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## A new score based on biomarker values to predict the prognosis of locally advanced cervical cancer

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2 **A new score based on biomarker values to predict the prognosis of locally**  
3 **advanced cervical cancer:**

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**A new prognostic score in cervical cancer**

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**Highlights**

- pretreatment values of leucocyte, platelet and hemoglobin.
- prospective study of 238 patients treated for locally advanced cervical cancer.
- our score includes 3 biomarkers permit to identify patients with high risk of relapse.

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**ABSTRACT**

**Objective:** To define a prognostic score based on pretreatment values of leucocyte, platelet and hemoglobin in locally advanced cervical cancer (LACC).

**Material and methods:** We conducted a prospective study of 238 patients for LACC with negative PET imaging in the para-aortic (PA) area and who were undergoing laparoscopic PA lymphadenectomies. All patients were treated with chemo-radiation and brachytherapy.

**Results:** Patients had clinical International Federation of Gynecology and Obstetrics stages IB2 (n =76), IIA (n=13), IIB (n=122), III (n=18) or IVA (n=9). We identified three biological parameters (at the time of diagnosis) with three cut-offs which impacted disease free survival (DFS) and overall survival (OS) : <12 g/dL for hemoglobin, >10,000/ $\mu$ L for leucocyte and >300x10<sup>9</sup>/L for platelet. A score is calculated, as shown in the table below, by adding the scores of all three biological parameters together (with a maximum score of three).

Score	0	1
Hemoglobin	$\geq 12$ g/dl	<12 g/dl
Leucocyte	$\leq 10,000$ / $\mu$ L	>10,000/ $\mu$ L
Platelet	<300x10 <sup>9</sup> /L	$\geq 300$ x10 <sup>9</sup> /L
<b>Total score</b>	<b>/3</b>	

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DFS at 36 months was 87.3% [78.3-97.4], 58% [45-74.6], 79.1% [71.1-88], 58% [45-74.6] and 56.8% [37.8-85.4] for scores of 0, 1, 2 and 3 respectively. OS at 36 months was 92.6% [84.9-100], 84% [76.6-92.1], 62.5% [48.9-79.9] and 67% [46.8-96] for scores of 0, 1, 2 and 3 respectively.

90 **Conclusion:** This score includes three biomarkers with easily remembered cut-offs  
91 that allow us to identify, at the time of diagnosis, those patients with a high risk of  
92 relapse (scores of two or three) and those requiring dose escalation.

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97 **INTRODUCTION**

98

99 For locally advanced cervical cancer (LACC), Chemoradiotherapy (CRT) is  
100 considered the standard treatment by many North American and European teams.<sup>1</sup>  
101 In 2018, the Phase III trial (NCT00193739), which compared CRT and neoadjuvant  
102 chemotherapy followed by radical surgery, confirmed the superiority of CRT in  
103 LACC.<sup>2</sup> Despite CRT, the 5-year Disease Free Survival rate was 76.7%. In this  
104 Phase III trial<sup>2</sup>, the location of relapse was local in 6 %, at a distance in 6.9% and  
105 both in 7.6%. To improve local control, new radiation therapy modalities such as  
106 image-guided brachytherapy were used.<sup>3</sup> To improve distance control, positron  
107 emission tomography (PET) imaging at initial diagnosis can be used as a triage to  
108 identify patients with metastasis at a distance, especially in the para-aortic nodes,  
109 which is the first prognostic factor of survival in LACC.<sup>4,5</sup> Moreover, for patients with  
110 negative PET in para-aortic, a laparoscopic para-aortic lymphadenectomy can be  
111 used to identify patients with metastasis of less than 5 mm. Indeed, the extension of  
112 radiation fields in the para-aortic areas offered the same survival to those patients as  
113 that for patients with negative para-aortic nodes.<sup>6</sup> Due to the inflammation caused by  
114 cervical cancer, biological parameters at diagnosis (including neutrophil, leukocyte,  
115 platelet and C-reactive protein) have been shown to be prognostic factors.<sup>7-9</sup>  
116 Moreover, anemia has long been identified as an independent prognostic factor.<sup>10</sup>  
117 The challenge was how to use these biological parameters to identify, at the time of  
118 diagnosis, those patients with a high risk of relapse and those requiring dose  
119 escalation. At the time of relapse Moore et al., developed a model based on five  
120 factors (race, PS, site of disease, prior radiosensitizer and interval between diagnosis  
121 and first recurrence) to predict the response to chemotherapy.<sup>11</sup> The Moore criteria

122 were prospectively validated by Tewari et al., to evaluate the benefit of the  
123 incorporation of bevacizumab with chemotherapy for relapse.<sup>12</sup> The aim of this study is  
124 to define a simple score using biological parameters at the time of diagnosis of  
125 LACC, to increase the quality of triage of patients.

126

## 127 **METHODS**

### 128 *Patients*

129 We prospectively included all patients with a diagnosis of LACC and the following  
130 criteria: stages IB2 to IVA cervical cancer (according to the 2009 International  
131 Federation of Gynecology and Obstetrics classification); classical histology as  
132 adenocarcinoma, squamous cell carcinoma or adenosquamous subtypes; no  
133 hemotologic malignancies, chronic infection or immunological disease; no  
134 extrapelvic disease on conventional imaging (abdominopelvic magnetic resonance  
135 imaging [MRI] or CT scan and pelvic MRI) and no PA (or extrapelvic) uptake on initial  
136 PET-CT imaging. No peritoneal carcinomatosis or ovarian metastasis at the  
137 laparoscopic staging which was done in order to perform a para-aortic  
138 lymphadenectomy.

139

### 140 *Treatment*

141 The cervical tumor was treated (if there was no PA node involvement after a staging  
142 laparoscopy) with pelvic external radiation therapy (45 to 50 Gy) with concomitant  
143 platinum-based chemotherapy (cisplatin at a dose of 40 mg/m<sup>2</sup> per week). Patients  
144 with histologic PA node metastasis after staging laparoscopic surgery were treated

145 using pelvic and PA CRT (45 to 60 Gy) with concomitant chemotherapy. This  
146 treatment could be then completed by a 15-Gy dose of uterovaginal brachytherapy  
147 (according to the International Commission on Radiation Units recommendations). A  
148 boost of external radiation therapy (up to 60 Gy) was optional in patients with  
149 suspicious pelvic nodes (on conventional or PET-CT imaging) and/or in patients with  
150 initial parametrial involvement. Completion surgery was only used if brachytherapy  
151 was not technically feasible or on patients exhibiting clinical and radiological (using  
152 MRI exams) residual disease six to eight weeks after the end of brachytherapy.

153

#### 154 *Definition of leukocyte, platelet and hemoglobin disorders*

155 All patients had a blood sample at the diagnosis of cervical cancer, prior to  
156 laparoscopic para-aortic staging, which was the first step of the treatment. Anemia  
157 was defined with thresholds of 12g/dl. Leukocytosis was defined as a leukocyte count  
158 exceeding 10 000/ $\mu$ l. The platelet disorder was defined as a platelet count exceeding  
159 400x10<sup>9</sup>/L.

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#### 162 *Follow-ups and statistical analyses :*

163 Follow-ups were scheduled every three months for two years, then every six months  
164 for three years and finally, once a year. Quantitative variables were described as  
165 mean (+/- sd) and compared with the Student's t-test or as median (IQR) and  
166 compared with the Wilcoxon's test depending on the assumption of normality.  
167 Qualitative variables were described as counts (percentages) and compared with the



168 Chi<sup>2</sup> test or Fisher's exact test as appropriate. Survival curves were calculated  
169 according to Kaplan-Meier and compared with the log-rank test from the date of  
170 treatment initiation to the date of: death for overall survival and death or first  
171 recurrence (whichever came first) for disease-free survival. The impact of quantitative  
172 variables on survival was estimated by a single variable Cox proportional hazard  
173 model with a restricted cubic spline to assess the monotonicity of the relation. Cut-  
174 offs were initially defined at the limits of laboratory normal values and subsequently  
175 estimated by a sensitivity analysis of the value, maximizing the difference between  
176 the curves. Hazard ratios and their 95% confidence intervals were estimated with a  
177 Cox PH model. All tests were bilateral and a p value lower than .05 was used to  
178 denote statistical significance. All analyses were done with R 3.4.4 (The R Core  
179 Team, Vienna, Austria).

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181

## 182 **RESULTS**

### 183 *Patients*

184 We included 238 patients. Table 1 shows patient characteristics. The mean age was  
185 45.9 years (+/- 9.9). The tumor histological type was squamous cell carcinoma in 189  
186 (80%) patients. Patients had clinical International Federation of Gynecology and  
187 Obstetrics stages IB2 (n =76), IIA (n=13), IIB (n=122), III (n=18), or IVA (n=9). The  
188 median tumor size was 48.9 mm (range 6 to 120). PET scans were done in the  
189 median time of 8.97 days after the first consultation; staging laparoscopic surgeries in  
190 the median time of 24 days. PET scans were positive in pelvic nodes for 89 patients  
191 (37.5%). After staging surgery, 21 patients (14%) had PA positive nodes. Sixteen  
192 hysterectomies (6.7%) were done after brachytherapy for suspicious residual tumors

193 on MRI 6 to 8 weeks after treatment. For only 6 patients (2.5%), histological residual  
194 tumors were found. The median follow-up was 53 months [range 48-59]. The rate of  
195 relapse was 22% with a median time of 8.24 months (range 0.03 to 67.9). Table 2  
196 lists the localization of recurrence..

#### 197 *Leukocyte, platelet and hemoglobin disorders and statistical analysis*

198 We identified three cut-offs which impacted disease free survival and overall survival:  
199 <12 g/dL for hemoglobin; >10,000/ $\mu$ L for leucocyte; >300x10<sup>9</sup>/L for platelet. For each  
200 of the three biological parameters a score of "0" or "1". A score of "1" is given for  
201 anemia (<12 g/dL), leukocytosis (>10,000/ $\mu$ L) and platelet  $\geq$ 300x10<sup>9</sup>/L. A score of  
202 "0" is given for hemoglobin  $\geq$ 12g/dl, leucocyte  $\leq$ 10,000/ $\mu$ L and platelet <300x10<sup>9</sup>/L  
203 The score is calculated by adding the scores of all three biological parameters  
204 together (with a maximum score of three).

205 Table 3 showed multivariate analysis including our score.

206 This score at the time of diagnosis is a prognosis of disease free survival and overall  
207 survival as shown in Figures 1 and 2 respectively.

208 The PFS for patients with a score of 0 was 94.1 % [87.8-100], 87.3% [78.3-97.4]  
209 87.3% [78.3-97.4] at 12, 36 and 60 months respectively. The PFS for patients with a  
210 score of 1 was 91.7% [86.4-97.4], 79.1% [71.1-88] and 73.1 % [64.1-83.4] at 12, 36  
211 and 60 months respectively. The PFS for patients with a score of 2 was 72.5% [60.7-  
212 86.5], 58% [45-74.6], and 55.1% [42-72.2] at 12, 36 and 60 months respectively]. The  
213 PFS for patients with a score of 3 was 63.9% [45.7-89.4], 56.8% [37.8-85.4], and  
214 56.8% [37.8-85.4] at 12, 36 and 60 months respectively].

215 The OS for patients with a score of 0 was 100 % [100-100], 92.6% [84.9-100] and  
216 92.6% [84.9-100] at 12, 36 and 60 months respectively. The OS for patients with a

217 score of 1 was 99% [97-100], 84% [76.6-92.1] and 82.3% [74.4-91] at 12, 36 and 60  
218 months respectively. The OS for patients with a score of 2 was 89.2% [80.7-98.6],  
219 62.5% [48.9-79.9], and 62.5% [48.9-79.9] at 12, 36 and 60 months respectively. The  
220 OS for patients with a score of 3 was 100% [100-100], 67% [46.8-96], and 58.7%  
221 [37.6-91.5] at 12, 36 and 60 months respectively.

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## 225 **DISCUSSION**

226 In our retrospective series, we suggested a prognostic score based on leucocyte,  
227 platelet and hemoglobin in locally advanced cervical cancer. Our score was easily  
228 used in routine practice due to the cut-offs we defined: anemia for hemoglobin  
229 ( $<12\text{g/dl} = 1$  point), leukocytosis for leucocyte ( $\geq 10\ 000/\mu\text{l} = 1$  point) and platelet  
230  $\geq 300 \times 10^9/\text{L} (= 1$  point). In routine practice, our score could be used as a triage to  
231 define patients with two or three points as at high risk of relapse. Indeed, patients  
232 with two or three points in our score had a dramatic decline of PFS and OS. In the  
233 literature, pre-treatment platelet, leucocyte and hemoglobin were all noted as  
234 prognostic factors.

235

### 236 *Platelet*

237 Cheng et al., recently published a meta-analysis and showed that a pretreatment  
238 thrombocytosis was an independent prognostic factor in cervical cancer.  
239 Unsurprisingly, the author found that pretreatment thrombocytosis was significantly  
240 associated with the FIGO stage, pelvic node status and tumor size . Unfortunately,  
241 the author did not give a platelet cut-off. The studies, which were included in the

242 meta-analysis, suggested a platelet cut-off ranging from 272 x10<sup>9</sup>/L to 400 x10<sup>9</sup>/L.<sup>8</sup>  
243 Kozasa et al., suggested a cut-off at 350 x10<sup>9</sup>/L as an independent prognostic factor  
244 in a series of 684 patients which included 306 stage IIB-IVB treated with  
245 radiotherapy followed by brachytherapy with or without chemotherapy.<sup>13</sup> Moreover,  
246 the author showed that platelet count was significantly superior in terms of prognosis  
247 than a ratio between platelet and lymphocyte.<sup>13</sup> Indeed, two studies showed that the  
248 platelet-lymphocyte ratio was an independent prognostic factor of OS (Zheng et al.,)  
249 and PFS and OS (Chen et al.,) but the two series only included early stage cervical  
250 cancer patients who underwent surgical treatment.<sup>14-15</sup> For our score, we chose a  
251 cut- off for platelet at 300x10<sup>9</sup>/L.

252

### 253 *Leukocyte*

254 Okazawa-Sakai analysed a series of 219 patients with LACC who were treated with  
255 radiotherapy. The multivariate analysis identified pelvic node metastasis, pre-  
256 treatment leukocytosis and pre-treatment neutrophilia as prognosis factors of distant  
257 relapse. Leukocytosis  $\geq 10\ 000/\mu\text{l}$  and neutrophils count  $> 7,500/\mu\text{l}$  were identified as  
258 cut-offs.<sup>16</sup> In the era of chemoradiation, our team published a series which included  
259 113 patients with LACC who were also treated with brachytherapy. In a multivariate  
260 analysis, we found the same cut-off for neutrophils count ( $\geq 7,500/\mu\text{l}$ ).<sup>9</sup> For our score,  
261 we chose leukocyte with a cut-off defined at  $\geq 10\ 000/\mu\text{l}$  which was defined as  
262 leukocytosis in non-hematological malignancies.<sup>15</sup>

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264

265 *Hemoglobin*

266 In 1999, Grogan et al., published a series of 605 patients with LACC who were  
267 treated with radiotherapy (11% received concurrent chemotherapy). The authors  
268 showed that the increase of survival from a hemoglobin level <12 g/dl to a level  
269  $\geq 12$ g/dl was 12%.<sup>10</sup> In 2017, Koulis et al., published a series of 257 LACC treated  
270 with chemoradiation followed by brachytherapy (in 98%).<sup>18</sup> In a multivariate analysis,  
271 an anemia at diagnosis (defined by a hemoglobin  $\leq 11,5$  g/L) was independently  
272 associated with survival (Hazard Ratio 2.76 (1.79 - 4.25) p <0.001).<sup>17</sup> For our  
273 score we chose 12 g/dl . Indeed, according to the World Health Organization (WHO),  
274 anemia is defined as hemoglobin (Hb) levels <12.0 g/dL in non-pregnant women.<sup>19</sup>

275

276 *Score and nomogram*

277 Zheng et al., suggested a nomogram to predict overall survival for early cervical  
278 cancer stage (IA1 to IIA). This nomogram included platelet, leucocyte and  
279 hemoglobin with cut-offs at 217 x10<sup>9</sup>/L, 110 g/L and 7,800/ $\mu$ L respectively. This  
280 nomogram was not tested in LACC. Furthermore, this series did not include data  
281 about treatment as doses of radiotherapy with or without chemotherapy and external  
282 boosts.<sup>20</sup> Koulis et al., in a series of 257 LAAC, showed that (on multivariate analysis)  
283 there was an additional risk of worse PFS 72% vs 42%, [HR 3.05 (95% CI 1.75–  
284 5.35), p < 0.001]and OS 68% vs 37% [HR 3.91 (95% CI 2.00–6.49), p < 0.001] at five  
285 years in patients who had both pre-treatment anemia (defined by an hemoglobin  
286  $\leq 11,5$  g/L) and leukocytosis (> 10 000/ $\mu$ l).<sup>18</sup>

287 Our score has several advantages. Firstly, it is robust due to the number of patients  
288 (n=237) who were treated with the same protocols using PET-CT (to ovoid patients

289 with para-aortic or distant metastasis) followed by a laparoscopic staging ( to ovoid  
290 patients with peritoneal carcinomatosis), chemoradiation followed by brachytherapy  
291 with the same modalities. Secondly, our score is simple due to our defined cut- offs :  
292 10 000/ $\mu$ l for leukocytosis and 12 g/dl for hemoglobin (according to the WHO  
293 definitions) and 300x10<sup>9</sup>/L for platelet. Thirdly, our score can identify patients with a  
294 high risk of relapse (patients with scores of two or three) at the time of diagnosis and  
295 may be benefit dose escalation as neoadjuvant chemotherapy, targeted therapy or  
296 immunotherapy. Two ongoing studies will give us data on new strategies using  
297 chemotherapy. The Phase III Interlace is evaluating weekly induction chemotherapy  
298 followed by standard chemoradiation versus standard chemoradioation alone.<sup>21</sup> The  
299 Phase III Outback trial is evaluating adjuvant chemotherapy following CRT as primary  
300 treatment for locally advanced cervical cancer compared to CRT alone. This study  
301 uses 4 cycles of carboplatin/paclitaxel.<sup>22</sup> Bevacizumab with chemotherapy  
302 significantly increased overall survival in first relapse.<sup>23</sup> Moreover, Bevacizumab  
303 alone significantly increased overall survival in second or more lines of  
304 chemotherapy.<sup>24</sup> Due to those results, Bevacizumab could be an option as an  
305 adjuvant treatment after CRT in patients identifying as at high risk of relapse  
306 (according to our score). The rationale for immunotherapy was supported by the rate  
307 of PD-L1 in squamous cell carcinoma. One ongoing Phase I trial is evaluating  
308 Ipilimumab in the primary treatment of LACC. This study will define the best dose of  
309 Ipilimumab to give together with CRT.<sup>25</sup>

310

311 **CONCLUSION**

312 Our score is simple and easy to use in routine practice. Our score includes three  
313 biological parameters with easily remembered cut-offs: leukocytosis > 10 000/ $\mu$ l,  
314 hemoglobin <12.0 g/dL and platelet>300x10<sup>9</sup>/L. Our score can identify, at the time  
315 of diagnosis, those patients with a high risk of relapse (scores of two or three) and  
316 those requiring dose escalation.

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319 *Conflict of interest statement*

320 Gouy and Morice: Consultancy for Roche

321 Maulard, Chargari, Pautier, Leary, Faron, Genestie, Alwohaibi: no conflict

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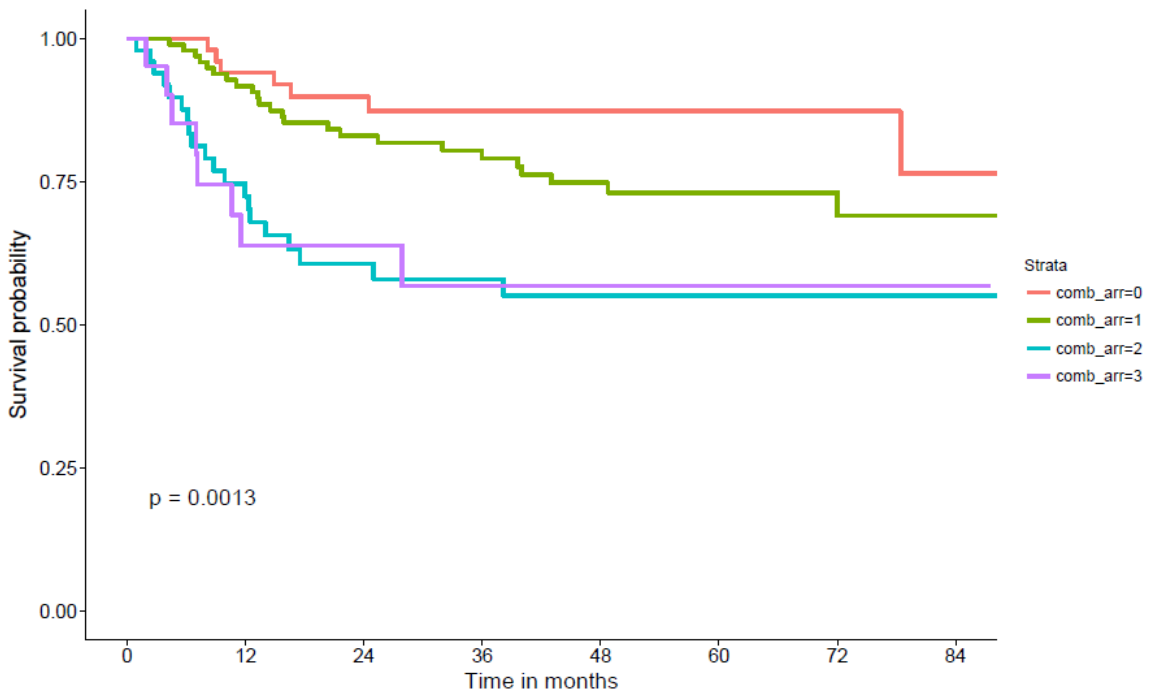
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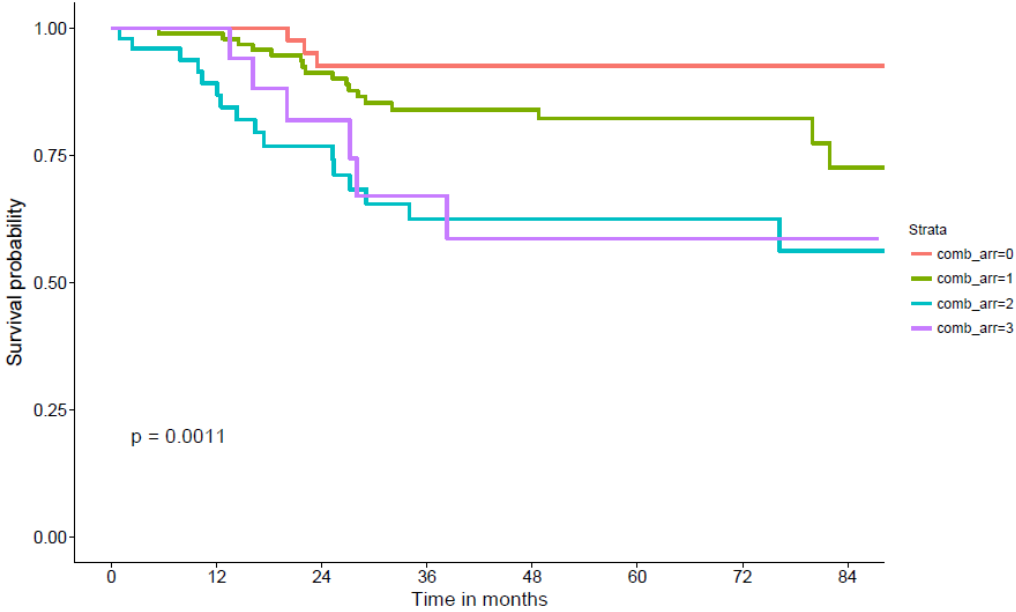
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**Figure 1: Disease free survival**



**Figure 2: Overall survival**



**Table 1: patients' characteristics**

<b>Demographic and Baseline Disease and treatment Characteristics</b>	
<b>Baseline characteristics</b>	
Mean age - year	45.9 (±9.9)
BMI - kg/m <sup>2</sup>	23.8 (23.1-26.7)
Tumor histologic type - no (%)	
Squamous cell carcinoma	189 (80)
Adenocarcinoma	48 (20)
FIGO – no (%)	
IB	76 (31)
IIA	13 (5.5)
IIB	122 (51)
III	18 (7.5)
IV	9 (4)
Size – no (%)	
Median size - mm	48.9 (6-120)
< 40mm	30 (12.7)
40-50mm	89 (37.5)
>50mm	103 (43.5)
Missing	15 (6.3)
<b>Treatment characteristics</b>	
Median time between 1 <sup>st</sup> consultation and PET scan - day	8.97 (1.75-17)
Median time between 1 <sup>st</sup> consultation and surgery* - day	24 (16-32)
Median time between PET scan and surgery* - day	15 (8-24)
Median time between surgery and CRT** - day	19 (13-28)
Positive PET scan – no (%)	89 (37.5)
Pelvic	89
Para aortic	0
Both	0
Positive nodes (histology) - no	21 (14)
Completion surgery after brachytherapy - no (%)	16 (6.7)
Residual disease after surgery*** - no (%)	6 (2.5)

**Table 2 : Relapses' characteristics**

<b>Follow up and relapse</b>		
<b>Median follow up – month (range)</b>		53 (48-59)
<b>Recurrence</b>		
<b>No (%)</b>		53 (22)
<b>Localization – no (%)</b>		
<b>Pelvic nodes</b>		21 (39)
<b>Para aortic nodes</b>		10 (18)
<b>Both</b>		3
<b>Distant</b>		26 (49)
<b>carcinosis</b>		6 (11)
<b>Median time in month</b>		8.24 (0.03-67.9)
<b>Death</b>		
<b>No(%)</b>		40 (16)
<b>Median time in month (range)</b>		21 (0.06-92.9)

**Table 3: multivariate analysis**

Variable	Category	HR	p
<b>score</b>	<b>0</b>	1	0.00036
	<b>1</b>	2.49 [CI 95% 0.72-8.56]	
	<b>2</b>	8.33 [CI 95% 2.39-29.07]	
	<b>3</b>	4.92 [CI 95% 1.16-20.91]	
<b>FIGO stage</b>	<b>IB</b>	1	<0.0001
	<b>II</b>	3.59 [CI 95% 1.44-8.98]	
	<b>III-IV</b>	10.92 [CI 95% 3.65-32.66]	
<b>Histology</b>	<b>adenocarcinoma</b>	1	0.75
	<b>squamous cell carcinoma</b>	0.86 [CI 95% 0.35-2.13]	
<b>Age</b>		0.98 [CI 95% 0.95-1.02]	0.32
<b>Node</b>	<b>negative</b>	1	0.9
	<b>positive</b>	1.06 [CI 95% 0.44-2.55]	