Cervical cancer recurrence – can we predict the type of recurrence?

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PURPOSE
We aimed to identify if there is an association between the severity of cervical cancer at diagnosis and the pattern of recurrence.

METHODS
We conducted a retrospective study of recurrent cervical cancers diagnosed between 2016 and 2018. We characterized the cases according to histology, size, FIGO stage (according to 2009 and 2018 FIGO classifications) and nodal involvement at diagnosis, symptoms at the time of recurrence, interval between the end of treatment and recurrence, imaging methods used, and location of the recurrence. Statistical analysis was performed between histology, size, FIGO stage and nodal involvement at diagnosis and time to recurrence and type of recurrence (locoregional versus lymph node, distant or multiple site involvement).

RESULTS
We included 48 patients with recurrent cervical cancer. At diagnosis, mean tumor size was 5 cm and 83% of the patients had squamous cell carcinoma. The FIGO stage changed in 43.8% of patients between the 2009 and the 2018 classifications. A mean of 26 months elapsed between the end of treatment and recurrence. Recurrence was symptomatic in 64.6% of patients. Imaging identified recurrence in 97.9% of patients. The most frequent recurrence sites were locoregional and lymph node metastases. We found a statistically significant association between 2009 FIGO stage and time to recurrence ($P = 0.030$) and lymph node involvement at diagnosis and type of recurrence ($P = 0.022$). As expected patients with more advanced disease recurred sooner, though this was only observed for the 2009 FIGO classification. Absence of lymph nodes at initial diagnosis was associated with locoregional recurrence, while presence of lymph node involvement was associated with lymph node, distant or multiple site involvement of recurrence. No other significant associations were found.

CONCLUSION
In our cohort of recurrent cervical cancer, we found an association between patients without lymph node metastases at initial diagnosis and locoregional recurrence. Further studies are needed in order to evaluate whether this association has predictive value.

U terine cervical cancer incidence has decreased in the Western world, but it remains the most frequent gynecological malignancy worldwide, accounting for 6.6% of female cancers (1), the fourth deadliest cancer in women (1, 2). This cancer has a bad prognosis as it is frequently diagnosed in advanced stages of disease, while uterine cervical cancer identified in the early stages has a good prognosis (3).

Imaging has a main role in the detection and evaluation of the extent of disease (3–5), aiding in the assignment of an International Federation of Gynecology and Obstetrics (FIGO) stage, with strong implications on patient management and treatment. FIGO staging has recently been updated from the 2009 classification (6) to the 2018 classification (7).

Follow-up of treated patients is guided by clinical assessment, with imaging performed when there is clinical suspicion of residual or recurrent disease, preferably targeted to the patient's complaints (7–10) and eventually followed by histological confirmation. Approximately a third of women treated for cervical cancer will have recurrence during follow-up (11), with most relapses occurring in the first two to three years after treatment (7, 12).

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The classification of the type of recurrence of cervical cancer is based on the location where the recurrent tumor is identified and it is classified as locoregional, distant, or lymph node involvement (3, 4, 7, 12–14). Computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography-computed tomography (PET-CT) are used in the diagnosis of cervical cancer recurrence (3, 13).

The distinction between residual and recurrent disease has prognostic implications. Recurrent disease is defined as tumor reappearance or development of metastatic disease more than six months after the end of treatment (2), while residual disease is detected in a period shorter than six months following the end of treatment. In this study, we only focus on recurrent disease.

The purpose of this study was to determine whether there is an association between the severity of disease at diagnosis and the pattern of recurrence.

Methods

This is a retrospective, institutional review board-approved (UIC/1253), single center study of recurrent cervical cancers diagnosed at our center between 2016 and 2018.

One hundred and twenty-two patients were diagnosed with either residual or recurrent disease between January 2016 and December 2018. We included patients who had first recurrence of cervical cancer after treatment between January 2016 and December 2018 with imaging studies available for review (staging and follow-up imaging). Patients with residual cervical

cancer (detection ≤6 months from the end of treatment), history of previous recurrences or with unavailable imaging studies for review were excluded.

Patient records were analyzed to determine age at initial diagnosis, histology of the tumor, FIGO stage (recorded classification was given according to 2009 FIGO classification), type of treatment and date of termination, symptoms and clinical evaluation associated with suspected recurrence, date of recurrence, and age at recurrence.

A retrospective consensus review of the imaging studies was performed to confirm 2009 FIGO stage at initial diagnosis and to determine the updated FIGO stage (2018 FIGO classification), also noted were the type of examination used (CT and/or MRI) at the time of recurrence, and the location of recurrence with subclassification into locoregional, lymph node and distant recurrence.

Both FIGO classifications (2009 and 2018 FIGO classifications) (6, 7) were analyzed to evaluate if an association could be identified between either classification and the type of recurrence and the time to recurrence. Our goal with analyzing both classifications was to assess if the recently published classification showed a higher association with these criteria.

A lesion was considered recurrence if it was identified *de novo* as compared to the staging examination while in cases treated with radiotherapy recurrence resembled the primary tumor (2). In case of adenopathies, a cutoff of 10 mm in the short axis was considered suspicious for recurrence in all sites, except for the inguinal nodes where a 15 mm cutoff was used. Some of the lesions were submitted to biopsy for histological confirmation of recurrence.

We aimed to evaluate whether there was any association between the diagnostic characteristics (i.e., tumor histology, FIGO stage considering both 2009 and 2018 classifications, dimension of primary tumor, and presence of adenopathies at diagnosis) and the recurrence outcomes (i.e., time to first recurrence and type of recurrence).

FIGO stage variables were grouped for statistical analysis into four or five categories. FIGO 2009 classification included stages I, II, III and IV; while for FIGO 2018 classification, stage III was subdivided into IIIA/IIIB and IIIC, which is a major difference between the two classifications.

The type of recurrence was classified into four categories: exclusively locoregional, exclusively lymph node involvement, exclu-

sively distant recurrence, and multiple sites involved. Due to our relatively small sample we only considered two categories in group comparison: exclusively locoregional versus the remainder sites of recurrence. We opted for this grouping because a localized, central pelvic recurrence is associated with favorable prognosis in patients with recurrent disease (15).

Statistical analysis

Descriptive statistics of the data are presented with absolute (n) and relative frequencies (%) for categorical variables, median (1st quartile–3rd quartile) or median (minimum-maximum) for quantitative non-normal variables and mean ± standard deviation for quantitative normal variables.

Given that in this study all patients had recurrence (i.e., there were no censored observations), time from diagnosis to first recurrence was treated as a quantitative and not as a time-to-event outcome. Also, as based on the normal Q-Q plot and Shapiro-Wilk normality test a normal distribution could not be assumed for time to recurrence and tumor dimension, as such we used non-parametric tests for group comparisons. The Mann-Whitney-Wilcoxon test with continuity correction (non-parametric alternative to the two-sample t-test) was used to evaluate differences in time to first recurrence between patients with or without adenopathies at diagnosis and with primary tumor dimension <4 cm or ≥4 cm. The Kruskal-Wallis test (non-parametric alternative to ANOVA) was used to evaluate differences in time to recurrence between histology and FIGO stage groups; whenever a statistical result was found in this test we conducted post-hoc two-by-two comparisons using Mann-Whitney-Wilcoxon test with continuity correction and P value adjustment for multiple comparison using the Hochberg method. We also used Spearman's rho rank correlation coefficient to assess the degree of association between the quantitative variables of tumor dimension at diagnosis (in cm) and time to first recurrence. Spearman's correlation coefficient is a nonparametric method that, contrary to Pearson's correlation coefficient, does not carry any assumptions about normal distribution of the data. Pearson's chi-square test and Fisher's exact test (suitable only for 2×2 contingency tables) were used to evaluate the association between type of recurrence and presence of adenopathies at diagnosis and tumor dimension <4 cm or ≥4 cm, respectively. Free-

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Main points

- Absence of lymph node metastases at diagnosis was significantly associated with locoregional recurrences; when initial lymph node involvement was identified at initial diagnosis, the recurrences were more common in the lymph nodes, in distant or multiple locations.

- Significant association was detected between the 2009 FIGO stages and time to recurrence.

- Despite tumor size, FIGO stage, and lymph node status being independent risk factors for recurrence, only 2009 FIGO stage was associated with time to recurrence, and lymph node status was associated with the type of recurrence.

- If confirmed in larger studies, these associations might enable the radiologists to focus their search when evaluating patients for recurrent disease.

Table 1. Distribution of patients according to 2009 FIGO (5) and to 2018 FIGO (6) classifications

| | | 2018 FIGO Stage | | | | | | | | | | | | |
		IA1 + IA2	IB1	IB2	IB3	IIA1	IIA2	IIB	IIIA	IIIB	IIIC1	IIIC2	IVA	IVB	Total
2009 FIGO Stage	IA1 + IA2	0	-	-	-	-	-	-	-	-	-	-	-	-	0
	IB1	-	2	2	-	-	-	-	-	-	-	-	-	-	4
	IB2	-	-	-	1	-	-	-	-	-	2	-	-	-	3
	IIA1	-	-	-	-	0	-	-	-	-	-	-	-	-	0
	IIA2	-	-	-	-	-	1	-	-	-	1	-	-	-	2
	IIB	-	-	-	-	-	-	12	-	-	14	1	-	-	27
	IIIA	-	-	-	-	-	-	-	1	-	1	-	-	-	2
	IIIB	-	-	-	-	-	-	-	-	2	1	1	-	-	4
	IVA	-	-	-	-	-	-	-	-	-	-	-	5	-	5
	IVB	-	-	-	-	-	-	-	-	-	-	-	-	1	1
Total		0	2	2	1	0	1	12	1	2	19	2	5	1	48

Table 2. Patients' symptoms at time of recurrence

Symptom	n (%)
Lumbar pain	9 (18.8)
Pelvic pain	5 (10.4)
Chest pain	4 (8.3)
Metrorrhagia	4 (8.3)
Lumbar and pelvic pain	2 (4.2)
Pain in other locations	3 (6.2)
Edema	2 (4.2)
Vaginal discharge	1 (2.1)
Thoracic mass	1 (2.1)
No symptoms	17 (35.4)

man-Halton extension of the Fisher's exact test with double sided P value calculation as proposed by Agresti (1992) was used to evaluate the association between type of recurrence and histology and FIGO stage classifications 2009 and 2018.

All tests were two-sided. We considered a significance level of 0.05 and, given the exploratory nature of the study, we did not perform any P value adjustment for multiple comparisons apart from the ones concerning the post-hoc two-by-two comparisons described above. All analyses were done using R (http://www.R-project.org/).

Results

Of the 122 patients evaluated, 74 patients were excluded: 54 because they presented with residual disease, 16 for lack of available staging imaging examinations and 4 because of multiple recurrences. After exclusion criteria were applied our sample consisted of 48 patients with a median age of 52.5 years (range, 31–85 years). Most patients had squamous cell carcinoma (n=40, 83.3%), followed by adenocarcinoma (n=6, 12.5%), and adenosquamous carcinoma (n=2, 4.2%); the mean tumor size at diagnosis was 5 cm (median, 4.7 cm; range, 0.5–11.9 cm).

Our cohort received their initial diagnoses between 2006 and 2017, with a mean of 26 months elapsing between the end of treatment and the diagnosis of recurrence (median, 15 months; range, 7–121 months).

After review of staging examinations, FIGO classification changed in 21 patients (Table 1). According to the 2009 FIGO classification, 27 patients (56.3%) were in stage IIB, while according to the updated 2018 FIGO classification, 21 were in stage IIIC (43.8%) and 12 were in stage IIB (25.0%).

Thirty-one patients were symptomatic at the time of recurrence (64.6%). The patients' main complaints are displayed on Table 2. Seventeen patients (35.4%) had no complaints, of which 10 (58.8%) had changes on clinical examination that prompted imaging evaluation and one had worsening kidney function. The remaining 6 patients (12.5%) had no complaints nor changes on physical examination, but recurrence was detected on imaging.
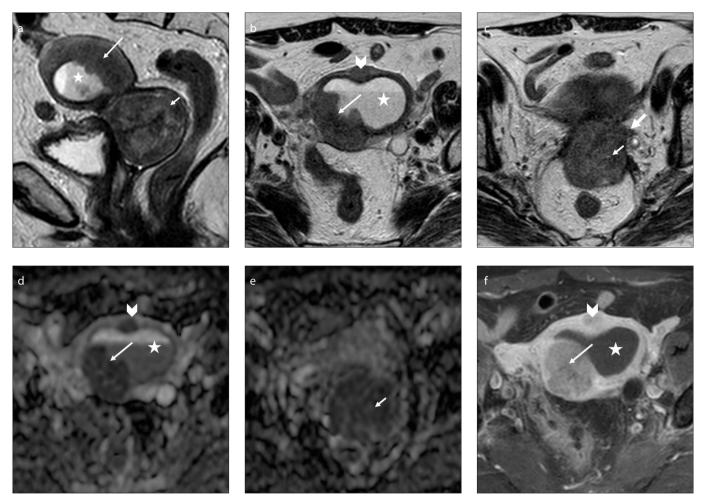
As there are no standardized tests to search for recurrence, different imaging protocols were used, directed at the patient's symptoms. All patients underwent radiologic studies to determine if recurrence was present. Imaging detected recurrence in 47 patients (97.9%). Pelvic MRI was performed in a total of 32 patients (66.7%), with DWI and DCE sequences except when gadolinium was contraindicated (n=5). CT was performed in 23 patients (47.9%) with the protocol guided by the clinical question (thoracic, abdominal and/or pelvic) with intravenous contrast administration in 15 cases (62.2% of CT examinations) and no contrast in 8 cases (34.8%). Both imaging modalities were used in 7 patients (14.6%).
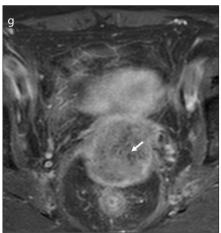
Recurrence was locoregional in 22 patients (46.8%), with 20 having a central recurrence (41.7%) (Fig. 1) and two extending to the pelvic side wall (4.2%) (Fig. 2). There were distant metastases in 16 patients (33.3%) and lymph node metastases in 24 patients (50.0%). Thirteen patients (27.1%) had more than one location involved (Fig. 3). The locations of recurrence are displayed on Table 3.

A significant correlation was detected between the 2009 FIGO stage and time to recurrence ($P = 0.030$) (Table 4); this was not observed when comparing 2018 FIGO stage with time to recurrence.

A statistically significant correlation was also identified between the presence of lymph node involvement at diagnosis and the type of recurrence (locoregional vs. other) with $P = 0.022$ (Table 5); patients without lymph node involvement at initial diagnosis were more likely to have locoregional recurrences while patients with lymph node involvement were more likely to recur in the lymph nodes, in distant or multiple locations.

The three histological subtypes of our cohort were not statistically different when analyzing time to recurrence or type of recurrence. The 2009 FIGO stage did not cor-

Figure 1. a–g. Locoregional recurrence on MRI. Sagittal (**a**) and axial (**b** and **c**) T2-weighted images, ADC map (**d** and **e**), and contrast-enhanced axial T1-weighted fat-suppressed images (**f** and **g**) at two different levels of a patient with cervical *(thin short arrows)*, uterine body *(long arrows)* and parametrial recurrence *(thick arrow)* of squamous cell carcinoma of the cervix, 12 months after completing treatment. There is a skip metastasis to the anterior wall of the uterine body *(arrowheads)* and the cervical tumor is causing upstream fluid retention *(star)*. No enlarged lymph nodes or distant metastases were identified.

relate with the type of recurrence and the 2018 FIGO staging did not show statistical association with either time to or type of recurrence. Tumor size at initial diagnosis was not associated with time to recurrence when analyzed as a categorical variable (Table 4) neither as a continuous variable (Spearman's rho= -0.13; $P = 0.390$); similarly, tumor size was not associated with the type

of recurrence as shown in Table 5. The presence of lymph nodes at diagnosis did not correlate with time to recurrence.

Discussion

The identification of recurrence has a major impact on the survival outcomes of patients treated for cervical cancer (3), with the prognosis depending upon the

site of recurrence and the ability to pursue potentially curative therapy. We set out to determine if the interval and the location of recurrence were associated with the histology, FIGO stage, size and presence of adenopathies of the initial tumor at diagnosis. To our knowledge this is the first study analyzing a cohort of exclusively recurrent patients of cervical cancer for this purpose.

Table 3. Recurrence distribution identified on imaging by location

	n (%)[a]
Locoregional recurrence distribution	
Locoregional recurrence incidence	22 (46.8)
Locoregional recurrence only	15 (31.9)
Uterine cervix	16 (34.0)
Parametria	8 (17.0)
Uterine corpus	5 (10.6)
Vagina	2 (4.3)
Ovaries	1 (2.1)
Bladder	1 (2.1)
Rectum	1 (2.1)
Pelvic wall recurrence	2 (4.3)
Lymph node recurrence distribution	
Lymph node recurrence incidence	24 (51.1)
Lymph node recurrence only	12 (25.5)
Lymph nodes, para-aortic	14 (29.8)
Lymph nodes, iliac	6 (12.8)
Lymph nodes, mediastinal	4 (8.5)
Lymph nodes, supraclavicular	4 (8.5)
Lymph nodes, retrocrural	2 (4.3)
Lymph nodes, inguinal	1 (2.1)
Lymph nodes, axillary	1 (2.1)
Distant recurrence distribution	
Distant recurrence incidence	16 (34.0)
Distant recurrence only	7 (14.9)
Lung	9 (19.2)
Liver	5 (10.6)
Peritoneum	4 (8.5)
Pleura	4 (8.5)
Bone	4 (8.5)
Adrenal glands	3 (6.4)
Thoracic wall	2 (4.3)
Kidneys	1 (2.1)
Recurrence at multiple locations	13 (27.7)

[a]In one patient recurrence was not identified on imaging, thus the total number of patients is 47 for this table. Due to multiple sites involved in some patients, percent recurrence at different sites do not add up to 100%.

The age distribution, tumor size at diagnosis and histological subtype distribution were as expected compared to those reported in the literature for recurrent cervical cancer (4, 11).

The main differences in FIGO staging system were due to the introduction of the lymph nodes in the classification as stage IIIC (IIIC1 and IIIC2) in the most recent classification, as depicted on Table 1.

In our cohort, a mean of 26 months elapsed between the end of treatment and the diagnosis of recurrence. In the literature, the reported mean time to recurrence is variable, ranging from 7 to 36 months (4, 10, 11). Typically, recurrences occur within the first 2–3 years after the initial treatment (8, 12, 16), and in 33 patients of our cohort (68.8%) a recurrence was identified within 2 years of finishing treatment and 43 had a recurrence within 5 years (89.6%).

Recurrence of cervical cancer is most frequently diagnosed in symptomatic patients (8, 9, 15, 16), with the most common reported symptom being pain (8, 16). In our population 31 patients had symptomatic recurrence (64.6%), most frequently related to pain (Table 2). In our asymptomatic patients, 10 (58.8%) showed changes at gynecological examination, indicating that physical examination accounts for the highest rate of asymptomatic disease detection (8).

Although not advocated for routine follow-up in asymptomatic patients (10), imaging is excellent at detecting recurrence, having identified 47 cases of recurrences in our sample (97.9%). There is no imaging protocol to diagnose cervical cancer recurrence and, this being a retrospective analysis, several imaging methods were used. MRI was the most frequently performed study at our institution, although in the reported literature the most frequently used imaging methods are CT and/or PET-CT (12, 16). MRI has better soft tissue resolution allowing for increased detection of local recurrence, especially when using functional sequences (e.g., DWI) (17) and in our opinion should be used whenever available.

Regarding the distribution of the recurring disease, we found 22 patients (46.8%) had locoregional recurrence, 16 had distant metastases (34%) and 24 had lymph node metastases (51.1%). Multiple sites of disease were involved in 13 patients (27.7%). This distribution is concordant with data published in the literature (4, 10). The most frequent sites of recurrence in the pelvis are in the central compartment (cervix, parametrium, uterus, vagina, ovaries), as shown in Table 3, similar to those reported by Schieda et al. (12). The second most common site of recurrence, following locoregional locations, is in the para-aortic lymph nodes (7), which was also seen in our cohort. Distant recurrence was found in 16 patients (34%), with the lung and the liver most frequently involved (Table 3), as previously reported (4).

We found a significant association between the 2009 FIGO stage and time to recurrence (Table 4); this was not observed when comparing 2018 FIGO stage with time to recurrence. FIGO stage has been described as a predictor of survival in cervical cancer (4) and this finding seems expected of the 2009 FIGO classification. The absence

Table 4. Association between diagnostic characteristics and time to recurrence

Diagnostic feature	n	Time to recurrence (months) Median (IQR)	P
Histology			
Squamous cell carcinoma	40	16.6 (12.3–38.2)	0.254
Adenocarcinoma	6	9.7 (8.7–15.5)	
Adenosquamous carcinoma	2	13.9 (13.5–14.3)	
FIGO stage (2009)			
I	7	36.8 (26.4–41.5)	0.030 [a]
II	29	16.5 (12.6–31.6)	
III	6	11.1 (8.9–13.0)	
IV	6	11.2 (9.7–19.7)	
FIGO stage (2018)			
I	5	36.8 (31.2–37.9)	0.177
II	13	17.4 (12.6–52.1)	
IIIA/IIIB	3	9.9 (9.2–11.6)	
IIIC	21	14.5 (12.4–23.8)	
IV	6	11.2 (9.7–19.7)	
Tumor dimension [b]			
<4 cm	11	13.1 (11.3–31.4)	0.769
≥4 cm	37	14.7 (10.4–37.9)	
Adenopathies			
Absent	23	16.5 (10.0–37.3)	0.769
Present	25	14.5 (12.0–23.8)	

IQR, interquartile range.
[a]Post-hoc two-by-two comparisons using Mann-Whitney-Wilcoxon test with continuity correction and P value adjustment for multiple comparison with Hochberg method indicated that this result was due to a statistically significant difference between FIGO stages I and III (P = 0.028). The adjusted P values concerning all the other comparisons were above 0.05 (I vs. II P = 0.304; I vs. IV P = 0.304; II vs. III P = 0.169; II vs. IV P = 0.699 and III vs. IV P = 0.699).
[b]Tumor size at initial diagnosis was not correlated with time to recurrence when analyzed as a continuous variable (Spearman's rho= -0.13; P = 0.390).

of a significant correlation when comparing the 2018 FIGO stages may be associated with the presence of more subgroups with an associated decrease in the number of patients per group, decreasing the power of analysis.

The main conclusion drawn from our statistical analysis was the statistically significant association between the presence/absence of lymph node metastases at diagnosis and the type of recurrence. In our opinion, this association is seen because patients with lymphadenopathy at initial diagnosis are more likely to have advanced disease and when recurrence is suspected these patients are more likely to be associated with advanced recurrence (including lymph node, distant and multiple sites of recurrence); on the other hand, patients with less advanced disease at initial diagnosis (absence of lymph node involvement) are more likely to recur locoregionally. This association, though not necessarily causative, may allow us to infer that if a patient without lymph node metastases at diagnosis is suspected of having a recurrence, this will more likely be locoregional, while patients with initial lymph node involvement will be more prone to recur in the lymph nodes or in distant or multiple locations. This notion needs further research to determine if a causative association is present. This is an interesting finding which if proven may in the future guide radiologists when evaluating cervical cancer patients on follow-up.
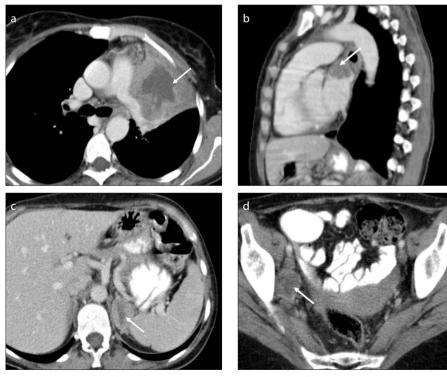
Figure 2. a–c. Pelvic wall recurrence of adenosquamous carcinoma of the cervix, 13 months after treatment. Coronal **(a)**, sagittal **(b)**, and axial reformatted **(c)** CT images show recurrence *(white arrow)* to the pelvic side wall. This pelvic wall recurrence has led to right uretero-hydronephrosis *(black arrow)* with presentation as lumbar pain.

Table 5. Association between diagnostic characteristics and type to recurrence

Diagnostic feature	n	Type of recurrence[a]		P
		Exclusively locoregional (n=15), n (%)	Other (n=32), n (%)	
Histology				
Squamous cell carcinoma	39	10 (66.7)	29 (90.6)	0.067
Adenocarcinoma	6	4 (26.7)	2 (6.2)	
Adenosquamous carcinoma	2	1 (6.7)	1 (3.1)	
FIGO stage (2009)				
I	7	2 (13.3)	5 (15.6)	0.773
II	28	8 (53.3)	20 (62.5)	
III	6	3 (20.0)	3 (9.4)	
IV	6	2 (13.3)	4 (12.5)	
FIGO stage (2018)				
I	5	1 (6.7)	4 (12.5)	0.087
II	13	7 (46.7)	6 (18.8)	
IIIA/IIIB	3	2 (13.3)	1 (3.1)	
IIIC	20	3 (20.0)	17 (53.1)	
IV	6	2 (13.3)	4 (12.5)	
Tumor dimension				
<4 cm	11	6 (40.0)	5 (15.63)	0.136
≥4 cm	36	9 (60.0)	27 (84.4)	
Tumor dimension, cm				
Median (1st–3rd quartiles)	---	4.3 (3.7–5.4)	4.9 (4.2–6.0)	0.263
Adenopathies				
Absent	23	11 (73.3)	12 (37.5)	0.022
Present	24	4 (26.7)	20 (62.5)	

[a]Type of recurrence as identified on imaging. In one patient the recurrence was not identified on imaging, and this analysis was performed with 47 patients.

Figure 3. a–d. Distant and lymph node recurrence. CT images (sagittal of the thorax and axial planes at different levels) of a patient with cardiac, lung and left adrenal metastases and obturator lymph node involvement *(white arrows)* of squamous cell carcinoma of the cervix, 15 months after treatment. There is a mass in the left lung apex that invades the heart (left atria) and a heterogeneous lesion on the left adrenal gland *de novo*. In the pelvis, only an obturator lymph node metastasis was noted.

The remainder of our statistical analysis could not find any significant correlation between our analyzed variables, which may be due to our relatively small sample size.

Previously described risk factors for recurrence include histological type, tumor size, and nodal status (3, 4, 12, 18). To assess if these factors were also associated with the location of and the time to recurrence, we only included patients with recurrence. In our population of patients with recurrence, we found a significant association between the 2009 FIGO staging classification and time to recurrence and between lymph node status and the location of recurrence.

To our knowledge no other previous study analyzed the relation of the type of recurrence and tumor criteria at initial diagnosis in a population exclusively of recurrent cervical cancer; we consider this relevant because the location of recurrence is related to different prognosis and patient management.

The major limitation of our study is the limited sample size with a wide distribution of FIGO stages at diagnosis. This study is also retrospective in nature and based on a single institution. Another limitation of our

analysis was the absence of stratification of the patients according the primary tumor treatment; this was a conscious decision because treatment varied widely in our small cohort and the state-of-the-art treatment evolved over the 10-year period in which our patients were diagnosed.

Despite these limitations we found a statistically significant association between lymph node metastases at diagnosis and the type of recurrence (absence of lymph node involvement was more likely to be associated with exclusively locoregional recurrence). We suggest that studies with larger cohorts should be conducted to confirm our results.

In conclusion, the detection and correct localization of recurrent cervical cancer is key to determine subsequent patient management. In our cohort, we found that a statistically significant association exists between the identification of lymph node metastases at diagnosis and the location of recurrence, helping to predict where the radiologists should focus their search for recurrent disease once it is clinically suspected.

Conflict of interest disclosure
The authors declared no conflicts of interest.

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