



HAL
open science

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

H T Nguyen-Xuan, L Benoit, Y Dabi, C Touboul, E Raimond, M Ballester, S Bendifallah, P Collinet, Y Kerbage, Lobna Ouldamer, et al.

► To cite this version:

H T Nguyen-Xuan, L Benoit, Y Dabi, C Touboul, E Raimond, et al.. How to predict para-aortic node involvement in advanced cervical cancer? Development of a predictive score. A FRANCOGYN study. *EJSO - European Journal of Surgical Oncology*, 2021, 47 (11), pp.2900-2906. 10.1016/j.ejso.2021.06.036 . hal-03336678

HAL Id: hal-03336678

<https://hal.science/hal-03336678v1>

Submitted on 5 Jan 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

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

4 **A FRANCOGYN study**

5 Nguyen-Xuan HT ^{1,2} , Benoit L ^{2,3} , Dabi Y ⁴ , Touboul C ³ , Raimond E ⁵ , Ballester M ⁶ ,
6 Bendifallah S ³ , Collinet P ⁷ , Kerbage Y ⁷ , Ouldamer L ⁸ , Bricou A ^{6,9} , Lavoue V ¹⁰ ,
7 Carcopino X ¹¹ , Huchon C ^{1,12,13} .

8 ¹ Department of Gynaecology and Obstetrics, Intercommunal Hospital Centre of Poissy-Saint-
9 Germain-en-Laye, 78300 Poissy, France

10 ²- Department of Gynaecology and Obstetrics, Assistance Publique – Hôpitaux de Paris,
11 Hôpital Européen Georges Pompidou

12 ³- Department of Gynaecology and Obstetrics, Tenon University Hospital, Assistance
13 Publique des Hôpitaux de Paris (AP-HP), University Pierre and Marie Curie, Paris 6, Institut
14 Universitaire de Cancérologie (IUC), Paris, France

15 ⁴- Department of Obstetrics and Gynecology, Centre Hospitalier Intercommunal, Créteil,
16 France

17 ⁵-Department of Obstetrics and Gynaecology, Institute Alix de Champagne University
18 Hospital, Reims, France

19 ⁶- Department of Obstetrics and Gynecology, Groupe hospitalier Diaconesses Croix Saint-
20 Simon, Paris, France

21 ⁷-Department of Obstetrics and Gynecology, Centre Hospitalier Régional Universitaire, Lille,
22 France

23 ⁸-Department of Obstetrics and Gynaecology, Centre Hospitalier Régional Universitaire de
24 Tours, Hôpital Bretonneau, Tours, France

25 ⁹- Department of Obstetrics and Gynecology, Jean-Verdier University Hospital, Assistance
26 Publique des Hôpitaux de Paris (AP-HP), Paris, France

27 ¹⁰- CRLCC Eugène-Marquis, Service de Gynécologie, CHU de Rennes, Université de
28 Rennes 1, Rennes, France

29 ¹¹-Department of Obstetrics and Gynecology, Hopital Nord, APHM, Marseille, France

30 ¹² EA 7285 Risques cliniques et sécurité en santé des femmes, University of Versailles-Saint-
31 Quentin en Yvelines

32 ¹³ Department of Obstetrics and Gynecology, Assistance Publique – Hôpitaux de Paris,
33 Hôpital LARIBOISIERE, University of Paris

34

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 (ρ <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 μ g/L
151 (range: 0 - 317 μ g/L) in N+ and 4.9 μ g/L (range: 0 - 153 μ g/L) in N- patients (ρ = 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 μ /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 (ρ <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 μ /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/m² (OR 0.5, 95%CI [0.29 – 0.84], ρ <0.01). Patients with a retro-
166 peritoneal lymphadenectomy had a statistically significant lower BMI (mean 24.6kg/m²) than
167 patients without (mean 25.7kg/m²) (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 μ /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 μ 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 (ρ =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 kg/m^2 and patients without, mean
233 BMI 25.7 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
299 E, Ballester M, Collinet P, Kerbage Y, Ouldamer L, Bricou A, Lavoue V, Carcopino X,
300 Huchon C

301

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

304

305

- 307 1. Bhatla N, Aoki D, Sharma DN, Sankaranarayanan R. Cancer of the cervix uteri. *Int J Gynaecol*
308 *Obstet Off Organ Int Fed Gynaecol Obstet.* oct 2018;143 Suppl 2:22- 36.
- 309 2. Marth C, Landoni F, Mahner S, McCormack M, Gonzalez-Martin A, Colombo N, et al. Cervical
310 cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*
311 *Off J Eur Soc Med Oncol.* 1 juill 2017;28(suppl_4):iv72- 83.
- 312 3. Meng Q, Liu X, Wang W, Hou X, Lian X, Sun S, et al. Evaluation of the efficacy of
313 prophylactic extended field irradiation in the concomitant chemoradiotherapy treatment of
314 locally advanced cervical cancer, stage IIIB in the 2018 FIGO classification. *Radiat Oncol Lond*
315 *Engl.* 16 déc 2019;14(1):228.
- 316 4. Frumovitz M, Querleu D, Gil-Moreno A, Morice P, Jhingran A, Munsell MF, et al.
317 Lymphadenectomy in locally advanced cervical cancer study (LiLACS): Phase III clinical trial
318 comparing surgical with radiologic staging in patients with stages IB2-IVA cervical cancer. *J*
319 *Minim Invasive Gynecol.* févr 2014;21(1):3- 8.
- 320 5. Leblanc E, Gauthier H, Querleu D, Ferron G, Zerdoud S, Morice P, et al. Accuracy of 18-fluoro-
321 2-deoxy-D-glucose positron emission tomography in the pretherapeutic detection of occult para-
322 aortic node involvement in patients with a locally advanced cervical carcinoma. *Ann Surg*
323 *Oncol.* août 2011;18(8):2302- 9.
- 324 6. Cibula D, Pötter R, Planchamp F, Avall-Lundqvist E, Fischerova D, Haie Meder C, et al. The
325 European Society of Gynaecological Oncology/European Society for Radiotherapy and
326 Oncology/European Society of Pathology Guidelines for the Management of Patients With
327 Cervical Cancer. *Int J Gynecol Cancer Off J Int Gynecol Cancer Soc.* mai 2018;28(4):641- 55.
- 328 7. Smits RM, Zusterzeel PLM, Bekkers RLM. Pretreatment retroperitoneal para-aortic lymph node
329 staging in advanced cervical cancer: a review. *Int J Gynecol Cancer Off J Int Gynecol Cancer*
330 *Soc.* juill 2014;24(6):973- 83.
- 331 8. Delpech Y, Tulpin L, Bricou A, Barranger E. [Lymph node surgical staging for locally advanced
332 cervical cancer]. *Gynecol Obstet Fertil.* janv 2010;38(1):30- 5.
- 333 9. Harrell FE, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models,
334 evaluating assumptions and adequacy, and measuring and reducing errors. *Stat Med.* 28 févr
335 1996;15(4):361- 87.
- 336 10. Steyerberg EW, Eijkemans MJ, Harrell FE, Habbema JD. Prognostic modelling with logistic
337 regression analysis: a comparison of selection and estimation methods in small data sets. *Stat*
338 *Med.* 30 avr 2000;19(8):1059- 79.
- 339 11. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic
340 (ROC) curve. *Radiology.* avr 1982;143(1):29- 36.
- 341 12. Gouy S, Morice P, Narducci F, Uzan C, Gilmore J, Kolesnikov-Gauthier H, et al. Nodal-staging
342 surgery for locally advanced cervical cancer in the era of PET. *Lancet Oncol.* mai
343 2012;13(5):e212-220.
- 344 13. Gonzalez-Benitez C, Salas P, Grabowski JP, Hernandez A, De Santiago J, Zapardiel I. Lack of
345 Survival Benefit of Para-Aortic Lymphadenectomy in Advanced Cervical Cancer. *Gynecol*
346 *Obstet Invest.* 2019;84(4):407- 11.

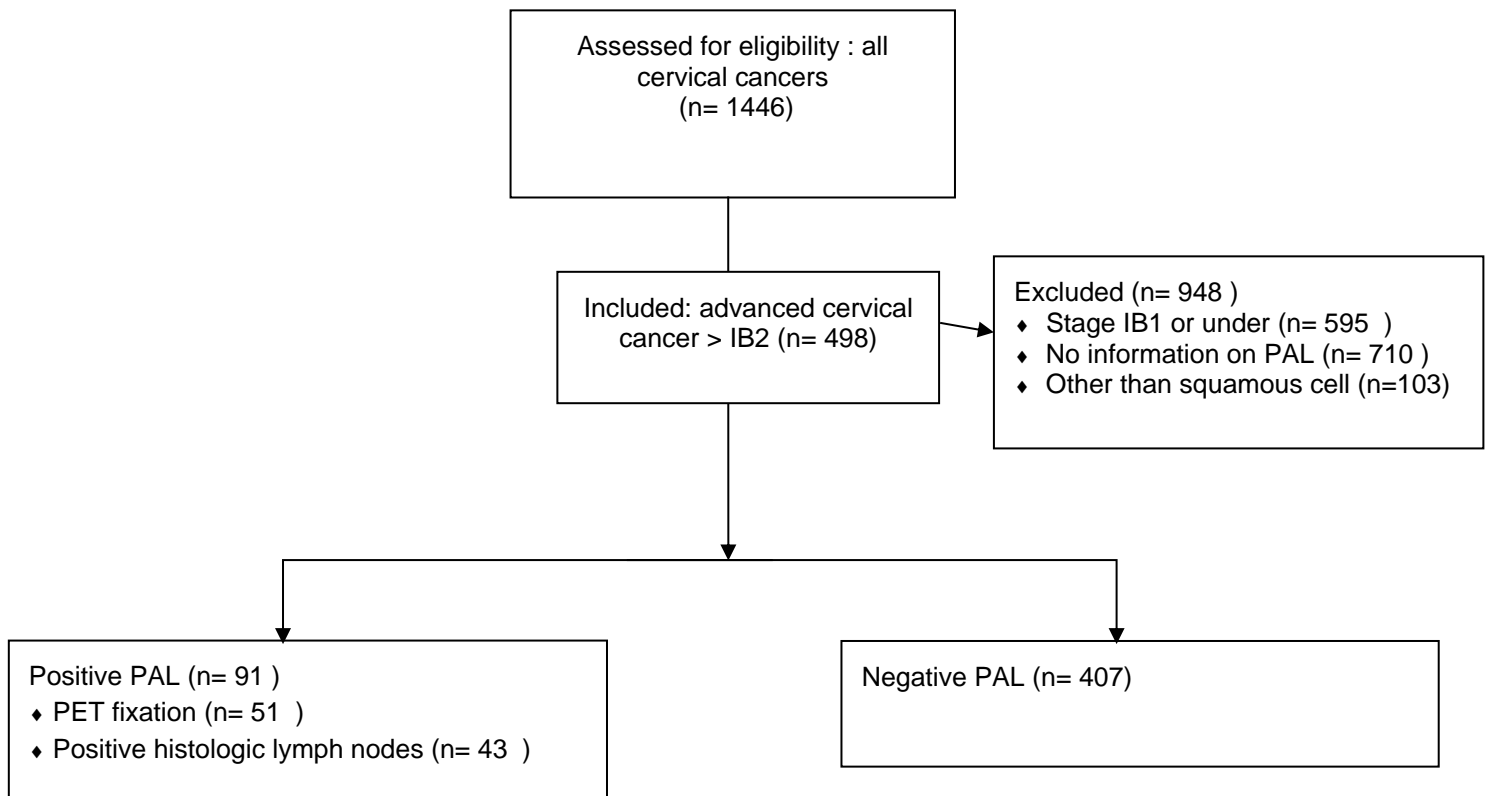
- 347 14. Brockbank E, Kokka F, Bryant A, Pomel C, Reynolds K. Pre-treatment surgical para-aortic
348 lymph node assessment in locally advanced cervical cancer. *Cochrane Database Syst Rev.* 28
349 mars 2013;(3):CD008217.
- 350 15. Gold MA, Tian C, Whitney CW, Rose PG, Lanciano R. Surgical versus radiographic
351 determination of para-aortic lymph node metastases before chemoradiation for locally advanced
352 cervical carcinoma: a Gynecologic Oncology Group Study. *Cancer.* 1 mai
353 2008;112(9):1954- 63.
- 354 16. Leblanc E, Narducci F, Frumovitz M, Lesoin A, Castelain B, Baranzelli MC, et al. Therapeutic
355 value of pretherapeutic extraperitoneal laparoscopic staging of locally advanced cervical
356 carcinoma. *Gynecol Oncol.* mai 2007;105(2):304- 11.
- 357 17. Lai C-H, Huang K-G, Hong J-H, Lee C-L, Chou H-H, Chang T-C, et al. Randomized trial of
358 surgical staging (extraperitoneal or laparoscopic) versus clinical staging in locally advanced
359 cervical cancer. *Gynecol Oncol.* avr 2003;89(1):160- 7.
- 360 18. Gouy S, Morice P, Narducci F, Uzan C, Martinez A, Rey A, et al. Prospective multicenter study
361 evaluating the survival of patients with locally advanced cervical cancer undergoing
362 laparoscopic para-aortic lymphadenectomy before chemoradiotherapy in the era of positron
363 emission tomography imaging. *J Clin Oncol Off J Am Soc Clin Oncol.* 20 août
364 2013;31(24):3026- 33.
- 365 19. De Cuypere M, Lovinfosse P, Goffin F, Gennigens C, Rovira R, Duch J, et al. Added value of
366 para-aortic surgical staging compared to 18F-FDG PET/CT on the external beam radiation field
367 for patients with locally advanced cervical cancer: An ONCO-GF study. *Eur J Surg Oncol J Eur
368 Soc Surg Oncol Br Assoc Surg Oncol.* 11 nov 2019;
- 369 20. Martinez A, Voglimacci M, Lusque A, Ducassou A, Gladieff L, Dupuis N, et al. Tumour and
370 pelvic lymph node metabolic activity on FDG-PET/CT to stratify patients for para-aortic surgical
371 staging in locally advanced cervical cancer. *Eur J Nucl Med Mol Imaging.* mai
372 2020;47(5):1252- 60.
- 373 21. Fu J, Wang W, Wang Y, Liu C, Wang P. The role of squamous cell carcinoma antigen (SCC Ag)
374 in outcome prediction after concurrent chemoradiotherapy and treatment decisions for patients
375 with cervical cancer. *Radiat Oncol Lond Engl.* 15 août 2019;14(1):146.
- 376 22. Choi KH, Lee SW, Yu M, Jeong S, Lee JW, Lee JH. Significance of elevated SCC-Ag level on
377 tumor recurrence and patient survival in patients with squamous-cell carcinoma of uterine cervix
378 following definitive chemoradiotherapy: a multi-institutional analysis. *J Gynecol Oncol.* janv
379 2019;30(1):e1.
- 380 23. Hong J-H, Tsai C-S, Lai C-H, Chang T-C, Wang C-C, Chou H-H, et al. Risk stratification of
381 patients with advanced squamous cell carcinoma of cervix treated by radiotherapy alone. *Int J
382 Radiat Oncol Biol Phys.* 1 oct 2005;63(2):492- 9.
- 383 24. Havrilesky LJ, Leath CA, Huh W, Calingaert B, Bentley RC, Soper JT, et al. Radical
384 hysterectomy and pelvic lymphadenectomy for stage IB2 cervical cancer. *Gynecol Oncol.* mai
385 2004;93(2):429- 34.
- 386 25. Berman ML, Keys H, Creasman W, DiSaia P, Bundy B, Blessing J. Survival and patterns of
387 recurrence in cervical cancer metastatic to periaortic lymph nodes (a Gynecologic Oncology
388 Group study). *Gynecol Oncol.* sept 1984;19(1):8- 16.

- 389 26. Wang W, Liu X, Meng Q, Zhang F, Hu K. Nomogram for predicting para-aortic lymph node
390 metastases in patients with cervical cancer. *Arch Gynecol Obstet.* 2018;298(2):381- 8.
- 391 27. Azaïs H, Ghesquière L, Petitnicolas C, Borghesi Y, Tresch-Bruneel E, Cordoba A, et al.
392 Pretherapeutic staging of locally advanced cervical cancer: Inframesenteric paraaortic
393 lymphadenectomy accuracy to detect paraaortic metastases in comparison with infrarenal
394 paraaortic lymphadenectomy. *Gynecol Oncol.* 2017;147(2):340- 4.
- 395 28. Petitnicolas C, Azaïs H, Ghesquière L, Tresch-Bruneel E, Cordoba A, Narducci F, et al.
396 Morbidity of Staging Inframesenteric Paraaortic Lymphadenectomy in Locally Advanced
397 Cervical Cancer Compared With Infrarenal Lymphadenectomy. *Int J Gynecol Cancer Off J Int*
398 *Gynecol Cancer Soc.* 2017;27(3):575- 80.
- 399 29. Shim S-H, Kim D-Y, Lee SJ, Kim S-N, Kang S-B, Lee S-W, et al. Prediction model for para-
400 aortic lymph node metastasis in patients with locally advanced cervical cancer. *Gynecol Oncol.*
401 *janv 2017;144(1):40- 5.*
- 402 30. Choi EK, Kim JK, Choi HJ, Park SH, Park B-W, Kim N, et al. Node-by-node correlation
403 between MR and PET/CT in patients with uterine cervical cancer: diffusion-weighted imaging
404 versus size-based criteria on T2WI. *Eur Radiol.* août 2009;19(8):2024- 32.
- 405 31. Liu B, Gao S, Li S. A Comprehensive Comparison of CT, MRI, Positron Emission Tomography
406 or Positron Emission Tomography/CT, and Diffusion Weighted Imaging-MRI for Detecting the
407 Lymph Nodes Metastases in Patients with Cervical Cancer: A Meta-Analysis Based on 67
408 Studies. *Gynecol Obstet Invest.* 2017;82(3):209- 22.
- 409 32. Perucho JAU, Chiu KWH, Wong EMF, Tse KY, Chu MMY, Chan LWC, et al. Diffusion-
410 weighted magnetic resonance imaging of primary cervical cancer in the detection of sub-
411 centimetre metastatic lymph nodes. *Cancer Imaging Off Publ Int Cancer Imaging Soc.* 6 avr
412 2020;20(1):27.
- 413 33. Lin G, Ho K-C, Wang J-J, Ng K-K, Wai Y-Y, Chen Y-T, et al. Detection of lymph node
414 metastasis in cervical and uterine cancers by diffusion-weighted magnetic resonance imaging at
415 3T. *J Magn Reson Imaging JMRI.* juill 2008;28(1):128- 35.
- 416 34. Whittaker CS, Coady A, Culver L, Rustin G, Padwick M, Padhani AR. Diffusion-weighted MR
417 imaging of female pelvic tumors: a pictorial review. *Radiogr Rev Publ Radiol Soc N Am Inc.*
418 *juin 2009;29(3):759- 74; discussion 774-778.*
- 419 35. Onal C, Guler OC, Reyhan M, Yapar AF. Prognostic value of 18F-fluorodeoxyglucose uptake in
420 pelvic lymph nodes in patients with cervical cancer treated with definitive chemoradiotherapy.
421 *Gynecol Oncol.* avr 2015;137(1):40- 6.

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)

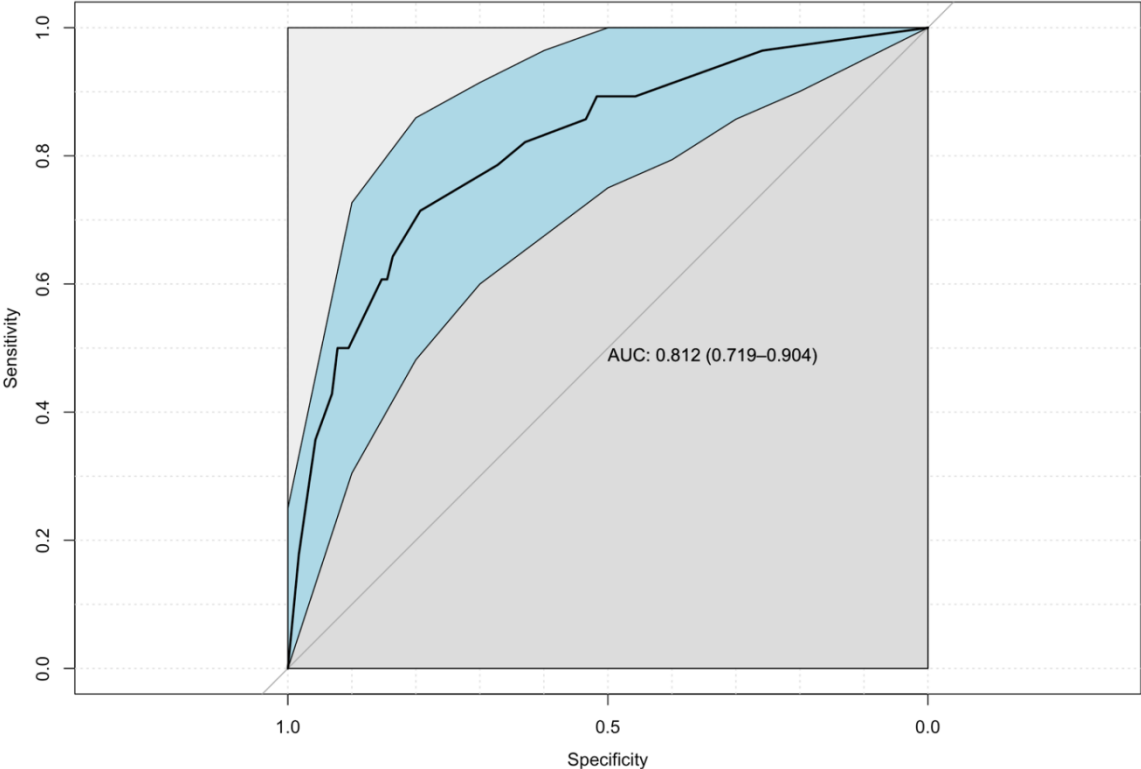
For patients with a low risk score (<3), the predicted probability of positive para-aortic node was 9.0% (IC95%=0.06-0.14). This threshold had a sensibility of 0.69 (IC95%=0.58-0.78) and a negative predictive value of 0.90 (IC95%=0.87-0.93).

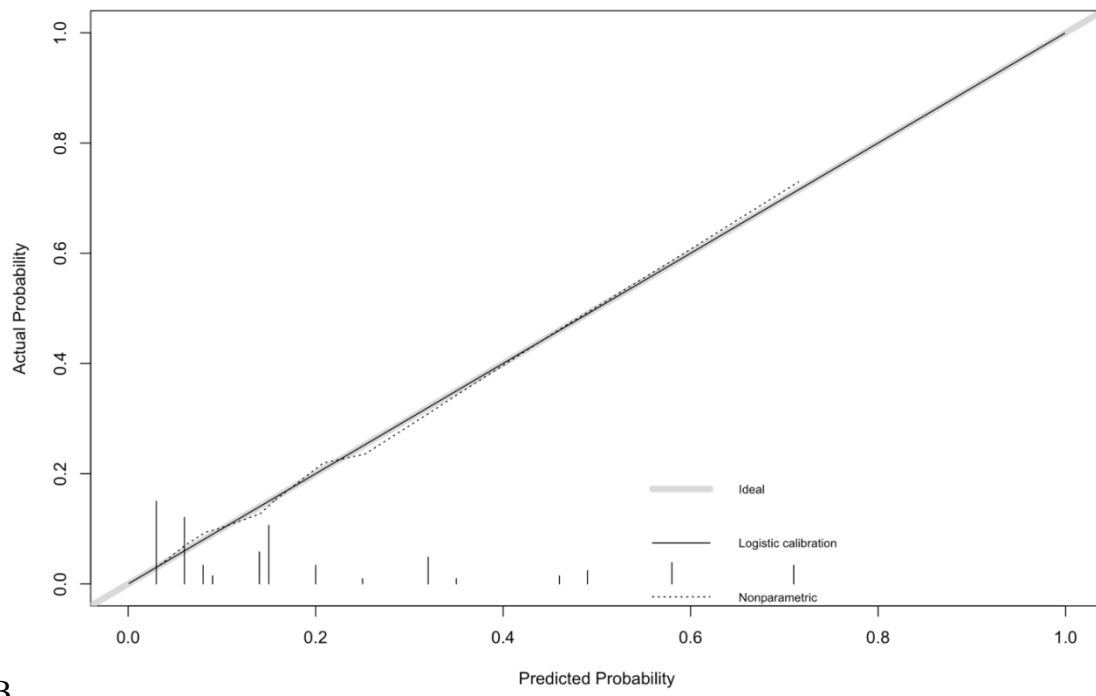
Patients with a score > 5 were considered high-risk and had a positive likelihood ratio of 3.13 (IC95%=1.88-5.21) with a high specificity 0.92 (IC95%=0.89-0.94).

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	0.02
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)	<0.001
SCC	Mean (+/- SD) Range	38.77 +/- 64.98 0-317	13.29 +/- 23.04 0-153	0.02
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)	0.04
MRI tumor size (mm)	Mean (+/- SD) Range	59.52 +/- 25.52 29-220	48.40 +/- 15.84 0-110	<0.001

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 (≤ 60 mm versus > 60 mm)	4.93	2.59-10.72
SCC (≤ 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