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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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## ABSTRACT

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

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

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

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

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

## Introduction

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

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

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

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

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

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

## **Patients and method**

### *Population*

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

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

### *Definitions*

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

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

### *Statistical analysis*

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

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

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

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

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

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

## **Results**

### *General results*

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

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

### *Patient characteristics*

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

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

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

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

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

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

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

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

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



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

#### *Development of the score (Figure 2)*

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

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

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

## Discussion

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

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

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

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

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

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

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

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

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

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

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

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

## **Conclusion**

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

## **Conflict of interest**

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

#### **Author contribution**

Wrote the paper: Nguyen-Xuan HT

Performed the statistical analysis: Benoit L, Huchon C

Conceived and designed the analysis: Huchon C

Performed the analysis: Huchon C

Contributed data or analysis tools: Nguyen-Xuan HT, Benoit L, Dabi Y, Touboul C, Raimond E, Ballester M, Collinet P, Kerbage Y, Ouldamer L, Bricou A, Lavoue V, Carcopino X, Huchon C

Collected data: Nguyen-Xuan HT, Benoit L, Dabi Y, Touboul C, Raimond E, Ballester M, Collinet P, Kerbage Y, Ouldamer L, Bricou A, Lavoue V, Carcopino X, Huchon C

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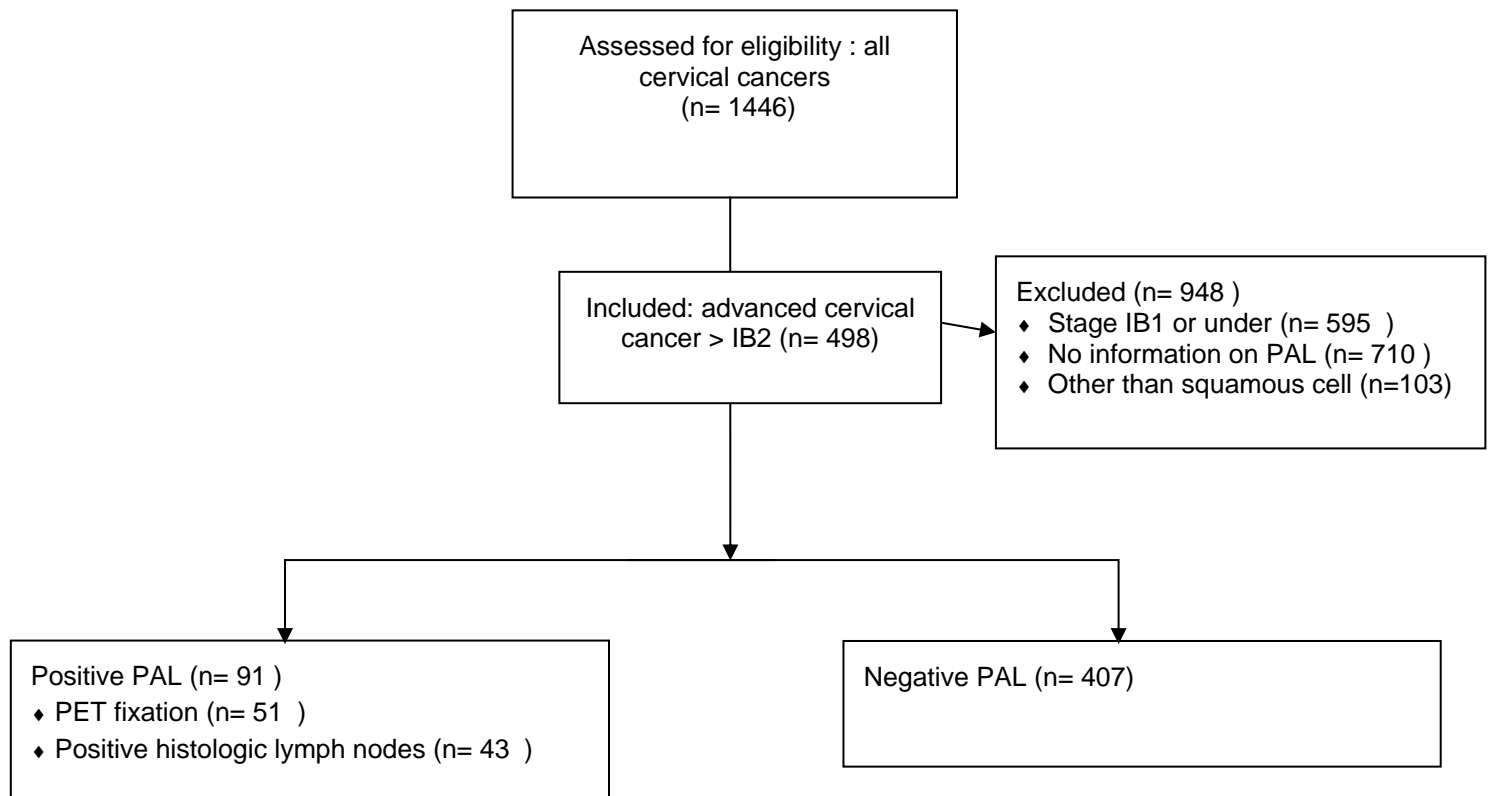


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422

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)

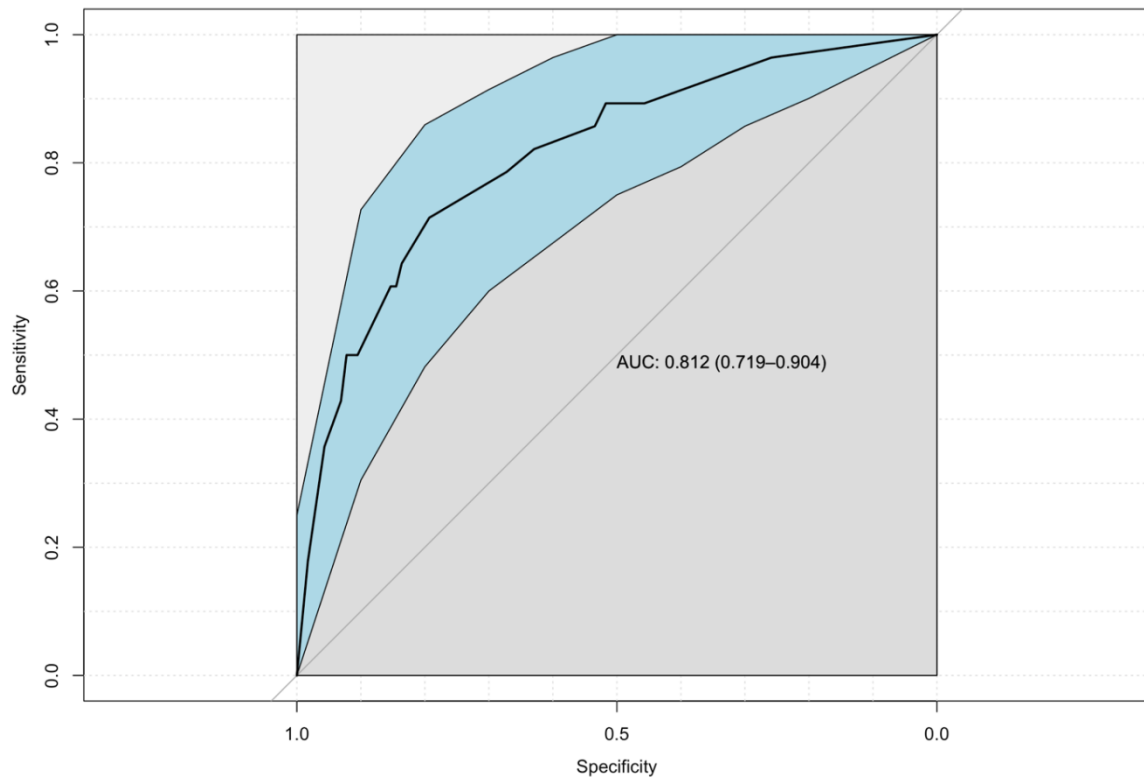
For patients with a low risk score (<3), the predicted probability of positive para-aortic node was 9.0% (IC95%=0.06-0.14). This threshold had a sensibility of 0.69 (IC95%=0.58-0.78) and a negative predictive value of 0.90 (IC95%=0.87-0.93).

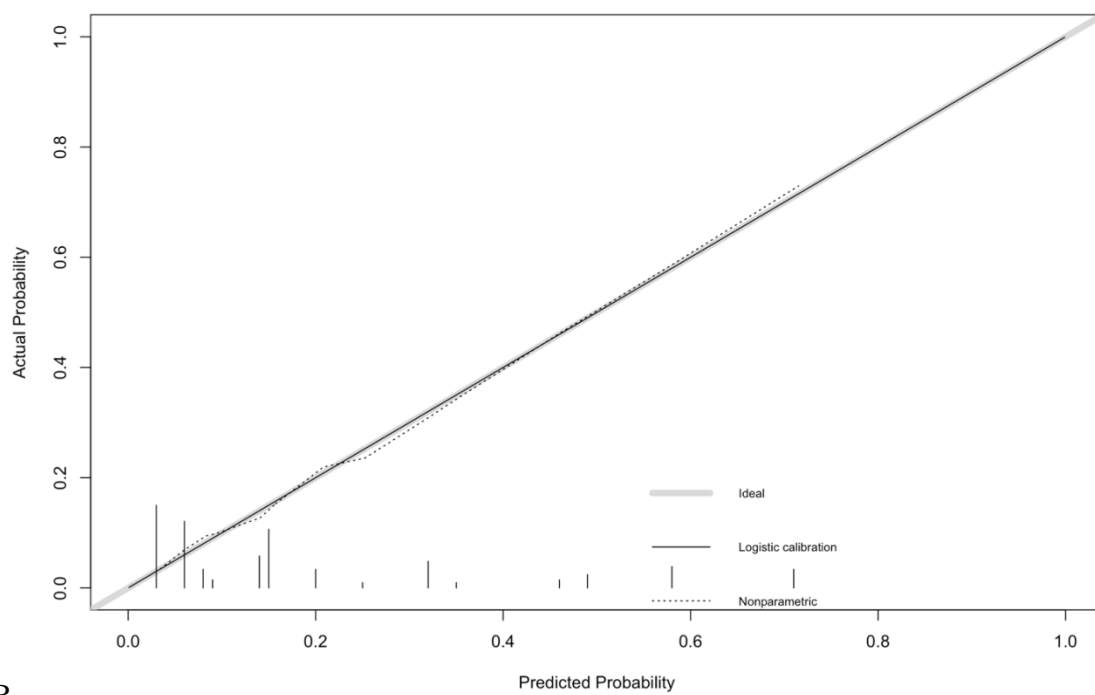
Patients with a score > 5 were considered high-risk and had a positive likelihood ratio of 3.13 (IC95%=1.88-5.21) with a high specificity 0.92 (IC95%=0.89-0.94).

**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