Accuracy of ^{18}F-FDG PET/CT for Diagnosing Inguinal Lymph Node Involvement in Penile Squamous Cell Carcinoma

Systematic Review and Meta-Analysis of the Literature

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Purpose: Metastatic involvement of the inguinal lymph nodes is associated with decreased survival and is a strong prognostic factor in penile squamous cell carcinoma. The aim of the current systematic review was to evaluate the accuracy of ^{18}F-FDG PET/CT for inguinal lymph node staging in penile squamous cell carcinoma and possible influential factors.

Materials and Methods: Medline, SCOPUS, Springer, Science Direct, and Google Scholar were searched using the key words "(penile or penis) and PET," with no date or language limitation. The meeting abstracts were not excluded either. Statistical pooling was performed using the random-effects model.

Results: Seven studies were included in the meta-analysis. One article had 2 different subgroups of patients, and each subgroup was considered as a separate study. Pooled sensitivity and specificity were 80.9% (95% confidence interval [CI]: 69.5%–89.4%) and 92.4% (95% CI: 86.8%–96.2%), respectively. Pooled sensitivity was 96.4% (95% CI: 81.7%–99.9%) for cN+ and 56.5% (95% CI: 34.5%–76.8%) for cN0 patients.

Conclusions: ^{18}F-FDG PET/CT imaging has relatively low sensitivity (especially in cN0 patients) for detection of inguinal lymph node involvement in penile cancer patients, which does not justify its routine use. However, patients with clinically palpable lymph nodes may benefit from ^{18}F-FDG PET/CT because the sensitivity in this subgroup of patients is high.

Key Words: inguinal lymph node dissection, meta-analysis, penile cancer, FDG PET, systematic review, PET/CT, squamous cell carcinoma, sensitivity, specificity

(*Clin Nucl Med* 2012;37: 436–441)

Squamous cell carcinoma (SCC) of the penis is a malignancy of the genitourinary system, which is uncommon in developed countries, but its incidence in some developing countries is much higher.[1] The age of presentation is mostly in the sixth decade of life, and a minority presents with metastatic involvement.[2] Metastatic involvement is a strong prognostic factor and is associated with decreased survival.[3]

Received for publication May 18, 2011; revision accepted August 17, 2011.

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The sponsor didn't have any role in the study design, in the collection, analysis and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication.

Conflicts of interest and sources of funding: Supported financially by the vice-chancellery of research of Mashhad University of Medical Sciences with the approval number 900007.

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ISSN: 0363-9762/12/3705-0436

Inguinal lymph node dissection is the procedure usually performed for penile cancer patients for prognosis determination, as well as therapeutic purposes.[4] It is worth mentioning that this procedure is not necessary in many penile cancer patients because 75% to 80% of cN0 patients do not have inguinal lymph node involvement.[5] This fact, as well as significant morbidity of inguinal lymph node dissection,[6] shows that patients would benefit from noninvasive methods of inguinal lymph node staging. Nomograms,[7] imaging modalities (MRI, PET/CT, CT, ultrasound),[8] and sentinel lymph node biopsy[9] have been used for this purpose with various results.

In the current study, we evaluated the diagnostic accuracy of ^{18}F-FDG PET/CT for inguinal lymph node staging of penile SCC by systematic search of the literature and meta-analysis of the results.

MATERIALS AND METHODS

Search Strategy, Selection Criteria, Data Abstraction

Medline, SCOPUS, Google Scholar, Springer, and Science Direct were searched with the free search terms of (PET and [penile or penis]), without any date or language limitation. Meeting abstracts were not excluded. References of relevant studies were hand searched for any possible missing citation. Corresponding authors of several studies were contacted for obtaining more complete data.

Studies with the following criteria were included:

1. Using ^{18}F-FDG PET/CT as the index test for inguinal lymph node staging.
2. Using inguinal lymph node dissection (or sentinel node biopsy) and/or follow-up of the patients as the gold standard.
3. Providing enough data to construct a 2 × 2 table for sensitivity and/or specificity calculation.
4. The malignancy of interest was SCC.

Retrieved articles were evaluated blindly by 2 of the authors. Any controversy was resolved by the third author. Possible duplicate publications were discussed, and only the most recent studies were included.

The Oxford Center for Evidence-Based Medicine checklist for diagnostic studies was used for quality assessment of the included studies.[10] This checklist has 5 major parts as follows:

1. Representative spectrum of the patients
2. Consecutive patient recruitment
3. Ascertainment of the gold standard regardless of the index test results
4. Independent blind comparison between the gold standard and index test results
5. Enough explanation of the test to permit replication

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Data on authors, publication year, method, characteristics of the patients, and information needed for sensitivity and/or specificity calculation were abstracted by 2 authors independently.

Statistical Analysis

We used the recommendations of Devillé et al for statistical analyses.[11] Considering various spectra of patients included in each study, we used the random-effects model (DerSimonian and Laird method[12]) for pooling the results. For heterogeneity evaluation, the Cochrane Q test was used, and significance level was set at $P = 0.05$. For quantifying the heterogeneity, the I^2 index was used.[13]

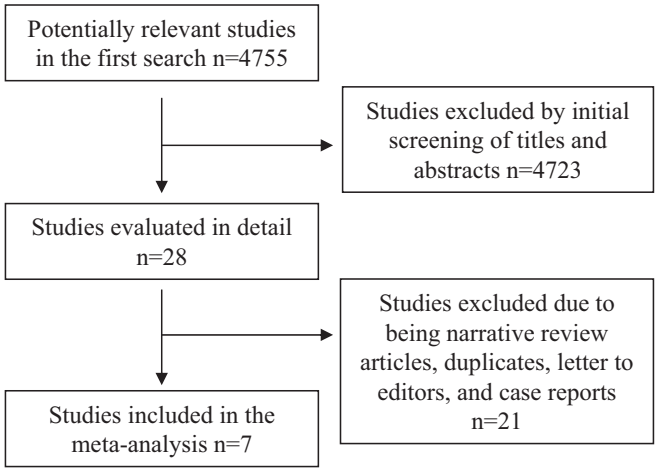

FIGURE 1. Flowchart of the study search strategy.

For evaluation of threshold effect, correlation between specificity and sensitivity in all included studies was evaluated.[14] For studies with enough information regarding threshold of PET positivity, ^{18}F-FDG PET/CT scan were imposed, and new diagnostic indices were recalculated.

Sensitivity, specificity, LR− (negative likelihood ratio), LR+ (positive likelihood ratio), and diagnostic odds ratio (DOR) were calculated for each study, and pooling was done for each. Summary receiver operating characteristics curve (SROC curve) fitting,[14] area under the curve (AUC) calculation, as well as Q* value[15] were also used for summarizing data.

For publication bias evaluation, funnel plots, Egger's regression intercept,[16] and Duval and Tweedie's trim and fill[17] method were used.

For statistical analyses, Comprehensive Meta-analysis (version 2) and Meta-Disc (version 1.4)[18] were used. All analyses were performed with the groins as the unit of calculations. Two subgroups of patients (namely, cN+ and cN0) were used for subgroup analysis. For calculating the proportion of between-study variance, which could be explained by subgroup analysis, we used the R^2 index as proposed by Borenstein et al.[13]

RESULTS

Figure 1 shows the diagram of meta-analysis search strategy. In all, 4755 studies in the first search seemed to be potentially relevant. A total of 4723 studies were excluded (irrelevant subjects) on the basis of initial screening of the titles and/or abstracts. Full texts of the remaining 28 studies were evaluated. Twenty-one studies were excluded for being narrative review articles, duplicates, letter to editors, and case reports. The remaining 7 articles (overall 115 patients and 213 groins) were included in the meta-analy-

TABLE 1. Quality Assessment of the Included Studies

Authors and Reference Number	Publication Year	Wide Spectrum of the Included Patients	Application of eference Standard to All Patients	Blind Comparison Between the Index Test and Reference Standard	Enough Explanation of the Tests	Consecutive Patient Recruitment	Mean Duration of Follow–Up in Months
Graafland et al[19]	2010	No (patients with palpable nodes or inoperable tumors)	4/8 inguinal dissection, 1/8 sentinel node biopsy, 3/8 follow–up	Yes	Yes	N/A	N/A
Schlenker et al[20]	2009	Yes	22/35 inguinal dissection, 13/35 follow–up	No	Yes	N/A	48.8
Dou et al[21]	2010	Yes	6/11 inguinal dissection, 5/11 follow–up	N/A	No	Yes	15
Leijte et al[22]	2009	No (only cN0 patients)	Inguinal dissection in 2 groins and sentinel node biopsy in the remainder	No	Yes	Yes	N/A
Graafland et al[23]	2009	No (only tumor positive inguinal nodes were included)	14/18 inguinal dissection, 4/18 follow–up	Yes	Yes	Yes	7
Thyavihally et al[24]	2009	Yes (this is the subgroup with positive inguinal nodes)	Inguinal dissection in all	N/A	No	N/A	N/A
Thyavihally et al[24]	2009	Yes (this is the cN0 subgroup)	Follow–up in all	N/A	No	N/A	12
Rosevear et al[25]	2011	No (only cN0 patients)	Inguinal dissection in all	N/A	No	Yes	N/A

N/A indicates not available.

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TABLE 2. Summary Data of the Included Studies as Well as Characteristics of the Patients

Authors and Reference Number	Mean Age of the Patients	^{18}F–FDG Dose in MBq	Total No. Groins	True–Positive Groins	False–Positive Groins	False–Negative Groins	True–Negative Groins	Sensitivity (95% CI)	Specificity (95% CI)
Graafland et al[19]	66	300–400 in 2 and 180–240 in 6	15	11	0	0	4	100% (71.5–100)	100% (39.8–100)
Schlenker et al[20]	60.6	200	70	15	1	2	52	88.2% (63.6–98.5)	98.1% (89.9–100)
Dou et al[21]	47–81	555	20	3	5	1	11	75% (19.4–99.4)	68.8% (41.3–89)
Leijte et al[22]	61	300–400 in 9 and 180–240 in 15	42	1	3	4	34	20% (5–71.6)	91.9% (78.1–98.3)
Graafland et al[23]	62	300–400 or 180–240	28	10	0	1	17	90.9% (58.7–99.8)	100% (80.5–100)
Thyavihally et al[24]	43	N/A	6	6	0	0	0	100% (54.1–100)	N/A
Thyavihally et al[24]	43	N/A	26	9	2	2	13	81.8% (48.2–97.7)	86.7 (59.5–98.3)
Rosevear et al[25]	N/A	N/A	6	0	0	3	3	0% (0–70.8)	100% (29.2–100)

N/A indicates not available.

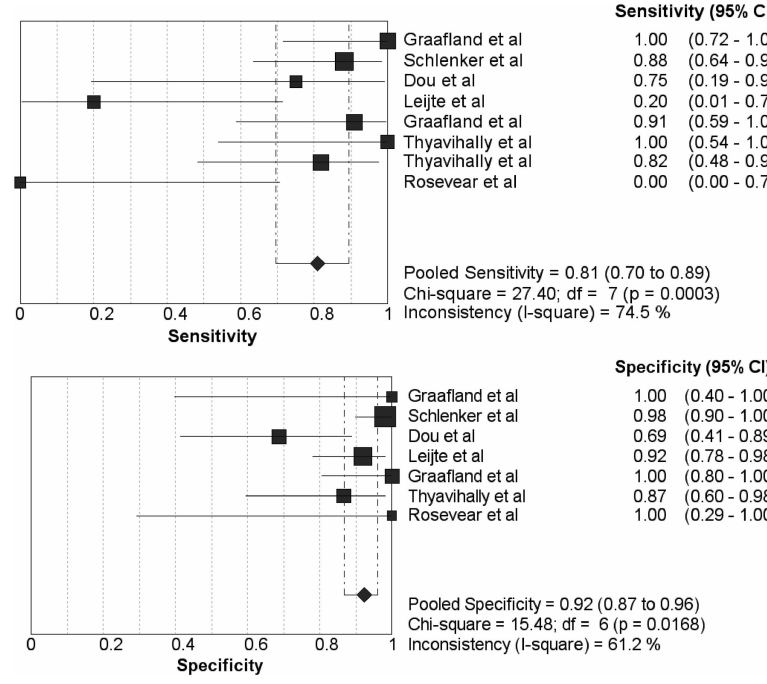

FIGURE 2. Forest plot of the sensitivity (top) and specificity (bottom) pooling. The black squares are sensitivity (top) or specificity (bottom) of individual studies, and their sizes correspond to the sample size. Lines on each side of the squares represent 95% CIs. The black diamonds are pooled sensitivity (top) and specificity (bottom) of the included studies, and the lines on each side represent 95% CI. I^2 indices represent the proportion of between-study variance, which cannot be attributed to sampling error and is truly due to variations between studies.

sis.[19–25] One study had 2 separate subgroups of patients (cN+ and cN0 patients) that were included in the meta-analysis separately.[21]

Quality assessment of the included studies is shown in Table 1. Summary data of the included studies as well as characteristics of the patients are shown in Table 2.

Diagnostic Accuracy

Figure 2 shows the forest plots of sensitivity and specificity of ^{18}F-FDG PET/CT in the diagnosis of inguinal lymph node involvement of penile SCC patients. Table 3 shows pooled summary indices of the meta-analysis.

SROC curve of the study is shown in Figure 3. AUC = 0.9089 and Q* was 0.8401.

Heterogeneity Evaluation and Subgroup Analysis

Considering Cochrane Q values as well as I^2 indices (Table 3), the included studies were heterogeneous, and for addressing this heterogeneity, we performed subgroup analysis regarding cN0 or cN+ patient groups. Table 4 shows subgroup analysis summary indices of the meta-analysis.

Threshold Effect

Spearman correlation coefficient between logit values of true-positive and false-positive rates was −0.429 (P = 0.337), which showed no statistically significant (implicit or explicit) threshold effect in the included studies. However, different thresholds were used by included studies; for example, Dou et al reported any increased uptake as positive scan,[21] Rosevear et al used standardized uptake value as the criteria of positivity (standardized uptake value of 1.5 in a lymph node was considered as inflammatory),[25] and Graafland et al as well as Leijte et al used semiquantitative evaluation (more than 1+) as the criterion of positivity.[19,22] We considered any increased activity as positive ^{18}F-FDG PET/CT,

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TABLE 3. Pooled Summary Indices of Diagnostic Performance of ^{18}F-FDG PET/CT for Inguinal Lymph Node Involvement Diagnosis

	Pooled Index	95% CI	Cochrane Q and *P*	I^2 Index
Sensitivity	0.809	0.695–0.894	27.41/<0.0003	74.5%
Specificity	0.924	0.868–0.962	15.48/0.017	61.2%
LR−	0.288	0.094–0.878	54.22/<0.0001	86.4%
LR+	6.461	2.088–19.993	14.90/0.021	59.7%
DOR	27.619	5.295–144.07	13.94/0.03	57%

TABLE 4. Subgroup Analysis of the Study Regarding cN0 or cN+ Patients

	cN0		cN+	
	Pooled Index	95% CI	Pooled Index	95% CI
Sensitivity	0.565	0.345–0.768	0.964	0.817–0.999
Specificity	0.859	0.756–0.930	1	0.839–1
LR−	0.615	0.279–1.356	0.101	0.027–0.378
LR+	3.029	1.510–6.078	16.960	2.54–113.242
DOR	7.532	2.040–27.808	229.20	17.743–2960.9

and recalculation of the results showed pooled sensitivity and specificity of 85.3% (95% confidence interval [CI]: 74.6%–92.7%) and 91% (95% CI: 85.2%–95.1%), respectively. Using the same criteria, pooled sensitivity and specificity for cN0 subgroup were 69.6% (95% CI: 47.1%–86.8%) and 83.1% (95% CI: 72.3%–90.9%), respectively.

Publication Bias

Publication bias is a major concern in all meta-analyses. Funnel plots of the included studies for sensitivity and specificity are shown in Figure 4. Egger's regression intercept for sensitivity and specificity funnel plots was −1.297 ($P = 0.278$) and 1.7596 ($P = 0.10$), respectively. Adjusted values of pooled sensitivity and specificity using Duval and Tweedie's trim and fill method were 77.1% [95% CI: 65.7%–85.6%] and 80.9% [95% CI: 75.3%–84.7%], respectively. These were about 3.8% and 11.5% lower than the observed pooled indices, respectively.

DISCUSSION

Inguinal lymph node involvement is the major prognostic factor in patients with penile SCC.[26] Inguinal lymph node dissection is considered the standard of care in patients who presented with palpable inguinal nodes. This approach showed significant survival benefit in contrast to many other solid tumors.[5] Although this survival benefit has also been shown for cN0 patients with nodal involvement in pathologic examination,[4,27] performing inguinal lymph node dissection in all cN0 patients is obviously an overtreatment (especially keeping in mind the considerable morbidity of this procedure) because up to 75% to 80% of these patients do not have pathologically involved inguinal nodes.[5,6] Due to the earlier mentioned facts, recommendations for inguinal lymph node management in cN0 patients vary significantly, and there is an obvious need for noninvasive imaging technique for better diagnosis of inguinal lymph node involvement in penile cancer patients.[26]

^{18}F-FDG PET/CT is an imaging modality with encouraging results in the staging of various cancers.[28] Several case reports of successful application of this imaging technique in penile SCC have been reported.[29–34] However, specific studies on the accuracy of ^{18}F-FDG PET/CT are scarce. Low incidence of this cancer is the major cause of this scarcity. In the current meta-analysis, we systematically searched for specific studies in this regard and statistically pooled the results.

No statistically significant threshold effect was noted in the included studies of the current systematic review.

We presented overall performance of ^{18}F-FDG PET/CT with SROC curve and AUC calculation. AUC was 0.9082 and Q* was 0.8401, which are fairly high. Pooled DOR of ^{18}F-FDG PET/CT was 27.619 [95% CI: 5.295–144.07], which also is high. DOR, AUC, and Q* are indices of diagnostic accuracy and should be considered alongside sensitivity and specificity because high overall performance of a test does not guarantee high sensitivity, which is the primary index of interest in our study.

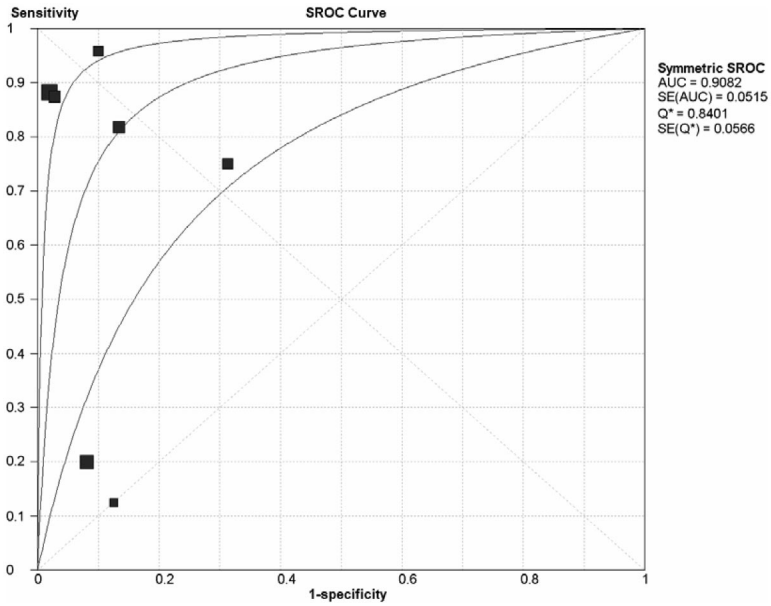

FIGURE 3. SROC curve of the meta-analysis. This is the plot of sensitivity against specificity of each study for evaluating possible threshold effect in the included studies. The curves represent the SROC curve (middle) and 95% CI. The SROC curve represents overall performance of the test. AUC is the area under the SROC curve, and the higher values of AUC (closer to 1) mean better performance of the test. Q* is the point on the SROC curve at which the sensitivity and specificity are equal to each other. Again higher values of Q* (closer to 1) show better performance of the test.

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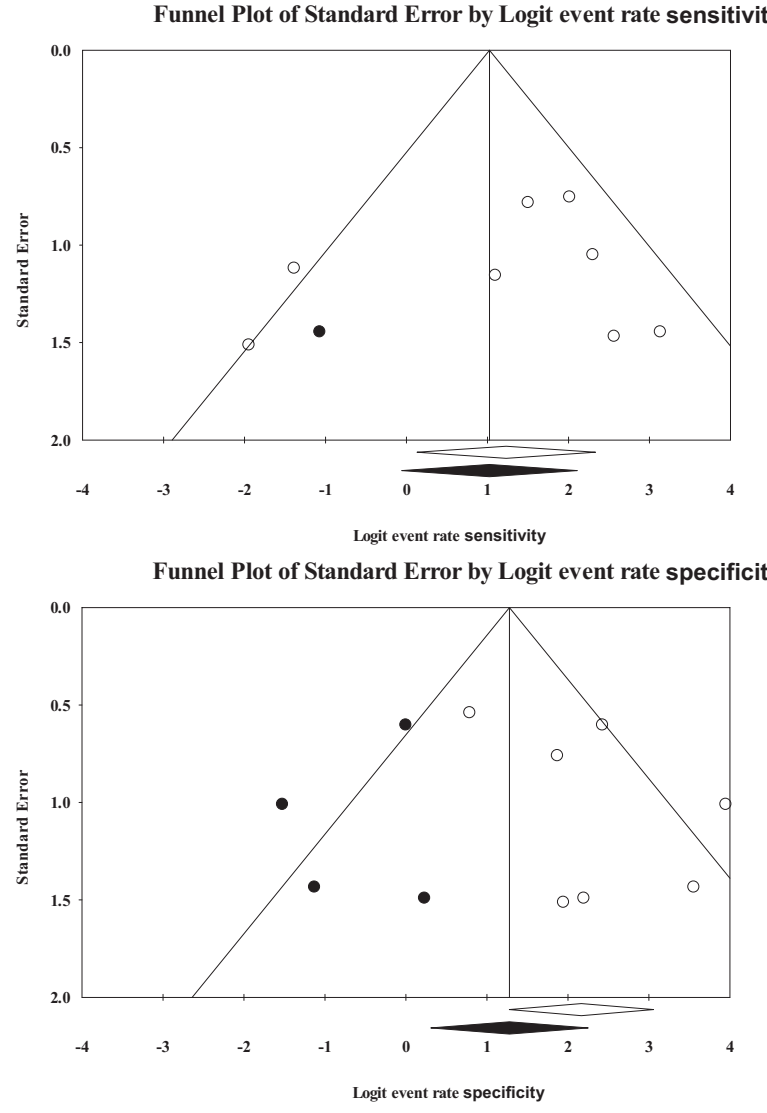

FIGURE 4. Funnel plot of the sensitivity (top) and specificity (bottom) pooling. These are the plots of logit sensitivity (top) and specificity (bottom) against standard errors. Any asymmetry in the plot can be due to publication bias. The black diamonds show trimmed pooled effect sizes after application of Tweedie's trim and fill method. This method represents the adjusted values of sensitivity (top) and specificity (bottom) after correction of possible publication bias. If the adjusted values show high deviation from the original ones, important publication bias can be implied.

Pooled sensitivity and LR− of ^{18}F-FDG PET/CT for diagnosis of inguinal involvement were 80.9% [95% CI: 69.5%–89.4%] and 0.288 [95% CI: 0.094%–0.878], respectively. These are not that high when compared with other approaches such as sentinel node biopsy[35,36] or nomograms.[37] Pooled specificity and LR+ of ^{18}F-FDG PET/CT for diagnosis of inguinal involvement were 92.4% [95% CI: 86.8%–96.2%] and 6.461 [95% CI: 2.088–19.993], respectively, which are high enough and mean that positive ^{18}F-FDG PET/CT inguinal nodes are most likely true-positive results. This low pooled sensitivity has been attributed to low spatial resolution of PET/CT scanners and missing micrometastases.[22]

Statistically significant Cochrane Q test as well as high I^2 indices showed considerable heterogeneity in the included studies. Subgroup analysis considering clinical condition of inguinal lymph nodes (cN0 or cN+ patients) was used for addressing this heterogeneity. As shown in Table 4, sensitivity of ^{18}F-FDG PET/CT for diagnosis of inguinal lymph node involvement was fairly high in cN+ patients (96.4% [95% CI: 81.7%–99.9%]), which was in contrast to those with clinically negative groins or cN0 patients (56.5% [95% CI: 34.5%–76.8%]). Subgroup analysis results also support the concept of limited value of PET/CT in diagnosis of micrometastases. The R^2 indices ($1-T^2_{within}/T^2_{total}$) for subgroup analyses considering sensitivity and specificity were 0.4511 and 0.7805, respectively, which mean that 45.11% and 78.05% of the between-study variance for sensitivity and specificity pooling could be explained by subgroup membership, respectively.

Study Limitations

Considering the low incidence of penile cancer, studies specifically reporting accuracy of ^{18}F-FDG PET/CT in penile cancer are scarce. We comprehensively searched several databases including Google Scholar, Science Direct, and SCOPUS to locate more studies. We also included meeting abstracts and contacted corresponding authors of several studies. However, the small number of included studies shows that the problem still persists and is the major limitation of our meta-analysis.

Another important limitation is the heterogeneity of the included studies. The heterogeneity of diagnostic studies comes from 2 different sources. First is the threshold effect, which means that different cutoff values (implicit or explicit) in each study can affect the results. We evaluated this effect, which was not statistically significant; however, recalculation of the results

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with different threshold setting showed increased sensitivity and decreased specificity, which denotes an important threshold effect. We also pooled the diagnostic performance with SROC and AUC, which are special ways to deal with threshold effect. The second source of heterogeneity is between-study variance regarding recruited patients, methods, etc. We used subgroup analysis regarding cN0 or cN+ patient groups to deal with this limitation. R^2 index showed that 45.11% and 78.05% of the between-study variance in sensitivity and specificity pooling could be explained by subgroup analysis.

In our opinion, despite high level of heterogeneity, the subgroup analysis, as well as threshold effect evaluation, was pretty successful for explaining this heterogeneity in our study. For example, the reason for 100% sensitivity in the Graafland et al study[23] was inclusion of only cN+ patients, and the reason for 0% sensitivity in the Rosevear et al study[25] was inclusion of cN0 patients as well as the threshold effect we mentioned earlier. Therefore, we decided to continue with meta-analysis in addition to qualitative systematic review of the literature, which is more intuitive for most readers.

Publication bias was also evaluated in the current study. Funnel plot for sensitivity and specificity pooling showed some asymmetry. However, Egger's regression intercepts were not statistically significant. Keeping in mind the low power of Egger's test for catching important publication bias, we also used Duval and Tweedie's trim and fill method, which showed that publication bias, if present, can have some effects on pooled diagnostic indices, especially specificity pooling. We included meeting abstracts and set no language limitation in our search to minimize this bias. However, this limitation still persists for our systematic review.

In conclusion, ^{18}F-FDG PET/CT imaging has relatively low sensitivity for detection of inguinal lymph node involvement in penile cancer patients, which does not justify its routine application in penile SCC. This is especially true for cN0 patients. However, patients with clinically palpable lymph nodes may benefit from ^{18}F-FDG PET/CT because the sensitivity in this subgroup of patients is fairly high.

ACKNOWLEDGMENTS

The authors thank Dou Y, Schlenker B, and Scher B for providing additional information for the current systematic review.

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