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F18-FDG-PET/CT in the evaluation of patients with suspected recurrent or persistent locally advanced cervical carcinoma

Lucely Cetina,* Alberto Serrano,* David Cantú-de-León,† Delia Pérez-Montiel,‡ Enrique Estrada,§ Jaime Coronel,* Martha Hernández-Lucio,‖ Alfonso Dueñas-González‖

* Oncología Médica y División de Investigación Clínica, † Departamento de Oncología Ginecológica, ‡ Departamento de Patología, § Departamento de Medicina Nuclear, Instituto Nacional de Cancerología. ‖ División de Investigación Básica, Instituto Nacional de Cancerología y Unidad de Investigación Biomédica en Cáncer, Instituto de Investigaciones Biomédicas, Universidad Nacional Autónoma de México.

ABSTRACT

Background. Cervical cancer (CC) represents the second most common neoplasm and the third cause of death by cancer among women. Recurrent or persistent disease depends on the clinical stage, but can be as high as 70%. Positron emission tomography/computed tomography (PET/CT) is an image study that can detect increased glucose uptake in tumor tissues. Material and methods. PET/CT was performed in patients with confirmed CC, who had been previously treated, who developed suspected symptoms of recurrence or persistent disease with or without evidence of disease on a CT scan. Sensitivity, specificity, predictive values from PET/CT, and CT scan were evaluated. Results. Sixteen patients with a mean age of 47.2 years were included in the study from April 2007 to June 2008. Thirteen patients (81.2%) were symptomatic. PET/CT was positive in 14/16 (85.7%), of these, 12 True positive (TP) and two, False positive (FP); meanwhile another two cases were True negative (TN) (12.5%). Cervix, retroperitoneal, iliac, obturator, and mediastinal lymph nodes were the most common anatomic sites detected by PET/CT. Mean number of anatomic sites with high Fluoro-deoxy-D-glucose (FDG) uptake was two sites (range 1-7 sites). PET/CT and CT scan had 100 and 91.7% sensitivity, respectively. Specificity for both was 50%. Positive predictive value (PPV) was 85.4 and 84.6%, respectively. Negative predictive value (NPV) was 100 and 66%, respectively, and accuracy was 88 vs. 81%, respectively. Conclusions. PET/CT has the capability for detecting recurrent or persistent cervical cancer; it detects increased metabolic activity mainly in primary site or lymph nodes. Further PET/CT evaluation is required to confirm the real

F18-FDG-PET/CT en la evaluación de pacientes con sospecha de recurrencia o persistencia de cáncer cervicouterino localmente avanzado

RESUMEN

Antecedentes. El cáncer cervical (CC) representa la segunda neoplasia más frecuente y la tercera causa de muerte por cáncer entre las mujeres. La enfermedad recurrente o persistente se encuentra en relación con la etapa clínica, pero puede ser alta hasta en 70%. La tomografía computada con emisión de positrones (PET/CT) es un estudio de imagen que puede detectar la absorción incrementada de glucosa en los tejidos neoplásicos. Material y métodos. Se realizó PET/CT en pacientes con CC confirmado, que habían sido previamente tratadas y que desarrollaron síntomas sugestivos de recurrencia o enfermedad persistente con o sin evidencia de la enfermedad en una tomografía computarizada. Se evaluaron la sensibilidad, especificidad, valores predictivos de PET/CT y tomografía computarizada. Resultados. Dieciséis pacientes con una edad promedio de 47.2 años se incluyeron en el estudio entre abril 2007 y junio 2008. Trece pacientes (81.2%) presentaron síntomas. PET/CT fue positivo en 14/16 (85.7%). De éstos, 12 catalogados como Verdaderos Positivos (TP) y dos, Falsos Positivos (FP); otros dos casos fueron catalogados como Verdaderos Negativos (TN) (12.5%). Los sitios anatómicos más frecuentes de captación detectados por el PET/CT fueron el cuello uterino, los ganglios linfáticos retroperitoneales, iliacos, obturadores y mediastinales. El número de sitios anatómicos promedio con alta captación de Fluoro-desoxi-D-glucosa (FDG) fueron dos (rango, 1-7 sitios). PET/CT y TC presentaron sensibilidad de 100 y 91.7%, respectivamente. Especificidad para ambos 50%; valor

impact of this study on the early detection of CC recurrence.

Key words. Positron emission tomography/computed tomography (PET/CT). Cervical cancer. Recurrence.

predictivo positivo (PPV) 85.4 y 84.6%, respectivamente. Valor predictivo negativo (NPV) 100 y 66%, respectivamente. Precisión 88 vs. *81%, respectivamente. Conclusiones. El PET/CT tiene la capacidad para detectar el cáncer de cérvix recurrente o persistente; detecta el aumento de la actividad metabólica, principalmente, en el sitio primario o los ganglios linfáticos. Es necesario realizar estudios adicionales sobre PET/CT y esta entidad para confirmar el impacto real de este estudio sobre la detección temprana de la recurrencia de CC.*

Palabras clave. Tomografía computada con emisión de positrones (PET/CT). Cáncer de cuello uterino. Recurrencia.

INTRODUCTION

Cervical cancer (CC) accounted for the second most frequent tumor worldwide; during the year 2007, 555,100 new cases were reported, which represented the third cause of death by cancer among women (309,800 deaths).[1,2] Eighty percent of new cases were registered in countries with fewer financial resources. In México 9,927 new cases were registered during the year 2003 (12.8% of tumors in female population), and 4,326 deaths (rate 8.7 x 100,000)[3] due to CC.

Recurrence of the disease is defined as tumoral growth or distant metastasis development at least 6 months after initial treatment; anatomical sites that exhibit higher frequency of recurrence are pelvis (central or lateral), pelvic lymph nodes (first or second relay), extra-pelvic nodes, and distant metastasis localized in peritoneum, liver, lungs, and/or bones as well.[4] The incidence of recurrent disease fundamentally depends on the initial stage; 10-20% is registered for stages IB-IIA, while incidence becomes as high as 50-70% for stages IIB–IVA.[5] The 2006 annual report of the International Federation of Gynecology (FIGO)[6] confirmed that the most important prognostic variable is the initial clinical stage: the 5-year survival rate is > 90% for stage IA; 89% for IB1; 75% for IB2; 73% for IIA; 65% for IIB; 40% for stages IIIA and -B, 22% for stage IVA, and only 9% for stage IVB.

Recurrent disease is suspected, clinically, by the presence of lumbar pain, sciatica pain, or limb edema; however, in some cases, patients remain asymptomatic. Radiologic studies have been used for detecting recurrent disease; among these, computed tomography (CT) and nuclear magnetic resonance imaging (NMRI)[7] are the most popular. However, they have limitations; for example, CT is not able to differentiate tumor activity from post-radiotherapy fibrosis, and magnetic resonance imaging (MRI) is not able to differentiate among necrosis, edema, hemorrhage, or inflammation.[4,8] On the other hand, positron emission tomography (PET) is a molecular imaging technique that employs radioactive molecules to detect images of molecular interactions of biological processes *in vivo*, thus being able to establish the functional metabolic behavior of tissues, which allows distinguishing recurrent disease with higher accuracy.[10]

A glucose analog, 2-18F-Fluoro-deoxy-D-glucose (FDG), is utilized to evaluate the metabolic activity in tumors. This particular glucose analog is not metabolized and by intracellular trapping, it avidly accumulates. making it possible to be measured by PET.[11] Progress in the knowledge of metabolic behavior of tumor cells establishes that these show increased glycolytic activity favored by several mechanisms, such as the increase of glucose transporting proteins at the cell surface [as example Glucose transporter 1 (GLUT 1) receptors] and the increase of several key enzymes such as hexokinase.[12] In squamous CC, it has been reported that 94% of primary lesions, whether recurrent or persistent, show Glut 1 over-expression, while normal tissue, or in cases with cervical intraepithelial neoplasia (CIN), over-expression is minimal, being no > 15% of basal layer cells –either normal or dysplastic tissues–.[13]

PET efficacy for detecting the recurrence of CC has been reported in some studies.[14-18] In order to reduce limitations of anatomical location of hyperuptake sites detected with PET, their fusion and integration with morphological information obtained by CT has been structured through a metabolic test, positron emission tomography/computed tomography (PET/CT), which is considered an effective imaging technique even for initial staging of cervical cancer.[19,20]

OBJECTIVE

The purpose of this study was to analyze the capability of PET/CT in detecting recurrence and/or

persistence of locally advanced CC treated with standard procedures.

MATERIAL AND METHODS

We conducted a retrospective study from April 2007 to June 2008 in women with confirmed locally advanced CC treated at the Instituto Nacional de Cancerología de México (INCan) and who underwent PET/CT due to suspicious persistent or recurrent disease. Patients had been treated according to international guidelines for their corresponding FIGO clinical stage. Criteria for requesting the PET/CT study were the following:

- Symptoms suggesting recurrence.
- Radiologic findings or clinical data suggesting recurrence.
- Positive Papanicolaou smear.

Abdominal and pelvic CT was also requested and findings were compared in all cases. Recurrent or persistent disease was confirmed by means of biopsy or documentation of progressive disease through serial imaging studies or clinical disease course.

We retrieved information from the clinical chart such as age, initial FIGO stage, histopathological type, treatment, overall survival (OS), symptoms related with the tumor activity, CT and PET/CT findings, number and size of positive sites, biopsy results, and the Maximum standardized uptake value (max SUV).

PET/CT technique

PET/CT with FDG was conducted in the INCan Nuclear Medicine Department using a Siemens BIOGRAPH 16 system. After Intravenous (IV) administration of a 370 MBq (10 mCi) dose of the F-18-labeled FDG, patient was placed to rest in an isolated room during 60 min in order to obtain the uptake phase.

CT images were obtained in simple phase, through 16 detectors, making axial cuts and coronal and sagittal reconstructions from cranium base to upper third of thighs. High-resolution bidimensional PET phase was conducted for 7 min, and finally, image reconstruction was carried out employing filtered back-projection. PET/CT studies were evaluated by two physicians, a Nuclear Medicine Specialist and a Radiologist.

PET/CT analysis

Max SUV indicates the activity found in a lesion and is expressed as related with injected dosage and the patient's weight. Values > 3.0 were considered positive for malignancy.

A study was considered as True positive (TP) in PET/CT when it showed at least one lesion with a positive biopsy. A False positive (FP) study was defined when at least one lesion considered as malignant in PET/CT was determined to be without malignancy by histopathologic study or clinical course. A True negative (TN) study showed no abnormal findings and the patient was followed-up without clinical evidence of malignant disease. False negative (FN) was considered when the study was reported as negative but the biopsy was positive or when the clinical evidence of malignant disease was unquestionable. These definitions are considered reliable and reported by other authors as valid.[8]

Statistical analysis

Statistical analysis was performed by means of descriptive methods. Sensitivity, specificity, positive and negative predictive values, and accuracy for detecting recurrent disease by PET/CT and computerized tomography (CT) were determined according to the following formulas:

- Sensitivity = (TP/TP + FN) x 100.
- Specificity = (TN/TN + FP) x 100.
- Positive predictive value (PPV) = (TP/TP + FP) x 100.
- Negative predictive value (NPV) = (TN/TN + FN) x 100.

Where:

- TP = True positive.
- TN = True negative.
- FP = False positive.
- FN = False negative.

Histopathologic findings and clinical course were considered as the gold standard for comparison.

RESULTS

A PET/CT study was requested in 26 cases, 10 cases were excluded from the analysis, two of these due to lack of the metabolic test, another two because this was used as primary staging method and

Table 1. Patients' characteristics.

Age (years)	Histology	FI-GO stage	Treatment	Indication PET/CT	DFI	Symptoms	CT	PET/CT
60	Squamous	IIB	Ch-RT	Recurrence	15	Present	FP	TN
49	Squamous	IIIB	Ch-RT	Persistence		Present	TP	TP
52	Squamous	IIIB	RT	Persistence		Present	TP	TP
42	Squamous	IB2	Ch-RT	Recurrence	6	Present	FN	TP
31	Squamous	IIB	Ch-RT-Sx	Recurrence	14	Absent	TP	TP
47	Squamous	IVB	Ch-RT	Persistence		Present	TP	TP
47	Squamous	IB2	Ch-RT	Persistence		Present	TP	TP
35	Squamous	IVA	Ch-RT	Persistence		Present	TP	TP
46	Squamous	IIB	Ch-RT	Recurrence	12	Present	TP	TP
52	Adeno	IIIB	Ch-RT	Persistence		Present	TP	TP
33	Squamous	IIB	Sx-RT	Persistence		Present	TP	TP
66	Squamous	IVB	Ch-RT	Progression		Present	TN	FP
57	Squamous	IIB	Ch-RT	Recurrence	10	Present	TP	TP
47	Squamous	IIB	Ch-RT	Persistence		Present	FP	FP
51	Squamous	IIB	Ch-RT	Recurrence	36	Absent	TP	TP
41	Squamous	IIB	Ch-RT	Persistence		Absent	TN	TN

CT: Computed tomography. **DFI:** Disease-free interval (months). **PET/CT:** Positron emission tomography/computer tomography. **Ch:** Chemotherapy. **RT:** Radiotherapy. Sx: Surgery. **TP:** True positive. **TN:** True negative. **FP:** False positive. FN: False negative. **Ad**eno: Adenocarcinoma.

planning for the radiation treatment, three additional cases because they lacked CT –although they had pelvic magnetic resonance imaging (MRI) or ultrasound (US)– and another three because they had no confirmatory biopsy.

The remaining 16 patients were included in this study; median age was 47.2 years (range 31-66 years); general characteristics are shown in table 1. All cases were staged as locally advanced tumors mainly stage IIB in eight cases (50%); predominant histology was squamous cell carcinoma (15/16 cases); initial treatment was concurrent chemoradiation in 13 patients (81.2%), chemoradiotherapy (Ch) followed by radical surgery in one patient, radiotherapy (RT) alone in one patient, and radical surgery and adjuvant RT in another patient. Complete clinical and cytological response was observed in six cases (37.5%), disease progression in one (6.2%), and persistence in the remaining nine patients (56.2%). The median recurrence-free interval was 13 months (range 6-36 months) among cases with complete response.

Persistence or disease recurrence was suspected in 13/16 cases (81.2%) by the referred symptoms, the more frequent being pelvic pain in eight cases (61.5%), vaginal discharge in five (38.4%), and lower limb edema and malaise in three (23.1%); furthermore, three patients had no symptoms. On the other hand, suspicion of recurrent or persistent disease was documented in 12/16 (75%) cases through the gynecological findings and in 13/16 (81.2%) by means of CT findings.

Suspicious anatomic sites detected by CT included the following: Uterine cervix in nine (56.2%); enlargement of retroperitoneal lymph nodes in nine (56.3%); RT-related changes in 5 (31.2%); loss of the inteface in contiguous tissues in four (25%); enlargement of obturator lymph nodes in four (25%); parametrial involvement in three (18.7%), and iliac lymph node enlargement in three cases (18.7%).

PET/CT was considered positive in 14 of the 16 patients (87.5%) (12 TP and 2 FP) and negative in 2/16 (12.5%) (2 TN). Table 2 depicts the anatomic sites detected by the metabolic study; the median number of hypermetabolic anatomical sites was 2.2

Table 2. Sites with increased metabolic activity detected by PET/CT.

Site	Number of patients (%)
Cervix	8 (50)
Retroperitoneal lymph nodes	5 (41.6)
Iliac lymph nodes	4 (33.3)
Mediastinal lymph nodes	2 (16.6)
Obturator lymph nodes	2 (16.6)
Uterine body	1 (8.3)
Lung	1 (8.3)
Vagina	1 (8.3)
Axillary lymph node	1 (8.3)
Retrocrural lymph node	1 (8.3)
Renal hilius lymph node	1 (8.3)
Supraclavicular lymph node	1 (8.3)
Pelvis	1 (8.3)

PET/CT: Positron emission tomography/computer tomography.

Table 3. Statistical analysis of CT and PET/CT in recurrent or persistent locally advanced cervical cancer.

	CT [95% CI]	PET/CT [95% CI]
Sensitivity	91.7 [76-100%]	100
Specificity	50 [1-99%]	50 [1-99%]
PPV	84.6 [65-100%]	85.4 [67–100%]
NPV	66.7 [41-92.3%]	100
Accuracy	81 [62.1-100%]	88 [71.3-100%]
Pearson's coefficient	0.064	0.009

CT: Computed tomography. **PET/CT:** Positron emission tomography/computed tomography. PPV: Positive predictive value. NPV: Negative predictive value. **CI:** Confidence interval.

(range 1-7 sites). The most frequent anatomic sites identified with hypermetabolic activity were uterine cervix in eight cases (50%), retroperitoneal lymph nodes in five (41.6%), iliac in four (33.3%), mediastinal in two (16.6%), and obturator lymph nodes in two cases (16.6%). Median max SUV was 6.9 (range 2.2-14). Positive PET/CT detected lesions size according to anatomic site:

- Lymph nodes, mean 22 mm (range 10-31 mm).
- Uterine cervix, mean 53 mm (range 50-66 mm).

In addition, a 31-mm pulmonary nodule and a 54-mm lesion in the vagina were identified.

Regarding the two patients with FP PET/CTs, one was a 47-year-old woman with stage IIB squamous carcinoma treated with concurrent Ch and vaginal brachytherapy; she referred mild pelvic pain 1 month after her treatment, and CT reported enlargement of obturator chains from 5-7 mm, slight enlargement of the cervix 3.8 x 3.5 cm, and this was associated with alterations in the adjacent fatty tissue, as well as thickening of the vaginal walls. PET/CT detected 5 x 2.5 cm uterine cervix with max SUV 2.2, posterior bladder wall with loss of soft-tissue interface and left parametrial thickening; biopsy reported only necrosis. The patient has been followed up for 18 months with no evidence of tumor activity.

The other FP case was a 66-year-old woman with IVB stage squamous carcinoma and left supraclavicular adenopathy, treated with concurrent chemoradiotherapy (Ch-RT) and vaginal brachytherapy; she developed left pelvic limb edema 2 months after treatment completion; CT identified thickened rectosigmoid walls, alteration in adjacent fat, tissue density, and bladder-wall thickening; PET/CT demonstrated uterine cervical-wall thickening and thickening of the vaginal canal, max SUV 4.5. In the physical examination, a recto-vaginal fistula was documented that led to a colostomy; during this procedure, biopsies were taken and reported as negative for neoplasm. The patient is alive and has been disease-free during the 8 months during which she has been followed up.

In patients with TP PET/CT, 11 had positive findings in the CT and only five had an association with the biopsy report. Quantitative PET/CT analysis, CT, and biopsies are shown in table 3. Metabolic test sensitivity was superior to that detected for CT [100 *vs.* 91.7% (95% Confidence interval [CI], 76-100%), respectively], while specificity was similar in both studies [50% (95% CI, 1-99)]; the PPV was 85.4% (95% CI, 67-100) and for CT, 84.6% (95% CI, 65-100), while the NPV was 100 and 66.7% (95% CI, 41–92.3), respectively; Pearson's correlation test showed statistical significance for PET/CT ($p = 0.009$).

Among the 12 TP PET/CTs, three of these patients were lost with no further treatment and nine patients were treated with Ch within a clinical trial (five cases) or standard therapy for recurrent cervical cancer (four cases). Both cases considered TN and one FP PET/CT were maintained under observation and are disease-free; the remaining FP case was subjected to colostomy for chronic RT effects. At present, only one patient has died as a direct consequence of disease, nine are lost to follow-up, and six are alive (37.5%); survival for the group with the positive PET/CT was 11.5 months (range 1-23 months), and in the group with negative or FP PET/CT, this was 14.5 months (range 9-19 months).

DISCUSSION

Recurrent or persistent cervical cancer is usually evaluated by means of CT and/or MRI, which can identify the presence of new abnormal masses or changes caused by cancer growth in an already known lesion;[21] but this type of imaging studies has limitations in differentiating tumor infiltration from reactive changes, fibrosis, and scar tissue;[8,14,22,23] additionally, both studies exhibit a reduced capability for discriminating lymph-node status, especially when the latter are relatively small.[14]

In our study, PET/CT showed high sensitivity and PNV for identifying recurrent or persistent disease, which allowed to locate hyperuptake areas in uterine cervix, retroperitoneal, iliac, mediastinal and/or obturator lymph nodes with greater frequency than the CT scan; also, the PET/CT showed a

specificity value identical to that of the CT, while its PPV was slightly superior to that of the CT.

The first report of PET in CC was informed by Sugawara, *et al.*, in 1999.[24] More than a dozen studies have reported the usefulness of PET for detecting CC recurrence or persistence, as shown in table 4;[8,14-18,21,24-30] reported sensitivity is highly variable and ranges from 80-100%; specificity from 57.1-100%, and accuracy, from 86.5-97.2%, respectively. Yen, *et al.*,[31] in a study of 150 cases, showed that PET reduces the CT or MRI downstage proportion from 38.4-15.2% and that it added a higher capacity for identifying pelvic recurrence.

In this study, PET/CT was able to identify, with higher frequency, hyperuptake areas from the primary site, and from retroperitoneal, iliac, mediastinal, and obturator nodes. In the literature, PET has informed to have a higher capability to detect lymph-node compromise[8,15,17,30] with 100% sensitivity for the increased metabolic-activity detection in hilar, scalene, mediastinal, and iliac lymph nodes, thoracic wall, liver, and vertebral spine, while its sensitivity is less (75-85%) in pulmonary lesions, retrovesicular region, and para-aortic nodes.[18,31] Lai, *et al.,*[32] found higher sensitivity and specificity as compared with CT or MRI for detecting any recurrent lesion (91 *vs.* 67%; p = 0.001), mainly from a metastatic type (92 *vs.* 60%; p = 0.0003), while all three imaging methods exhibited a similar capacity for identifying local lesions (90 *vs.* 84%; p = 0.631). PET maintains its potential to detect lymph nodes (77.3 *vs.* 45.5%; p = 0.043), distant metastasis (66.7 *vs.* 26.7%; p = 0.028), and local tumors (100 *vs.* 74%; p = 0.462), even in second or third recurrent episodes.[33]

Sakurai, *et al.*,[15] informed that metabolic activity and standardized uptake value (SUV) depend on tumor-lesion size (> 1 cm); SUV was reported to have an average of 3.90 and 2.31 in tumor and non-tumor lesions, respectively (p > 0.05). In our study, SUV in recurrent or persistent lesions was 6.4 in average.

PET is based on the increased glucose uptake by malignant cells, but lack of anatomical information and accurate location of suspicious lesions have comprised PET deterrents.[21] To date, only two studies have reported the PET/CT diagnostic value for detecting CC recurrence.[21,26] Chung, *et al.*,[21] in 52 cases with evident recurrence –by means of clinical, cytological, serological, or imaging studies– reported sensitivity of 90.3%, specificity of 81%, and accuracy of 86.5%. Kitajima, *et al.,* in his study with 52 patients compared the diagnostic capability of PET and PET/CT; the authors informed sensitivity, specificity, and accuracy for PET of 80, 77.8, and 78.8%, respectively, while the figures for PET/CT were 92, 92.6, and 92.3%, respectively, with no statistical difference with respect to sensitivity, but

Table 4. Sensitivity, specificity, predictive values, and accuracy based on FDG-PET or PET/CT in suspected cervical cancer recurrence in the literature.

Author	Year	Number of cases	Sensitivity	Specificity	PPV	NPV	Accuracy
Kitajima[25]	2009	90	90.9	93.5			92.2
Kitajima[26]	2008	52	92	92.6			92.3
Chung[21]	2007	52	90.3	81	87	85	86.5
Chung[14]*	2006	76	96.1	84.4	91.3	92.7	91.7
Sakurai[15]*	2006	25	91.5	57.1			87
Unger[16]*	2004	26 Asx	80	100	100	88.9	
		21Sx	100	85.7	93.3	100	
Wong[27]*	2004	Local rec.	82	97			92
		Sys. rec	100	90			94
Chang[28]*	2004	27	94	78	89	88	
Yen[29]*	2004	55	89.4	98.2	91.3	97.8	96.7
Havrilevsky[17]*	2003	28	85.7	86.7	85.7	86.7	
Ryu[18]*	2003	249	90.3	76.1	35	98.2	
Sun[30]*	2001	20	90	100			
Park[8]*	2000	36	100	94.4			97.2
Cetina, *et al.*	2010	16	100	50	85.7	100	88

*Report based on positron emission tomography (PET). FDG/PET: Fluoro-deoxy-D-glucose/positron emission tomography. PET/CT: Positron emission tomography/computed tomography. PPV: Positive predictive value. NPV: Negative predictive value. Local Rec: Local recurrence. Sys. rec: Systemic recurrence. Asx: Asymptomatic. Sx: Symptomatic.

with a statistical difference in specificity and accuracy ($p = 0.00077$ and 0.00051, respectively).[26] An updated version of this study has been published recently; the study included 90 patients with results that continued to favor PET/CT.[25]

Our study has the limitations inherent in the number of analyzed cases and its retrospective nature, which could have exerted an influence on the observed results; in addition, we did not register the clinical impact that PET/CT can have on the therapeutic decisions made or on the role of PET/CT as a prognostic factor for survival. Observations found in this work are similar to those reported in the world literature, and among these, the following: PET/CT has the capability to detect recurrent tumor activity in asymptomatic patients.

The advantages of adequate recognition and localization of recurrent lesions by PET or PET/CT are reflected in the therapeutic approach and the patient's survival. In our study, we did not record the therapeutic impact related with the metabolic study, as previously mentioned; however, other authors have reported that PET or PET/CT can change the therapeutic approach in up to 65.5% of cases[21,26,29,32] because it reduces the need of further diagnostic tests and unnecessary treatments. Chung, *et al.*,[14] reported a study that included 76 cases with recurrence CC; among these, 20 patients were asymptomatic with a positive PET, of them, eight underwent pelvic exenteration, considering five cases successful; the remaining patients were treated with Ch, RT, or palliative surgery, and survival for these patients was 85.6% at 3 years. Hussain, *et al.*,[34] sustain that PET could be considered as the most reliable study for determining the best candidates for pelvic exenteration.

Early detection for recurrent or persistent disease evidently has an impact on the treatment options offered to patients, and could be considered a prognostic factor as well, because survival expectations in symptomatic patients are very limited when compared with those for asymptomatic patients, that is, 11 *vs.* 42 months ($p = 0.001$), respectively.[35] A multicenter study observed that 50% of 327 patients with recurrent disease were asymptomatic.[36]

The presence of symptoms suggesting recurrent disease has a sensitivity of 71% and specificity of 95%, while these diagnostic parameters are lower for pelvic examination and vaginal cytology[37] because they depend on the physicians' medical experience and also on RT-induced tissue changes. These limitations in diagnostic capability are present even for CT and MRI, especially in asymptomatic patients;[16,18] this has encouraged different groups to evaluate PET as a follow-up method for early identification of the persistence and/or recurrence of CC.

Brooks, *et al.*,[38] detected 9 of 78 asymptomatic patients with recurrent disease (12%) and 21 of 25 symptomatic patients (84%) by means of PET; the 3-year survival estimation was 100% among asymptomatic patients and 35% for those with symptoms ($p < 0.05$). Grigsby, *et al.*,[39] among 152 symptom-free cases followed by PET/CT, identified 20 patients with persistent tumor with a 5-year survival that was less in those with persistence (92 *vs.* 43%), and this was 0% for patients with new areas of abnormal uptake; in this study, FDG persistent uptake at 3 months after local treatment showed to be an important predictive factor for death due to CC death in the multivariate analysis. With the intention of optimizing PET use, it has been suggested that it be conducted in groups of patients with a high risk of recurrence.[29] At present, the main recommendation is to perform PET/CT in cases with suspicion of recurrence, and in some instances as a follow-up study.[9]

CONCLUSIONS

PET/CT has higher sensitivity and NPV compared with CT for detecting CC recurrence or persistence and permits differentiating CC and differentiation at the lymph-node level with higher accuracy than other clinical, serological, or imaging methods. We consider that PET/CT must be performed in all symptomatic patients with any evidence or suspicious manifestations of disease, and that the usefulness of PET/CT as a follow-up method in patients with cervical cancer must be evaluated in comparative and prospective clinical trials.

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Correspondence and reprint request:

David Cantú-de-León, MD
Departmento de Oncología Ginecológica
Instituto Nacional de Cancerología
Av. San Fernando No. 22
Col. Sección XVI, Tlalpan
14080 México, D.F.
Phone: (+52) (55) 5628-0400 Ext.: 277
Fax: (+52) (55) 5573-7037
E-mail: dcantude@yahoo.com

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