

[¹⁸F]Fluciclovine-PET Guided Salvage Lymph Node Dissection Following Radical Prostatectomy



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INTRODUCTION

Despite advances in standard-of-care treatment for prostate cancer, including pelvic radiotherapy and radical prostatectomy with lymph node dissection, biochemical recurrence remains a problem with some studies reporting up to 30% of patients with biochemical recurrence at 10-years following treatment. Upon detection of a rise in serum prostate-specific antigen following treatment, clinicians are left with the dilemma of how best to treat these patients. Frequently, these patients are restaged with CT of the abdomen and pelvis or MRI of the pelvis in addition to a nuclear medicine bone scan. However, detection of recurrent disease both within the prostate gland/prostatectomy bed and in the region of pelvic lymph nodes remains challenging and is limited by size criteria per RECIST 1.1. [¹⁸F]Fluciclovine PET imaging has improved detection of these previously occult metastases and helped guide treatment planning. In some select patients, a targeted lymphadenectomy may be the treatment of choice if the PET-avid disease is limited to a solitary lymph node site of spread. However, this concept has not been well described in the literature and here we provide 3 cases and short-term outcomes of patients that underwent [¹⁸F]fluciclovine PET guided surgical excision of their biochemically recurrent prostate cancer.

CASE PRESENTATIONS

Patient 1

A 62-year-old male with biopsy Gleason 3 + 4 = 7, Grade Group 2, prostate cancer underwent a robotic-assisted radical

prostatectomy with pelvic lymph node dissection in 2009. Postoperative pathology demonstrated pathologic T2, Gleason 3 + 4 = 7, Grade Group 2, surgical margin negative, and lymph node negative prostate cancer. Postoperative serum prostate specific antigen (PSA) was undetectable at a level of <0.01 ng/mL. Beginning in 2013, routine surveillance revealed a slowly rising serum PSA which escalated to 1.23 ng/mL by April 2017 with doubling time of approximately 6 months. Conventional staging imaging obtained at this time failed to demonstrate site of recurrent disease. The patient then underwent [¹⁸F]fluciclovine PET/CT, which revealed a PET-avid lymph node in the perirectal space (Fig. 1). The patient subsequently underwent targeted surgical excision in June 2017. Postoperative pathology confirmed metastatic nodal focus of prostate cancer spread and serum PSA once again returned to undetectable levels at first assessment postoperatively and has remained undetectable for 18 months thereafter.

Patient 2

A 61-year-old male with biopsy Gleason 4 + 3 = 7, Grade Group 3, prostate cancer underwent a robotic-assisted radical prostatectomy with lymph node dissection in 2009. Postoperative pathology demonstrated pathologic T3, Gleason 4 + 3 = 7, Grade Group 3, surgical margin negative, and lymph node negative prostate cancer. Initially following surgery, serum PSA became undetectable to <0.01 ng/mL, however it began to rise again in 2011. The patient then underwent salvage radiation therapy to the pelvis for biochemical recurrence with a return to undetectable PSA levels. In 2015, PSA surveillance revealed a second biochemical recurrence, with levels reaching 3.2 ng/mL in December 2017. At this time, the patient underwent [¹⁸F]fluciclovine PET/CT, which demonstrated a solitary suspicious right external iliac chain lymph node (Fig. 2). The patient was subsequently underwent a salvage pelvic lymph node dissection, from which the resultant pathology confirmed metastatic prostate cancer spread to one right external iliac lymph node. Serum PSA returned to undetectable levels postoperatively.

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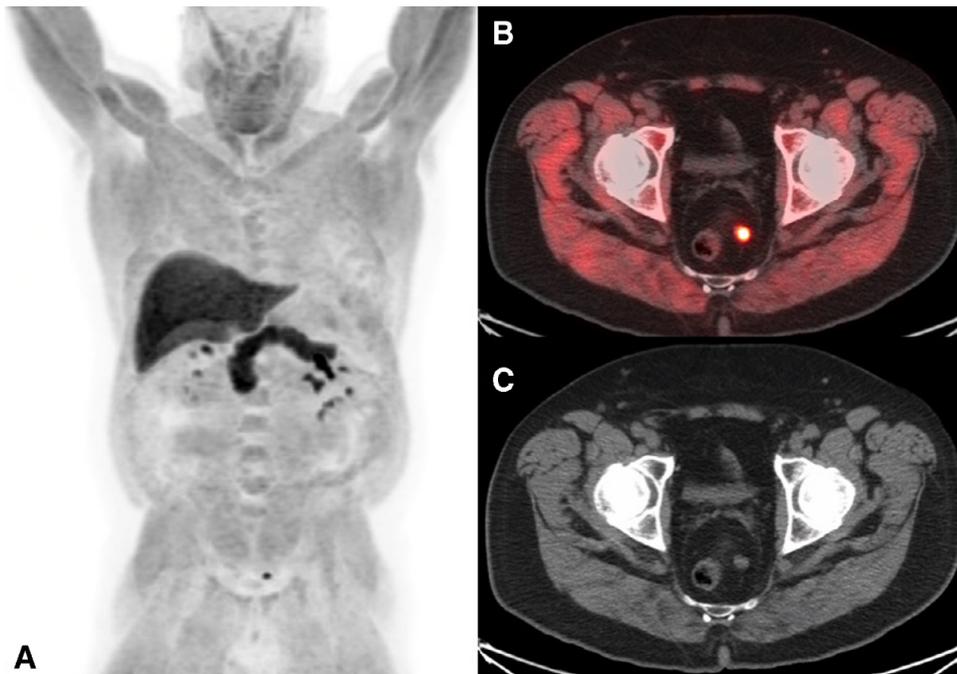


Figure 1. Maximum intensity projection (A), fused [^{18}F]fluciclovine PET/CT (B), and CT (C) image of patient 1 which demonstrates a fluciclovine-avid lymph node in the perirectal space. (Color version available online.)

Patient 3

A 64-year-old male with biopsy Gleason 4 + 3 = 7, Grade Group 3, prostate cancer underwent a robotic-assisted

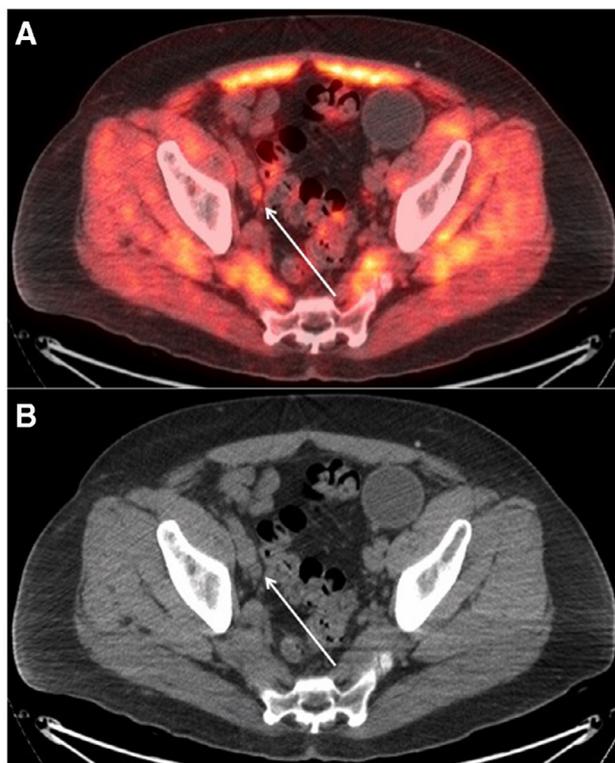


Figure 2. Fused [^{18}F]fluciclovine PET/CT (A) and CT (B) image of patient 2 which demonstrates a fluciclovine-avid lymph node in the right external iliac chain (arrow). (Color version available online.)

radical prostatectomy with lymph node dissection in 2007. Postoperative pathology demonstrated pathologic T2, Gleason 4 + 3 = 7, Grade Group 3, surgical margin negative, and lymph node negative prostate cancer. Postoperative serum PSA was undetectable at <0.01 ng/mL. In 2011, the patient developed a biochemical recurrence with a rise in PSA to a level of 0.4 ng/mL. Patient then underwent salvage radiation therapy to the pelvis, achieving a secondary nadir serum PSA of 0.2 ng/mL. In 2013, a subsequent rise in serum PSA to 0.9 ng/mL was observed and conventional staging imaging at this time was negative for recurrence. The patient was intermittently placed on androgen deprivation therapy, but was unable to tolerate this treatment approach due to side effects. A subsequent CT obtained demonstrated a prominent 11 mm perirectal lymph node. The patient then underwent follow-up [^{18}F]fluciclovine-PET/CT in 2017 (Fig. 3A and B), which showed marked tracer activity in the suspicious lymph node seen on CT. Subsequently, the patient underwent an image-targeted lymphadenectomy. Postoperative pathology confirmed malignancy within the lymph node specimen, which stained positive for immunohistochemical markers suggestive of possible metastatic melanoma. Postoperatively, the patient's serum PSA continued to rise. Therefore, a follow-up [^{18}F] fluorodeoxyglucose PET/CT was performed and showed minimal activity in the lymph node (Fig. 3C and D) and follow-up [^{18}F]fluciclovine-PET/CT was obtained, which redemonstrated intense activity in a perirectal nodule (Fig. 3E and F). These findings are most consistent with inadequately resected lymph node harboring metastatic prostate cancer. The patient was then referred for consideration of additional salvage radiation therapy.

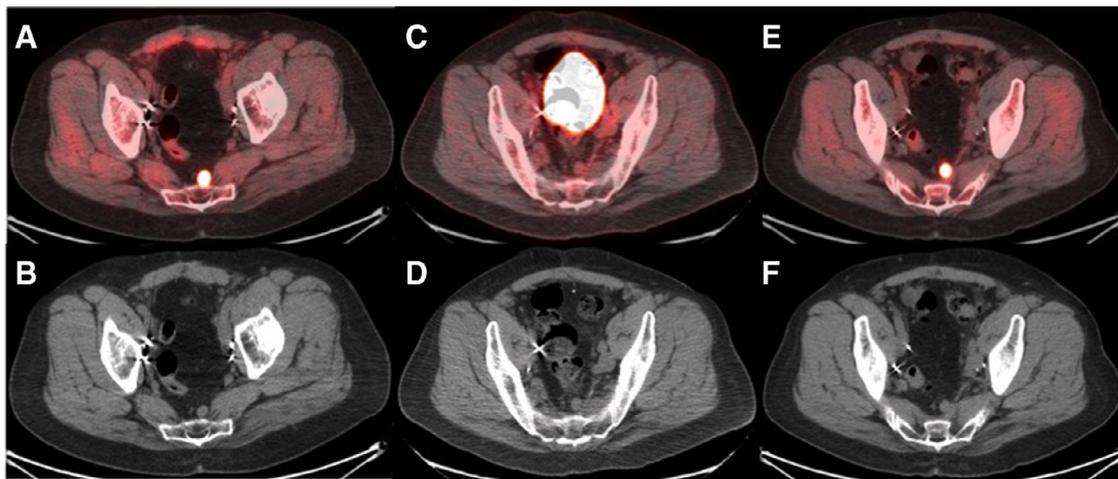


Figure 3. Initial fused [^{18}F]fluciclovine PET/CT (A) and CT (B) images which demonstrate a fluciclovine-avid lymph node in the presacral space. Follow-up fused [^{18}F]FDG PET/CT (C) and CT (D) images demonstrate minimal tracer activity in the presacral lymph node. Follow-up fused [^{18}F]fluciclovine PET/CT (E) and CT (F) images demonstrate persistent activity in the presacral lymph node following attempted surgical resection. (Color version available online.)

DISCUSSION BY SOROUSH RAIS-BAHRAMI, MD

[^{18}F]Fluciclovine was approved in May 2016 by the United States Food and Drug Administration for patients with biochemically recurrent cases of prostate cancer based upon rising PSA. Conventional imaging modalities used for staging indication in the setting of prostate cancer biochemical recurrence including CT, MRI, and [$^{99\text{m}}\text{Tc}$] nuclear medicine bone scan have been limited in sensitivity and specificity, as detection of cancer persistence or recurrence in the prostate bed and/or pelvic lymph nodes relies on size and morphologic criteria of anatomic findings in the postoperative field. PET imaging offers the advantage of earlier detection and localization of recurrent malignancy, particularly in subcentimeter lymph nodes. Thus, fluciclovine-PET/CT and PET/MRI have become increasingly utilized for the restaging of men with biochemically recurrent prostate cancer.¹

Several PET radiotracers have been studied for evaluation of prostate cancer. The earliest tracer, [^{18}F]fluorodeoxyglucose (FDG), is a mainstay in oncologic imaging, but use is limited in prostate cancer with only poorly differentiated and/or aggressive tumors consistently demonstrating substantial FDG uptake.² Subsequently, [^{11}C]choline and [^{18}F]choline were developed and evaluated for use in patients with prostate cancer. Choline analogs function as a substrate for cell membrane metabolism, a process that is upregulated in prostate cancer cells. Although results were improved from studies with [^{18}F]FDG, sensitivity and specificity remained limited.³⁻⁵ Additionally, very few clinical centers offer choline-PET imaging, which significantly limits availability to patients and providers.

[^{18}F]Fluciclovine is an amino acid analog that targets the ASCT2 and LAT1 transporters, both of which are upregulated in prostate cancer cells. These transporters are involved with glutamine uptake at the cell membrane

and fluciclovine acts as a substrate for the transporters. Importantly, [^{18}F]fluciclovine is not metabolized intracellularly or incorporated into proteins.⁶ Several studies thus far have evaluated the diagnostic performance of fluciclovine-PET/CT in the setting of biochemical recurrence. A prospective study by Nanni et al demonstrated superior diagnostic performance of [^{18}F]fluciclovine-PET/CT for patients with biochemically recurrent prostate cancer when compared to [^{11}C]choline-PET/CT.⁷ Fluciclovine has also been evaluated in comparison to a historical prostate cancer SPECT imaging agent, [^{111}In]capromab (Prostascint) and was shown to be superior in the detection of both intraprostatic and extraprostatic biochemical recurrence.^{8,9} Many of the studies in patients with biochemically recurrent prostate cancer have focused on the impact [^{18}F]fluciclovine-PET/CT had on patients for salvage radiotherapy planning. A study by Akin-Akintayo et al demonstrated that [^{18}F]fluciclovine-PET changed management decisions in 40.5% of patients with biochemically recurrent prostate cancer.¹⁰ However, only 2 case reports exist in the literature that describe [^{18}F]fluciclovine-PET/CT guided lymph node dissection in patients with clinically biochemically recurrent prostate cancer.^{11,12}

There is an evolving paradigm shift in the treatment of patients with oligometastatic prostate cancer. Based on the results from the STAMPEDE trial, patients with oligometastatic prostate cancer (limited node positive, visceral metastasis negative) demonstrated greater than expected failure-free survival when treated with radiotherapy combined with ADT vs ADT alone.¹³ However, the extent of both nodal and distant metastatic disease is underestimated on conventional imaging with CT, MRI, and nuclear medicine bone scan. In patients with both newly diagnosed prostate cancer and biochemically recurrent disease, [^{18}F]fluciclovine demonstrated lymph node metastases not detected on conventional, standard-of-care

staging imaging.^{14,15} This information is important to the treating radiation oncologist, as underestimation of the metastatic disease burden could potentially result in undertreatment. Additionally, there is emerging data on performing radical prostatectomy and pelvic lymph node dissection in patients with suspicion of limited lymph node involvement preoperatively, with several studies reporting positive lymph nodes outside the standard dissection template and up to 13% of metastatic lymph nodes found outside the template of an extended pelvic lymph node dissection.¹⁶⁻²⁰ Advanced preoperative imaging with molecular or functional imaging, including [¹⁸F]fluciclovine, shows great potential for improving pretreatment staging of these patients to improve a durable oncologic response.²¹ There are currently ongoing studies of [¹⁸F]fluciclovine PET imaging in the primary staging setting (NCT03264456 and NCT03081884), particularly for those with high-risk prostate cancer, to better define potential extraprostatic spread or oligometastatic lymph node involvement not appreciated on conventional staging scans. Although these studies are examining the potential role of these imaging studies in changing clinical decision-making and potentially directing targeted lymph node sampling or dissection templates, oncologic outcomes proving the value of this added imaging modality for primary staging is not yet mature.

A large study prior to salvage lymph node dissection demonstrated a risk of early recurrence following salvage lymph node dissection of 25% with preoperative PET imaging serving an important role of risk stratification prior to salvage lymphadenectomy in predicting early recurrence.²² Future studies with longer-term clinical follow-up are needed to determine the potential oncologic benefit of PET imaging in patients with prostate cancer beyond the routine serum PSA follow-up. We recognize this as prostate cancer, even in cases of limited regional spread one or very few pelvic lymph nodes, may have an indolent clinical course. As such, there may be a clinically impactful role in targeted salvage lymph node removal or radiotherapy as the more prostate cancer specific PET imaging develops and is widely employed in the staging of patients with biochemically recurrent prostate cancer.

Finally, the development of several PET radiotracers for prostate cancer may enable surgeons to perform intraoperative molecular imaging to assist in targeting areas of recurrent or metastatic cancer foci. The concept of fluorescent molecular probes for intraoperative identification of malignancy has been studied in several malignancies in the preclinical setting, including colorectal and head and neck cancers.^{23,24} A [⁶⁸Ga]prostate specific membrane antigen (PSMA)-11-derived dual-labeled radiopharmaceutical was developed that had properties of a PET-imaging agent combined with a fluorescent dye conjugate was studied and demonstrated feasibility and high potential for use in the preoperative, intraoperative, and postoperative detection of prostate cancer.²⁵ Additionally, PSMA-directed PET radiotracers have been studied in a potential theranostic setting, where the diagnostic PET would be performed with a [⁶⁸Ga]-tagged PET radiotracer and the

therapeutic targeted radiation therapy would be provided by substituting the [⁶⁸Ga] with a beta emitter, lutetium-177.²⁶ This theranostic approach is currently FDA-approved for clinical use in patients with gastroenteropancreatic neuroendocrine tumors utilizing [⁶⁸Ga]DOTA-TATE and [¹⁷⁷Lu]DOTA-TATE. Thus, it is conceivable that the theranostic approach may have a significant role in the management of patients with metastatic prostate cancer as PSMA radiopharmaceuticals seek FDA-approval.

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