Whole-body [18F]fluoro-2-deoxyglucose positron emission tomography scan as combined PET-CT staging prior to planned radical vulvectomy and inguinofemoral lymphadenectomy for squamous vulvar cancer: a correlation with groin node metastasis

M.W. Kamran, F. O'Toole, K. Meghen, A.N. Wahab, F.A. Saadeh, N. Gleeson

Division of Gynecological Oncology, Department of Obstetrics & Gynecology, Trinity College & St James's Hospital, Dublin (Republic of Ireland)

Summary

Surgery is the mainstay of treatment for vulvar cancer. FIGO staging requires histopathological detail of the primary tumor and inguinofemoral lymph nodes but groin node dissection carries a substantial risk of short and long-term morbidity. The trend in current practice is towards sentinel lymphadenectomy for cancers with a low risk of metastases. Full lymphadenectomy is undertaken if the sentinel lymph node contains metastasis. The predictive value of 18F-FDG-PET in preoperative assessment of the groin in vulvar squamous cancer was assessed in retrospect at a single institution. A period of three years prior to the introduction of sentinel lymph node mapping was chosen in order to have full histopathological assessment of inguinal and femoral lymph nodes available as the gold standard for correlation with positron emission tomography-computerized tomography (PET-CT) to determine the accuracy of the enhanced radiological technique. In patients with histologically proven metastases to groin nodes, comparisons between PET-CT positive (True-positive/TP) and negative (False-negative/FN) groups vis-à-vis histology showed a tendency towards higher FDG avidity in the vulvar lesions, more bilateral nodes, multiple metastases, larger metastases and more extra-capsular extension in the TP group. Calculations per patient for PET-CT yielded a sensitivity of 50% and specificity at 100%. The positive predictive value (PPV) was 100% and the negative predictive value (NPV) was 57.1%. The test accuracy was 70% per patient. The high positive predictive value of PET-CT can be used to advance treatment planning prior to surgical staging of patients identified with Stage III disease. The poor sensitivity makes it unsuitable as a substitute for staging lymphadenectomy.

Key words: PET-CT; Vulvar Cancer; Specificity; Positive Predictive Value.

Introduction

Carcinoma of the vulva accounts for 5% of all gynecological malignancies [1]. Squamous is the predominant histological type accounting for 75% of these cancers [2]. FIGO staging for vulvar cancer (2010) includes tumor size, lymph node status, and the presence of local and distant metastases [3]. Lymph node status is the best predictor of survival and histological assessment of nodes is an integral part of the staging surgery [4]. Stage III disease is defined by lymphatic metastases. Clinical palpation is inaccurate [5]. Radiological detection on ultrasound or magnetic resonance imaging (MRI) of central necrosis is strongly suggestive of metastasis but improved radiological assessment is needed for the assessment of smaller or undetectable lymph nodes [6-12]. Positron emission tomography (PET) demonstrates metabolic activity in tumors and integration of the modality with computerized tomography (CT) accurately localizes that active tumor. This newer imaging modality has been shown to enhance the staging and management of malignancies such as malignant melanoma [13-15] and squamous cancers at other sites [16,17]. Cervical cancer is the most frequent squamous cancer of the genital tract and PET-CT has established a place in the pretreatment assessment of that disease [18-23]. The value of PET-CT in the preliminary assessment of squamous cancer of the vulva remains to be established. De Hullu *et al.* reported sensitivity of 75% and specificity of 62% per groin assessed using L-[1-11C]-tyrosine as a tracer in PET detection per groin assessed in twenty-three patients [24]. Cohn *et al.* reported sensitivity of 67% and specificity of 95% per groin and sensitivity of 80% and specificity at 90% per patient assessed with FDG-PET in 15 patients [25].

Radical vulvectomy or modification thereof with groin lymphadenectomy is the mainstay of treatment for squamous cancer that invades the vulvar stroma to > one mm in depth. Groin node dissection carries significant morbidity; infection, lymphedema, lymph cysts, cellulitis, and psychosexual dysfunction are frequent adverse outcomes [26-28]. Cellulitis, wound dehiscence and lymphocyst occur in the early to intermediate postoperative period. The interruption of lymph channels results in lower limb and vulvar edema. The vulvar lymphedema usually resolves but chronic lymphedema of the lower limb is not infrequent

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and can be a very disabling sequel. Lymphatic drainage is unilateral for small lesions distant from the midline [29]. Unilateral lymphadenectomy is the standard of care for small lateralized lesions. The majority of women undergoing lymphadenctomy in the absence of clinical suspicion of metastases have negative histology rendering this morbid procedure unnecessary for cure in the majority of patients. Mapping and excision of sentinel nodes (SLN) in the groin is feasible and limiting lymphadenectomy to SLN is now considered [30-36]. Sentinel lymphadenectomy is under review in a prospective multicentre observational study (GroinSS-vii) and the standard of care emerging for patients with vulvar lesions less than four cm and no detectable lymph nodes is based on SL analysis by frozen section, standard hematoxylin-eosin (H&E), and ultrastaging pathological examinations. Full lymphadenectomy is progressed when SLN metastases are detected [37]. If SLN positivity is established after falsely negative intraoperative frozen section, a second surgery is required. Improved radiological imaging with high predictive values could facilitate streamlining of some patients to full lymphadenectomy without recourse to preliminary SLN. A test with high sensitivity is sought to define the lowest risk group who might be spared lymphadenectomy altogether.

The authors undertook this review of outcomes in women with vulvar cancer > one mm stromal invasion and no clinical suspicion of groin metastases who underwent combined PET-CT in the evaluation of groin node and distant metastasis in a tertiary cancer center in Ireland. The study period was the interval between the introduction of PET-CT and the commencement of SLN in the authors' clinical practice. Patients underwent surgical staging of their squamous vulvar cancers with full ipsilateral lymphadenectomy for small lateralized lesions and bilateral lymphadenectomy for central lesions within one cm of the midline. The aim was to determine the sensitivity, specificity, and predictive value of the modality in the detection of groin node metastases and thereby the identification of Stage III disease prior to definitive surgery for squamous vulvar cancer.

Materials and Methods

All patients with squamous vulvar cancer and more than one mm of stromal invasion undergoing radical excision of their cancer and regional lymphadenectomy without prior treatment were identified from the gynecological oncology data base. Patients who had undergone chemotherapy and/or radiotherapy prior to surgery were excluded. The period between the introduction of PET-CT and commencement of sentinel node mapping was chosen to facilitate correlation between PET-CT and histopathological examination of the complete inguinofemoral lymph nodes. Clinical data were extracted from the database and patient records and included age, parity, body mass index (BMI), co-morbidities, smoking status, and details of the operative procedure. Patients without overt lymph node metastasis based on clinical exam (with/without additional ultrasound and MRI at the discretion of their attending clinician) who had undergone PET-CT preoperatively were identified. Their PET-CT findings including size and fluorodeoxyglucose (FDG) avidity of vulvar tumor and lymph nodes were reviewed from radiological records. Other radiological abnormalities were noted. Comparison was made with histopathological outcomes to calculate the results.

18F-FDG-PET/CT image protocol

Fluoro-2-deoxyglucose positron emission tomography scans were performed on a VCT 64-slice PET/CT. After fasting for six hours the patient received an intravenous injection approximately 350 MBq of ^{18}F-FDG. Pre-injection blood glucose was measured. Scans were performed approximately 60 minutes after injection of the radionuclide. Whole body PET imaging extended from the base of the skull to the mid-thighs. Low dose CT images were acquired over the same range for attenuation correction and anatomical localization. The PET images were reconstructed with iterative methods after correction for scatter, dead-time, decay, and random coincidences. The images were reformatted into axial data-sets and were reviewed on a advanced workstation using the PET VCAR module by radiologists experienced in PET/CT imaging. The diagnosis of pathologic lymph node on 18F-FDG-PET/CT images was based on the presence of focal increased tracer uptake on PET images, measured as maximum standardized uptake value (SUV_{max}) and corresponding to the lymph nodal chains on CT images, but independent of lymph node size on CT.

Clinical, surgical, and histopathological protocol

All patients had full clinical examination by a gynecological oncologist, full blood count, plasma glucose, renal and hepatic biochemistry. Surgery was radical excision of the vulvar lesion with two cm horizontal margin beyond the tumor and excision down to the deep fascia or periosteum. The groin incision was elliptical and all adipose and lymph tissue was removed from the superficial inguinal and deep femoral spaces. All specimens were processed in a routine fashion and stained with H&E before microscopic examination by gynecological pathologists. The lymph nodes were reported as normal, reactive (follicular or sinusoidal hyperplasia) or malignant. The total number of lymph nodes harvested and size and number of metastases were recorded. Histopathological results were reviewed and decisions on adjuvant treatment were made at the multidisciplinary tumor board meetings.

Statistical analysis

For the purpose of statistical analysis, a true-positive (TP) was a patient with malignant lesion in a lymph node detected on PET-CT and found to be positive for metastasis at histological analysis. A false-positive (FP) was a patient with a lesion seen on PET-CT tissue but found to be negative for lymphatic metastasis at histologic analysis. A true-negative (TN) was indicated when no lesion was seen on PET-CT and the result of the histologic analysis of lymph nodes was negative for metastasis. A false-negative (FN) was a patient with histologically proven lymphatic metastasis that was not visible on PET-CT. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of PET-CT imaging in the diagnosis of groin node metastases were calculated.

Results

Twenty patients out of 58 cases of squamous vulvar cancer had a pre-op FDG PET-CT and full surgery comprising vulvectomy and groin node dissection without

Table 1. — Patient demographics and clinical details of vulvar lesion and PET-FDG avidity of vulva and groins.

Patient Number	**Outcome of PET vis-à-vis histopathology of groin nodes**	**Age at diagnosis**	**BMI (Kg/m²)**	**Vular lesion(s) location and size of largest lesion**	**FDG avidity of vulvar lesion**	**Groin node FDG avidity (SUV max)**
1	True Positive	72	24	Unifocal, posterior fourchette 3.5cm	12.6	3
2	True Positive	56	29	Multifocal, extending to perineum, lower vagina largest 2cm	4.5	2.4
3	True Positive	77	27	Unifocal, lateral 2.5cm	4.3	3.1
4	True Positive	69	31	Multifocal, bilateral anterior & central labial	18.5	3.2
5	True Positive	50	26	Unifocal, anterior central 1.5 cm	14.5	2.6
6	True Positive	61	35	Multifocal,unilateral 2cm	11.8	2.6
7	False Negative	41	21	Unifocal, central anterior, 1.5cm	7.8	Negative
8	False Negative	67	29	Multifocal, bilateral & central anterior 3.5 cm	4.2	Negative(1)
9	False Negative	63	26	Multifocal, lateral & central anterior <1cm	0	Negative(2)
10	False Negative	83	26	Unifocal, lateral 1.5cm	0	Negative
11	False Negative	49	28	Multifocal, lateral 3.5 cm	14.7	Negative
12	False Negative	89	23	Multifocal, lateral 3.5 cm	9.8	Negative
13	True Negative	72	24	Unifocal, central anterior, 1.5 cm	4.4	Negative
14	True Negative	45	31	Multifocal, bilateral 2.5cm	2.5	Negative
15	True Negative	50	28	Unifocal, lateral 2cm	0	Negative
16	True Negative	57	26	Unifocal, lateral 1.5 cm	3.2	Negative
17	True Negative	43	23	Multifocal, lateral & central posterior to perimeum	9	Negative
18	True Negative	67	36	Unifocal, central anterior, 3.5 cm	8	Negative (3)
19	True Negative	43	20	Unifocal, central extending to lower vagina	4.8	Negative
20	True Negative	38	35	Unifocal, central posterior scar only,no residual seen		0 Negative

(1) Rectal lesion on PET-CT; (2) Pulmonary Lesion - primary adenocarcinoma of lung; (3) Pulmonary lesion - granuloma.

Table 2. — PET–CT in preoperative assessment of vulvar cancer: details of surgery and histo-pathological outcomes. Patients 1-6: true positive; 6-12: false negative; 12-20: true negative PET groin node assessment.

Patient Number	Surgery	Grade	LVSI	Vulvar depth of invasion (mm)	Metastatic lymph nodes: number and laterality	Max diameter of nodal metastasis (mm)	Total nodes removed	Extracapsular extension
1	RVE;BGND	2	Positive	5	3, bilateral	24/26/18	13 R/11L	Present
2	RVE;VGTAC;CBD;BGND	2	Negative	6	1	>5mm	9R/11L	Absent
3	RVE;BGND	2	Negative	7	5, bilateral	>5mm	9R/7L	Present
4	RVE;BGND	3	Positive	15	2, bilateral	0.5 & 3mm	4R/7L	Absent
5	RVE;BGND	3	Negative	6	1	>5mm	9R/10L	Absent
6	RVE;BGND	2	Positive	5	2 bilateral	22/16	13 R/9L	Absent
7	RVE;BGND	2	Negative	4.5	1	3mm	13R/9	Absent
8	RVE;BGND	2	Negative	4	1	4mm	9R/10L	Absent
9	RVE;BGND	3	Positive	8	1	4 & 2mm in single node	6R/9L	Absent
10	RVE;BGND	2	Positive	12	9, bilateral	20mm	10R/6L	Present
11	RVE;BGND	2	Negative	3	1	5mm	7R/6L	Absent
12	RVE;BGND	2	Negative	23	2, unilateral	5 & 4 mm	9R/11L	Absent
13	RVE;BGND	1	Negative	3	0	N/A	7R/6L	N/A
14	RVE;BGND	2	Negative	8	0	N/A	8R/9L	N/A
15	RVE;UGND	1	Negative	4	0	N/A	10R	N/A
16	RVE;UGND	1	Negative	7	0	N/A	6L	N/A
17	RVE;CBD;BGND	3	Negative	3	0	N/A	6R/5L	N/A
18	RVE;BGND	1	Negative	7	0	N/A	12R/14L	N/A
19	RVE;URT;VGTAC;CBD;BGND	2	Positive	18	0	N/A	5R/10L	N/A
20	RVE;BGND	2	Negative	3	0	N/A	16R/11 L	N/A

RVE: radical excision of vulvar lesion; UGND: unilateral groin node dissection; BGND: bilateral groin node dissection; URT: distal urethrectomy; VGTAC: partial vaginectomy/ partial excision anal canal and/or sphincter; CBD: colostomy bowel diversion.

prior chemotherapy or radiotherapy between January 2010 and March 2012. A summary of the results is shown in Tables 1 and 2. Patients ranged in age from 38 to 83 (median 59) years. BMI ranged from 21-36 (median 26.5) kg/m^2. Twelve were current or past smokers. Two patients had unilateral groin node dissection (UGND). Eighteen patients had complete BGND: 16 at primary surgery and two after an interval following the detection of metastases in their first groin. The vulvar malignant lesions were unifocal in eleven. The lesions were unifocal and lateral in four, but two of these progressed to completion bilateral groin node dissection (BGND) on finding unilateral lymph node metastases. Twelve patients had lesions in or within one cm of the midline either anteriorly or posteriorly (central component). Some cancers encroached on the urethra (n = 1) or vagina (n = 2) and abutted the anal sphincter (n = 3). Radical excision of these clinical Stage II cancers necessitated distal urethrectomy (n = 1) and partial excision of anal sphincter with temporary bowel diversion (n = 3).

FDG avidity was measurable in 16 vulvas with SU-V_{max} range 2.5-14.7 (mean 8.4) and six groins with SU-V_{max} range 2.4-3.0 (mean 2.1). Fourteen patients had no FDG avid groin lymph nodes: 13 of these had no measurable disease on CT and one patient had an eight-mm lymph node with normal architecture (fatty hilum) deemed to be reactive/normal. Six women had FDG avid lymph nodes: four nodes were single, two multiple, and all measured less than two cm. PET-CT detected bilateral nodes in three patients. Extranodal extension was not detected on radiology. Three patients had unrelated lesions outside of the vulva/groins: one synchronous primary adenocarcinoma of lung, one granuloma of lung, and one rectal lesion with subsequent negative MRI and endoscopy.

Histopathological findings were of squamous grade 1 (n = 4), grade 2 (n = 12), and grade 3 (n = 4). All grade 1 cancers occurred in Stage I/II. Cancers with lymph node metastases were grade 2 (n = 8) and grade 3 (n = 4). Lymphovascular space invasion (LVSI) was described in six patients: one of eight Stage I/II cancers and five of 12 Stage III cancers. The maximum depth of stromal invasion ranged from three to 23 mm: 3-18 (median 5.5) mm in Stage I/II and 3-23 (median 5.5) mm in Stage III cancers. Metastasis to lymph nodes were single unilateral (n = 5), multiple in single node (n = 1), single in two nodes unilateral (n = 1), single in two nodes bilateral (n = 2), and multiple in bilateral nodes (n = 3). Extracapsular extension was present in three patients.

In patients with histologically proven metastases to groin nodes, comparisons between PET-CT positive (true-positive /TP) and negative (false-negative / FN) groups vis-à-vis histology yielded the following: the average vulvar SUV in TP was 11 (4.3 - 18.5) and 5.5 (0 - 14.7) in FN. Metastatic lymph nodes were bilateral in four of six (67%) TP and one of six (17%) FN, contained multiple metastases in four of six (67%) TP and two of six (33%) FN and largest metastases measured 11 (range 3 - 26) mm in TP compared to 6.6 (range 3-20) mm in FN group. Extracapsular extension was present in two of six (33%) TP and 1/6 (17%) FN. The average deepest invasion in the primary tumor was 7.3 (5 - 15) mm in TP and 9.1 (3 - 23) in the FN group.

The calculations per patient for PET-CT yielded a sensitivity of 50% and specificity at 100%. The PPV was 100% and the NPV was 57.1%. The test accuracy was 70% per patient.

Discussion

Progress in the surgical management of many cancers is marked by less radical excision of tissues. Modifications in the radical surgical approach to vulvar cancers have been evolving since the 1980s [38, 39]. Complete vulvectomy is replaced by radical wide excision with maximal effort to preserve coital and orgasmic sexual function. The need for full groin lymphadenectomy is under review with lymph node sparing surgery being assessed in an international prospective trial (GroinSS-vii). Better radiological assessment of lymph node status has the potential to enhance the individualized approach to management of vulvar cancer surgery. A test with a sufficiently high PPV would allow patients with metastases to progress to full lymphadenectomy without recourse to sentinel node (SLN) sampling. A test with an excellent NPV could identify a lowest risk group that could be spared lymphadenectomy altogether

This evaluation of CT-PET in preoperative assessment of vulvar squamous cancer in a single institution over three years was undertaken prior to the introduction of sentinel lymph node mapping into our clinical practice. This was a window of opportunity to compare CT-PET with the histopathological results of full inguinofemoral lymphadenectomy. Analysis was restricted to those without clinical suspicion of lymph node metastases who underwent PET-CT scanning prior to surgery. Other studies have reported figures calculated per lymph node or per groin [24,25]. The authors wanted to determine whether pre-treatment PET-CT could determine Stage III categorization prior to surgery and they analyzed the results per patient.

Three quarters of vulvar cancers are Stage I-II [40]. That only 34% of the present authors' referred patients were eligible for this retrospective review reflects their unit's referral pattern. Early-stage microinvasive disease is referred from their allied vulvar and colposcopy clinics and their tertiary referral status is skewed towards more advanced and metastatic cancers. Patients with microinvasive disease (< one mm stromal invasion) and patients with locally advanced disease who underwent chemother-

apy or radiotherapy prior to surgery were excluded. Full groin histopathological status was regarded as the gold standard against which to compare PET-CT.

The pattern that emerged from this study was for PET detection of metastases when the primary tumor was more FDG-avid (higher SUVmax) and metastases were larger, multiple or bilateral. The low NPV and test accuracy rule out a potential role for PET- CT in identifying the lowest risk group who might be spared any sampling of lymph nodes and we are pursuing SLN based management in that group [41]. De Hullu *et al.* speculated that attenuation due to proximity of bony structures might contribute to the poorer performance of PET-CT in the pelvic region compared to other anatomical sites [24]. The high PPV is interpreted with caution because the group size is small but the authors consider it reasonable to progress to full bilateral lymphadenectomy when a groin is PET positive without preliminary recourse to SLN. That approach saves on hospital resources including nuclear medicine scanning, shortens operating time, and avoids the need for a second operation that arises when frozen section on SLN yields a false negative result. The treatment of patients with advanced-stage disease is a challenge and while chemotherapy and radiotherapy are used with increasing frequency in this group [40, 42, 43], there is insufficient evidence to eschew lymphadenectomy completely. Other series have found that high yield lymphadenectomy is beneficial in this group and higher rates of groin recurrence are observed when surgical removal is replaced by radiation alone [44, 45]. The present authors continue to offer a thorough inguinofemoral lymph node dissection for Stage III disease but treatment is individualized based on patient performance status and discussion by the multidisciplinary group.

Larger studies of PET-CT incorporating full groin node dissection are unlikely to emerge now that SLN based surgical management has become widespread. Detection of additional lesions adds value to PET-CT scanning as evidenced by the patient in this series with a synchronous lung cancer. ^{18}F-FDG is taken up by inflammatory reactive cells as well and may lead to additional diagnostic testing for some patients. Other authors have recommended histological evaluation by biopsy of apparent metastases in other cancers including cervical malignancy [46]. Distant metastasis of vulvar cancer outside of the groin and pelvis is extremely rare at first presentation of the disease and only occurs in advanced/recurrent cancer in this (NG) author's experience [47]. Low levels of FDG uptake on the vulvar surface can be due to urinary contamination by excreted ^{18}F-FDG and may account for some surface false positivity in the vulva. However, radiological assessment of the vulvar lesion is not a priority as visual inspection will supersede the radiological findings in that organ.

Conclusion

The sensitivity and NPV of PET-CT are too low to identify women at lowest risk of groin node metastasis in vulvar cancer in order to avoid lymphadenectomy. A positive test predicts metastases, advancing the diagnosis of Stage III disease to the preoperative phase for some women and can be used to facilitate more robust therapeutic decision making prior to their surgery for vulvar cancer

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Address reprint requests to:
M.W. KAMRAN, M.D.
St James's Hospital
James's Street
Dublin 8 (Republic of Ireland)
e-mail: waseemkamran@dubgyn.org