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From FIGO-2009 to FIGO-2018 in women with early-stage cervical cancer; Does the revised staging reflect risk groups?

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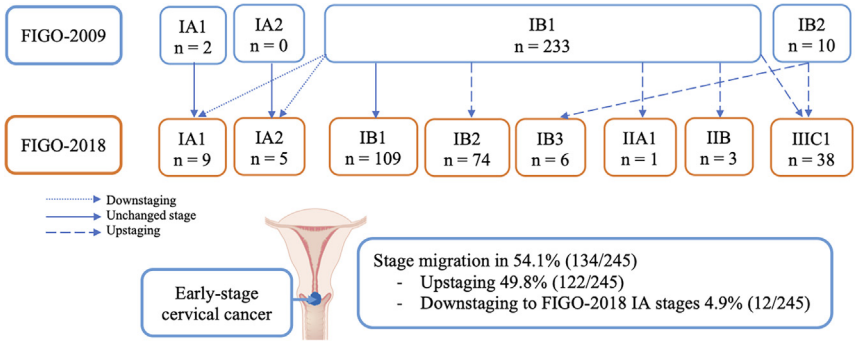
HIGHLIGHTS

- The revised FIGO-2018 system causes stage migration for a large proportion of women with early-stage cervical cancer.
- Upstaging occurred in 49.8% (122/245) and downstaging to FIGO-2018 IA stages in 4.9% (12/245).
- Women who were downstaged to FIGO-2018 IA stages did not have nodal metastatic disease.
- The attention on depth of invasion rather than horizontal dimension seems to correctly reflect the risk of nodal metastases.
- Nodal metastases which are initially identified by imaging should be histologically verified.

GRAPHICAL ABSTRACT



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ABSTRACT

Objectives. We aimed to evaluate if the revised staging according to FIGO-2018 in early-stage cervical cancer correctly predicts the risk for nodal metastases.

Methods. We reallocated 245 women with early-stage cervical cancer from FIGO-2009 to FIGO-2018 stages using data from a national, prospective cohort study on sentinel lymph node (SLN) mapping. We used univariate and multivariate binary regression models to investigate the association between FIGO-2018 stages, tumor characteristics, and nodal metastases.

Results. Stage migration occurred in 54.7% (134/245) (95% CI 48.2–61.0), due to tumor size or depth of invasion (71.6%, 96/134) and nodal metastases (28.4%, 38/134). Imaging preoperatively upstaged 7.3% (18/245); seven had nodal metastatic disease on final pathology. Upstaging occurred in 49.8% (122/245) (95% CI 43.4–56.2%) and downstaging to FIGO-2018 IA stages in 4.9% (12/245) (95% CI 2.6–8.4). The tumor size ranged

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Sentinel lymph node mapping
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from 3.0–19.0 mm in women with FIGO-2018 IA tumor characteristics, and none of the 14 women had nodal metastases. In multivariate analysis, risk factors significantly associated with nodal metastases were FIGO-2018 ≥ IB2 (RR 5.01, 95% CI 2.30–10.93, $p < 0.001$), proportionate depth of invasion >2/3 (RR 1.88, 95% CI 1.05–3.35, $p = 0.033$), and lymphovascular space invasion (RR 5.56, 95% CI 2.92–10.62, $p < 0.001$).

Conclusions. The FIGO-2018 revised staging system causes stage migration for a large proportion of women with early-stage cervical cancer. Women who were downstaged to FIGO-2018 IA stages did not have nodal metastatic disease. The attention on depth of invasion rather than horizontal dimension seems to correctly reflect the risk of nodal metastases.

1. Introduction

The International Federation of Gynecology and Obstetrics (FIGO) revised the cervical cancer staging in 2018 [1,2]. The fundamental changes in the revised FIGO-2018 staging system are (a) all women with a microscopically detected tumor with depth of invasion ≤5 mm are allocated to stage IA regardless of horizontal tumor size; (b) in stage IB, visible tumors with depth of invasion ≤5 mm and tumors with >5 mm depth of invasion are categorized into three sub-stages according to the greatest dimension of tumor size: ≤20 mm (IB1); >20 and ≤40 mm (IB2); and >40 mm (IB3); (c) lymph node involvement (macro- and micrometastases) on histopathology (with p notation) or imaging (with r notation) upstages women to a new stage category of IIIC; and (d) findings on imaging and final histopathology are included in the final staging.

The purpose of the revision is to improve staging with better differentiation of prognostic outcomes [3]. However, several matters of controversy have been raised. For example, with this paradigm shift to only involving depth of invasion as the cut-off for IA stages, a proportion of women with comparatively large microscopic horizontal width are downstaged. Questions arise on how to treat these women since the evidence on this matter is scarce. With the implementation of the FIGO-2018 staging system, the Danish Gynecologic Cancer Group proposed a national recommendation for the treatment of women in FIGO-2018 stages [4]. The primary national treatment adaptation is a more conservative surgical approach to the uterus in women with microscopic tumors up to 20 mm with superficial depth of invasion (≤5 mm). The recommendations include a cone biopsy, cervical amputation, or simple hysterectomy in women with tumor size ≤20 mm, type A-B radical hysterectomy or trachelectomy in tumors >7–20 mm with LVSI, and SLN mapping in all women with tumors >7–20 mm [5]. This is a cautious adaptation to FIGO-2018 while awaiting international results from studies applying conservative surgical management in women with low risk of metastases such as no lymphovascular space invasion (LVSI), depth of invasion ≤10 mm and tumor size ≤20 mm (SHAPE, GOG-278, and ConCerv) [6–8].

The overall purpose of this paper is to evaluate if the stage migration related to the implementation of FIGO-2018 in early-stage cervical cancer correctly reflects risk groups as indicated by the presence of lymph node metastases. We use lymph node metastases as a surrogate marker for recurrence. Our aim is to establish whether depth of invasion – rather than width and depth – more correctly reflects the risk of lymph node metastases. Further, we analyze different combinations of intermediate-risk factors, including tumor size, LVSI, and proportionate depth of invasion, to evaluate the association of these with the presence of lymph node metastases.

2. Methods

2.1. Study design and setting

We prospectively included women with FIGO-2009 IA2 with LVSI, IB1, IB2, or IIA1 cervical cancer in a national multicenter cohort study (SENTIREC CERVIX) on SLN mapping from March 2017 to January 2021 [9,10]. In Denmark, the treatment of cervical cancer is centralized to three cancer centers, and all centers participated in this study. In this paper, we reallocated women from FIGO-2009 to FIGO-2018 stages, incorporating all surgical and imaging findings. Women staged FIGO-2018 IA only included microscopic tumors ≤5 mm in depth of invasion, not visible on preoperative evaluation. Women with FDG-PET/CT positive findings were downstaged from IIIC1 if final pathology did not reveal any lymph node metastases. The study was approved by the Regional Committees on Health Research Ethics for Southern Denmark (S-20150207) and the Data Protection Agency (15/52037). Study data were collected and managed using REDCap (Research Electronic Data Capture) tools hosted at Odense Explorative Network (OPEN) [11,12].

2.2. Procedures

Women with FIGO-2009 IA2-IB1 tumor size ≤20 mm underwent SLN mapping as the staging procedure, while women with FIGO-2009 IB1 with tumors >20 mm, IB2, and IIA1 received SLN mapping, radical pelvic lymphadenectomy, and systematic removal of any FDG-PET/CT positive lymph nodes [10,13]. We performed the SLN mapping procedure using minimally invasive surgery. A 1.25 mg/ml concentration of indocyanine green was injected into the cervix at positions three and nine 'o'clock. We adhered to a SLN mapping algorithm with removal of any suspicious lymph nodes and ipsilateral pelvic lymphadenectomy in cases where the SLNs were not identified [10,14]. All women underwent preoperative FDG-PET/CT using diagnostic contrast-enhanced CT according to the European procedure guidelines for tumor imaging with FDG-PET/CT [15].

Pathologists specializing in gynecologic oncology re-reviewed all histological specimens (biopsies or cone biopsies) at one of the three centralized cervical cancer centers and assessed all histological specimens from surgery. All SLNs were histologically evaluated using a national standardized ultrastaging protocol [10,16]. Non-SLNs were evaluated with routine HE-staining only. Macrometastasis (MAC) was defined as lymph node metastasis ≥2.0 mm, micrometastasis (MIC) as 0.2 to <2.0 mm, and isolated tumor cells <0.2 mm. Per protocol, we only reported the largest metastasis per woman. LVSI was immunohistochemically verified in all cases.

Adhering to national guidelines, women with high- or a combination of intermediate-risk factors on final pathology were allocated to postoperative chemo- and radiotherapy [16,17]. The presence of MIC or isolated tumor cells was considered a high-risk factor per protocol. According to national guidelines, intermediate-risk factors were defined as the combination of either tumor size >20 mm, proportionate depth of invasion >1/3 and LVSI or tumor size >30 mm and proportionate depth of invasion >2/3. These intermediate-risk factors have been nationally applied in Denmark since 2000 and were defined based on Sedlis criteria [16,17].

2.3. Statistical methods

Demographics and patient characteristics were compared in women with and without nodal metastases using Wilcoxon rank-sum test for continuous variables and the chi-squared test for categorical variables. We used Fisher's exact test in categorical variables with expected values under five. To evaluate the association between tumor size, depth of invasion, and the risk of lymph node metastases, we used logistic regression models with a cubic spline of three knots. Using univariate and

multivariate binary regression models, we calculated the risk ratio of FIGO-2018 stages and tumor characteristics associated with lymph node metastases. In the univariate regression models, the reference group in each variable was all women who did not fulfill the criteria of the defined variable. We calculated tumor volume by multiplying the histologically assessed three-dimensional measurements; anterior-posterior, cranial-caudal, and lateral-lateral. The median volume was calculated and used as the cut-off in the binary regression analysis. Our sample size allowed a maximum of three variables in the multivariate analyses. The following three variables of clinical interest were chosen; FIGO-2018 ≥ IB2, LVSI, and proportionate depth of invasion >2/3, as we expected tumor size >20 mm and depth of invasion >5 mm to be reflected in FIGO-2018 ≥ IB2. We proposed risk stratification models for lymph node metastases and used binary regression models to calculate risk ratios for each model. All statistical analyses were performed using STATA, version 16.0 (STATA Inc., Texas, USA).

3. Results

The study population consisted of 245 women. Table 1 presents demographic and clinical characteristics. Among the 245 included women, 15.5% (38/245) had nodal metastases. Women with and without nodal metastases did not differ in age, Body Mass Index (BMI), or Charlson Comorbidity Index (CCI). The two groups differed significantly regarding tumor size, depth of invasion, presence of LVSI, and microscopic parametrial invasion (Table 1).

3.1. The transition from FIGO-2009 to FIGO-2018

Fig. 1 illustrates the distribution of women in FIGO-2009 stages and their reallocation according to the FIGO-2018 staging system. Stage migration occurred in 54.7% (134/245) (95% CI 48.2–61.0). This was due to tumor size or depth of invasion in 71.6% (96/134) and the presence of

Table 1
Demographic and clinical characteristics of women with early-stage cervical cancer.

	Women without LNM (n = 207)		Women with LNM (n = 38)		P-value[a]
	Median	(range)	Median	(range)	
Age (years)	44	(26–84)	49	(27–80)	0.22
Body mass index (kg/m^2)	25	(18–46)	24	(20–37)	0.18
	n	(%)	n	(%)	*P*-value
Smoking					
Never smoker	103	(49.76%)	19	(50.00%)	0.89[b]
Previous smoker	58	(28.02%)	9	(23.68%)	
Smoker	39	(18.84%)	9	(23.68%)	
Unknown status	7	(3.38%)	1	(2.63%)	
Charlson Comorbidity Index (CCI)					
CCI > 1	6	(2.90%)	3	(7.89%)	0.15[b]
FIGO-2009					
IA1[d]	2	(0.97%)	0	(0.00%)	0.07[b]
IA2	0	(0.00%)	0	(0.00%)	
IB1	199	(96.14%)	34	(89.47%)	
IB2	6	(2.90%)	4	(10.53%)	
Type of hysterectomy					
Simple hysterectomy	7	(3.38%)	0	(0.00%)	0.04[b]
Radical hysterectomy	192	(92.75%)	35	(92.11%)	
Conization only	8	(3.86%)	1	(2.63%)	
Aborted surgery	0	(0.00%)	2	(5.26%)	
Histology					
Squamous cell carcinoma	120	(57.97%)	26	(68.42%)	0.57[b]
Adenocarcinoma	75	(36.23%)	11	(28.95%)	
Adenosquamous carcinoma	7	(3.38%)	0	(0.00%)	
Clear cell carcinoma	1	(0.48%)	0	(0.00%)	
Other[e]	4	(1.93%)	1	(2.63%)	
	Median	(range)	Median	(range)	P-value[a]
Tumor size on final pathology (mm)	18	(0–63)	26	(9–56)	<0.001
Cervical invasion					
Median depth of invasion in mm (range)	6	(0–34)	10	(2–25)	<0.001
Median proportional depth of invasion (%)	44	(0−100)	71	(12−100)	<0.001
	n	(%)	n	(%)	P-value
Parametrial lymph node metastases	0	(0.00%)	5	(13.16%)	<0.001[b]
Microscopic parametrial invasion	3	(1.46%)	6	(16.67%)	<0.001[b]
LVSI	48	(23.19%)	27	(71.05%)	<0.001[c]
Adjuvant therapy (External beam radiation and concomitant chemotherapy)	40	(19.32%)	37[f]	(97.37%)	<0.001[c]

LNM: Lymph Node Metastases; LVSI: Lymphovascular Space Invasion.
[a] Wilcoxon rank-sum test.
[b] Fisher's exact test, due to expected values under five.
[c] Chi-squared test.
[d] Stage IA1 was not a part of the inclusion criteria, these women were included due to conization without free margins, with no residual tumor on final pathology.
[e] Glassy cell carcinoma (n = 1), Low differentiated carcinoma (n = 1), Primary mesonephric carcinoma (n = 1), Sarcomatoid planocellular carcinoma (n = 1), Serous carcinoma (n = 1).
[f] One woman deselected adjuvant therapy.

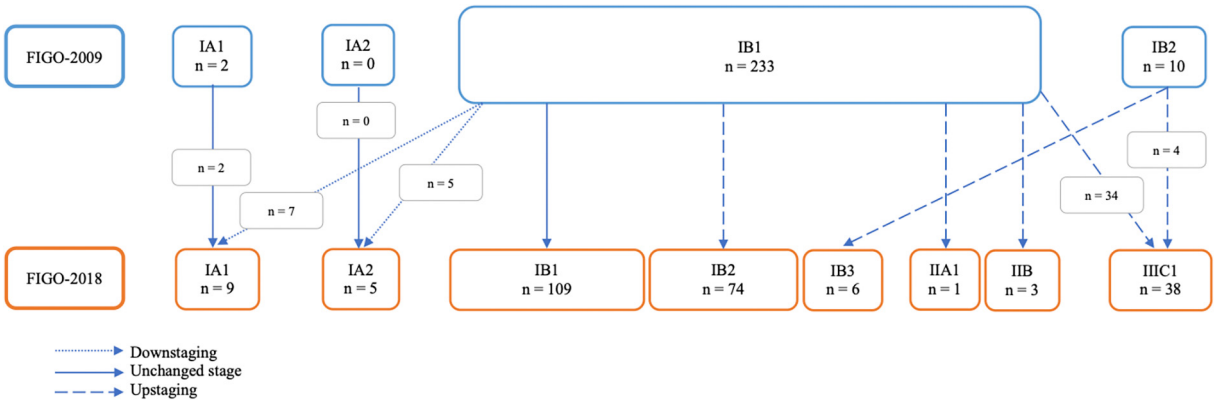

Fig. 1. Transition of stages from FIGO-2009 to FIGO-2018 in women with early-stage cervical cancer.

lymph node metastases in 28.4% (38/134). Downstaging to FIGO-2018 IA stages was observed in 4.9% (12/245) (95% CI 2.6–8.4), and upstaging occurred in 49.8% (122/245) (95% CI 43.4–56.2%). Preoperative FDG-PET/CT imaging initially upstaged in 7.3% (18/245), of whom seven had metastatic disease on final pathology.

3.2. Lymph node metastases

Lymph node metastases were identified in 38/245 (15.5%) of women on final pathology (MAC: 73.7% (28/38), MIC: 26.3% (10/38)). No women had isolated tumor cells only. Table 2 shows the FIGO-2018 stages, tumor characteristics, and MAC and MIC proportions prior to upstaging to IIIC1. In stage IA1, the median tumor size was 12.0 mm (range 3.0–19.0 mm) and 10.0 mm (range 9.0–14.0 mm) in stage IA2. None of the 14 women with FIGO-2018 IA stages had nodal metastases. Nodal metastases were detected in 6.0% (7/116) of women with FIGO-2018 stage IB1. The tumor size ranged from 9.0–20.0 mm in the seven women with nodal metastases, of which six were SLNs. The metastatic non-SLN was detected in the parametrium, identified by the radical hysterectomy procedure in a woman with a tumor size of 20 mm and depth of invasion of 13 mm. Nodal metastases were detected in 24.5% of women with stage IB2 and 14.3% of women with stage IB3.

Fig. 2 illustrates the association between lymph node metastases, tumor size, and depth of invasion. As it appears, the risk of nodal metastases increases in tumors >12 mm, with the steepest slope at 20 mm, and a flattening of the curve at 25 mm. A total of 80 women had tumor size 12–20 mm, of whom 61.2% (49/80) had depth of invasion ≤5 mm. Five of these 80 women (6.3%) had nodal metastases, of which four were SLNs, and their depth of invasion in the cervical tumor ranged from 4 to 13 mm. Regarding depth of invasion, the risk of nodal metastases increases steeply at >5 mm with a flattening of the curve at 10 mm. In total, 111 women had a depth of invasion from 5 to 10 mm with a median tumor size of 20 mm. Seventeen of the 111 women (15.3%) had nodal metastases, of which 14 were SLNs.

3.3. Parametrial invasion and lymph node metastases in the parametrium

Nine of 245 women (3.6%) were upstaged according to FIGO-2018 due to microscopic parametrial invasion, and six of these women also had pelvic lymph node metastases (Table 3). In addition, five of 245 women (2.0%) were upstaged to FIGO-2018 IIIC1 due to one lymph node metastasis in the parametrium, identified by the radical hysterectomy procedure. In the 14 women with parametrial invasion or nodal metastasis in the parametrium, the horizontal tumor size ranged from 20 to 56 mm, and the depth of invasion ranged from 2 to 14 mm.

Table 2
Tumor characteristics and incidence of lymph node metastases in FIGO-2018 stages of early-stage cervical cancer.

FIGO-2018[a]	Lymph node metastases				LVSI n (%[c])	Depth of invasion in mm, median (range)	Tumor size in mm, median (range)
	LNM +/−	n (%)	MAC	MIC			
			n (n SLN[b])	n (n SLN[b])			
IA1	−	9 (100.0%)			1 (11.1%)	2.0 (1.0–3.0)	12.0 (3.0–19.0)
	+	0 (0.0%)	0 (0)	0 (0)			
IA2	−	5 (100.0%)			1 (20.0%)	4.0 (4.0–5.0)	10.0 (9.0–14.0)
	+	0 (0.0%)	0 (0)	0 (0)			
IB1	−	109 (94.0%)			22 (20.2%)	4.5 (0.0–11.0)	13.0 (0.4–20.0)
	+	7 (6.0%)	5 (4)	2 (2)	4 (57.1%)	5.0 (4.0–13.0)	19.0 (9.0–20.0)
IB2	−	74 (75.5%)			21 (28.4%)	8.0 (1.0–29.0)	25.0 (21.0–40.0)
	+	24 (24.5%)	17 (7)	7 (7)	16 (66.7%)	10.5 (2.0–25.0)	27.5 (21.0–37.0)
IB3	−	6 (85.7%)			0 (0.0%)	14.5 (4.0–34.0)	44.0 (42.0–63.0)
	+	1 (14.3%)	1 (1)	0 (0)	1 (100.0%)	17.0 (17.0–17.0)	45.0 (45.0–45.0)
IIA1	−	1 (100%)			1 (100.0%)	13.0 (13.0–13.0)	36.0 (36.0–36.0)
	+	0 (0.0%)	0 (0)	0 (0)			
IIB[d]	−	3 (33.3%)			2 (66.7%)	11.0 (7.0–12.0)	36.0 (22.0–40.0)
	+	6 (66.7%)	5 (4)	1 (1)	6 (100.0%)	9.5 (7.5–14.0)	38.5 (26.0–56.0)
All women	−	207 (84.5%)			48 (23.2%)	5.8 (0.0–34.0)	18.0 (0.4–63.0)
	+	38 (15.5%)	28 (16)	10 (10)	27 (71.1%)	9.5 (2.0–25.0)	26.5 (9.0–56.0)

LNM: Lymph Node Metastases; SLN: Sentinel Lymph Node; LVSI: Lymphovascular Space Invasion.
[a] Women with lymph node metastases have not been upstaged to IIIC1 for the purpose of this analyses.
[b] Number of nodal metastases found in SLNs only.
[c] Proportion of women with LVSI in women with and without lymph node metastases, respectively.
[d] Women were included according to FIGO-2009 IB1/IB2 and were upstaged postoperatively due to microscopic parametrial invasion according to FIGO-2018 staging.

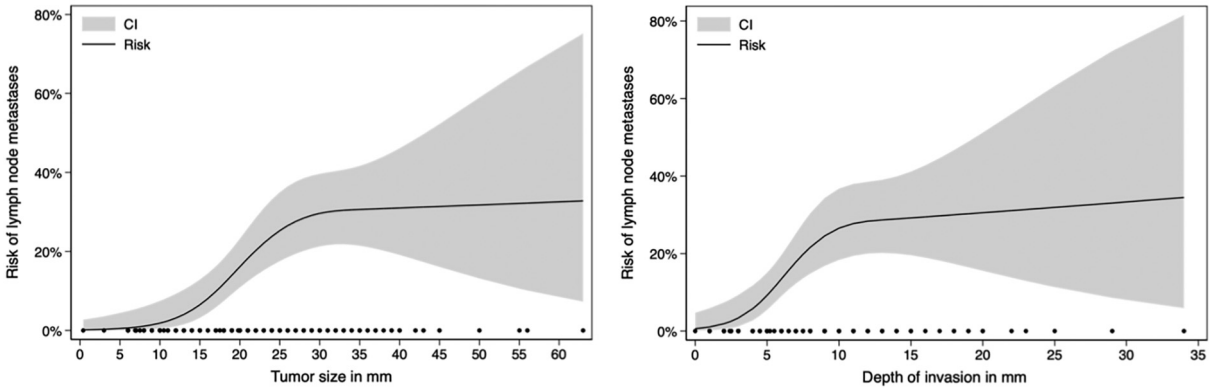

Fig. 2. Association between tumor size, depth of invasion, and lymph node metastases in women with early-stage cervical cancer.

3.4. Association between FIGO-2018 stages, tumor characteristics, and lymph node metastases

In univariate binary regression models, FIGO-2018 ≥ IB2 ($p < 0.001$), parametrial invasion ($p < 0.001$), LVSI ($p < 0.001$), tumor size >20 mm ($p < 0.001$), depth of invasion >5 mm ($p = 0.002$), proportionate depth of invasion >2/3 ($p < 0.001$), and cervical tumor volume over the median of 23.5 mm^3 ($p < 0.001$) significantly increased the risk of having nodal metastases (Table 3). FIGO-2018 ≥ IB2, LVSI, and proportionate depth of invasion >2/3 remained significant in the multivariate model. FIGO-2018 stage ≤ IB1 ($p < 0.001$), tumor size ≤20 mm ($p < 0.001$), depth of invasion ≤5 mm ($p = 0.002$), and proportionate depth of invasion ≤1/3 ($p = 0.022$) were significantly associated with a low risk of nodal metastases.

Table 4 shows the association between combinations of risk factors and lymph node metastases. Both models with different combinations

Table 3
FIGO-2018 staging and risk factors associated with lymph node metastases in women with early-stage cervical cancer.

Variable	Total number of women	Women with LNM, n (%)	Univariate binary regression model		Multivariate binary regression model[a]	
			RR (95% CI)	p-value	RR (95% CI)	p-value
FIGO-2018[b]						
≤ IB1	130	7 (5.4%)	0.20 (0.09–0.44)	< 0.001	1.00 (Ref)	
≥ IB2	115	31 (27.0%)	5.01 (2.30–10.93)	< 0.001	2.64 (1.13–6.20)	0.025
Histology						
Squamous cell carcinoma	146	26 (17.8%)	1.47 (0.79–2.77)	0.24		
Adenocarcinoma	86	11 (12.8%)	0.75 (0.39–1.44)	0.39		
Adenosquamous carcinoma	7	0 (0%)	NA	0.60[c]		
Clear cell carcinoma	1	0 (0%)	NA	1.0[c]		
Other[d]	5	1 (20.0%)	1.30 (0.22–7.68)	0.77		
Microscopic parametrial invasion						
No	236	32 (13.6%)	0.20 (0.12–0.36)	< 0.001		
Yes	9	6 (66.7%)	5.18 (2.93–9.16)	< 0.001		
LVSI						
No	170	11 (6.5%)	0.18 (0.09–0.34)	< 0.001	1.00 (Ref)	
Yes	75	27 (36.0%)	5.56 (2.92–10.62)	< 0.001	4.12 (2.16–7.84)	< 0.001
Tumor size						
≤20 mm	130	7 (5.4%)	0.20 (0.09–0.44)	< 0.001		
>20 mm	115	31 (27.0%)	5.01 (2.30–10.93)	< 0.001		
Depth of invasion						
≤5 mm	108	7 (6.5%)	0.29 (0.12–0.63)	0.002		
>5 mm	137	31 (22.6%)	3.49 (1.60–7.62)	0.002		
Proportionate depth of invasion						
≤1/3	74	5 (6.8%)	0.35 (0.14–0.86)	0.022	1.00 (Ref)	
>1/3 but ≤2/3	102	11 (10.8%)	0.57 (0.30–1.10)	0.093		
>2/3	69	22 (31.9%)	3.51 (1.96–6.27)	< 0.001	1.88 (1.05–3.35)	0.033
Cervical tumor volume						
<23.5 mm^3	118	5 (4.2%)	0.16 (0.07–0.40)	< 0.001		
≥23.5 mm^3 (= median volume)	127	33 (26.0%)	6.13 (2.48–15.18)	< 0.001		

Abbreviations: LNM, Lymph Node Metastases; RR, Risk Ratio; LVSI, Lymphovascular Space Invasion.

[a] Multivariate logistic regression model with dependent variable lymph node metastases (yes/no) and independent variables FIGO-2018 stages, LVSI, and proportionate depth of invasion >2/3. Sample size allowed a maximum of three variables, we chose these as we expected tumor size >20 mm and depth of invasion >5 mm to be reflected in FIGO-2018 ≥ IB2.

[b] Women with lymph node metastases have not been upstaged to IIIC1 for the purpose of this analyses. FIGO-2018 was pooled into ≤IB1 and ≥ IB2 due to low number of lymph node metastases in stage IA1, IA2, IB3, IIA1 and IIB.

[c] Fisher's exact test due to expected values under 5.

[d] Glassy cell carcinoma (n = 1), Low differentiated carcinoma (n = 1), Primary mesonephric carcinoma (n = 1), Sarcomatoid planocellular carcinoma (n = 1), Serous carcinoma (n = 1).

Table 4
Association between risk stratification models and lymph node metastases in women with early-stage cervical cancer.

Risk stratification models		Total number of women	Women with LNM, n (%)	Binary regression model for risk ratio	
				RR (95% CI)	p-value
Low-risk factors	No LVSI Depth of invasion ≤10 mm Tumor ≤20 mm	101	3 (2.8%)	0.12 (0.04–0.39)	< 0.001
Low-risk factors with LVSI	+ LVSI Depth of invasion ≤10 mm Tumor ≤20 mm	27	3 (11.1%)	NA	1.0[a]
Intermediate-risk factors	Tumor >20 mm + LVSI Proportionate cervical invasion >1/3	43	21 (48.8%)	5.80 (3.35–10.04)	< 0.001
Intermediate-risk factors	Tumor >30 mm Proportionate cervical invasion >2/3	31	11 (35.5%)	2.8 (1.56–5.08)	0.001
Visible tumors ≤20 mm with depth of invasion ≤5 mm[b]		74	4 (5.4%)	0.27 (0.10–0.74)	0.011
Visible tumors >20 mm with depth of invasion ≤5 mm[b]		20	3 (15.0%)	NA	1.0[a]

Abbreviations: LNM, Lymph Node Metastases; RR, Risk Ratio; LVSI, Lymphovascular Space Invasion.
[a] Fisher's exact test due to expected values under 5.
[b] Not including women with microscopic tumors (stage IA).

of intermediate-risk factors were significantly associated with nodal metastases ($p < 0.001$ and $p = 0.001$, respectively). The low-risk model defined as depth of invasion ≤10 mm, tumor size ≤20 mm and no LVSI was significantly associated with a low risk of nodal metastases ($p < 0.001$).

3.5. Women with a depth of invasion ≤ 5 mm irrespective of tumor size

As previously mentioned, no women with FIGO-2018 IA stages had nodal metastases. We then considered all women with a depth of invasion ≤5 mm irrespective of tumor size, i.e., visible or non-visible tumors. In this group, nodal metastases were detected in 7/108 (6.5%) women. The tumor size ranged from 0.4–42.0 mm (median 13 mm) in the 101 women without nodal metastases, while the tumor size was 9.0–24.0 mm (median 20 mm) in the seven women with nodal metastases. Six of seven metastases were SLNs, while the non-SLN was identified in the parametrium of a woman with a tumor size of 20 mm. None of the 108 women had parametrial invasion. Table 4 shows the association between tumors with any horizontal width but with depth of invasion ≤5 mm and lymph node metastases. In these women, tumor size ≤20 mm was significantly associated with a low risk of nodal metastases ($p = 0.011$).

4. Discussion

We evaluated the risk of lymph node metastases according to the revised FIGO-2018 staging and tumor characteristics in a large sample of 245 women with early-stage cervical cancer. All women were included in the nationwide multicenter prospective SENTIREC study with strict eligibility criteria and underwent surgery according to protocol regarding SLN mapping and national guidelines on surgery of the uterus and cervix. All SLNs were examined by ultrastaging, and LVSI was verified by immunohistochemistry in all cases [10,16]. Hence, the staging procedure, the surgical approach, and the histopathological methods were aligned across centers. We demonstrated that a substantial proportion of the women underwent stage migration. In the following, we will discuss some of the controversies that have arisen from the FIGO-2018 adaptation.

Focusing on risk of lymph node metastases in women with low-stage disease according to FIGO-2018, we demonstrated that women who were downstaged to IA did not have any nodal metastases. Even FIGO-2018 stage IB1 was significantly associated with a very low (6.0%) risk of nodal metastases. Further, if all 108 women with depth of invasion ≤5 mm had been downstaged to FIGO-2018 IA regardless of a preoperatively visible tumor, the risk of nodal metastases would still be very low (6.5%). Our study demonstrated that the risk of nodal metastases seems to rise at a depth of invasion >5 mm and tumor size of >12 mm. Further, our results indicate that the risk of nodal metastases increases more steeply with increasing depth of invasion rather than tumor size. Thus, the revised FIGO-2018 staging for the early stages seems to correctly reflect risk groups as indicated by the presence of lymph node metastases.

Approximately 5% of the women were downstaged to FIGO-2018 IA stage in our study. Several women had comparatively large tumors, which would usually allocate to more extensive surgery with radical hysterectomy and pelvic lymphadenectomy for FIGO-2009 stage IB [18–20]. The papers describing and advising on the revised FIGO-2018 staging did not provide any new recommendations regarding treatment. A potential introduction of more conservative surgical treatment to the uterus and pelvic nodes underlines the importance of ascertaining the risk of metastases in these women. Several ongoing prospective studies (SHAPE, GOG-278, and ConCerv) are investigating the safety of these more conservative surgical treatments to the uterus in women with so-called low-risk factors such as no LVSI, depth of invasion ≤10 mm and tumor size ≤20 mm [6–8]. To our knowledge, this is the first prospective study to show that women with these combined low-risk factors are significantly associated with a very low risk of nodal metastases. Further, the prospective SENTICOL trial recently demonstrated that bilateral negative SLNs and tumor size ≤20 mm predicted a very low risk of parametrial involvement [21]. Likewise, in our study, none of the 108 women with depth of invasion ≤5 mm had microscopic parametrial invasion. Our results suggest that a more conservative approach to the uterus is adequate in women with FIGO-2018 IA stages with tumor size ≤20 mm and no LVSI. Of notice, the present study primarily concerns the risk of lymph node metastases as a surrogate marker for risk of recurrence and survival. Awaited recurrence and survival data from our study, along with data from the SENTICOL and SENTIX trials, will provide further guidance regarding SLN mapping [22,23].

There is no definition of parametrial involvement in the revised FIGO-2018 staging. Women with microscopic invasion of the parametrium on final histology are allocated to stage IIB, while nodal metastases identified in the parametrium presumably allocate the women to stage IIIC1. It is unknown whether the women with one nodal MAC or MIC in the parametrium and no positive pelvic nodes share the same survival as women with positive pelvic nodes or should be considered stage IIB [24]. Five such women in our study population had tumor characteristics as FIGO-2018 IB1 and IB2 but were allocated to stage IIIC1 due to one parametrial lymph node metastasis. The finding of parametrial lymph node metastases underlines the importance of

careful SLN mapping in women undergoing surgery for stage IB cervical cancer with a meticulous inspection of the parametrial area, particularly if a conservative surgical approach to the cervix/uterus is considered.

As proposed by Sedlis et al. (GOG-92) in 1999, combinations of intermediate-risk factors (tumor size, proportionate depth of invasion, and LVSI) for recurrence have been used to allocate women who have undergone surgery for early-stage cervical cancer and who were lymph node- and margin negative, to postoperative chemo- and radiotherapy [17]. The potential benefit of adjuvant chemo-radiation has not been evaluated in a randomized setting since the GOG-92 study [25]. The GOG-92 study has been criticized for an imbalance between the groups regarding LVSI and intermediate-risk factors, which may have contributed to differences in survival outcomes. Further, recurrence rates of 15.0% in the adjuvant chemo-radiation group and 39.0% in the surgery alone group may indicate a lack of surgeon proficiency or standardization. The follow-up of the GOG-92 study found a reduced risk of recurrence following adjuvant therapy while overall survival was not improved significantly [26]. During the years, several retrospective studies have re-evaluated the prognostic significance of these intermediate-risk factors [27,28]. Cibula et al. showed a 5-year disease-free survival rate of 95.7% (95% CI 91.9–99.4%) in 127 node-negative women with FIGO-2009 stage IB cervical cancer with positive intermediate-risk factors (LVSI and deep depth of invasion or LVSI and tumor size ≥20 mm or tumor size ≥40 mm) who received radical surgery only [28]. The survival rate did not differ significantly from the 104 women in the control group undergoing adjuvant therapy. Lately, Nasioudis et al. performed a large comparative study based on The National Cancer Database evaluating the outcome of surgery-only versus surgery combined with adjuvant chemo-radiation in node-negative, margin-negative women with FIGO-2018 stage IB and intermediate-risk factors defined as tumor size 20–40 mm and LVSI or tumor size >40 mm [29]. Nasioudis et al. showed no difference in overall survival between these two groups. In the present prospective study, we found that FIGO-2018 ≥ IB2 (tumor size >20 mm), proportionate depth of invasion >2/3, and immunohistochemically verified LVSI were significantly associated with nodal metastases while the absence of LVSI strongly predicted disease-free nodes. The SENTICOL study showed similar results in their univariate analyses, though only FIGO-2018 IIB and LVSI predicted lymph node metastases [30]. However, it remains controversial how this information should be translated into a clinical setting. Although LVSI is confirmed as a significant risk factor for nodal metastases, this does not necessarily negatively impact the rate of recurrence and survival as long as those with metastases are identified and treated accordingly.

While it is important to raise the attention towards the significance of lymph node staging for certain risk groups, we should also consider the large group of women who *do not* have lymph node metastases despite intermediate-risk factors. These women may not need adjuvant chemo-irradiation as a routine. Tumor size, depth of invasion, and the presence of LVSI may all be known when the treatment decision is taken and may urge clinicians to opt for primary chemoradiation. The present study shows that a large proportion of women with intermediate-risk factors do not have lymph node metastases. In a recent commentary, Cibula [25] mentions that the selection of women with a higher risk of recurrence is currently much more accurate than decades ago when the intermediate-risk factors were implemented. Modern imaging has become more accurate in detecting and precluding parametrial invasion and non-free margins, which are still considered high-risk negative prognostic factors for recurrence. Further, the adoption of the SLN mapping technique provides much more precise information on nodal metastatic status [25,31]. In a previous paper, we demonstrated that SLN mapping adhering to the algorithm had a sensitivity of 96.3% and a negative predictive value of 98.7% in 103 women with tumors >20 mm [10]. Additionally, SLN mapping led to increased detection of lymph node metastases, with 26.3% of all nodal metastases detected by ultrastaging. Hence, while underlining the importance of lymph node staging, including bilateral SLN mapping and adherence to the SLN mapping algorithm, we advocate for omitting routine adjuvant chemoradiation in women with intermediate-risk factors who are comprehensively staged if no lymph node metastases are identified.

The introduction of FIGO stage IIIC in women with nodal-positive cervical cancer is controversial. From a clinical point of view, it is questionable that, e.g., one micrometastasis in the pelvic region impairs the prognosis of the patients more than uni- or bilateral tumor extension to the pelvic sidewall. Several authors have retrospectively evaluated survival outcomes for women with cervical cancer stage III and could not confirm a consistent association between FIGO-2018 stage IIIA, B, and C and survival outcomes: The 5-year survival rate was 40.7–46.0% in stage IIIA, 41.4–55.0% in stage IIIB versus 60.8–62.0% in IIIC1, and 35–37.5% in IIIC2 [32,33]. This indicates that women in stage IIIC1 represent a heterogeneous group with varying survival rates. In our study, 18 women were preoperatively suspected of having stage IIIC1 disease due to FDG-PET/CT imaging alone. Though, only seven of these women had nodal metastatic disease on final pathology. We have previously demonstrated that FDG-PET/CT in this group of low-risk patients is limited; 73.3% of FDG-PET/CT positive lymph nodes were false-positive, corresponding to a positive predictive value of 26.7% [10]. Therefore, imaging alone does not seem to be the optimal modality for allocating women with presumably early-stage cervical cancer to neither primary or adjuvant chemo-radiation. Of notice, many women with stages ≤ IB who have undergone a prior diagnostic cone-biopsy may have FDG-positive nodes. Still, only a minority have nodal metastases that will be accurately identified by SLN mapping. It is therefore recommended that FDG-positive lymph nodes in women with early-stage cervical cancer should be histologically examined. A two-step procedure with removal of SLNs and FDG-positive nodes may be considered in selected cases before final decision regarding further surgical or oncological treatment [18]. Allocation to stage IIIC1 should correctly reflect survival, and adjustment of stage IIIC may be considered in future revision of FIGO-2018 for cervical cancer.

4.1. Strengths and limitations

The main strength of this study is its design as a national multicenter prospective study. Our inclusion rate was high, with a participation of 94.6% of all women referred to the three centralized centers [10]. Furthermore, all women underwent preoperative diagnostic FDG-PET/CT imaging, allowing us to evaluate the number of women who would be preoperatively upstaged to IIIC1 on imaging alone. All specimens underwent central pathology revision at one of the three centers, and they all agreed to adhere to a national ultrastaging protocol. The presence of LVSI was immunohistochemically verified in all cases.

Limitations included that the study was not designed to investigate implications of the new risk allocations according to FIGO-2018. Therefore, some groups are small, which precluded a more comprehensive multivariate analysis. Further, the prognostic importance of MIC and ITC is debated; unfortunately, our sample size limited us in specifically investigating risk factors for low-volume metastases. Finally, the overall low incidence of metastatic disease in early-stage cervical cancer may limit interpretation of significance in regression analyses in variables where the incidence of nodal metastases is low or not present at all. We used lymph node metastases as a surrogate marker for recurrence. Other high-risk factors for recurrence include microscopic parametrial invasion and positive surgical margins. These risk factors occurred at a low rate in our study population, i.e., parametrial invasion in 3.7%, and could therefore not be used as end-points.

5. Conclusion

The FIGO-2018 revised staging system causes stage migration for a large proportion of women with early-stage cervical cancer. The attention on depth of invasion rather than horizontal dimension seems to

correctly reflect the risk of nodal metastases. Nodal metastases which are initially identified by imaging should be histologically verified. Results from this study may further contribute to treatment decisions in women with early-stage cervical cancer.

Declaration of Competing Interest

There are no conflicts of interest to disclose.

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