Diagnostic performance of ultrasonography in pre-operative assessment of lymph nodes in patients with cervical cancer

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ABSTRACT

Objectives To assess the diagnostic performance of ultrasonography in pre-operative assessment of lymph nodes in patients with cervical cancer, to compare the outcomes for pelvic and para-aortic regions, and to detect macrometastases and micrometastases separately.

Methods Patients were retrospectively included if they met the following inclusion criteria: pathologically verified cervical cancer; ultrasonography performed by one of four experienced sonographers; surgical lymph node staging, at least in the pelvic region—sentinel lymph node biopsy or systematic pelvic lymphadenectomy or debulking. The final pathological examination was the reference standard.

Results 390 patients met the inclusion criteria between 2009 and 2019. Pelvic node macrometastases (≥2 mm) were confirmed in 54 patients (13.8%), and micrometastases (≥0.2 mm and <2 mm) in another 21 patients (5.4%). Ultrasonography had sensitivity 72.2%, specificity 94.0%, and area under the curve (AUC) 0.831 to detect pelvic macrometastases, while sensitivity 53.3%, specificity 94.0%, and AUC 0.737 to detect both pelvic macrometastases and micrometastases (pN1). Ultrasonography failed to detect pelvic micrometastases, with sensitivity 19.2%, specificity 85.2%, and AUC 0.522. There was no significant impact of body mass index on diagnostic accuracy. Metastases in para-aortic nodes (macrometastases only) were confirmed in 16 of 71 patients who underwent para-aortic lymphadenectomy. Ultrasonography yielded sensitivity 56.3%, specificity 98.2%, and AUC 0.772 to identify para-aortic node macrometastases.

Conclusion Ultrasonography performed by an experienced sonographer can be considered a sufficient diagnostic tool for pre-operative assessment of lymph nodes in patients with cervical cancer, showing similar diagnostic accuracy in detection of pelvic macrometastases as reported for other imaging methods (18F-fluorodeoxyglucose positron emission tomography/CT or diffusion-weighted imaging/MRI). It had low sensitivity for detection of small-volume macrometastases (largest diameter <5 mm) and micrometastases. The accuracy of para-aortic assessment was comparable to that for pelvic lymph nodes, and assessment of the para-aortic region should be an inseparable part of the examination protocol.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Although ultrasonography is considered to be an adequate alternative to MRI for pre-operative local staging of cervical cancer, there is very limited evidence on its diagnostic accuracy in assessment of pelvic lymph nodes, and no relevant evidence on assessment of para-aortic lymph nodes.

WHAT THIS STUDY ADDS

⇒ This is the first study to systematically evaluate diagnostic performance of ultrasonography in pre-operative assessment of both pelvic and para-aortic lymph nodes in patients with cervical cancer. The diagnostic performance is assessed for pelvic macrometastases, micrometastases, and the sum of both (pN1) per patient and per pelvic side. It is a retrospective analysis of a large prospective single institution registry.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The outcomes of the study demonstrate that transrectal (or transvaginal) and transabdominal ultrasonography performed by experienced sonographers yield similar diagnostic accuracy to detect metastatic pelvic and para-aortic lymph nodes as other state-of-the-art imaging methods. Since all imaging methods share the same limitations in assessment of lymph nodes, it is clinically meaningful to incorporate ultrasonography in pre-operative locoregional work-up of patients with cervical cancer. For future research, prospective comparison of all imaging methods in one cohort, assessment of inter-operator variability, and cost effectivity is needed.

INTRODUCTION

The presence of metastases in pelvic and para-aortic nodes is one of the most significant prognostic factors for recurrence and adverse overall survival in patients with cervical cancer. Recent analysis of a large prospective registry documented 5-year overall survival of 92.0% and 74.0%, for node-negative early-stage (T1a–T1b2, T2a1) and locally advanced (T1b3, T2a2, T2b) cervical cancers, respectively, and 77.0% and 67.0%, respectively, for the same groups of cervical cancers with node metastases.[1]

For patients with node involvement, definitive chemoradiotherapy is indicated regardless of the local extent of disease, including early stages.[2]

Locally advanced cervical cancers T1b3 and higher (except T2a1) are usually treated by chemoradiation regardless of the node status.[3] Radical surgery should be omitted in these conditions to avoid severe morbidity caused by the combination of both modalities with no significant benefit for survival. However, detection of metastatic nodes helps to guide radiotherapy and tailor the radiation field with boosting.[4]

Nowadays, pre-operative staging based on MRI, or ultrasonography (USG) is recommended for local staging in almost all patients with cervical cancer. For locally advanced cervical cancers or in early stages with suspicious nodes on MRI or USG, fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) or CT should be considered.[5 6] Previous meta-analyses of FDG-PET/CT studies showed for all node regions moderate pooled sensitivities of 57.0–76.0% and high pooled specificities of 87.0–96.0%.[7–11] There were no significant differences in diagnostic performance of FDG-PET/CT between pelvic and para-aortic regions (pooled sensitivities 55.0–76.0% and 59.0–85.0%, respectively, pooled specificities 93.0–97.0% and 86.0–98.0%, respectively).[9–11]

Another option for evaluating nodes in cervical cancer is diffusion-weighted imaging MRI (DWI/MRI) combining morphological and functional characteristics.[12] Meta-analysis by Shen et al demonstrated for pelvic DWI/MRI moderate pooled sensitivity of 86.0% and specificity 84.0%.[13] In other meta-analyses, conventional MRI showed for all regions lower pooled sensitivities of 56.0–61.0% but higher pooled specificities of 89.0–93.0% (for pelvic

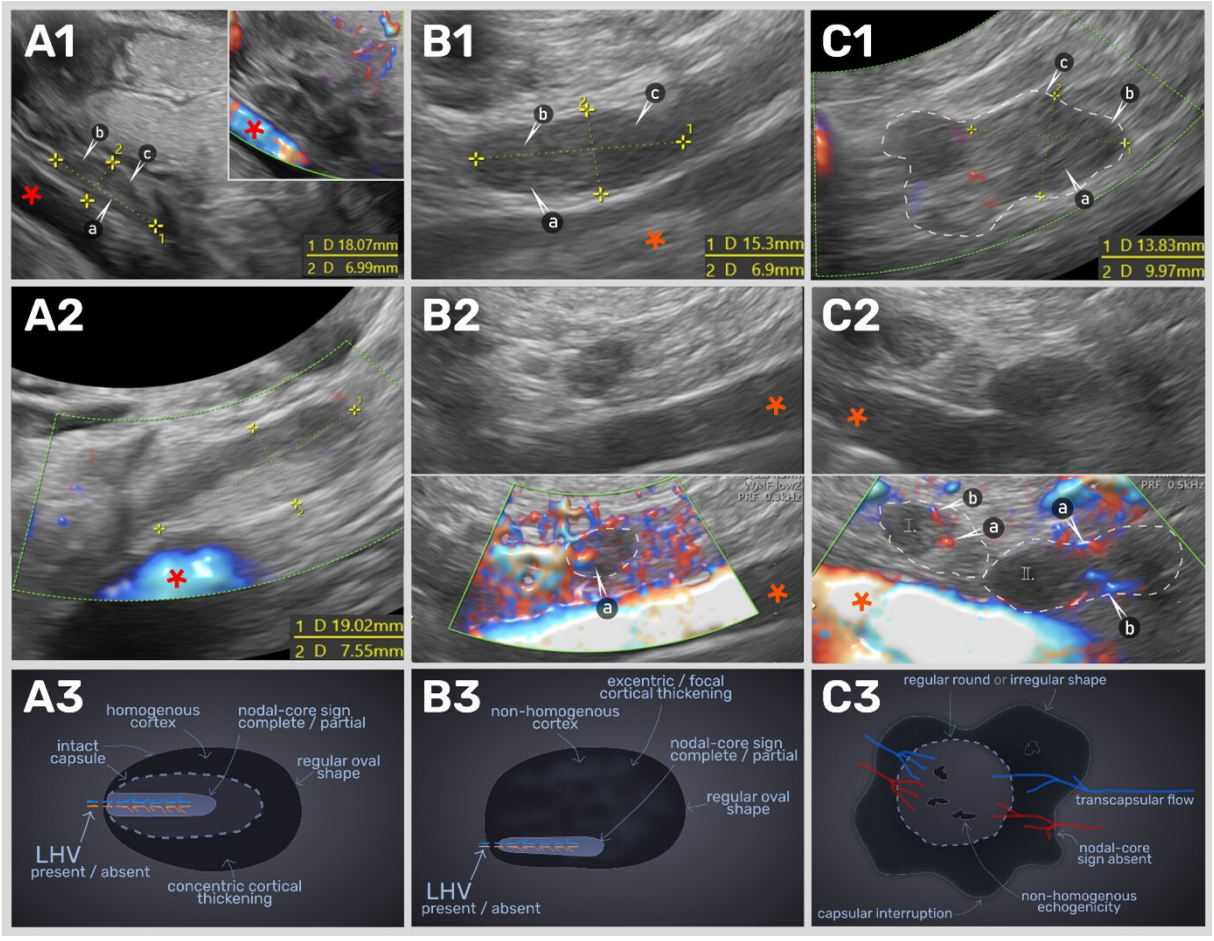

Figure 1 Gray scale ultrasonography (USG), Doppler images, and schematic drawings of pelvic lymph nodes. (A) USG negative lymph nodes: A1 lymph node in right obturator fossa bordered by calipers in yellow – (a) medulla, (b) homogeneous cortex, (c) intact capsule; A2 lymph node in left obturator fossa bordered by calipers in yellow, both show oval shape, partial nodal-core sign, and both are negative in patients with cervical squamous cell carcinoma; A3 schema of typical features of USG negative lymph nodes. (B) USG probably infiltrated lymph nodes (overlapping features of infiltrated and non-infiltrated lymph nodes): B1 lymph node in left external iliac region bordered by calipers in yellow – (a) medulla, (b) non-homogeneous cortex with eccentric thickening, (c) intact capsule, verified macrometastasis of cervical squamous cell carcinoma; B2 lymph node in left obturator fossa bordered by white dashed line—round shape, (a) hilar blood flow, verified micrometastasis of cervical squamous cell carcinoma; B3 most common features of USG probably infiltrated lymph nodes. (C) USG certainly infiltrated lymph nodes: C1 lymph node in left external iliac region bordered by white dashed line, intranodal metastases measured by yellow calipers – (a) nodal-core sign absent, non-homogeneous echogenicity, (b) irregular lobulated shape, (c) capsule interruption, verified macrometastasis of squamous cell carcinoma; C2 two lymph nodes in left obturator fossa (I and II) bordered by white dashed lines— partial grouping, combined blood flow—(a) hilar and (b) transcapsular, verified macrometastasis of cervical squamous cell carcinoma in both lymph nodes; C3 typical features of USG certainly infiltrated lymph nodes. *External iliac artery and vein.

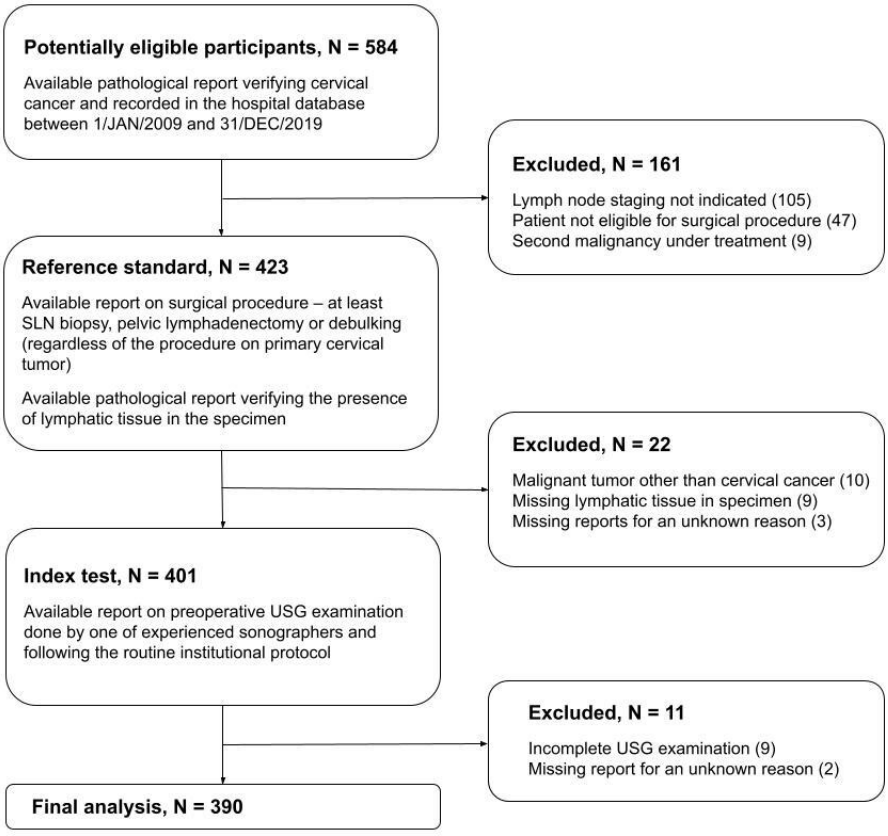

Figure 2 Flowchart of study cohort selection.

nodes 61.0–62.0% and 88.0–93.0%, respectively, for para-aortic nodes 40.0–54.0% and 91.0–94.0%, respectively).[9 11 14]

There is sufficient evidence that transvaginal or transrectal USG has the same or even better accuracy than MRI in local staging.[15–18] On the other hand, the diagnostic performance of USG in assessment of nodes has not yet been thoroughly investigated.[19 20] The aim of the study was to analyze the accuracy of USG in detection of pelvic and para-aortic node involvement in a large set of patients with cervical cancer based on our clinical practice.

METHODS

In accordance with the journal's guidelines, we will provide our data for independent analysis by a selected team by the Editorial Team for the purposes of additional data analysis or for the reproducibility of this study in other centers if such is requested. This study was approved by the ethics committee of the General University Hospital in Prague (project No. 190/23 S-IV).

Cohort Selection

We retrospectively retrieved prospectively created data from patients who were diagnosed with cervical cancer, underwent surgery with pathological verification of nodes, and had pre-operative USG for staging purposes.

Ultrasonography

All the patients in the study had transrectal and transabdominal USG as a routine part of pre-operative work-up. USG images were obtained with a GE Logic9 and VolusonE8 ultrasound machine (GE Medical Systems) equipped with an endoluminal microconvex probe of 5–9 MHz frequency and a transabdominal convex probe of 5 MHz frequency. The transrectal approach was preferred to reduce the risk of contact bleeding from the tumor and better visualization of the distal part of the cervix.[16] Each patient was examined by one of four experienced sonographers (FF, DF, RK, and MZ) using a predefined institutional protocol. Expertise of all operators corresponded to level 3 of European Federation of Societies for Ultrasound in Medicine and Biology.[21]

The protocol consisted of assessment of primary cervical tumor and regional nodes plus distant abdominal staging.[22] Nodes were classified, using transrectal and transabdominal USG, as negative or not seen, probably infiltrated, and certainly infiltrated, based on the subjective assessment by the operator. The criteria included measurements of the long and short axis, evaluation of the shape, regularity of the borders, homogeneity and echogenicity of internal architecture in 2D gray scale mode, and vascularization in Doppler mode (Figure 1). Probably or certainly infiltrated pelvic nodes were localized to the left or right pelvic side (Online supplemental video 1).

Surgical Procedures

All patients in the study underwent a surgical procedure, including at least sentinel lymph node (SLN) biopsy, systematic pelvic lymphadenectomy, or sampling of enlarged (suspicious) pelvic nodes, regardless of the cervical surgery (none, conization, simple or radical trachelectomy, simple or radical hysterectomy). The extent of pelvic surgery was in line with contemporary institutional guidelines. The surgeons always recorded the location of removed pelvic nodes if systematic lymphadenectomy was not performed.

Table 1 Main clinical and pathological characteristics of study population

Characteristics		Median (fifth; ninth)/n (%)
Age, years		42.0 (28.0; 71.0)
Body mass index		24.8 (18.6; 35.0)
FIGO staging 2018	IA1	13 (3.3%)
	IA2	15 (3.8%)
	IB1	86 (22.1%)
	IB2	125 (32.1%)
	IB3	38 (9.7%)
	IIA1	4 (1.0%)
	IIA2	1 (0.3%)
	IIB	29 (7.4%)
	IIIA	0 (0.0%)
	IIIB	1 (0.3%)
	IIIC1	56 (14.4%)
	IIIC2	19 (4.8%)
	IVA	2 (0.5%)
	IVB	1 (0.3%)
Histological type	Squamous cell carcinoma	292 (74.9%)
	Adenocarcinoma	81 (20.8%)
	Adenosquamous carcinoma	8 (2.1%)
	Neuroendocrine carcinoma	9 (2.3%)
Tumor diameter*	< 20 mm	119 (30.5%)
	20–39 mm	160 (41.0%)
	≥ 40 mm	111 (28.5%)
Grade	1	48 (12.3%)
	2	165 (42.3%)
	3	177 (45.4%)
LVSI	No	186 (47.7%)
	Yes	184 (47.2%)
	Unknown	20 (5.1%)

*Based on the pathological assessment or ultrasonography assessment if surgery of cervical tumor not performed.
FIGO, International Federation of Gynecology and Obstetrics; LVSI, lymphovascular space invasion.

Systematic para-aortic lymphadenectomy was carried out only in patients with positive pelvic nodes based on intra-operative pathological assessment of obtained SLN and/or any suspicious pelvic nodes. Based on the pre-operative imaging (probably or certainly infiltrated para-aortic nodes) or intra-operative gross assessment by the surgeon, sampling of enlarged (suspicious) para-aortic nodes was performed in selected patients, balancing the clinical benefit and staging purposes.

Pathological Assessment

In cases of SLN biopsy, pathological ultrastaging was based on the protocol published previously.[23] Pathological reports always contained the number of removed nodes and the largest diameter of the largest node. If node involvement was found, number and location of infiltrated nodes plus the size of the largest node metastasis was recorded. Node metastases (pN1) were classified as macrometastases (the largest diameter ≥2 mm) or micrometastases (≥0.2 mm and <2 mm). Nodes with isolated tumor cells (the largest diameter <0.2 mm) were considered negative (pN0).[24] The final pathological outcomes were always considered the reference standard.

Statistical Analysis

Categorical variables were reported as nominal and percentage. Continuous variables were reported as median estimate supported by the 5th and 95th percentile range. Receiver operating characteristics curves with 95.0% confidence intervals were calculated separately for transrectal and transabdominal USG, for detection of macrometastases, micrometastases, and the sum of macrometastases and micrometastases (pN1), separately per patient and per site. The predictive power of USG in assessment of pelvic nodes in early and locally advanced stages, as well as in the pelvic and para-aortic region, was compared using two-sample Z test. The effect of body mass index, histological type, lymphovascular space invasion, cervical tumor size, and parametrial involvement on diagnostic performance of USG was analyzed by two-sample Z test. McNemar's paired test was used to compare the performance of USG to predict node involvement if certainly only, or certainly plus probably infiltrated, nodes were considered positive. Statistical Package for the Social Sciences was applied for statistical analysis. P values <0.05 were accepted as the boundary for statistical significance.

RESULTS

We performed a retrospective analysis of data from a prospective registry collected between 2009 and 2019 and identified 390 patients fulfilling all inclusion criteria (Figure 2). Available clinical and pathological characteristics are summarized in Table 1.

In the whole study population, 90 patients (23.1%) underwent solely SLN biopsy, 44 patients (11.3%) had systematic pelvic lymphadenectomy, and 256 (65.6%) had a combination of both procedures. Pelvic node macrometastases were confirmed in 54 patients (13.8%) and micrometastases in another 21 patients (5.4%). Altogether 75 patients (19.2%) had pathologicaly positive pelvic nodes (pN1; macrometastases and/or micrometastases). The solitary presence of isolated tumor cells (pN0) was found in an additional 11 patients (2.8%). The median largest diameter of uninvolved pelvic nodes was 10.0 mm (6.0; 30.0), and infiltrated pelvic nodes were not significantly larger with median largest diameter 10.0 mm (6.0; 35.8). Median largest diameter of pelvic node metastases was 4.0 mm (0.3; 33.4).

Transrectal USG detected pelvic nodal macrometastases or pN1 with sensitivity 72.2% and 53.3%, respectively, specificity 94.0% and 94.0%, respectively, and area under curve (AUC) 0.831 and 0.737, respectively, evaluated per patient. The results were not significantly different if evaluated per pelvic site, meaning right and left half of the pelvis (Table 2). USG failed to detect the majority of pelvic node micrometastases with sensitivity 19.2%, specificity 85.2% and AUC 0.522.

The outcomes were substantially different for early stages (T1a–T1b2, T2a1; n=267) and locally advanced cervical cancers (T1b3, T2a2, T2b and higher; n=123). Transrectal USG yielded significantly

Table 2 Diagnostic performance of transrectal ultrasonography to detect pelvic node metastases evaluated per patient and per site in the whole study population

	Per patient (n=390)		Per site (n=780)	
	Results	**95% CI**	**Results**	**95% CI**
Detection of pelvic macrometastases only (54 patients)				
Sensitivity	72.2%	60.3% to 84.2%	72.0%	61.8% to 82.2%
Specificity	94.0%	91.5% to 96.6%	95.9%	94.4% to 97.4%
PPV	66.1%	54.0% to 78.2%	65.1%	54.8% to 75.3%
NPV	95.5%	93.2% to 97.7%	97.0%	95.7% to 98.3%
ACC	91.0%	88.2% to 93.9%	93.6%	91.9% to 95.3%
AUC	0.831	0.758 to 0.904	0.839	0.778 to 0.901
DOR	41.1	19.5 to 86.8	59.9	32.0 to 112.1
Detection of pelvic macrometastases and/or micrometastases (pN1, 75 patients)				
Sensitivity	53.3%	42.0% to 64.6%	52.9%	43.3% to 62.5%
Specificity	94.0%	91.3% to 96.6%	95.9%	94.4% to 97.4%
PPV	67.8%	55.9% to 79.7%	66.3%	56.1% to 76.4%
NPV	89.4%	86.1% to 92.7%	93.0%	91.1% to 94.9%
ACC	86.2%	82.7% to 89.6%	90.1%	88.0% to 92.2%
AUC	0.737	0.663 to 0.810	0.744	0.682 to 0.805
DOR	17.8	9.3 to 34.1	26.0	15.1 to 44.6

ACC, accuracy; AUC, area under curve; DOR, diagnostic OR ; NPV, negative predictive value; PPV, positive predictive value.

lower sensitivity (p<0.001) and higher specificity (p<0.001) to identify pelvic node macrometastases or pN1 in early compared with locally advanced stages (Table 3). It was caused by the much lower prevalence of node macrometastases; furthermore, the majority were of low volume, with the largest diameter <5 mm (macrometastases in 11 patients; 4.1%), and relatively higher prevalence of solitary micrometastases (10 patients; 3.7%) compared with locally advanced stages (macrometastases in 43 patients; 35.0% vs micrometastases only in 11 patients; 8.9%). The largest median diameter of pelvic node metastases in early stages (1.3 mm (0.2; 12.8)) was significantly lower than in locally advanced stages (5.0 mm (0.4; 34.9)), although there were no significant differences in the median largest diameters of pelvic nodes between these two subgroups (10 mm (6.0; 29.4) vs 10 mm (6.0; 32.2)).

We analyzed different factors that could affect the diagnostic performance of transrectal USG to detect pN1. There were no significant differences in sensitivity and specificity in relation to body mass index with cut-off value ≥25 (p=0.144; p=0.089, respectively; Online supplemental table S1), histological type (p=0.505; p=0.340, respectively; Online supplemental table S2) and lymphovascular space invasion (p=0.638; p=0.114, respectively; Online supplemental table S3). The only important factors affecting the accuracy of transrectal USG were related to the local stage of the disease, including the largest diameter of the cervical tumor with cut-off value ≥40 mm (p=0.001; p<0.001, respectively; Online supplemental table S4) and parametrial involvement (p<0.001; p<0.001, respectively; Online supplemental table S5). We compared the diagnostic performance of transrectal USG to detect pN1 in terms of certainty of subjective expert assessment (probably or certainly infiltrated versus only certainly infiltrated nodes considered positive). If all nodes classified by USG as probably or certainly infiltrated are considered positive, the sensitivity to detect pN1 was markedly higher (53.3% vs 41.3%; p=0.008) with acceptable, lower specificity (94.0% vs 97.5%; p=0.003; Online supplemental table S6).

Systematic para-aortic lymphadenectomy or para-aortic nodal sampling was performed in 71 patients (18.2%) and metastases (all of them macrometastases) were found in 16 of them (22.5%). In the para-aortic region, pathological ultrastaging was not performed so the micrometastases or isolated tumor cells could not be detected. The median largest diameter of all para-aortic nodes was 11.0 mm (7.0; 30.0) and median largest diameter of para-aortic node macrometastases was 6.5 mm (3.0; 17.5). USG-positive para-aortic nodes were debulked in 10 of 71 patients (nine true positive, 1 false positive). There was no case of isolated para-aortic nodal involvement without positive pelvic lymph nodes based on pre-operative imaging or intra-operative gross assessment. Transabdominal USG yielded sensitivity 56.3%, specificity 98.2%, AUC 0.772 for para-aortic metastatic node detection (Online supplemental table S7).

DISCUSSION

Summary of Main Results

This is the first study to systematically evaluate the diagnostic performance of USG performed by an experienced sonographer in pre-operative assessment of pelvic and para-aortic nodes in patients with cervical cancer. We demonstrated that the sensitivity and specificity of transrectal USG assessed per patient to detect pelvic node macrometastases was 72.2% and 94.0%, respectively. The corresponding values to detect altogether macrometastases and/or micrometastases (pN1) were 53.3% and 94.0%,

Table 3 Diagnostic performance of transrectal ultrasonography to detect pelvic node metastases separately in early and locally advanced stages of cervical cancer evaluated per patient

Detection of pelvic node macrometastases only				
	Early stages (n=267) 11 patients with macrometastases		**Locally advanced stages (n=123) 43 patients with macrometastases**	
	Results	**95% CI**	**Results**	**95% CI**
Sensitivity	18.2%	0.0% to 41.0%	86.0%	75.7% to 96.4%
Specificity	98.4%	96.9% to 100.0%	80.0%	71.2% to 88.8%
PPV	33.3%	0.0% to 71.1%	69.8%	57.5% to 82.2%
NPV	96.6%	94.3% to 98.8%	91.4%	84.9% to 98.0%
ACC	95.1%	92.5% to 97.7%	82.1%	75.3% to 88.9%
AUC	0.583	0.391 to 0.776	0.830	0.751 to 0.909
DOR	14.0	2.3 to 86.7	24.7	8.9 to 68.5
Detection of pelvic node macrometastases and/or micrometastases (pN1)				
	Early stages (n=267) 21 patients with pN1		**Locally advanced stages (n=123) 54 patients with pN1**	
	Results	**95% CI**	**Results**	**95% CI**
Sensitivity	9.5%	0.0% to 22.1%	70.4%	58.2% to 82.5%
Specificity	98.4%	96.8% to 100.0%	78.3%	68.5% to 88.0%
PPV	33.3%	0.0% to 71.1%	71.7%	59.6% to 83.8%
NPV	92.7%	89.6% to 95.9%	77.1%	67.3% to 87.0%
ACC	91.4%	88.0% to 94.8%	74.8%	67.1% to 82.5%
AUC	0.539	0.404 to 0.675	0.743	0.652 to 0.834
DOR	6.4	1.1 to 37.0	8.6	3.8 to 19.4

ACC, accuracy; AUC, area under curve; DOR, diagnostic OR ; NPV, negative predictive value; PPV, positive predictive value.

respectively. Transabdominal USG had sensitivity 56.3% and specificity 98.2% to identify para-aortic node involvement (macrometastases). The sensitivity to detect pelvic node involvement (pN1) was significantly lower in early stages than in locally advanced stages (9.5% vs 70.4%), which was predominantly caused by the presence of significantly smaller node metastases (median largest diameter 1.3 vs 5.0 mm) and significantly higher proportion of solitary micrometastases in early stages (10/21 patients; 47.6% vs 11/54 patients; 20.4%).

We confirmed that the size of pelvic nodes was not a reliable feature to distinguish between benign and malignant (median largest diameter 10.0 mm vs 10.0 mm). A substantial portion of the infiltrated pelvic nodes was not bulky (largest diameter <15 mm). USG assessment of nodes was based on criteria, including shape, regularity of border (integrity of capsule), homogeneity of internal architecture composed of medulla and cortex, type of cortical thickening, and Doppler characteristics (vascular score and vascular architecture) as were described for USG assessment of inguinal nodes.[25]

Results in the Context of Published Literature

Very limited evidence is available for transrectal or transvaginal USG to assess pelvic nodes, and no evidence for transabdominal USG to assess para-aortic ones. Pálsdóttir et al investigated the accuracy of USG in pelvic node assessment on 104 patients before pathological verification. Subjective evaluation by an experienced sonographer had sensitivity 42.9% and specificity 96.1% in this study population, including mainly early-stage cancers (n=104, 16 patients with International Federation of Gynecology and Obstetrics (FIGO) 2018 stage ≥IB3).[26]. Testa et al prospectively compared transvaginal USG and conventional MRI in 68 patients with cervical cancer (33 early, 35 locally advanced). For USG assessment, the criteria to identify metastatic nodes included among others the minimal axial size >10 mm, but Doppler parameters were not considered. USG and MRI correctly identified only 1 (respectively 3) of 11 patients with node metastases, reaching sensitivity 9.0% and 23.0%, respectively, and false positivity rate 0.0% and 4.0%, respectively.[17] In a European multicenter trial on diagnostic performance of transvaginal or transrectal USG and conventional MRI in local staging of cervical cancer, all patients with bulky nodes on pre-operative imaging were excluded. Of 188 patients in the study, 32 had node metastases (mostly micrometastases) in final pathology, three had been suspected on USG and four on MRI.[15]

Regarding other imaging methods, in a recent prospective trial comparing FDG-PET/CT and DWI/MRI with pathological assessment in a small cohort of patients with cervical cancer (n=40, 4 patients with FIGO 2018 stage ≥IB3), the authors reported sensitivity 30.0% and 20.0%, respectively, and false positivity rate 0.0% and 3.0%, respectively.[27] Pre-operative diagnosis of infiltrated nodes was made using morphologic descriptors (absence of fatty hilum, non-homogeneous appearance, presence of necrosis, or irregular margins) and functional features (high signal intensity on the high b value DWI/MRI or increased tracer uptake higher than

background on FDG-PET/CT). The sensitivity would have been even lower (10%), if assessment had been based only on size criteria: short axis >10 mm or size ratio.[27] In another prospective trial recruiting only patients with locally advanced cervical cancers (n=153) and using pathology as a reference, FDG-PET/CT had in the pelvis and para-aortic regions, sensitivity 83.0% and 50.0%, respectively, and specificity 63.0% and 89.0%, respectively.[28] The outcomes of imaging methods strongly depend on the ratio of early and locally advanced stages, strict adherence to the pathology as reference standard, and the proportion of SLN biopsies with pathological ultrastaging.[7–11 13 14]

Strengths and weaknesses

As USG is a mandatory part of pre-operative work-up at our center, the study population represents a consecutive cohort of patients with cervical cancer indicated and eligible for nodal staging or sampling. The main strengths include large sample size, standardized protocol of USG scanning, surgical techniques, and pathological ultrastaging and reporting.[24] Furthermore, the proportion of patients with SLN biopsy was high (88.7%). A high number of specialized experienced sonographers is another strength of this work, supporting the reproducibility of USG for staging purposes. Our study does have several limitations. Owing to the retrospective design, we were not able to investigate which USG features were most reliable to identify infiltrated nodes. Moreover, other state-of-the-art imaging methods were not systematically used in the study.

Implications for Practice and Future Research

The high specificity of USG in the pelvic and para-aortic region, comparable to other imaging methods, means that positive pre-operative imaging is reliable enough to predict node involvement, so that indication for surgery and extent of surgical procedure can be pre-operatively modified. Furthermore, the accuracy of USG to assess pelvic nodes was not significantly different when assessed per patient or per site, so USG can be used to navigate the surgeon in cases of node debulking.

Low sensitivity suggests that negative pre-operative imaging is insufficient to exclude node involvement and cannot replace surgical staging. This fact emphasizes the importance of the SLN biopsy, particularly in the early stages.[29] Low sensitivity of USG and other imaging methods to detect para-aortic metastases in cases of pelvic node involvement might favor the surgical para-aortic staging to tailor the radiation field and potentially improve para-aortic and distant control, avoiding unnecessary morbidity.[30 31]

To establish the role of USG in pre-operative node staging of cervical cancer, a prospective comparison of all three imaging methods USG, DWI/MRI, and FDG-PET/CT in one cohort is needed. The promising outcomes of USG arising from this study are being currently validated in a multicentric trial (NCT05573451).

CONCLUSION

USG performed by an experienced sonographer can be considered a sufficient diagnostic tool for pre-operative assessment of nodes in patients with cervical cancer, showing similar diagnostic accuracy in detection of pelvic macrometastases as reported for other imaging methods (FDG-PET/CT or DWI/MRI). It had low sensitivity for detection of small-volume macrometastases (<5 mm) and micrometastases. The accuracy of para-aortic lymph nodes' assessment was comparable to that for pelvic lymph nodes and assessment of the para-aortic region should be an inseparable part of examination protocol.

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Correction notice This article has been corrected since it first published. The open access licence type has been changed to CC BY-NC. 25th July 2024.

Contributors FF, RK, MZ, and DF performed the examinations; FF, DC, and DF were involved in planning and supervised the work; JJ performed the statistical analysis; FF and DF processed the experimental data; FF (guarantor responsible for overall content) drafted the manuscript and designed the figures. All authors discussed the results and commented on the manuscript.

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