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Initial Institutional Experience with 18F-Fluciclovine PET-CT in Biochemical Recurrence of Prostate Cancer

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Objectives: 18F-fluciclovine (fluciclovine) is an amino acid analog approved by the Food and Drug Administration for use as a radiotracer in positron emission tomography (PET) in men with biochemical recurrence of suspected prostate cancer. The purpose of this study was to investigate the initial institutional experience with 18F-fluciclovine in the evaluation of prostate cancer with biochemical recurrence.

Methods: This study was a retrospective review of 135 patients who underwent 18F-fluciclovine PET-computed tomography (PET-CT) at a single institution from August 2018 through January 2020. Prognostic information, including prostate-specific level antigen (PSA) at the time of diagnosis, initial risk, initial Gleason score, and initial stage, was reviewed as well as the PSA level at the time of the scan. The images were reviewed by two radiologists with fellowship training in nuclear medicine and additional training to interpret the fluciclovine studies. A minority of studies were reviewed by a third fellowship-trained radiologist under the guidance of the two nuclear medicine–trained radiologists. In cases with abnormal radiopharmaceutical uptake in lymph nodes, the short-axis dimension of the lymph node or largest lymph node with abnormal uptake was noted. If CT or bone scan was performed within 4 months of the 18F-fluciclovine PET-CT, findings on the alternate imaging were compared with the results of the 18F-fluciclovine PET-CT.

Results: Our institutional positivity rate was 75.6%, with 64 (67.4%) patients with metastatic disease and 71 (52.6%) patients with local recurrence detected by fluciclovine. As expected, the rate of positive examinations increased with increasing PSA values measured at the time of imaging ($P < 0.001$). Of the 54 patients with nodal disease, 35 had nonpathologically enlarged lymph nodes measuring <1 cm in maximum short-axis dimension. In more than half of the patients in this study, with conventional imaging, fluciclovine either discovered otherwise undetectable metastatic disease or suggested the presence of local recurrence.

Conclusions: Our single-institution experience with 18F-fluciclovine PET-CT has the largest number of patients to date in the literature and demonstrates the ability of fluciclovine to help guide clinical management in the detection of early recurrent disease.

Key Words: biochemical recurrence, 18F fluciclovine PET-CT, prostate cancer

After a definitive treatment of prostate cancer (PCa), biochemical recurrence (BCR) may occur in up to approximately 20% to 30% of men as a harbinger of subsequent metastatic disease.[1,2] If the site or sites of oligometastatic disease can be identified early at a time with lower tumor cell burden, then treatment can be initiated at an earlier time.[3–5] In an effort to identify oligometastatic disease with higher sensitivity at an earlier time, molecular imaging is increasingly being applied in the management of PCa.

Key Points

- Our single-institution experience with 18F-fluciclovine positron emission tomography-computed tomography has demonstrated its ability to help guide clinical management in the detection of early recurrent disease in prostate cancer.
- Our detection rates are comparable to the experiences of other institutions reported in the literature.
- The ability of fluciclovine to detect nonpathologically enlarged metastatic lymph nodes allows radiation fields to target oligometastatic sites of disease.
- 18F-fluciclovine positron emission tomography-computed tomography is widely used in biochemical recurrence and as a caution should be interpreted by radiologists with specific training in fluciclovine interpretation to avoid high false positive rates of physiological uptake.

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S.T.L. has received compensation from the National Institutes of Health. The remaining authors did not report any financial relationships or conflicts of interest.

Accepted March 22, 2021.

0038-4348/0–2000/114-703

DOI: 10.14423/SMJ.0000000000001314

There are several molecular agents used in the evaluation of PCa. 68Ga-prostate-specific membrane antigen has been used increasingly, but it is not approved by the Food and Drug Administration (FDA). 11C-Choline is used as a radiotracer for positron emission tomography-computed tomography (PET-CT) and is based on the upregulated enzymes of choline metabolism seen in PCa.[6] It was approved by the FDA in 2012 for imaging patients with recurrent PCa.[7] Although 11C-choline has been shown to be preferentially taken up in PCa with improved performance over conventional imaging, its performance in the detection of PCa relapse has been shown to be inferior to 18F-fluciclovine (fluciclovine) for detecting recurrences per patients as well as per lesion.[8]

Fluciclovine is an amino acid analog approved by the FDA for use as a radiotracer in PET in men with suspected PCa recurrence following prior treatment. Fluciclovine can help guide management in patients with BCR and has been shown to significantly change radiotherapy management decisions.[9] A multicenter prospective trial demonstrated that fluciclovine changed management in 59% of patients.[10]

The purpose of this study was to investigate the initial institutional experience with fluciclovine in the evaluation of PCa BCR. The goals of the study are as follows:

- Review our initial experience after approximately 17 months of using the new agent.
- Compare our results with other institutions as a quality assurance process.
- Evaluate our results to plan the future course of our precision medicine (PM) initiatives in PCa management.

Methods

This institutional review board–approved, Health Insurance Portability and Accountability Act of 1996–compliant study was a retrospective review of 135 patients who underwent fluciclovine PET-CT at a single institution from August 2018 through January 2020. In total, 32 patients primarily received care at the institution and 103 patients were referred for fluciclovine imaging from providers outside the institution.

Prognostic information, including prostate-specific level antigen (PSA) at the time of diagnosis, initial risk, initial Gleason score, and initial stage, was reviewed. The results of the fluciclovine PET-CT were evaluated. Examinations were considered positive if there was nonphysiologic uptake of fluciclovine, either in the prostate or prostate bed, lymph nodes, or other distant sites. Local recurrence was defined as uptake in the prostate or prostatectomy bed. Metastatic disease was defined as either nodal or extranodal nonphysiologic uptake.

The χ^2 test was used to evaluate prognostic information and imaging outcomes, with $P \leq 0.05$ considered statistically significant. The Pearson χ^2 test was used to evaluate the PSA level at the time of the scan and positive imaging findings on the examination. Data were analyzed using SPSS 24.0 software (IBM SPSS Statistics, Armonk, NY).

In cases with abnormal radiopharmaceutical uptake in lymph nodes, the short-axis dimension of the lymph node (or largest lymph node, in cases of multiple lymph nodes) with abnormal uptake was noted. If CT or bone scan was performed within 4 months of the fluciclovine PET-CT, findings on the alternate imaging were compared with the results of the fluciclovine PET-CT.

Imaging Protocol

Patients fasted for 4 hours before imaging. Imaging was acquired from 3 to 5 minutes following intravenous radiopharmaceutical administration and was performed from the mid-thighs to the skull vertex. The first bed stop was acquired at the proximal thighs/pelvis, with each sequential stop in a more superior location until the skull vertex was imaged. Diagnostic CT was performed for attenuation correction and localization. All of the imaging was acquired on a General Electric Discovery 690 scanner (GE Healthcare, West Milwaukee, WI).

Results

A total of 135 patients underwent fluciclovine imaging at our institution in a 15-month period (Table 1). The average time from

Table 1. Patient demographics

Patient age, y	**69 (SD 6.8)**
Stage	
	I: 8
	II: 29
	III: 45
	IV: 7
	Unknown: 46
Initial Gleason score	
	6: 15
	7: 51
	8: 15
	9: 20
	10: 5
	Unknown: 29
Initial risk	
	Very low risk: 5
	Low risk: 4
	Intermediate risk: 24
	High risk: 64
	Unknown risk: 35
Initial treatment	
	Prostatectomy: 84
	Brachytherapy: 18
	External beam radiation therapy: 8
	Androgen-deprivation therapy: 7
	Combination therapy: 11
	Unknown therapy: 7
Mean PSA at diagnosis	16.5 ng/mL (SD 19.6)
Mean PSA at scan	6.3 ng/mL (SD 12.9)
Mean time from diagnosis to scan	7.2 y (5.1 y)

PSA, prostate-specific antigen; SD, standard deviation.

Table 2. Fluciclovine PET/CT interpretation

Fluciclovine PET-CT interpretation	N = 135
Nodal metastatic disease only	47
Nodal metastatic disease with extranodal metastatic disease	7
Extranodal metastatic disease only	10
Local recurrence prostate/prostate bed	38
No abnormal radiopharmaceutical uptake	29
Indeterminate for metastatic disease	4

PET-CT, positron emission tomography-computed tomography.

PCa diagnosis to fluciclovine imaging was 7.2 years. Of the 135 patients, 29 had no fluciclovine evidence of recurrence, 38 had local disease recurrence only, 4 had studies indeterminate for recurrence, and 64 patients had metastatic disease.

Of the patients with metastatic disease, 47 patients had metastatic nodal disease, 7 patients had metastatic nodal disease and extranodal metastatic disease, and 10 patients extranodal metastatic disease only (Table 2). Of the 54 patients with nodal disease, 35 had nonpathologically enlarged lymph nodes measuring <1 cm in maximum short-axis dimension. Patients with evidence of local recurrence or metastatic disease on fluciclovine were

Table 3. Prognostic information and local recurrence

	Yes (%) n = 38; 28.1%	No (%) n = 97; 71.9%	*P*
Initial staging			0.019
Stage I	3 (7.9)	5 (5.2)	
Stage II	10 (26.3)	19 (19.6)	
Stage III	6 (15.8)	38 (39.2)	
Stage IV	0 (0.0)	7 (7.2)	
Unknown stage	19 (50.0)	28 (28.9)	
Initial Gleason score			0.074
6	6 (15.8)	9 (9.3)	
7	14 (36.8)	37 (38.1)	
8	2 (5.3)	14 (14.4)	
9	2 (5.3)	17 (17.5)	
10	1 (2.6)	4 (4.1)	
Unknown Gleason score	13 (34.2)	16 (16.5)	
Initial risk (D'Amico classification)			0.044
Very low risk	2 (5.3)	3 (3.1)	
Low risk	2 (5.3)	3 (3.1)	
Intermediate risk	8 (21.1)	15 (15.5)	
High risk	10 (26.3)	54 (55.7)	
Unknown risk level	16 (42.1)	22 (22.7)	
PSA at diagnosis			0.006
PSA <1	5 (13.2)	32 (33.0)	
PSA 1–2	2 (5.3)	18 (18.6)	
PSA >2	26 (68.4)	39 (40.2)	
Unknown PSA	5 (13.2)	8 (8.2)	

PSA, prostate-specific antigen.

Table 4. Prognostic information and metastatic disease

	Yes n = 64; 47.4%	No n = 71; 52.6%	*P*
Initial staging			0.005
Stage I	2 (3.1)	6 (8.5)	
Stage II	13 (20.3)	16 (22.5)	
Stage III	28 (43.8)	16 (22.5)	
Stage IV	6 (9.4)	1 (1.4)	
Unknown stage	15 (23.4)	32 (45.1)	
Initial Gleason score			0.073
6	5 (7.8)	10 (14.1)	
7	21 (32.8)	30 (42.3)	
8	10 (15.6)	6 (8.5)	
9	14 (21.9)	5 (7.0)	
10	3 (4.7)	2 (2.8)	
Unknown Gleason score	11 (17.2)	18 (25.4)	
Initial risk (D'Amico classification)			0.002
Very low risk	2 (3.1)	3 (4.2)	
Low risk	1 (1.6)	4 (5.6)	
Intermediate risk	7 (10.9)	16 (22.5)	
High risk	42 (65.6)	22 (31.0)	
Unknown risk level	12 (18.8)	26 (36.6)	
PSA at diagnosis			0.077
PSA <1	13 (20.3)	24 (33.8)	
PSA 1–2	14 (21.9)	6 (8.5)	
PSA >2	32 (50.0)	33 (46.5)	
Unknown PSA	5 (7.8)	8 (11.3)	

PSA, prostate-specific antigen.

those who initially had higher risk and higher stage disease (Tables 3 and 4). More patients initially presented with Gleason score 8 or 9 disease in the metastatic group and 6 or 7 in the nonmetastatic group, although this finding was not statistically significant ($P = 0.073$).

As expected, the rate of positive examinations increased with increasing PSA values measured at the time of imaging (Table 5). Of the 29 patients with no abnormal radiopharmaceutical uptake, 19 had PSA values of <1 at the time of the examination

Table 5. Rate of positivity by PSA at time of scan

PSA at scan, ng/mL	No. examinations	No. positive examinations	Positivity rate, %	*P*
<1	37	19	51.4	<0.001
1–2	20	16	80.0	
>2	65	61	93.8	
Unknown	13	10	76.9	

PSA, prostate-specific antigen.

and 2 had PSA values that were not provided. A total of 31 patients had conventional imaging in the 4 months before the fluciclovine PET-CT. Of these patients, 29 had CT scans and 28 had bone scans. There were 7 patients found to have metastatic nodal disease not suspected on conventional CT. Nine patients had local recurrence not suspected on conventional CT. Two patients who were suspected to have metastatic disease based on CT or bone scan had an alternative diagnosis suggested by fluciclovine PET-CT.

Discussion

Our institutional positivity of fluciclovine studies was 75.6% (Table 5). Our findings were similar to a previous single-center study that found positivity rates of 77.4%, with a positivity range of 34% to 85% seen in additional studies. We saw a higher rate of positive lymph nodes of 40%, with a range in the literature from 20% to 25% and a rate of uptake of 28% in the prostate/prostate bed, with a range in the literature reported from 10% to 75%.[8,11,12] In more than half of the patients in this study with conventional imaging, fluciclovine either confirmed otherwise undetectable metastatic disease or suggested the presence of local recurrence. The ability of fluciclovine to detect nonpathologically enlarged metastatic lymph nodes, which represented 65% of examinations with metastatic lymph nodes, emphasizes its clinical utility. This detection of metastatic lymph nodes allows radiation clinical target volumes to be enlarged, enabling correct treatment to the correct target. The adjustment of radiation fields can be made with confidence, given that the reported specificity of lymph node uptake of fluciclovine is 96.7%.[13]

PM concepts are being increasingly applied in PCa, as PM can improve outcomes in PCa.[14–16] Molecular imaging could become an important component in applying PM because conventional imaging is inadequate in defining oligometastatic disease.[17] This study demonstrates the feasibility of fluciclovine in establishing extraprostatic disease, an important step in the application of PM. It additionally highlights the potential to detect disease that would not be apparent on conventional imaging, including nonpathologically enlarged metastatic lymph nodes.

Although fluciclovine is specific in the detection of extraprostatic disease, it demonstrates high sensitivity and relatively low specificity for prostate bed uptake—90.2% and 40%, respectively.[11] Of the 38 patients with local recurrence suspected on fluciclovine, 13 patients had also undergone brachytherapy, which is thought to be a confounding factor given the associated inflammation from brachytherapy.[17,18]

This study demonstrated the potential utility of fluciclovine; however, there were cases in which the imaging did not provide additional clinical data. There were 8 patients with a PSA of ≥1 with imaging reports that did not establish the site of a known BCR. One was retrospectively determined to have metastatic lymph node disease. Of the 7 remaining patients, 3 had PSAs between 1 and 1.1 ng/mL.

Even though there is no PSA threshold for fluciclovine, positive uptake is more likely in patients with a PSA >1.[11] In our study, 37 patients had PSA values of <1 when undergoing fluciclovine imaging. Of these patients, 18 had abnormal uptake and 19 had no abnormal radiopharmaceutical uptake, with a rate of positivity of 48.6%. Our rate of positivity compared favorably with a prior study that found a rate of positivity of 37.5% in patients with a PSA <1.[11] The interpretation of negative results when the patient's PSA value is <1 remains a challenge, and understanding the diagnostic limitations of fluciclovine in this setting is essential both for radiologists and clinicians.

There are several limitations of this study. Staging data were unavailable for some patients because some patients were referred for imaging from providers outside the institution. The low sample size of patients with alternate imaging also limits the interpretation of these findings. Long-term follow-up data were not available at the time of this study, given that it represents the early institutional experience. Most significantly, patients did not undergo biopsy to confirm diagnoses, because this was not feasible in a retrospective review. Using biopsy as a reference standard is an aim for future studies.

Summary and Conclusions

Our single-institution experience with fluciclovine PET-CT has demonstrated its ability to help guide clinical management in the detection of early recurrent disease in PCa. Our detection rates are comparable to the experiences of other institutions reported in the literature. The ability of fluciclovine to detect nonpathologically enlarged metastatic lymph nodes allows radiation fields to target oligometastatic sites of disease. Fluciclovine PET-CT is widely used in BCR, and as a caution should be interpreted by radiologists with specific training in fluciclovine interpretation to avoid high false positive rates of physiological uptake.

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