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Predictive factors of unexpected lymphatic drainage pathways in early-stage cervical cancer

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HIGHLIGHTS

- Sentinel lymph nodes are mostly found in the interiliac and external iliac area.
- Atypical topography of sentinel lymph nodes concerns up to 24.5% of patients.
- Sentinel lymph nodes in atypical areas are more frequent with tumor size ≥20 mm.
- Multiparity may have an impact on uterine lymphatic drainage.
- Sentinel lymph node biopsy may detect metastatic nodes in aberrant topography.

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ABSTRACT

Objectives. The purpose of this study was to describe sentinel lymph nodes (SLN) topography in patients with early-stage cervical cancer and to determine factors associated with atypical lymphatic drainage pathway (LDP).

Methods. We analyzed the data of two prospective multicentric trials on SLN biopsy for cervical cancer (SENTICOL I and II) in women undergoing surgery for early-stage cervical cancer. SLN detection was realized with a combined labeling technique (Patent blue and radioactive tracer). Patients having bilateral SLN detection were included. Univariate and Multivariate analysis were performed by patients and by side to assess clinical and pathologic factors that may predict atypical LDP.

Results. Between January 2005 and July 2012, 326 patients with 1104 intraoperative detected SLNs fulfilled the inclusion criteria. The SLNs were mainly located in the interiliac or external iliac area in 83.2%. The other localizations were: 9.2% in the common iliac area, 3.9% in the parametrium, 1.6% in the promontory area, 1.5% in the paraaortic area and 0.5% in other areas. Thirty-five patients (10.7%) had atypical SLN without SLN in typical area on one or both sides. In multivariate analysis, tumor size ≥20 mm appeared as an independent factor of having at least one exclusive atypical LDP (ORa = 3.95 95%CI = [1.60–9.78], p = 0.003). Multiparity decreased significantly the probability of having at least one exclusive atypical LDP (ORa = 0.16 95%CI = [0.07–0.39], p < 0.0001).

Conclusions. Tumor size larger than 20 mm and nulliparity increase the risk of having exclusive atypical LDP in early-stage cervical cancer.

1. Introduction

Cervical cancer is the second most common cancer among women and the third cause of cancer-related deaths in females with approximately 527,600 new cases and 265,700 deaths each year [1]. Lymph node involvement is one of the main major prognosis factors for early-stage cervical cancer [2,3]. According to main guidelines [4,5], surgery is the preferred treatment for early-stage cervical cancer (up to FIGO stage IIA1), especially in young patients. Lymph node staging is performed to assess the prognosis and guide the treatment [5]. Considering that pelvic lymphadenectomy generates several complications, the sentinel lymph node (SLN) technique has been introduced for

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20 years and is increasingly used in cervical cancer. One of the interests of SLN is to highlight the aberrant drainage territories that are not systematically dissected during routine lymphadenectomies [6]. Although most of SLNs are located in the interiliac and external iliac area, SLNs have also been described in "unexpected" territories such as sacral, promontory and paraaortic areas [7].

The purpose of the present study was to describe SLNs topography in a large multicentric prospective cohort of patients with early-stage cervical cancer and to determine factors associated with atypical lymphatic drainage pathway (LDP).

2. Material and methods

2.1. Population study

We retrospectively analyzed the data of two multicentric prospective trials on SLN biopsy for FIGO IA-IIA cervical cancer (SENTICOL I & II). Design of the both studies have already been described elsewhere [8,9]. Patients with early cervical cancer (stage Ia1 with lymphovascular emboli, IB1 and IIA1) were included consecutively from 7 French gynecological oncology centers for SENTICOL I and 23 French gynecological oncology centers for SENTICOL II.

Briefly, SENTICOL I was a prospective multicenter study assessing the diagnostic value of SLN biopsy in early-stage cervical cancer. One hundred and forty-five patients were enrolled between January 2005 and May 2007 and a systematic pelvic lymphadenectomy was performed after SLN biopsy as well as lymphadenectomy of areas containing one or more SLNs [12]. SENTICOL II was a prospective randomized multicenter study assessing morbidity and quality of life [13]. Two hundred and sixty-seven patients were enrolled and 206 patients with negative SLN at frozen-section examination were randomized between SLN biopsy only (105 patients) and SLN biopsy with additional pelvic lymphadenectomy (101 patients).

In both studies, number and location of SLNs were prospectively recorded in a pre-specified analysis. In this article, patients with early-stage cervical cancer and bilateral SLN detection were included. Bilateral detection was defined as intraoperative detection SLNs in both hemi-pelvises. Patients who had unilateral or no SLNs detected were excluded because LDP could not be assessed intraoperatively. Approval to conduct this study was obtained from the Paris Descartes Ethical Committee (Comité de Protection des Personnes HEGP-Broussais). Patients included in the two studies signed an informed consent stating the use of data for secondary analyses.

2.2. Data analysis

All data were collected from two prospective multicentric databases. Demographic characteristics, surgical history, and clinical data including FIGO stage were extracted. Operative records were reviewed, and data about the type of surgical approach, the type of surgery performed (hysterectomy or trachelectomy) and the operating time was collected.

Sentinel lymph node was detected by a combined labeling technique. The radioactive tracer (colloidal rhenium sulfide labeled with technetium [99mTc] (Nanocis®, Cis Bio International, Gif sur Yvette, France)) was injected using a 25-gauge needle into the four cardinal points of the uterine cervix either on the day before surgery (120-MBq; long protocol) or morning of surgery (60-MBq; short protocol). Lymphoscintigraphy was performed routinely, and the results were given to the surgeons before the surgical procedure. At the beginning of the surgical procedure, 2.5% Patent Blue (2 mL diluted in 2 mL of saline) was injected into the four cardinal points of the cervix.

Intraoperatively, the pelvic and para-aortic nodes were examined before and after opening of the peritoneum, the pararectal, paravesical spaces and exposure of the parametria. SLNs were identified based on the blue color of the lymphatic channels and nodes and on radioactivity detected using an endoscopic gamma detection device. SLNs were selectively removed and the absence of residual in vivo radioactivity was checked. Frozen section analysis was performed either routinely or only on suspected metastasis nodes depending on the center.

To describe SLN location, we used the area classification suggested by Marnitz et al. [7]: paraaortic (area 1), common iliac (from the bifurcation of the aorta to the bifurcation of the iliac vessels, area 2), external iliac (along the external iliac vessels, area 3), interiliac (nodes medial to the external iliac artery and vein, in the obturator fossa and over the bifurcation of the common iliac artery, area 4), internal iliac (medial to the internal iliac vessels down to the uterine artery bifurcation, including the presacral nodes, area 5), and parametrium (nodes medial to the bifurcation of the uterine artery, area 6). Areas 3 and 4 were considered to be located in typical sites whereas the other areas (areas 1, 2, 5, and 6) were defined as atypical sites. Classic LDP was defined by the presence of SLNs exclusively in typical sites (area 3 and 4). Atypical LDP was defined by the presence of one or more SLNs in atypical sites (area 1, 2, 5 and 6). Common iliac SLNs were considered to belong to classic LDP if they were associated with SLNs in the interiliac or external iliac area whereas isolated common iliac SLNs (without any SLNs in the interiliac or external iliac area) were considered as belonging to atypical LDP. In the same way, paraaortic SLNs were considered as atypical if they were isolated without any SLNs in the external, interiliac or common iliac area.

SLNs were analyzed after hematoxylineosin-saffron (HES) staining of 200-μm sections. SLNs negative by HES were examined by immunohistochemistry with anti-cytokeratin AE1-AE3 antibodies. Non-SLNs were cut once and were examined by HES only. Isolated tumor cells (ITCs) were defined as <0.2 mm, micrometastases as between 0.2 and 2 mm, and macrometastases as >2 mm [10].

Pathological data was reviewed (tumor histology, lymphovascular space invasion (LVSI), parametrial status, vaginal margin status, surgical margin status and tumor size).

2.3. Statistical analysis

We performed two analyses: a patient-specific analysis and a side-specific analysis, considering all hemi-pelvises (right and left for each patient). In both analyses, we assessed clinico-pathologic variable associated with the presence or not of exclusive atypical LDP.

Qualitative variables were expressed as n (%) and quantitative data as mean [range]. The chi-square test (or Fisher's test if the sample size was too small) was used to compare qualitative variables. The Student's *t*-test was applied to compare quantitative variables.

Variables yielding p values lower than 0.2 by univariate analysis were entered into a multivariate logistic regression model to determine variables independently associated with the presence or not of exclusive atypical LDP. Values of p lower than 0.05 were considered as significant.

Data were recorded in an Excel files and statistical analyses were performed using XLStat Biomed software (AddInsoft V19.4).

3. Results

Between January 2005 and July 2012, 412 patients were enrolled in the both studies: 145 in SENTICOL I and 267 in SENTICOL II. Three hundred and twenty-six patients had bilateral SLN detection and were finally included for analysis.

3.1. Patient and surgical characteristics

The median age was 41.5 years [22–85 years] and the median Body-Mass Index (BMI) was 22.6 kg/m^2 [14.6–42.2 kg/m^2]. Eighty-seven patients (26.7%) were nulliparous. Most of the patients had FIGO stage IB1 disease (273 patients, 83.7%). The majority of patients had squamous cell carcinoma (216 patients, 66.3%). Thirty-three patients (10.1%) had only lymph node staging, 4 patients (1.2%) a simple

Table 1
SLN status and topography.

Predictive variable	Total patients N = 326 Total SLN N = 1104		Patient-specific: Patients with no SLNs in atypical areas N = 246		Patient-specific: Patients with at least one SLN in atypical areas N = 80		p	Side-specific: Side with no SLNs in atypical areas N = 559		Side-specific: Side with at least one SLN in atypical areas N = 93		p
	n Mean ± SD	[%] [range]	n Mean ± SD	[%] [range]	n Mean ± SD	[%] [range]		n Mean ± SD	[%] [range]	n Mean ± SD	[%] [range]	
Type of SLN												
Blue and hot	650	58.9	471	62,0	179	53,4	0.03	539	62,2	111	50,7	0.007
Hot	265	24	170	22,4	95	28,4		190	21,9	65	29,7	
Blue	180	16.3	119	15,7	61	18,2		137	15,8	43	19,6	
Not specified	9	0.8										
Topography of SLN												
Interiliac/external iliac area	918	83.2	724	94,3	194	57,7	<0.0001	828	93,6	90	41,1	<0.0001
Common iliac area	102	9.2	44	5,7	58	17,3		57	6,4	45	20,5	
Parametrial area	43	3.9	0	0,0	43	12,8		0	0,0	43	19,6	
Promontory area	18	1.6	0	0,0	18	5,4		0	0,0	18	8,2	
Paraaortic area	17	1.5	0	0,0	17	5,1		0	0,0	17	7,8	
Other	6	0.3	0	0,0	6	1,8		0	0,0	6	2,7	
Total	1104	100	768	100	336	100						
Number of removed nodes												
Number of SLN per patient	3.8 ± 1.8	[2–11]	3.6 ± 1.6	[2–11]	4.5 ± 2.1	[2−10]	<0.0001	–	–	–	–	–
Number of SLN per hemipelvis	1.9 ± 1.3	[1–9]	–	–	–	–	–	1.8 ± 1.1	[1–9]	2.4 ± 1.8	[1–8]	<0.0001
Node status												
Patients with positive SLN												
Yes	53	16.3	38	15,4	15	18,8	0.49	–	–	–	–	–
No	273	83.7	208	84,6	65	81,3		–	–	–	–	
Side with positive SLN												
Yes	64	9,8	–	–	–	–	–	54	9,7	10	10,8	0.74
No	588	90,2	–	–	–	–		505	90,3	83	89,2	
Number positive SLN												
Yes	68	6.2	48	6,3	20	6,0	0.85	57	6,4	11	5,0	0.43
No	1036	93.8	720	93,8	316	94,0		828	93,6	208	95,0	
Type of positive SLN												
Macrometastasis	31/68	45.6	20/48	41,7	11/20	55,0	0.32	23/57	40,4	8/11	72,7	0.17
Micrometastasis	19/68	27.9	16/48	33,3	3/20	15,0		17/57	29,8	2/11	18,2	
ITC	18/68	26.5	12/48	25,0	6/20	30,0		17/57	29,8	1/11	9,1	
Topography of positive SLN												
Topography of overall metastasis												
Interiliac/external iliac area	60/68	88.2	46/48	95,8	14/20	70,0	0.005	55/57	96,5	5/11	45,5	<0.0001
Common iliac area	3/68	4.4	2/48	4,2	1/20	5,0		2/57	3,5	1/11	9,1	
Parametrial area	3/68	4.4	0/48	0,0	3/20	15,0		0/57	0,0	3/11	27,3	
Promonotory area	1/68	1.5	0/48	0,0	1/20	5,0		0/57	0,0	1/11	9,1	
Paraaortic area	1/68	1.5	0/48	0,0	1/20	5,0		0/57	0,0	1/11	9,1	
Topography of macrometastasis												
Interiliac/external iliac area	26/31	83.9	20/20	100	6/11	54,5	0.003	23/23	100,0	3/8	37,5	<0.001
Parametrial area	3/31	9.7	0/20	0	3/11	27,3		0/23	0,0	1/8	12,5	
Promonotory area	1/31	3.2	0/20	0	1/11	9,1		0/23	0,0	1/8	12,5	
Paraaortic area	1/31	3.2	0/20	0	1/11	9,1		23/23	100,0	3/8	37,5	
Topography of micrometastasis												
Interiliac/external iliac area	17/19	89.5	14/16	87,5	3/3	100	0.71	15/17	88,2	2/2	100,0	0.99
Common iliac area	2/19	10.5	2/16	12,5	0/3	0		2/17	11,8	0/2	0,0	
Topography of ITCs												
Interiliac/external iliac area	17/18	94.4	12/12	100	5/6	83.3	0.72	17/17	100	0/1	0	0.06
Common iliac area	1/18	5.6	0/12	0	1/6	16.7		0/17	0	1/1	100	

Table 2
Description of patients with metastatic SLN in atypical localisation.

Patient	Age (years)	BMI (kg/m^2)	Parity	FIGO stage	Histologic type	Tumor size	Number of total positive SLN	Localisation of positive SLN in atypical area	Type of positive SLN in atypical area	Positive SLN in interiliac or external area associated
1	39	24.0	Nulliparous	IIB	Squamous cell carcinoma	50	1	Common iliac area	ITCs	No
2	38	25.0	Nulliparous	IB1	Squamous cell carcinoma	4	1	Parametrial area	Macrometastasis	No
3	30	28.1	Nulliparous	IB1	Adenocarcinoma	20	2	Parametrial area	Macrometastasis	Yes
4	49	38.8	Multiparous	IIB	Squamous cell carcinoma	21	3	Parametrial area	Macrometastasis	Yes
5	36	31.1	Multiparous	IB1	Adenocarcinoma	26	1	Promontory area	Macrometastasis	No
6	54	17.0	Multiparous	IB1	Squamous cell carcinoma	26	2	Paraaortic area	Macrometastasis	Yes

trachelectomy, 53 patients (16.3%) a radical trachelectomy, 10 patients (3.1%) a simple hysterectomy and 226 (69.3%) a radical hysterectomy. At final pathologic examination, 58 patients (20.6%) had a tumor size larger than 20 mm. There were a parametrial spread in 12 patients (3.7%), a vaginal spread in 12 patients (3.7%) and positive surgical margin in 14 patients (4.3%).

3.2. SLNs topography and status

In 326 patients, 1104 SLNs were detected and removed (Table 1). The mean number of removed SLN per patient was 3.8 ± 1.8 [2–11] and per hemipelvis was 1.9 ± 1.3 [1–9]. SLNs were mainly located in the interiliac or external iliac area (918/1104, 83.2%). One hundred and two SLNs (9.2%) were found in common iliac area. Among them, 62 common iliac SLNs were associated with SLNs in the interiliac or external iliac area and therefore were considered as following classical lymphatic drainage pathway whereas 40 common iliac SLNs were isolated and were considered as atypical. In addition to that, 33 SLNs were specifically located in the parametrium (3.9%), 18 SLNs in the promontory area (1.6%) and 17 SLNs (1.5%) were isolated in the paraaortic area. Three SLNs were identified in the right paracervix 0.3%. The topography of 3 SLNs was not precised. The majority of patients had exclusively bilateral classic LDP (246 patients, 75.5%) whereas 80 patients (24.5%) had at least one atypical LDP. In this

Table 3
Univariate analysis of predictive factors of having at least one exclusive atypical LDP per patients.

Predictive variable	Total population N = 326		Patients with bilateral classic LDP N = 291		Patients with at least one exclusive atypical LDP N = 35		p
	n Mean ± SD	[%] [range]	n Mean ± SD	[%] [range]	n Mean ± SD	[%] [range]	
Age [years]							
Mean	43.6 ± 11.8	[22–85]	43.6 ± 11.6	[23–85]	43.7 ± 13.7	[22–79]	0.96
<50	248	76.1	222	76.3	26	74.3	0.63
50–70	68	20.9	61	21.0	7	20.0	
≥70	10	3.1	8	2.7	2	5.7	
BMI [kg/m^2]							
Mean	23.6 ± 5.0	[14.6–42.2]	23.8 ± 5.1	[14.6–42.2]	22.4 ± 3.5	[16.0–31.1]	0.11
≤25	234/325	72.0	204/290	70.3	30	85.7	0.06
>25	91/325	28.0	86/290	29.7	5	14.3	
Parity							
0	87	26.7	65	22.3	22	62.9	<0.0001
≥1	239	73.3	226	77.7	13	37.1	
Menopausal status							
Yes	88	27.0	79	27.1	9	25.7	0.86
No	238	73.0	212	72.9	26	74.3	
History of previous pelvic surgery							
0	180	55.2	158	54.3	22	62.9	0.34
≥1	146	44.8	133	45.7	13	37.1	
FIGO stage							
IA1 with emboli – IA2	35/314	11.1	32/282	11.3	3/32	9.4	0.66
IB1	273/314	86.9	244/282	86.5	29/32	90.6	
IIA	6/314	1.9	6/282	2.1	0/32	0.0	
Histology							
Squamous cell carcinoma	216/310	69.7	194/278	69.8	22/32	68.8	0.62
Adenocarcinoma	87/310	28.1	77/278	27.7	10/32	31.3	
Other type	7/310	2.3	7/278	2.5	0/32	0.0	
Preoperative LEEP							
Yes	193/310	62.3	175/278	62.9	18/32	56.3	0.46
No	117/310	37.7	103/278	37.1	14/32	43.8	
Preoperative brachytherapy							
Yes	51/263	19.4	46/238	19.3	5/25	20.0	0.94
No	212/263	80.6	192/238	80.7	20/25	80.0	
Type of surgical approach							
Minimal invasive surgery	299/325	92.0	264/290	91.0	35	100.0	0.06
Laparotomy	26/325	8.0	26/290	9.0	0	0.0	
Node status							
Patients with positive SLN							
Yes	53	16.3	47	16.2	6	17.1	0.88
No	273	83.7	244	83.8	29	82.9	
Final pathologic exam							
Tumor size							
<20 mm	223/281	79.4	208/255	81.6	15/26	57.7	0.0004
≥20 mm	58/281	20.6	47/255	18.4	11/26	42.3	
LVSI							
Yes	87/292	29.8	79/265	29.8	8/27	29.6	0.98
No	205/292	70.2	186/265	70.2	19/27	70.4	
Parametrial invasion							
Yes	12/283	4.2	10/257	3.9	2/26	7.7	0.36
No	271/283	95.8	247/257	96.1	24/26	92.3	
Vaginal invasion							
Yes	12/276	4.3	10/250	4.0	2/26	7.7	0.38
No	264/276	95.7	240/250	96.0	24/26	92.3	
Positive margin							
Yes	14/282	5.0	11/256	4.3	3/26	11.5	0.1
No	268/282	95.0	245/256	95.7	23/26	88.5	

subgroup of 80 patients, 45 patients (13.8%) had classic LDP associated with atypical LDP on one or both sides, 32 patients (9.8%) had exclusively atypical LDP on one side and 3 patients (0.9%) had exclusively atypical LDP on both sides. Among the 652 hemipelvises assessable, 93 hemipelvises (14.3%) had at least one atypical LDP. Among these 93 hemipelvises, 36 hemipelvises had exclusively atypical LDP. Significantly more SLNs were removed in patients with atypical LDP (4.5 ± 2.1 SLNs vs 3.6 ± 1.6, p < 0.0001) and more SLN were removed in hemipelvises with atypical LDP (2.4 ± 1.8 SLNs vs 1.8 ± 1.1, p < 0.0001).

In this cohort of 326 patients with 1104 detected SLNs, 68 positive SLNs (6.3%) were found in 53 patients (16.3%) (Table 1). Eleven patients had 2 positive SLNs and 2 patients had 3 positives SLNs. Eleven patients had bilateral positive SLNs. Among the 68 positive SLNs, 31 were macrometastasis (45.6%), 19 were micrometastasis (27.9%) and 18 were isolated Tumoral cells (ITCs) (26.5%). Positive SLNs were mainly found in interiliac and external iliac area (60/68, 88.2%), whereas there were only 3 positive SLNs in the parametrial area (3/68, 4.4%), 1 positive SLN in the promontory area (1/68, 1.5%) and 1 positive SLN in the paraaortic area (1/68, 1.5%). Three positive SLNs were located in the common iliac area (3/68, 4.4%): two were synchronous with a positive SLN in external area and one was isolated. There were no differences between patients without and with SLNs in atypical area in terms of rate of positive SLN and type of positive SLN. If only interiliac and external iliac area were harvested, 83.2% of SLN and 88.2% of metastatic SLN were found. In addition, if common iliac, parametrial and promontory areas were also harvested, 97.9% of SLN and 98.6% of metastatic SLN were found.

In the subgroup of 80 patients with at least one atypical LDP, 20 SLNs were positive in 15 patients (4.6%). Among these 20 positive SLNs, 6 positive SLNs were located in atypical areas. Among these 15 patients with positive SLNs, 6 patients had positive SLNs in atypical areas, including 3 patients who had exclusively positive SLNs in atypical area (Table 2).

3.3. Patients-specific analysis

Thirty-five patients (10.7%) had atypical SLN without SLN in typical area on one or both sides. In univariate analysis, the factors which were significantly associated with an exclusive atypical LDP on one or both sides were the parity and the tumor size (Table 3). Nulliparous patients had significantly more exclusive atypical LDP (22/87, 25.3%) than multiparous patients (13/239, 5.4%), p < 0.0001. In patients with exclusive atypical LDP, the rate of tumor larger than 20 mm was significantly higher (42.3% vs 18.4%, p = 0.0004). BMI and the type of surgical approach may have an impact but did not reach statistical significance rate. Less exclusive atypical LDP tended to be found in patients with BMI > 25 kg/m^2 (5/91, 5.5%) than in patients with BMI ≤ 25 kg/m^2 (30/234, 12.8%), p = 0.06. More exclusive atypical LDP seemed to be found in patients operated by minimal invasive approach (35/299, 11.7%) than by open surgery (0/26, 0%), p = 0.06.

In multivariate analysis, tumor size ≥20 mm appeared as an independent factor of having at least one exclusive atypical LDP (ORa = 3.95 95%CI = [1.60–9.78], p = 0.003) (Table 4). Multiparity and BMI ≥ 25 kg/m^2 decreased significantly the probability of having at least one exclusive atypical LDP (ORa = 0.16 95%CI = [0.07–0.39], p < 0.0001 and ORa = 0.17 95%CI = [0.03–0.9], p = 0.04 respectively).

3.4. Side-specific analysis

Among the 652 hemipelvises assessable, exclusive atypical LDP were found in 38 hemi-pelvises (5.8%). As previously found in patients-specific analysis, results of the univariate analysis confirmed a significative association between exclusive atypical LDP in each side with nulliparity and tumor size larger than 20 mm (Table 5). Moreover, less exclusive atypical LDP were significantly retrieved in each hemipelvis in patients with BMI > 25 kg/m^2 (5/182, 2.7%) than in patients with BMI ≤ 25 kg/m^2 (33/468, 7.1%), p = 0.04. The same trend with minimal invasive approach was also found without reaching statistical significance rate. Furthermore, parametrial and vaginal invasion tended to be more frequent in hemipelvises with exclusive atypical LDP (10.7% vs 3.9%, p = 0.08 and 10.7% vs 4%, p = 0.09 respectively).

By multivariate analysis, variable which were independently associated with exclusive atypical LDP in each hemipelvis were parity and tumor size (Table 6). The rate of exclusive atypical LDP by side was decreased in case of multiparity (ORa = 0.17, 95%CI = [0.07–0.39], p < 0.0001). Tumor size larger than 20 mm increased the probability of exclusive atypical LDP in each hemipelvis (ORa = 2.52, 95%CI = [1.04–6.10], p = 0.04). BMI > 25 kg/m^2 tended to decrease the incidence of exclusive atypical LDP in each hemipelvis but this variable did not reach significativity (p = 0.06).

4. Discussion

Through this prospective cohort of 326 patients, this study shows that atypical LDP of the uterine cervix concerns up to 24.5% of patients with early-stage cervical cancer and 8.9% of positive SLNs are found in atypical area. To our best knowledge, the present study is the first study that precisely assesses predictive factors of atypical LDP. Over the last century, many classifications of uterine lymphatic drainage have been described [11–17]. Although the terminology is different according to the authors, all these works support the concept of concomitant atypical lymphatic drainage. More recently, Geppert et al. suggested a uterine lymphatic drainage pathway classification based on SLN mapping in endometrial cancer [11]. They injected ICG into the cervix or the uterine fundus. They distinguished the upper paracervical pathway (UPP), the lower paracervical pathway (LPP) and the Infundibulo-pelvic pathway (IPP). The UPP follows the uterine artery and drains to external and/or obturator lymph nodes with a continued course lateral to the common iliac artery and then to the lateral precaval and paraaortic areas. The LPP goes through the sacrouterine ligament to the internal iliac and/or presacral draining nodes before continuing medial to the common iliac artery and then to the medial paraaortic and precaval areas. The IPP has a course along the fallopian tube and upper broad ligament via the Infundibulo-pelvic ligament to its origin.

Ouldamer et al. performed a meta-analysis to determine the frequency of atypical localizations of SLNs in patients with early-stage cervical cancer [18]. They analyzed 27 articles which included 1301 patients with 3012 SLNs. They showed that 83.7% of SLNs were found in classic areas of the pelvis (obturator, external iliac, and internal iliac), 6.6% in the common iliac area, 4.3% in the parametrial area, 2.0% in the paraaortic area, 1.3% in the presacral area, 0.2% in the hypogastric area, 0.07% in the inguinal area, and 0.07% in the cardinal ligament area. Their results were in accordance with ours. We did not find any SLNs in the inguinal area or in the circumflex iliac area as described by Takeshita et al. [19].

Table 4
Multivariate analysis of predictive factors of having at least one SLN in atypical area per patients.

Variable	ORa	IC 95%	p
BMI [kg/m^2]			
≤25	1		
>25	0.17	0.03–0.9	0.04
Parity			
0	1		
≥1	0.16	0.07–0.39	<0.0001
Type of surgical approach			
Minimal invasive surgery	1		
Laparotomy	0.41	0.02–7.87	0.56
Tumor size			
<20 mm	1		
≥20 mm	3.95	1.60–9.78	0.003

We highlighted that tumor size ≥20 mm have an impact on lymphatic drainage pathway in early-stage cervical cancer. In a retrospective cohort of 350 patients, Dostalek et al. assessed SLN biopsy in cervical tumors in 3 subgroups of <20 mm, 20–39 mm and ≥40 mm tumor size. They shew that bilateral detection rate and false negative rate were similar between the 3 subgroups and concluded that SLN biopsy was reliable in lymph node staging in tumors larger than 20 mm [20]. Lymphatic vessels may be obstructed by cancer cells and it may result in a modification of tumor lymphatic drainage. Furthermore, large tumors can have a central necrotic part that may alter the diffusion of patent blue or/and radiocolloid [21]. Tumor cells migration could use other lymphatic drainage pathway than that run to interiliac or external iliac area. This theory may explain that parametrial invasion tended to be more frequent in case of SLNs in atypical area, although this difference did not reach statistical significance.

Surprisingly, we found that multiparity decreased significantly the rate of SLNs identified in atypical area. During pregnancy, uterine vascular and lymphatic network is modified [22]. This phenomenon was already described by Cuneo and Marcille in 1901 and they described that in non-pregnant uterus, lymphatics vessels were very thin but during gestation they were hyperplasic [12]. Volchek et al. suggested that during pregnancy, endometrial stromal cell decidualization may involve in loss of lymphatics in decidua especially around the spiral arteries but lymphatics vessels were still present and larger in the non-decidualized

Table 5
Univariate analysis of predictive factors of having at least one atypical SLNs per side.

Predictive variable	Total side N = 652		Side with classic LDP N = 614		Side with exclusive atypical LDP N = 38		p
	n Mean ± SD	[%] [range]	n Mean ± SD	[%] [range]	n Mean ± SD	[%] [range]	
Age [years]							
Mean	43.6 ± 11.8	[22–85]	43.6 ± 11.7	[22–85]	43.6 ± 13.3	[22–79]	0.98
<50	496	76.1	468	76.2	28	73.7	0.72
50–70	136	20.9	128	20.8	8	21.1	
≥70	20	3.1	18	2.9	2	5.3	
BMI [kg/m^2]							
Mean	23.6 ± 5.0	[14.6–42.2]	23.7 ± 5.0	[14.6–42.2]	23.0 ± 4.9	[16–31.1]	0.11
≤25	468/650	72	435/612	71.1	33	86.8	0.04
>25	182/650	28	177/612	28.9	5	13.2	
Parity							
0	174	26.7	150	24.4	24	63.2	<0.0001
≥1	478	73.3	464	75.6	14	36.8	
Menopausal status							
Yes	176	27.0	166	27.0	10	26.3	0.92
No	476	73.0	448	73.0	28	73.7	
History of previous pelvic surgery							
0	360	55.2	336	54.7	24	63.2	0.31
≥1	292	44.8	278	45.3	14	36.8	
FIGO stage							
IA1 with emboli – IA2	70/628	11.1	67/593	11.3	3/35	8.6	0.60
IB1	546/628	86.9	514/593	86.7	32/35	91.4	
IIA	12/628	1.9	12/593	2.0	0/35	0.0	
Histology							
Squamous cell carcinoma	432/620	69.7	407/585	69.6	25/35	71.4	0.65
Adenocarcinoma	174/620	28.1	164/585	28.0	10/35	28.6	
Other type	14/620	2.3	14/585	2.4	0/35	0.0	
Preoperative LEEP							
Yes	386/620	62.3	365/585	62.4	21/35	60.0	0.78
No	234/620	37.7	220/585	37.6	14/35	40.0	
Preoperative brachytherapy							
Yes	134/500	26.8	128/476	26.9	6/24	25.0	0.84
No	366/500	73.2	348/476	73.1	18/24	75.0	
Type of surgical approach							
Minimal invasive surgery	598/650	92.0	560/612	91.5	38	100.0	0.06
Laparotomy	52/650	8.0	52/612	8.5	0	0.0	
Node status							
Patients with positive SLN							0.88
Yes	64	9.8	60	9.8	4	10.5	
No	588	90.2	554	90.2	34	89.5	
Final pathologic exam							
Tumor size							
<20 mm	448/561	79.9	432	81.4	16/30	53.3	0.0002
≥20 mm	113/561	20.1	99	18.6	14/30	46.7	
LVSI							
Yes	174/584	29.8	166/555	29.9	8/29	27.6	0.79
No	410/584	70.2	389/555	70.1	21/29	72.4	
Parametrial invasion							
Yes	24/566	4.2	21/538	3.9	3/28	10.7	0.08
No	542/566	95.8	517/538	96.1	25/28	89.3	
Vaginal invasion							
Yes	24/552	4.3	21/524	4.0	3/28	10.7	0.09
No	528/552	95.7	503/524	96.0	25/28	89.3	
Positive margin							
Yes	28/564	5.0	24/536	4.5	4/28	14.3	0.02
No	536/564	95.0	512/536	95.5	24/28	85.7	

Table 6
Multivariate analysis of predictive factors of having at least one SLN in atypical area per side.

Variable	ORa	IC 95%	p
BMI [kg/m^2]			
≤25	1		
>25	0.21	0.04–1.06	0.06
Parity			
0	1		
≥1	0.17	0.07–0.39	<0.0001
Type of surgical approach			
Minimal invasive surgery	1		
Laparotomy	0.41	0.02–7.22	0.54
Tumor size			
<20 mm	1		
≥20 mm	2.52	1.04–6.10	0.04
Parametrial invasion			
No	1		
Yes	3.07	0.49–19.07	0.23
Vaginal invasion			
No	1		
Yes	1.51	0.22–10.27	0.67

hypersecretory endometrium [23]. Some authors provided evidence about the relation between lymphangiogenesis and lymphatic spread in endometrial cancer [24,25]. We feel that all these complex mechanisms associated with lymphatic vessels modification during pregnancy may have an impact on lymphatic drainage pathway in cervical cancer as suggested our results.

According to our results, BMI ≥ 25 kg/m^2 decreased significantly the rate of SLNs identified in atypical area. Independently of the technique of SLN detection (Fluorescent with Indocyanine green (ICG) or colorimetric with blue dye), Eriksson et al. showed that increasing BMI were significantly associated with a decreasing of bilateral detection of SLNs in patients with uterine cancer but ICG would provide better results than blue dye in the specific population of obese patients [26]. Due to the period of both studies SENTICOL I and II, our patients had SLN detection technique with combined labeling technique (blue dye and radiotracer) and not ICG. This point constitutes one of the limitations of our study. Recently, the FILM trial has proven that ICG should become the gold-standard for SLN mapping in uterine cancer [27]. In fact, we support the idea that less SLNs were found in atypical area in case of BMI ≥ 25 kg/m^2 because less SLNs may have been globally found in this group of patients due to the fact that visualization of all areas may be suboptimal and the thick layer of retroperitoneal fat may obscure channels.

Another limitation is the retrospective analysis of two databases which were not designed to our specific objectives. However, all data related to SLNs localization were prospectively recorded in a quality-checked database and patients came from multiple expert centers with high surgical skills in SLN biopsy.

Our findings stress the importance of SLN biopsy in the detection of metastatic nodes in aberrant topography that would not be removed during routine pelvic lymphadenectomy. This technique may reduce the false-negative case of lymph node staging and residual disease missing which leads to an undertreatment of patients.

To improve the identification of SLNs in unexpected sites, we suggest opening first the entire retroperitoneal space along the external iliac vessels and to identify the ureter and the obliterated umbilical artery. This approach allows observing the early drainage from the cervix through the parametrium by following the dye progression in the channels before any node is taken to ensure that the true draining SLN is identified and not missed. Although the false negative rate may be limited by increasing the number of SLNs sampled especially in teams with low experience, not all detected nodes (blue and/or hot SLN) should be taken but only the first draining node in the channel pathway has to be removed and labeled as SLN. This strategy permits to perform a real SLN-mapping and avoids considering as SLNs non-SLNs which correspond in fact to distal migration of tracer beyond the true SLN. However, in case of truly separate channels which may correspond to distinct LDP, more SLNs should be sample. If no SLNs are found in the external iliac, interiliac and common iliac area, dissection of the promontory area and paraaortic area should be performed to avoid missing SLN in atypical topography.

5. Conclusion

In patients with early-stage cervical cancer, most of SLNs are found in expected areas but atypical LDP of the uterine cervix concerns up to 24.5% of these patients. Tumor size larger than 20 mm and nulliparity increase the risk of having exclusive atypical LDP in early-stage cervical cancer.

Author contribution

Study concepts	Balaya V., Mathevet P., Bats AS., Lécuru F.
Study design	Balaya V., Mathevet P., Bats AS., Lécuru F.
Data acquisition	Mathevet P., Lécuru F., Bats AS., Magaud L.,
Quality control of data and algorithms	Magaud L., Lécuru F., Mathevet P., Balaya V., Ngô C.
Data analysis and interpretation	Balaya V., Lécuru F., Mathevet P., Bats AS., Bonsang-Kitzis H., Delomenie M., Montero Macias R.
Statistical analysis	Bonsang-Kitzis H., Balaya V.
Manuscript preparation	Balaya V., Lécuru F. Mathevet P.
Manuscript editing	Balaya V., Lécuru F., Delomenie M., Ngô C., Bats AS. Bonsang-Kitzis H., Montero Macias R.
Manuscript review	Lécuru F., Bats AS., Mathevet P.

Conflict of interest

None.

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