Clues pointing to simple hysterectomy to treat early-stage cervical cancer

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Abstract. Radical hysterectomy and pelvic lymphadenectomy is recommended for stage Ia2-Ib1 cervical cancer while parametrial involvement (PI) is rare. Our aim was to evaluate criteria to select women with low risk of PI that could benefit from simple hysterectomy. Factors associated with low risk of PI were analyzed in a series of 37 patients with stage Ia2-Ib1 cervical cancer undergoing radical hysterectomy and sentinel lymph node procedure from 2003 to 2008. PI was associated with tumor size ($p<0.001$) and lymphovascular space invasion (LVSI) ($p=0.007$). PI was found in 4.5% of patients with tumor size ≤2 cm versus 33% with tumor size >2 cm ($p=0.04$). The negative predictive value was 100% for absence of LVSI (95% CI: 0.83-1) and for combinations: tumor size ≤2 cm and SN negative (95% CI: 1-1), tumor size ≤2 cm and no LVSI (95% CI: 0.86-1), tumor size ≤2 cm and tumor grade 1-2 and no LVSI (95% CI: 0.82-1), and tumor size ≤2 cm and PLN negative and no LVSI (95% CI: 0.83-1). Among various combinations, a tumor size ≤2 cm and absence of LVSI appears the most relevant to predict parametrial status.

Introduction

Radical hysterectomy and pelvic lymphadenectomy is the gold standard to treat patients with early-stage cervical cancer (stage Ia2 and Ib1) (1-3). Although the anatomical concept of the parametrium has recently been discussed (4,5), parametrectomy remains an integral part of surgical treatment and defines the radicality of hysterectomy (1). Parametrium involvement (PI) is low in the early stages of cervical cancer (6-8) affecting only 8% of women with negative pelvic lymph nodes in early-stage (9-11). However, parametrectomy is the most difficult step of radical hysterectomy and the main source of complications: severe perioperative complications occurred in 10-15% of patients and late urologic and rectal dysfunctions related to nerve injury in 20-30% raising the issue of its legitimacy (12-14). Moreover, previous studies support that reduction in radicality did not seem to impact on prognosis while the incidence of complications decreased (6,7,13).

The main challenge for the oncologist is therefore to identify which women with early-stage cervical cancer carry a low risk of PI and could thus benefit from simple hysterectomy without compromising prognosis. Strnad *et al* questioned the relevance of systematic parametrectomy in early-stage cervical cancer when tumor size measured <2 cm, stromal infiltrationwas <16 mm and there was no lymphovascular space invasion (LVSI) (3). However, they did not take into account pelvic lymph node (PLN) status which is directly associated with the risk of PI. Recently, it has been suggested that the sentinel node (SN) procedure is a potential tool to tailor the radicality of hysterectomy (3,15).

We were therefore prompted to evaluate the criteria identifying women with a low risk of PI who could benefit from simple hysterectomy in a series of patients with early stages of cervical cancer treated by radical hysterectomy and sentinel node procedure.

Materials and methods

Between July 2003 and July 2008, 37 of 105 women with cervical cancer referred to the gynecology unit of Tenon Hospital, France had early-stage cervical cancer corresponding to FIGO (International Federation of Gynecology and Obstetrics) stage Ia2 to Ib1. Eligibility criteria were: squamous, adenosquamous or adenocarcinoma histology and no contra-indication to surgery. Women with stage Ia1 were excluded from the study as parametrectomy was not indicated in these patients in accordance with our protocol, as were those with FIGO Ib2 to IV stages and patients treated exclusively with concurrent chemoradiotherapy. All gave their informed consent before treatment. All 37 women had biopsy- or conization-proven cervical cancer and underwent preoperative blood sampling, chest X-ray examination, and pelvic magnetic resonance imaging (MRI). Tumor size was assessed by both pelvic examination and MRI. The medical records were prospectively recorded in a database to determine age, body

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mass index (BMI), FIGO stage, tumor size in cm, surgical procedure, pathologic findings [tumor histology, histological grade: well differentiated (grade 1), moderately differentiated (grade 2) and poorly differentiated (grade 3)], presence of LVSI, histological tumor size, stromal infiltration, PI, vaginal involvement, surgical margins, and PLN status including SN status, and operative time. PI was defined as tumor cells within the parametrium. The protocol was approved by the ethics committee.

Patients underwent initial laparoscopic pelvic lymphadenectomy and SN procedure and vaginal or laparoscopic radical hysterectomy. In women wishing to preserve their childbearing potential, a radical vaginal trachelectomy was performed as a fertility sparing treatment. After final histology analysis, patients with adverse prognostic factors underwent adjuvant therapy (radiotherapy and/or chemotherapy). SN biopsy and pathological SN examination methods were performed as previously described (15). In accordance with the Philadelphia Consensus Conference and previous studies on SN procedure in cervical cancer (16,17), the following definitions of lymph node metastases were used: macrometastases as a single focus of metastatic disease per node measuring >2 mm, micrometastases as a focus of metastatic disease ranging from 0.2 mm to ≤2 mm and, in accordance with Marchiole *et al*, submicrometastases as metastases measuring ≤0.2 mm (including the presence of single non-cohesive tumor cells) (16,18,19). SNs were considered positive when they contained macrometastases, micrometastases or submicrometastases. When SN involvement was detected intra-operatively by imprint cytology, paraaortic lymphadenectomy was performed.

Comparisons between continuous and dichotomous variables were based on the Student-t test or the Mann-Whitney U-test. Comparisons between dichotomous variables were based on the Pearson Chi-square test or Fisher's test. We reported factors associated with a low risk of PI as tumor size ≤2 cm, absence of LVSI, tumor grade 1 or 2, negative SN at final histology, negative PLN at final histology. We also studied the combined variables as tumor size ≤2 cm and SN negative at final histology; tumor size ≤2 cm and PLN negative at final histology; tumor size ≤2 cm and absence of LVSI; tumor size ≤2 cm and tumor grade 1 or 2 and absence of LVSI; and finally tumor size ≤2 cm and PLN negative at final histology and absence of LVSI. We calculated a number of false negatives (FN), true negatives (TN), false positives (FP) and true positives (TP) and calculated a sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) with a 95% confidence interval of NPV. We also reported a negative likelihood ratio (NLR) and its 95% confidence interval. A p-value <0.05 was considered to denote a significant difference. Statistical analysis was performed using the R package with the Survival, Design, Hmisc, Rpart, and Verification libraries (http://lib.stat.cmu.edu/R/CRAN/).

Results

The median age of the 37 patients was 50.3 years (range: 29-89 years). Two patients (5.4%) had FIGO stage Ia2 and 35 (94.6%) patients had FIGO stage Ib1. Among the 37 patients, tumor size was ≤2 cm in 22 patients (59.5%) and >2 cm in 15 patients (40.5%). Median tumor size was 1.75 cm (range: 0.4-3.5 cm). All the patients underwent a pre-operative MRI that did not detect PI. The histological type of cervical cancer was squamous cell carcinoma in 25 cases (67.6%) and adenocarcinoma in 12 (32.4%). The tumor was poorly, moderately and well differentiated in seven cases (18.9%), nine cases (24.3%) and 17 cases (45.9%), respectively. Tumor grade was not available in four cases (10.8%). Thirty-one patients (83.8%) underwent laparoscopic radical hysterectomy, three patients underwent Amreich Schauta operation and three vaginal radical trachelectomy. The mean operative time was 241 min (range: 150-350) including the operating time for SN procedure and intra-operative imprint cytology. LVSI was found in 11 cases (29.7%). Six of the 37 patients (16.2%) had PI and these six also had LVSI. Clinical and pathological data were compared by tumor size ≤2 cm and >2 cm. Age, PI and operative time were higher in patients with tumor size >2 cm (Table I).

At least one SN was detected in 32 patients. The identification rate was 86.7%. The mean number of SN removed was 2.7 per patient (range: 1-8). Six (18.8%) of the 32 patients had at least one positive SN. The histological results for SN and non-SN are given in Table II. Intra-operative examination by imprint cytology of SN was positive for only one of the six SN-positive patients including three macrometastases. Sensitivity and NPV of imprint cytology were 0.167 (95% confidence interval: 0.04-0.17) and 0.865 (95% confidence interval: 0.84-0.87) respectively, with an FN rate of 13.5%. The patient with SN metastases detected by imprint cytology underwent paraaortic lymphadenectomy with 15 negative paraaortic lymph nodes. Among the six patients with positive SN at final histology, three had macrometastasis, two had micrometastasis detected by H&E and one patient had submicrometastasis detected by IHC. All patients underwent bilateral pelvic lymphadenectomy of external iliac, interiliac, and superficial obturator nodes, and a mean of 9.6 nodes were removed per patient (range: 2-21). No patient had positive pelvic non-SNs. Therefore, the FN rate of the SN procedure was 0. The mean number of SNs removed was higher in patients with tumor size ≤2 cm than in patients with tumor size >2 cm [3.2 (range: 1-8) versus 1.9 (range: 1-5), p<0.001]. The identification rate was similar in both groups: 19 of the 22 patients (86.4%) with tumor size ≤2 cm and 13 of the 15 patients (86.7%) with tumor size >2 cm. A trend for a higher bilateral SN detection was noted in patients with tumor size ≤2 cm versus tumor size >2 cm (68.4% versus 30.8% respectively, p=0.07). PLN involvement was found in 18.2% (4/22) of patients with tumor size ≤2 cm and 13.3% (2/15) of patients with tumor size >2 cm (p=1). Among the four positive-SN patients with tumor size ≤2 cm, macrometastasis and micrometastasis in H&E was detected in two patients each. Among the two positive-SN patients with tumor size >2 cm, macrometastasis and submicrometastasis in IHC was detected in each patient (p=0.6).

PI was strongly associated with tumor size (p<0.001), presence of LVSI (p=0.007), and vaginal involvement (p=0.04) but not with SN or PLN involvement, histology or histological grade (Table III). PI was found in 4.5% of patients (1/22) with a tumor size ≤2 cm versus 33% of patients (5/15)

Table I. Clinical and pathological data of the 37 patients with cervical cancer FIGO stage Ia2 and Ib1: overall and tumor size ≤2 cm versus >2 cm.

Characteristics	Total (n=37)	Patients with tumor ≤2 cm (n=22)	Patients with tumor >2 cm (n=15)	p
Mean age, years (range)	51.6 (29-89)	46.3 (29-89)	58.4 (34-76)	<0.001
Body mass index (kg/m^2)	24.2 (17-37)	25 (17-38)	22.8 (17-27)	<0.001
FIGO stage				0.5
Ia2	2 (5.4%)	2 (9.1%)	0	
Ib1	35 (94.6%)	20 (91.9%)	15	
Tumor size (cm)				
Mean (range)	1.6 (0.07-3.5)	1 (0.07-2)	2.8 (2.2-3.5)	
Histology				1
Squamous cell carcinoma	25 (67.6%)	15 (68.2%)	10 (66%)	
Adenocarcinoma	12 (32.4%)	7 (31.8%)	5 (34%)	
Histological grade				1
Well differentiated	17 (45.9%)	9 (40.1%)	8 (53.3%)	
Moderately differentiated	9 (24.3%)	5 (22.7%)	4 (26.7%)	
Poorly differentiated	7 (18.9%)	4 (18.2%)	3 (20%)	
Not graded	4 (10.8%)	4 (18.2%)	0	
Localization				1
Cervical	23 (62.2%)	14 (63.6%)	9 (60%)	
Endocervical	14 (37.8%)	8 (36.4%)	6 (40%)	
Preoperative conization	13 (35.1%)	12 (54.5%)	1 (6.7%)	0.04
LVSI				1
Present	11 (29.7%)	6 (27.3%)	5 (33.3%)	
Absent	26 (70.3%)	16 (72.7%)	10 (66.7%)	
Parametrial involvement[a]				0.03
Present	6 (16.2%)	1 (4.5%)	5 (33.3%)	
Absent	31 (83.8%)	21 (95.5%)	10 (66.7%)	
Vaginal involvement[a]				0.19
Present	6 (16.2%)	2 (9.1%)	4 (26.7%)	
Absent	31 (83.8%)	20 (90.9%)	11 (73.3%)	
Type of surgery				0.27
Radical hysterectomy	31 (83.8%)	18 (81.8%)	13 (86.7%)	
Amreich Schauta	3 (81.1%)	1 (4.5%)	2 (13.3%)	
Trachelectomy	3 (81.1%)	3 (13.7%)	0	
Operative time, min (range)	241 (150-360)	237 (150-360)	248 (210-340)	<0.001

LVSI, lymphovascular space involvement; [a]at final hystology.

with a tumor size >2 cm (p=0.04). Among the 11 patients (29.7%) with LVSI, six (55.5%) had PI. No PI was reported in the 26 patients without LVSI. Clinical and pathological data of the six patients with PI are reported in the Table IV. The patient with a tumor size ≤2 cm had poorly differentiated epidermoid carcinoma. All patients had LVSI. One of the six patients had PLN involvement (one macrometastasis SN).

To apply a pragmatic clinical approach, we particularly studied variables classically reported as determinant factors associated with a low risk of PI: tumor size ≤2 cm, absence of LVSI, tumor grade 1 or 2, SN negative at final histology, PLN negative at final histology and combined variables as tumor size ≤2 cm and SN negative at final histology; tumor size ≤2 cm and PLN negative at final histology; tumor size

Table II. Histology of sentinel and non-sentinel lymph nodes and outcome of 37 patients with cervical cancer FIGO stage Ia2 and Ib1: overall and tumor size ≤2 cm versus >2 cm.

Characteristics	Total (n=37)	Patients with tumor ≤2 cm (n=22)	Patients with tumor >2 cm (n=15)	p
Sentinel node (SN)				
At least one SN detected	32	19	13	1
Identification rate	86.5%	86.4%	86.7%	
Mean nb of SN (range)	2.7 (1-8)	3.2 (1-8)	1.9 (1-5)	<0.001
Patients with bilateral SN	17 (53.1%)	13 (68.4%)	4 (30.8%)	0.07
Nb of patient with positive SN	6 (18.8%)	4 (21.1%)	2 (15.4%)	1
Nb of patients with macrometastases in H&E	3 (50%)	2	1	0.6
Nb of patients with micrometastases in H&E	2 (33%)	2	0	
Nb of patients with micrometastases in H&E	0	0	0	
Nb of patients with isolated tumor cells	1 (17%)	0	1	
Non-sentinel lymph nodes (non-SN)				
Nb of patients	37 (100%)	22 (100%)	15 (100%)	
Nb of non-SN removed	347	204	143	
Mean nb of non-SN (range)	9.6 (2-21)	9.3 (2-16)	10.2 (4-21)	<0.001
Nb of patients with positive non- SN	0	0	0	
Pelvic lymph nodes (PLN) = SN + non-SN				
Nb of patient with positive PLN	6 (16.2%)	4 (18.2%)	2 (13.3%)	1
$SN^+/non\text{-}SN^+$	0			
$SN^+/non\text{-}SN^-$	6 (16.2%)	4 (18.2%)	2 (13.3%)	
$SN^-/non\text{-}SN^+$	0			
$SN^-/non\text{-}SN^-$	26 (70.2%)	15 (68.2%)	11 (73.3%)	
no SN/PLN^-	5 (13.5%)	3 (13.6%)	2 (13.3%)	
no SN/PLN^+	0			
False-negative rate	0	0	0	

SN, sentinel node; LVSI, lymphovascular space involvement; Nb, number; H&E, hematoxylin and eosin; IHC, immunohistochemistry.

≤2 cm and absence of LVSI; tumor size ≤2 cm and tumor grade 1 or 2 and absence of LVSI; and finally tumor size ≤2 cm and PLN negative at final histology and absence of LVSI (Table V). The NPV was 100% for absence of LVSI (95% confidence interval: 0.83-1) and for four combinations of variables: tumor size ≤2 cm and SN negative (95% confidence interval: 1-1), tumor size ≤2 cm and absence of LVSI (95% confidence interval: 0.86-1), tumor size ≤2 cm and tumor grade 1 or 2 and absence of LVSI (95% confidence interval: 0.82-1), and tumor size ≤2 cm and PLN negative at final histology and absence of LVSI (95% confidence interval: 0.83-1). The last combination applied to patients undergoing a vaginal trachelectomy (Table V).

Discussion

The present study has demonstrated that pre-operative characteristics of early cervical cancer stages are useful to select a subgroup of patients for whom systematic parametrectomy could be avoided.

We show that combinations of clinical and histological variables are more relevant to predict PI than the use of a single variable. Using single variables, only the absence of LVSI had a NPV of 100% in predicting the absence of PI while tumor size <2 cm, low tumor grade, and negative SLN or PLN status had lower NPVs. This is in accordance with previous studies showing that LVSI was directly related to the risk of lymph node involvement (18). Moreover, previous studies have underlined that lymph node metastases were correlated to PI (20). Using multivariate analysis, LVSI emerged as a major predictive factor of survival (21). To preclude the risk of underestimation of PI using a single variable, several combinations were tested. An NPV of 100% was found for four combinations: i) tumor size ≤2 cm and SN negative at final histology; ii) tumor size ≤2 cm and absence of LVSI; iii) tumor size ≤2 cm and tumor grade 1 or 2 and absence of LVSI; iv) tumor size ≤2 cm and PLN negative at final histology and absence of LVSI. Among these combinations, two are potentially available pre-operatively to select patients at low risk of PI: tumor size ≤2 cm and absence

Table III. Clinical and pathological data of the 37 patients with cervical cancer FIGO stage Ia2 and Ib1: overall and patients with parametrial involvement versus without parametrial involvement.

Characteristics	Total (n=37)	Patients with parametrial involvement (n=6)	Patients without parametrial involvement (n=31)	p
Mean age, years (range)	51.6 (29-89)	64.5 (44-89)	48.6 (29-77)	<0.001
Body mass index (kg/m^2)	24.2 (17-37)	22 (18-29)	24.5 (17-38)	<0.001
FIGO stage				1
Ia2	2 (5.4%)	0	2 (6.5%)	
Ib1	35 (94.6%)	6 (100%)	29 (93.6%)	
Tumor size (cm)				<0.001
Mean (range)	1.6 (0.07-3.5)	2.75 (1.5-3.5)	1.56 (0.07-3.1)	
Histology				1
Squamous cell carcinoma	25 (67.6%)	4 (66.7%)	21 (67.7%)	
Adenocarcinoma	12 (32.4%)	2 (33.3%)	10 (32.3%)	
Histological grade				0.67
Well differentiated	17 (45.9%)	2 (33.3%)	15 (48.4%)	
Moderately differentiated	9 (24.3%)	1 (16.7%)	8 (25.8%)	
Poorly differentiated	7 (18.9%)	2 (33.3%)	5 (16.1%)	
Not graded	4 (10.8%)	1 (16.7%)	3 (9.7%)	
Localization				1
Cervical	23 (62.2%)	4 (66.7%)	19 (61.3%)	
Endocervical	14 (37.8%)	2 (33.3%)	12 (37.7%)	
Preoperative conization	13 (35.1%)	1 (16.7%)	12 (38.7%)	0.37
LVSI				0.007
Present	11 (29.7%)	6 (100%)	5 (16.1%)	
Absent	26 (70.3%)	0	26 (83.9%)	
Vaginal involvement				0.04
Present	6 (16.2%)	3 (50%)	3 (9.7%)	
Absent	31 (83.8%)	3 (50%)	28 (90.3%)	
Type of surgery				0.7
Radical hysterectomy	31 (83.8%)	5 (83.3%)	26 (83.8%)	
Amreich Schauta	3 (81.1%)	1 (16.7%)	2 (6.5%)	
Trachelectomy	3 (81.1%)	0	3 (9.7%)	
Operative time, min (range)	241 (150-360)	220 (150-260)	245 (160-360)	<0.001
Sentinel node (SN)				
At least one SN detected	32	4	28	0.17
Identification rate	86.5%	66.7%	90.3%	
Mean nb of SN (range)	2.7 (1-8)	2 (1-3)	2.8 (1-8)	<0.001
Patients with bilateral SN	17 (53.1%)	2 (33.3%)	15 (48.4%)	1
Nb of patient with positive SN	6 (18.8%)	1 (25%)	5 (17.9%)	1
Nb of patients with macrometastases in H&E	3 (50%)	1	2 (40%)	1
Nb of patients with micrometastases in H&E	2 (33%)	0	0	
Nb of patients with micrometastases in H&E	0	0	2 (40%)	
Nb of patients with isolated tumours cells	1 (17%)	0	1 (20%)	

Table III. Continued.

Characteristics	Total (n=37)	Patients with parametrial involvement (n=6)	Patients without parametrial involvement (n=31)	p
Non-sentinel lymph nodes (non-SN)				
Nb of patients	37 (100%)	6 (100%)	31 (100%)	
Nb of non-SN removed	347	71	276	
Mean nb of non-SN (range)	9.6 (2-21)	14.2 (10-20)	8.9 (2-16)	<0.001
Nb of patients with positive non-SN	0	0	0	
Pelvic lymph nodes (PLN) = SN + non-SN				
Nb of patient with positive PLN	6 (16.2%)	1 (16.7%)	5 (16.1%)	1
$SN^+/non\text{-}SN^+$	0	0	0	
$SN^+/non\text{-}SN^-$	6 (16.2%)	1 (16.7%)	5 (16.1%)	
$SN^-/non\text{-}SN^+$	0			
$SN^-/non\text{-}SN^-$	26 (70.2%)	3 (50%)	23 (74.2%)	
No SN/PLN^-	5 (13.5%)	2 (33.3%)	3 (9.7%)	
No SN/PLN^+	0	0		
False-negative rate	0	0	0	

SN, sentinel node; LVSI, lymphovascular space involvement; Nb, number; H&E, hematoxylin and eosin; IHC, immunohistochemistry.

Table IV. Clinical, pathological data and outcome of patients with parametrial involvement according to the tumor size ≤2 cm or >2 cm.

Age	FIGO stage	Tumor size (cm)	Cell type	Histological grade	LVSI	Nb of SN removed	Results of SN	Results of non-SN	Outcome
Tumor size ≤2 cm									
89	IB1	1.5	SCC	Poorly	+	Not detected		Negative	RFS
Tumor size >2 cm									
45	IB1	2.8	Adenoc	Moderately	+	1	Negative	Negative	
44	IB1	3	SCC	Well	+	3 (bilaterally)	Macro	Negative	
60	IB1	2.7	Adenoc	Not graded	+	2 (bilaterally)	Negative	Negative	RFS
76	IB1	3	SCC	Well	+	2	Negative	Negative	Death
73	IB1	3.5	SCC	Poorly	+	Not detected		Negative	RFS

SCC, squamous cell carcinoma; adenoc, adenocarcinoma; LVSI, lymphovascular space involvement; SN, sentinel lymph node; non-SN, non-sentinel lymph node; RFS, relapse-free survival.

of LVSI and tumor size ≤2 cm and tumor grade 1 or 2 and absence of LVSI. Among these two combinations, tumor size ≤2 cm and absence of LVSI appeared particularly relevant due to a narrow 95% confidence interval (CI) while adding tumor grade increased the CI width. Our results support the use of this combination to select patients that could benefit from a simple hysterectomy. Moreover, although our series included only two patients who underwent vaginal radical trachelectomy, our results raise the issue of the possible use of conization in patients fulfilling these criteria due to the low risk of PI.

Using the combination of a tumor size ≤2 cm and absence of LVSI to select early-stage cervical cancer patients for a simple hysterectomy might expose them to the risk of under-treatment if PLN involvement is not taken into account. Positive PLNs have been reported as a major predictive factor of a high risk of PI (3,6,13,22-24). However, in our study, only one patient with PI had positive SLN (macro-metastases) while five had PI with negative PLN. Rob *et al* reported that none of their negative-SLN patients with tumor size <3 cm had PI (24). In a subgroup of patients with tumor size <2 cm and stromal invasion <50%, Strnad *et al* found

Table V. Predictive factors of low risk of parametrial involvement in patients with early-stage cervical cancer.

Variables	Nb of patients	Nb of FN	NPV (95% confidence interval)	
Single variable				
Tumor <2 cm	22	1	0.95	(0.85-0.99)
Absence of LVSI	11	0	1	(0.83-1)
Tumor grade 1 or 2	25	3	0.88	(0.82-0.95)
Negative SN[a]	26	3	0.83	(0.85-0.95)
Negative PLN[a]	31	5	0.84	(0.81-0.9)
Combination of variables				
Tumor <2 cm and absence of LVSI	15	0	1	(0.86-1)
Tumor <2 cm and grade 1 or 2 and absence of LVSI	11	0	1	(0.82-1)
Tumor <2 cm and negative SN[a]	15	0	1	(1-1)
Tumor <2 cm and negative PLN[a]	18	1	0.94	(0.82-0.99)
Tumor <2 cm and absence of LVSI and negative PLN[a]	14	0	1	(0.85-1)

[a]At final histology; Nb, number; LVSI, lymphovascular space involvement; SN, sentinel lymph node; PLN, pelvic lymph node; FN, false negative; NPV, negative predictive value.

that PI was observed in 27% (3/11) of patients with positive SLN versus 0% (0/80) in patients with negative SLN (3). Stegman *et al* reported that only 5 of 799 patients (0.63%) with early cervical carcinoma <2 cm, infiltration depth <10 mm and negative PLN had PI (11). Finally, Panici *et al* reported PI in only 3% of cases with negativePLN versus 100% of cases in positive PLN (13). All these data (3,11,13,24) raise the issue of histological techniques to assess lymph node status both intra-operatively and on final histology. In the present study, none of the six patients with positive SLN were detected by intra-operative histology reflecting the low accuracy of imprint cytology. However, serial sectioning and IHC allowed three of the five SLN-positive patients without PI to be identified, reinforcing the contribution of ultrastaging Hence, there is a need for a better assessment of lymph node status. One option could be to opt for an initial pelvic lymphadenectomy with the SLN procedure followed by a second surgery after final histology. This option could be relevant for patients wishing to preserve their childbearing potential due to the less aggressive nature of conization compared to radical trachelectomy, but appears questionable for the vast majority of patients related to cumulative risks associated with a second surgery (11).

To avoid a two-step surgical treatment of early-stage cervical cancer, it might be necessary to increase the accuracy of intra-operative histology. In this study, accuracy of imprint cytology was poor. Sensitivity and NPV were 0.17 (95% CI: 0.04-0.17) and 0.86 (95% CI: 0.84-0.87) respectively, with an FN rate of 13.5%. Hence, combinations including SLN status appeared less relevant due to the low accuracy of imprint cytology to detect lymph node involvement. Previous studies have underlined the contribution of intra-operative histology based on frozen section but this is associated with loss of tissue sample for definitive histology (13,25-27). The sensitivity, NPV and FN rates of frozen section reported by Panici *et al* were 90, 97, and 4.2%, respectively (13). In various series, FN rates ranged from 4.2 to 32% (13,25-27). To improve the accuracy of intra-operative histology, several biological techniques based on RT-PCR have been proposed using both cytokeratin 19 and human papillomavirus but were not able to differentiate between types of metastases (15,28). Although issues remain about the relevance of micrometastases in women with cervical cancer (16), differentiating between true macrometastases and multiple micrometastasis or submicrometastasis seems particularly relevant as previous clinical studies have underlined the risk of recurrence and poor survival according to the type of metastases (16). To remedy this concern, in breast cancer, correlation has been established between the number of copy cells and the size of metastases but requires confirmation in cervical cancer.

Some limitations of the present study have to be underlined. First, we did not take into account MRI features suggestive of PI. Postema *et al* reported that the sensitivity of MRI to detect PI was 89% compared to 44% for pelvic examination alone but included both early and advanced stages of cervical cancer (29). In the present study, all the patients with early-stage cervical cancer underwent a pre-operative MRI that did not detect PI. Second, the small sample size did not allow us to draw definitive conclusions. However, from a statistical viewpoint, our pragmatic proposal seems robust enough. Finally, the present study represents the experience of one team with potential bias linked to department recruitment and requires confirmation on the usefulness of our combination by others teams.

In conclusion, our results support that the combination of pre-operative characteristics of early-stage cervical cancer could be useful to select patients for less aggressive surgery and hence potentially contribute to a decrease in surgical morbidity. Moreover, among the various combinations studied, a tumor size ≤2 cm and the absence of LVSI appears easy to assess and the most relevant predictor of parametrial status.

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