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Stratification of lymph node metastases as macrometastases, micrometastases, or isolated tumor cells has no clinical implication in patients with cervical cancer: Subgroup analysis of the SCCAN project

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HIGHLIGHTS

- Classification of metastases to MAC, MIC and ITC is of no clinical value in cervical cancer.
- DFS did not differ between patients with MAC or MIC and was shorter than in N0.
- DFS was significantly shorter in patients with metastases ≥0.4 mm compared to N0.
- No subcohort with better prognosis than the rest of the N1 cohort was identified.
- LN metastases have a significant negative impact on DFS regardless of the size.

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ABSTRACT

Background. In cervical cancer, presence of lymph-node macrometastases (MAC) is a major prognostic factor and an indication for adjuvant treatment. However, since clinical impact of micrometastases (MIC) and isolated tumor-cells (ITC) remains controversial, we sought to identify a cut-off value for the metastasis size not associated with negative prognosis.

Methods. We analyzed data from 967 cervical cancer patients (T1a1L1-T2b) registered in the SCCAN (Surveillance in Cervical CANcer) database, who underwent primary surgical treatment, including sentinel lymph-node (SLN) biopsy with pathological ultrastaging. The size of SLN metastasis was considered a continuous variable and multiple testing was performed for cut-off values of 0.01–1.0 mm. Disease-free survival (DFS) was compared between N0 and subgroups of N1 patients defined by cut-off ranges.

Results. LN metastases were found in 172 (18%) patients, classified as MAC, MIC, and ITC in 79, 54, and 39 patients, respectively. DFS was shorter in patients with MAC (HR 2.20, $P = 0.003$) and MIC (HR 2.87, $P < 0.001$), while not differing between MAC/MIC ($P = 0.484$). DFS in the ITC subgroup was neither different from N0

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($P = 0.127$) nor from MIC/MAC subgroups ($P = 0.449$). Cut-off analysis revealed significantly shorter DFS compared to N0 in all subgroups with metastases ≥0.4 mm (HR 2.311, $P = 0.04$). The significance of metastases <0.4 mm could not be assessed due to limited statistical power (<80%). We did not identify any cut-off for the size of metastasis with significantly better prognosis than the rest of N1 group.

Conclusions. In cervical cancer patients, the presence of LN metastases ≥0.4 mm was associated with a significant negative impact on DFS and no cut-off value for the size of metastasis with better prognosis than N1 was found. Traditional metastasis stratification based on size has no clinical implication.

1. Introduction

Nodal spread is a key factor that defines the treatment strategy of patients with early-stage cervical cancer [1]. Since other high-risk factors, parametrial infiltration and incomplete tumor resection, are now almost eliminated by proper clinical staging, and the management of patients with intermediate risk factors is still being debated [2,3], lymph node (LN) involvement remains the major reason for adjuvant treatment administration.

Routine implementation of sentinel LN (SLN) biopsy combined with pathologic ultrastaging has increased the accuracy of LN staging due to the detection of small metastases, which would otherwise be missed by standard assessment [4,5]. At the same time, SLN biopsy in cervical cancer is still not standard-of-care treatment method and its safety without systematic pelvic lymphadenectomy is currently being evaluated by ongoing SENTIX and SENTICOL III prospective trials [6,7]. Thus, 98% of patients included in this study underwent both SLN biopsy and systematic pelvic lymphadenectomy. SLN biopsy was used as inclusion criterion since low volume metastases are mostly detected only by pathological ultrastaging.

Unsurprisingly, improved detection of small volume metastases has provoked a debate about whether there is a minimum cut-off for metastasis size that that does not have a negative impact on prognosis and does not require adjuvant treatment. Such a cut-off would also determine requirements for the intensity of pathologic assessment.

The classification of LN metastases in cervical cancer was adopted from a consensus on SLN in breast cancer [8], in which nodal metastases are classified based on their size as macrometastases (MAC; >2 mm), micrometastases (MIC; >0.2 to ≤2 mm), or isolated tumor cells (ITC; ≤0.2 mm). MIC and ITC are considered as low-volume metastases (LVM). For MIC, several studies recently demonstrated that metastases between 0.2 and 2 mm carries a similar negative prognostic impact to that of larger lesions (MAC) [9–13]. However, the impact of ITC was assessed in a small number of studies, which were underpowered to detect a significant result [11–13].

In this study, we used a large cohort of patients with early-stage cervical cancer, the retrospective international SCCAN (Surveillance in Cervical CANcer) study, which contained data from 967 patients who underwent SLN biopsy and pathological ultrastaging. Our aim was to identify a potential cut-off value for the minimal size of metastasis that was not associated with a negative prognosis in terms of DFS.

2. Materials and methods

2.1. Study design and patients

The SCCAN study is an international, multicenter, retrospective cohort study that evaluated the recurrence patterns of cervical cancer survivors. The SCCAN study consortium consisted of 20 tertiary centers, located in Europe, Asia, North America, and Latin America.

Patients were retrospectively included if they met the following inclusion criteria: (i) pathologically confirmed cervical cancer treated between 2007 and 2016; (ii) TNM stage T1a to T2b based on preoperative assessment according to American Joint Committee on Cancer – Cervix Uteri Cancer Staging; and (iii) primary surgical management, including fertility-sparing procedures. Patients were eligible irrespective of the type of adjuvant treatment, neoadjuvant chemotherapy, tumor type, LN status, or LN staging. Patients were ineligible if they had precancer disease, they underwent definitive radiotherapy/chemoradiation, or primary surgical treatment was abandoned intra-operatively. The database comprised data from 4343 patients with early-stage cervical cancer. The design of the SCCAN study was published in more detail in a previous report [14].

For the present study, additional inclusion criterion was successful identification of at least one SLN, which was subsequently processed according to the pathologic ultrastaging protocol. Minimal criteria for the ultrastaging protocol were defined for the sites to join the study: (i) the entire SLN had to be processed; (ii) at least four paraffin block levels; and (iii) routine use of immunohistochemistry.

The protocol was approved by the institutional review board at the lead institution (General University Hospital in Prague, Czech Republic; approval number: 2183/18S-IV) in 2019. Institutional review board approval at the participating sites was a prerequisite for participation. Due to the retrospective nature of the study, the institutional review boards waived the need for informed consent. The study was performed in accordance with the Declaration of Helsinki.

2.2. Data collection

The type of radical parametrectomy was classified according to the Querleu–Morrow classification system [15,16]. The number of negative and positive sentinel and non-sentinel LNs and the size of largest nodal metastasis were retrieved from the database. Patients were then classified into MAC, MIC, ITC, and N0 subgroups according to the size of the largest LN metastasis detected in the SLN or parametrial LN. MAC was defined as a metastasis >2 mm in diameter, MIC as a metastasis of >0.2 to ≤2 mm, and ITC as individual tumor cells or small clusters of cells ≤0.2 mm in diameter. Histopathological data (histotype, grade, lymphovascular space invasion, maximum tumor diameter, and stage) were retrieved from the SCCAN database. Further details on the SLN procedure analyzed: tracer type, size of nodal metastasis, and the description of ultrastaging protocol.

2.3. Ultrastaging protocol

At the macroscopic level, SLNs were sliced in regular (2 or 3 mm) intervals at 11 of 12 participating centers. Equal parts (halves or thirds) were produced by gross processing at the other center. In all sites, the entire SLN was sectioned, and no tissue was left unexamined. At least four paraffin block levels were assessed at the microscopic level. The interval between single levels ranged from 50 to 250 μm. Up to five slides were prepared from each level and at least one slide was processed using immunohistochemistry.

2.4. Data analyses

Standard measures of summary statistics were used to describe primary data, including the relative and absolute frequencies, and the

arithmetic mean with the standard deviation. Associations between size of the metastasis and the DFS were determined using Cox proportional hazard model and expressed as hazard ratios (HR) with 95% confidence intervals (CI) and corresponding *P*-values. DFS was calculated as the time from surgery to the date of disease recurrence. DFS was assessed using the Kaplan–Meier method and compared among subgroups using the log-rank test.

Additionally, patients in the N1 cohort (i.e., MAC, MIC, or ITC) were combined and reassessed to investigate the impact of the size of LN metastases on prognosis. Patients were clustered into subgroups with nodal metastases less or equal to specified cut-off values (*x* mm) ranging from 0.01 mm to 1 mm at 0.01 mm intervals. The DFS in each subgroup was compared with that of the N0 subgroup and the remainder of the N1 cohort using Kaplan–Meier curves, log-rank tests, and Cox proportional hazard model with HR, 95% CI, and the corresponding *P* value. The statistical power of the analysis was recorded for each analysis. A value of $P = 0.05$ was used as the limit of statistical significance in all of the analyses.

3. Results

3.1. Patient characteristics

Of 4343 patients included in the SCCAN database, we analyzed data from 967 patients with pathologically confirmed cervical cancer who underwent SLN biopsy followed by pathological ultrastaging. The main patient characteristics are summarized in Table 1. The majority of patients had squamous cell carcinoma (62%) or adenocarcinoma (30%). The mean ± standard deviation maximum tumor size was 20.6 ± 13.7 mm. The predominant surgical procedure was radical hysterectomy (86%). SLNs were identified using blue dye, radioactive colloid, and indocyanine green in 718 (74%), 480 (50%) and 219 (23%) patients, respectively. A dual tracer technique was used in 47% of patients. A mean of 3.2 SLNs were identified per patient. Pelvic and paraaortic lymphadenectomy was completed in 98% and 6% of patients. No metastatic involvement (N0) was confirmed in 795 patients (82%). None of the 21 patients who did not undergo pelvic lymphadenectomy had SLN metastasis or experienced recurrence.

The pelvic LN metastases were classified as MAC, MIC, and ITC in 79 (8%), 54 (6%), and 39 (4%) patients, respectively. Of these 172 patients, SLN ultrastaging was falsely negative in 4 of them, with negative SLN but positive (MAC) in other pelvic LN. The sensitivity, false negative rate, and negative predictive value of SLN ultrastaging for pelvic LN status were 98%, 2%, and 99%, respectively.

A total of 153 (16%), 135 (14%), and 18 (2%) patients underwent radiation, chemoradiation, or systemic treatment in the adjuvant setting. Adjuvant treatment was administered to 94% patients with MAC (74), 81% patients with MIC (44), and 69% patients with ITC (27). All patients with any type of metastasis who experienced recurrence underwent adjuvant treatment (Supplementary table 1). Among 151 patients in the N0 subgroup who received adjuvant (chemo)radiation (19%), 11 (7%) had parametrial infiltration and 140 patients (93%) had a combination of intermediate risk prognostic factors [2].

Nine traditional prognostic markers were evaluated in univariable analysis for predicting DFS (Supplementary table 2). Only surgical approach ceased to be significant. The highest prognostic risk, described as hazard ratio (HR), was found for maximum tumor size, tumor histotype, and number of positive pelvic LNs.

3.2. Prognostic impact of LVM

With a median follow-up of 52 months, 117 patients were diagnosed with recurrence, including 18 patients with MAC (23%), 15 patients with MIC (28%), and 7 patients with ITC (18%) as the biggest type of LN metastasis. Mean number of positive lymph nodes in the MAC, MIC and ITC group was 2.2, 1.4 and 1.3, respectively. Patients with MAC (HR 2.20, $P = 0.003$) or MIC (HR 2.87, $P < 0.001$) had significantly higher risk of recurrence compared with the N0 subgroup (Fig. 1). DFS was not significantly different between the MAC and MIC subgroups (HR 0.76, $P = 0.484$).

Furthermore, DFS in the ITC subgroup was not significantly different from that of the N0 ($P = 0.127$) or MIC/MAC subgroups ($P = 0.449$) (Fig. 1).

We then reassessed the N1 cohort (i.e., MAC, MIC, and ITC) to investigate the prognosis of patients with small LN metastases by dividing the patients into subgroups based on cut-off values ranging from 0.01 mm to 1 mm at intervals of 0.01 mm. The DFS of these subgroups were compared with the N0 cohort (Fig. 2) and the rest of the N1 cohort (Fig. 3). All subgroups with cut-off values of ≥0.4 mm had significantly shorter DFS compared with the N0 subgroup; the HR was 2.311 (95% CI 1.157–4.618) at the cut-off value of 0.4 mm. The prognosis could not be assessed in subgroups with metastases <0.4 mm because these subgroups were insufficiently powered to yield significant results based on log-rank tests (power < 80% and $P > 0.05$). Furthermore, we found no threshold cut-off value for separating a subgroup of patients with a minimum size of metastasis with significantly better prognosis than the N1 cohort (Fig. 3).

Table 1
Basic characteristics of the patients ($N = 967$).

Characteristics		N (%)/mean ± SD
Stage	T1a	129 (13%)
	T1b1	415 (43%)
	T1b2	302 (31%)
	T1b3	62 (6%)
	T2a	24 (2%)
	T2b	35 (4%)
Tumor diameter	mm	20.6 ± 13.7
Grade	1	149 (15%)
	2	405 (42%)
	3	245 (25%)
Histological type	Squamous cell	603 (62%)
	Adenocarcinoma	287 (30%)
	Adenosquamous	50 (5%)
	Neuroendocrine	18 (2%)
	Sarcoma	2 (<1%)
	Other	7 (1%)
LVSI	Positive	349 (36%)
Lymph node status[1]	MAC	79 (8%)
	MIC	54 (6%)
	ITC	39 (4%)
	Negative	795 (82%)
Type of uterine procedure	Conization/trachelectomy	37 (4%)
Surgical approach	Simple hysterectomy	24 (2%)
	Radical trachelectomy	70 (7%)
	Radical hysterectomy[2,3]	836 (86%)
	Open	574 (59%)
	Laparoscopic	199 (21%)
	Robotic	194 (20%)
SLN tracer type	Dye	718 (74%)
	Radiocolloid	480 (50%)
	Indocyanine green	219 (23%)
Dual tracer		450 (47%)
Number of SLN detected		3.2 ± 2.2
Pelvic lymphadenectomy performed		946 (98%)
Adjuvant treatment	Radiotherapy	153 (16%)
	CRT	135 (14%)
	CT	18 (2%)
	CRT + outback CT	5 (1%)
Patients with recurrence		117 (12%)

CRT, chemoradiation; CT, chemotherapy; ITC, isolated tumor cells; LVSI, lymphovascular space invasion; MAC, macrometastases; MIC, micrometastases; SD, standard deviation; SLN, sentinel lymph node.
[1] Largest type of metastasis.
[2] Including radical parametrectomy.
[3] Including conization, simple hysterectomy and simple trachelectomy.

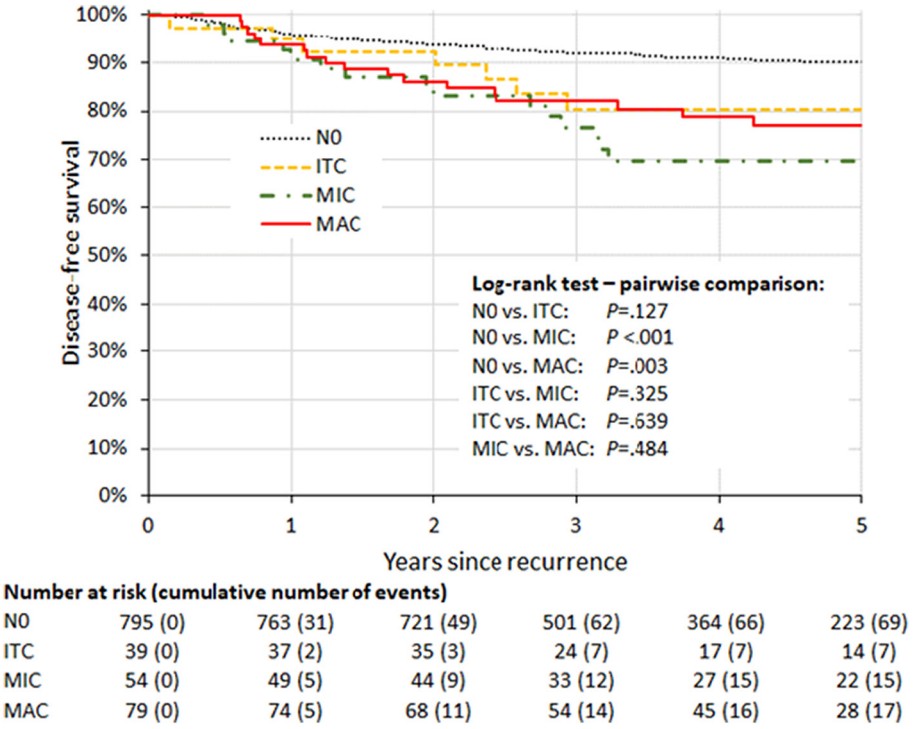

Fig. 1. Kaplan–Meier estimates of disease-free survival in the N0, MAC, MIC, and ITC subgroups.
ITC, isolated tumor cells; MAC, macrometastases; MIC, micrometastases.

4. Discussion

Based on data from this retrospective, international, multicenter SCCAN study, we demonstrated that any size of SLN metastasis above 0.4 mm is significantly associated with shorter DFS compared to N0 patients. Even this large cohort was not sufficiently powered to analyze the prognostic impact of metastatic lesions below the cut-off value of <0.4 mm due to the limited number of eligible cases and events. We also did not identify any threshold for a minimum size of metastasis below which the prognosis would be more favorable than in the N1 cohort.

Because N1 status substantially changes the treatment management of the cervical cancer patients, it has been intensely debated whether all LN metastases have a similar clinical impact according to their size. N1 category in gynecological cancer has been divided into MAC, MIC, and ITC, based on consensus made in breast cancer, and these categories have been studied separately in terms of their impact on prognosis. However, it is important to mention that even in breast cancer the concept of micrometastases was based on an arbitrary cut-off with no clear explanation to support this value [17]. This was also true for differentiating between ITC and MIC, with no supporting evidence regarding its prognostic value.

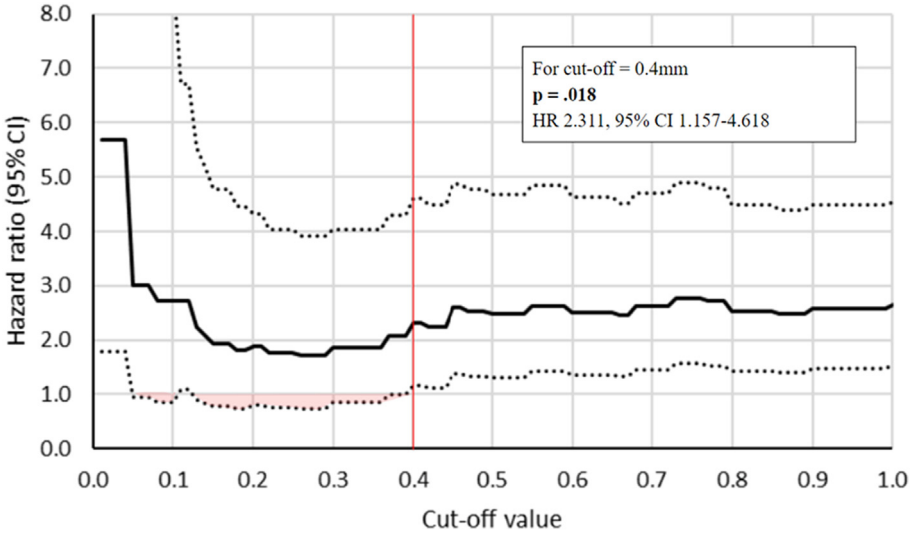

Fig. 2. Results of Cox proportional hazard model for subgroups of patients with LN metastases smaller or equal to the specified cut-off value in mm (*x* axis) compared with the N0 cohort. Confidence intervals below 1.0 (unsignificant) are marked in red.
CI, confidence interval; HR, hazard ratio. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

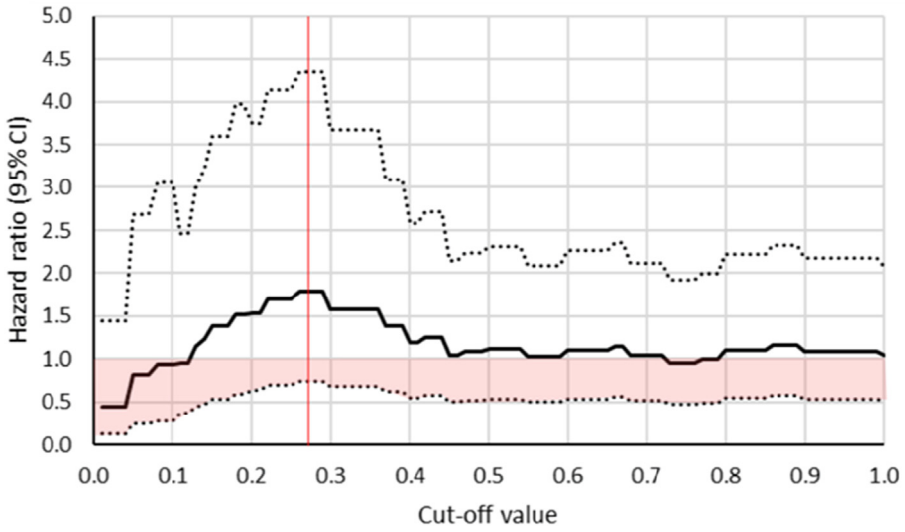

Fig. 3. Results of the Cox proportional hazard model for subgroups of patients having LN metastases smaller or equal than the cut-off value (x axis) compared to the rest of the N1 cohort (> cut-off value) as a reference group. Confidence intervals below 1.0 (unsignificant) are marked in red.
CI, confidence interval. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

A recent meta-analysis evaluating the impact of LVM in cervical cancer patients [18] in 11 published papers confirmed the negative impact of MIC on both DFS and overall survival compared with N0 status (HR 2.60, 95% CI 1.55–4.34). Our study supports this observation, demonstrating that MIC is associated with a similar prognosis to that of MAC (HR 2.87 and 2.20, respectively), and prompted our conclusion that the discrimination between MAC and MIC for guiding further clinical management has little impact, given the comparable prognosis of both subgroups.

The prognosis of patients with even smaller LN metastases (i.e., ITC) was, in prior reports, based on a small cohorts that were insufficient for appropriate statistical analysis [10,13]. In an attempt to overcome the low number of patients with ITC in the evaluated papers, the authors of the above-mentioned meta-analysis [18] pooled the ITC and MIC into a LVM category. They highlighted the worse prognostic impact of MIC alone compared with the LVM category (HR for MIC vs. MIC&ITC: 4.10 vs. 2.60 for DFS and 6.94 vs. 5.65 for overall survival, respectively) and concluded that patients with ITC should be considered as N0 patients. However, their interpretation may be misleading because no statistical analysis was performed to compare the ITC category with the rest of the N1 cohort. Despite the lower recurrence rate in the ITC subgroup in our study (18% vs. 23% for MAC and 28% for MIC), we found that DFS in the ITC subgroup was not significantly different to the remaining N1 cohort ($p = 0.449$) or the N0 subgroup ($p = 0.127$), implying that ITC cannot be merged with either N1 or N0.

Because the upper limit of 0.2 mm is an artificial cut-off, we tried to identify a minimum cut-off size below which the prognosis would be significantly better than the N1 cohort. We found that all subgroups of patients with metastatic lesions ≥0.4 mm had significantly shorter DFS compared with the N0 subgroup. The subgroups with lower upper limits below 0.4 mm were too small to yield conclusive results. Though, at the same time, we were unable to identify a cut-off value that could define subcohorts of LN metastases (i.e., 0–x mm) showing better prognosis than the rest of the N1 cohort.

The impact of our findings for clinical practice can be interpreted from two opposite perspectives. It can be argued that since the significant impact of very small metastasis (either the ITC category below 0.2 mm, or 0.4 mm according to this study) was not proven, these lesions should be categorized as N0. We believe that the interpretation should be otherwise and even these very small lesions should be considered N1 until any future study will identify a threshold for a minimum metastatic size which is not associated with higher risk of recurrence. In addition, it should be emphasized that the ability to detect ITC depends on the intensity of the ultrastaging protocol. Pathological protocols, mainly interval between the levels, will never be sufficiently sensitive, even in experimental settings, to detect all ITC. As a consequence, some ITC will always remain undetected in the N0 group, and this may diminish the difference in patient outcomes between the N0 and N1 subgroups.

The current study represents the largest cohort of patients with cervical cancer who underwent SLN ultrastaging. The main limitation of this study is its retrospective design. However, a prospective study designed to address a prognostic impact of LVM would be extremely demanding, if not unrealistic, given the declining incidence of cervical cancer, low frequency of LVM, overall excellent prognosis of patients with early stages, and inability to detect ITC completely, as described above. Another potential limitation is the fact that 41% of patients underwent surgery via minimally invasive approach, since the results of the LACC trial [19] were not known at the time of the treatment. In order to assess the impact of risk factors other than LN involvement, univariable analysis of the factors associated with DFS was performed and surgical approach did not turn to be significant.

In conclusion, in the current study of 967 patients with at least one SLN identified and processed by ultrastaging, we found that the presence of LN metastasis of ≥0.4 mm is associated with a significantly increased risk of disease recurrence. Therefore, stratifying patients with N1 cervical cancer into the MAC and MIC categories has no clinical value in terms of prognosis. Moreover, no threshold for a minimal size of metastasis with significantly better prognosis than N1 group was found. We therefore suggest that the management of all lymph node positive patients should be uniform irrespective of the size of the metastasis until a sufficiently powered study can define a cut-off value below which the size of LN metastases is not associated with worse prognosis.

Data availability statement

Data on the study are available upon reasonable request to the corresponding author.

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CRediT authorship contribution statement

Lukáš Dostálek: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft. **Klára Benešová:** Data curation, Formal analysis, Visualization. **Jaroslav Klát:** Investigation. **Sarah H. Kim:** Investigation. **Henrik Falconer:** Investigation. **Jan Kostun:** Investigation. **Ricardo dos Reis:** Investigation. **Ignacio Zapardiel:** Investigation. **Fabio Landoni:** Investigation. **David Isla Ortiz:** Investigation. **Luc R.C.W. van Lonkhuijzen:** Investigation. **Aldo Lopez:** Investigation. **Diego Odetto:** Investigation. **Martina Borčinová:** Data curation, Formal analysis, Writing – original draft. **Jiri Jarkovsky:** Formal analysis, Visualization. **Sahar Salehi:** Investigation. **Kristýna Němejcová:** Investigation. **Sylva Bajsová:** Investigation. **Kay J. Park:** Investigation. **Veronika Javůrková:** Investigation. **Nadeem R. Abu-Rustum:** Funding acquisition, Investigation. **Pavel Dundr:** Investigation. **David Cibula:** Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Writing – original draft.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2022.11.017.

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