^{18}F-Fluciclovine PET for Assessment of Prostate Cancer with Histopathology as Reference Standard

A Systematic Review

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KEYWORDS

• Prostate cancer • PSMA • PET/CT • PET/MR imaging • Personalized medicine • Fluciclovine PET • Histopathology

KEY POINTS

- ^{18}F-fluciclovine PET has high sensitivity, but low specificity for localization of known primary prostate cancer.
- ^{18}F-fluciclovine PET has high specificity, but low sensitivity for detection of primary lymph node metastases.
- Few ^{18}F-fluciclovine studies have systematic sector-based histopathology that allows calculation of sensitivity and specificity.

BACKGROUND

Prostate cancer is the most common cancer in men, and has the second-highest mortality among male malignant carcinomas.[1] At initial diagnosis, the extent and spread of the cancer are key factors in deciding the appropriate treatment. For localized disease, the main treatment modalities are radical prostatectomy, external beam radiotherapy, or brachytherapy. About one-third of patients develop recurrence after primary definitive treatment.[2] Localization of recurrent disease is critical to the subsequent therapeutic strategy and prognosis because focal salvage treatment options are emerging.[3,4]

In the past, the role of PET for prostate cancer imaging has been limited. However, in recent years, several new PET tracers have emerged that offer improved diagnostic performance for detecting localized disease and metastases at initial diagnosis and localize disease recurrence.[5] One of these PET tracers is trans-1-amino-3-^{18}F-fluorocyclobutanecarboxylic acid (anti-^{18}F-FACBC, ^{18}F-fluciclovine). ^{18}F-fluciclovine is a radiolabeled amino acid analogue that exploits the increased demand of amino acids in tumor tissue for prostate cancer imaging[6] (**Fig. 1**). Long half-life and limited urinary excretion are also desirable features of ^{18}F-fluciclovine.[7] At present,

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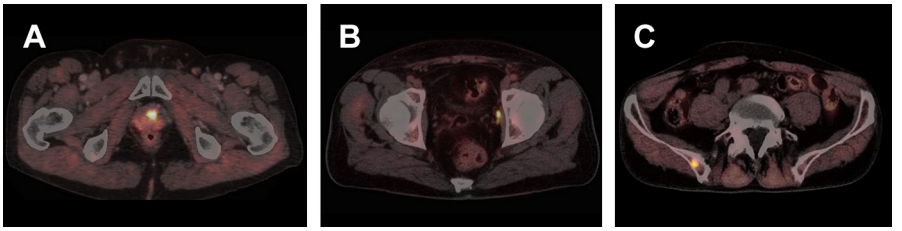

Fig. 1. ^{18}F-fluciclovine PET/CT images showing local recurrence (*A*), a lymph node metastasis (*B*), and a sclerotic bone metastasis (*C*).

^{18}F-fluciclovine is approved in the United States for specific indications: suspected prostate cancer recurrence based on increased prostate-specific antigen (PSA) level.[8]

This article summarizes studies of diagnostic accuracy of ^{18}F-fluciclovine PET for assessment of patients with prostate cancer with systematic sector-based histopathology as reference standard.

EVIDENCE ACQUISITION

Search Strategy

The systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[9] An information specialist (H.S.) planned and performed the systematic literature searches in MEDLINE (Ovid), Embase (Ovid), Cochrane Database of Systematic Reviews (Wiley), Cochrane Central Register of Controlled Trials, including references from ClinicalTrials.gov and The World Health Organization (WHO) International Clinical Trials Registry Platform (Wiley) and Scopus (Elsevier). Search terms were discussed in detail with 2 of the reviewers (A.J.T., T.S.) and the authors searched for a combination of subject headings, where applicable, and text words, including synonyms, for "fluciclovine f 18 AND prostate cancer." The following strategy was used in MEDLINE (Ovid) and adapted to the other databases: "(((((fluciclovine or fluorocyclobutane* or FACBC) adj3 (F-18 or 18F)) or ge-148 or ge148 or F-FACBC or axumin or NMK-36 or NMK36 or NMK-36c or "1-amino-3-fluorocyclobutane-1-carboxylic acid").mp.) OR ((exp Prostatic Neoplasms/or (prostat* adj3 (neoplasm* or cancer* or tumo?r* or carcinom*)).mp.) and FACBC.mp.))." Filters to exclude animal studies were applied in MEDLINE and Embase. All searches were performed on July 14 2020. The complete search strategy for all databases can be obtained from the corresponding author. The results from all searches were imported into EndNote and duplicates were removed. The remaining references were imported in the Rayyan screening software.[10]

Eligibility Criteria

The PICO (patient, intervention, comparator, outcome) framework was used to define the eligibility criteria: the study must consist of patients with prostate cancer (P), the patients must have had ^{18}F-fluciclovine PET (I), the comparator must be systematic sector-based histopathology (C), and the outcome must be diagnostic performance given as sensitivity and specificity (O). Furthermore, the study must report sector-based data either as individual data or as summary diagnostic accuracy and contain at least 10 patients fulfilling all these criteria. In case of studies with mixed settings (primary/recurrence, prostate bed/lymph nodes), each subgroup must fulfill all criteria. Only original articles in English were eligible. Editorials, letters, review articles, comments, conference proceedings, and case reports were excluded, because study quality could not be assessed.

Screening and Study Selection

The screening and article selection was performed by 3 independent evaluators (A.J.T., E.H., T.S.) and conflicts were resolved by consensus. After an initial screening of titles and abstracts, the remaining articles were read in full text and excluded with reasons when appropriate.

Quality Assessment

Two evaluators (E.H., T.S.) in consensus used the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool[11] to assess the risk of bias in 4 domains: patient selection, index test, reference standard, and reference test timing. For the 3 first domains, applicability concerns were also assessed.

Data Extraction

For each selected study, the following information was collected:

- Basic study characteristics: investigators, year of publication, country, study design (prospective/retrospective), clinical setting

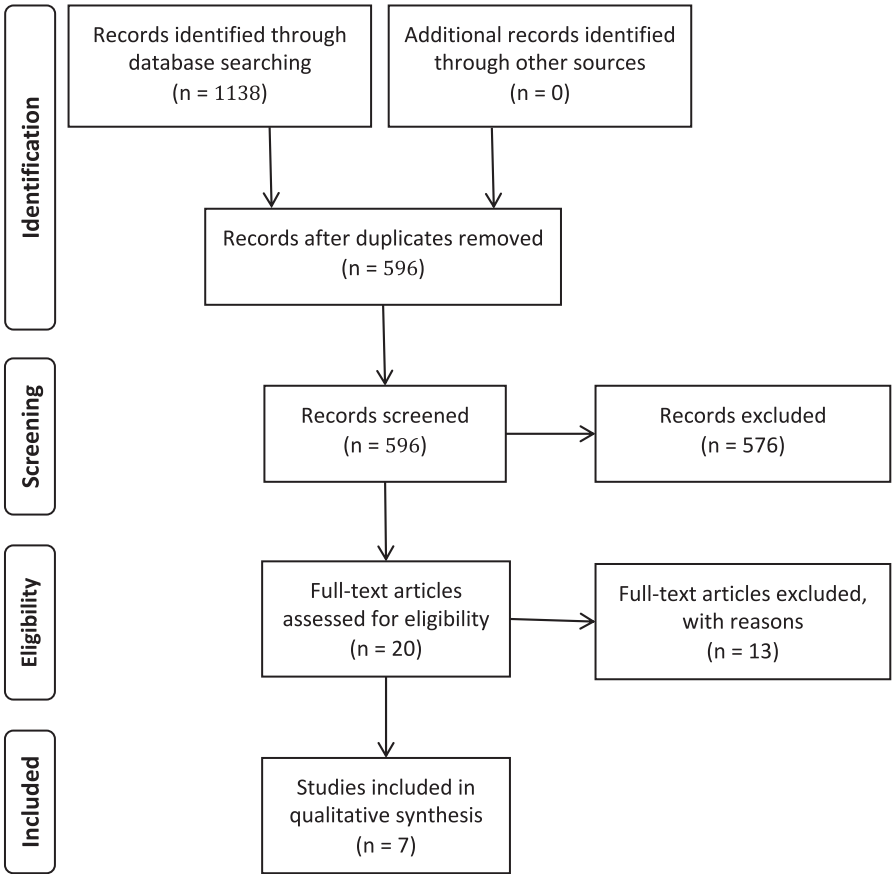

Fig. 2. PRISMA flow chart of studies for the systematic review of ^{18}F-fluciclovine PET for assessment of prostate cancer with systematic sector-based histopathology as reference standard.

(primary/recurrence), anatomy (prostate/lymph nodes), and imaging modality.
- Clinical and pathologic data: number of patients, age, prostate specific antigen (PSA), Gleason score, and tumor stage.
- Diagnostic accuracy data: number of true-positives, true-negatives, false-positives, and false-negatives (2 × 2 contingency tables). Investigators of studies that only reported summary diagnostic data were asked to provide additional data.

Data Synthesis and Analysis

Sensitivity and specificity with 95% confidence interval (CI) were calculated from the 2 × 2 contingency tables for each of the included studies using the MedCalc Diagnostic test evaluator calculator[12] or extracted from studies where 2 × 2 data were not available. Forest plots were drawn to show the variation and explore heterogeneity for sensitivity and specificity.

EVIDENCE SYNTHESIS

Search Results

The results for the identification and selection of studies are shown in **Fig. 2**. Initially, a total of 1138 records were retrieved by the systematic search. The number was reduced to 596 after removal of duplicates. Screening of titles and abstracts excluded 576 records. The remaining 20 records were read in full text and 13 were excluded. The reasons for exclusion were no systematic sector-based histopathology[13–22] or inappropriate study design and/or not within the scope of the review.[23–25]

Table 1
Study characteristics

Author	Journal	Country	Design	Setting	Anatomy	Modality
Alemozaffar, et al,[30] 2020	J Urol	United States	Prospective	Primary	Lymph nodes	PET/CT
Jambor, et al,[32] 2018	EJNMMI	Finland	Prospective	Primary	Prostate	PET/CT + PET/MR imaging
Schuster, et al,[26] 2013	AJNMMI	United States	Prospective	Primary	Prostate	PET/CT
Selnaes, et al,[31] 2018	Eur Radiol	Norway	Prospective	Primary	Lymph nodes	PET/MR imaging
Suzuki, et al,[27] 2016	Jpn J Clin Oncol	Japan	Prospective	Primary	Prostate + lymph nodes	PET/CT
Suzuki, et al,[28] 2019	Jpn J Clin Oncol	Japan	Prospective	Primary	Lymph nodes	PET/CT
Turkbey, et al,[29] 2014	Radiology	United States	Prospective	Primary	Prostate	PET/CT

Description of Included Studies

Study and patient characteristics for the 7 included studies are presented in **Tables 1** and **2**. The 7 eligible studies included a total of 212 patients. All studies were prospective. Five studies used PET/computed tomography (CT),[26–30] 1 study used PET/magnetic resonance (MR) imaging,[31] and 1 study used both PET/CT and PET/MR imaging.[32] The mean age of the study cohorts ranged from 60.8 to 68 years and the mean PSA level ranged from 8.2 to 21.4 ng/mL. The 2×2 contingency data for localizing intraprostatic tumors and lymph node metastases are presented in **Tables 3** and **4**.

Table 2
Patient and tumor characteristics

		Age (y)		PSA (ng/mL)			
Author	N	Mean	Range	Mean	Range	Gleason Score (%)	Tumor Stage
Alemozaffar, et al,[30] 2020	57	62	7[c]	15.0[a]	7.4–27.6[b]	7a (16), 7b (20), 8 (2), ≤9 (63)	NR
Jambor, et al,[32] 2018	26	65[a]	49–76	12.1[a]	4.1–35.0	7a (38), 7b (35), 8 (4), 9 (23)	pT2 (23), pT3a (38), pT3b (38)
Schuster, et al,[26] 2013	10	61	40–70	8.2	2.3–16.6	6 (27), 7a (22), 7b (11), 8 (25), 10 (15)	NR
Selnaes, et al,[31] 2018	28	66[a]	55–72	14.6[a]	3.7–56.9	7 (42), 8 (31), 9 (27)	pT2 (27), pT3a (27), pT3b (42), pT4 (4)
Suzuki, et al,[27] 2016	42	66	51–74	21.4	3.8–93.9	6 (7), 7 (41), 8 (23), 9 (25), 10 (5)	T1c (14), cT2 (50), cT3a (24), cT3b (14)
Suzuki, et al,[28] 2019	28	68	57–77	17.9	1.2–82.4	≤6 (3), 7 (41), 8 (28), 9 (28)	T1c (14), cT2 (50), cT3a (32), cT3b (5)
Turkbey, et al,[29] 2014	21	62	44–73	13.5	3.6–37.3	6 (14), 7 (57), 8 (24), 9 (5)	NR

Abbreviation: NR, not reported.
[a] Median.
[b] (Q1-Q3).
[c] Standard deviation.

Table 3
Two-by-two contingency data of ^{18}F-fluciclovine for localization of intraprostatic tumor lesions

Author	N	Modality	Sectors	TP	FP	FN	TN	Total
Jambor, et al,[32] 2018	26	PET/CT	12	143	64	22	83	312
		PET/MR imaging	12	138	5	26	143	312
Suzuki, et al,[27] 2016	43	PET/CT	6	173	7	14	64	258
Turkbey, et al,[29] 2014	21	PET/CT	20	NR	NR	NR	NR	420
Schuster, et al,[26] 2013	10	PET/CT, 4 min	12	71	32	8	7	118
		PET/CT, 16 min	12	68	25	13	14	120
		PET/CT, 28 min	12	65	20	15	20	120
		PET/CT, 40 min	12	63	25	17	15	120

Abbreviations: FN, false-negative; FP, false positive; TN, true negative; TP, true positive.

Quality Assessment/Risk of Bias

The quality assessment of the 7 studies regarding risk of bias as indicated by QUADAS-2 analysis is summarized in **Table 5**. The risk of bias regarding patient selection, index test, reference standard, and flow and timing was low except for 1 study that had unclear risk of bias for patient selection and flow and timing.[26] For this study, the risk of bias for patient selection as well as for flow and timing was scored as unclear because of unavailability of data on patient enrollment or time between imaging and surgery. Concerns regarding applicability for index test and reference standard were low in all studies. For 2 studies there was unclear concern of applicability of patient selection because image findings at CT were used for study inclusion.[27,28]

DIAGNOSTIC ACCURACY

Intraprostatic Tumor Localization: Primary Cancer

The accuracy of ^{18}F-fluciclovine PET to localize intraprostatic lesions was investigated by Schuster and colleagues,[26] Suzuki and colleagues,[27] Turkbey and colleagues,[29] and Jambor and colleagues.[32] Those study cohorts consisted of patients with histologically confirmed prostate cancer, and Schuster and colleagues,[26] Turkbey and colleagues,[29] and Jambor and colleagues[32] included lesions with longest diameter greater than 0.5 cm at histopathology. Jambor and colleagues[32] included PET/MR imaging in addition to PET/CT. Three of the studies included dynamic data acquisition,[26,29,32] but the set of images used for lesion detection was different: 1 to 15 minutes summed images in Turkbey and colleagues,[29] 5 frames times 4 minutes in Jambor and colleagues,[32] and acquired at 4, 16, 20, and 28 minutes after injection in Schuster and colleagues.[26] Suzuki and colleagues[27] used whole-body acquisition starting from the thigh immediately after acquisition of CT. Hematoxylin-eosin–stained tissue sections of the resected gland were used as reference standard, with Turkbey and colleagues[29] and Jambor and colleagues[32] using whole-mount histopathology. The prostate gland was divided into 6,[27] 12,[26,32] or 20 sectors.[29] MR-CT coregistration[26,29] or visual assessment[32] was used to allocate the lesions detected on PET to 1 or more of these sectors. Sector-based diagnostic sensitivity and specificity for these 4 studies are summarized in **Fig. 3**.

Table 4
Two-by-two contingency data of ^{18}F-fluciclovine PET for detection of primary lymph node metastases

Author	N	Modality	Sectors	TP	FP	FN	TN	Total
Alemozaffar, et al,[30] 2020	57	PET/CT	4	NR	NR	NR	NR	228
Selnaes, et al,[31] 2018	28	PET/MR imaging	8	6	0	14	185	205
Suzuki, et al,[28] 2019	28	PET/CT	6	4	5	3	28	40[a]
Suzuki, et al,[27] 2016	42	PET/CT	6	0	1	9	234	244

[a] Different from 28 × 6 because only sectors with lymph nodes between 5 and 9 mm at CT were included.

Table 5
Quality of the included studies using the Quality Assessment of Diagnostic Accuracy Studies-2 tool

	Risk of Bias				Applicability Concern		
Study	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Alemozaffar, et al,[30] 2020	Low	Low	Low	Low	Low	Low	Low
Jambor, et al,[32] 2018	Low	Low	Low	Low	Low	Low	Low
Schuster, et al,[26] 2013	Unclear	Low	Low	Unclear	Low	Low	Low
Selnaes, et al,[31] 2018	Low	Low	Low	Low	Low	Low	Low
Suzuki, et al,[27] 2016	Low	Low	Low	Low	Unclear	Low	Low
Suzuki, et al,[28] 2019	Low	Low	Low	Low	Unclear	Low	Low
Turkbey, et al,[29] 2014	Low	Low	Low	Low	Low	Low	Low

Risk of bias and applicability concern are for patient selection, index test, reference standard, and flow and timing.

Schuster and colleagues[26] found the highest combined sensitivity and specificity for 28 minutes. Although there was a significant correlation between ^{18}F-fluciclovine uptake of the malignant sectors and Gleason score, the correlation coefficients for all 4 time points were weak (r<0.5).[29] Both Turkbey and colleagues[29] and Schuster and colleagues[26] reported large overlap between ^{18}F-fluciclovine uptake for malignant and nonmalignant sectors.[26,29] In the FLUCIPRO study, Jambor and colleagues[32] found that PET/CT and PET/MR had similar sensitivity, but that PET/MR had significantly higher specificity (mean, 0.95; 95% CI, 0.91–0.98).[32]

Detection of Primary Lymph Node Metastases

The accuracy of ^{18}F-fluciclovine PET to detect and localize lymph node metastases was investigated by Alemozaffar and colleagues,[30] Selnaes and colleagues,[31] Suzuki and colleagues,[27] and Suzuki and colleagues.[28] All 4 studies recruited among patients referred to prostatectomy and extended lymph node dissection. There were many differences between the studies, including eligibility criteria, data acquisition, data analyses, and percentage of patients with nodal disease. Selnaes and colleagues[31] included high-risk patients, Alemozaffar and colleagues[30] included patients with unfavorable intermediate-risk to very-high-risk cancer without definitive findings of systemic

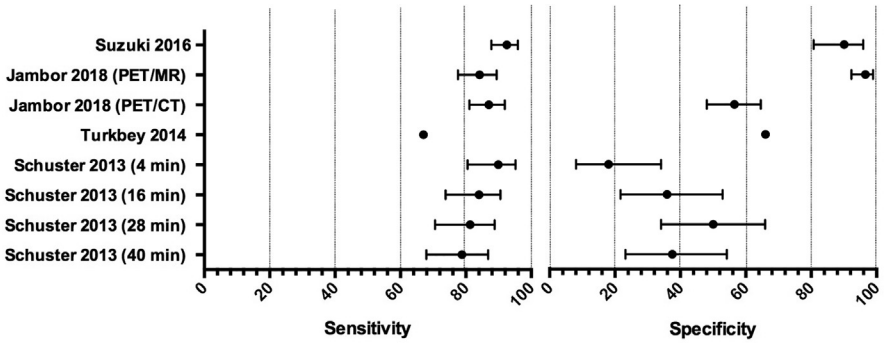

Fig. 3. Sensitivity and specificity of ^{18}F-fluciclovine for localizing primary intraprostatic tumor extent. The dots mark mean values and the whiskers are 95% CIs.

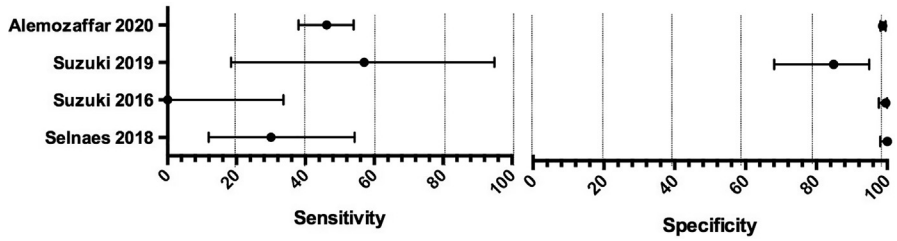

Fig. 4. Sensitivity and specificity of ^{18}F-fluciclovine for detection of primary lymph nodes. The dots mark mean values and the whiskers are 95% CIs.

metastases on conventional imaging, whereas the requirement of Suzuki and colleagues[27] was no findings indicating metastases at conventional imaging. Lymph nodes with longest diameters between 5 and 9 mm at CT were required in Suzuki and colleagues.[28] Acquisition time per bed ranged from 2 to 5 minutes. For the detection of lymph nodes Alemozaffar and colleagues[30] used acquisition at 5 minutes in addition to early (immediately after injection) and delayed pelvic imaging (22.5 minutes), Selnaes and colleagues[31] used 5 to 10 minutes summed images, Suzuki and colleagues[28] used images acquired at 10 minutes, and Suzuki and colleagues[27] used whole-body imaging completed by 30 minutes after injection. The number of lymph node sectors was 4[30] 6,[27,28] or 8[31]. Alemozaffar and colleagues,[30] Selnaes and colleagues,[31] and Suzuki and colleagues[28] included all sectors in their analyses and defined a sector as true-positive if 1 or more lymph nodes were positive in that sector on imaging and 1 or more nodes were positive on histopathology, whereas Suzuki and colleagues[27] only included sectors with lymph nodes within the predefined size range at CT in the analyses and defined the sector as positive if the node identified at CT was positive at histopathology. This approach yielded a total of 40 sectors in the study cohort of 28 patients. The percentage of patients with nodal disease was 16.7% (7 out of 42) in Suzuki and colleagues,[27] 54% (31 out of 57) in Alemozzafar and colleagues,[30] 38% (10 out of 26) in Selnaes and colleagues,[31] and 21% (6 out of 28) in Suzuki and colleagues.[28] The sector-based sensitivity and specificity for the 4 included studies are shown in **Fig. 4**.

DISCUSSION

The literature search identified 7 studies of patients with prostate cancer in which systematic sector-based histopathology had been used to confirm findings at ^{18}F-fluciclovine PET. For all studies, ^{18}F-fluciclovine PET was performed as part of the preoperative assessment of primary prostate cancer: 3 for intraprostatic lesion detection, 3 for lymph nodes detection, and 1 investigating both intraprostatic lesion and lymph node detection. There was a large variation in sensitivity and specificity among the included studies.

In this systematic review, only studies that had systematic sector-based histopathology as reference standard are included. This limitation is necessary in order to complete a 2 $\times$ 2 contingency table with true-positives, true-negatives, false-positives, and false-negatives that enable calculation of sensitivity and specificity. The use of other end points than systematic sector-based histopathology is problematic. The authors found 3 categories of such end points that are frequently used: first, comparison between 2 tracers or modalities without reference standard. Second, the term detection rate, where any positive findings are considered as true-positives. Third, altered treatment based on image findings, which by nature is self-affirming.

All 7 studies that fulfilled the inclusion criteria for this systematic review were performed in patients with known primary prostate cancer. The main finding from the 4 studies investigating intraprostatic tumor localization was high sensitivity and large variation in specificity. However, there are some factors that contribute to the high sensitivity that may limit the transferability to other cohorts. First, the readers knew that all patients had prostate cancer. Second, benign hyperplasia, commonly present in this age group, has similar ^{18}F-fluciclovine uptake to tumor (**Fig. 5**). Defining the cutoff for pathologic uptake is a trade-off between false-positives and false-negatives and thus is decisive for sensitivity and specificity. In a different setting such as screening for prostate cancer, the reader would probably use a higher cutoff for pathologic uptake in order to reduce false-positives and thereby reduce the sensitivity. Two of the studies[27,32] reported specificity greater than 80%. The study cohort of Suzuki and colleagues[27] consisted of overall large primary tumors and divided the prostate into only 6 sectors. This approach led to nearly 70% true-

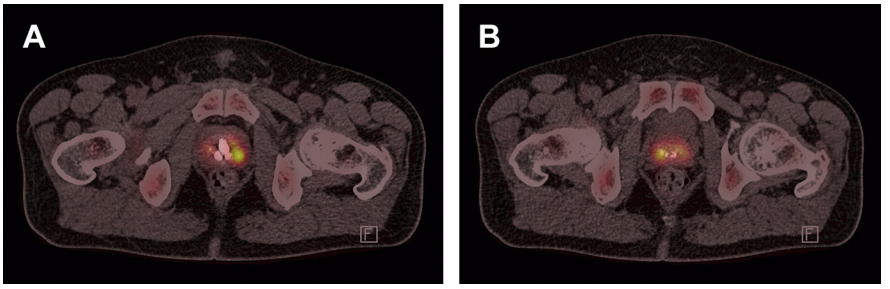

Fig. 5. Images in a 66-year-old-man with a serum PSA level of 12.0 ng/mL. High ^{18}F-fluciclovine uptake in a focus in the left peripheral zone (*A*) histopathologically confirmed to be Gleason 4 + 3. Similarly high ^{18}F-fluciclovine in the right side of the transitional zone (*B*) histologically confirmed to be benign hyperplasia.

positive sectors, which, in combination with few false-positive sectors, contributed to the high specificity. Jambor and colleagues[32] reported high specificity for PET/MR imaging only, not for PET/CT, indicating that the additional information from MR imaging probably was the reason for the high accuracy.

The main finding from the 4 studies investigating primary lymph node metastases was high specificity but very low sensitivity. This indicates that a certain amount of tumor is needed in order for the lymph node metastases to be detected at 18F-fluciclovine PET/CT. This is supported by Alemozaffar and colleagues,[30] who found that the detection rate was closely linked to the diameter of the metastatic foci: 83.3% for foci greater than 9 mm compared with 23.7% for foci of 3 mm or less. Selnaes and colleagues[31] also reported a relationship between size and detectability. In a large study of 4686 lymph nodes, Thoeny and colleagues[33] showed that most metastases were 3 mm or less. This finding may explain why Suzuki and colleagues[27] did not detect any of the 7 lymph node metastases in their cohort of 42 patients.

At present, the US Food and Drug Administration (FDA)–approved indication for ^{18}F-fluciclovine PET is men with biochemical recurrence after local treatment.[8] During the past decade, several studies have evaluated use of ^{18}F-fluciclovine PET in this setting and found it to offer a reliable cancer detection rate both for locally persistent disease (prostate/bed) and extraprostatic disease.[14,16–18,20,22] The diagnostic performance has been reported to be superior to that of CT,[19] multiparametric MR imaging,[14] choline PET,[18] and ^{111}In–capromab pendetide single-photon emission CT/CT.[20] The lack of systematic sector-based histopathology as reference standard made these studies ineligible for the current systematic review.

In the clinical setting of biochemical recurrence, it is difficult to obtain systematic histopathology: For local recurrence in the prostate/prostate bed, biopsies are seldom performed. Early PSA recurrence after prostatectomy is considered as recurrence within the prostatic bed and treated with salvage radiation therapy, often without image investigation or biopsies. Intraprostatic recurrence after primary radiation therapy often leads to systemic oncologic treatment without systematic prostate biopsies. Salvage prostatectomy, which would provide histopathologic reference, is seldom performed because of risk of serious side effects. However, for pelvic lymph nodes, it is feasible to obtain the required 2 × 2 contingency table using extended pelvic lymph node dissection as reference standard. The authors found no such studies in the recurrence setting, but 4 in the primary setting (see **Table 1**). Two major studies of ^{18}F-fluciclovine in the recurrence setting[18,20] reported divergent findings that exemplify this challenge, and how dependent the findings are on study cohort and reference standard. Whereas Schuster and colleagues[20] reported high sensitivity and specificity, Nanni and colleagues[18] reported negative imaging in more than half of the patients.

For distant metastases (M+) it is impossible to assess the rate of false-negatives. In this context, imaging is mainly used to evaluate treatment response of systemic disease and to identify oligometastatic patients suited for image-guided focal treatment. The clinical usefulness of imaging cannot be assessed by sensitivity and specify in these settings. Clinical follow-up and survival are needed.

A recent review in *Lancet Oncology* concluded that the PET radioligand Ga-68- prostate-specific membrane antigen (PSMA) increasingly has replaced both fluciclovine and choline for prostate cancer assessment because of its higher sensitivity and specificity over a range of PSA levels.[34] The authors performed an equivalent systematic literature search for PSMA[35] to their search for

fluciclovine. The search yielded 14 studies for primary prostate, 13 for primary lymph nodes, and 8 for lymph node recurrence. To our knowledge, there are only 2 studies that compare fluciclovine and PSMA in the same patients, both in recurrence settings.[36,37] Pernthaler and colleagues[36] found in a study of 58 patients that ^{18}F-fluciclovine had a superior detection rate for local recurrence, whereas the results for nodal disease and bone metastases were similar to 68Ga-PSMA-11. In another study of 50 patients, Calais and colleagues[37] found a similar detection rate for local recurrence, but more than twice as high for lymph nodes and for extrapelvic metastasis for ^{68}Ga-PSMA-11. None of these studies met the inclusion criteria of our reviews because of the lack of systematic sector-based histopathology. The authors therefore conclude that there is little evidence for superiority of any of the 2 tracers; however, the body of evidence for PSMA is substantially larger than for ^{18}F-fluciclovine.

In conclusion, our literature search, investigating the PET tracer ^{18}F-fluciclovine in patients with prostate cancer, identified only a few studies that had systematic sector-based histopathology allowing calculation of sensitivity and specificity. In primary prostate, the sensitivity was high, but the specificity was limited. In primary lymph nodes, the sensitivity was low.

DISCLOSURE

The authors declare that they have no conflicts of interest that relates to the subject matter of the present review.

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