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The Value of FDG PET/CT in Penile Cancer: An Update

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Penile cancer is a rare malignancy predominantly of squamous cell histology, whose prognosis is strongly influenced by lymph node involvement. Conventional imaging methods such as CT, MRI, and ultrasound have limitations in assessing metastatic spread. [^{18}F]FDG PET/CT, a metabolic imaging technique, has shown increasing value in the staging, restaging, and treatment monitoring of penile cancer. Evidence, although limited, demonstrates high sensitivity and specificity, particularly in detecting inguinal and pelvic lymph node metastases, outperforming conventional imaging in most cases. [^{18}F]FDG PET/CT also aids in identifying distant metastases and distinguishing viable tumor tissue from post-treatment fibrosis. Preliminary data suggest a prognostic role of SUVmax values in correlating with tumor aggressiveness and survival outcomes. Current guidelines recommend its use mainly in patients with nodal involvement or inconclusive conventional imaging. Overall, [^{18}F]FDG PET/CT represents a complementary tool that enhances staging accuracy, risk stratification, and treatment planning in penile cancer.

INTRODUCTION

Penile cancers (PC) are rare malignancies, most commonly of squamous cell carcinoma (SCC) histology. Penile SCC accounts for approximately 95% of all PC cases, with an incidence rate of 0.80 per 100,000 person-years in 2020 [1]. Several risk factors have been associated to the development of PC. Among those, smoking habits, the absence of circumcision, poor penile hygiene and chronic inflammation, phimosis and immunosuppression have to be listed. Furthermore, in Europe and certain Asian countries, the incidence has been reported to be on the rise due to Human Immunodeficiency Virus (HIV) and Human Papilloma Virus (HPV) being major public health issues [2,3]. Although global incidence remains low, PC represents a significant cause of morbidity and mortality in developing countries. One of the prognostic determinants of the disease is lymph node (LN) involvement. LN metastases are the most common route of dissemination in PC patients, typically affecting the groin unilaterally or bilaterally. Micrometastases involve up to 25% of patients with clinically impalpable inguinal LN at diagnosis [4].

Imaging plays a pivotal role in the staging and restaging of PC. Several imaging methods can be used for this purpose. Conventional modalities — including, Computed Tomography (CT), Magnetic Resonance Imaging (MRI) and ultrasonography (US) — are frequently used but often insufficient to fully delineate the metastatic burden. In this context, 2-deoxy-2-[18F]fluoro-D-glucose ([^{18}F]FDG) Positron Emission Tomography / Computed Tomography (PET/CT) has been increasingly used for

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staging and restaging purposes as a metabolic imaging agent [5].

BIOLOGICAL BASIS OF [^{18}F] FDG PET/CT

[^{18}F]FDG is a radioactive glucose analogue that mimics intracellular glucose metabolism and accumulates in malignant cells due to their increased glucose tenure. [^{18}F]FDG PET/CT is a well-established hybrid imaging modality in oncology, with proven diagnostic value, and is widely applied for both malignant and non-malignant clinical purposes. [^{18}F]FDG is the most commonly used radiopharmaceutical in routine molecular imaging and has increasingly gained importance in the context of personalized cancer therapy [6].

Penile SCC, similar to other types of SCC, typically exhibits high FDG uptake due to its high proliferative capacity [7–9]. This characteristic renders [^{18}F]FDG PET/CT valuable not only for the assessment of the primary tumor but in particular for the detection of metastatic sites [9,10]. Appropriate patient selection is critical, and the suitability of [^{18}F]FDG PET/CT should be carefully considered based on specific clinical criteria and available evidence.

The clinical applications of [^{18}F]FDG PET/CT in penile cancer can be summarized across different scenarios including staging, restaging and treatment response assessment (Table 1).

The role of [^{18}F]FDG PET/CT will be discussed in the next paragraphs, according to the different clinical scenarios.

[^{18}F]FDG PET/CT FOR STAGING PENILE CANCER

The utility of [^{18}F]FDG PET/CT in evaluating primary penile tumors remains limited. The main drawback lies in its relatively low spatial resolution, which hampers accurate assessment of local tumor extension and potential involvement of adjacent structures [11]. Additionally, the presence of radioactive urine in the vicinity may hinder the visualization of the primary lesion. At present, clinical evaluation through physical examination — capable of determining tumor size, anatomical location, and extent of local invasion — remains a cornerstone in the diagnostic workup. Complementary imaging modalities, particularly ultrasound and MRI, continue to represent the gold standard for primary tumor assessment [12,13].

Inguinal lymph node involvement represents the most important prognostic factor in newly-diagnosed PC patients. In patients who present with palpable nodes, inguinal lymph node dissection remains the standard of care [4]. However, in cN0 patients, inguinal lymph node dissection could be an overtreatment (especially considering the considerable morbidity of this procedure) because up to 75% to 80% of these patients do not have regional pathological involvement. Therefore, non-invasive imaging tools capable of accurately assessing the extent of metastatic spread to the inguinal lymph nodes are pivotal in PC patients.

Since the introduction into clinical practice, [^{18}F]FDG PET/CT has demonstrated increasing utility in the staging of PC, particularly in assessing lymph node involvement (Figure 1, Table 2). Inguinal lymph node metastases represent a key prognostic factor in newly diagnosed PC patients, and several studies have evaluated the diagnostic performance of [^{18}F]FDG PET/CT in this context. A 2024 american population-based study of Bologna et al [14] reported that, among 17494 patients with diagnosis of PC and 5965 with penile intraepithelial neoplasia, [^{18}F]FDG PET/CT was the second most used imaging technique for staging after ultrasound and before MRI and conventional CT (8.13%, 11.7%, 5.02% and 5.98%), in particular for evaluation of lymph-nodes involvement and distant metastases, as supported by literature.

Concerning staging of lymph node metastases, a recent meta-analysis [15] showed good diagnostic performances of [^{18}F]FDG PET/CT with a pooled sensitivity of 87% (95%CI 0.79-0.92) and the pooled specificity was 88% (95%CI, 0.79-0.93).

Scher et al [16] first explored the role of this imaging method in 2005, in a cohort of 13 patients with suspected (n=10) or confirmed (n=3) PC. They reported a very high accuracy for the detection of lymph node metastases, as 15 of

Table 1 Clinical Scenarios for [^{18}F]FDG PET/CT in Penile Cancer.

Clinical Scenario	Purpose	Advantages of PET/CT	Limitations
Initial Staging	Evaluation of the primary tumor and lymph node metastases	Ability to demonstrate FDG-avid lesions; whole-body imaging in a single session	Inability to detect micrometastases; false positives due to inflammation/infection
Restaging	Detection of local recurrence, distant metastases, or postoperative residual disease	Differentiation between fibrosis and viable tumor tissue	Reduced sensitivity in small lesions
Assessment of Treatment Response	Monitoring metabolic response after chemotherapy/ radiotherapy	Ability to demonstrate metabolic regression earlier than morphological shrinkage	Response criteria (EORTC, PERCIST) are not well validated in penile cancer

EORTC = European Organization for. Research and Treatment of Cancer; PERCIST = Positron Emission Tomography Response Criteria in Solid Tumors.

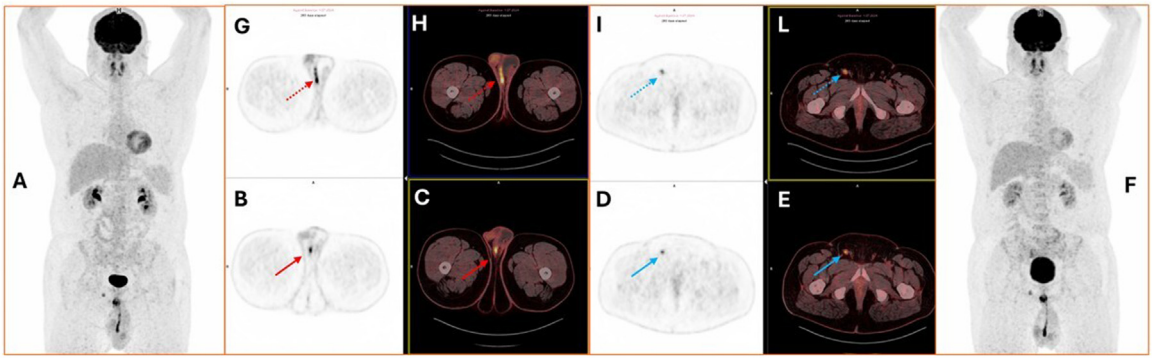

Figure 1 A 47-year old male with a diagnosis of penile cancer performed a baseline [^{18}F]FDG PET/CT (Maximum intensity projection, MIP (**A**)) showing a focal uptake at primary lesion (SUVmax 11.84, MTV 3.53; red arrow) and a right inguinal lymph node metastasis (widest axial diameter 1.17 cm; SUVmax: 7.24; blue arrow) at fused PET/CT images (**B-E**). A restaging [^{18}F]FDG PET/CT showed progression of disease both at the primary lesion (SUVmax: 14.09 MTV: 5.03 (red dashed arrows) and right inguinal metastatic LN (widest axial diameter: 1.5 cm; SUVmax: 7.6, blue dashed arrows). MIP (**F**) and transaxial fused PET/CT images (**G-L**) detecting progression of disease.

16 [^{18}F]FDG-avid lymph nodes were confirmed metastatic at histology, with a sensitivity of 89% for superficial inguinal lymph-nodes. In 2009 Leijte et al [17] evaluated 24 cN0 patients and found [^{18}F]FDG PET/CT highly specific (92%) with a negative predictive value of 89%, but very low sensitivity and PPV due to the negativity of small metastases (<10mm). A subsequent study by Schlenker et al [18] involving 35 patients confirmed high sensitivity (82.1%) and specificity (98.1%) for inguinal lymph node metastases. Further confirmations have been reported in the literature by several authors in more recent years [19–24].

Other works compared [^{18}F]FDG PET/CT with conventional imaging modalities used to stage PC, in particular CT. Overall, these works evidenced that, for inguinal nodal involvement, [^{18}F]FDG PET/CT outperformed conventional imaging in terms of sensitivity and specificity. In 2012 Souillac et al [25] compared [^{18}F]FDG PET/CT with conventional CT in 30 patients, demonstrating superior specificity (87.5% vs. 77.5%) but lower sensitivity (75% vs 100%) in cN0 patients (n=22). Instead, in cN+ cases (n=8) [^{18}F]FDG PET/CT reached both sensitivity and specificity of 100%, while CT showed lower sensitivity (85.7%) and equal specificity. Of note, [^{18}F]FDG PET/CT upstaged to pN2 2 cN0 and 3 cN1 cases, determining an up-staging in 9.1% and 37.5% of cases, respectively. Another study by Jakobsen et al [26] involving 143 PC patients demonstrated a superior [^{18}F]FDG PET/CT sensitivity and specificity with respect to conventional CT (88.5% and 70.5% per groin vs 57.7% and 47.5% per groin, respectively), and lower false -negative (FN) rate (11.5% vs 42.3% per groin, respectively).

Beyond inguinal lymph node staging, [^{18}F]FDG PET/CT has also been investigated for broader applications in PC management and some studies focused on the evaluation of pelvic lymph node involvement and distant metastases.

Table 2 Results of [^{18}F]FDG PET/CT for Staging Inguinal and pelvic Lymph-Nodes.

	Year	Study Design	Patients	N	Overall Sensitivity	Overall Specificity	PPV	NPV
Scher et al [15]	2005	P	13	inguinal	89%	100%	100%	80%
Thyavihally et al [21]	2009	R	16	inguinal	82%	87%	82%	87%
Leijite et al [16]	2009	P	24 (cN0)	inguinal	20%	92%	25%	89%
Graafland et al [26]	2009	R	21	pelvic	91%	100%	100%	94%
Graafland et al [23]	2010	R	8	inguinal	100%	100%	100%	100%
Dou et al [22]	2010	R	11	inguinal	75%	69%	37.5%	92%
Souillac et al [24]	2012	P	22 (cN0) 8 (cN+)	inguinal	91%	91%	67%	98%
Schlenker et al [17]	2012	P	35	inguinal	88%	98%	94%	96%
Zhang et al [18]	2016	P	48	pelvic	93%	85%	86%	92%
Jakobsen et al [29]	2016	P	129 (cN0)	inguinal	94.4% per groin (combined to SLNB)	-	-	98% (combined to SLNB)
Drager et al [19]	2018	P	41 (cN0)	both	84%	79%	44%	91%
Jakobsen et al [25]	2021	R	143	inguinal	88%	71%	40%	96%
Ottenhof et al [27]	2022	R	61	pelvic	85%	75%	65%	90%

Abbreviations: cN0 clinically non palpable lymph nodes; cN+ clinically palpable lymph node; FN: false negative; NPV: Negative predictive value; P: prospective; PPV: Positive predictive value; R: retrospective; SLNB: Sentinel lymph node biopsy.

Regarding the role of [^{18}F]FDG PET/CT in detecting pelvic lymph node metastases Graafland et al [27] demonstrated a sensitivity, specificity, and diagnostic accuracy of 91%, 100%, and 96%, respectively, with a positive predictive value (PPV) and negative predictive value (NPV) of 100% and 94%. Similarly, Ottenhof et al [28] in 2022 reached values of sensitivity, specificity, PPV and NPV of 85%, 75%, 65% and 90%, respectively, higher than those previously published for conventional CT and MRI [29]. A 2022 meta-analysis by Lee et al [15] confirms these data by highlighting a pooled sensitivity and specificity of 89% and 83% for the detection of pelvic lymph node involvement.

Taking into account the detection of distant metastases some studies [26,27] evidence that [^{18}F]FDG PET/CT identified distant metastases and synchronous malignancies missed by conventional CT, reinforcing its role in comprehensive staging and treatment planning. Ottenhof et al [28] reported a PPV of 93% for detection distant metastases on [^{18}F]FDG PET/CT and sensitivity, specificity, NPV and PPV resulted 83%, 60%, 75% and 73% respectively, with an accuracy of 74% in identifying, overall, pelvic lymph node and distant metastases.

In conclusion, [^{18}F]FDG PET/CT demonstrates superior performance compared to conventional imaging in detecting lymph node metastases in patients with penile cancer, showing comparable accuracy in both inguinal and pelvic regions. It also holds promise for identifying distant metastatic sites, thereby informing treatment decisions within a multimodal therapeutic framework. Its diagnostic value is currently more evident in cN+ patients, whereas in cN0 cases, alternative locoregional staging approaches—such as sentinel lymph node biopsy (SLNB)—may be more appropriate to minimize the risk of false negatives [30]. A key limitation of [^{18}F]FDG PET/CT remains its reduced sensitivity for detecting micrometastatic disease.

[^{18}F]FDG PET/CT FOR RESTAGING PENILE CANCER

Regional Recurrence

The incidence of local relapse after surgical treatment varies widely in PC patients, with reported rates between 5% and 30%. Most regional recurrences occur within the first two years following treatment, regardless of whether patients were managed with surveillance or invasive nodal staging. Although less common, regional recurrence may also arise beyond two years, and therefore continued follow-up in these patients is recommended [31]. The highest rate of regional recurrence (9%) has been reported in patients managed with surveillance, whilst the lowest rate (2.3%) is observed in patients who underwent invasive nodal staging with modified inguinal lymphadenectomy or dynamic sentinel lymph node biopsy and were found to be node-negative. The main features in terms of risk are tumor stage, surgical margins and lymph node involvement [32]. Local recurrence can usually be detected easily by physical examination, either by the patient or the clinician. Patient education is therefore a critical component of follow-up, and individuals should be instructed to seek specialist evaluation immediately if any changes are observed. However, imaging is highly relevant in clinically challenging cases. In the assessment of local recurrence after surgery or radiation therapy, the use of US and fine-needle aspiration cytology (FNAC) has improved the early detection rate of regional recurrence [33,34]. In suspicious cases, ^{18}F-FDG PET/CT might offer an advantage over conventional imaging in distinguishing postoperative inflammation and fibrosis from viable tumor relapse. Scher and colleagues [16] reported of 3 patients restaged with [^{18}F]FDG PET/CT for the suspect of recurrence following partial penile amputation. [^{18}F]FDG PET/CT revealed no abnormal uptake at the surgical site, despite MRI raising suspicion of local recurrence in one case; biopsy subsequently excluded malignancy. However, data currently available are insufficient to establish whether [^{18}F]FDG PET/CT might be an accurate diagnostic tool for assessing local recurrence of PC.

Distant Recurrence

Regarding distant metastases, the lungs represent the most common site of spreading, followed by the liver and bones (Figure 2). The likelihood of distant metastases increases particularly in advanced stages and in patients with multiple nodal involvements. [^{18}F]FDG PET/CT enables accurate whole-body imaging in a single session, which is highly valuable for detecting distant metastases in the lungs, liver, and bones. Moreover, the metabolic characterization of suspicious small nodules identified by conventional CT can alter clinical decision-making in the restaging process.

Nevertheless, the available literature on distant penile cancer metastases detected by [^{18}F]FDG PET/CT is currently almost limited to case reports [35–38]. In a study by Graafland et al [27], among 18 patients with pathologically confirmed inguinal lymph node metastases, distant metastases were identified in five patients at [^{18}F]FDG PET/CT. Of these five metastases, four were subsequently confirmed by CT or histopathology. Despite the small sample size, these findings support the value of [^{18}F]FDG PET/CT in accurate M staging.

In the largest series reported by Zhang et al. [19], [^{18}F]FDG PET/CT was compared with conventional CT in 42 patients with suspicious lesions on CT or MRI, which introduces a potential selection bias. When histopathology or follow-up imaging was used as the reference standard, the sensitivity and specificity of [^{18}F]FDG PET/CT across all metastatic sites (including lymph nodes, lungs, and bones) were 85% and 86%, respectively. On a per-patient analysis, sensitivity and specificity were found to be 82% and 93%, respectively. However, the patients enrolled in the study were imaged in different phases of disease (staging vs restaging), thus limiting the generalizability of the data reported.

While whole-body imaging in a single session provides advantages such as sensitivity based on metabolic activity and the ability to evaluate early treatment response, limitations remain. These include low sensitivity for

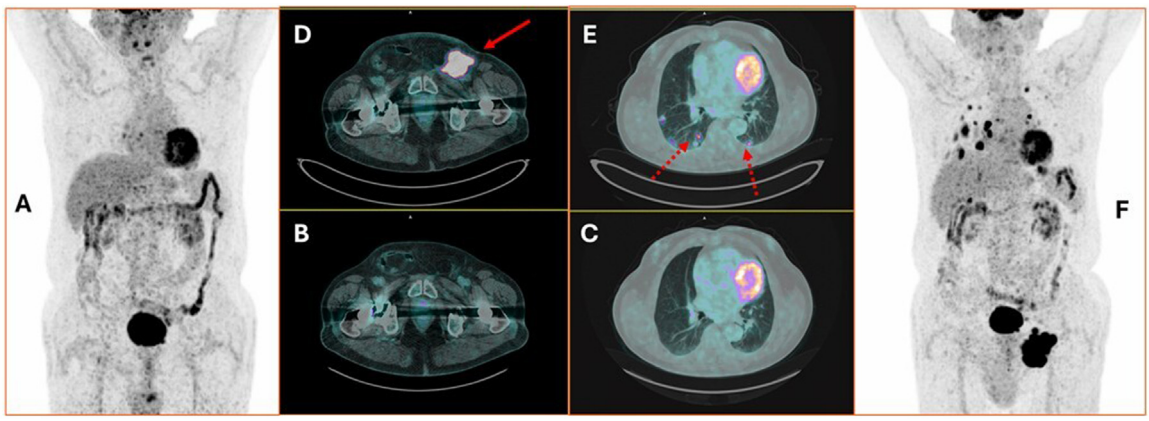

Figure 2 An 88-year-old man was diagnosed with primary PC in 2020 and executed a staging [^{18}F]FDG PET/CT. MIP (**A**) and transaxial fused PET/CT images (**B-C**) showing the presence of only primary tumor. A subsequent [^{18}F]FDG PET/CT (transaxial fused PET/CT images (**D-E**) and MIP (**F**) showed the appearance of metastatic left inguinal LN (red arrow) and multiple bilateral lung metastases (red dashed arrows) consistent with progression/relapse of disease. He died approximately 3 months after lung metastases developed.

micrometastases, false positives in cases of inguinal inflammatory changes, high costs, and limited availability. Nevertheless, the European Association of Urology (EAU) [39] and the National Comprehensive Cancer Network (NCCN) guidelines [40] currently endorse the use of [^{18}F]FDG PET/CT in the context of suspected recurrence in patients with inconclusive results at conventional imaging or known metastatic lymph node disease at diagnosis. Particularly, [^{18}F]FDG PET/CT has been reported to influence clinical management by excluding pelvic and distant metastases prior to surgical decision-making. Nevertheless, multicenter studies involving large cohorts of PC patients are required to confirm this indication.

THE ROLE OF [^{18}F]FDG PET/CT IN TREATMENT RESPONSE AND FOLLOW-UP IN PENILE CANCER

The potential role of [^{18}F]FDG PET/CT in evaluating treatment response in PC is promising but not supported by robust evidence. As in other oncological diseases, [^{18}F]FDG PET/CT might represent a successful tool in monitoring treatment response in penile tumors. In a case report, a 55-year-old male patient with bilateral inguinal LN metastases and classified as T3N3M0 was considered unsuitable for radical resection of the inguinal metastases and treated with neoadjuvant chemotherapy (NAC). Both CT and [^{18}F]FDG PET/CT scans demonstrated a remarkable reduction in inguinal metastases following NAC, suggesting a potential role of metabolic imaging in this scenario [41].

Graafland et al [24] investigated the role of [^{18}F]FDG PET/CT in monitoring neoadjuvant treatment response in patients with advanced PC in a small cohort of 8 patients. In patients with primarily inoperable but non-metastatic disease, induction chemotherapy is typically required before surgery, which remains the cornerstone of curative management in those with limited metastatic burden [2,3,42]. Accurate response monitoring is crucial in this subset of patients. Patients classified as responders, based on imaging, typically continue chemotherapy followed by surgery, whereas non-responders stop chemotherapy and receive palliative treatment only. In the cohort analyzed, [^{18}F]FDG PET/CT detected abnormal [^{18}F]FDG uptake consistent with malignancy in all eight patients. After two chemotherapy cycles, six patients demonstrated a metabolic response and two did not. [^{18}F]FDG PET/CT assessment was accurate in all cases; CT was concordant in seven patients but underestimated response in three responders. Five of six responders subsequently completed four chemotherapy cycles followed by surgery, with histopathology confirming metabolic response. These preliminary findings highlight the potential role of [^{18}F]FDG PET/CT in guiding treatment stratification for penile cancer. Confirmation in larger prospective cohorts will be essential to establish its clinical utility, since conventional imaging is limited in this context, as complete remission cannot be reliably confirmed in normal-sized lymph nodes and treatment response in necrotic lesions is difficult to quantify [43,44].

[^{18}F]FDG PET AS A PROGNOSTIC TOOL IN PENILE CANCER

In 2020 Bandini et al [45] selected from a multicenter database 334 patients with cN+ PC with clinical and follow-up information. Among these, 48 performed [^{18}F]FDG PET/CT and in 16 [^{18}F]FDG uptake was found in inguinal and pelvic lymph nodes. Their analysis identified an increased risk (>50%) of 24-month overall mortality (OM) in patients with cN2 and CN3 results at [^{18}F]FDG PET/CT, with a benefit

from potential NAC, concluding that staging [^{18}F]FDG PET/CT may represent a useful prognostic tool enabling selection of patients to be addressed to NAC.

In order to assess the effectiveness of [^{18}F]FDG PET/CT as a prognostic marker on PC, Salazar et al in 2019 [46] compared metabolic PET results with histopathology and clinical outcomes. They prospectively evaluated 5 PC patients that underwent [^{18}F]FDG PET/CT before surgery. Primary lesions exhibited significantly higher SUVmax (pSUVmax) values in more advanced stages, with a mean SUVmax of 9.2 in pT0−1a compared to 15.2 in pT1b−4 ($p = 0.019$). Similarly, SUVmax analysis of inguinal lymph nodes (nSUVmax) demonstrated good performance in identifying metastatic involvement, with a mean nSUVmax of 5.5 in pN0 cases - imputable to local inflammation - versus 12.0 in pN>1 cases ($p = 0.039$). Therefore, SUVmax values directly correlated with more aggressive histological features and may aid the differential diagnosis of pathological versus phlogistic inguinal lymph nodes. In the ROC analysis, an optimal cut-off value of 6.5 was identified ($p = 0.015$) for confirming metastatic involvement of inguinal lymph nodes, yielding a sensitivity of 76.9% and a specificity of 77.8%. This threshold demonstrated superior accuracy compared to clinical evaluation alone, particularly in cN+ patients. Survival analysis identified a pSUVmax of 16.6 ($p = 0.0001$) and a nSUVmax of 6.5 ($p = 0.019$) as optimal cut-off values for predicting cancer-specific survival. Univariate analysis confirmed that both pSUVmax and nSUVmax were significant predictors of mortality and lymph node metastasis. However, in multivariate analysis, nSUVmax remained an independent predictor of inguinal lymph node involvement ($p = 0.043$), while pSUVmax was independently associated with cancer-related death ($p = 0.05$). These findings support the prognostic value of [^{18}F]FDG PET/CT metabolic parameters in PC.

In 2024 another study by Salazar et al [47] focused on the correlation between [^{18}F]FDG uptake and tissue expression of markers involved in glucose metabolism and proliferation. 51 consecutive PC patients underwent [^{18}F]FDG PET/CT scanning for initial staging and were submitted to surgery as first treatment. As reported in previous studies, higher values of SUVmax correlated with higher tumor grades, with a link between higher Ki-67 and GLUT-1 levels. These findings confirm the potential relevance of [^{18}F]FDG PET/CT in identifying aggressive tumor types and guiding treatment in penile cancer.

Collectively, these findings underscore the dual diagnostic and prognostic utility of [^{18}F]FDG PET/CT in PC. Beyond its role in staging and restaging, semiquantitative PET metrics—particularly SUVmax values derived from primary tumors and nodal sites—may contribute to risk stratification and guide clinical decision-making, such the use of chemotherapy regimens in a neo- or adjuvant settings in those with unfavorable prognostic profile. Given the rarity of this malignancy, further validation in larger prospective cohorts will be essential to establish standardized SUVmax thresholds and to integrate [^{18}F]FDG PET/CT into evidence-based management algorithms.

FINAL REMARKS AND CONCLUSIONS

The rarity of PC has considerably limited the feasibility of prospective investigations aimed at exploring its diagnosis, staging, treatment, and follow-up. As a result, robust evidence on the role of imaging in this disease remains scarce. The recommendations of the major international guidelines vary regarding the routine use of [^{18}F]FDG PET/CT, with differences in indications for staging, recurrence, and surveillance (Table 3 [12,40,42]).

The literature consistently demonstrates that PC, both at the primary site and within regional lymph nodes, exhibit marked [^{18}F]FDG avidity. This strongly supports the potential role of [^{18}F]FDG PET/CT in disease staging. Nevertheless, PET has some intrinsic limitations: its spatial resolution reduces sensitivity for small metastatic deposits, and false positives findings may occur in the setting of inflammation, such as reactive lymph nodes. These limitations are not unique to PC but are shared across other malignancies commonly evaluated with [^{18}F]FDG PET and known to an expert physician.

Staging [^{18}F]FDG PET might be crucial in patients with clinical suspect of inguinal metastases, along with SNLB.

Table 3 Summary of Current Guidelines on the Use of [^{18}F]FDG PET/CT.

Guideline	Role of [^{18}F]FDG PET/CT	Notes
EAU (2024) [12]	Not recommended for routine initial staging but is advised for staging in cN+ patients. It may also be useful in cases of recurrence or advanced disease, particularly in those with confirmed nodal involvement or inconclusive findings on conventional imaging.	Highlights the limitation in detecting micro-metastases
NCCN (2024) [40]	Recommended in patients with palpable lymph nodes for risk stratification and treatment response assessment; tt may be used for restaging in cases of suspected metastatic disease or when conventional imaging yields inconclusive findings.	Emphasizes combined use with CT/MRI
AFU (2024–2026) [42]	Applicable for nodal evaluation and recurrence; particularly important during 5-year follow-up	Not an alternative to sentinel lymph node biopsy

However, another important consideration concerns the reliability of inguinal examination. Although some reports advocate using clinical positivity as a criterion for referring patients to [^{18}F]FDG PET/CT imaging, this approach is problematic. Inguinal palpation is frequently unreliable—particularly in obese patients—and may result in both false-positive and false-negative assessments. As reported by Algaba et al [48], between 20% and 96% of patients present with palpable lymph nodes at initial diagnosis; however, histologically confirmed nodal metastases are found in only 17% to 45% of these cases. Therefore, limiting [^{18}F]FDG PET/CT referral exclusively to patients with palpable lymph nodes is increasingly difficult to justify.

While only a few small-sample studies have focused on staging, even fewer have evaluated the effectiveness and clinical utility of [^{18}F]FDG PET/CT in recurrence and restaging of PC. Post-treatment surveillance of PC is largely dependent on meticulous clinical examination, both by the treating physician and, to some extent, by patient self-inspection. In this context, [^{18}F]FDG PET/CT may offer additional benefit in accurately identifying the location and extent of suspected recurrence. However, routine surveillance with [^{18}F]FDG PET/CT cannot be recommended yet, and this imaging should be reserved only to selected patients where recurrence is clinically suspected.

Finally, the observed association between advancing tumor stage and grade and the likelihood of nodal metastases suggests that [^{18}F]FDG PET/CT may be particularly valuable when performed after histopathological confirmation, in patients with high-grade disease. In this context, [^{18}F]FDG PET/CT could help in risk stratification and optimization of subsequent management strategies, as already demonstrated in other malignancies [49]. Moreover, Salazar findings [50] underscore the dual diagnostic and prognostic utility of [^{18}F]FDG PET/CT in penile squamous cell carcinoma, in particular when corroborated by semiquantitative PET metrics, like SUVmax values.

In summary, [^{18}F]FDG PET/CT should be considered a complementary imaging modality rather than a stand-alone tool in the management of PC. When judiciously applied, it offers the potential to enhance risk stratification, guide personalized treatment strategies, and ultimately improve patient outcomes. Although current evidence remains limited and its definitive role in routine clinical practice has yet to be established, available data consistently highlight the [^{18}F]FDG-avid nature of penile lesions. This biological characteristic supports the rationale for prospective studies involving sufficiently powered cohorts to better delineate the true clinical utility of [^{18}F]FDG PET/CT in PC and facilitate its integration into diagnostic and therapeutic pathways. Nevertheless, the rarity of PC continues to pose a significant challenge to the implementation of large-scale investigations. Future research efforts should prioritize the development of novel radiotracers, hybrid imaging platforms, and AI-driven analytical approaches to broaden the diagnostic and prognostic capabilities of [^{18}F]FDG PET/CT, paving the way for its more prominent role within multidisciplinary oncologic care.

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CRediT authorship contribution statement

Ilham Badrane: Investigation, Methodology, Writing – original draft, Writing – review & editing. **Alberto Nieri:** Data curation, Investigation, Writing – original draft, Writing – review & editing. **Domenico Albano:** Data curation, Methodology, Supervision, Writing – original draft, Writing – review & editing. **Esra Arslan:** Investigation, Methodology, Writing – original draft. **Valentina Ceriani:** Investigation, Writing – original draft. **Federica Lancia:** Methodology, Writing – review & editing. **Corrado Cittanti:** Methodology, Writing – review & editing. **Mirco Bartolomei:** Methodology, Writing – review & editing. **Luca Urso:** Conceptualization, Data curation, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing.

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