up to inferior mesenteric artery) LNE was performed independently of pelvic lymph node status in 27 (81.8%) of these TMMR patients. In 7 (2.7%) patients, a previously unknown cervical carcinoma was found after conventional hysterectomy, these patients underwent a parametrectomy with partial colpectomy in a second procedure (parametrectomy after previous hysterectomy). In 2 (0.8%) patients, radical hysterectomy (RH) followed a caesarean section (RH following cesarean section). 16 (6.1%) patients had intraoperative complications (e.g. blood loss requiring transfusion, bladder injury) and 35 (13.4%) patients suffered a postoperative complication requiring an intervention. 11 (4.2%) patients received adjuvant chemotherapy, 16 (6.1%) patients received pelvic irradiation and 122 (46.7%) patients received combined chemoradiation.

Incidence and localization of lymph node metastasis

A pelvic lymphadenectomy was performed in all 261 patients. A median of 36 pelvic lymph nodes [interquartile range (IQR) 27–44, range 10–70] were removed. 86 (33.0%) patients showed pelvic lymph node metastases, with a median of 2 positive nodes (IQR = 1–5, range 1–17). An additional paraaortic lymphadenectomy was performed in 82 (31.4%) patients and in 13 (15.9%) cases paraaortic lymph node metastases were found (median = 2, IQR = 1–3.5, range = 1–9); all 13 patients with paraaortic lymph node metastases also had pelvic lymph node metastases. Overall, a median of 38 (IQR = 29–47, range 10–107) lymph nodes (pelvic and paraaortic lymph nodes combined) were removed in the 261 patients, and a median of 2 (IQR 1–5, range 1–25) positive nodes were found in the 86 patients that showed lymph node involvement.

The external iliac artery and obturator fossa were the most frequent regions of lymph node metastases with 57.0% and 54.7%, respectively, of all 86 node-positive patients. The areas of the internal and common iliac artery

Table 1 Baseline characteristics of patients with cervical carcinoma (*n* = 261)

Variable	
Age (years)	
Median	46
Range	26–84
Body mass index (kg/m^2)	
Median	24.8
Range	15.1–50.8
Unknown (*n*)	1
Type of surgery, *n* (%)	
Laparotomic (open) radical hysterectomy	179 (68.6%)
Laparoscopic (including robotic) radical hysterectomy	40 (15.3%)
Total mesometrial resection (TMMR)	33 (12.6%)
Parametrectomy after previous hysterectomy	7 (2.7%)
Radical hysterectomy (RH) following cesarean section	2 (0.8%)
Clinical FIGO stage, *n* (%)	
IA1	8 (3.1%)
IA2	10 (3.8%)
IB1	132 (50.6%)
IB2	31 (11.9%)
IIA1	18 (6.9%)
IIA2	5 (1.9%)
IIB	57 (21.8%)
Final (histologically confirmed) FIGO stage, *n* (%)	
IA1	9 (3.4%)
IA2	13 (5.0%)
IB1	94 (36.0%)
IB2	37 (14.2%)
IIA1	5 (1.9%)
IIA2	11 (4.2%)
IIB	91 (34.9%)
IIIB	1 (0.4%)
Histological grading, *n* (%)	
*G*1	11 (4.2%)
*G*2	126 (48.3%)
*G*3/*G*4	120 (46.0%)
Missing	4 (1.5%)
Histological type, *n* (%)	
Squamous	192 (73.6%)
Adenocarcinoma	47 (18.0%)
Other	22 (8.4%)
Tumor-free margins, *n* (%)	
Yes	244 (93.5%)
No	16 (6.1%)
Missing	1 (0.4%)
Lymphovascular space invasion (LVSI), *n* (%)	
No	111 (42.5%)
Yes	150 (57.5%)
Vascular space invasion (VSI), *n* (%)	
No	223 (85.4%)

Table 1 (continued)

Variable	
Yes	37 (14.2%)
Unknown	1 (0.4%)
Lymphadenectomy procedure, *n* (%)	
Pelvic only	179 (68.6%)
Pelvic and para-aortic	82 (31.4%)
Number of pelvic lymph nodes removed	
Median	36
Range	10–70
Pelvic lymph nodes	
Negative nodes only, *n* (%)	175 (67.0%)
At least one positive node, *n* (%) (median, range)	86 (33.0%) (2, 1–17)
Para-aortic lymph nodes removed	
No	179 (68.6%)
Yes	82 (31.4%)
Number of para-aortic lymph nodes removed	
Median	12
Range	1–52
Para-aortic lymph nodes ($n=82$)	
Negative nodes only, *n* (%)	69 (84.1%)
At least one positive node, *n* (%) (median, range)	13 (15.9%) (2, 1–9)
Number of pelvic and paraaortic lymph nodes removed	
Median	38
Range	10–107
Adjuvant treatment, *n* (%)	
No chemo- or radiotherapy	108 (41.4%)
Chemotherapy only	11 (4.2%)
Radiotherapy only	16 (6.1%)
Chemoradiation	122 (46.7%)
Missing	4 (1.5%)

were affected less often, with 44.2% and 24.4% of node-positive patients, respectively. Only rarely affected regions with 5.8% of patients with lymph node metastases were the circumflex iliac nodes distal to the external iliac nodes (CINDEIN), while presacral lymph node metastases were present in only one patient (1.1%). Out of the 13 patients with paraaortic lymph node involvement, 8 (61.5%) and 10 (76.9%) patients had positive nodes below and above the inferior mesenteric artery, respectively.

Associations of patient and tumor characteristics with lymph node involvement

Table 2 shows the results of univariable analyses regarding the associations between the presence of any lymph node metastases and patients or tumor characteristics. Presence of lymph node metastases was significantly associated with both preoperative FIGO stage ($p=0.001$) and final pathological tumor stage ($p<0.001$), status of resection margin ($p=0.002$), LVSI ($p<0.001$) and VSI ($p<0.001$). The association between the presence of lymph node metastases and the total number of lymph nodes removed was nearly significant in univariable analysis ($p=0.058$). A multivariable logistic regression model with presence of positive nodes (yes/no) as a binary response variable showed that LVSI ($p<0.001$) and BMI ($p=0.035$) were significant independent predictors for the presence of positive nodes. The total number of lymph nodes removed ($p=0.097$), resection status ($p=0.097$) and vascular space invasion ($p=0.058$) were almost significant predictive factors, whereas there was no evidence of a predictive value for age, histopathological grading, histological type, and clinical FIGO stage (Table 3). To assess the prognostic value of LVSI for the clinically meaningful subgroups of patients with a preoperatively obtained FIGO stage < IIB/≥ IIB, we additionally ran two separate multivariable logistic regressions. The model for patients with a preoperatively obtained FIGO stage < IIB clearly confirmed the prognostic value of LVSI ($p<0.001$); VSI was an almost significant predictive factor ($p=0.053$), while the other parameters showed no predictive value (all $p>0.1$). In contrast, the model for patients with a preoperatively obtained FIGO stage ≥ IIB revealed no significant predictive value for LVSI ($p=0.122$), with only the total number of removed lymph nodes ($p=0.027$) and resection status ($p=0.035$) significantly predicting the presence of positive nodes in these patients.

We also performed a multivariable logistic regression with presence of paraaortic positive nodes (yes/no) as a binary response variable that included only the 82 patients with paraaortic lymphadenectomy. All 13 patients with positive paraaortic nodes had evidence of LVSI. Because of this quasi-complete separation of the data by LVSI, we used likelihood ratio tests to assess the statistical significance of parameters (see methods). The model showed that only LVSI ($p=0.005$) and number of removed paraaortic nodes ($p=0.018$) significantly predicted the presence of positive paraaortic lymph nodes; there was no significant effect of age, BMI, histopathological grading, histological type, clinical FIGO stage, resection status, or VSI (all $p>0.30$).

Discussion

In this study, we found that lymph node metastases in the pelvis were present in 86 out of 261 (33.0%) cervical carcinoma patients, with 2 of these patients having clinical FIGO stage IA and the remaining patients FIGO stages IB–IIB cervical cancer. Paraaortic lymph node metastases were found in 13 (15.9%) of the 82 patients that received an additional paraaortic lymphadenectomy, and all patients with positive paraaortic lymph nodes had also pelvic lymph

Table 2 Baseline characteristics of patients and clinicopathological variables according to lymph node involvement

Variable	Patients with negative lymph nodes only $n = 175$	Patients with positive lymph nodes $n = 86$	p value[a]
Age (years)			0.562[b]
Median	46	46	
Range	26–80	29–84	
Body mass index (kg/m^2)			0.566[b]
Median	24.6	25.4	
Range	15.1–50.8	16.2–42.2	
Clinical FIGO stage, n (%)			0.001[c]
IA	16 (9.1%)	2 (2.3%)	
IB	118 (67.4%)	45 (52.3%)	
IIA	13 (7.4%)	10 (11.6%)	
IIB	28 (16.0%)	29 (33.7%)	
Final (histologically confirmed) FIGO stage, n (%)			< 0.001[c]
IA	21 (12.0%)	1 (1.2%)	
IB	107 (61.1%)	24 (27.9%)	
IIA	9 (5.1%)	7 (8.1%)	
IIB	38 (21.7%)	53 (61.6%)	
III/IV	0 (0.0%)	1 (1.2%)	
Type of surgery, n (%)			0.144[c]
Laparotomic (open) RH	118 (67.4%)	61 (70.9%)	
Laparoscopic (including robotic) RH	32 (18.3%)	8 (9.3%)	
TMMR	18 (10.3%)	15 (17.4%)	
Parametrectomy after hysterectomy	6 (3.4%)	1 (1.2%)	
RH following cesarean section	1 (0.6%)	1 (1.2%)	
Histological type, n (%)			0.145[c]
Squamous	125 (71.4%)	67 (77.9%)	
Adenocarcinoma	37 (21.1%)	10 (11.6%)	
Others	13 (7.4%)	9 (10.5%)	
Histological grading, n (%)			0.118[c]
$G1$	9 (5.1%)	2 (2.3%)	
$G2$	90 (51.4%)	36 (41.9%)	
$G3/G4$	73 (41.7%)	47 (54.7%)	
Missing	3 (1.7%)	1 (1.2%)	
Tumor-free margins, n (%)			0.002[c]
Negative	169 (96.6%)	75 (87.2%)	
Positive	5 (2.9%)	11 (12.8%	
Missing	1 (0.6%)	0 (0.0%)	
LVSI, n (%)			< 0.001[c]
No	101 (57.7%)	10 (11.6%)	
Yes	74 (42.3)	76 (88.4%)	
Vascular space invasion, n (%)			< 0.001[c]
No	162 (92.6%)	61 (70.9%)	
Yes	13 (7.4%)	24 (27.9%)	
Missing	0 (0.0%)	1 (1.2%)	
Number of pelvic lymph nodes removed			0.699[b]
Median	36.0	35.5	
Range	10–70	11–69	
Paraaortic lymph nodes removed			< 0.001[c]
No	142 (81.1%)	37 (43.0%)	
Yes	33 (18.9%)	49 (57.0%)	

Table 2 (continued)

Variable	Patients with negative lymph nodes only $n = 175$	Patients with positive lymph nodes $n = 86$	p value[a]
Number of paraaortic lymph nodes removed			0.073[b]
Median	4	7	
Range	1–52	1–46	
Total number of lymph nodes removed			0.058[b]
Median	38.0	42.0	
Range	10–102	11–107	

[a]All tests without unknowns

[b]Mann–Whitney U test

[c]Chi square test

Table 3 Multivariable logistic regression model with lymph node involvement (yes/no) as a binary response variable

Variable	Odds ratio	95% CI	p
Age at diagnosis (years)	1.013	0.986–1.042	0.351
BMI (kg/m^2)	0.938	0.884–0.995	0.035
Total number of lymph nodes removed	1.017	0.997–1.038	0.097
Clinical FIGO stage			0.495
IB versus IA	2.894	0.533–15.140	0.208
IIA versus IA	3.300	0.519–21.000	0.206
IIB versus IAa	3.854	0.675–21.996	0.129
Grading			0.614
G2 versus G1	0.700	0.069–7.090	0.763
G3/G4 versus G1	0.961	0.094–9.785	0.973
Histological type			0.479
Adenocarcinoma versus squamous	0.846	0.325–2.203	0.731
Other versus squamous	1.885	0.616–5.771	0.267
LVSI			
Yes versus no	9.051	3.940–20.789	< 0.001
Vascular space invasion			
Yes versus no	2.253	0.973–5.214	0.058
Tumor-free margins			
Yes versus no	3.009	0.818–11.069	0.097

node metastases (i.e. there were no isolated paraaortic lymph node metastases). The incidence of lymph node metastases in FIGO stages IB to IIB cervical cancer is described at 15–31%, with increasing incidence in higher tumor stages [17]. Thus, our findings are in line with the previous reported numbers. Taken together, these results show that almost 70–85% of all patients with LNE undergo an unnecessary surgical procedure with potential short- and long-term complications only for diagnostic assessment of lymph node status.

The median number of 36 removed pelvic lymph nodes in our study is clearly above that of other studies [18–20]. In addition, the median number of 12 removed paraaortic lymph nodes in patients with paraaortic lymphadenectomy is also high comparable to other studies [21]. However, there are no clear recommendations for a minimum number of pelvic and/or paraaortic lymph nodes to be removed in national and international guidelines [9, 22]. Nevertheless, the results of Matsuo et al., like our data, show a significant correlation between the number of paraaortal lymph nodes removed and the presence of metastases [21].

Lymph node status is the most important prognostic factor in cervical carcinoma [2]. Positive pelvic lymph node status reduces 5-year overall survival to 52% compared to 89% for node-negative patients [15]. In particular, paraaortic lymph node metastases have an extreme poor prognosis (2 years OS of 14% with paraaortic LNE) [23]. Based on results that demonstrate a poor prognosis in cervical cancer patients with lymph node metastases, lymph node involvement is incorporated in the recently published revised cervical cancer staging recommendations of the FIGO Gynecologic Oncology Committee. Stage IIIC1 is assigned to cases with only pelvic positive nodes and stage IIIC2 is assigned to cases where paraaortic nodes are also involved [3]. The updated FIGO classification, which also offers the possibility to include the radiological findings of the nodal status, raises considerable difficulties. Since CT and especially MRI have considerable weaknesses [10] in the prediction of lymph node status, histopathological prognostic factors are particularly important in therapy decisions.

According to current international guidelines, surgical therapy should be considered as primary treatment up to and including FIGO stage IIA [22]. For tumors larger than 4 cm (FIGO IB2, IIA2), the therapy decision should individually be determined depending on the presence of additional risk factors such as LVSI, cervical stroma invasion, or suspected lymph nodes [22] with the aim of preventing multimodal therapies [8]. In a survey of German gynaecological clinics, Mangler et al. showed that 45.6% of centres preferred radical hysterectomy and adjuvant chemoradiation in FIGO stage IIB [24], even though there is no oncological advantage over primary chemoradiation [25]. In 2014, the German guideline amended “preferred” to the “recommendation” of primary chemoradiation for FIGO stage IIB [9]; however, primary surgical therapy for stages IB2, IIA2 and IIB remains an option in cases with proven negative lymph nodes. Based on the previous German guideline recommendations, patients with cervical cancer up to FIGO stage IIB and clinically unsuspicious abdominal lymph nodes were treated with primary surgery.

The distribution of lymph node metastases shows mostly positive nodes in the region of external iliac artery (57.0%) and obturator fossa (54.7%) which correlates with other studies [26, 27]. These localizations were also found in studies regarding the sentinel concept, where Marnitz et al. could demonstrate that more than 80% of the sentinel lymph nodes were detected in the external pelvic, interiliac and obturator region [28]. A further study has also identified the region of the external and internal iliac vessels and the obturator fossa as the most common site of lymph node metastases in patients with FIGO stage IB [29]. On the other hand, the circumflex iliac nodes distal to the external iliac nodes (CINDEIN) in our collective are the least likely to show lymph node metastases. This is consistent with another study in which this region was explicitly investigated, with the result that ultimately only 0.6–1.2% positive lymph nodes were detected in these regions in stages FIGO IA–IIA [30].

In our study, univariable analyses revealed significant associations between presence of lymph node metastases and several clinicopathological factors (preoperative FIGO stage, final pathological tumor stage, status of resection margin, LVSI and VSI). However, a multivariable logistic regression model showed that only BMI and LVSI were significant independent predictive factors for lymph node involvement. In particular, LVSI (found in 57.5% of our patients) with an odds ratio of 9.05 was highly predictive for lymph node involvement. In addition, LVSI was found to be the only significant clinicopathological predictor (besides the number of removed paraaortic nodes) for the presence of paraaortic lymph node metastases, which are associated with a particularly poor prognosis. LVSI has already been described as intermediate risk factor in other studies [11, 31] and is part of several risk models for optimal therapy planning [2, 32]. However, these risk models are so far not used in clinical routine, either due to low sensitivity or the risk of over-treatment [33]. Interestingly, risk factors for therapy recommendations are evaluated differently in different countries. While the National Comprehensive Cancer Network (NCCN) guidelines in the USA, the European Society of Medical Oncology (ESMO) guidelines and the German guidelines of the Arbeitsgemeinschaft für Gynäkologische Onkologie (AGO) cite a positive resection margin as an indication for concomittant chemoradiation, the Japan Society of Gynecologic Oncology (JSGO) does not consider this factor [2]. The number of lymph nodes removed (< 15) is considered a risk factor in the AGO guidelines, whereas this is irrelevant in the American, Japanese or European guidelines [2]. To assess the risk of nodal involvement based on LVSI, the LVSI status should be determined at the biopsy or the cone. LVSI—proven in the cone—was found to be a significant prognostic factor for parametrial infiltration [34]. However, Bidus et al. could show that the negative predictive values for assessing LVSI based on biopsy, cold knife cone (CKC) or loop electrical excision procedure (LEEP) were only 0.45, 0.83 and 0.57, respectively [35]. As a consequence, it seems to be important that sufficient tissue is removed to determine all prognostically relevant histological factors as a basis for further therapy decisions, with particular emphasis on the examination of LVSI. On the other hand—and to our knowledge this has not yet been demonstrated—LVSI was only a significant ($p < 0.001$) prognostic factor for the prediction of lymph node metastases in the clinical stages FIGO < IIB, but not ($p = 0.122$) for the stages FIGO IIB or higher. This shows that the prognostic value of LVSI in higher stages seems to be limited.

The fact that we did not know which method (biopsy or cone) was used to assess LVSI is one limitation of our study. Furthermore, the retrospective character and the lack of information on known risk factors such as deep stromal infiltration are limiting our study. However, the strength of the study lies in the relatively large number of patients with histologically confirmed FIGO IA–IIB cervical cancer that received lymphadenectomy with high numbers of removed lymph nodes.

The future of nodal staging in operable cervical cancer clearly lies in the sentinel technique. The advantages are obvious: reduced morbidity through the removal of only single lymph nodes, targeted removal of the key lymph nodes, detection of micrometastases or isolated tumour cells through ultrastaging by the pathologist, to name but a few. Nevertheless, the achievement of a bilateral pelvic detection of sentinel lymph nodes, the unclear prognostic value of micrometastases and isolated tumor cells and the selection of the optimal tracer are among other issues that have not yet been conclusively clarified to implement this method by standard in any treatment [36]. Especially in situations where sentinel lymph nodes can only be unilaterally visualized and risk factors such as obesity or LVSI are present at the same time, a systematic lymphadenectomy should be performed on this side.

Conclusion

This retrospective single center study confirmed the prognostic value of LVSI in cervical cancer with FIGO stage IA–IIB and demonstrated an association of LVSI not only with the presence of any positive nodes but also specifically with the presence of paraaortic lymph node metastases, which per se indicate a poor prognosis. In contrast, other clinicopathological factors such as preoperative FIGO stage, age, histopathological grading and histological type were not associated with positive lymph nodes. The high predictive value of LVSI with regard to lymph node involvement in early cervical cancer patients should be taken into account for therapy decisions. As the presence of lymph node metastases detected during surgery has a great impact on following treatment, the avoidance of multimodal therapy should have high priority. The incorporation of the sentinel concept might lead to a reduction in morbidity and at the same time precisely detect the typical anatomical localizations of potential lymph node metastasis.

Author's contribution PW: Protocol/project development, Data collection or management, Data analysis, Manuscript writing/editing. WJ: Protocol/project development, Manuscript editing. CS: Manuscript editing, Protocol development. ADG: Data collection, Manuscript editing. NDG: Data collection, Manuscript editing. TWPF: Data analysis, Statistics, Manuscript editing.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This retrospective analysis was approved by the ethic committee of the university of Ulm, Germany. Number 133/16.

Informed consent Informed consent was not possible in this study due to retrospective data collection.

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