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

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

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

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

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

59 **Results:** Between January 2005 and July 2012, 326 patients with 1104 intraoperative detected SLNs
60 fulfilled the inclusion criteria. The SLNs were mainly located in the interiliac or external iliac area in
61 83.2%. The other localizations were: 9.2% in the common iliac area, 3.9% in the parametrium, 1.6% in
62 the promontory area, 1.5% in the paraaortic area and 0.5% in other areas. Thirty-five patients (10.7%)
63 had atypical SLN without SLN in typical area on one or both sides. In multivariate analysis, tumor size
64 ≥ 20 mm appeared as an independent factor of having at least one exclusive atypical LDP (ORa =
65 3.95 95%CI = [1.60 – 9.78], $p = 0.003$). Multiparity decreased significantly the probability of having at
66 least one exclusive atypical LDP (ORa = 0.16 95%CI = [0.07 – 0.39], $p < 0.0001$).

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

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71 **Key-words:** « Cervical cancer », « Sentinel Lymph Node », « Lymphatic drainage »,
72 « SENTICOL », « Radical hysterectomy »

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74

75 **Introduction**

76

77 Cervical cancer is the second most common cancer among women and the third cause of
78 cancer-related deaths in females with approximately 527 600 new cases and 265 700 deaths each
79 year (1). Lymph node involvement is one of the main major prognosis factors for early-stage cervical
80 cancer (2,3). According to main guidelines (4,5), surgery is the preferred treatment for early-stage
81 cervical cancer (up to FIGO stage IIA1), especially in young patients. Lymph node staging is
82 performed to assess the prognosis and guide the treatment (5). Considering that pelvic
83 lymphadenectomy generates several complications, the sentinel lymph node (SLN) technique has
84 been introduced for 20 years and is increasingly used in cervical cancer. One of the interests of SLN is
85 to highlight the aberrant drainage territories that are not systematically dissected during routine
86 lymphadenectomies (6). Although most of SLNs are located in the interiliac and external ilac area,
87 SLNs have also been described in “unexpected” territories such as sacral, promontory and paraaortic
88 areas (7).

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

92

93 **Material and methods**

94

95 **Population study**

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

101 Briefly, SENTICOL I was a prospective multicenter study assessing the diagnostic value of SLN
102 biopsy in early-stage cervical cancer. One hundred and forty-five patients were enrolled between
103 January 2005 and May 2007 and a systematic pelvic lymphadenectomy was performed after SLN
104 biopsy as well as lymphadenectomy of areas containing one or more SLNs (12). SENTICOL II was a

105 prospective randomized multicenter study assessing morbidity and quality of life(13). Two hundred
106 and sixty-seven patients were enrolled and 206 patients with negative SLN at frozen-section
107 examination were randomised between SLN biopsy only (105 patients) or SLN biopsy with additional
108 pelvic lymphadenectomy (101 patients).

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

116

117 **Data analysis**

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

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

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

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

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

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

155

156 **Statistical analysis**

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

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

163 Variables yielding p values lower than 0.2 by univariate analysis were entered into a multivariate
164 logistic regression model to determine variables independently associated with the presence or not of

165 exclusive atypical LDP. Values of p lower than 0.05 were considered as significant.

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

168 **Results**

169
170 Between January 2005 and July 2012, 412 patients were enrolled in the both studies: 145 in
171 SENTICOL I and 267 in SENTICOL II. Three hundred and twenty-six patients had bilateral SLN
172 detection and were finally included for analysis.

173

174 **Patient and surgical characteristics**

175 The median age was 41.5 years [22 – 85 years] and the median Body-Mass Index (BMI) was
176 22.6 kg/m² [14.6 – 42.2 kg/m²]. Eighty-seven patients (26.7%) were nulliparous. Most of the patients
177 had FIGO stage IB1 disease (273 patients, 83.7%). The majority of patients had squamous cell
178 carcinoma (216 patients, 66.3%). Thirty-three patients (10.1%) had only lymph node staging, 4
179 patients (1.2%) a simple trachelectomy, 53 patients (16.3%) a radical trachelectomy, 10 patients
180 (3.1%) a simple hysterectomy and 226 (69.3%) a radical hysterectomy. At final pathologic
181 examination, 58 patients (20.6%) had a tumor size larger than 20 mm. There were a parametrial
182 spread in 12 patients (3.7%), a vaginal spread in 12 patients (3.7%) and positive surgical margin in 14
183 patients (4.3%).

184

185 **SLNs topography and status**

186 In 326 patients, 1104 SLNs were detected and removed (Table 1). The mean number of
187 removed SLN per patient was 3.8 ± 1.8 [2-11] and per hemipelvis was 1.9 ± 1.3 [1-9]. SLNs were
188 mainly located in the interiliac or external iliac area (918/1104, 83.2%). One hundred and two SLNs
189 (9.2%) were found in common iliac area. Among them, 62 common iliac SLNs were associated with
190 SLNs in the interiliac or external iliac area and therefore were considered as following classical
191 lymphatic drainage pathway whereas 40 common iliac SLNs were isolated and were considered as
192 atypical. In addition to that, 33 SLNs were specifically located in the parametrium (3.9%), 18 SLNs in

193 the promontory area (1.6%) and 17 SLNs (1.5%) were isolated in the paraaortic area. Three SLNs
194 were identified in the right paracervix 0.3%. The topography of 3 SLNs was not precised. The majority
195 of patients had exclusively bilateral classic LDP (246 patients, 75.5%) whereas 80 patients (24.5%)
196 had at least one atypical LDP. In this subgroup of 80 patients, 45 patients (13.8%) had classic LDP
197 associated with atypical LDP on one or both sides, 32 patients (9.8%) had exclusively atypical LDP on
198 one side and 3 patients (0.9%) had exclusively atypical LDP on both sides. Among the 652
199 hemipelvises assessable, 93 hemipelvises (14.3%) had at least one atypical LDP. Among these 93
200 hemipelvises, 36 hemipelvises had exclusively atypical LDP. Significantly more SLNs were removed in
201 patients with atypical LDP (4.5 ± 2.1 SLNs vs 3.6 ± 1.6 , $p < 0.0001$) and more SLN were removed in
202 hemipelvises with atypical LDP (2.4 ± 1.8 SLNs vs 1.8 ± 1.1 , $p < 0.0001$).

203 In this cohort of 326 patients with 1104 detected SLNs, 68 positive SLNs (6.3%) were found in
204 53 patients (16.3%) (Table 1). Eleven patients had 2 positive SLNs and 2 patients had 3 positives
205 SLNs. Eleven patients had bilateral positive SLNs. Among the 68 positive SLNs, 31 were
206 macrometastasis (45.6%), 19 were micrometastasis (27.9%) and 18 were isolated Tumoral cells
207 (ITCs) (26.5%). Positive SLNs were mainly found in interiliac and external iliac area (60/68, 88.2%),
208 whereas there were only 3 positive SLNs in the parametrial area (3/68, 4.4%), 1 positive SLN in the
209 promontory area (1/68, 1.5%) and 1 positive SLN in the paraaortic area (1/68, 1.5%). Three positive
210 SLNs were located in the common iliac area (3/68, 4.4%): two were synchronous with a positive SLN
211 in external area and one was isolated. There were no differences between patients without and with
212 SLNs in atypical area in terms of rate of positive SLN and type of positive SLN. If only interiliac and
213 external iliac area were harvested, 83.2% of SLN and 88.2% of metastatic SLN were found. In
214 addition, if common ilac, parametrial and promontory areas were also harvested, 97.9% of SLN and
215 98.6% of metastatic SLN were found.

216 In the subgroup of 80 patients with at least one atypical LDP, 20 SLNs were positive in 15
217 patients (4.6%). Among these 20 positive SLNs, 6 positive SLNs were located in atypical areas.
218 Among these 15 patients with positive SLNs, 6 patients had positive SLNs in atypical areas, including
219 3 patients who had exclusively positive SLNs in atypical area (Table 2).

220

221 **Patients-specific analysis**

222 Thirty-five patients (10.7%) had atypical SLN without SLN in typical area on one or both sides.

223 In univariate analysis, the factors which were significantly associated with an exclusive atypical LDP
224 on one or both sides were the parity and the tumor size (Table 3). Nulliparous patients had
225 significantly more exclusive atypical LDP (22/87, 25.3%) than multiparous patients (13/239, 5.4%), p
226 <0.0001 . In patients with exclusive atypical LDP, the rate of tumor larger than 20 mm was significantly
227 higher (42.3% vs 18.4%, $p = 0.0004$). BMI and the type of surgical approach may have an impact but did
228 not reach statistical significance rate. Less exclusive atypical LDP tended to be found in patients with
229 BMI $> 25 \text{ kg/m}^2$ (5/91, 5.5%) than in patients with BMI $\leq 25 \text{ kg/m}^2$ (30/234, 12.8%), $p = 0.06$. More
230 exclusive atypical LDP seemed to be found in patients operated by minimal invasive approach
231 (35/299, 11.7%) than by open surgery (0/26, 0%), $p = 0.06$.

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

237

238 Side-specific analysis

239 Among the 652 hemipelvises assessable, exclusive atypical LDP were found in 38 hemi-
240 pelvises (5.8%). As previously found in patients-specific analysis, results of the univariate analysis
241 confirmed a significative association between exclusive atypical LDP in each side with nulliparity and
242 tumor size larger than 20 mm (Table 5). Moreover, less exclusive atypical LDP were significantly
243 retrieved in each hemipelvis in patients with BMI $> 25 \text{ kg/m}^2$ (5/182, 2.7%) than in patients with BMI
244 $\leq 25 \text{ kg/m}^2$ (33/468, 7.1%), $p = 0.04$. The same trend with minimal invasive approach was also found
245 without reaching statistical significance rate. Furthermore, parametrial and vaginal invasion tended to
246 be more frequent in hemipelvises with exclusive atypical LDP (10.7% vs 3.9%, $p = 0.08$ and 10.7% vs
247 4%, $p = 0.09$ respectively).

248 By multivariate analysis, variable which were independently associated with exclusive atypical
249 LDP in each hemipelvis were parity and tumor size (Table 6). The rate of exclusive atypical LDP by
250 side was decreased in case of multiparity (ORa = 0.17, 95%CI = [0.07 – 0.39], $p < 0.0001$). Tumor size
251 larger than 20 mm increased the probability of exclusive atypical LDP in each hemipelvis (ORa = 2.52,
252 95%CI = [1.04 – 6.10], $p = 0.04$). BMI $> 25 \text{ kg/m}^2$ tended to decrease the incidence of exclusive

253 atypical LDP in each hemipelvis but this variable did not reach significance ($p= 0.06$).

254

255 Discussion

256

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

272 Ouldamer et al. performed a meta-analysis to determine the frequency of atypical localizations
273 of SLNs in patients with early-stage cervical cancer (18). They analyzed 27 articles which included
274 1301 patients with 3012 SLNs. They showed that 83.7% of SLNs were found in classic areas of the
275 pelvis (obturator, external iliac, and internal iliac), 6.6% in the common iliac area, 4.3% in the
276 parametrial area, 2.0% in the paraaortic area, 1.3% in the presacral area, 0.2% in the hypogastric
277 area, 0.07% in the inguinal area, and 0.07% in the cardinal ligament area. Their results were in
278 accordance with ours. We did not find any SLNs in the inguinal area or in the circumflex iliac area as
279 described by Takeshita et al. (19).

280 We highlighted that tumor size ≥ 20 mm have an impact on lymphatic drainage pathway in
281 early-stage cervical cancer. In a retrospective cohort of 350 patients, Dostalek et al. assessed SLN

282 biopsy in cervical tumors in 3 subgroups of < 20 mm, 20-39 mm and \geq 40 mm tumor size. They shew
283 that bilateral detection rate and false negative rate were similar between the 3 subgroups and
284 concluded that SLN biopsy was reliable in lymph node staging in tumors larger than 20 mm (20).
285 Lymphatic vessels may be obstructed by cancer cells and it may result in a modification of tumor
286 lymphatic drainage. Furthermore, large tumors can have a central necrotic part that may alter the
287 diffusion of patent blue or/and radiocolloid (21). Tumor cells migration could use other lymphatic
288 drainage pathway than that run to interiliac or external iliac area. This theory may explain that
289 parametrial invasion tended to be more frequent in case of SLNs in atypical area, although this
290 difference did not reach statistical significance.

291 Surprisingly, we found that multiparity decreased significantly the rate of SLNs identified in
292 atypical area. During pregnancy, uterine vascular and lymphatic network is modified (22). This
293 phenomenon was already described by Cuneo and Marcille in 1901 and they described that in non-
294 pregnant uterus, lymphatics vessels were very thin but during gestation they were hyperplastic (12).
295 Volchek et al. suggested that during pregnancy, endometrial stromal cell decidualization may involve
296 in loss of lymphatics in decidua especially around the spiral arteries but lymphatics vessels were still
297 present and larger in the non-decidualized hypersecretory endometrium (23). Some authors provided
298 evidence about the relation between lymphangiogenesis and lymphatic spread in endometrial cancer
299 (24,25). We feel that all these complex mechanisms associated with lymphatic vessels modification
300 during pregnancy may have an impact on lymphatic drainage pathway in cervical cancer as suggested
301 our results.

302 According to our results, BMI \geq 25 kg/m² decreased significantly the rate of SLNs identified in
303 atypical area. Independently of the technique of SLN detection (Fluorescent with Indocyanine green
304 (ICG) or colorimetric with blue dye), Eriksson et al. showed that increasing BMI were significantly
305 associated with a decreasing of bilateral detection of SLNs in patients with uterine cancer but ICG
306 would provide better results than blue dye in the specific population of obese patients (26). Due to the
307 period of both studies SENTICOL I and II, our patients had SLN detection technique with combined
308 labeling technique (blue dye and radiotracer) and not ICG. This point constitutes one of the limitations
309 of our study. Recently, the FILM trial has proven that ICG should become the gold-standard for SLN
310 mapping in uterine cancer (27). In fact, we support the idea that less SLNs were found in atypical area
311 in case of BMI \geq 25 kg/m² because less SLNs may have been globally found in this group of patients

312 due to the fact that visualization of all areas may be suboptimal and the thick layer of retroperitoneal
313 fat may obscure channels.

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

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

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

335

336 **Conclusion**

337

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

341

342 Author contribution

343 Study concepts: Balaya V., Mathevet P., Bats AS., Lécuru F.
344 Study design: Balaya V., Mathevet P., Bats AS., Lécuru F.
345 Data acquisition : Mathevet P., Lécuru F., Bats AS., Magaud L.,
346 Quality control of data and algorithms: Magaud L., Lécuru F., Mathevet P., Balaya V.,
347 Ngô C.
348 Data analysis and interpretation: Balaya V., Lécuru F., Mathevet P., Bats AS.,
349 Bonsang-Kitzis H., Delomenie M.,
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351 Statistical analysis: Bonsang-Kitzis H., Balaya V.
352 Manuscript preparation: Balaya V., Lécuru F. Mathevet P.
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355 Manuscript review: Lécuru F., Bats AS., Mathevet P.
356

357 Conflict of Interest: none

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359 REFERENCES

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- 361
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- 362 1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA*
363 *Cancer J Clin.* 2015 Mar;65(2):87–108.
364 2. Benedetti-Panici P, Maneschi F, Scambia G, Greggi S, Cutillo G, D’Andrea G, et al. Lymphatic spread
365 of cervical cancer: an anatomical and pathological study based on 225 radical hysterectomies with systematic
366 pelvic and aortic lymphadenectomy. *Gynecol Oncol.* 1996 Jul;62(1):19–24.
367 3. Ho C-M, Chien T-Y, Huang S-H, Wu C-J, Shih B-Y, Chang S-C. Multivariate analysis of the
368 prognostic factors and outcomes in early cervical cancer patients undergoing radical hysterectomy. *Gynecol*
369 *Oncol.* 2004 May;93(2):458–64.
370 4. Marth C, Landoni F, Mahner S, McCormack M, Gonzalez-Martin A, Colombo N. Cervical cancer:
371 ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2017 Jul
372 1;28(suppl_4):iv72-iv83.
373 5. Cibula D, Pötter R, Planchamp F, Avall-Lundqvist E, Fischerova D, Haie Meder C, et al. The European
374 Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology/European Society of
375 Pathology Guidelines for the Management of Patients With Cervical Cancer. *Int J Gynecol Cancer.* 2018
376 May;28(4):641.
377 6. Bats A-S, Mathevet P, Buenerd A, Orliaguet I, Mery E, Zerdoud S, et al. The sentinel node technique
378 detects unexpected drainage pathways and allows nodal ultrastaging in early cervical cancer: insights from the
379 multicenter prospective SENTICOL study. *Ann Surg Oncol.* 2013 Feb;20(2):413–22.
380 7. Marnitz S, Köhler C, Bongardt S, Braig U, Hertel H, Schneider A, et al. Topographic distribution of
381 sentinel lymph nodes in patients with cervical cancer. *Gynecol Oncol.* 2006 Oct;103(1):35–44.
382 8. Lécuru F, Mathevet P, Querleu D, Leblanc E, Morice P, Daraï E, et al. Bilateral negative sentinel nodes
383 accurately predict absence of lymph node metastasis in early cervical cancer: results of the SENTICOL study. *J*
384 *Clin Oncol Off J Am Soc Clin Oncol.* 2011 May 1;29(13):1686–91.
385 9. Mathevet P, Lécuru F, Magaud L, Bouttitie F. Sentinel lymph node biopsy for early cervical cancer:
386 Results of a randomized prospective, multicenter study (Senticol 2) comparing adding pelvic lymph node
387 dissection vs sentinel node biopsy only. *Gynecol Oncol.* 2017 Jun;145, Supplement 1:2–3.
388 10. Hermanek P, Hutter RV, Sobin LH, Wittekind C. International Union Against Cancer. Classification of

389 isolated tumor cells and micrometastasis. *Cancer*. 1999 Dec 15;86(12):2668–73.

390 11. Geppert B, Lönnerfors C, Bollino M, Arechvo A, Persson J. A study on uterine lymphatic anatomy for
391 standardization of pelvic sentinel lymph node detection in endometrial cancer. *Gynecol Oncol*.
392 2017;145(2):256–61.

393 12. Cunéo B, Marcille M. Topographie des ganglions ilio-pelviens. *Bull Mem Soc Anat, Paris, G Steinheil*
394 1901; 3: 653–663.

395 13. Leveuf J, Godard H. Les lymphatiques de l'utérus. *Rev Chir*. 61:219–48.

396 14. Lécuru F, Neji K, Robin F, Darles C, Bièvre P de, Taurrelle R. Drainage lymphatique de l'utérus. *J*
397 *Gynécologie Obstétrique Biol Reprod*. 2008 Aug 3;26(4):418.

398 15. Ercoli A, Delmas V, Iannone V, Fagotti A, Fanfani F, Corrado G, et al. The lymphatic drainage of the
399 uterine cervix in adult fresh cadavers: anatomy and surgical implications. *Eur J Surg Oncol J Eur Soc Surg*
400 *Oncol Br Assoc Surg Oncol*. 2010 Mar;36(3):298–303.

401 16. Bonneau C, Cortez A, Lis R, Mirshahi M, Fauconnier A, Ballester M, et al. Lymphatic and nerve
402 distribution throughout the parametrium. *Gynecol Oncol*. 2013 Dec;131(3):708–13.

403 17. Kraima AC, Derks M, Smit NN, Van Munsteren JC, Van der Velden J, Kenter GG, et al. Lymphatic
404 drainage pathways from the cervix uteri: implications for radical hysterectomy? *Gynecol Oncol*. 2014
405 Jan;132(1):107–13.

406 18. Ouldamer L, Marret H, Acker O, Barillot I, Body G. Unusual localizations of sentinel lymph nodes in
407 early stage cervical cancer: a review. *Surg Oncol*. 2012 Sep;21(3):e153-157.

408 19. Takeshita S, Todo Y, Okamoto K, Sudo S, Yamashiro K, Kato H. Incidence of metastasis in circumflex
409 iliac nodes distal to the external iliac nodes in cervical cancer. *J Gynecol Oncol*. 2016 Jul;27(4):e42.

410 20. Dostálek L, Zikan M, Fischerova D, Kocian R, Germanova A, Frühauf F, et al. SLN biopsy in cervical
411 cancer patients with tumors larger than 2cm and 4cm. *Gynecol Oncol*. 2018;148(3):456–60.

412 21. Red-Horse K. Lymphatic vessel dynamics in the uterine wall. *Placenta*. 2008 Mar;29 Suppl A:S55-59.

413 22. Volchek M, Girling JE, Lash GE, Cann L, Kumar B, Robson SC, et al. Lymphatics in the human
414 endometrium disappear during decidualization. *Hum Reprod Oxf Engl*. 2010 Oct;25(10):2455–64.

415 23. Koukourakis MI, Giatromanolaki A, Sivridis E, Simopoulos C, Gatter KC, Harris AL, et al. LYVE-1
416 immunohistochemical assessment of lymphangiogenesis in endometrial and lung cancer. *J Clin Pathol*. 2005
417 Feb;58(2):202–6.

418 24. He Y, Rajantie I, Ilmonen M, Makinen T, Karkkainen MJ, Haiko P, et al. Preexisting lymphatic
419 endothelium but not endothelial progenitor cells are essential for tumor lymphangiogenesis and lymphatic
420 metastasis. *Cancer Res*. 2004 Jun 1;64(11):3737–40.

421 25. Eriksson AGZ, Montovano M, Beavis A, Soslow RA, Zhou Q, Abu-Rustum NR, et al. Impact of
422 Obesity on Sentinel Lymph Node Mapping in Patients with Newly Diagnosed Uterine Cancer Undergoing
423 Robotic Surgery. *Ann Surg Oncol*. 2016 Aug;23(8):2522–8.

424 26. Frumovitz M, Plante M, Lee PS, Sandadi S, Lilja JF, Escobar PF, et al. The FILM Trial: A randomized
425 phase III multicenter study assessing near infrared fluorescence in the identification of sentinel lymph nodes
426 (SLN). *Gynecol Oncol*. 2018 Jun 1;149:7.

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Predictive variable	PATIENT-SPECIFIC						SIDE-SPECIFIC					
	Total Patients N = 326 Total SLN N = 1104		Patients with no SLNs in atypical areas N = 246		Patients with at least one SLN in atypical areas N = 80		P	Side with no SLNs in atypical areas N = 559		Side with at least one SLN in atypical areas N = 93		P
	n	[%]	n	[%]	n	[%]		n	[%]	n	[%]	
Mean ± SD	[range]	Mean ± SD	[range]	Mean ± SD	[range]	Mean ± SD	[range]	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	<i>0.72</i>	17/17	100	0/1	0	
Common iliac area	1/18	5.6	0/12	0	1/6	16.7		0/17	0	1/1	100	<i>0.06</i>

Table 1. SLN status and topography

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

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

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	
50 – 70	68	20.9	61	21.0	7	20.0	0.63
≥ 70	10	3.1	8	2.7	2	5.7	
BMI [kg/m²]							
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	<i>0.94</i>
	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	<i>0.06</i>
	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	<i>0.88</i>
	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	<i>0.0004</i>
	≥ 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	<i>0.98</i>
	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	<i>0.36</i>
	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	<i>0.38</i>
	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	<i>0.1</i>
	No	268/282	95.0	245/256	95.7	23/26	88.5	

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/m²]			
≤ 25	1		
> 25	0.17	0.03 – 0.9	<i>0.04</i>
Parity			
0	1		
≥ 1	0.16	0.07 – 0.39	<i>< 0.0001</i>
Type of surgical approach			
Minimal Invasive Surgery	1		
Laparotomy	0.41	0.02 – 7.87	<i>0.56</i>
Tumor size			
< 20 mm	1		
≥ 20 mm	3.95	1.60 – 9.78	<i>0.003</i>

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	
50 – 70	136	20.9	128	20.8	8	21.1	0.72
≥ 70	20	3.1	18	2.9	2	5.3	
BMI [kg/m²]							
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							
Yes	64	9.8	60	9.8	4	10.5	0.88
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/m²]			
≤ 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