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Prognostic significance of low volume sentinel lymph node disease in early-stage cervical cancer☆

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ABSTRACT

Objective: Evaluate prognostic significance of low volume disease detected in sentinel nodes (SN) of patients with early stages cervical cancer. Although pathologic ultrastaging of SN allows for identification of low volume disease, including micro-metastasis and isolated tumor cells (ITC), in up to 15% of cases, prognostic significance of these findings is unknown.

Methods: A total of 645 records from 8 centers were retrospectively reviewed. Enrolled in our study were patients with early-stage cervical cancer who had undergone surgical treatment including SN biopsy followed by pelvic lymphadenectomy and pathologic ultrastaging of SN.

Results: Macrometastasis, micrometastasis, and ITC were detected by SN ultrastaging in 14.7%, 10.1%, and 4.5% patients respectively. False negativity of SN ultrastaging reached 2.8%. The presence of ITC was not associated with significant risk, both for recurrence free survival and overall survival. Overall survival was significantly reduced in patients with macrometastasis and micrometastasis; hazard ratio for overall survival reached 6.85 (95% CI, 2.59–18.05) and 6.86 (95% CI, 2.09–22.61) respectively. Presence of micrometastasis was an independent prognostic factor for overall survival in a multivariable model.

Conclusion: Presence of micrometastasis in SN in patients with early stage cervical cancer was associated with significant reduction of overall survival, which was equivalent to patients with macrometastasis. No prognostic significance was found for ITC. These data highlight the importance of SN biopsy and pathologic ultrastaging for the management of cervical cancer.

Introduction

Sentinel node (SN) biopsy is increasingly used in the management of cervical cancer [1-4]. It may improve the accuracy of staging by identification of lymph nodes in atypical localizations, which can therefore be missed during systematic pelvic lymphadenectomy [2,5]. It is used for triaging the patients toward surgery or radiotherapy [6], and selecting candidates for fertility sparing treatment [7-9]. Several prospective randomized studies are ongoing, the aims of which are to determine the oncologic safety of avoiding systematic pelvic lymphadenectomy in patients without involvement of the SN.

Identification of 2 to 4 sentinel nodes allows for their extensive processing by pathologic ultrastaging (multiple serial sectioning with immunohistochemical assessment). Pathologic ultrastaging increases detection rate of low volume disease, which includes micrometastasis and isolated tumor cells (ITC) [10]. In patients with FIGO stages IA2-IIB cervical cancer, micrometastasis are being detected in SN of 4%–15% of patients [11,12]. However, significance of low

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volume disease for prognosis of the disease has not been established, and therefore its implication for adjuvant treatment is not known.

The aim of our multicenter retrospective cohort study was to collect data from gynecologic oncology centers that perform SN biopsy and pathologic ultrastaging in cervical cancer patients, and to use these data to determine the significance of micrometastasis and isolated tumor cells for the disease prognosis.

Methods

Patients and therapeutic procedures

Enrolled were patients with early-stage cervical cancer (FIGO stages IA–IIB) in whom surgical treatment was performed, including SN biopsy followed by systematic pelvic lymphadenectomy. Only patients with histologically confirmed squamous carcinoma, adenocarcinoma, or adenosquamous carcinoma, in whom SN were processed by the ultrastaging protocol, and data on the follow-up were available, were included. A total of 645 records from 8 centers (Ostrava (195), Prague (119), Amsterdam/Utrecht (115), New York (90), Toulouse (57), Krakow (48), Paris [21]) were included in the final analysis.

Blue dye alone or combined technique with radioisotope was used for SN detection. Removal of SN(s), by laparotomy or laparoscopy, was followed by systematic pelvic lymphadenectomy in combination with simple hysterectomy [3], simple trachelectomy [22], radical trachelectomy (88), or radical hysterectomy (532). Adjuvant therapy (radiotherapy or chemoradiotherapy) was administered according to the institutional guidelines.

The prognostic variables evaluated in this study included age, tumor size, FIGO stage, type of surgery, lymph node status, histological type, grade, lymph-vascular space invasion (LVSI) (based on hematoxilin–eosin staining), vaginal involvement, parametrial involvement, administration of adjuvant treatment and type of adjuvant treatment.

Lymph nodes processing and definition of low volume disease

All SN negative for metastasis on the initial routine section stained by hematoxylin and eosin (H&E) were further examined according to the pathologic ultrastaging protocol of the respective institutions. The entire node was cut at regular intervals which varied at individual centers between 150 and 500 μm; in 7 out of 8 centers and 98% of cases the intervals measured ≤250 μm. Three consecutive sections (5 μm thick) were obtained at each level. The first slide was stained with H&E while the second was used for immunohistochemical staining for cytokeratin. Pelvic non-sentinel nodes (nSN) were processed identically in all institutions by single section of each node examined by a routine H&E staining. Protocols for sentinel node biopsy and evaluation were approved by ethical committees of the individual institutions.

Low volume disease included both micrometastasis (MM) and isolated tumor cells (ITC), as defined for breast cancer by the American Joint Committee on Cancer (AJCC) [13]. Macrometastasis were defined as tumor deposits >2.0 mm; micrometastasis were defined as deposits between 0.2 and 2.0 mm; and isolated tumor cells were defined as deposits no larger than 0.2 mm, including the presence of single non-cohesive cytokeratin-positive tumor cells.

Status of non-sentinel nodes (nSN) reflected results from pathologic processing of all removed pelvic nodes except for SN, while sentinel node status referred to the results obtained from ultrastaging of all detected SN. Final lymph node status combined results from all pelvic nodes together (SN + nSN) and following categories were recognized: a) negative: if all SN and other pelvic nodes (nSN) were free of metastasis, b) micrometastasis or ITC: if micrometastasis or ITC were identified in SN and all other pelvic nodes (nSN) were free of metastasis, and c) macrometastasis: if macrometastasis was found either in SN or in nSN or in both.

Statistical methods

Standard summary statistics were used to describe data. ML-χ^2 test was applied to assess mutual associations between binary or categorical variables in contingency tables or to measure trend changes in frequency tables over categories of ordinal stratifying factor. The diagnostic power of age as a potential predictor was assessed on the basis of Receiver Operating Characteristics (ROC) curves. The ROC analysis was performed using the ROC web calculator [14] for curve fitting, SPSS 17.02 [15] for the AUC computation and testing. The computation was based on bi-normal assumption. A value $\alpha = 0.05$ was used as limit of statistical significance in all performed analyses.

Kaplan–Meier method was used to describe profiles of time-to-event end-points, i.e., overall survival and relapse-free survival. Overall survival was defined as time interval between time of diagnosis and death (due to any reason). Relapse-free survival was calculated as time interval between time of diagnosis and time when recurrence of the disease was identified and diagnosed. Standard, guideline-based, clinical follow-up was realized and so time-to-event data address outcomes from regular clinical monitoring. Log rank test was applied to compare survival reached in different groups of patients in stratified survival analyses. Bonferroni-corrected threshold $\alpha = 0.008$ was applied in case of multiple comparison of survival curves in analyses stratified according to stage. Both univariable and multivariable proportional hazard Cox regression models were applied to quantify association of potential risk factors and survival endpoints. Estimates of hazard ratio (supplied with 95% confidence intervals) were tested in Wald χ^2 test. Parameters with potential risk power (providing at least $p<0.10$ in univariable Cox regression) were examined for mutual correlation and interaction terms were coded and tested for significantly correlated pairs of variables. The final set of significant predictive factors was subjected to stepwise selection algorithm in multivariable Cox regression (driven by maximum likelihood ratio test).

Results

Initial description of sample data set

Basic group characteristics are summarized in Table 1. Majority of the sample is formed by Stage I tumors (stage I: 91.5%) of squamous histology (71.3%). Median follow-up for the whole group reached 40 months. The spectrum of patients was heterogeneous in age (range, 23 to 93 years); therefore, all analyses that focused on overall survival endpoints were controlled for the influence of age as background prognostic risk factor.

Macrometastasis, micrometastasis, and isolated tumor cells were detected by SN ultrastaging in 14.7%, 10.1%, and 4.5% of patients, respectively. In 23 (3.6%) cases, the low volume disease (ITC = 4; MM = 19) was detected in SN by ultrastaging but the macrometastasis was found in another pelvic lymph node, so the final lymph node status was corrected. As a result, final lymph node status combining results from SN and all pelvic non-sentinel nodes was classified as negative in 67.9%, macrometastasis in 21.1%, micrometastasis in 7.1%, and ITC in 3.9% of cases. There were 18 patients (2.8%) with false-negative ultrastaging results in whom macrometastasis was detected in some pelvic node (nSN) despite of negativity of SN.

FIGO stage appeared to be not only a significant prognostic factor (Fig. 1) but also a significant cofactor associated with the other parameters (Table 2). Older age, squamous histology, and presence of LVSI tended to be significantly more frequent in more advanced stages (Table 2). Metastatic involvement of nSN also increased with stage.

Adjuvant combined radiotherapy or chemoradiation was given to 33.0% of patients. Considering the final lymph node status, 85.3% of patients with macrometastasis, 82.6% with micrometastasis, 52% with ITC and 10.5% with negative pelvic nodes received adjuvant

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Table 1
Basic characteristics of the group ($N = 645$).

Parameter	Statistics[a]	
Subjects		
	Follow-up (months)[b]	40 (0.6; 116)
	Age (years)	46 (23; 93)
	> 50 years	$N = 236$ (36.6%)
	> 65 years	$N = 66$ (10.2%)
Histology		
	Adeno	$N = 165$ (25.5%)
	Squamous	$N = 461$ (71.5%)
	Adenosquamous	$N = 19$ (3.0%)
Clinical staging		
Stage I		$N = 590$ (91.5%)
	IA1	$N = 25$ (3.9%)
	IA2	$N = 30$ (4.6%)
	IB1	$N = 477$ (74.0%)
	IB2	$N = 58$ (9.0%)
Stage II		$N = 55$ (8.5%)
	IIA	$N = 36$ (5.6%)
	IIB	$N = 19$ (2.9%)
Pathologic staging		
	LVSI	$N = 169$ (26.2%)
	Parametrial involvement	$N = 46$ (7.1%)
	Vaginal involvement	$N = 36$ (5.6%)
LN status: SN ultrastaging		
	Negative	$N = 456$ (70.7%)
	Macrometastasis	$N = 95$ (14.7%)
	Micrometastasis	$N = 65$ (10.1%)
	ITC	$N = 29$ (4.5%)
LN status: non-sentinel nodes (nSN)		
	Positive	$N = 89$ (13.8%)
LN status: final status		
(SN ultrastaging and pelvic nSN)		
	Macrometastasis	$N = 136$ (21.1%)
	Micrometastasis	$N = 46$ (7.1%)
	ITC	$N = 25$ (3.9%)
	Negative	$N = 438$ (67.9%)
Therapy		
	Adjuvant therapy	$N = 213$ (33.0%)

[a] Continuous parameters are described using median and min/max range; categorical parameters are described by number of cases (N) and percentages of given categories.
[b] The data survey included all cases retrospectively reported from participating centres with overall follow-up up to 120 months.

Table 2
Characteristics of the group according to FIGO stage ($N = 645$).

Parameter		% within clinical stages				p Value[1]
		IA	IB1	IB2	IIAB	
Age						
	> 50 years	23.6% [a]	35.4% [a]	34.5% [a]	61.8% [b]	0.003
	> 65 years	10.9% [ab]	9.2% [a]	5.2% [a]	23.6% [b]	0.014
Histology	Adeno	34.6% [a]	29.6% [a]	29.3% [a]	10.9% [b]	0.011
LVSI		18.2% [a]	23.9% [a]	36.2% [b]	43.6% [b]	0.003
Positive pelvic nSN		5.5% [a]	11.9% [ab]	17.2% [b]	34.6% [c]	< 0.001
Final lymph node status						
(SN ultrastaging and pelvic nSN)						
	Macrometastasis	9.1% [a]	19.5% [b]	24.1% [b]	43.6% [c]	< 0.001
	Micrometastasis	3.6% [a]	6.2% [a]	12.1% [a]	12.7% [a]	
	ITC	3.6% [a]	3.6% [a]	5.2% [a]	5.5% [a]	
	Negative	83.7% [a]	70.7% [b]	58.6% [b]	38.2% [c]	

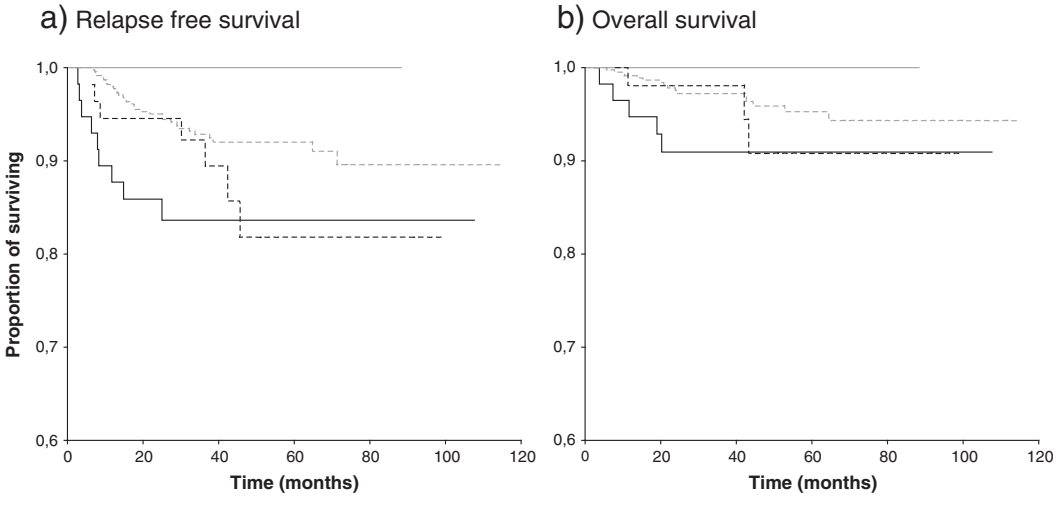
[a-c] Marks of statistical significance of mutual differences among FIGO categories (ML-χ^2 test; $p<0.05$): values marked by the same letter are not mutually significantly different.
[1] ML-χ^2 test for the overall trend differences among clinical stages.

therapy. Both administration and type of adjuvant treatment were included in univariable and multivariable analysis, but no significant multivariable-adjusted effect on the time-to-event end-points was found.

Descriptive analysis of survival endpoints

Both relapse-free survival (RFS) and overall survival (OS) were displayed using standard Kaplan–Meier curves (Fig. 1). Survival data stratified according to final lymph node status are shown in Fig. 2. The predictive potential of lymph node status was even more significant ($p = 0.001$ both for RFS and OS) than FIGO stage.

The presence of micrometastasis and macrometastasis was associated with significantly reduced overall survival. These two categories of lymph node status (macrometastasis versus micrometastasis) could not be mutually statistically distinguished in the effect on overall survival rate ($p = 0.886$). Both were also highly significantly different from negative lymph node status ($p<0.001$).



Mutual comparison of categories (p values):

	IA	IB1	IB2
IIAB	0.019	0.187	0.582
IB2	0.001*	0.021	
IB1	0.083		

Mutual comparison of categories (p values):

	IA	IB1	IB2
IIAB	0.049	0.183	0.389
IB2	0.011	0.038	
IB1	0.214		

* Mark of statistical significance: p values lower than Bonferroni –corrected threshold p = 0.008

Fig. 1. Survival endpoints stratified according to FIGO stage.

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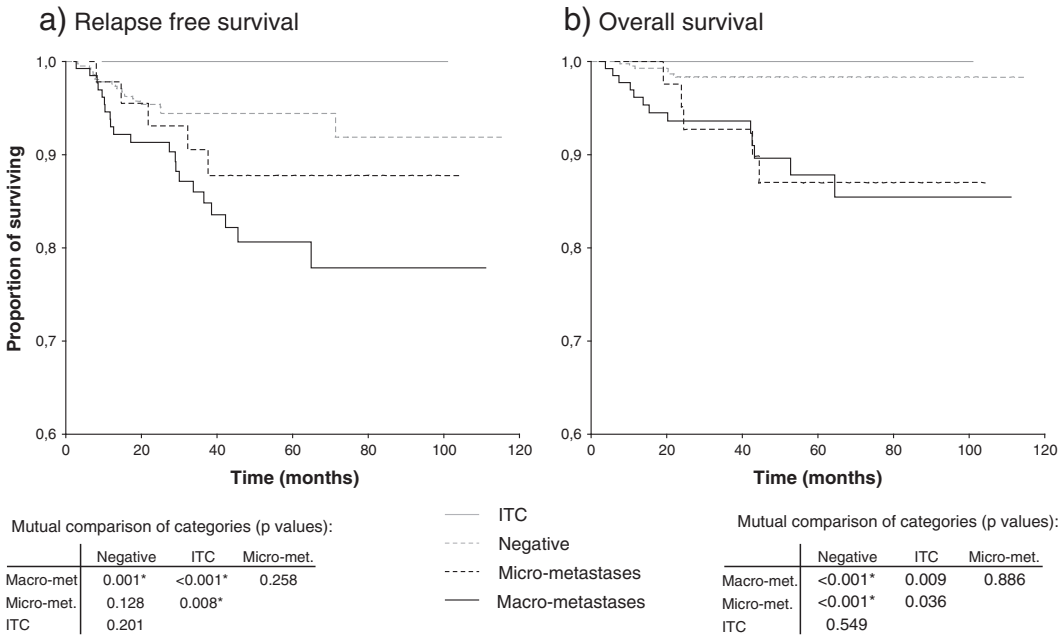

Mutual comparison of categories (p values):

	Negative	ITC	Micro-met.
Macro-met	0.001*	<0.001*	0.258
Micro-met.	0.128	0.008*	
ITC	0.201		

Mutual comparison of categories (p values):

	Negative	ITC	Micro-met.
Macro-met.	<0.001*	0.009	0.886
Micro-met.	<0.001*	0.036	
ITC	0.549		

* Mark of statistical significance: p values lower than Bonferroni –corrected threshold p = 0.008

Fig. 2. Survival endpoints stratified according to final lymph node status (based on SN ultrastaging and pelvic nSN evaluation).

Similar results were obtained for RFS, but the presence of micrometastasis did not reach statistical significance. RFS of patients with micrometastasis was neither significantly different from those with negative lymph nodes ($p = 0.128$), nor from those with macrometastasis ($p = 0.258$).

The presence of ITC was not associated with any significant risk, both for RFS and OS. No significant difference was found between cases with ITC and those with negative lymph nodes in both RFS ($p = 0.201$) and OS ($p = 0.549$). RFS of patients with ITC was longer than in those with micrometastasis with boundary Bonferroni-corrected significance level ($p = 0.008$).

Hazard ratio associated with potential prognostic factors

All potential prognostic factors entered univariable Cox regression models estimating hazard ratio (RR) both for RFS and OS (Table 3). Most of the parameters resulted in statistically significant RR, except for histology type, LVSI and vaginal involvement. Age was a significant risk factor both for RFS and OS, therefore multivariable analyses included age as an obligatory cofactor. Besides the age, lymph node status was the most significant factor for both OS and RFS. Metastatic involvement of non-sentinel pelvic nodes (nSN), or presence of macrometastasis and micrometastasis in SN was associated with significantly increased RR both in OS and RFS, except for RR for RFS in patients with micrometastasis.

As many of the significant estimates of RR in Table 3 can be closely related to each other, multivariable Cox regression analysis was applied to identify mutually independent risk factors and estimate multivariable-adjusted RRs (Table 4). Statistically significant multivariable models were successfully constructed for both RFS and OS, with high overall significance ($p < 0.001$). Presence of macrometastasis and micrometastasis proved to be independent and significant prognostic factors for OS, while macrometastasis was also significant prognostic factor for RFS. Age was included in both models, and both models provided age-adjusted RR. Another factor significant on multivariable analysis was advanced FIGO stage.

Discussion

A large cohort of 645 patients with early-stage cervical cancer who underwent surgical treatment including SN biopsy and microstaging allowed for the analysis of prognostic significance of detected micrometastasis and ITC. The presence of micrometastasis was associated with significantly reduced overall survival, which corresponded to the patients with macrometastasis, while no increased risk was associated with the detection of ITC.

Prevalence of micrometastasis in SN from patients with early-stage cervical cancer has been presented in small study populations only, and varied between 4% and 15% [12]. The implication of the presence of micrometastasis or ITC for the prognosis or management decisions regarding adjuvant treatment has been a subject of much debate. Much more data on low volume disease are available from patients with breast cancer [16-18] in whom they concluded that micrometastasis are likely to represent an incremental detriment to prognosis [19,20]. In patients with cervical cancer, the prognostic significance of micrometastasis was so far analyzed only on small samples based on re-evaluation of the specimen from pelvic nodes without SN detection. Juretzka et al. performed serial sectioning of all pelvic nodes in 49 patients with negative lymph nodes on routine pathology assessment and found micrometastasis in 4 (8%) of them [21]. At a median follow-up time of 40 months, recurrent disease was observed in 2 of 4 (50%), versus 3 of 45 (7%) patients with or without micrometastasis. Marchiole et al. compared a group of 26 patients with recurrence and same number of controls matched for age, histology, stage, and tumor diameter [22]. They retrospectively collected all lymph node blocks, which had been considered uninvolved, and submitted them to serial sectioning and immunohistochemistry. They found a total of 6 micrometastasis, all in the group with recurrence; this finding created increased hazard ratio of recurrence (RR = 2.44) for the presence of micrometastasis. Recently, Horn et al. re-examined original slides from a group of 281 surgically treated patients with pelvic node involvement. Their intention was to measure the size of the metastasis [23]. At a median follow-up of 821 months they observed significantly decreased 5-year OS in patients with

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Table 3
Univariable analysis of relapse-free survival (RFS) and overall survival (OS) in relation to potential risk factors[a].

Parameter	*Reference category*	RFS		OS	
		HR (95% CI)[a]	*p* Value	HR (95% CI)[a]	*p* Value
Age (continuous)	–	1.03 (1.01; 1.04)	0.018	1.07 (1.04; 1.10)	<0.001
Age (categories)					
> 50 years	*≤ 50 years*	2.39 (1.34; 4.28)	0.003	7.44 (2.54; 21.81)	<0.001
> 65 years	*≤ 65 years*	1.71 (0.80; 3.66)	0.162	3.35 (1.39; 8.09)	0.007
Adenocarcinoma	*Other histology*	0.87 (0.44; 1.69)	0.674	0.60 (0.21; 1.77)	0.359
Clinical stage					
IB2	*Stage IB1*	2.33 (1.11; 4.89)	0.025	2.53 (1.02; 6.88)	0.049
IIAB		1.72 (0.76; 3.90)	0.192	1.46 (0.42; 5.00)	0.550
IA2		–		–	
IB2 and IIAB	*Stage IB1 and IA2*	2.23 (1.22; 4.06)	0.005	2.17 (1.03; 4.95)	0.032
LVSI	*No LVSI*	0.83 (0.43; 1.64)	0.608	0.57 (0.19; 1.68)	0.310
Parametrial involvement	*No parametrial involvement*	3.51 (1.79; 6.88)	<0.001	2.76 (1.03; 7.43)	0.043
Vaginal involvement	*No vaginal involvement*	1.63 (0.69; 3.85)	0.262	2.15 (0.73; 6.32)	0.163
Positive pelvic nSN	*Negative pelvic nSN*	3.47 (1.92; 6.26)	<0.001	5.09 (2.28; 11.39)	<0.001
Final lymph node status[c]					
Macrometastasis	*Negative findings*	3.15 (1.73; 5.74)	0.001	6.85 (2.59; 18.05)	<0.001
Micrometastasis		3.15 (0.73; 5.14)	0.186	6.86 (2.09; 22.61)	0.002
ITC[b]		–		–	

[a] HR: hazard ratios estimated on the basis of univariable Cox proportional hazard regression; CI: confidence interval.
[b] All patients in this category survived without any event, HR not estimated.
[c] SN micro staging and pelvic nSN.

macrometastasis (48%) and micrometastasis (64%) when compared to the patients without metastatic disease (87%). The latter study should be interpreted with caution, however, as only original slides from routine evaluation were available, no serial sectioning was performed, and node negative cases were not re-evaluated. In conclusion, although some preliminary data have shown a worse prognosis of patients with micrometastasis, all available studies suffer either from small samples size or have other serious limitations. Moreover, the significance of low volume disease detected by serial sectioning in SN has not been addressed in any of these studies.

In our study, ITC was detected in 4.5%, micrometastasis in 10% and macrometastasis in 15% of patients in SN by ultrastaging. The presence of ITC was not associated with statistically significant prognostic risk for either RFS or OS. Identical prevalence of ITC has been found in all FIGO stages equally, in contrast to the increasing prevalence of both micrometastasis and macrometastasis in more advanced stages. Most importantly, detection of micrometastasis was associated with poorer prognosis, which did not reach statistical significance for RFS, but OS was equally reduced as in patients with macrometastasis. Presence of micrometastasis was an independent prognostic factor which reached a univariable and multivariable-adjusted RR of 6.86 ($p=0.002$ and 4.60 ($p=0.015$); this was even more significant than the effect of FIGO stage.

Our findings highlight the importance of sentinel node biopsy for the management of patients with early-stage cervical cancer. Detection of SN and subsequent ultrastaging may identify a subgroup of patients with micrometastasis which would be overlooked by routine pathologic processing, although they are in the same prognostic category as those with macrometastasis.

There are several limitations of our study caused by the retrospective and multicenter nature of data collection. The sample size provided by participating centers was significantly different and unbalanced. Therefore, the study did not allow for relevant comparison of centers on reached survival. However, including unique codes of centers as qualitative cofactors of constructed predictive models did not indicate any significant differences among them or bias associated with samples from individual centers. Also, disparities in pathology processing of lymph nodes could have influenced the results, as the detection of low volume disease remains dependent on the technique employed

Table 4
Multivariable analysis of relapse-free survival (RFS) and overall survival (OS) in relation to potential risk factors[a].

Parameters included in model	Coefficient (SE; *p* level)	Multivariable adjusted HR (95% CI)
4a. Relapse-free survival		
Macrometastasis	0.91 (0.30; $p=0.002$)	2.47 (1.38; 4.42)
Age > 50 years	0.73 (0.29; $p=0.014$)	2.08 (1.16; 3.75)
Stage IB2 and IIAB	0.55 (0.24; $p=0.048$)	1.73 (1.01; 2.92)
Overall model statistics		
- Log-likelihood of Null model / final model	295.0/285.7	
χ^2 test (*p* value)	$\chi^{2\ (\text{d.f.}=3)}=18.6$ ($p<0.001$)	
4b. Overall survival		
Age (in years)	0.06 (0.01; $p=0.002$)	1.06 (1.03; 1.10)
Macrometastasis	1.66 (0.48; $p=0.008$)	5.27 (1.99; 14.00)
Micrometastasis	1.52 (0.62; $p=0.015$)	4.60 (1.34; 15.77)
Stage IB2 and IIAB	1.04 (0.45; $p=0.044$)	2.82 (1.01; 7.95)
Overall model statistics		
Log-likelihood of Null model / final model	146.8 / 128.1	
χ^2 test (*p* value)	$\chi^{2\ (\text{d.f.}=4)}=34.4$ ($p<0.001$)	

CI: confidence interval.
[a] Multivariable proportional hazard Cox regression models.

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[24]. Therefore, protocols used for lymph node evaluation have been revised from all collaborating institutions. Routine evaluation of nSN was identical in all centers. Protocols for SN processing were comparable, differing mostly in step sectioning protocol, but having the intervals for serial sectioning ≤250 μm in the vast majority of cases (98%), which is mostly considered sufficient to screen for micrometastasis [13,24]. Also, the oncological outcome may be influenced by variations in treatment protocols between the centers. Therefore, type of surgical procedure, administration and type of adjuvant treatment have been involved in the multivariable analysis and did not appear in any of the models. Moreover, adjuvant treatment was given to the equal proportion of patients with macrometastasis and micrometastasis.

In conclusion, our data represent the largest prognostic assessment of the presence of low volume lymph node disease in patients with early-stage surgically treated cervical cancer. It should be emphasized that none of ongoing prospective studies are designed to address this topic. Presence of micrometastasis in SN in the absence of macrometastasis in any of the pelvic nodes was associated with significantly decreased overall survival, which was equivalent to the overall survival of patients with macrometastasis. No prognostic significance of ITC has been observed.

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Conflict of interest statement
The authors declare that there are no conflicts of interest.

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