Lymph Node Assessment with ^{18}F-FDG-PET and MRI in Uterine Cervical Cancer

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Abstract. *Background: To assess pelvic (P) and/or paraaortic (PA) lymph node (LN) involvement in patients with primary stage IA–IVA cervical cancer, ^{18}F-fluorodeoxyglucose (FDG)-PET, and MRI were compared with histological results. Materials and Methods: Forty patients were prospectively evaluated. Twenty-eight patients underwent radio-chemotherapy (RT-CT) after initial staging and lymph node dissection (LND). Results: PLN metastases were present in 6/31 patients. Sensitivity, specificity, positive and negative predictive values (PPV, NPV) and accuracy in detecting PLN metastases were 67%, 84%, 50%, 91% and 81%, with MRI, and 33%, 92%, 50%, 85% and 81%, with FDG-PET. PALN metastases were present in 5/27 patients. Sensitivity, specificity, PPV, NPV and accuracy were 60%, 73%, 33%, 89% and 70% with MRI and 100%, 77%, 50%, 100% and 81% with FDG-PET in detecting PALN metastasis. Conclusion: FDG-PET is less accurate than MRI for PLN, but more accurate for PALN; FDG-PET cannot replace PA surgical procedures, but could guide them.*

One of the greatest challenges in the management of cervical cancer is pelvic (P) and paraaortic (PA) lymph node (LN) evaluation. Nodal involvement detected by ^{18}F-fluorodeoxyglucose (FDG)-PET in cervical cancer is related to clinical stage and stratifies patient recurrence and survival outcomes for all disease stages (1). In advanced cancer, PALN metastasis is not only a prognostic factor, but it also modifies the radiation therapy field. For this reason, inaccurate assessment of LN involvement can lead to suboptimal treatment (2). MRI is the best imaging modality for defining tumour volume and the depth of stromal invasion; however, the definition of node invasion is mostly based on size, explaining the low sensitivity of 60% with this technique (3). Metastasis in a normal-sized LN can be missed, and inflammatory LN enlargement cannot be reliably distinguished from cancer infiltration with MRI imaging.

FDG-PET is a glucose metabolic rate-based functional imaging technique of malignant cells and has become a diagnostic technique for node evaluation superior to MRI or CT in various malignancies such as lymphoma and lung cancer. Various publications have shown controversial results regarding the sensitivity and specificity of PET in node evaluation in the initial management of cervical cancer (4-7). FDG-PET is currently recommended by the National Comprehensive Cancer Network (NCCN) as part of the pre-treatment assessment for patients with clinical stage IB2 or higher cervical cancer, but its therapeutic implication remains challenging.

This prospective study was designed to estimate the accuracy of FDG-PET for PLN and PALN metastasis detection in patients with uterine cervical cancer compared with MRI. Surgicopathological findings were used as the standard of reference. Comparison between the sensitivity and specificity of both examinations was recorded, and correlation was made with the histology after LND.

Materials and Methods

Patients. The study was performed between September 2004 and December 2007 at the Limoges University Hospital. It included patients, who had a primary, previously-untreated and histologically-confirmed uterine cervical cancer. The Committee for Medical Research Ethics of Limoges approved the study. The patients were managed according to the International Federation of Gynaecology

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and Obstetrics (FIGO) staging system. Initial FDG-PET and MRI imaging were performed in all the patients before treatment. The first patient group (stage IA to IB1) received total hysterectomy with conventional PLN. In cases of metastatic PLNs extemporaneously determined, PA lymphadenectomy and adjuvant radio-chemotherapy (RT-CT) were required. The second group (stage IB2 to IVA) received PA and/or P lymphadenectomy, and RT-CT. After RT-CT, a second FDG-PET imaging and MRI evaluation were performed. The patients underwent extra facial hysterectomy at least 6 weeks after the end of RT-CT and brachytherapy.

PET imaging. The detection limit of FDG-PET in locating tumours or metastases can be around half a centimetre in diameter. Two types of camera were used. In the first PET with coincidence detection using a double head gamma camera (DHC) with a ¾-inch-thick NaI crystal equipped with septa (Axis, Philips Medical System, Cleveland, OH, USA) was employed. This camera was acquired in 1999 and no correction attenuation device was included. The reconstructed transverse spatial resolution of the DHC system is 4.8 mm in the centre. DHC was used in Limoges from the beginning of the study to September 2005 and included 19 patients. Dedicated PET replaced DHC, and was used after September 2005 on 21 patients. Imaging and acquisitions were performed on an integrated FDG-PET/CT using Biograph 6 TEP/TDM (Siemens Medical Imaging Systems, Knoxville, TN, USA). Transaxial PET resolution was 4.5 mm. The fused data on PET/CT improved the anatomic localization of PET abnormalities and reduced the number of equivocal PET interpretations.

The patients were injected with FDG (5.5 MBq/Kg). All the patients fasted at least 6 h before the examination. The peripherical glucose level was systematically assessed. PET was performed only when the blood glucose level did not exceed 140 mg/dl. The FDG studies were acquired 60-115 min post injection. To improve image quality and force diuresis, 0.5 mg of Furosemide per kilogram of body weight (maximum, 40 mg) was injected through an intravenous line, 45 min before data acquisition. DHC and dedicated PET imaging and acquisitions have been described previously (8, 9).

For DHC and PET/CT, the criterion for LN involvement on FDG imaging was FDG uptake greater than that of the surrounding tissue and corresponding to the LN structure on CT when CT was performed.

MRI. The MRIs were performed with a 1.5 Tesla system (Philips Achieva Best, Eindhoven, NL) using a phased-array body coil. For pelvic and abdominal transaxial, sagittal and coronal sections, T2-spin echo, T1-spin echo and T1-spin echo with intravenous gadolinium injection and fat suppression sequences were used. The slice thickness was 5 mm. The criterion for LN involvement on MRI was a short axis diameter greater than 8 mm of the LN with gadolinium uptake (10). Tumour volume was calculated using a geometric model of an ellipsoid: tumour volume=(4/3) $\pi.R_1 . R_2 . R_3$ (with R_1 R_2 and R_3= tumour radius in 3 axes).

Surgical technique. P and PA lymphadenectomies were performed by extra peritoneal laparoscopy (58%) or laparotomy (42%). PALND extended from the left renal vein to the iliac bifurcation (internal – external). PLND extended from the iliac bifurcation to the obturator hole. The external, internal iliac and obturator nodes were classified as P nodes. The common iliac and lomboaortic nodes were classified as PA nodes. This classification was used in the MRI, FDG and surgical evaluations.

Treatment by radio-chemotherapy. The chemotherapy protocol included weekly cisplatin (CDDP) alone (40 mg/m^2/week) or carboplatin (CBCA) alone (area under the curve=2.0) for 5 weeks or the combination of CDDP and 5-fluorouracile (5-FU) (CDDP 20 mg/m^2/day with 5-FU 500 mg/m2/day for 5 days on days 1 to 5, and on days 29 to 33).

External radiation therapy (ERT) was performed with photon energies superior to or equal to 10 mV. Pelvic radiation delivered 45 Gy in 25 fractions *via* a four-field box technique. The superior limit was L4-L5 and the inferior limit depended on the vaginal and or distal parametrial involvement. The field of RT was extended to T12-L1 when PALN involvement was proved. For high dose rate brachytherapy, dosimetry used the ICRU 38 (International Commission on Radiation Units and Measurements) recommendations. Brachytherapy was delivered in 2 fractions of 10 Gy.

Histopathological evaluation. The nodes were macroscopically distinguished and separated. All the nodes were totally examined by conventional techniques and haematoxylin-eosin-safran (HES) staining.

Statistics. The quantitative values are expressed as medians and range. The qualitative values are expressed as percentages and numbers. The imaging methods were evaluated for sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy with their 95% confidence interval (CI), which was calculated using the exact method. Comparisons were made using the Mann-Whitney *U*-test for continuous outcomes. The inter-rater agreement for qualitative variable was assessed using Cohen's Kappa coefficient. A *p*-value of less than 0.05 was considered statistically significant. Analyses were performed with SAS V9 software (SAS Institute, Cary, NC, USA) and MedCalc software (V9.4.2 Frank Schoongans, Mariakerke, BE).

Results

Patients. In total, 42 patients with uterine cervical cancer were enrolled in this study, but two withdrew. Table I summarizes the characteristics of the patients. Eleven patients were classified as stage IA-IB1 and placed in group I. Twenty-nine were classified as stage IB2-IVA and placed in group II. The median delays between FDG, MRI and surgery are shown in Figure 1. P lymphadenectomy was performed on the 11 patients in group I and on 20 patients in group II associated with PA dissection. PA lymphadenectomy alone was performed on 7 patients in group II. Two patients had no PA lymphadenectomy because of technical problems. Eight P lymphadenectomies, in group II, were conducted after RT-CT. LND resulted in the removal of a median of 7 (range, 1-27) P nodes and 7 (range, 1-21) PA nodes. Twenty-eight out of the 29 patients underwent RT-CT after initial staging. Out of these, 21 patients received CDDP plus 5-FU, 7 received platin weekly (6 CDDP and 1 CBCA), and 1 patient refused chemotherapy. All these 29 patients received 45 Gy onto the pelvic field and 4 also had radiation to the PA field (45 Gy). Twenty-two patients had complementary radiotherapy using brachytherapy (21 patients) and/or ERT (2 patients). The median duration of treatment by RT-CT was 36 (range, 29-92) days.

Table I. *Baseline patient characteristics*.

Characteristic	n	%
Total number of patients	40	
Median age at diagnosis, years	53 (32-77)	
Initial FIGO* stage		
Group I		
IA	1	3
IB1	10	25
Group II		
IB2	4	10
IIB	22	55
IIIB	2	5
IVA	1	3
Histology		
Adenocarcinoma	12	30
Squamous cell carcinoma	28	70
Differentiation of the primary tumor		
Poor	11	28
Intermediate	7	18
Well	14	35
Unknown	8	20

*The International Federation of Gynecology and Obstetrics.

Table II. *Pelvic and paraaortic lymph node assessment*.

Pelvic lymph node	Positive Histology		Negative Histology	
	MRI+	MRI–	MRI+	MRI–
PET+	2	0	1	1
PET–	2	2	3	20
Paraaortic lymph node	**Positive Histology**		**Negative Histology**	
	MRI+	MRI–	MRI+	MRI–
PET+	3	2	3	2
PET–	0	0	3	14

Initial evaluation. Pelvic lymph node assessment: PLN metastases were present in 6/31 patients (19%) (Table II); of these, 2 were FDG-positive and 4 MRI-positive. In the 25 histologically negative, 23 were considered FDG-negative and 21 MRI-negative.

The 2 false-positive FDG nodes were inflammatory nodes (one was also a false-positive MRI). Among the 4 false-negative FDG nodes: 2 showed histological supracentimetric involvement, 2 were smaller than 0.5 cm, and one was considered positive only after immunohistochemical staining. Two of these 4 false negatives were true-positive MRI. The 2 false-negative MRI nodes were also negative on FDG-PET, and both were infracentimetric. The 4 false-positive MRI nodes were inflammatory nodes >1 cm (one was a false-positive FDG).

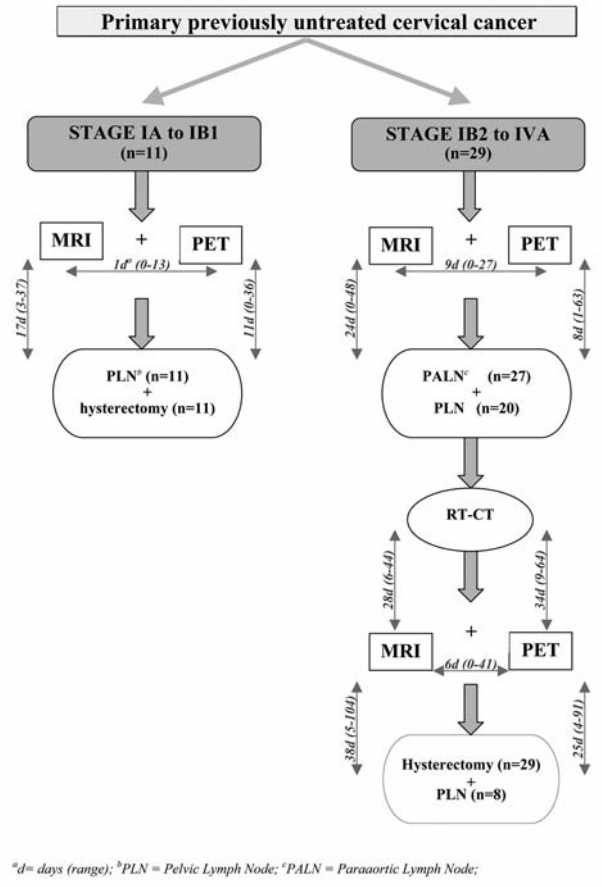

Figure 1. *Flowchart of patients according to stage*.

On a patient-based analysis, the sensitivity, specificity, PPV, NPV and accuracy to detect PLN metastasis were 33% (95% CI, 6.0-75.9), 92% (95% CI, 72.5-98.6), 50% (95% CI, 9.2-90.8), 85% (95% CI, 65.4-95.1) and 81% (95% CI, 62.5-92.6), respectively with FDG-PET and 67% (95% CI, 24.1-94.0), 84% (95% CI, 63.1-94.7), 50% (95% CI, 17.4-82.6), 91% (95% CI, 70.5-98.5) and 81% (95% CI, 62.5-92.6), respectively with MRI.

The Kappa correlation coefficient between imaging modalities and histopathological assessment after surgery was 0.29 (NS) for FDG-PET and 0.45 (p=0.011) for MRI. The value for the Kappa correlation coefficient was 0.40 (95% CI, 0.07-0.72), indicating a moderate level of agreement between MRI and FDG-PET.

Paraaortic lymph node assessment. PALN metastases were present in 5/27 patients (18.5%) (Table II). FDG-PET correctly identified PALN metastasis in these 5 patients and a representative example is shown in Figure 2. Five additional FDG positive PALN were found. As described in Table III, these patients presented with huge tumours, the

Table III. *Characteristics of patients with false-positive FDG-PET paraaortic lymph nodes.*

Patient	FIGO* stage	MRI tumor size (mm)	Histological PLN‡	Number PALN§ resected	MRI PALN	Histological PALN
N°3	IIb	75	+	17	+	Reactional
N°10	IIb	40	–	6	+	Reactional
N°20	IIb	76	+	10	+	Negative
N°25	IIb	56	ND	6	+	Reactional
N°30	IVa	65	–	14	–	Reactional

*The International Federation of Gynecology and Obstetrics; ‡pelvic lymph node; §paraaortic lymph node.

number of LN resected ranged from 6 to 17, and 4 had inflammatory nodes (as shown in Figure 3). Four out of the five were also false positives on MRI.

Six false-positive and 2 false-negative nodes were noted with MRI. The 6 false-positive MRI detected nodes were found to be inflammatory nodes. The 2 false-negative nodes with MRI were true positives with FDG-PET; one of them had a metastasis <0.5 cm.

On a patient-based analysis, the sensitivity, specificity, PPV, NPV and accuracy to detect PALN metastasis were 100% (95% CI, 46.3-100.0), 77% (95% CI, 54.2-91.3), 50% (95% CI, 20.1-79.9), 100% (95% CI, 77.1-100.0) and 81% (95% CI, 61.9-93.7), respectively with FDG-PET and 60% (95% CI, 17.0-92.7), 73% (95% CI, 49.6-88.4), 33% (95% CI, 9.0-69.1), 89% (95% CI, 63.9-98.1) and 70% (95% CI, 49.8-86.3), respectively with MRI.

The Kappa correlation coefficient between imaging modalities and histopathological assessment after surgery was 0.56 (p=0.00029) for FDG-PET and 0.25 (NS) for MRI. The value for the Kappa correlation coefficient was 0.43 (95% CI, 0.08-0.79), indicating a moderate level of agreement between MRI and FDG.

Evaluation after CT-RT. Pelvic lymph node assessment: Eight P lymphadenectomies were performed and one was histologically positive. FDG-PET and MRI were performed respectively in 6 and 7 patients. One false-negative FDG-PET and true-positive MRI was noted. Another one was false-positive FDG-PET and MRI (delay between imaging and surgery was 54 days and 66 days for FDG-PET and MRI respectively) and 2 were only false-positive MRI.

Cervical tumour assessment. Histological evaluations were performed in the 29 patients, in group II. The median delay between surgery and the end of RT-CT was 62 days (range, 13-134) overall for group II, without difference between patients with or without residual tumour. Sixteen cervical tumours showed histological residual disease. FDG-PET was performed in 14/16 patients and only 4 were true positives. MRI was performed in the 16 patients and 10 were true positives.

Thirteen patients had no residual histological cervical disease. Among them, 3 had false-positive FDG-PET and 4 had false-positive MRI.

The false positive imaging could be partially explained by a median delay between the imaging and surgery of 43 days (range, 22-54) for FDG-PET and 35 days (range, 21-66) for MRI. The false negative imaging could be explained by technical resolution: 2 of the false-negative MRI were <0.5 cm.

Follow-up. Patients were followed up from diagnosis for a median of 36 (range, 3-75) months. Recurrent disease was noted in 11 patients at a median of 25 (11-41) months, one in group I and 10 in group II. Seven patients had centropelvic recurrences (one in group I and 6 in group II), 4 had PLN recurrences and 3 had metastases (liver, n=1; lung, n=3).

Discussion

Previous published reports with PET and PET/CT in the evaluation of PALN do not show marked differences for sensitivity from 75% to 85% with PET (5, 11) and from 57% to 100% with PET/CT (12, 13) or specificity from 92% to 96% and 50% to 99%, respectively, for the two machines. In the present study, no difference was found between the two machines in terms of false positive and false negative PA and PLN. Nonetheless, PLN sensitivity was 33% globally with DHC and PET-CT, but increased to 67% in patients evaluated with dedicated PET-CT.

For PLN evaluation, FDG-imaging sensitivity and specificity in the patient-based analysis was 33% and 92%, respectively. The 2 false-positive cases were inflammatory LNs. Two out of the four false-negative PET cases were <0.5 cm in size (less than the spatial resolution of the machine). These results were lower than those achieved in previously published prospective (13-15), and retrospective studies (16-19), which showed a range of 50% to 100% sensitivity, and 89% to 100% specificity. The heterogeneity of the selected patients in published studies, which included stage IVA and metastatic patients with a higher prevalence of involved LN, may explain these differences.

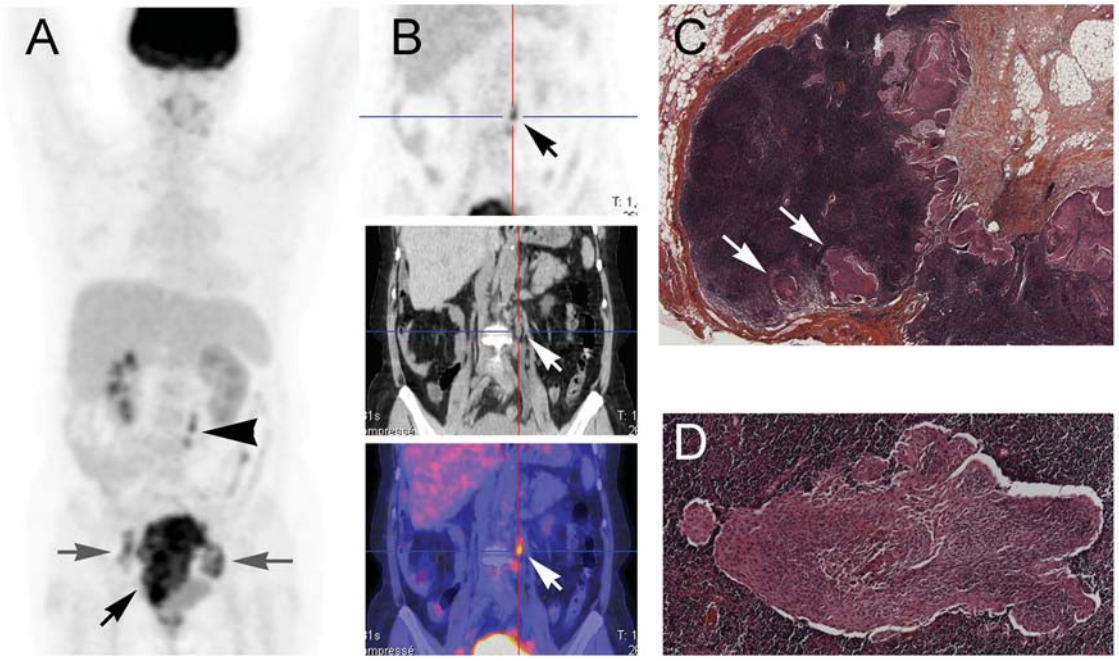

Figure 2. *Paraaortic lymph node metastases of cervical squamous cell carcinoma, FIGO stage IIIb. Cervical cancer (black arrow) with pelvic lymph node (grey arrows) and paraaortic lymph node (PALN) uptake (black head arrow) shown on anterior maximum intensity projection (MIP) view of FDG PET (A). PALN detected on FDG (black arrow, top), on CT (white arrow, centre) and fused data (white arrow, bottom) coronal slices (B). Squamous cell PALN metastases (white arrows) confirmed on pathological HES examination ×25 (C) and ×100 (D).*

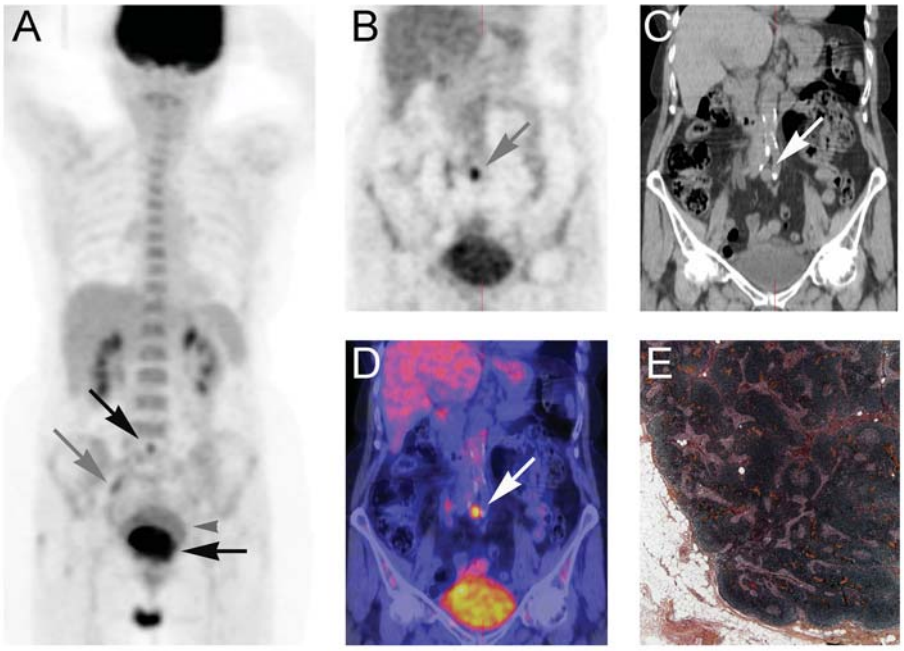

Figure 3. *Inflammatory paraaortic lymph node of cervical squamous cell carcinoma, FIGO stage IVA. Cervical cancer (horizontal black arrow) with right pelvic lymph node (grey arrow) and paraaortic lymph node (PALN) uptake (black arrow) shown on anterior maximum intensity projection (MIP) view of FDG-PET (A). Note that urine was diluted in bladder (grey head arrow) after diuretic injection (A). PALN (arrow) was detected on FDG (B), on CT (C) and in fused data (D) coronal slices. Finally, PALN was inflammatory on pathological HES examination ×25 (E).*

In the present study the histopathological results were chosen as the gold standard, to which the imaging modalities were compared, and rather than just to comparing the two imaging modalities (7, 20) or using clinical follow-up (21). In the present study, the MRI sensitivity and specificity for metastatic PLN involvement were 67% and 84%, respectively, in accordance with studies previously published (12, 14, 22). In the study of Reinhardt *et al*. (14), histological evaluation was performed only when nodes were palpable by surgeons, resulting in no false positive cases.

PALN staging is fundamental in planning extended radiation field therapy (20) and no differences were noted between DHC and PET evaluation. In the present study, FDG imaging sensitivity, specificity, PPV and accuracy in detecting PALN were 100%, 77%, 50% and 81%, respectively. In the literature, retrospective studies showed values ranging from 25% to 50% for sensitivity, 83% to 89% for specificity and 50% for PPV (17, 19). In prospective studies, values ranged from 58% to 100% for sensitivity, 92% to 100% for specificity and 50% to 94% for PPV (5, 11-13). Increased PET sensitivity is related to an increase in the prevalence of PALN metastasis (23). The accuracy of PET-CT imaging in predicting the PLN status is very low in patients with early-stage cervical cancer (24). Patients with stage III-IVA disease may have more large size nodes improving PET sensitivity.

The present results highlighted 5 patients with false-positive FDG, four of which presented inflammatory nodes (Figure 3). One was histologically normal and MRI-positive but 25 months later, presented with a local PA recurrence. In this patient non-optimal initial retroperitoneal surgery was a possibility. The observed rate of false positive (22%) was equivalent to that described by Kang *et al*. but no false negative cases were identified compared to the 8% of the literature (23).

For PA staging, MRI imaging sensitivity, specificity, PPV and accuracy were 66%, 73%, 33% and 70%, respectively. In the 6 false-positive MRI, one patient (who was FDG negative) presented with a PA recurrence 37 months later. In this patient the same question as previously, concerning a non-optimal initial retroperitoneal surgery could be raised. False positive imaging rate does not inform decisions about planning the radiotherapy field, which is only based on the surgicopathological results.

After RT-CT, the present sample was small but, as described by Motton *et al*. (25) FDG-PET results did not seem reliable enough to be the basis of surgical decisions.

In this study, MRI was more accurate than FDG-PET for PLNs, and FDG-PET was more accurate than MRI for PALNs involvement. Pooling the data of MRI and FDG did not significantly improve the sensitivity and specificity for node involvement. However, FDG-PET in conjunction with MRI could improve the detection of extrapelvic metastasis, mainly PALN.

PALN staging is very important for extended radiation field; otherwise, after initial PLN staging only the pelvic areas are systematically included in radiation fields. The question is whether PET could potentially replace the surgical procedure before RT-CT. The survival effect of a complete surgical LN resection is not proved (26).

In higher cancer stages, FDG enables the detection of metastatic LN involvement and visceral localization (excluded in this study), and can guide the surgical approach. Nevertheless, differentiating between malignant nodes and focally-increased glucose metabolism caused by an inflammatory node reaction remains challenging, even with a PET-CT scan. It would actually be better to routinely associate FDG-PET with MRI evaluations only in higher staged cervical tumours for LN evaluation, although the impact on the patient's survival remains unclear.

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