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Original Article



The risk of lymph node metastasis in the new FIGO 2018 stage IA cervical cancer with >7 mm diameter

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ABSTRACT

Objective: In the 2018 FIGO staging system, cervical cancers with ≤ 5 mm depth of invasion (DOI) and a diameter of >7 mm, first classified as stage IB, are classified as stage IA. In this group, it is unclear what the risk of lymph node metastasis (LNM) is. This retrospective cohort study aims to determine the incidence of LNM and to study the association between disease-related characteristics and LNM.

Methods: Women diagnosed with FIGO 2009 IB cervical cancer, with ≤ 5 mm DOI and a diameter >7 mm, treated with a radical hysterectomy and pelvic lymphadenectomy between 1985 and 2020 were selected from the databases of the Amsterdam University Medical Center and the University Medical Center Groningen. The specimens of patients with LNM were revised by expert pathologists. The incidence of LNM was calculated. The associations between LNM and DOI, diameter, histological type, clinical visibility and lymphovascular space invasion (LVSI) were evaluated by calculating odds ratios using logistic regression.


Results: Of the 389 patients included, 10 had pathologically confirmed LNM (2.6%, 95% confidence interval=1.3%–4.5%). In case of LVSI, univariate analysis showed an increased risk of LNM ($p=0.003$ and $p=0.012$, respectively). No difference in LNM was found between lesions diagnosed by microscopy and clinically visible lesions. No LNM were found in patients without LVSI and a DOI of ≤ 3 mm.

Conclusion: For patients with stage IA cervical cancer with a diameter >7 mm, we recommend considering a pelvic lymph node assessment in case of DOI >3 mm and/or presence of LVSI.

Keywords: Adenocarcinoma; Lymph Node Metastasis; Neoplasm Invasiveness; Squamous Cell Carcinoma; Survival; Uterine Cervical Neoplasms

Synopsis

Cervical cancers with ≤ 5 mm DOI and >7 mm diameter are newly classified as FIGO stage IA. The LNM incidence in stage IA cervical cancers with a diameter >7 mm is 2.6%. LNM is associated with LVSI, but not with clinical visibility of the tumor. Lymph node assessment is advised in case of DOI >3 mm or presence of LVSI.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Author Contributions

Conceptualization: Y.R., V.J., M.C.H.; Data curation: N.L., B.M.C., B.J., V.J., M.C.H.; Formal analysis: N.L., B.M.C., B.J.; Investigation: N.L.; Methodology: N.L., V.J., M.C.H.; Supervision: Y.R., V.J., M.C.H.; Validation: V.J.; Visualization: V.J., M.C.H.; Writing - original draft: N.L.; Writing - review & editing: N.L., Y.R., B.M.C., B.J., V.J., M.C.H.

INTRODUCTION

To define patient groups with a similar prognosis, cervical tumors are staged according to the International Federation of Gynecology and Obstetrics (FIGO) staging system for cervical cancer. In 2018 this staging system changed from a clinical staging system (FIGO 2009) into a system based on clinical, imaging, and pathological variables [1,2]. In this new FIGO staging system, diameter is no longer a determining factor in differentiating between stage IA and IB in tumors ≤ 5 mm depth of invasion (DOI) [1,2]. As a result, tumors diagnosed only by microscopy, without invasion beyond the uterus, with ≤ 5 mm DOI and >7 mm diameter, which were classified as stage IB in the 2009 FIGO staging, are now classified as FIGO stage IA.

Although the FIGO staging is primarily meant to be a prognostic scoring system, it is also used as a guide for treatment decisions. In general, early stages (stage I-IIA) are treated surgically, while locally advanced and late stages ($>IIA$) are treated by concomitant chemoradiotherapy [3].

Lymph node involvement is one of the most important prognostic factors in cervical cancer. The presence of lymph node metastases is associated with decreased overall survival and increased risk of recurrence [4]. For FIGO 2009 stage IA tumors, the recommendation to perform a pelvic lymphadenectomy was mainly dependent on the presence of lymphovascular space invasion (LVSI), as LVSI increases the risk of lymph node metastasis (LNM), from 1.3% in the absence of LVSI to 12% in patients with LVSI [5].

Wenzel et al. [6] showed 3.5% LNM in a group of patients that was first classified as stage IB (FIGO 2009) and now stage IA (FIGO 2018). However, in a study by Sponholtz et al., [7] no lymph node metastases was found in the newly stage IA. Therefore, more studies are needed to determine the risk of LNM, and consequently, whether a pelvic lymph node assessment is recommended for patients with tumors previously (2009) classified as stage IB1, but now classified as stage IA.

In addition, more research is needed to make recommendations on the preferred treatment strategy depending on whether a tumor is clinically visible or not.

This study aims to determine the incidence of lymph node metastases in patients with tumors confined to the cervix, with ≤ 5 mm DOI and with >7 mm diameter. Moreover, this study will focus on the association between the presence of LNM and tumor characteristics, such as DOI, diameter, histological type, LVSI, and clinical visibility of the lesion. Based on the results we aim to make recommendations regarding lymph node assessment in this patient group.

MATERIALS AND METHODS

1. Design and setting

A retrospective cohort study was performed by analyzing data from the electronic patient records of the Amsterdam University Medical Center (UMC) and the University Medical Center Groningen (UMCG). All consecutive patients, newly diagnosed with FIGO (2009) IB cervical cancer between February 1985 and August 2020 and treated by (open) radical hysterectomy, radical trachelectomy, simple hysterectomy, cervical conization or large loop excision of the transformation zone (LLETZ), combined with a complete pelvic lymphadenectomy, were identified. In case of LNM, parametrial involvement or tumor in the resection margin,

adjuvant (chemo)radiotherapy was recommended. At the UMCG the Sedlis criteria were also used to recommend adjuvant radiotherapy [8]. All patients with an adenocarcinoma, squamous cell carcinoma, or adenosquamous cell carcinoma of the cervix, with ≤ 5 mm DOI and >7 mm diameter were included in the study. If information regarding clinical visibility of the lesion was available, patients were further subdivided into a group in which the diagnosis was only made by microscopy, and another group in which the tumor was clinically visible. Patients were excluded if no hysterectomy was performed, no lymph nodes were examined, the DOI was unknown, or if neoadjuvant chemotherapy was administered.

2. Ethical approval

Ethical approval for the study was obtained from the Institutional Review Board (IRB) of the Amsterdam UMC (reference number W20_448 # 20.495). Written informed consent was waived by the IRB, because, according to Dutch law, this is not obligated in case anonymized patient data are used, keeping in mind the rules of good clinical practice.

3 Data collection

The medical records of the included patients were reviewed. The following data were retrieved from these records: age at diagnosis, clinical visibility of the lesion, primary treatment, date of surgery, adjuvant therapy, last follow-up date, date of recurrence, and date of death. A tumor was considered clinically visible when a suspect lesion was seen at routine gynecological examination.

Pathology reports were evaluated, and the following data were retrieved: histological subtype, diameter (in millimeters), DOI (in millimeters), presence of positive lymph nodes, and presence of LVSI. The Amsterdam UMC pathologic specimens from 1985 till 1992 were previously reviewed by an expert gynecologic pathologist [9], whereas pathologic specimens from 1992 till 2020 were analyzed prospectively by expert gynecologic pathologists and discussed in a multidisciplinary board. All UMCG pathologic specimens were analyzed by an expert gynecologic pathologist. For this study, all specimens of patients with positive lymph nodes were reviewed again by an expert pathologist (J.B; M.C.G.B.). If any of these cases turned out to have a DOI of >5 mm, they were excluded from the study. Four cases with LNM were not revised since there were no specimens available. In this case, the DOI, diameter and LVSI described in the original report was used.

4. Statistical analysis

Descriptive statistics were used to summarize the basic demographic details. The incidence of LNM was calculated with 95% confidence interval (CI) for the whole population. The associations of DOI, diameter, histological type, clinical visibility of the lesion and LVSI with LNM were evaluated by calculating the odds ratios (OR) with 95% CI using logistic regression. P-values <0.05 were considered statistically significant. IBM SPSS Statistics 26 (IBM Corp., Armonk, NY, USA) was used for this study. In accordance with the journal's guidelines, we will provide our data for the reproducibility of this study in other centers if such is requested.

RESULTS

1. Patient selection

A total of 1,291 patients with 2009 FIGO stage IB were identified, of which 389 (30.1%) patients had a DOI ≤ 5 mm and diameter >7 mm (**Fig. 1**). In 265 of 389 patients a description

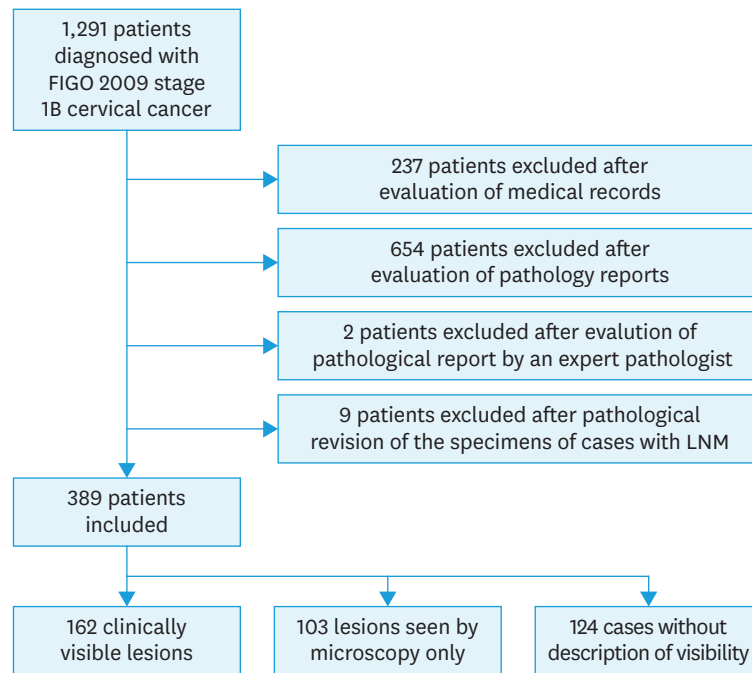


Fig. 1. Patient selection. FIGO, International Federation of Gynecology and Obstetrics; LNM, lymph node metastasis.

of whether the tumor was seen by microscopy only or was clinically visible was found in the medical records.

Pathology of tumor specimens of 19 patients with positive lymph nodes were reviewed. Nine of nineteen reviewed cases turned out to have a DOI of >5 mm, these cases were excluded. Although described as LVSI negative in the original report, three reviewed cases turned out to have LVSI.

2. Patient and disease-related characteristics

The median age at diagnosis was 41 years (range 23–86 years). The median follow-up duration was 62 months. Patient characteristics are shown in **table 1**. The most common primary treatment was a radical hysterectomy with pelvic lymphadenectomy (93.8%). Some patients received a simple trachelectomy (3.3%), simple hysterectomy (0.8%) or conization or re-LLETZ (2.1%) with pelvic lymphadenectomy. Of all patients, 3.6% received adjuvant radiotherapy and 0.5% patients received adjuvant chemoradiation. The five-year recurrence free survival was 97.7% (95% CI=95.7%–98.8%). The five-year survival rate was 97.7% (95% CI=95.7%–98.8%).

Table 2 shows the disease-related characteristics. The most prevalent histological subtype was squamous cell carcinoma (68.6%). All patients had a DOI of ≤5 mm, but in 18 cases the exact DOI (≤3 mm or >3 mm) was unknown. LVSI was found in 23.9% of the patients. In 38.9% cases the lesion was seen by microscopy only.

3. Lymph node metastasis

The incidence of pathologically confirmed LNM was 2.6% (95% CI=1.3%–4.5%). **Figs. S1** and **S2** show how the cases with LNM are distributed among different tumor characteristics groups. No difference in risk of =LNM was found between tumors with a DOI of ≤3 mm (0.6%) and tumors with a DOI of >3 and ≤5 mm (3.9%, p=0.074). The incidence of LNM was

Table 1. Patient characteristics

Characteristics	Full cohort (n=389)
Primary treatment	
Radical hysterectomy type B2	153 (39.3)
Radical hysterectomy type C2	212 (54.5)
Trachelectomy	13 (3.3)
Simple hysterectomy	3 (0.8)
Cervical conization/LLETZ	8 (2.1)
Adjuvant therapy	
Radiotherapy	14 (3.6)
Chemoradiation	2 (0.5)
No	372 (95.9)
Missing	1
Positive lymph nodes	
Yes	10 (2.6)
No	379 (97.4)
Recurrence	
Yes	11 (2.8)
No	378 (97.2)
Outcome	
Disease-related death	7 (1.8)
Intercurrent death	17 (4.4)
No death	365 (93.8)

Values are presented as number (%).

LLETZ, large loop excision of the transformation zone; LNM, lymph node metastasis.

Table 2. Disease-related characteristics

Disease-related characteristics	Full cohort (n=389)	Presence LNM*
Histological subtype		
Squamous cell carcinoma	267 (68.6)	7/267 (2.6)
Adenocarcinoma	122 (31.4)	3/122 (2.5)
Depth of invasion[†]		
≤3 mm	166 (44.7)	1/166 (0.6)
>3 mm - ≤5 mm	205 (55.3)	8/205 (3.9)
Missing	18	1/18
Diameter		
<2 cm	291 (74.8)	6/291 (2.1)
≥2 cm	98 (25.2)	4/98 (4.1)
Lymphovascular space invasion		
Yes	93 (23.9)	7/93 (7.5)
No	296 (76.1)	3/296 (1.0)
Diagnosis		
Lesion is seen by microscopy only	103 (38.9)	4/103 (3.9)
Lesion is clinically visible	162 (61.1)	3/162 (1.9)
Missing	124	124

Values are presented as number (%).

LNM, lymph node metastasis.

*Rate (95% confidence interval); [†]Depth of invasion was ≤5 mm in all cases, also in those where exact measurement was unknown.

similar in the different histological subtypes. No cases with LNM were found in the tumors with a DOI of ≤3 mm without LVSI.

In the univariate analysis, the presence of LVSI increased the risk of LNM (OR=7.95; 95% CI=2.01–31.40). Other characteristics were not associated with LNM (**Table 3**).

Of the 34 patients with LVSI and a DOI of ≤3 mm, one patient with squamous cell carcinoma had LNM (2.9%). Of the 57 patients with LVSI and a DOI of >3 mm and ≤5 mm, five patients had LNM (8.8%). There was no difference between these two groups (p=0.405).

Table 3. Univariate analysis lymph node metastases

Disease related characteristics	Univariate analysis		
	OR	95% CI	p-value*
Histological subtype			0.925
Adenocarcinoma	1.00		
Squamous cell carcinoma	1.07	0.27–4.20	
Depth of invasion			0.074
≤3 mm	1.00		
>3 mm–≤5 mm	6.70	0.82–54.13	
Diameter			0.284
<2 cm	1.00		
≥2 cm	2.02	0.56–7.32	
Lymphovascular space invasion			0.003
No	1.00		
Yes	7.95	2.01–31.40	
Microscopic or macroscopic tumor			0.325
Lesion seen by microscopy only	1.00		
Lesion is clinically visible	0.47	0.10–2.131	

CI, confidence interval; LNM, lymph node metastasis; OR, odds ratio.

*Logistic regression.

No difference in risk of LNM was found between lesions seen by microscopy only and clinically visible lesions (3.8% versus 1.9% respectively, $p=0.332$).

DISCUSSION

1. Main results

Our results show an incidence of LNM of 2.6% in 389 patients with cervical cancer with ≤5 mm DOI and >7 mm diameter. The risk of LNM was increased in case of LVSI. Clinical visibility had no impact on the risk of LNM and in our study histological subtype was not associated with a higher risk of LNM. No cases of LNM were found in cervical cancers with a DOI ≤3 mm without LVSI. No difference in LNM was found between patients with LVSI and a DOI of ≤3 mm and patients with LVSI and a DOI of >3 mm and ≤5 mm.

2. Interpretations and implications

We could only identify three studies that analyzed the incidence of LNM in patients with 2009 stage IB cervical cancer with a DOI of ≤5 mm and >7 mm diameter (FIGO 2018 stage IA) [6,7,10]. However, these studies were done in smaller study populations than our study.

In a prospective cohort study on sentinel lymph node mapping, Sponholtz et al. [7] identified only 12 cases that would be classified as stage IA in the 2018 FIGO staging system of 233 patients with 2009 FIGO stage IB1. No LNM were found in this group of 12 patients. Stolnicu et al. [10] found an incidence of LNM of 0.8% in cervical tumors reallocated from stage IB (2009) to IA (2018). In a population-based study by Wenzel et al., [6] a 3.5% risk of LNM was found in a cohort of 170 patients.

Wenzel et al. [6] found a higher risk of LNM in adenocarcinoma (7.6%) than in squamous cell carcinoma (1.7%). In the absence of LVSI, they found no LNM in patients with squamous cell carcinoma. Consequently, they recommended omitting a lymph node dissection in patients with squamous cell carcinoma without LVSI. In contrast to these findings by Wenzel et al., [6] we observed no difference in risk of LNM between the histological types.

Many studies show that LVSI is a high-risk factor for LNM [11-15]. In the cohort from the study by Wenzel et al. [6] there was a higher incidence of LNM in tumors with LVSI (9.3%) compared to the group without LVSI (1.7%). We also found a higher risk of LNM in univariate analysis, confirming the importance of LVSI as a predictor for LNM. Both our study and the study by Wenzel et al. [6] found no LNM in cervical cancers without LVSI and with a DOI of ≤ 3 mm.

The official description of FIGO stage IA is “Invasive carcinoma that can be diagnosed only by microscopy, with maximum DOI ≤ 5 mm.” [1,2]. This implies that clinically suspect lesions are always at least a stage IB. A study by Takahashi et al. [16] reclassified 25 FIGO 2009 stage IB tumors with a size of < 2 cm. Of these 25 patients, 9 (36.0%) were reclassified as stage IA. Stolnicu et al. [10] performed a retrospective study on 416 cases with a FIGO 2009 stage IA carcinoma, and strictly used the FIGO guidelines by reclassifying all clinically visible tumors as stage IB. 30.3% of cases were reclassified as stage IA. These percentages are similar to our study (30.3%) but differ greatly from the percentage reclassified in the study by Sponholtz et al. [7] (5.2%). This may be due to the different interpretations of what “microscopy only” means and raises questions on how to define “clinically suspect.” For example, does “clinically suspect” also include lesions that are not suspect with the naked eye, but are suspect in colposcopy? How can we classify the patient where directed biopsies of a suspect lesion only show pre-invasive disease, but a conization shows a tumor with a DOI of 4 mm and a diameter of 20 mm? What about a cervical lesion which is not suspect at gynaecological examination, but is seen on MRI, and has a DOI of 3 mm and diameter of 8 mm?

In contrast to the study by Wenzel et al. [6] we also compared lesions which were clinically suspicious with lesions which could only be diagnosed by microscopy. Interestingly, our data did not show a difference in risk on LNM for the group of patients with clinically suspicious lesions versus the group that was diagnosed with microscopy only. This outcome challenges the condition “diagnosed by microscopy only” for stage IA in the FIGO classification.

Based on the results in our relatively large cohort, we recommend performing a pelvic lymph node assessment, by either a lymphadenectomy or a sentinel node procedure, in all patients with cervical cancer with a DOI of ≤ 5 mm and a diameter of > 7 mm, except in the absence of LVSI and a DOI of ≤ 3 mm. **Fig. 2** shows a flowchart with our recommendation on the performance of a pelvic lymph node assessment in this population. Importantly, a risk of LNM of 2.6% can be interpreted as a risk high enough to perform lymph node assessment but can also be seen as a relatively low risk. As lymph node assessment may result in morbidity, for example lymphedema, doctors and patients may take this into account in making treatment decisions regarding pelvic lymph node assessment in this group.

Since there are only a few cases with LNM in our population, more research in larger and preferably prospective series is needed to allow firm conclusions on the treatment of cervical cancer with a DOI of ≤ 5 mm and a diameter of > 7 mm.

3. Strengths and weaknesses

The strength of this research is the review of pathology specimen by expert pathologists in each medical center of cases with LNM and of cases in which the reports were inconclusive. Although all samples were initially or in retrospect examined by an expert pathologist, for this study we performed a revision of the lymph node positive cases. This allowed for the application of new insights and harmonization of methods. Especially in a retrospective study, a quality control like this can enhance the homogeneity of our results. The exclusion

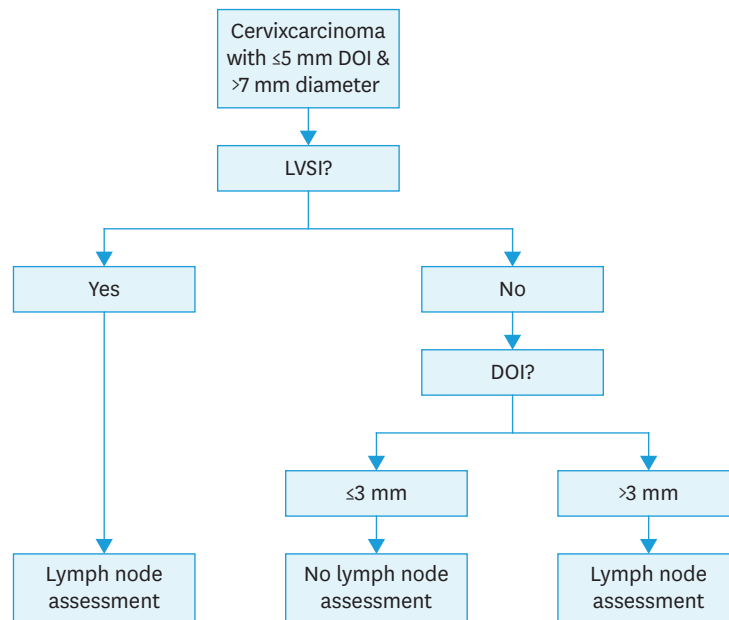


Fig. 2. Recommendations for lymph node assessment. DOI, depth of invasion; LVSI, lymphovascular space invasion.

of cases and correction of data after revision demonstrates the importance of revision by expert pathologists. We could not find another study that collaborated so closely with expert pathologists to get more accurate results. Revision of all cases with positive lymph nodes resulted in a lower incidence of LNM and a higher incidence of LVSI in our research group. However, since we only revised cases with positive lymph nodes, we assume that the incidence of LNM could be higher after revision of all cases and exclusion of cases that do not fit the inclusion criteria.

Another strength is that it is a multicenter study which allowed for enhancement of generalizability and sharing of knowledge between these centers.

To our knowledge this is the largest study that evaluated the incidence of LNM in cervical cancers with a DOI of ≤ 5 mm and a diameter of > 7 mm.

The limitation in this study is its retrospective nature. The quality of the data depends on the quality of the data in the medical records and pathology reports.

The incidence of LNM in patients with cervical cancer with ≤ 5 mm DOI and a diameter > 7 mm is 2.6%. Clinical visibility is not associated with a higher risk of LNM. LVSI increases the risk of LNM. We recommend a pelvic lymph node assessment in all patients with cervical cancer with a DOI of ≤ 5 mm and a diameter of > 7 mm, except in the absence of LVSI and a DOI of ≤ 3 mm. However, the incidence of LNM leaves room for shared decision-making regarding lymph node assessment.

SUPPLEMENTARY MATERIALS

Fig. S1

Figure portrays the percentage of LNM in all cases with LVSI. The cases are further subdivided into (from above to below) histology, DOI and diameter. The percentage portrays (number of cases with LNM)/(total number of cases in the subgroup). For example, the bottom left box shows that there was 1 case with LNM out of all 23 patients with squamous cell carcinoma, with LVSI, a DOI of ≤ 3 mm and a diameter of < 20 mm.

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Fig. S2

Figure portrays the percentage of LNM in all cases without LVSI. The cases are further subdivided into (from above to below) histology, DOI and diameter. The percentage portrays (number of cases with LNM)/(total number of cases in subgroup). For example, the bottom left box shows that there were no cases with LNM out of all 75 patients with squamous cell carcinoma, without LVSI, a DOI of ≤ 3 mm and a diameter of < 20 mm.

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