Original Article

Utility of the PET/CT in vulvar cancer management

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Objective: To describe the clinical impact of PET/CT in the management of patients with vulvar cancer.

Material and methods: Retrospective analysis of 13 PET/CT studies with 18F-FDG (6 staging and 7 suspected recurrence) corresponding to 10 patients diagnosed with vulvar cancer by biopsy, with a mean age of 64.5 years. The preoperative PET/CT study was analyzed qualitatively according to the lesion region. Surgical excision was carried out, covering all the suspected areas according to the PET/CT study. This was compared with the histopathologic analysis.

Results: Abnormal vulvar PET/CT uptake was found in 9 out of the 13 studies and invasion of adjacent structures in 5 of them (urethra, perianal, vagina). The inguinal–femoral lymph nodes were considered as affected in 3 studies and one pelvic lymph node was also affected. Four of the studies had extralymphatic involvement: 3 in lung and 1 in ischiorectal fossa. The PET/CT showed a 100% sensitivity for the detection of the vulvar lesion in squamous cell carcinomas and 60% in non-squamous cell ones. There was a false positive result for local invasion due to urine contamination. One of the studies with lung metastases was related to a synchronous breast tumor. All the pathological lymph node levels detected in the PET/CT study were confirmed in the histopathology study. No new lesions were identified by surgery. PET/CT changed the therapeutic management in 8/13 studies (61.5%).

Conclusions: PET/CT is postulated as a useful imaging test for the management of vulvar cancer, mainly in the identification of nodal metastases. It may affect both surgical planning and clinical management. Larger series are needed to confirm our findings.

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Resumen

Utilidad de la PET/CT en el manejo del cáncer de vulva

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Palabras clave:
Cáncer de vulva
PET/CT
Metastasis ganglionares
Manejo terapéutico

Objetivo: Describir el impacto clínico de la PET/CT en el manejo de las pacientes con cáncer de vulva.

Material y métodos: Análisis retrospectivo de 13 estudios de PET/CT con 18F-FDG (6 de estadificación y 7 por sospecha de recurrencia), correspondientes a 10 pacientes diagnosticadas de cáncer de vulva mediante biopsia, con una edad media de 64,5 años. Se analizó cualitativamente el estudio PET/CT preoperatorio, según la región de la lesión. Se realizó exéresis quirúrgica, abordando todas las zonas sospechosas según el estudio de PET/CT. Se comparó con el análisis histopatológico.

Resultados: Se encontró captación patológica vulvar en 9 de los 13 estudios, e invasión de estructuras adyacentes (uretra, perineal o vagina) en 5 de ellos. En 3 estudios se consideró afectado los ganglios inguinofoemorales, y en uno de ellos apareció también afectación ganglionar pélvica. Cuatro de los estudios presentaron diseminación extralinfática: 3 en el pulmón y uno en la fosa isquiorectal. La PET/TC mostró una sensibilidad para la detección de la lesión vulvar del 100% en carcinoma epidermoide y del 60% en el no epidermoide. Se encontró un falso positivo en cuanto a invasión local debido a contaminación urinaria. Uno de los estudios con metástasis pulmonares procedía de un tumor de mama sincrónico. Todos los niveles ganglionares patológicos detectados en la PET/TC fueron confirmados en el estudio histopatológico. No se identificaron nuevas lesiones en la cirugía. La PET/TC cambió el manejo terapéutico en 8 de los 13 estudios (61,5%).

Conclusions: La PET/TC se postula como una prueba de imagen útil en el manejo del cáncer de vulva, particularmente en la identificación de la afectación ganglionar, pudiendo influir tanto en la planificación quirúrgica como en el manejo clínico. Se necesitan series más extensas que confirmen nuestros hallazgos.

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Introduction

Vulvar cancer is the fourth malignant gynecological tumor following the cancers of the uterus, ovary and cervix and represents 3–5% of gynecological cancers and less than 1% of all cancers in women. Although the percentage of invasive vulvar cancer has
remained stable in the last decades, the incidence of in situ carcinoma or intraepithelial vulvar neoplasm has doubled in the last years. The mean age of the patients is 65 years, although this seems to be decreasing.1

The risk factors with the greatest impact associated with the prognosis of this disease are both lymph node status and the nature of the primary lesion (size and stromal invasion).2 Inguinal lymph node palpation is not recommended as a diagnostic method since 24–41% of enlarged lymph nodes in these patients do not present tumoral infiltration.3 The concept of the sentinel lymph node in the diagnosis of lymph node involvement in vulvar cancer is currently in the process of validation.

In early stages without lymph node complications the rate of overall survival at 5 years is about 90%, progressively decreasing to less than 53% in patients with lymph node involvement.4 Surgical staging is therefore the only procedure in which the principal prognostic factors are evaluated. Standard surgical treatment consists in radical partial vulvectomy associated or not with ipsilateral or bilateral inguinofemoral lymphadenectomy based on the proximity of the lesion to the midline and tumor stage.6 10–20% of the patients in the initial stages of vulvar cancer present inguinal lymph node micrometastasis and approximately 30% of the patients undergoing curative intent surgery present lymph node dissemination during surgical staging, thereby constituting the greatest prognostic factor of the disease.7,8

Considering the low incidence of vulvar cancer, there are few data on the utility of imaging studies such as CT, MR or PET in the staging or the follow-up of these patients. The aim of this study was to assess the diagnostic yield of PET/CT with 18F-FDG in the management of patients with vulvar cancer and determine its possible impact on the diagnosis and treatment of these patients.

Material and methods

We performed a retrospective analysis of 13 PET/CT studies done on 10 patients diagnosed with vulvar cancer by biopsy. Six studies were of patients with a new diagnosis and 7 with suspicion of recurrence due to previous vulvar cancer. Five of the relapses were treated with surgery and 2 with surgery plus radiotherapy. The mean age of the patients studied was 64.5 years (range: 30–81 years). The histological types found in the preoperative biopsy of the 10 patients were: 4 epidermoid carcinomas, one verrucous carcinoma, one melanoma, 2 Paget’s disease, one eccrine mucinous carcinoma and one vulvar sarcoma.

Thirteen studies were carried out in a total of 10 patients since one woman with epidermoid cancer underwent 3 PET/CT studies: at diagnosis, following neoadjuvant chemotherapy and 8 months after recurrence of the treated vulvar lesion. Another patient diagnosed with verrucous cancer underwent 2 PET/CT studies: one at diagnosis and the other during the recurrence 2 years later.

All the patients underwent the PET/CT study within less than 15 days with respect to the curative intent surgery. Images were acquired 60 min after the intravenous administration of 370 MBq of 18F-FDG, at 3 min per field using low dose CT in a Discovery ST PET/CT equipment (GE Healthcare). Water was used as the negative oral contrast prior to image acquisition.

The findings were analyzed by 2 independent observers by qualitative analysis of the lesions considered pathologic and were classified according to their localization: vulva, inguinofemoral lymph nodes, pelvic lymph nodes, invasion of adjacent structures and other distant localizations.

Surgical resection was performed as either radical vulvectomy or partial radical vulvectomy or hemivulvectomy with excision of the lesion and margins of more than 1 cm associated or not with ipsilateral or bilateral inguinofemoral lymphadenectomy based on the proximity of the lesion to the midline and tumor stage. All zones suspicious of malignancy were also surgically resected according to the results of the PET/CT study. The surgical procedures performed included: 6 hemivulvectomies, 4 radical vulvectomies, 4 left inguinal lymphadenectomies, 2 right inguinal lymphadenectomies and one pelvic lymphadenectomy.

The PET/CT findings were postoperatively compared with the histopathological analysis considered as the reference method. After surgery the patients were followed for a period of no less than 6 months.

Results

The results of the PET/CT are described in Table 1. Nine of the 13 studies were considered to have pathological uptake; 5 studies were performed in patients with recurrence of previously treated vulvar cancer.

The 4 PET/CT studies which did not demonstrate significant hypermetabolism in the vulvar lesion were the 2 Paget’s diseases, the verrucous carcinoma and the eccrine mucinous carcinoma.

The morphology of uptake in the vulvar lesion varied greatly, having a linear (1 study), nodular (5 studies) appearance with a poorly delimited plaque or mass form (3 studies) (Fig. 1).

Invasion by contiguity was diagnosed by PET/CT in 5 of the 13 studies. Three corresponded to the same patient with epidermoid cancer, another to melanoma and the last to a epidermoid cancer. Invasion of the perineal raphe, the urethra, the vaginal introitus and the anus was observed.

With regard to lymph node involvement, 3 studies suggested ipsilateral inguinofemoral lymph node involvement, corresponding to 1 epidermoid cancer, 1 nodular melanoma and 1 Paget’s disease. In the latter case involvement of the external iliac and left obturator lymph nodes was visualized (Fig. 2).

Five studies presented extra-lymph node findings. One tumoral implant was observed in the left ischiorectal fossa in a patient with epidermoid cancer (Fig. 3). Three studies showed pulmonary nodules suggestive of metastasis, corresponding to one epidermoid cancer, one nodular melanoma and sarcoma. In one of the studies an adrenal mass was observed with marked glucidic avidity.

Comparison with histologic results

The PET/CT findings were compared with the histopathological analysis of the lesion following surgery, considering this analysis as the method of reference (Table 1).

Diagnosis of the primary lesion

PET/CT correctly identified the malignant vulvar lesion in 9 of the 13 studies (69.23%). Of the 4 patients not presenting pathologic hypermetabolism in the tumor (30.76%) 3 were patients with well-differentiated tumors (2 Paget’s disease and 1 verrucous carcinoma), Two studies were carried out in the patient with verrucous carcinoma, one for staging of a millimetric lesion in which the lesion was not detected, and the other was performed in a centimetric lesion for suspicion of recurrence 2 years later, detecting pathologic hypermetabolism. The fourth patient in whom the vulvar lesion was not detected corresponded to an eccrine mucinous carcinoma determined by biopsy, and the tumor was not found in the surgical piece.

Infiltration by contiguity

Invasion by contiguity to neighboring structures was correctly diagnosed in 4 of the 13 studies (3 corresponded to the same patient
Table 1
PET/CT findings, anatomopathological correlation and treatments.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Study n.</th>
<th>PET/CT findings in region of vulvar cancer</th>
<th>PET/CT findings outside the vulva: lymph node involvement and distant metastasis</th>
<th>Surgical and non-surgical treatments performed after PET/CT, anatomopathological findings after surgery and changes in treatment due to PET/CT findings</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Histological type of vulvar tumor</td>
<td>Staging/recurrence PET/CT in vulvar region</td>
<td>Inguino-femoral lymph nodes</td>
</tr>
<tr>
<td>P1</td>
<td>1</td>
<td>Epidermoid</td>
<td>Recurrence (S + RT + CT) + Right focal region</td>
<td>+Left inguinal</td>
</tr>
<tr>
<td>P2</td>
<td>1</td>
<td>Epidermoid</td>
<td>Staging + Central focal region</td>
<td>–</td>
</tr>
<tr>
<td>P3</td>
<td>1</td>
<td>Epidermoid</td>
<td>Staging 1st PET: +Large vulvar mass with infiltration of the vaginal introitus and anus (after neoadjuvant CT)</td>
<td>–</td>
</tr>
<tr>
<td>P4</td>
<td>1</td>
<td>Epidermoid</td>
<td>Re-staging 2nd PET: +Large vulvar mass with infiltration of vaginal introitus and the anus</td>
<td>–</td>
</tr>
<tr>
<td>P5</td>
<td>1</td>
<td>Nodular melanoma Eccrine mucinous</td>
<td>Recurrence (S) + Left focal region and perineum</td>
<td>+Left inguinal</td>
</tr>
<tr>
<td>P6</td>
<td>1</td>
<td>Staging</td>
<td>Staging</td>
<td>–</td>
</tr>
<tr>
<td>P7</td>
<td>1</td>
<td>Verrucous</td>
<td>Staging 1st PET: –</td>
<td>–</td>
</tr>
<tr>
<td>P8</td>
<td>1</td>
<td>Paget’s disease</td>
<td>Recurrence (S)</td>
<td>–</td>
</tr>
<tr>
<td>P9</td>
<td>1</td>
<td>Paget’s disease</td>
<td>Recurrence (S)</td>
<td>–</td>
</tr>
<tr>
<td>P10</td>
<td>1</td>
<td>Sarcoma</td>
<td>Recurrence (S)</td>
<td>+Right linear region</td>
</tr>
</tbody>
</table>

+, pathological hypermetabolism; –, no findings; ++, histological confirmation of malignancy; –−, no histological evidence of tumoral disease; Study n., study number; S, surgery; Patient, patient number; CT, chemotherapy; RT, radiotherapy; LND, lymph node dissection.
with epidermoid carcinoma and the other to a melanoma). One false positive result was observed on characterizing uptake as infiltration of the urethra in an epidermoid cancer which could not be demonstrated by histological analysis.

**Lymph node involvement**

Regarding the assessment of lymph node metastases at all the pathologic lymph node levels detected on PET/CT, both those visualized in inguinofemoral lymph nodes (3 out of 13) and those in the pelvic lymph node chains (1 out of 13) were confirmed in the post surgical histopathologic study. Involvement of lymph node levels other than those visualized by the PET/CT were not identified during surgery or in the histopathologic studies.

**Distant metastasis**

The patient presenting the hypermetabolic adrenal mass was studied by MR, being characterized as an adrenal adenoma supported by a follow-up of more than 36 months in which no changes suggesting another etiology were observed. The tumoral implant in the ischiorectal fossa was also confirmed by pelvic MR. High resolution CT was performed in the 3 studies presenting lesions suggestive of pulmonary metastasis to confirm the findings. In one of these patients a biopsy of one pulmonary nodule was also carried out, corresponding to a synchronous breast tumor not identified by PET/CT. The other 2 studies with pulmonary nodules were attributed to metastasis of vulvar cancer considering the absence of another probable etiology in the extension study and progression in follow-up CT studies.

**Modification of the treatment**

With regard to the changes in therapeutic approach following the PET/CT findings, the treatment was modified in 8 of the 13 studies performed (61.5%) (Table 1). In 2 studies detecting pulmonary metastasis vulvar surgery was ruled out and systemic chemotherapy was initiated. In the third...
study with pulmonary metastases, surgery of the vulvar tumor was carried out in addition to chemotherapy since the metastases were demonstrated to be due to a synchronous breast tumor. The treatment was modified in the patient presenting the implant in the ischiorectal fossa, was treated with neoadjuvant chemotherapy and delayed surgery. In another patient a possible unknown area of recurrence was observed in the perineal raphe. Extensive surgery and adjuvant radiotherapy were planned in the 3 patients with inguinofemoral and pelvic involvement.

**Discussion**

Ninety percent of vulvar carcinomas are squamous or epidermoid cell carcinomas. In our group only 50% of the patients presented the most common histological type, with the remaining 50% showing infrequent histology, probably related to our hospital being one of reference for this disease.

It is also of note that 3 out of the 4 studies without pathologic uptake in the vulvar lesion in our study coincided with a well-differentiated tumor or with scarce superficial intraepithelial tumor load which may explain this scarce glucidic avidity. One of these lesions was also millimetric which may have impeded detection of the lesion. The fourth patient in whom the vulvar lesion was not detected corresponded to an eccrine mucinous carcinoma diagnosed on biopsy, with no tumor being found in the surgical piece probably due to complete tumor resection during the biopsy and prior to the PET/CT. Discarding this last case since there was no vulvar tumor at the time of the study, the PET/CT correctly identified the vulvar lesion in 76.9% of the studies.

With respect to the false positive result found on characterization of an infiltration of the urethra not demonstrated in the histological study, this finding may be explained by urinary contamination in the zone given the difficulty in isolating the perineum and the vulva from the exit of the urine. This aspect should be taken into account as a possible cause of false positive results on evaluation of these studies.

The model of the spread of vulvar cancer is influenced by the histology. Well-differentiated lesions tend to disseminate along the surface with minimum invasion while undifferentiated lesions tend to have a greater probability of invasion to adjacent organs or through the lymphatic system toward the inguinofemoral and pelvic lymph nodes. The fact that joint evaluation of lymphatic involvement and tumor size is the prognostic factor of greatest impact in vulvar cancer and that the staging of these patients is always surgical makes the use of these imaging techniques prior to this surgical approach very important. Current data indicate that the rate of survival of patients with lymph node metastasis is less than 50%.

Although several MR approaches have been made in vulvar cancer in the last years, data regarding the sensitivity of these approaches vary greatly which may be explained by the different parameters used. Bipat et al. studied MR in the assessment of lymph node involvement in 60 patients with vulvar carcinoma and, among other parameters, reported a sensitivity of 52%. These authors concluded that, at present, standard MR has no role in this disease. With regard to CT there is no literature of diagnostic value in this type of cancer.

There are also few reports on the study of the utility of PET/CT in cancer of the vulva probably in relation to its low incidence. In
2002 Cohn et al. described a series of 15 patients diagnosed with epidermoid cancer of the vulva evaluated by PET study (not PET/CT). They reported a sensitivity of 67%, a specificity of 95% and a positive predictive value of 86% in the detection of lymph node involvement.

During the 41st annual meeting of the Society of Gynecologic Oncology in March 2010 Viswanathan et al. (Dana Farber Cancer Institute of Boston) presented the largest retrospective series to date. The abstract included 51 patients diagnosed with vulvar carcinoma. The patients were divided into 3 groups according to PET/CT study prior to surgery (16 patients), post surgery (19 patients) and not surgical due to PET/CT findings (16 patients). The predictive value described was 95% for the epidermoid carcinoma and 71% for the adenosquamous and adenosquamous combined. It is of note that 88% of the presurgical studies presented uptake in the vulvar lesion, with 2 false negative results. In addition, inguinofemoral lymph node involvement was found in 38% of the studies. Of the 19 studies undertaken after surgery, 84% presented some type of tumor involvement, and in 68% residual disease was observed in the vulva. The results of the PET/CT led to a change in the therapeutic management of 18 of the 19 patients in this group. Their complete results could not be reproduced since these were collected in a report and have not yet been published.

Our results are similar to those presented by the Dana Farber Cancer Institute, being promising in both the detection of the primary lesion and for the discrimination of lymph node involvement, with an important impact on the therapeutic management of the patients due to the PET/CT findings. In this latter case the contribution of PET/CT seems to be undoubtful with respect to both the surgical planning, attempting to minimize the morbidity or surgical extent, as well as the avoidance of unnecessary surgery due to tumor stage or in the association of neoadjuvant or adjuvant chemotherapy and/or radiotherapy.

Conclusion

In light of the results of our study and despite the small sample size we believe that PET/CT may be a very useful imaging test in the management of vulvar cancer, particularly in the identification of metastatic lymph node involvement, contributing to both surgical planning and clinical management including the association of other treatments. Nonetheless, more extensive series are needed to confirm our findings.

Conflict of interests

The authors declare no conflict of interests.

References