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## How to predict para-aortic node involvement in advanced cervical cancer? Development of a predictive score. A FRANCOGYN study

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# 1 **How to predict para-aortic node** 2 **involvement in advanced cervical cancer?** 3 **Development of a predictive score.**

## 4 **A FRANCOGYN study**

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35

36 **ABSTRACT**

37 Introduction - Node involvement is one of the main prognostic factors for cervical  
38 cancer. Para-aortic lymph node (PALN) assessment is crucial for treating advanced cervical  
39 cancer, to define irradiation fields. Objective of this study was to develop a score predicting  
40 para-aortic lymph node involvement in patients with advanced cervical cancer.

41 Patients and method – We performed a multicenter, retrospective, study on 9 French  
42 centers from 2000 to 2015, including patients with advanced squamous cell cervix carcinoma  
43 who had PALN status assessed by imaging and/or by surgery. Factors associated with a risk  
44 of PALN involvement were determined by univariate and multivariate analysis using a  
45 logistic regression model. A score was then developed and validated.

46 Results – A total of 1446 patients treated for cervical cancer were included. Of these,  
47 498 had an advanced squamous cell cervical cancer. Ninety-one patients (18.3%) had positive  
48 PALN. After univariate and multivariate analysis, tumor size on pelvic MRI, initial SCC, and  
49 suspected pelvic node involvement on PET-CT were included in our score. This model  
50 allowed the population to be divided into 3 risk groups. Area under the ROC curve of the  
51 score was 0.81 (95%CI=0.72 – 0.90). In the low-risk group, 9% (28/287) had PALN  
52 involvement, whereas in the high-risk group, 43% (22/51) had PALN involvement.

53 Conclusion – We developed a simple score predicting PALN involvement in advanced  
54 cervical cancers. Three risk groups can be defined, and patients considered to be at low risk  
55 may avoid para-aortic staging as well as extensive field irradiation.

56

57 Keywords: advanced cervical cancer, predictive model, para-aortic lymph node

## 58 **Introduction**

59 Node involvement is one of the main prognostic factor for cervical cancer, along with  
60 histological tumor size, depth of stromal invasion and presence of emboli [1].

61 Para-aortic lymph node (PALN) assessment is essential in treating advanced cervical  
62 cancer. Patients with positive lymph nodes can benefit from an extended-field radiation on the  
63 PALN [2,3] and it is of paramount importance to select patients who would most benefit from  
64 aortic irradiation. However, systematic irradiation of these nodes is associated with a  
65 significant increase in morbidity, with a risk of grade 3 and 4 toxicity according to Common  
66 Terminology Criteria For Adverse Events (CTCAE) classification of 15% (especially  
67 digestive toxicity) [4]. Two options, still debated, can be used for PALN assessment: surgical  
68 para-aortic lymphadenectomy, or the use of positron emission tomography-coupled computed  
69 tomography (PET-CT) imaging. However, these two techniques have several limitations. The  
70 main risk of PET-CT is its low sensitivity, estimated around 33% according to a multicentric  
71 study [5]. Due to the high risk of false negative, patients with a negative PET-CT should  
72 undergo a surgical para-aortic node staging. Current recommendations state that patients  
73 should undergo a PET-CT. In case of a PALN involvement, patients benefit from an extended  
74 field radiotherapy. In case of a negative PET-CT, patients should undergo a surgical para-  
75 aortic staging lymphadenectomy [2,6].

76 Surgical node staging is not devoid of risk and is associated with a high per-operative  
77 and post-operative morbidity [7]. Moreover, the benefit of removal of metastatic PALN on  
78 overall survival and recurrence-free survival has not been clearly demonstrated [8].

79 The current trend in the management of gynecological cancers is towards therapeutic  
80 de-escalation. The use of predictive models could be useful in predicting invasion of PALN,

81 avoiding staging surgery in low-risk patients and helping in the decision-making process of  
82 extended irradiation.

83 The objective of this study was to develop a score predicting PALN involvement in  
84 patients with advanced cervical cancer.

## 85 **Patients and method**

### 86 *Population*

87 We conducted a multicenter, retrospective study in 9 French centers (FRANCOGYN  
88 group) from 2000 to 2015 (Creteil University Hospital, Tenon University Hospital, Poissy  
89 University Hospital, Reims University Hospital, Lille University Hospital, Tours University  
90 Hospital, Bondy University Hospital, Rennes University Hospital, and Marseille Public  
91 Hospital North). Adult patients with advanced squamous cell carcinoma of the cervix  
92 (International federation of gynecology and obstetrics, FIGO 2009 Ib2 to IV stage), who had  
93 PALN status evaluated by imaging and/or by surgery staging between 2000 and 2015 were  
94 included. Patients with other histologic type, localized cervical cancer or without information  
95 on PALN involvement were excluded.

96 The research protocol was approved by the Institutional Review Board (IRB) of the  
97 French College of Obstetrics and Gynaecology (CEROG 2020-GYN-0601).

98

### 99 *Definitions*

100 Patients were considered node-positive (N+) if the PET-CT was positive for the para-  
101 aortic area and/or had positive PALN at surgical staging. Suspected positive pelvic node on  
102 PET-CT were not considered as positive on PALN. Node-negative patients (N-) were defined

103 as patients with negative nodes at surgical staging after PET-CT negative. Patients were  
104 considered to have an advanced cervical cancer if they had a stage Ib2 to IV 2009 FIGO  
105 cervical cancer. The 2009 classification was used since it does not depend on the node status.

106

### 107 *Statistical analysis*

108 Development of the model: Factors associated with a risk of para-aortic node  
109 involvement were determined by univariate analysis.

110 A student-t test and chi 2 test were used to compare the continuous and categorical  
111 values, respectively. Continuous variables were transformed into categorical variables  
112 according to the optimal threshold on the ROC curve.

113 Multivariate analysis was carried out using a logistic regression model, including  
114 significant variables upon univariate analysis to select the best combination of predictors. A  
115 *p-value* less than or equal to 0.05 was considered significant. A score was developed from the  
116 odds ratio (OR) of the logistic regression model. A stepwise selection method was used to  
117 select the best combination of predictors. Missing data were considered as negative. In the  
118 final model, only factors with a significant *p-value* ( $p \leq 0.05$ ) were selected.

119 Accuracy of the model: The performance of the model was tested by its discrimination  
120 and calibration [9,10]. The discrimination was assessed using the area under the curve (AUC)  
121 of the receiver operating curve (ROC) [11]. Calibration was studied using a graphical plot  
122 which showed the difference between the predicted outcome and the actual outcome. The  
123 mean and maximal error was calculated. The performance of the model was evaluated by its  
124 AUC. Sensitivity, specificity, negative and positive likelihood ratios were also assessed.

125            Validation of the model: An internal validation was performed with 1000 bootstrap  
126 resamples to obtain relatively unbiased estimates. The bootstrapping method provides an  
127 estimate of the average optimism of the AUC-ROC [9].

128            All statistical analyses were carried out using an Excel database and Rstudio version  
129 1.1.447.

130

## 131            **Results**

### 132            *General results*

133            Between 2000 and 2015, 1446 patients treated for cervical cancer were included. Of  
134 these, 498 had an advanced squamous cell cervical cancer (i.e. with a FIGO 2009 stage  
135 greater than or equal to IB2) (Figure 1).

136            Ninety-one patients had positive PALN (18.3 %): 51 had positive nodes on PET-CT  
137 and 43 on definitive histology.

### 138            *Patient characteristics*

139            Patient characteristics are summarized in Table 1. The mean age of patients at  
140 diagnosis was 53 ( $\pm$  14) and 54 ( $\pm$  14) years old for N+ and N- patients, respectively. Of the  
141 498 patients included in the study, 267 (53.6%) had not had a pap-smear test within 3 years  
142 and 11% (n=55) had a normal pap-smear less than 3 years before the cancer.

143            Two hundred and eighty-nine patients had both a lymphadenectomy and a PET-CT,  
144 126 had only a PET-CT and 83 had only a lymphadenectomy.

### 145            *Pre-operative assessment and surgical staging (Table 1)*

146 The mean tumor size on pelvic MRI was 59.5 mm ( $\pm$  25.5) in N+ versus 48.4 mm  
147 ( $\pm$ 15.8) in N- patients and was significantly different ( $\rho$ <0.001). Suspicious pelvic lymph  
148 nodes on pelvic MRI were present in 42.6% (n=212) of the patients, of whom 29.7% (63/212)  
149 were N+.

150 The squamous cell carcinoma (SCC) tumor marker had a median value of 15.2  $\mu$ g/L  
151 (range: 0 - 317  $\mu$ g/L) in N+ and 4.9  $\mu$ g/L (range: 0 - 153  $\mu$ g/L) in N- patients ( $\rho$  = 0.02). After  
152 analyzing the ROC curve, the optimal threshold for differentiating positive and negative  
153 PALN for the SCC tumor marker was 8 $\mu$ /L.

154 PET-CT was performed in 90.1% (n=82) of N+ patients and 81.6% (n=332) of N-  
155 patients. Of the 91 patients with positive para-aortic nodes, 34% (31/91) had positive lymph  
156 node staging with negative PET-CT. Positive pelvic lymph nodes (PLN) on PET-CT was  
157 present in 54.9% (n=50) of N+ patients and 26.3% (n=107) of N- patients ( $\rho$ <0.001). The  
158 mean standard uptake value (SUV max) at the cervix was 12.78 (range: 0 - 42.9).

159 Primary PALN staging was performed in 300 patients (60%) and was positive in 43  
160 cases.

#### 161 *Predictive factors of para para-aortic lymph node involvement (Table 2)*

162 After univariate analysis, the predictive factors for PALN involvement were tumor  
163 size greater than 60mm (OR 2.69, 95%CI [1.60 – 4.52]), SCC marker > 8 $\mu$ /L (OR 4.6, 95%CI  
164 [2.14 – 9.90]), positive PLN on PET-CT (OR 3.27, 95%CI [1.98 – 5.39]) and body mass  
165 index (BMI) > 25 kg/m<sup>2</sup> (OR 0.5, 95%CI [0.29 – 0.84],  $\rho$ <0.01). Patients with a retro-  
166 peritoneal lymphadenectomy had a statistically significant lower BMI (mean 24.6kg/m<sup>2</sup>) than  
167 patients without (mean 25.7kg/m<sup>2</sup>) (p=0.04).



168 In multivariate analysis, factors associated with node involvement were: tumor size  
169 greater than 60 mm (aOR=5.27 (95%IC = 1.96 – 14.16)), SCC marker > 8 $\mu$ /L (aOR=2.55  
170 (95%IC = 0.97 – 6.73)) and positive PLN on PET-CT (aOR=2.91 (95%IC = 1.07 – 7.90)).

171 *Development of the score (Figure 2)*

172 All variables significant on multivariate analysis were included in our model. Points  
173 assigned to each criterion corresponded to the round of their respective odds ratios. Five  
174 points were given if the tumor size was greater than 6 cm on pelvic MRI, 3 points were given  
175 if PLN involvement was suspected on PET-CT, and 2 points were given if the SCC rate was  
176 greater than 8  $\mu$ g/L. Thus, the model had a total of 10 points.

177 This model allowed the population to be divided into 3 risk groups. Patient with a  
178 score inferior to 3 were considered at low risk with a 9% probability of PALN involvement  
179 with a sensitivity of 69% (95% CI = 0.58 – 0.78) and a negative predictive value of 90%  
180 (95% CI = 0.87 - 0.93). A score between 3 and 5 placed the patients in an intermediate risk  
181 population with a 26% probability of PALN involvement. Patients with a score greater than 5  
182 were considered at high risk with a 43% probability of PALN involvement with a high  
183 specificity 0.92 (95%CI = 0.89 – 0.94).

184 Performance of this score, determined by the area under the ROC curve (AUC), was  
185 0.81 (95% CI= 0.72 - 0.90). After 1000 bootstrap validation, the AUC was 0.80 (95%IC =  
186 0.71-0.89). This suggests that the model is robust and well discriminating in this population.  
187 The calibration curve showed no significant difference ( $\rho$ =0.93) between the predicted  
188 probabilities and the observed proportions with a mean error of 0.007 and a maximum error of  
189 0.016.

190

191           **Discussion**

192           This study presents a simple score that can be used in clinical practice to predict  
193 PALN invasion in locally advanced cervical cancer (LACC). We included variables that are  
194 part of the routine extension assessment of advanced cervical cancer, such as tumor size,  
195 positive PLN on PET-CT and high SCC rate, into our score. A low risk group of patients  
196 (score < 3) with a predicted probability of para-aortic lymph node involvement of 9% was  
197 then defined. Patients in the high-risk group (score >5) had a predicted probability of 43%.

198           The benefit of surgical staging in terms of survival is still debated [12–15]. Indeed,  
199 some believe that PALN staging surgery improves the prognosis and in particular the overall  
200 survival and recurrence-free survival [16]. Others find that the prognosis is deteriorated [17].  
201 This surgical staging may induce intraoperative complications such as vascular, digestive or  
202 postoperative wounds and delay concomitant radio-chemotherapy. One review reported a  
203 complication rate between 4 and 24% with a predominance of lymphoceles [7].

204           The false-negative (FN) rate of the PET-CT varies between 12 and 17% [18,19]. In our  
205 study, the rate of false negatives of PET-CT was 15.3%, concordant with these findings. The  
206 PLN on PET-CT is of particular interest. Indeed, Gouy et al suggested that positive PLN on  
207 PET-CT, increased the FN rate to 22% whereas, negative pelvic nodes decreased it to 9%  
208 [12]. PLN involvement is therefore a determining factor in assessing the risk of para-aortic  
209 involvement. Likewise, we found that the false-negative rate of PET-CT for para-aortic  
210 evaluation was 22.9% in case of positive pelvic node and 10.9% for negative pelvic node on  
211 PET-CT. Importance of PLN involvement in predicting PALN involvement has been  
212 previously showed in several studies, concordant with our findings [20]. Nevertheless, this  
213 imaging technique is not available in all centers, especially in developing countries, which  
214 could limit the wide use of our score.

215           Regarding the SCC marker, its dosage is not part of the recommendations for initial  
216 cervical cancer assessment [2] but can be used in follow-up if it is initially informative. An  
217 initial elevation of SCC is frequently associated with advanced stage, large tumor volume,  
218 lymph node and lymphovascular involvement [21]. In our study, a SCC rate greater than 8  
219  $\mu\text{g/L}$  was a predictive factor of PALN involvement. This rate may seem high since the rate  
220 associated with distant injury or recurrence is generally between 2 and 4  $\mu\text{g/L}$  [22,23].  
221 However, this threshold presented the most accurate discrimination for differentiating positive  
222 and negative PALN.

223           The final predictive factor of our score was tumor size greater than 6 cm on pelvic  
224 MRI. Evaluation by pelvic MRI is part of the standard local-regional spread assessment for  
225 locally advanced cervical cancers. The risk of pelvic and PALN involvement increases with  
226 tumor size [8,24–26].

227           BMI was significant only upon univariate analysis. It must be noted however that this  
228 characteristic can be biased. Indeed, patients with a higher BMI were more likely to not  
229 undergo a para-aortic lymphadenectomy due to a potentially added morbidity. Patients with a  
230 higher BMI could therefore have more negative PALN since they did not benefit from a retro-  
231 peritoneal lymphadenectomy. However, the BMI remained low in our population (patients  
232 with a retro-peritoneal lymphadenectomy mean BMI 24.6  $\text{kg/m}^2$  and patients without, mean  
233 BMI 25.7  $\text{kg/m}^2$ ).

234           In the era of personalized medicine, it is essential to provide a tailored treatment for  
235 each patient. Pre-therapeutic identification of an at-risk population is the cornerstone of this  
236 personalization. Our score allowed us to classify patients into 3 risk groups. A low risk (9%  
237 predicted probability of para-aortic involvement) group, an intermediate risk (26%) and a  
238 high-risk group (43%). This score presents a satisfactory discriminatory power (AUC = 0.81

239 95%CI = 0.71 – 0.90) and an excellent calibration. In clinical practice, it could therefore be  
240 estimated that patients with a low risk of para-aortic involvement could avoid extended field  
241 irradiation to these lymph node areas. The question arises for patients with a high or  
242 intermediate risk. It could be argued that high-risk patients could be expected to have  
243 extended irradiation to the para-aortic areas. However, this group had a risk of only 43%. This  
244 would imply an unjustified risk of irradiation in up to half of the patients and extended field  
245 irradiation to para-aortic area is not without risk [4]. Staging surgery would therefore still  
246 have a place for intermediate and high risks. To reduce morbidity, an infra-mesenteric  
247 lymphadenectomy could be discussed, as proposed by some [27,28] and European Guidelines  
248 [2]. Ideally, our score would have been able to indicate surgical staging only to patients with  
249 an intermediate risk and to perform prophylactic irradiation of the para-aortic areas in case of  
250 high risk.

251 Several predicting models have been previously developed. Wang et al developed a  
252 nomogram to predict PALN involvement. However, all stages of cervical cancer were  
253 included. PALN was only assessed by imaging (TEP-CT or CT) [26]. As previously stated,  
254 assessment of node involvement by imaging is far from perfect. A Korean team developed a  
255 score based on tumor size and PALN involvement on PET-CT with patient who underwent  
256 para-aortic lymphadenectomy in LACC [29]. Likewise, the main limitation of this study is that  
257 patients with LACC did not undergo surgical staging. These two studies may have under-  
258 estimated the FIGO stage and may have included patients with an initially advanced cervical  
259 cancer. Our study included patients assessed by imaging and/or surgery.

260 Limitations of our study include its retrospective design and the absence of an external  
261 validation of the score. Despite our large population size, the small number of events (91  
262 positive para-aortic nodes) rendered it impossible to divide the population into a training and  
263 validation set. Moreover, the high number of missing information on PALN involvement

264 could have biased our results. As discussed above, the predictive SCC threshold used in our  
265 score is very high compared to the literature. A systematic SCC dosage in the initial  
266 assessment could help to refine this threshold. Furthermore, the score was developed only in  
267 patients with squamous cell carcinoma of the cervix because of the small proportion of other  
268 histological types. Therefore, the score results cannot be extrapolated to these patients. Our  
269 score cannot be used in daily clinical practice in its current form due to the absence of an  
270 external validation. However, it can be used in complex situations to help weigh the decision.

271 As this score is based on imaging data, the addition of more efficient imaging to  
272 determine lymph node involvement could be of interest such as pelvic MRI with diffusion-  
273 weight imaging (DWI-RMI) [30–34]. Likewise, the use of the SUVmax at the tumor and PLN  
274 seems promising [20,35].

## 275 **Conclusion**

276 We developed a simple score predicting PALN involvement in advanced cervical  
277 cancers. Patients can be classified into 3 risk groups depending on their probability of lymph  
278 node invasion. Patients considered to be at low risk may avoid para-aortic staging as well as  
279 extensive field irradiation to these lymph nodes. This score is simple to use because the  
280 factors are part of the standard extension assessment of this pathology: tumor size on pelvic  
281 MRI, pelvic lymph node involvement on PET-CT and finally the SCC dosage. A prospective  
282 study and external validation are needed to confirm the performance and clinical value of  
283 such a model.

284

## 285 **Conflict of interest**

286           The authors declare that they have no conflicts of interest that might be relevant to the  
287 contents of this article.

288

289           **Author contribution**

290   Wrote the paper: Nguyen-Xuan HT

291

292   Performed the statistical analysis: Benoit L, Huchon C

293

294   Conceived and designed the analysis: Huchon C

295

296   Performed the analysis: Huchon C

297

298   Contributed data or analysis tools: Nguyen-Xuan HT, Benoit L, Dabi Y, Touboul C, Raimond  
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301

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304

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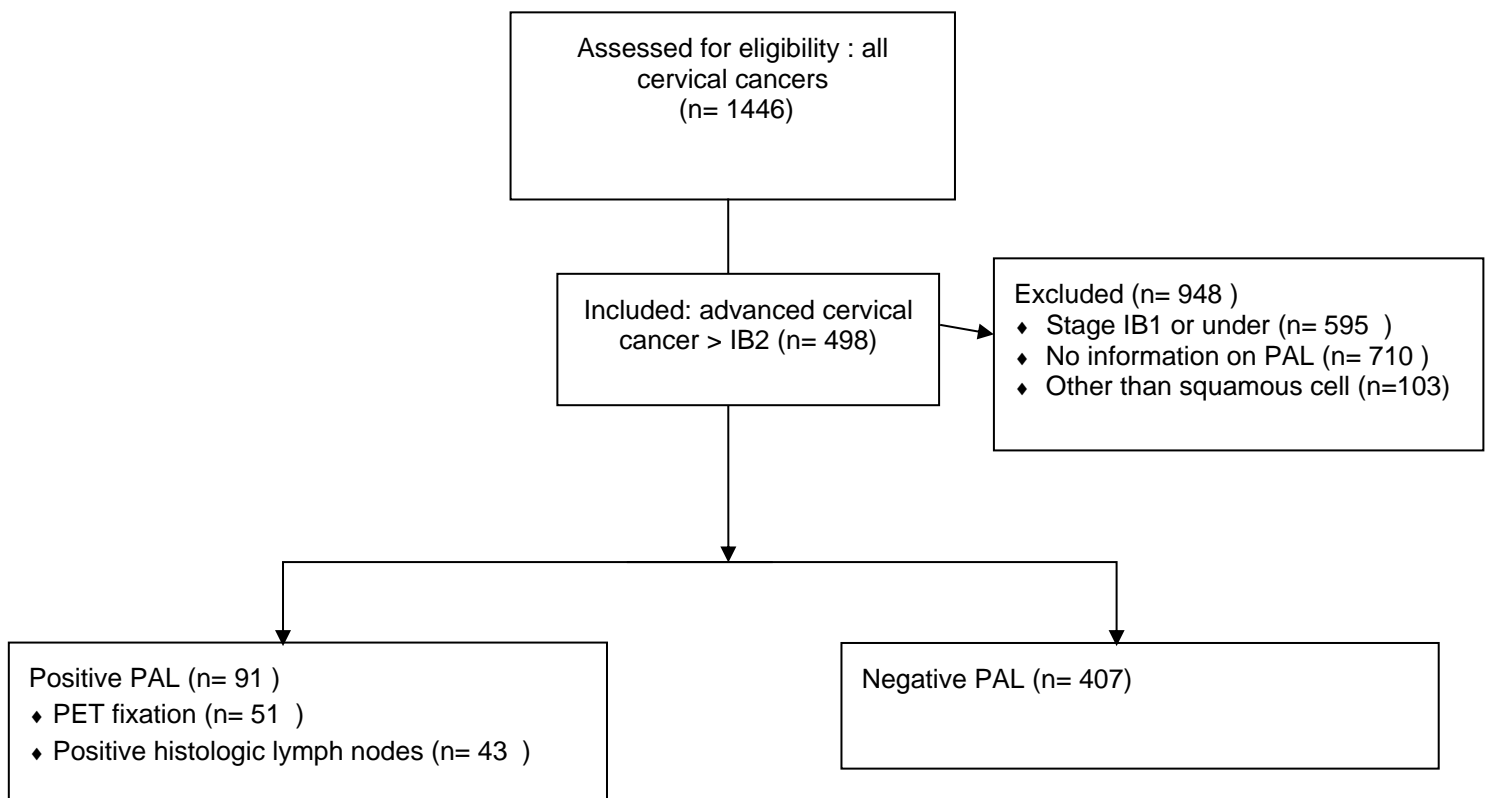


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422

423

Figure 1. Flow chart



Abbreviations: PET = positron emission tomography, PAL= para- aortic lymph nodes

Figure 2: Score predicting the invasion of para-aortic lymph nodes in advanced squamous cervical cancer.

Variable	Score
Tumor size > 6 cm	5
Positive pelvic nodes on TEP	3
SCC > 8	2

Low risk: score < 3: probability 9.0% (28/287)  
Intermediate-risk 3-5: probability 26% (42/161)  
High-risk >5: probability 43% (22/51)

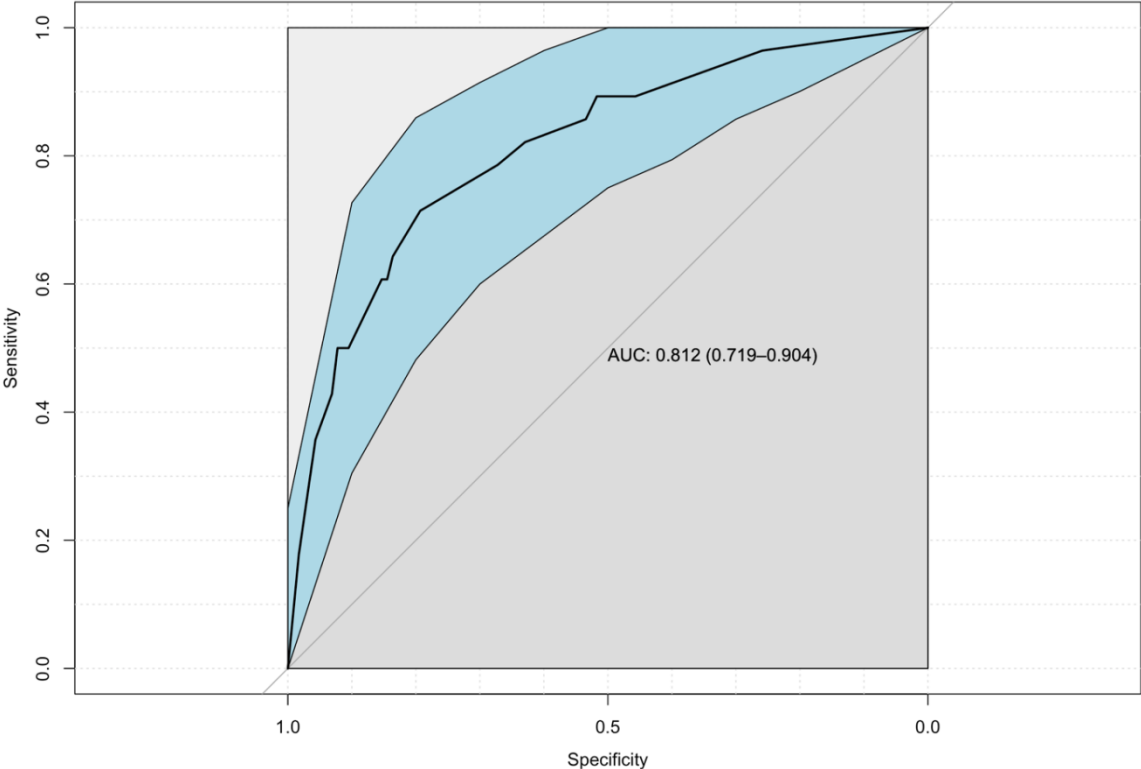
For patients with a low risk score (<3), the predicted probability of positive para-aortic node was 9.0% (IC95%=0.06-0.14). This threshold had a sensibility of 0.69 (IC95%=0.58-0.78) and a negative predictive value of 0.90 (IC95%=0.87-0.93).

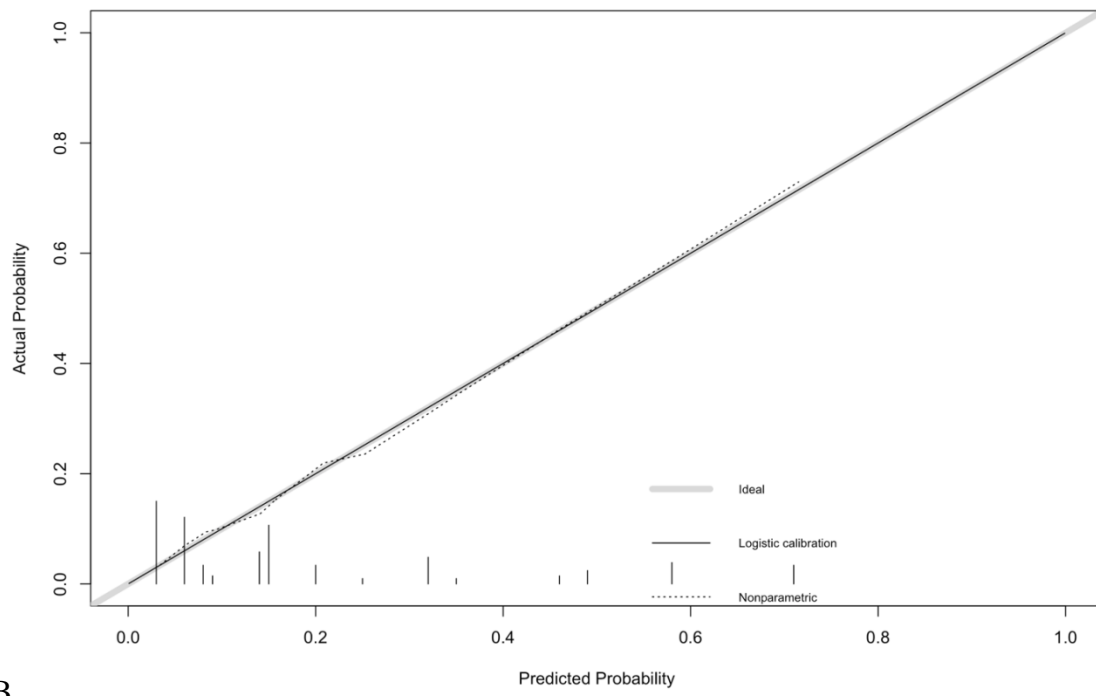
Patients with a score > 5 were considered high-risk and had a positive likelihood ratio of 3.13 (IC95%=1.88-5.21) with a high specificity 0.92 (IC95%=0.89-0.94).

**Figure 3:** Discrimination and validation of the model predicting the invasion of para-aortic lymph nodes in patients presenting an advanced squamous cervical cancer

- A. ROC curve of the model. The predictive model had a AUC of 0,81 (95% CI 0.71-0.90)
- B. Calibration of the model. The horizontal axis represents the predicted probability of para-aortic lymph node invasion and the vertical axis represents the actual probability. Perfect prediction would correspond to the 45-degree broken line. The dotted and solid lines indicate the observe (apparent) nomogram performance before and after bootstrapping.

A.





**B**

**Table 1.** Population characteristics

Characteristics		Positive PAL N=91 (18.3%)	Negative PAL N=407 (81.7%)	<i>p</i>
Age	Mean (+/- SD) Range	53 +/- 14 26-94	54 +/- 14 23-96	0.31
Menopause		47 (51.65)	230 (56.51)	0.42
BMI	Mean (+/- SD) Range	23.75 +/- 5.21 15-36	25.35 +/- 5.81 12-46	<b>0.02</b>
Previous pregnancies		72 (79.12)	342 (84.02)	0.35
Grade	1 2 3 NA	16 (17.58) 24 (26.37) 24 (26.37) 27 (29.68)	63 (15.48) 114 (28.01) 113 (27.76) 117 (28.75)	0.64
Lympho-vascular invasion	Invasion	12 (13.18)	27 (6.63)	0.09
Positive pelvic nodes on PET scanner		50 (54.94)	107 (26.29)	<b>&lt;0.001</b>
SCC	Mean (+/- SD) Range	38.77 +/- 64.98 0-317	13.29 +/- 23.04 0-153	<b>0.02</b>
FIGO stage 2009	IB2 IIA IIA1 IIA2 IIB IIIA IIIB IVA IVB	5 (5.49) 1 (1.1) 0 (0) 2 (2.2) 47 (51.65) 2 (2.2) 9 (9.89) 18 (19.78) 7 (7.6)	47 (11.55) 9 (2.21) 9 (2.21) 9 (2.21) 241 (59.21) 3 (0.74) 22 (5.41) 59 (14.50) 8 (1.96)	<b>0.04</b>
MRI tumor size (mm)	Mean (+/- SD) Range	59.52 +/- 25.52 29-220	48.40 +/- 15.84 0-110	<b>&lt;0.001</b>

*Abbreviations:* SD= standard deviation, BMI= body mass index, SCC = squamous cell carcinoma, MRI = magnetic resonance imaging, PET = positron emission tomography, PAL= para- aortic lymph nodes

Table 2. Multivariate analysis of factors associated with positive para-aortic lymph nodes in patients with advanced squamous cervical cancer.

Variables	Multivariate analysis	
	Adjusted Odds ratio	95% CI
Tumor size on MRI ( $\leq 60$ mm versus $> 60$ mm)	4.93	2.59-10.72
SCC ( $\leq 8$ versus $> 8$ )	3.18	1.29-7.79
Positive pelvic nodes on TEP	2.45	1-6.01

Abbreviations: SCC = squamous cell carcinoma, MRI = magnetic resonance imaging, PET = positron emission tomography, 95%CI = 95% confidence interval