The diagnostic value of core needle biopsy in cervical cancer: a retrospective analysis

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Abstract

Objective: To evaluate the accuracy, sensitivity, specificity, and predictive value of preoperative core needle biopsy (CNB) assessment of histological characteristics in primary cervical cancer. Setting: Retrospective cohort study. Population: Women older than 18 with primary cervical cancer enrolled in the prospective Leipzig School MMR study and had CNBs taken before their operation. Methods: We reviewed 318 cases of cervical carcinoma with available pathology reports from preoperative CNB assessment and from final postoperative evaluation of the hysterectomy specimen. Setting the postoperative comprehensive pathological evaluation as reference, we analysed CNB assessment of histological tumor characteristics. In addition, we performed multivariable logistic regression to identify factors influencing the accuracy in identifying lymphovascular space invasion (LVSI) and tumor grade. Main outcome measures: Accuracy, sensitivity, specificity, and predictive values of CNB assessment of histological tumor characteristics and the variables influencing these. Results: CNB was highly accurate in discriminating histological subtype. Sensitivity and specificity were 98.8% and 89% for squamous cell carcinoma (SCC), 92.9% and 96.6% for adenocarcinoma (AC), 33.3% and 100% in adenosquamous carcinoma respectively. Neuroendocrine carcinoma was always recognized correctly. The accuracy of the prediction of lymphovascular space invasion (LVSI) was 61.9% and was positively influenced by tumor size in preoperative MRI and negatively influenced by strong peritumoral inflammation. High tumor grade was diagnosed accurately in 73.9% of cases and was influenced by histological tumor type. Conclusions: CNB is an accurate sampling technique for histological classification of cervical cancer and represents a reasonable alternative to other biopsy techniques. Funding: “Stiftung gynäkologische Onkologie” (non-profit-organization).

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Setting: Retrospective cohort study.

Population: Women with primary cervical cancer enrolled in the prospective Leipzig School MMR study who had CNBs taken prior to their operation.

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Results: CNB was highly accurate in discriminating histological subtype. Sensitivity and specificity were 98.8% and 89% for squamous cell carcinoma (SCC), 92.9% and 96.6% for adenocarcinoma (AC), 33.3% and 100% in adenosquamous carcinoma respectively. Neuroendocrine carcinoma was always recognized correctly. The accuracy of the prediction of lymphovascular space invasion (LVSI) was 61.9% and was positively influenced by tumor size in preoperative MRI and negatively influenced by strong peritumoral inflammation. High tumor grade was diagnosed accurately in 73.9% of cases and was influenced by histological tumor type.

Conclusions: CNB is an accurate sampling technique for histological classification of cervical cancer and represents a reasonable alternative to other biopsy techniques.

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Keywords: cervical cancer; core needle biopsy; lymphovascular space invasion; tumor grading;

peritumoral inflammation

Tweetable abstract

This retrospective study analyses 318 cases of primary cervical carcinoma with core needle biopsies prior to operative therapy. The aim was to establish the accuracy of this biopsy technique for this cancer type. Core needle biopsy accurately predicted histological tumor type in 94.7% of cervical cancers. The accuracy of core needle biopsy in predicting lymphovascular space invasion in cervical cancers is 61.9%. Strong peritumoral inflammation significantely decreses the detection rate of lymphovascular space invasion. Core needle biopsy correctly assesses tumor grade of cervical cancers in 73.9% of cases.

Introduction:

Cervical carcinoma is a major cause of disability, morbidity, and mortality among women with an estimated number of deaths of 311,000 worldwide in 2018 .

In patients diagnosed with cervical cancer the treatment strategy depends on locoregional and distant disease extent. Several pathological characteristics have been studied to predict advanced disease (e.g. lymph node

metastasis), poor prognosis, or disease recurrence. Of these, the most commonly reported prognostic factors are lymphovascular space invasion (LVSI) and tumor grade.

However, most studies examine conization, trachelectomy or radical hysterectomy specimens and few authors have focused on preoperative biopsy samples in predicting the tumor grade or LVSI in cervical cancer. Pretreatment biopsy specimens are frequently the only tissue samples available for analysis, since many patients do not undergo surgery due to national and international guidelines which generally recommend primary chemo-radiotherapy for locally advanced cervical cancer, i.e. tumors staged IB2, IIA2, II B, III B and IV A according to the Féderation Internationale de Gynécologie et d'Obstetrique (FIGO) 2009 criteria. . Knowledge about how histological characteristics assessed in different biopsy techniques correlate with those in final hysterectomy specimens is therefore important if clinical decision making is based on these factors.

Core needle biopsy (CNB) is a safe and accurate way to obtain tissue specimens and is well established in the preoperative evaluation of abnormalities of the breast . Additional studies reported high accuracies of CNB in the evaluation of other neoplasms such as peripheral nerve sheath tumors , thyroid and pulmonary nodules . However, to date no studies evaluating the accuracy of CNB in cervical cancer have been published.

This study aims to evaluate the test performance of preoperative CNB in cervical carcinoma.

Methods:

This investigation represents a retrospective subgroup analysis of patients enrolled in the prospective observational Leipzig School Mesometrial Resection (MMR) study. All patients were cared for at the Department of Gynecology at the University Hospital Leipzig and were treated by total or extended mesometrial resection (TMMR, EMMR), or by laterally extended endopelvic resection (LEER). These are surgical treatments for cervical cancer based on the theory of ontogenetic cancer fields. The study outcomes along with a detailed description of the techniques have been published . All consecutive patients who presented to our institution with primary cervical cancer staged FIGO (Féderation Internationale de Gynécologie et d'Obstetrique) IB1 – IIB and who were older than 18 years of age were eligible for inclusion. In addition, selected patients with cancer staged FIGO III A, III B, and IV A were included in the trial if they were not candidates for primary (chemo-) radiotherapy or declined such treatment and insisted on surgery. Patients were excluded if they were not fit for surgical treatment. The study protocol and its amendments were approved by the ethics committee of the University of Leipzig (012/13-28012013, 171-2006, 192/2001, and 151/2000) and are registered with the German Clinical Trials Register (DRKS00015171).

For this current analysis, a computer search of the study database was performed. Patients were excluded if they had received preoperative chemotherapy, if a pathological report was not available, and if the CNB did not contain any tumor tissue. If only single histopathological characteristics (e.g. tumor grade, peritumoral inflammation) were not available, the patient was excluded from analyses involving this missing characteristic.

As specified in the MMR study protocol, all patients had undergone preoperative staging diagnostics which always included an examination under general anesthesia during which core needle biopsies of the cervix were taken using an automated spring-loaded biopsy device (Bard Magnum ® Biopty Gun, Bard, UK) with a 14 Gauge needle. The core needle biopsies were completely processed with embedding of multiple cores within one cassette in cases where multiple cores were obtained. From each block three step sections were performed with intervals of about 200µm between the steps (figure 1). No immunohistochemical stains were routinely performed for establishing the diagnosis. Both the core needle biopsies and the hysterectomy specimens were analysed under the supervision of a dedicated gynecologic pathologist (LCH) and the reports were reviewed for this study. Specimens were examined for histological cancer type, (conventional) tumor grade, lymphovascular space invasion, and peritumoral inflammatory response (figure 2). Peritumoral inflammatory response was classified according to previous publications as absent, weak, moderate or strong . Additionally, conventional tumor grading was performed as described before and G1- and G2-tumors were merged into one group thus adopting the binary grading model suggested by Horn et al. . These data were included in the database and compared with the same pathological parameters of the subsequent surgical specimens.

All patients underwent magnetic resonance imaging (MRI) as part of the preoperative staging procedures. Both tumor size and suspected parametrial involvement were included into the analysis.

We calculated the sensitivity, specificity, accuracy, positive (PPV) and negative (NPV) predictive value for every pathological parameter and used Fisher's exact test to compare sensitivities and specificities. To quantify the concordance between the pathology findings in CNB and hysterectomy specimens we used the observed agreement and (unweighted) Cohen´s kappa. To establish agreement quality for each kappa-value we applied the classification suggested by Landis and Koch. In this classification kappa-values of less than 0.2 correspond to a slight agreement, 0.21–0.4 to a fair agreement, 0.41–0.6 to a moderate agreement, 0.61–0.8 to substantial agreement and 0.81–1.0 almost perfect agreement . Furthermore, we performed a multivariable logistic regression analysis to investigate whether additional variables influenced CNB accuracy and to compute the adjusted odds ratios (aOR) of these variables. As previously proposed, variables were included in the multivariable logistic regression if they were associated with these parameters in an univariable model with a p-value of <0.25 . We ensured that events per variable were always more than 10 in multivariable logistic regression analysis in order to avoid bias of the coefficients . P-values of <0.05 were regarded as statistically significant.

Statistical analysis was performed with the program R . Kappa statistics were computed with the "IRR"-package. The most appropriate thresholds of continuous variables (specifically tumor size in the MRI) for the logistic regression were computed with ROC-curve analysis using the "pROC"-package. The "blorr"-package was used to perform collinearity diagnostics. Categorical data is given as percentages while continuous data is reported as numbers.

Funding was provided by the non-profit organization "Stiftung gynäkologische Onkologie".

Results:

The reports of 458 patients were identified between 1999 and 2017. In six cases CNB had not been performed (e.g. biopsies had already been performed before the examination under general anesthesia). Further 134 cases were excluded, since no tumor was detected in the CNB specimen. This false negative results of the CNB could partially be explained by the fact that 73.1% of these patients had a conization prior to the examination under general anesthesia, thus removing a significant part of the tumor mass before CNBs could be performed. Eventually, the reports of 318 patients were included in the study.

Histological tumor type, LVSI and tumor grade were known in all 318 patients in both CNB and hysterectomy specimen. Peritumoral inflammation could be evaluated in 284 CNBs and 290 hysterectomy specimen. Patient and tumor characteristics are compiled in table 1.

The sensitivity of CNB in recognizing a squamous cell carcinoma (SCC) and adenocarcinoma (AC) as such was 98.8% and 92.9%, respectively. Neuroendocrine carcinoma was recognized correctly by CNB in both cases. There were 15 cases of adenosquamous cervical carcinoma in our study group. The CNB recognized five of them correctly (33.3%), but classified four (26.7%) as SCC and six (40%) as AC. Specificity of the CNB for the various histological types was 89% for SCC, 96.6% for AC, and 100% for adenosquamous and neuroendocrine cervical carcinoma. Overall, the CNB accurately predicted histological tumor type in 94.7% of cases.

The overall sensitivity and specificity for the detection of LVSI in CNB were 56% and 83.8% respectively. The accuracy corresponded to 61.9% (kappa 0.26). PPV and NPV were 92.7% and 34.1% respectively.

Univariable logistic regression showed that presence of strong peritumoral inflammation, advanced clinical stage (FIGO IIB and higher), parametrial involvement on MRI, tumor size over 3.8 cm on MRI and number of CNB were associated with correct LVSI assessment. In multivariable logistic regression the presence of strong peritumoral inflammation and a tumor size larger than 3.8 cm had a statistically significant influence on correct LVSI assessment (table 2).

A tumor size of more than 3.8cm as determined by MRI was associated with an increase of an accurate

diagnosis (aOR 2.1, 95% confidence interval [CI]: 1.11 – 4.03).

The presence of strong peritumoral inflammation negatively influenced correct LVSI status prediction of the CNB (aOR 0.46, 95% CI: 0.22 – 0.95)). This decrease in accuracy was predominantly caused by a significantly lower sensitivity, which decreased from 63.2% to 38.5% when strong peritumoral inflammation was present (p=0.0067). Conversely, specificity didn't change significantly (80.6% vs. 84.6%, p=1.0).

When analyzing the performance of CNB predicting tumor grade we adopted the dual classification suggested by Horn et al. subdividing tumor grades in high grade (G3) and low grade (G1-2). The overall sensitivity and specificity of CNB predicting a high-grade (G3) tumor were 53% and 89.7% respectively. The accuracy corresponded to 73.9% (kappa 0.45). PPV and NPV were 78.9% and 72.4% respectively.

Univariable logistic regression showed that strong peritumoral inflammation, LVSI, advanced clinical stage (FIGO IIB and higher), parametrial involvement on MRI, and post-conization status were associated with correct diagnosis of a high-grade-tumor through CNB. Also we observed that, in the univariable model, SCC in the CNB influenced tumor grade recognition negatively (OR 0.43, 95% CI: 0.2 – 0.85, p=0.021) while AC improved it (OR 2.29, 95% CI: 1.12 – 5.19, p=0.032). Since these two variables were highly collinear, we only included the variable describing the presence of SCC in our multivariable model, since this seemed to have the highest influence on tumor grade recognition. Multivariable logistic regression (table 2) concluded that SCC-histology in the CNB impaired correct grading (aOR 0.31, 95% CI: 0.1 – 0.76).

Discussion:

Main findungs:

In this study, we show that CNB represents an accurate diagnostic tool for cervical cancer. Since CNB specimens are characterized by a relatively large size and inclusion of deep stromal tissue, they are useful in determining cancer associated histological features such as involvement of vascular and nervous structures.

We found that CNB has high accuracy in discriminating the major histological subtypes of cervical carcinoma. The sensitivity and specificity of CNB in recognizing the most common histological types were high (SCC: 98.8% and 89% respectively; AC: 92.9% and 96.6% respectively). Not surprisingly, adenosquamous cervical carcinomas were misclassified in 66.7% of cases (10 out of 15) as either SCC or AC. Both cases of neuroendocrine carcinoma were identified as such by the CNB.

In the only study evaluating the performance of superficial cervical biopsies, Bidus et al. found that this technique had a sensitivity, specificity, NPV and PPV of 14%, 96%, 45% and 83% in the detection of LVSI respectively . In our study, sensitivity was considerably higher (56%) while specificity was seemingly slightly lower (83.8%). Predictive values however are difficult to compare, since the study of Bidus and colleagues had a considerably lower prevalence of LVSI due to fact that most cases were early cervical cancers.

While data regarding superficial biopsies of cervical cancer are scarce, the accuracy of excision specimens regarding the detection of LVSI has been studied by various authors. Bai et al. and Kim et al. studied conization in stage IA2 – IB1 cervical cancers while Bidus et al. also included stage IB2 – IIA (7.1% of cases) . In these studies, sensitivity and specificity of conization ranged from 37.5 – 70.5% and 80 – 88% respectively. Our data show that CNB has a sensitivity of 56% and a specificity 83.8% suggesting similar performance in recognizing LVSI compared with conization. Interestingly, PPV and NPV of conization ranged between 43 – 75% and 57 – 90% respectively while those of CNB differed substantially in our study. We observed a PPV and NPV of 92.7% and 34.1% respectively for this sampling technique. However, it should be taken into account that prevalence of LVSI, which has a major influence on its predictive values, was very high in our study (78.6%) because of a high proportion of advanced cervical carcinomas (table 1). In contrast, those studies evaluation the accuracy of conization observed LVSI in 15.8 – 18.8% of their cases . The kappa value for LVSI assessment in our study was 0.26 (fair agreement). In summary our data suggest that CNB may have a similar accuracy to conization in recognizing LVSI.

As our findings suggest, it is plausible that increasing tumor size assessed by MRI improves the accuracy

of LVSI assessment by CNB, since the tumor may show more pronounced invasion of lymphatic vessels in an advanced stage. However, the drop in sensitivity for detection of LVSI caused by strong peritumoral inflammation has not been described in cervical cancer so far and warrants further investigation.

It is still controversial whether LVSI has prognostic relevance in cervical cancer . Various authors found that LVSI was statistically associated with parametrial and vaginal involvement, lymph node metastasis , and disease recurrence . Additionally, German guidelines state that LVSI can be used in cervical cancer in conjuncture with other risk factors to determine the need of adjuvant radiation . Furthermore, studies like the GOG #92 trial observed a benefit of adjuvant pelvic radiotherapy in the presence of multiple clinical-pathological risk factors including LVSI .

CNB showed an accuracy of 73.9% regarding the correct distinction between low-grade (G1 and G2) and high-grade (G3) tumors with a kappa of 0.45 (moderate agreement). To the best of our knowledge, this has never been studied in cervical cancer for neither superficial biopsy nor conization. However, this corresponded to the results of CNB in grading other tumors. A meta-analysis of the concordance of tumor grade between CNB and excision specimen in breast cancer showed pooled agreement of 71% with a kappa of 0.54 .

Interestingly, tumor grade seemed to be more difficult to assess correctly in SCC than in other carcinomas. Tumor grade is a widely known histopathologic factor in cervical carcinomas whose prognostic value has been discussed. Some authors found that high tumor grade had a prognostic impact on parametrial involvement, survival and recurrence while others failed to show this associations in cervical cancer .

Strenghts and limitations:

The number and location of cores taken were not standardized. This might have negatively influenced the accuracy, although we did not find any correlation between the number of CNBs taken and their accuracy in predicting LVSI or tumor grade. Furthermore, the accuracy of CNB analysed in this study could only be compared with the accuracy of other tissue sampling techniques (e.g. cervical biopsy, conization) analysed in different studies. Obviously, this comparison has its limitations, as the assessment of accuracies could vary significantly between studies.

The MMR-trial, which is executed at our institution since 1999, enables us to treat patients with locally advanced disease surgically. Hence, our study sample is characterized by a high number of women with tumors staged FIGO IIB or higher (43.1%). Our findings are therefore unique as such patients are usually submitted to primary chemo-radiotherapy. In contrast, other studies investigating the accuracy of biopsy or excision specimens have been limited by the inclusion of lower tumor stages only . Furthermore, this is to the best of our knowledge the first study showing which characteristics of both tumor and patient may have an influence on the accuracy of histopathological examination in cervical cancer.

Interpretation:

Conization can be associated with relevant complications such as bleeding during and after the procedure and the risk of intra- and postoperative hemorrhage can be expected to be higher in the presence of an advanced cervical cancer which often causes bleeding on its own . However, diagnostic conization may be justified in early cervical cancers, when tumor size can only be evaluated with pathological examination of a conization specimen. However, this procedure may not be appropriate in larger tumors, since cervical CNB may be sufficient to evaluate histopathological parameters as LVSI or tumor grade. In our opinion, CNB does not represent a technique for the primary diagnosis of cervical cancer, as ordinary cervical biopsy may be sufficient for this purpose. We believe that the main benefit of the CNB lies in the further categorization of the cervical tumor, which could be essential in those cases, where therapy must be chosen based on tumor biology.

Conclusion:

CNB has excellent accuracy in predicting histological tumor type in cervical carcinomas. The performance in predicting LVSI and tumor grading is comparable to data published for diagnostic conization and

superficial cervical biopsy. Additionally, we show that strong peritumoral inflammation negatively affects LVSI-assessment while SCC-histology impairs tumor grading. We therefore advocate that CNB is a reasonable alternative for histopathological classification of cervical cancers if diagnostic conization is not mandatory for the staging of early tumors.

Conflict of interest statement:

MH and BW received payments from the non-profit-organization "Stiftung gynäkologische Onkologie".

BA received honoraria from Pfizer Inc, Roche AG, Novartis AG, AstraZeneca PLC, Amgen Inc and Daiichi Sankyo Co Ltd.

LCH, PS and ML have no conflicts to disclose.

Authors' contribution:

ML and BW were responsible for the conception of the study, the systematic literature review, the acquisition of the data, the statistical analysis and the drafting of the manuscript. PS contributed substantially to the gathering of the data. LCH was involved in the review of histologic specimens, completed missing data in the pathology reports, provided the pictures and important expertise for the interpretation of histopathological data. BA and MH oversaw the project, were involved in the critical revision of the manuscript and contributed to the final submission. All authors reviewed and approved the final manuscript.

Details of ethics approval:

Ethical approval for the MMR study (including its amendments) was granted by the Ethics committee of the University of Leipzig (151/2000, 192/2001, and 012/13-28012013; Initial approval was granted on 22nd September 2000 and the subsequent amendments were approved on the 17th October 2007 and the 6th of March 2013). Written informed consent was obtained from each patient before inclusion into the study.

Table 1

Patient- and tumor characteristics	**Patient- and tumor characteristics**	**Patient- and tumor characte**
		Age - years (median, IQR)
		Preoperative conization - no. (%
		Suspected parametrial involveme
		Tumor size (MRI) - cm (median
Histologic subtype n=318	Histologic subtype n=318	Squamous cell carcinoma
		Adenocarcinoma
		Adenosquamous carcinoma
		Neuroendocrine carcinoma
Stage of disease (FIGO) no. (%) n=318	Stage of disease (FIGO) no. (%) n=318	IA
		IB1
		IB2
		IIA
		IIB
		IIIA
		IIIB
		IV
Histological tumor stage n=318	Histological tumor stage n=318	pT1b1
		pT1b2
		pT2a1
		pT2a2
		pT2b

		pT3b
		pT4
Lymphovascular space invasion (LVSI) present	CNB	
n=318	Hysterectomy	
Tumor grading	CNB	G1-2 (low-grade carcinoma)
n=318		G3 (high-grade carcinoma)
	Hysterectomy	G1-2 (low-grade carcinoma)
		G3 (high-grade carcinoma)
Peritumoral inflammation	CNB	absent
n=284		mild
		moderate
		severe
n=290	Hysterectomy	absent
		mild
		moderate
		severe
Number of CNBs	1	
n=318	2	
mean= 3.4	3	
	4	
	5	
	6	
	>=7	

Table 1: Patient- and tumor characteristics

IQR = interquantile range

MRI = magnetic resonance imaging

Table 2

Multivariable logistic regression model for correct assessment of lymphovascular space invasion (LVSI)	**Mu**
	Est
Presence of strong peritumoral inflammation in CNB	-0.7
Tumor size on MRI (> 38mm)	0.7
Suspected parametrial involvement on MRI	0.0
Advanced disease (FIGO [?] IIB)	0.2
Number of CNBs	0.0
Multivariable logistic regression model for correct assessment of tumor grading	**Mu**
	Est
Squamous cellular cancer in CNB	-1.1
Conization performed prior staging	0.7
LVSI in CNB	-0.4
Presence of strong peritumoral inflammation in CNB	-0.4
Advanced disease (FIGO [?] IIB)	0.0
Suspected parametrial involvement on MRI	-0.4

Table 2: Multivariable logistic regression model for correct assessment of lymphovascular space invasion (LVSI) and tumor grading