European Journal of Nuclear Medicine and Molecular Imaging (2019) 46:855–863
https://doi.org/10.1007/s00259-018-4128-7

ORIGINAL ARTICLE

^{18}F-FDG PET/CT as a prognostic factor in penile cancer

André Salazar[1] · Eduardo Paulino Júnior[2] · Paulo Guilherme O. Salles[3] · Raul Silva-Filho[4] · Edna A. Reis[5] · Marcelo Mamede[4]

Received: 8 March 2018 / Accepted: 7 August 2018 / Published online: 24 August 2018

Abstract

Purpose Penile cancer (PC) is a rare neoplasm with an aggressive behavior and variable prognosis. Lymph node (LN) involvement and pathological features of the primary lesion have been proven to be the most important survival factors. Positron emission tomography/computed tomography with fluorodeoxyglucose labelled with fluorine-18 (^{18}F-FDG PET/CT) provides information on tumor staging and works as a prognostic factor, with promising results in other carcinomas. The aim of the present study is to evaluate PET/CT as a prognostic factor in PC.

Methods Fifty-five patients (mean age 56.6 y) diagnosed with penile squamous cell carcinoma were prospectively evaluated from 2012 to 2014. All subjects underwent ^{18}F-FDG PET/CT before treatment and were regularly followed after surgery.

Results Out of the 53 patients selected, 17 (32.1%) had localized disease (cT1–2) and 24 (45.3%) had palpable nodes (cN+). Partial penile amputation was performed in 38 patients (71.7%) and inguinal lymphadenectomy (LND) in 30 (56.6%). From the LND group, 16 (53.3%) presented with positive neoplastic cells (pN+). Patients with more aggressive disease had a significantly ($p = 0.019$) higher ^{18}F-FDG tumor uptake ($pSUV_{max}$), while inguinal LN uptake ($nSUV_{max}$) was able to recognize metastatic LN ($p = 0.039$). Some pathological prognostic features, when presented, have shown significant changes in $pSUV_{max}$ values. Receiver operating characteristic (ROC) curves were performed and specific cutoff values of $pSUV_{max}$ were evaluated to determine sensitivity and specificity. Regarding regional LNs, PET/CT presented a 76.2% accuracy in cN+ patients. After a 39-month follow up, $pSUV_{max}$ of 16.6 ($p = 0.0001$) and $nSUV_{max}$ of 6.5 ($p = 0.019$) were established as the ideal values to predict cancer-specific survival. The multivariate analysis confirmed $nSUV_{max}$ as a predictor for LN metastasis ($p = 0.043$) and $pSUV_{max}$ as a mean to estimate survival rate ($p = 0.05$).

Conclusion This study showed promising results on the use of ^{18}F-FDG PET/CT as a prognostic tool for PC, using specific cutoff values of $pSUV_{max}$ and $nSUV_{max}$.

Keywords ^{18}F-FDG · PET/CT · Penile cancer · Prognostic value · Survival

Introduction

Penile cancer (PC) is a rare neoplasm in developed western countries [1]. However, prevalence is significantly higher in South America, Africa and some parts of Asia. In Brazil, PC represents up to 2% of all cancers among men, occurring mainly in less developed regions [2].

With a silent course and aggressive behavior, PC strongly impacts male health [3]. The course of this disease varies and is difficult to determine. Lymph node (LN) involvement is the most important prognostic factor and its evaluation presents a major challenge for therapeutic strategy [4, 5]. Patients with clinically negative LN (cN–) can have node metastasis up to 25% of the time and subjects with palpable nodes (cN+) could

✉ Marcelo Mamede
mamede.mm@gmail.com

1 Urology Section, Mario Penna Institute, Belo Horizonte, Brazil

2 Pathology and Forensic Department, School of Medicine, Federal University of Minas Gerais, Belo Horizonte, Brazil

3 Pathology Section, Mario Penna Institute, Belo Horizonte, Brazil

4 Anatomy and Imaging Department, School of Medicine, Federal University of Minas Gerais, Avenida Prof. Alfredo Balena, room 190, Belo Horizonte 175, Brazil

5 Statistics Department, Exact Science Institute, Federal University of Minas Gerais, Belo Horizonte, Brazil

present exclusively with non-metastatic inflammatory reaction in approximately 40% of cases [6].

Inguinal lymphadenectomy (ILND) is not routinely performed and is related to high morbidity [7]. The presence of nodal involvement greatly impacts survival, which ranges from around 85% in patients with negative nodes (pN–) to less than 40% in those with positive ones (pN+). An accurate preoperative staging is essential to select patients who will benefit from surgical treatment, avoiding unnecessary procedures without distant metastasis [8].

Positron emission tomography (PET) with fluorodeoxyglucose (FDG), a glucose analogue, labeled with fluorine-18 (^{18}F-FDG) is a nuclear imaging technique based on the analysis of tumoral cell glucose metabolism [9, 10], and provides a metabolic pattern for tumor growth and aggressiveness [11]. The maximum standardized uptake value (SUV_{max}), a semi quantitative measure of ^{18}F-FDG tumor uptake, has shown promising data as a prognostic factor in other squamous cell carcinomas (SCCs) [12, 13].

In PC, ^{18}F-FDG PET/computed tomography (CT) has been used to evaluate lymphatic involvement with positive results [14]. However, inflammatory reaction can reduce accurate metastatic LN detection [15]. Up to this date, there are no ^{18}F-FDG PET studies in PC presenting SUV_{max} cutoff values or confirming this imaging modality as a determiner for long-term survival, a well-established point in other neoplasms [12, 13, 16, 17].

In order to assess the effectiveness of ^{18}F-FDG PET as a prognostic marker on PC, the present study compares metabolic PET results with histopathology and clinical outcome.

Materials and methods

Sample population

Fifty-five consecutive patients with a mean age of 56.6 ± 13.6 years (26–84 range) were prospectively evaluated from October 2012 to October 2014. All subjects had histopathological confirmation of penile SCC, and underwent clinical examination, CT scans of the thorax, abdomen and pelvis, and ^{18}F-FDG PET/CT before treatment.

No neoadjuvant chemotherapy or antimicrobial drugs were administered prior to surgical resection. The local ethics committee approved this study and all patients signed an informed consent declaration to participate.

^{18}F-FDG PET/CT imaging

^{18}F-FDG PET/CT was performed 76 ±13 min after intravenous injection of 3.7 MBq/Kg (mean 304.14 ± 88.8 MBq) of ^{18}F-FDG. All patients had been fasting for at least 6 h before administration. Acquisition time of the whole-body PET was 2 min per bed position in a Discovery 690 GE PET/CT scanner (GE Healthcare, Milwaukee, WI, USA). The images were reconstructed in a 192 × 192 matrix, using an ordered subsets expectation maximization (OSEM)-like algorithm, with 2 iterations and 24 subsets. The CT scan utilized a low-dose protocol for the attenuation map [90 kV, 10–120 mAs (smart mA) with 3.75-mm section thickness] and imaging fusion. Semi-quantitative analysis used a standardized uptake value (SUV), corrected by the lean body mass at the highest pixel value (SUV_{max}) to assess the primary lesion ($pSUV_{max}$) or the regional inguinal nodes ($nSUV_{max}$). The $nSUV_{max}$ was correlated with the presence of nodal involvement in a single patient. The formulae used and implemented to calculate the lean body mass in PET images can be found elsewhere [18, 19]. All images were evaluated by two independent readers (experienced nuclear physician and radiologist), blinded to the clinical findings and to histopathologic results.

Surgical procedure and histopathology

All patients underwent a local tumor resection by the same surgical team at two reference centers following the European Association of Urology Guidelines on PC (4). Inguinal lymphadenectomy was performed following three criteria: 1) cN– patients with primary lesion up to pT1a received clinical follow up; 2) cN– patients with pT1b or above lesions were submitted to lymphadenectomy; 3) cN+ patients underwent lymphadenectomy. The results obtained with PET/CT did not influence patient management. Two experienced pathologists, unaware of the clinical and PET results, performed the histopathological analysis. Tumor-node-metastasis (TNM) classification (AJCC Cancer Staging Manual, 7th ed.) and the current World Health Organization (WHO) Urological Malignancies Staging System criteria for tumor grading were adopted [20, 21].

Follow-up and survival analysis

After surgical treatment, patients were followed with on a 3-month interval during the first year, and semiannually from the second year onwards. CT scans was done every 6 months until the end of second year, then as clinically indicated. Clinical outcome starting point was established as the date of ^{18}F-FDG PET/CT examination. Disease progression was defined as local recurrence and/or distant metastasis, proven by histopathology, conventional imaging [CT or magnetic resonance (MR)] or clinical examination. Meanwhile, disease-free was defined as absence of local recurrence, LN or metastatic involvement until the last clinical appointment. For the survival analysis, the primary endpoint was cancer-specific survival, related to recurrence after the treatment and consequent cancer-specific death.

Statistical analysis

Descriptive statistical analysis was performed for all variables. Normality testing was also checked before comparative tests.

ANOVA and the Student's *t* test (parametric analysis) as well as Kruskal–Wallis and Mann–Whitney (non-parametric analysis) were used to evaluate differences between quantitative variables. Receiver operating characteristic (ROC) curves were calculated in order to verify significant cutoff points for classification. The values obtained were further tested to determine the sensitivity, specificity, accuracy, and predictive values of PET/CT. Survival study (Kaplan–Meier) was applied for significant prognostic factors. Uni- and multivariate logistic regression analyses were performed for potential risk variables to predict binary outcomes. IBM SPSS (version 20.00) software was used for the statistical analysis.

Results

Patient characteristics

Fifty-five patients were initially screened. Two were excluded: one abandoned the study group; the other had high serum glucose levels (>190 mg/dL), impacting correct PET/CT analysis.

Clinical examination had shown 17 (32.1%) subjects with localized tumor (cT1–2) and 24 (45.3%) were cN+. The majority of patients ($n = 38$, 71.7%) underwent partial penile amputation, while the remaining underwent local resection (11.3%) or total penile amputation (17.0%). Histopathology confirmed squamous cell carcinoma in all primary lesions. Thirty patients (56.6%) were submitted to inguinal lymphadenectomy (90% bilateral procedure), 16 (53.3%) being positive for neoplastic cells.

^{18}F-FDG PET/CT characteristics and SUV cutoff values

Levels of agreement between readers were very good (Kappa above 0.81) for both analyses: primary lesion (Kappa: 1.0, CI: 1.0 to 1.0) and LN (Kappa: 0.83, CI: 0.664 to 0.990). Table 1 shows a summary of the metabolic results for all patients based on the TNM staging system. Primary lesions with more advanced stages had higher $pSUV_{max}$ values with significant statistical difference between groups. In PC, the TNM classification has specific points; the T1 category is stratified into two risk groups with different prognoses depending on the presence or absence of lymphovascular invasion and histological tumoral grade [21]. Tumors infiltrating subepithelial connective tissue, blood and lymphatic vessels and those with poor differentiation (pT1b and above) showed higher $pSUV_{max}$ compared to less aggressive lesions ($p < 0.019$, Table 1).

The ^{18}F-FDG PET/CT inguinal LN uptake ($nSUV_{max}$) analysis showed lower absolute values compared to the $pSUV_{max}$, but with a more pronounced standard deviation (Table 1). Patients without node metastasis (pN0) had an $nSUV_{max}$ lower than half of those with a more advanced stage (pN3; Table 1). The $nSUV_{max}$ was able to recognize metastatic LN involvement in PC ($p = 0.039$; Table 1).

Table 1 Semiquantitative analysis of ^{18}F-FDG PET/CT and TNM classification of penile cancer patients

Staging	N	%	$pSUV_{max}$ Mean	SD	*p* value
pT (tumor)					
In situ	2	3.8	4.2	2.1	0.043[&]
1a	7	13.2	10.6	7.4	
1b	2	3.8	9.7	4.0	
2	27	50.9	15.5	7.4	
3	15	28.3	15.3	5.5	
Total	53	100.0	–	–	
pT (tumor)					
pT (0-1a)	9	17.0	9.2	7.1	0.019[$]
pT (1b-4)	44	83.0	15.2	6,7	
Total	53	100.0	–	–	
			$nSUV_{max}$ Mean	SD	
pN (lymph node)					
0	24*	69.8	5.5	2.3	
1	1	1.9	6.0	–	0.005[#]
2	5	9.4	10.1	7.0	0.005[@]
3	10	18.9	13.6	11.0	
Total	40	100.0	–	–	
pN (lymph node)					
0	24*	60.0	5.5	2.3	
≥1	16	40.0	12.0	9.5	0.039[L]
Total	40	100.0	–	–	

*: available $nSUV_{max}$; pNx = 23; &: ANOVA; $: *t* test for pT ≥ 1b; #: ANOVA excluding group pN = 1; @: Bonferroni post hoc test between pN = 0 and pN = 3; L: *t* test for pN ≥ 1

Table 2 Semiquantitative analysis of ^{18}F-FDG PET/CT and prognostic pathological characteristics of penile cancer

Variables	Status	N*	pSUVmax		*p* value[&]
			Mean	SD	
Perineural invasion	–	18	11.5	7.3	0.047
	+	35	15.5	6.6	
Angiolymphatic invasion	–	21	12.5	7.6	0.182
	+	32	15.2	6.6	
Dartos infiltration	–	18	9.2	5.6	0.001
	+	29	16.3	6.8	
Lamina propia infiltration	–	4	5.0	1.8	0.007
	+	48	14.8	6.8	
Sponge body infiltration	–	15	10.8	8.1	0.024
	+	36	15.6	6.1	
Corpora cavernosa infiltration	–	19	9.8	5.4	0.000
	+	29	17.4	5.6	

*: the remaining cases for each variable are not applicable; &: *t* test

Table 3 ROC values for the evaluation of prognostic pathological characteristics using the semiquantitative values of ^{18}F-FDG PET/CT in penile cancer patients

Variables	n	Cutoff	AUC	*p* value$	Sensitivity (%)	Specificity (%)
Perineural invasion	53	11.9	0.699	0.018	71.4	61.1
Sponge body infiltration	52	11.6	0.762	0.003	77.8	75.0
Dartos infiltration	50	11.6	0.770	0.001	82.8	71.4
Corpora cavernosa infiltration	49	12.2	0.859	0.0001	82.8	75.0
Lamina propia infiltration	52	7.1	0.927	0.005	85.4	100.0

AUC: area under curve; $: asymptotic test for AUC = 0.05

Pathological prognostic features (perineural invasion, angiolymphatic invasion, dartos infiltration, lamina propria infiltration, sponge body infiltration and corpora cavernosa infiltration), when present, showed significant variability of $pSUV_{max}$ (Table 2). More aggressive tumors, with these factors positive, had statistically higher ^{18}F-FDG uptake (except for angiolymphatic invasion; Table 2).

ROC curves were designed using $pSUV_{max}$ and pathological features (Table 3 and Figs. 1 and 2). Lamina propria infiltration presented the best sensitivity and specificity, with the lowest $pSUV_{max}$ cutoff value. On the other hand, corpora cavernosa infiltration had the highest cutoff point (Table 3).

Regarding the evaluation of regional LNs, PET/CT was able to determine positive results for cN+ patients. ROC analysis using $nSUV_{max}$ was able to determine cN+ patients ($n = 22$) with metastasis (pN+, $p = 0.015$, cutoff value of 6.5) (Table 4) with sensitivity and specificity of 76.9 and 77.8%, respectively. Similar finding was not observed for cN− patients.

The $nSUV_{max}$ cutoff value of 6.5 was verified among the pN results (Table 5). Clinical evaluation showed low accuracy to confirm metastatic LN involvement. The use of an $nSUV_{max}$ cutoff value of 6.5 was more accurate than clinical examination alone in the confirmation of nodal involvement, particularly in the subgroup of cN+ patients.

Survival analysis

The median follow-up period was 39 months. Nineteen patients stayed disease-free, 2 abandoned the study, 18 recurred and/or progressed and 14 died (13 due to cancer and 1 from other cause). The Kaplan–Meier analysis showed $pSUV_{max}$ of 16.6 ($p = 0.0001$) and $nSUV_{max}$ of 6.5 ($p = 0.019$) as the best cutoff values to predict cancer-specific survival (Table 6, Fig. 3).

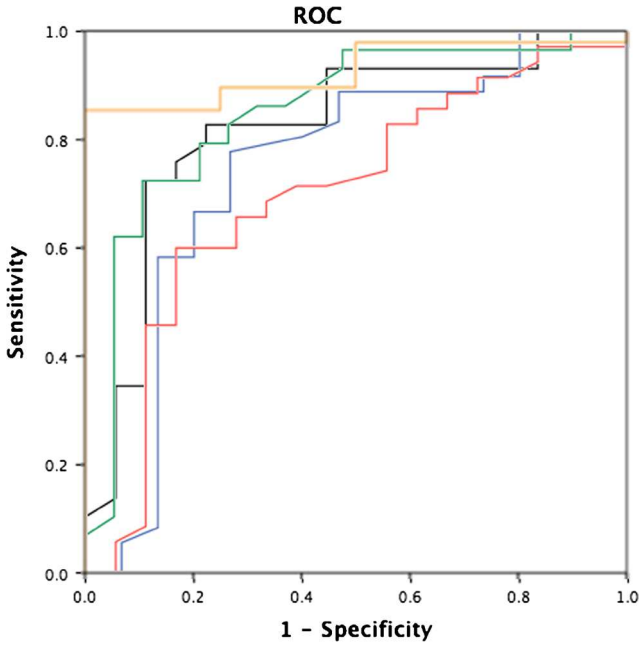

Fig. 1 Receiver operating characteristic curve for penile SUV_{max} and pathological prognostic factors. Note: Cavernous body infiltration (green line); sponge body infiltration (blue line); lamina propria infiltration (orange line); dartos infiltration (black line) and perineural invasion (red line)

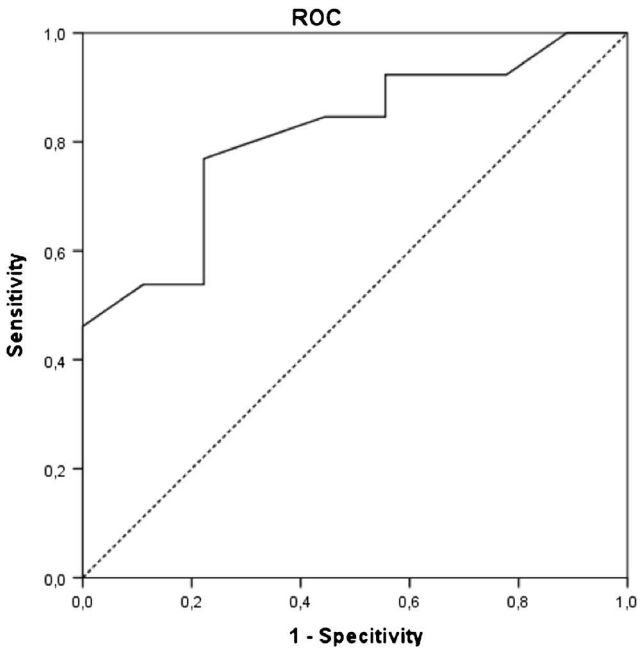

Fig. 2 Receiver operating characteristic curve analysis of lymph node SUV_{max} in cN+ patients

Table 4 ROC values for the evaluation of inguinal nodes involvement using the semiquantitative values of ^{18}F-FDG PET/CT in penile cancer patients

Variables		N	Cutoff	AUC	*p* value$	Sensitivity (%)	Specificity (%)
$pSUV_{max}$	cN−	29	11.6	0.404	0.591	50.0	66.7
	cN+	24	16.6	0.664	0.173	69,2	72.7
$nSUV_{max}$	cN−	18	4.1	0.678	0.343	73.3	66.7
	cN+	22	**6.5**	0.812	0.015	76.9	77.8

AUC: area under curve; $pSUV_{max}$: penile SUV_{max}; $nSUV_{max}$: lymph node SUV_{max}; cN−: clinical negative node; cN+: clinical positive node

Table 5 Diagnostic characteristics of pathological LN involvement with clinical and ^{18}F-FDG PET/CT evaluation

Parameters	Clinical	$nSUV_{max}$ (cutoff of 6.5)	$nSUV_{max}$ (cutoff of 6.5 in cN+)
TP	13	10	10
TN	6	11	6
FP	8	3	2
FN	3	6	3
Sensitivity	81.3%	62.5%	76.9%
Specificity	42.9%	78.6%	75.0%
PPV	61.9%	76.9%	83.8%
NPV	81.3%	62.5%	76.9%
Accuracy	63.3%	70.0%	76.2%

$nSUV_{max}$: inguinal nodel SUV_{max}, cN+: positive clinical node; TP: true positive, TN: true negative, FP: false positive, FN: false negative, PPV: positive predict value, NPV: negative predict value

Death and LN metastasis prediction

Binary logistic regression analyses were performed with two outcomes: inguinal node metastasis and cancer-specific death. Considering both results, $pSUV_{max}$ and $nSUV_{max}$ were significant predictors in a univariate analysis as all other histopathological predictors. However, in a multivariate analysis, $nSUV_{max}$ predicted ($p = 0.043$) inguinal node metastasis, while $pSUV_{max}$ ($p = 0.05$) predicted death (Table 7). A similar finding was not observed for $pSUV_{max}$ and the histopathological variables (thus, not included in the model).

Discussion

Prognosis in PC patients is extremely challenging to determine, probably due to tumor heterogeneity and specific behaviors: fast dissemination and great lymphatic spread. Routinely, treatment is based on clinical examination, which has however a low sensitivity to predict histopathological findings. Scher et al. (2005) analyzed the use of ^{18}F-FDG PET/CT in PC staging. The authors correlated the ^{18}F-FDG uptake (SUV_{max}) of the primary tumors and inguinal LNs to relapses of 30 patients. They concluded that ^{18}F-FDG PET/CT would be a promising tool for depicting metastatic LNs. However, the authors did not infer cutoff points of SUV_{max} as predictors of neither histopathological findings nor unfavorable prognosis [22].

In the present series, ^{18}F-FDG PET/CT was able to detect locally aggressive tumors with worst prognosis. For the 44 pT1b (and above) patients, $pSUV_{max}$ was significantly higher, showing a positive use of PET to evaluate the primary tumor. Patients with a more favorable prognosis could benefit from organ-sparing surgery, enabling a more adequate penile stump. It is important to point it out that initial misdiagnosis is related to early local recurrence and more aggressive tumor behavior with negative clinical impact [23, 24].

Table 6 ^{18}F-FDG PET/CT semiquantitative data and survival analyses in penile cancer patients

Variable	Cut-off	Median (months)	95% CI (months)	*p* value*
$pSUV_{max}$	11.6	NR	NR	0.002
	11.9	NR	NR	0.001
	12.2	27.0	NR	0.004
	16.6	18.0	13.1~22.9	0.0001
$nSUV_{max}$	6.5	16.0	12.9~19.7	0.019

$pSUV_{max}$: penile SUV_{max}; $nSUV_{max}$: lymph node SUV_{max}; NR: not reached; 95% CI: 95% confidence Interval; *: log-rank test

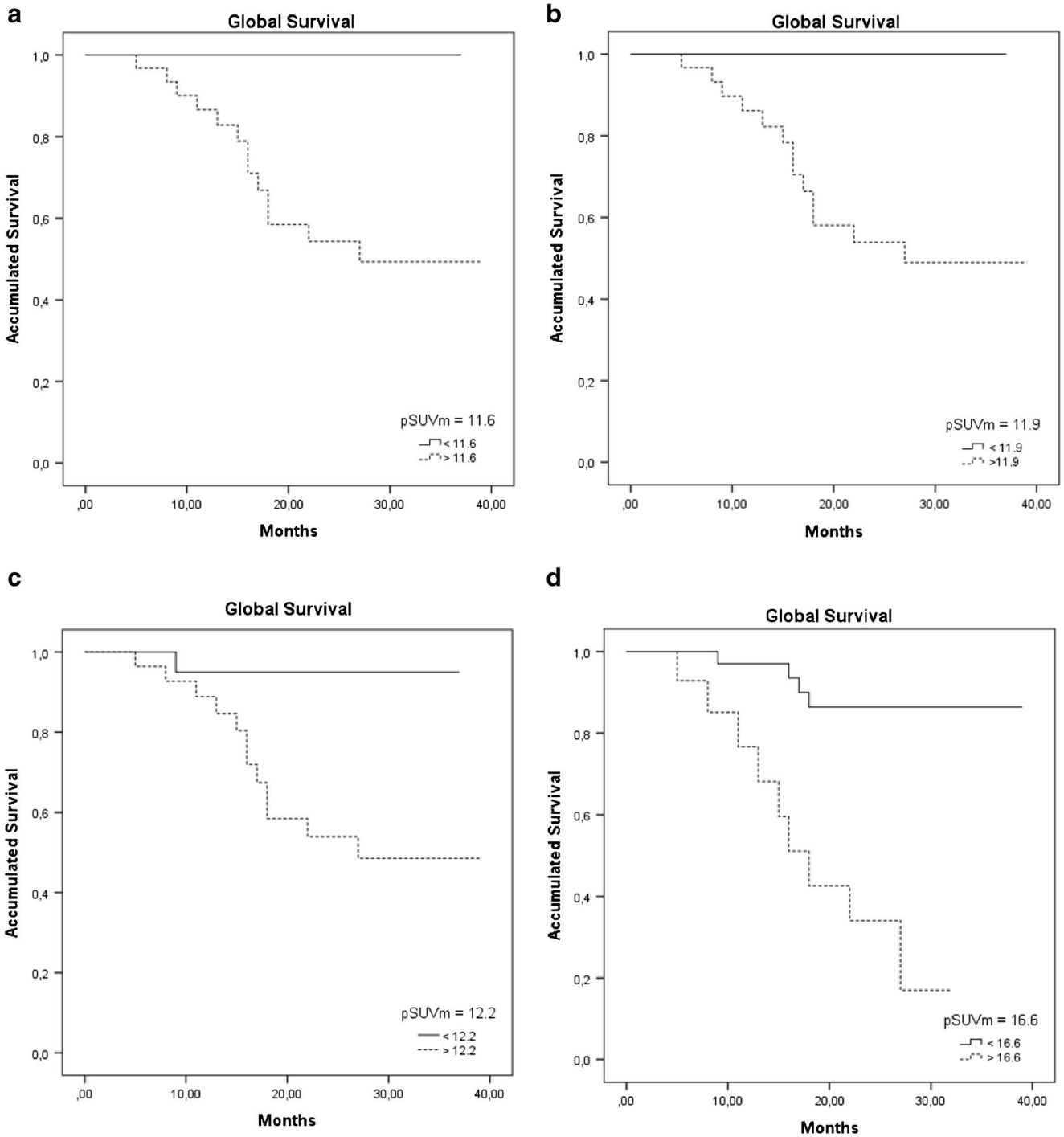

Fig. 3 Survival curves of penile SUV_{max} ($pSUV_{max}$). Note: **a**) $pSUV_{max} = 11.6$; **b**) $pSUV_{max} = 11.9$; **c**) $pSUV_{max} = 12.2$; **d**) $pSUV_{max} = 16.6$

MR imaging (MRI) or penile doppler ultrasound (PDU) with artificial erection were able to detect primary tumor cavernosa infiltration with good accuracy [25]. However, these tests may be difficult to reproduce and are based on anatomical aspects of local dissemination, which may not detect a tumor with more aggressive metabolic behavior in initial phases. The present results represent individual metabolic characteristics of the tumor and not only anatomical aspects of the image. ^{18}F-FDG PET/CT was able to refine pathological characteristics of aggressiveness (tumors with a higher pathological grade or vascular lymph invasion - pT1b), and not only tumors invading corpora cavernosa (pT2) [26].

Pathological prognostic features already stated, and even part of the current prognostic index [27, 28], regarding nodal metastasis and survival, were correlated with semiquantitative values (SUV_{max}) of metabolic pattern in this series. Except for

Table 7 Binary logistic regression analyses of inguinal node metastasis and death

Dependent variables	Predictor variables	Simple	Multiple	
		p value	*p* value	OR (95% CI)
pN	$pSUV_{max}$	0.047	NI	0.30 (1,01 ~ 1.67)
	$nSUV_{max}$	0.024	0.043	
	Perineural invasion	0.019	NI	
	Angio invasion	0.05	NI	
	CC infiltration	0.013	NI	
	SB infiltration	0.045	NI	
Death	$pSUV_{max}$	0.003	0.05	0.16 (1.00 ~ 1.36)
	CC infiltration	0.02	NI	

OR: Odds ratio; CI: confidence interval; pN: pathological lymph nodes; NI: not included in the model; CC: corpora cavernosa; SB - Sponge Body

angiolymphatic invasion, $pSUV_{max}$ showed significant higher values in all histopathologically positive samples (Table 2). It is important to emphasize the strong correlation between anatomical depth of the tumor and worse prognosis. Evaluation of $pSUV_{max}$ was compatible with these positive results for the majority of pathological variables related to anatomic involvement. In addition, perineural invasion is recognized as an independent factor of mortality, and PET/CT was congruent with this finding. In a previously unpublished way, the present study was able to define potential cutoff values that can be useful to predict prognostic pathological characteristics in PC patients, with reasonable sensitivity and specificity (Table 3, Fig. 1).

Inguinal node metastasis are the most relevant prognostic factor in PC [26–29]. In this series, 16 patients presented positive cancer cells and had significantly higher $nSUV_{max}$ (Table 1). Among them, 13 patients had clinical suspicion of LN invasion at initial evaluation (cN+). ^{18}F-FDG PET/CT showed diagnostic sensitivity of 76.9% and specificity of 75.0% using an $nSUV_{max}$ cutoff value of 6.5 (Table 5). Soulliac et al. evaluated 30 SCC patients with ^{18}F-FDG PET/CT. The authors observed 8 cN+ and found 100% of sensitivity and specificity after lymphadenectomy [30]. These differences in accuracy could be attributed to intense local inflammatory process and/or patient selection. In addition, the present work was able to define a cutoff value with reasonable sensitivity and specificity to predict malignancy in LNs before lymphadenectomy (Table 4), data never previously shown.

Clinically negative patients (cN−) represent a group of great interest. Despite clear difference in ^{18}F-FDG uptake in the LNs of cN− subjects, unfortunately, the null hypothesis of mean equality could not be rejected. Jakobsen et al. [31] prospectively evaluated the use of ^{18}F-FDG PET/CT to stage invasive PC in 128 cN− patients. PET/CT was compared to sentinel node biopsy. The authors found 94.4% sensitivity and a 5.6% false negative rate. In the present study, 73.3 and 66.7% sensitivity and specificity, respectively, were found using $nSUV_{max}$. This mismatch could be explained by a smaller number of patients evaluated, and suggests a trend of improvement with a higher number of cases. Besides, van Westreenen et al. showed that high ^{18}F-FDG uptake in the primary tumor often minimizes the uptake in regional

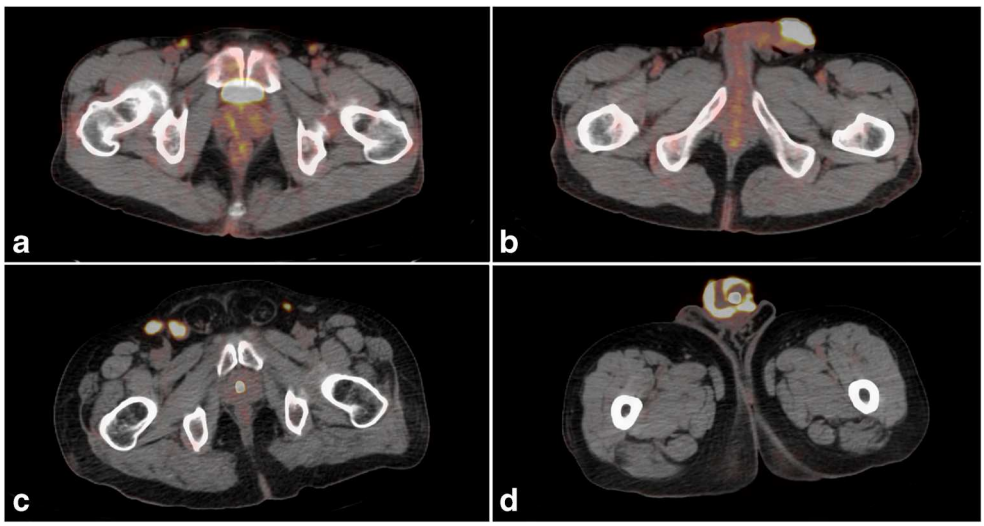

Fig. 4 Typical ^{18}F-FDG PET/CT imaging of penile cancer patients. Note: **a** and **b** correspond to a 51-year-old patient (pT2N0M0, $pSUV_{max}$: 12.3, right $nSUV_{max}$: 3.2, left $nSUV_{max}$: 3.4) submitted to partial amputation and bilateral inguinal lymphadenectomy. There was no evidence of recurrence during the follow-up period. **c** and **d** correspond to a 77-years-old patient (pT3N2M0, $pSUV_{max}$: 18.6, right $nSUV_{max}$: 14.6, left $nSUV_{max}$: 8.3) submitted to partial amputation and bilateral inguinal lymphadenectomy. This patient recurred and died 13 months later

nodes. This might explain the data differences and suggests that a study designed using this methodology—LN uptake before and after resection of the primary penile tumor—will probably increase accuracy [32]. The difficulty of evaluating cN− patients has already been observed in other series. Sadeghi et al. performed a systematic review in 2012 with the most relevant papers about the use of ^{18}F-FDG PET/CT in PC. They arrived at the same low sensitivity in cN− and suggested that ^{18}F-FDG PET/CT should not be routinely used in these scenarios [33].

Predicting clinical outcome in oncologic patients is a milestone. By using potential cutoff values in the different situations mentioned above, we were able to confirm the clinical use of ^{18}F-FDG PET/CT to predict overall survival. In this clinical setting, $pSUV_{max}$ of 16.6 was the best predictor ($p = 0.0001$), followed by $nSUV_{max}$ of 6.5 ($p = 0.019$). Similar findings were verified for other cutoff values of $pSUV_{max}$ (11.6 and 11.9), but with lower statistical power. Thus, this is the first work to show the value of ^{18}F-FDG PET/CT as a clinical marker to estimate mortality in PC patients (Fig. 4).

Using SUV_{max} cutoff points, ^{18}F-FDG PET/CT improved the accuracy of the inguinal node evaluation in this sample. Comparing the $nSUV_{max}$ values found (Table 5) with Sadeghi's results [33], our sensitivity and specificity were slightly lower. These differences could be related to the use of SUV cutoff points, since this methodology was not used in previous series (based exclusively on qualitative analysis). Thus, the results of the use of $nSUV_{max}$ presented here, although unpublished and promising, should be analyzed with caution and suggest that further evaluations are necessary to consolidate these findings.

Prognostic evaluation models have been proposed in PC, but those are lacking a metabolic pattern of the primary tumor evaluation [34]. Improved guidelines could be used to guide surgical treatment strategies and to rationalize the use of chemotherapeutic schemes, even in an adjuvant scenario. The addition of ^{18}F-FDG PET/CT results in cancer management has already been confirmed in renal tumors with excellent results [35, 36]. By using pathological prognostic features and semiquantitative PET parameters ($pSUV_{max}$ and $nSUV_{max}$), the present study was able to demonstrate $pSUV_{max}$ as a potential predictor to cancer survival in uni- and multivariate analysis. Thus, these findings corroborate to the use of ^{18}F-FDG PET/CT metabolic parameters as important variables to be incorporated in the current nomograms for PC patients.

It is important to point out that the measurements obtained from PET data has some limitations: 1) due to the inherent heterogeneity of cancer, viable and metabolically active tumor cells share space with necrosis and normal tissue, thus the SUV_{max}, which represents the most metabolically active voxel in the lesion, might not represent the entire heterogeneous tumor metabolic activity; 2) On the other hand, partial volume effect could have underestimated lesions that are smaller than the spatial resolution of the PET system.

Conclusion

This study showed promising results on the use of ^{18}F-FDG PET/CT as a prognostic tool for PC, especially by establishing specific cutoff values of $pSUV_{max}$ and $nSUV_{max}$.

Acknowledgments The authors thank Rodrigo Corradi, M.D., and Sofia Lage for the text revision.

Compliance with ethical standards

The authors declare no conflict of interest. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

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