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**PROGNOSTIC VALUE OF POSTTREATMENT FDG-PET IMAGING  
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**ABSTRACT**

**Objectives:** To evaluate the performances of posttreatment FEDG-PET to predict the prognosis of patients treated with concurrent chemoradiotherapy (CT/RT) for locally advanced cervical cancer.

**Materials and methods:** The medical records of 131 patients treated in 9 French academic institutions for IB2-IIB cervical cancer and for which a posttherapy FEDG-PET was performed were reviewed. All patients received CT/RT, possibly completed with vaginal brachytherapy (VBT) and completion surgery. Posttreatment FEDG-PET was performed within 3 months after completion of CT/RT or VBT. Incomplete metabolic response (IMR) was defined as the persistence of FEDG uptake.

**Results:** An IMR was identified in 44 (33.6%) cases. IMR was associated with higher risk of recurrence (aHR=2.8; 95%CI: 1.3-5.7; p=0.006) and death (aHR=4.5 ;95%CI: 1.4-13.8; p=0.009). Completion surgery was performed in 61 (46.9%) patients with histologic cervical residual disease identified in 31 (50.8%). FEDG-PET sensitivity and specificity in predicting cervical residual disease following CT/RT was 48.4% (95%CI: 30.8-66) and 80% (95%CI: 65.7-94.3), respectively.

**Conclusions:** In patients treated with CT/RT for locally advanced cervical cancer, despite limited performances to predict cervical residual disease, posttreatment FEDG-PET is predictive of patients' prognosis and long-term outcome.

**Keywords:** Cervical cancer; prognosis; FEDG-PET; chemoradiation

## Introduction

With 527 624 cases diagnosed in 2012 and 265 672 deaths, cervical cancer is the fourth most frequent cancer in women worldwide and therefore represents a major public health issue [1,2]. Despite recent advances in prevention, diagnosis and treatment, cervical cancer remains associated with severe prognosis and treatment morbidity [1,2]. Although management of early stage cervical cancer is still not standardised, concurrent chemoradiotherapy (CT/RT) is now considered as the therapy of choice for locally advanced cervical cancer [2–6]. Standard treatment consists of 45 to 50 Gy external radiotherapy with concomitant weekly administration of cisplatin-based chemotherapy. To date, the role of completion surgery following CT/RT remains debated, mostly due to morbidity concerns. Although the presence of residual disease after treatment is directly related to the risk of relapse and poor survival, there is still insufficient evidence that completion hysterectomy improves the survival of women with locally advanced cervical cancer who had received CT/RT [7–9]. Despite highly effective initial treatment, approximately one third of patients will recur, generally within the first two years [10]. Patterns of recurrence vary from local, to nodal and, distant recurrences [11,12].

The evaluation of the crude efficiency of CT/RT is one of the current challenges in advanced cervical cancer management. Tools for reliable identification of patients with post-CT/RT residual disease are needed, as such situation will highly impact patients' prognosis, requiring adaptation of management and follow-up. Currently widely used for the initial staging of locally advanced cervical cancer, especially for the characterization of initial pelvic and para-aortic nodal status, recent data suggest FDG-PET CT scan to be efficient in predicting patients' prognosis with an incomplete metabolic response being highly predictive of recurrence and survival [10,13–21]. Less is known about the ability of posttreatment FDG-PET to predict the

presence of pathologically assessed residual disease. This is mainly explained by the absence of systematic completion surgery in most studies and therefore the impossibility of genuine histologic assessment of CT/RT efficiency. Despite very little evidence, current data suggest FEDG-PET to have a low sensitivity for the prediction of residual disease, while specificity is better [22–24]. Finally, in identifying patients with post-CT/RT residual disease and poorer prognosis, it is questionable whether posttreatment FEDG-PET could help to identify which patients may benefit from completion hysterectomy after CT/RT for locally advanced cervical cancer.

The aim of this study was to evaluate the performances of posttreatment FEDG-PET to predict the long-term prognosis of patients treated with CT/RT for locally advanced cervical cancer. Secondary objectives were to evaluate the diagnostic performances of FEDG-PET to predict the presence of pathologically assessed cervical residual disease and to evaluate whether it could help in triaging patients who could benefit from completion surgery.

## **Materials and methods**

### **Patients**

A retrospective multicentre study including patients from 9 French academic institutions was conducted. The medical records of all 1446 patients treated for histologically proven cervical cancer between April 1996 and May 2016 were reviewed. A total of 131 patients with locally advanced cervical cancer (FIGO IB2, IIA and IIB) and for which a posttreatment FEDG-PET was performed after the completion of CT/RT were included. All posttreatment FEDG-PET were performed as part of the patients' routine clinical evaluation at the discretion of the attending physician. The study protocol received ethical approval from the Institutional Review

Board of the “Collège National des Gynécologues et Obstétriciens Français” (CEROG 2016-GYN-0502).

All patients had a cervical biopsy and pre-treatment pelvic MRI. Initial staging was established based on the results of systematic physical examination combined with pre-treatment pelvic MRI. Tumour size and FIGO stage were established based on the results of pre-treatment MRI according to the 2009 FIGO classification system [25]. Because of the retrospective nature of our study, the new 2018 FIGO classification could not be used. When indicated, laparoscopic lymph node staging was performed including pelvic and/or aortic laparoscopic lymph node dissection. The following definitions to describe the LN status were applied: patients were considered node positive (N+) when nodal involvement was identified on the pre-treatment FEDG-PET and/or after positive surgical pelvic and/or aortic nodal staging; they were considered node negative (N-) in case of negative surgical nodal staging; finally nodal status was considered unknown (Nx) in case of negative pre-treatment FEDG-PET without complementary surgical nodal staging or when neither pre-treatment FEDG-PET nor surgical nodal staging were performed.

Treatment modalities were established by a multidisciplinary committee according to French guidelines. CT/RT consisted in pelvic conformational radiotherapy at the total dose of 45 Grays (25 fractions) in 5 weeks combined with 40 mg/m<sup>2</sup> per week of cisplatinium ± 5FU depending on institutions. Additionally, some patients received 15 grays vaginal brachytherapy (VBT). Although all patients received CT/RT, patients could undergo the following treatment strategies: exclusive CT/RT; CT/RT completed with VBT; CT/RT without VBT and with completion surgery; CT/RT followed by VBT and completion surgery.

The decision whether to perform completion surgery was based on the standards of care of each institution. Whilst some departments systematically perform completion hysterectomy, others considered completion surgery only in selected cases of post-treatment residual disease or

progression. Data regarding completion surgery and histologic results of hysterectomy specimens when completion surgery was performed (presence and size of residual disease) were collected.

Posttreatment FEDG-PET was performed within 3 months following completion of CT/RT or VBT when performed in order to assess treatment response. An incomplete metabolic response was defined as persistent cervical and/or nodal FEDG uptake. Cervical incomplete response was defined as a persistent cervical FEDG uptake and nodal incomplete response as a persistent nodal FDG uptake whether pelvic and/or paraaortic.

Follow-up included visits every 3 months during the first 3 years, every 6 months during the 2 following years and annually after 5 years. Follow-up protocol included systematic physical examination and measures of SCC serum levels every 6 months in case of initially elevated SCC. Imaging including FEDG-PET and pelvic MRI was performed in case of clinically suspected recurrence.

### **Statistical analysis**

5-year recurrence-free (RFS) and overall (OS) survivals were estimated. RFS and OS were estimated for the following variables: age, BMI, menopausal status, FIGO stage, histology, tumour size, nodal status, treatment modality and results of posttreatment FEDG-PET (complete or incomplete metabolic response). Multivariate analysis was conducted including variables that are significant RFS and OS prognostic factors in our study and in literature. OS was defined as the time from primary treatment to death or date of last follow-up. RFS was defined as time from primary treatment to recurrence and was censored at the date of last follow-up or death without recurrence. FEDG-PET diagnostic performances in predicting histologic residual disease were evaluated using sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). The reference standard was the presence or



absence of residual disease on hysterectomy specimens after completion surgery. Patient characteristics were reported using sample size (%) for categorical variables and mean  $\pm$  standard deviation for continuous variables. Chi2 statistics were used to compare indicators of diagnostic performances. Kaplan-Meier estimates were used to estimate the event-time distributions, and log-rank test was used to compare the differences among the different groups in terms of RFS and OS. Hazard Ratios (*HR*) in univariate analysis and adjusted Hazard ratios (*aHR*) in multivariate analysis were estimated using Cox model. A p value of  $<0.05$  was considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics version 20.0 (IBM Inc., New York, NY, USA).

## Results

### Patients

A total of 131 patients were included in the study. Patient characteristics are reported in Table 1. Posttreatment FEDG-PET identified an incomplete metabolic response in 44 (33.6%) cases. A cervical and nodal incomplete metabolic response was identified in 42 (32.1%) and 18 (14.8%) cases, respectively. Only 2 patients were diagnosed with isolated nodal incomplete response. No cases of distant FEDG uptake were observed. Completion surgery was performed in 61 (46.9%) patients and histologic cervical residual disease was identified in 31 (50.8%) of these. Mean size of the histologic residual disease was 7.9 mm ( $\pm 13.4$ ). Median post-treatment follow-up was 35 months (95%CI: 26-45). The 5-year RFS and OS were 55.6% and 74.6%, respectively. Among the 47 patients identified with recurrent disease, 17 were found with local recurrence only. Compared with patients with complete metabolic response at posttreatment FEDG-PET, the proportion of patients who developed local recurrence following incomplete

metabolic response was not statistically different: 8 (47.1%) vs. 9 (52.9%), respectively (p=0.526).

### **Recurrence free survival**

An incomplete metabolic response on the post therapy FEDG-PET was associated with higher risk of recurrence (HR: 3.1; 95%CI: 1.7-5.5; p<0.001) (Table 2). Compared to those with complete metabolic response, patients with an incomplete metabolic response had lower 5-year RFS: 67.4% vs. 29.7%, respectively (p<0.001) (Figure 1A). The other factors found to significantly impact the risk of recurrence were BMI (HR: 0.93; 95%CI: 0.88-0.99; p=0.025) and nodal status (HR: 4.4; 95%CI: 2.3-8.4; p<0.001 for N+ patients). There was no significant difference in terms of RFS for age, parity, menopausal status, FIGO stage, histology, tumour size and treatment modality (Table 2). The 5-year RFS for N-, Nx and N+ patients were 73.8%, 49.4% and 29.3%, respectively (p<0.001). In multivariate analysis, only nodal status (aHR: 3; 95%CI: 1.4-6.3; p=0.003 for N+ patients) and incomplete metabolic response on posttreatment FEDG-PET (aHR: 2.8; 95%CI: 1.3-5.7; p= 0.006) were identified as independent prognostic factors of recurrence (Table 2).

### **Overall survival**

The identification of an incomplete metabolic response on the posttreatment FEDG-PET was associated with an increased risk of death (HR: 5.6; 95%CI: 2.2-13.8; p<0.001) (Table 3). The 5-year OS for patients with an incomplete metabolic response was 52.5% vs 85.1% for patients with a complete metabolic response (p<0.001) (Figure 1B). The other variables identified as prognostic factors of OS were: age (HR: 0.95; 95%CI: 0.91-0.95; p=0.009) and nodal status (HR: 5.4; 95%CI: 1.7-16.9; p=0.004 for N+ patients and HR: 6.4; 95%CI: 1.8-22.7; p=0.004 for Nx patients). The 5-year OS for N-, Nx and N+ patients were respectively 92.3%, 54.2%

and 55.8% ( $p=0.002$ ). There was no significant difference in terms of OS for BMI, FIGO stage, histology, tumour size and treatment modalities (Table 3). Independent prognostic factors of death were age (aHR: 0.91; 95% CI :0.86-0.96;  $p=0.001$ ), nodal status (aHR: 13.7; 95% CI: 2.4-79.4;  $p=0.003$  for Nx patients) and an incomplete metabolic response on post treatment FEDG-PET (aHR: 4.5 ;95% CI: 1.4-13.8;  $p=0.009$ ) (Table 4).

### **Diagnostic performances of FEDG-PET in predicting histologic cervical residual disease**

Correlation between posttreatment FEDG-PET results and histologic findings among patients who had undergone completion surgery are summarized in Table 3. FEDG-PET sensitivity and specificity in predicting cervical histologic residual disease after completion of CT/RT was 48.4% (95% CI: 30.8-66) and 80% (95% CI: 65.7-94.3), respectively. Positive and negative predictive values were 71.4% (95% CI: 52.1-90.8) and 60% (95% CI: 44.8-75.2), respectively. Neither histology type, tumour size, nor size of residual disease were found to have a significant impact on the diagnostic performances of posttreatment FEDG-PET.

### **Impact of completion surgery depending on post therapy FEDG findings**

Among the 61 patients who underwent completion surgery, 5-year RFS for patients with and without histologic residual disease after specimen analysis were 41% and 78.4%, respectively ( $p=0.008$ ). The 5-year OS was 59.6% vs. 90.9%, respectively ( $p=0.05$ ). Although not significant, among the 44 patients identified with incomplete metabolic response on post therapy FEDG-PET, completion surgery was associated with better 5-year RFS (40% vs. 14%, respectively,  $p=0.05$ ) and OS (64.5% vs. 40.8%, respectively,  $p=0.11$ ) (Figure 2).

## **Discussion**

This study demonstrates posttreatment FEDG-PET is efficient in predicting the prognosis and outcome of patients with locally advanced cervical cancer treated with systematic CT/RT. Thus, the identification of an incomplete response was significantly associated with decreased RFS and OS. This notable finding is in accordance with previously published literature [13–20,26]. However, compared to previously reported data, the impact of the identification of an incomplete metabolic response on posttreatment FEDG-PET was not the most significant factor for developing recurrence and death from cervical cancer when compared with other patient characteristics and treatment modalities [14,15,26]. This can be explained by the fact that we only considered the results of the sole initial posttreatment FEDG-PET performed within 3 months following the completion of CT/RT while previous studies had considered the results of repeated FEDG-PET imaging performed during patients' surveillance. This point therefore raises the question of the best timing to perform posttreatment FEDG-PET. In accordance with previous literature, we found FEDG-PET to have a low sensitivity for the prediction of residual disease and high specificity [22–24]. As neither the histological type, nor the size and dimensions of residual histologic disease were found to impact the accuracy of posttreatment FEDG-PET, the possible causes of false assessment of the tumour's response remain uncertain. One thing to consider is the possibility of false positive results due to FEDG-PET performed within a too short interval following CT/RT. As differences in time interval between the completion of CT/RT and posttreatment FEDG-PET are very likely in our retrospective cohort, it is questionable whether the timing of posttreatment FEDG-PET might influence its diagnostic performances. Unfortunately, the timing between the end of CT/RT and post posttreatment FEDG-PET was not available for our patients, making it currently impossible to answer to this question. This point should to be considered with caution when interpreting our results.

The benefit of completion surgery following CT/RT for locally advanced cervical cancer remains widely debated and uncertain. Put in balance with its related morbidity and in the

absence of genuine evidence of any improvement of patient's survival and prognosis, the indication of completion surgery cannot be systematically recommended [7–9]. In identifying patients with increased risk of recurrence and death, it is questionable whether posttreatment FEDG-PET could be valuable for the selection of patients that might benefit from completion surgery. Among patients with incomplete response on posttreatment FEDG-PET, although non-significant, those who underwent completion surgery had an improved prognosis, showing lower recurrence rate and lower risk of death. Showing a trend towards an improvement of the prognosis related to completion surgery in that specific group, our results suggest the use of posttreatment FEDG-PET to be promising for selecting patients who could be offered completion surgery. It is however impossible to draw any genuine conclusion from this finding as the small number of patients included, the retrospective nature of our study and the lack of randomization are likely to bias our findings, these results should therefore be considered with caution. To our knowledge, our study is the first to correlate completion surgery with patients' long-term prognosis depending on posttreatment FEDG-PET findings. Previous studies only extrapolated the possibility to indicate completion surgery from the accuracy of posttreatment FEDG-PET to identify residual disease [22,23]. Although our findings show posttreatment FEDG-PET to be insufficiently accurate to select patients who could benefit of completion surgery, we believe the trend towards improved prognosis among patients with identified residual disease to be promising and worthwhile being considered for further prospective randomized trials.

When considering our results, it is questionable whether the difference between the identification of incomplete cervical and/or nodal response might influence the significance of posttreatment FEDG-PET findings. Although, the identification of isolated incomplete nodal response is clinically relevant, this point has been poorly evaluated to date. It appears that, as for cervical evaluation, posttreatment FEDG-PET demonstrates high specificity and low

sensitivity for the identification of residual histologic nodal disease [22,23]. Unfortunately, our findings did not allow to investigate this question as only 18 patients were identified with incomplete nodal response to CT/RT, with most of them being also found with concomitant incomplete cervical response. Only two patients out of the 44 were found with isolated incomplete nodal response on posttreatment FEDG-PET. As lymphadenectomy was not systematically performed at the time of completion surgery, we could not estimate the performance of posttreatment FEDG-PET in predicting nodal histologic residual disease. Thus, when evaluating the ability of PET-FEDG to predict cervical histologic residual disease following CT/RT among the 61 patients who had undergone completion surgery, our analysis was restricted to the sole identification of cervical response on posttreatment FEDG-PET. Estimating the impact of isolated incomplete posttreatment nodal response on prognosis was not possible either. For these reasons, we chose not to differentiate cervical from the nodal response to CT/RT when estimating the ability of posttreatment FEDG-PET in predicting patients' prognosis and outcome. It is however noticeable that the impact on the risk of recurrence and death was not modified when only considering patients with isolated cervical incomplete response.

## **Conclusions**

In patients treated with CT/RT for locally advanced cervical cancer, despite limited performances to predict cervical residual disease, posttreatment FEDG-PET is predictive of patients' prognosis and long-term outcome. Our study did not show any value of posttreatment FEDG-PET for triaging patients that could benefit from completion surgery. Prospective randomized studies are needed to evaluate the benefits of FEDG-PET in this specific indication.

## **REFERENCES**

- [1] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018. doi:10.3322/caac.21492.
- [2] Green JA, Kirwan JM, Tierney JF, Symonds P, Fresco L, Collingwood M, et al. Survival and recurrence after concomitant chemotherapy and radiotherapy for cancer of the uterine cervix: a systematic review and meta-analysis. *Lancet* 2001;358:781–6. doi:10.1016/S0140-6736(01)05965-7.
- [3] Gadducci A, Cosio S, Cionini L, Genazzani AR. Neoadjuvant chemotherapy and concurrent chemoradiation in the treatment of advanced cervical cancer. *Anticancer Res* 2001;21:3525–33.
- [4] Green J, Kirwan J, Tierney J, Vale C, Symonds P, Fresco L, et al. Concomitant chemotherapy and radiation therapy for cancer of the uterine cervix. *Cochrane Database Syst Rev* 2005:CD002225. doi:10.1002/14651858.CD002225.pub2.
- [5] Chemoradiotherapy for Cervical Cancer Meta-analysis Collaboration (CCCMAC). Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: individual patient data meta-analysis. *Cochrane Database Syst Rev* 2010:CD008285. doi:10.1002/14651858.CD008285.
- [6] Lukka H, Hirte H, Fyles A, Thomas G, Elit L, Johnston M, et al. Concurrent cisplatin-based chemotherapy plus radiotherapy for cervical cancer--a meta-analysis. *Clin Oncol (R Coll Radiol)* 2002;14:203–12.
- [7] Kokka F, Bryant A, Brockbank E, Powell M, Oram D. Hysterectomy with radiotherapy or chemotherapy or both for women with locally advanced cervical cancer. *Cochrane Database Syst Rev* 2015:CD010260. doi:10.1002/14651858.CD010260.pub2.
- [8] Motton S, Houvenaeghel G, Delannes M, Querleu D, Soulé-Tholy M, Hoff J, et al. Results of surgery after concurrent chemoradiotherapy in advanced cervical cancer: comparison

of extended hysterectomy and extrafascial hysterectomy. *Int J Gynecol Cancer* 2010;20:268–75.

[9] Sun L, Sheng X, Jiang J, Li X, Liu N, Liu Y, et al. Surgical morbidity and oncologic results after concurrent chemoradiation therapy for advanced cervical cancer. *Int J Gynaecol Obstet* 2014;125:111–5. doi:10.1016/j.ijgo.2013.07.041.

[10] Eifel PJ, Winter K, Morris M, Levenback C, Grigsby PW, Cooper J, et al. Pelvic irradiation with concurrent chemotherapy versus pelvic and para-aortic irradiation for high-risk cervical cancer: an update of radiation therapy oncology group trial (RTOG) 90-01. *J Clin Oncol* 2004;22:872–80. doi:10.1200/JCO.2004.07.197.

[11] Kobayashi R, Yamashita H, Okuma K, Ohtomo K, Nakagawa K. Details of recurrence sites after definitive radiation therapy for cervical cancer. *J Gynecol Oncol* 2016;27:e16. doi:10.3802/jgo.2016.27.e16.

[12] de Foucher T, Bendifallah S, Ouldamer L, Bricou A, Lavoue V, Varinot J, et al. Patterns of recurrence and prognosis in locally advanced FIGO stage IB2 to IIB cervical cancer: Retrospective multicentre study from the FRANCOGYN group. *Eur J Surg Oncol* 2018. doi:10.1016/j.ejso.2018.11.014.

[13] Schwarz JK, Siegel BA, Dehdashti F, Grigsby PW. Metabolic response on post-therapy FDG-PET predicts patterns of failure after radiotherapy for cervical cancer. *Int J Radiat Oncol Biol Phys* 2012;83:185–90. doi:10.1016/j.ijrobp.2011.05.053.

[14] Grigsby PW, Siegel BA, Dehdashti F, Mutch DG. Posttherapy surveillance monitoring of cervical cancer by FDG-PET. *Int J Radiat Oncol Biol Phys* 2003;55:907–13.

[15] Schwarz JK, Siegel BA, Dehdashti F, Grigsby PW. Association of posttherapy positron emission tomography with tumor response and survival in cervical carcinoma. *JAMA* 2007;298:2289–95. doi:10.1001/jama.298.19.2289.

[16] Liu F-Y, Su T-P, Wang C-C, Chao A, Chou H-H, Chang Y-C, et al. Roles of posttherapy



<sup>18</sup>F-FDG PET/CT in patients with advanced squamous cell carcinoma of the uterine cervix receiving concurrent chemoradiotherapy. *Eur J Nucl Med Mol Imaging* 2018;45:1197–204. doi:10.1007/s00259-018-3957-8.

[17] Kunos C, Radivoyevitch T, Abdul-Karim FW, Faulhaber P. <sup>18</sup>F-fluoro-2-deoxy-D-glucose positron emission tomography standard uptake value ratio as an indicator of cervical cancer chemoradiation therapeutic response. *Int J Gynecol Cancer* 2011;21:1117–23. doi:10.1097/IGC.0b013e31821dc8b5.

[18] Siva S, Deb S, Young RJ, Hicks RJ, Callahan J, Bressel M, et al. <sup>18</sup>F-FDG PET/CT following chemoradiation of uterine cervix cancer provides powerful prognostic stratification independent of HPV status: a prospective cohort of 105 women with mature survival data. *Eur J Nucl Med Mol Imaging* 2015;42:1825–32. doi:10.1007/s00259-015-3112-8.

[19] Beriwal S, Kannan N, Sukumvanich P, Richard SD, Kelley JL, Edwards RP, et al. Complete metabolic response after definitive radiation therapy for cervical cancer: patterns and factors predicting for recurrence. *Gynecol Oncol* 2012;127:303–6. doi:10.1016/j.ygyno.2012.08.006.

[20] Dhull VS, Sharma P, Sharma DN, Maharjan S, Suman Kc S, Patel C, et al. Prospective evaluation of <sup>18</sup>F-fluorodeoxyglucose positron emission tomography-computed tomography for response evaluation in recurrent carcinoma cervix: does metabolic response predict survival? *Int J Gynecol Cancer* 2014;24:312–20. doi:10.1097/IGC.0000000000000038.

[21] Grigsby PW. The prognostic value of PET and PET/CT in cervical cancer. *Cancer Imaging* 2008;8:146–55. doi:10.1102/1470-7330.2008.0022.

[22] Motton S, De Lapparent T, Brenot-Rossi I, Buttarelli M, Al Nakib M, Jacquemier J, et al. <sup>18</sup>F-fluoro-2-deoxy-d-glucose-positron emission tomography and locally advanced cervical cancer. *Int J Gynecol Cancer* 2009;19:8–12. doi:10.1111/IGJ.0b013e318197f276.

[23] Ferrandina G, Petrillo M, Restaino G, Rufini V, Macchia G, Carbone A, et al. Can

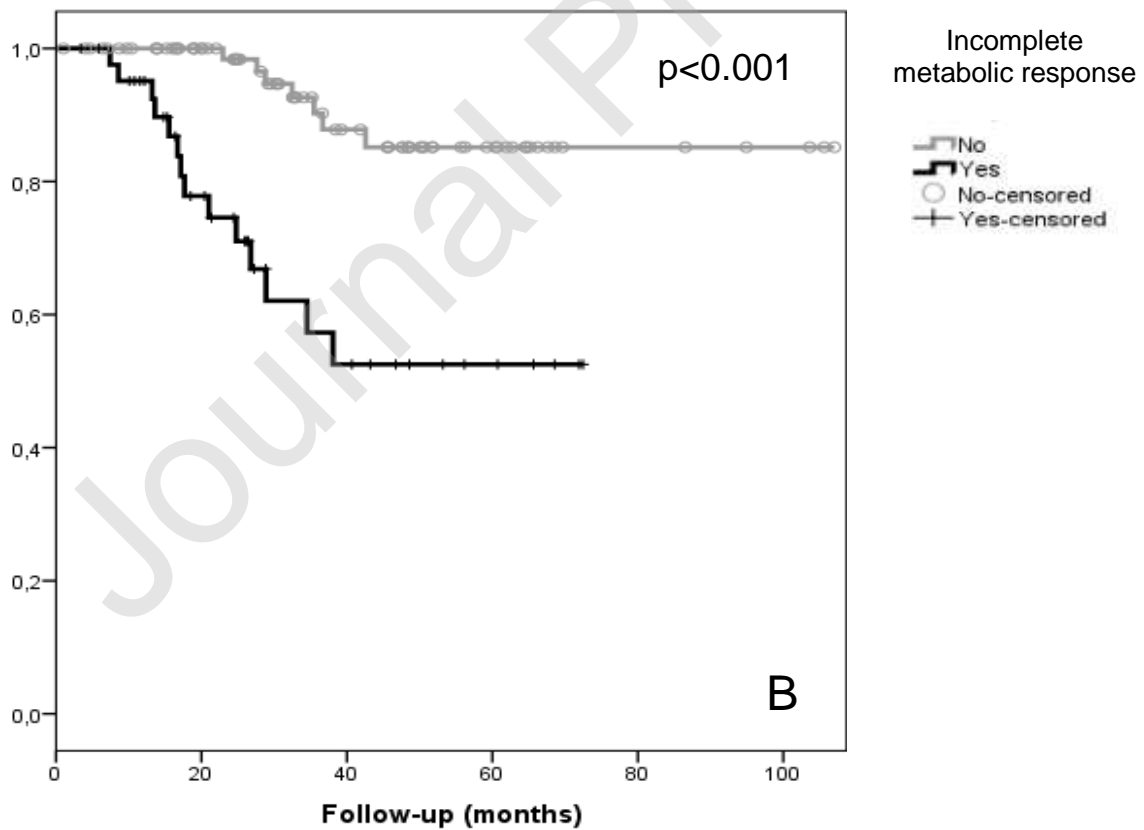
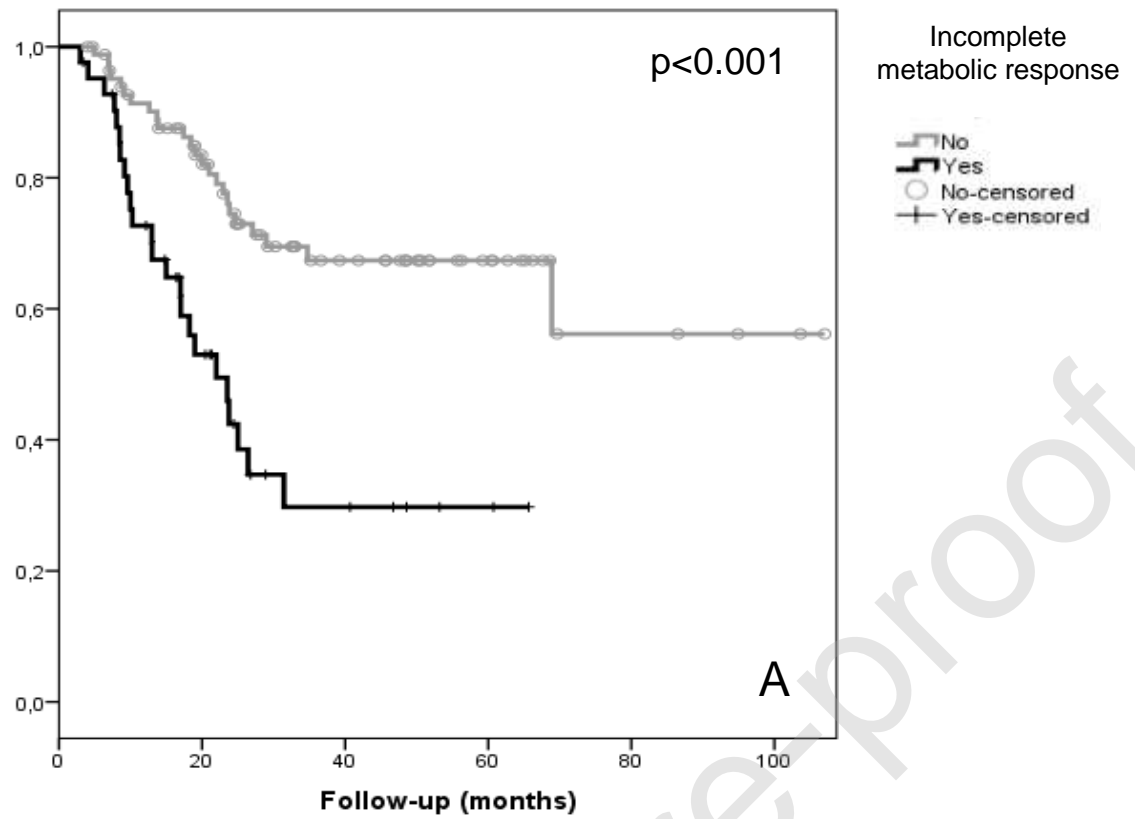
radicality of surgery be safely modulated on the basis of MRI and PET/CT imaging in locally advanced cervical cancer patients administered preoperative treatment? *Cancer* 2012;118:392–403. doi:10.1002/cncr.26317.

[24] Vandecasteele K, Delrue L, Lambert B, Makar A, Lambein K, Denys H, et al. Value of magnetic resonance and <sup>18</sup>F-FDG PET-CT in predicting tumor response and resectability of primary locally advanced cervical cancer after treatment with intensity-modulated arc therapy: a prospective pathology-matched study. *Int J Gynecol Cancer* 2012;22:630–7. doi:10.1097/IGC.0b013e3182428925.

[25] Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. *Int J Gynaecol Obstet* 2009;105:103–4.

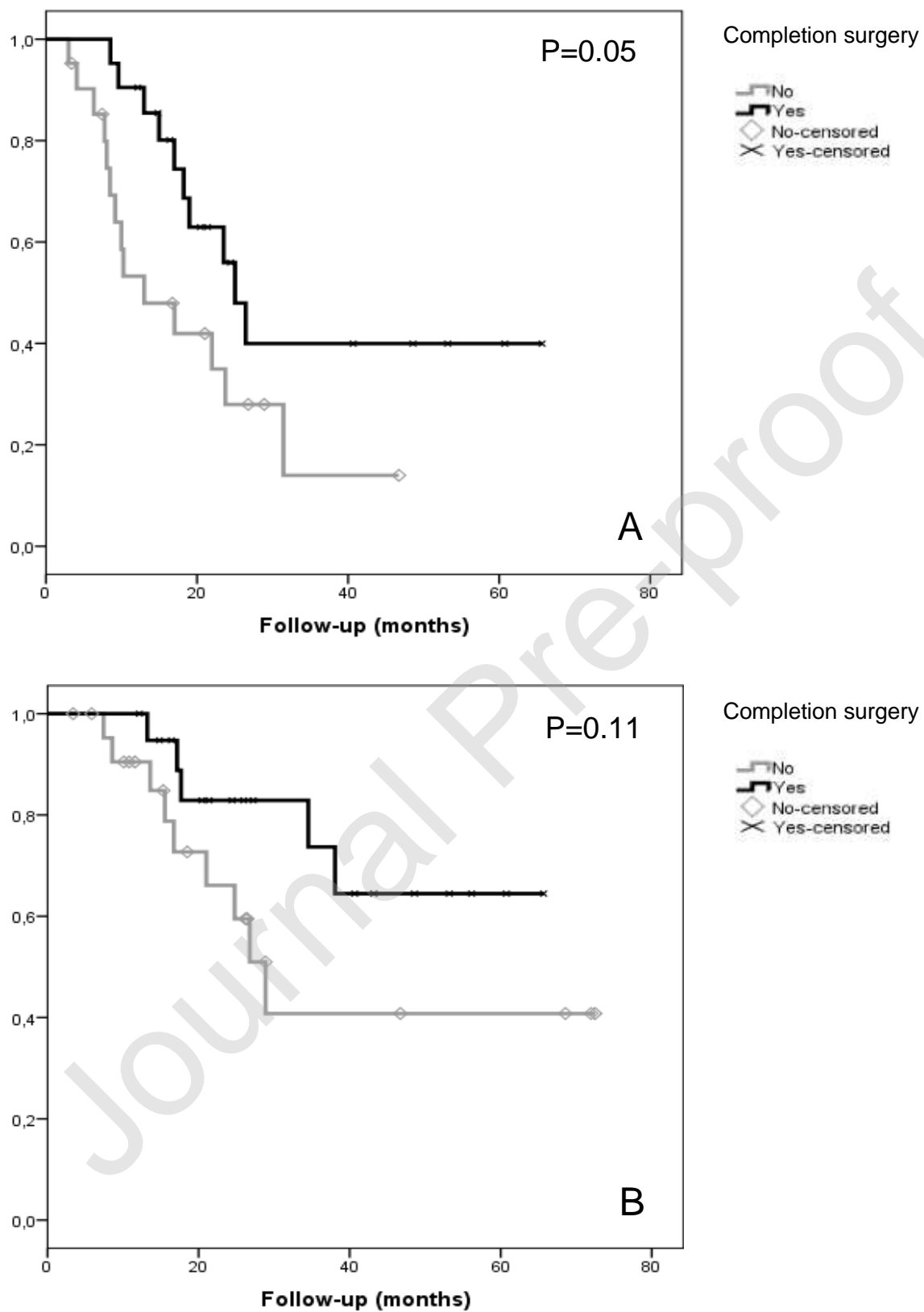
[26] Grigsby PW, Siegel BA, Dehdashti F, Rader J, Zoberi I. Posttherapy [18F] fluorodeoxyglucose positron emission tomography in carcinoma of the cervix: response and outcome. *J Clin Oncol* 2004;22:2167–71. doi:10.1200/JCO.2004.09.035.

**Figure 1.** Recurrence-free (A) and overall (B) survivals based on posttreatment FEDG-PET results



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**Figure 2.** Impact of completion surgery on recurrence-free (A) and overall (B) survivals among patients identified with incomplete metabolic response at posttreatment FEDG-PET



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<b>Age (years) mean (<math>\pm</math>SD)</b>	51.9 ( $\pm$ 11.9)
<b>BMI (kg/m<sup>2</sup>) mean (<math>\pm</math>SD)</b>	26.3 ( $\pm$ 6)
<b>Parity mean (<math>\pm</math>SD)</b>	2.3 ( $\pm$ 1.7)
<b>Menopausal</b>	70 (53.4)
<b>FIGO stage</b>	
IB2	21 (16)
IIA	12 (9.2)
IIB	98 (74.8)
<b>Histology</b>	
Squamous cell carcinoma	100 (76.3)
Other types*	31 (23.6)
<b>Tumor size** (mm)</b>	
Mean ( $\pm$ SD)	45.6 ( $\pm$ 12.4)
$\geq$ 40	86 (68.8)
<b>Nodal status †</b>	
N-	67 (51.1)
Nx	19 (14.5)
N+	45 (34.4)
<b>Treatment modality</b>	
Exclusive CT/RT	13 (9.9)
CT/RT+VBT	57 (43.6)
CT/RT+Completion surgery	10 (7.6)
CT/RT+VBT+Completion surgery	51 (38.9)
<b>Posttreatment FEDG-PET</b>	
Incomplete cervical metabolic response	42 (32.1)
Incomplete nodal metabolic response	18 (14.8)
Incomplete metabolic response §	44 (33.6)
<b>Completion surgery</b>	
Completion hysterectomy	61 (46.9)
Pathologically assessed cervical residual disease	31 (50.8)
Residual tumor size (mm) mean ( $\pm$ SD) £	19.1 ( $\pm$ 16.3)

**Table 1.** Patient characteristics (n=131)

Values are expressed as n (%) unless otherwise indicated

SD: standard deviation; BMI: Body Mass Index; CT/RT: chemoradiation therapy; VBT: vaginal brachytherapy

\* Adenocarcinomas (n=26) and other histology type (n=5)

\*\* Measured on initial pelvic MRI

† N+ (N+ on initial FEDG-PET or N- on initial FEDG-PET and N+ after surgical nodal staging or N+ after surgical nodal staging) ; N- (negative surgical nodal staging); Nx (no initial FEDG-PET and no surgical nodal staging or negative initial FEDG-PET with no surgical nodal staging)

§ Incomplete cervical and/or nodal metabolic response

£ n=13

	<b>HR (95 %CI)</b>	<b>p</b>	<b>aHR (95 %CI)</b>	<b>p</b>
<b>Age</b> (for each extra year)	0.99 (0.96-1.01)	0.346	0.99 (0.96-1.02)	0.506
<b>BMI</b> (for 1 kg/m <sup>2</sup> extra)	0.93 (0.88-0.99)	0.025	0.94 (0.88-1.00)	0.059
<b>Parity</b> (for 1 extra birth)	0.86 (0.71-1.04)	0.120	-	-
<b>Menopausal</b>	0.8 (0.5-1.5)	0.544	-	-
<b>FIGO stage</b> *		0.669		0.584
IB2	1 (ref.)	-	1 (ref.)	-
IIA	0.6 (0.2-2)	0.397	0.5 (0.1-2.2)	0.354
IIB	0.9 (0.4-2)	0.849	0.9 (0.4-2.5)	0.903
<b>Squamous cell carcinoma</b> **	0.7 (0.4-1.3)	0.209	0.5 (0.2-1.2)	0.113
<b>Tumor size</b> (for each extra mm)	1.02 (1.00-1.05)	0.074	0.99 (0.96-1.02)	0.598
<b>Nodal status</b> †		<0.001		0.013
N-	1 (ref.)	-	1 (ref.)	-
Nx	2.2(0.9-5.4)	0.093	2.7 (0.9-8.0)	0.074
N+	4.4(2.3-8.4)	<0.001	3.0 (1.4-6.3)	0.003
<b>Treatment modality</b> §		0.698		0.754
Exclusive CT/RT	1 (ref.)	-	1 (ref.)	-
CT/RT+VBT	0.8 (0.3-1.9)	0.585	1.3 (0.4-4.1)	0.674
CT/RT+Completion surgery	1.0 (0.2-3.8)	0.954	0.6 (0.1-3.3)	0.550
CT/RT+VBT+Completion surgery	0.6 (0.2-1.5)	0.298	1.0 (0.3-3.8)	0.950
<b>Incomplete metabolic response on posttreatment FEDG-PET</b> £	3.1 (1.7-5.5)	<0.001	2.8 (1.3-5.7)	0.006

**Table 2.** Recurrence-free survival prognostic factors

aHR: Adjusted Hazard Ratio; HR: Hazard Ratio; BMI: Body Mass Index; CT/RT: chemoradiation therapy; VBT: vaginal brachytherapy

\* Compared to IB2 (reference)

\*\* Compared to other histology type

† Compared to N- patients (reference)

§ Compared to patients treated with exclusive CT/RT (reference)

£ Incomplete cervical and/or nodal metabolic response



	<i>HR</i> (95 %CI)	p	<i>HRa</i> (95 %CI)	p
<b>Age</b> (for each extra year)	0.95 (0.91-0.95)	0.009	0.91 (0.86-0.96)	0.001
<b>BMI</b> (for 1 kg/m <sup>2</sup> extra)	0.98 (0.91-1.06)	0.639	1.04 (0.94-1.14)	0.469
<b>Parity</b> (for 1 extra birth)	1 (0.77-1.31)	0.991	-	-
<b>Menopausal</b>	0.5 (0.2-1.3)	0.154	-	-
<b>FIGO stage</b> *		0.297		0.951
IB2	1 (ref.)	-	1 (ref.)	-
IIA	0.2 (0-2)	0.194	0.9 (0.1-9.7)	0.907
IIB	0.5 (0.2-1.4)	0.219	0.8 (0.2-3.2)	0.753
<b>Squamous cell carcinoma</b> **	0.5 (0.2-1.4)	0.19	0.3 (0.1-1.2)	0.084
<b>Tumor size</b> (for each extra mm)	1.04 (1.00-1.07)	0.037	0.99 (0.95-1.04)	0.783
<b>Nodal status</b> †		0.007		0.014
N-	1 (ref.)	-	1 (ref.)	-
Nx	6.4 (1.8-22.7)	0.004	13.7 (2.4-79.4)	0.003
N+	5.4 (1.7-16.9)	0.004	3.6 (0.9-13.8)	0.063
<b>Treatment modality</b> §		0.363		0.949
Exclusive CT/RT	1 (ref.)	-	1 (ref.)	-
CT/RT+VBT	0.7 (0.2-2.5)	0.563	1.3 (0.2-7.4)	0.790
CT/RT+Completion surgery	1.6 (0.3-7.9)	0.571	1.1 (0.1-10.6)	0.961
CT/RT+VBT+Completion surgery	0.5 (0.1-1.9)	0.302	0.9 (0.1-6.8)	0.888
<b>Incomplete metabolic response on posttreatment FEDG-PET</b> £	5.6 (2.2-13.8)	<0.001	4.5 (1.4-13.8)	0.009

**Table 3.** Overall survival prognostic factors

HR: Hazard Ratio; HRa: Adjusted Hazard; BMI: Body Mass Index; CT/RT: concomitant chemoradiation; VBT: vaginal brachytherapy

\* Compared to IB2 (reference)

\*\* Compared to other histology type

† Compared to N- patients (reference)

§ Compared to patients treated with exclusive CT/RT (reference)

£ Incomplete cervical and/or nodal metabolic response

		Cervical residual disease on hysterectomy specimen n (%)		
		No	Yes	Total
Incomplete metabolic response on posttreatment FEDG-PET	No	24 (80)	16 (51.6)	40
	Yes	6 (20)	15 (48.4)	21
	Total	30	31	61

**Table 4.** Diagnostic performances of post-therapy FEDG-PET in predicting cervical residual disease in completion hysterectomy specimens following concomitant chemoradiation.

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