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Review article

Axumin: A promising diagnostic imaging agent for prostate cancer recurrence

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Key words: Axumin, Prostate cancer recurrence, Positron emission tomography, Imaging agent, Fluciclovine F-18, Gamma rays.

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Abstract

Prostate cancer is the second most common cancer among men in the United States and fifth most common cancer worldwide. Most primary prostate cancers can be successfully treated, but recurrence occurs in up to one-third of patients. The location and extent of the disease cannot always be detected by conventional imaging, however, and of those who experience recurrence, approximately one-third develop metastatic prostate cancer. Axumin (fluciclovine (F-18)) is the first, novel imaging agent approved for use in patients with suspected recurrent prostate cancer based on elevated blood prostate specific antigen (PSA) levels following initial treatment for the disease. It employs the technique of positron emission tomography (PET) imaging to detect the prostate cancer recurrence in suspected men. High PSA in the blood is a sign that cancer is coming back or spreading. The agent was developed to enable visualization of the increased amino acid transport that occurs in many cancers, including prostate cancer. Post injection of Axumin, the drug is taken up by the prostate cancer cells by transporters (eg, LAT-1, ASCT2), which are up-regulated in prostate cancer cells compared with surrounding normal tissues. Then the drug emits a small amount of energy in the form of gamma rays. This energy is detected by the PET/CT scanner, and a computer will produce a detailed image. Better understanding of a recurrence can facilitate management decisions that include surgery, radiotherapy, or chemotherapy. The molecule is being investigated for other potential cancer indications, such as glioma.

Introduction

Prostate cancer is a type of cancer that develops in the prostate gland which is found in the male reproductive system. During a man's lifetime, the risk of developing prostate cancer is 1 in 6, making it the second leading cause of cancer death in men, exceeded only by lung cancer. About 85% of men with prostate cancer are diagnosed after the age of 65 [1]. It is a significant burden to men's health. It represents the most frequently diagnosed non dermatological malignancy and the second leading cause of death due to cancer in men. The natural progression of prostate cancer in most men is relatively slow. Most tumors remain organ confined and will never surface clinically during the patient's lifetime, either because they are indolent or because death occurs from competing causes before clinical manifestation of the malignancy[2-5].

In the era of screening with prostate-specific antigen (PSA), many men now present with disease that previously may not have been detected. This presents a diagnostic and therapeutic dilemma for clinicians [6, 7].Based on the low specificity of PSA in detecting PCa, numerous novel diagnostic biomarkers found to be valuable in researches and are clinically applied to detect the patients with a disease or abnormal condition. The various biomarkers used are prostate acid phosphate (PAP), prostate specific antigen(PSA), complexed prostate specific antigen (cPSA), (-2) pro PSA (p2PSA), alpha-methyl-coA racemase (AMACR), prostate cancer antigen 3(PCA3), metastasis associated lung adenocarcinoma transcript 1 (MALAT1), single nucleotide polymorphism (SNP), loss of hetero-zygosity (LOH), kallikrein-related peptidase2 (KLK2), prostate-specific membrane antigen (PSMA), glutathione s-transferase pi 1 (GSTP1), golgi phosphoprotein 2 (GOLPH2), circulating tumor cells (CTC), ribonucleic acid (RNA), deoxyribonucleic acid (DNA), messenger RNA (mRNA) [8].Although a variety of biomarkers have been proposed, advances in imaging play an increasingly important role.

The evaluation of distant disease, where nuclear imaging has the potential to have the greatest impact. Nuclear imaging involves the injection of a small amount of radioactive material, known as a "radiopharmaceutical," into the patient. The distribution of this material within the body is then detected by specialized imaging cameras, thus allowing for noninvasive quantitative and qualitative assessment of the extent of disease. Radiopharmaceuticals labeled with positron-emitting radionuclides are specifically detected by positron emission tomography (PET) cameras that are often combined with x-ray computed tomography (PET/CT). The relatively better resolution and quantitative capabilities make PET a desirable molecular imaging modality. PET should be

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distinguished from the other major category of radionuclide imaging, single-photon emission computed tomography (SPECT), in which gamma-ray-emitting radionuclides are coupled to targeting agents. SPECT cameras, which can also be combined with CT, however, have inferior resolution and sensitivity compared to PET [6, 7].

The clinical relevance of either approach lies in the ability to conjugate positron or single-photon radionuclides to biologically significant molecules with high affinities for their targets, thereby enabling the noninvasive detection of specific markers associated with cancers. Because neoplastic growth typically relies on abnormal upregulation of many cellular processes, PET and SPECT tracers specific to these molecular signatures have emerged as important tools in the evaluation of both localized and metastatic cancer [9,10].

Pathophysiology

Similar to benign hyperplasia, carcinoma of the prostate is predominantly a disease of older man. Prostate cancer is extremely common; it is estimated that a 50-year-old man has a 40% chance of developing prostate cancer during his lifetime. The exact cause is often unknown [1].

The malignant transformation of prostate epithelial cells, as with other forms of cancer, is a result of a complex series of initiator and promoter events with generic and environmental influences. Approximately 5 to 10% of prostate cancer cases are estimated to be related to inherited genetic factors or prostate cancer susceptibility genes. One major locus of susceptibility is found at chromosome 1q24, designated as HPC1 (hereditary prostate cancer). This mutation is associated with a younger age at diagnosis, a higher tumor grade, and most advanced stage at diagnosis. Several other chromosome regions, which have been linked to susceptibility in inherited and sporadic forms of prostate cancer, have also been identified [1].

The protein ZIP1 is responsible for the active transport of zinc into prostate cells. Prostate cancer cells are generally devoid of zinc. This allows prostate cancer cells to save energy not making citrate, and utilize the new abundance of energy to grow and spread. RUNX2 is a transcription factor that prevents cancer cells from undergoing apoptosis thereby contributing to the development of prostate cancer. The PI3k/Akt signaling cascade works with the transforming growth factor beta/SMAD signaling cascade to ensure prostate cancer cell survival and protection against apoptosis. The androgen receptor helps prostate cancer cells to survive and is a target for many anticancer research studies [11].

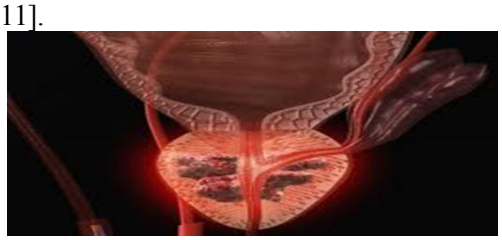


Figure 1. Androgen deprivation therapy (ADT) and radiation therapy to treat prostate cancer

Symptoms

Prostate cancer has very few signs or symptoms in the early stages. Early detection of this cancer is rather difficult. Signs and symptoms of prostate cancer depend on the extent and spread of prostate cancer [12].

Signs and symptoms for prostate cancer may include:

1. **Frequent urination:** You experience the need to urinate very frequently. This feeling is intensified specifically at night. You may wake up many times to visit the toilet.
2. **Incontinence:** Urinary incontinence is your inability to control the urge to urinate. Often, this causes accidents, as you are unable to reach the bathroom in time to urinate.
3. **Difficulty starting urination:** Growth of the prostate gland often causes difficulties in starting urination. This growth stresses on the urethra and constricts it. This is the cause for difficulty in starting urination. Further, it also causes difficulty in maintaining the urine stream. Sometimes, you pass blood in your urine.
4. **Discomfort during urination:** You may feel uncomfortable or encounter pain or a burning sensation during urination. This condition is dysuria. Although this is not a very common symptom of prostate cancer, it is present in few cases. However, this is predominant in benign prostatic hyperplasia. You would often feel you are unable to empty the bladder completely.
5. **Painful erections and ejaculations:** Growth or enlargement of the prostate gland affects blood flow into the penis. You may have trouble having erections or they may be less rigid. Constriction of the urethra narrows down the ejaculation channel. Therefore, passage of semen during ejaculation is narrowed and forced. This is the reason for pain during ejaculation.
6. **Impotence:** Impotence is the inability to have a satisfactory erection for penetration during intercourse. Sudden occurrence of impotence may be a symptom of the presence of prostate cancer. There could also be less semen during ejaculation as prostatic disease affects the flow of ejaculatory fluid produced by the prostate gland and seminal vesicles.
7. **Blood in the Semen:** This condition is Hematospermia. The blood in the semen would not be visible to the naked eye.
8. **Urinary Infections:** Constriction of urethra by prostate gland could cause formation of cystitis. This leads to urinary infections.

Advanced prostate cancer may cause these specific symptoms:

1. **Pain in the lower back and spinal regions:** As prostate cancer spreads, it can cause cancerous growth of cells in other body parts. This growth could extent to the bones of the pelvic and spinal region. This gives rise to severe pain in these regions.

2. **Numbness and pain in legs and thighs:** Prostate cancer causes severe pain and a numb feeling in the thighs and legs. You may suddenly not able to move your legs. It could also cause swelling of the legs.
3. **Sudden inability to pass urine:** This symptom appears from nowhere. You are unable to pass urine. However, you do not experience any pain.
4. **Bone fractures:** Prostate cancer advances into the bone tissue and makes them weak and vulnerable to frequent fractures. Bone pain remains intense [12].

Risk Factors

1. Age is the principle risk factor. The older a man is, the higher is his risk. Prostate cancer is rare among men under the age of 45, about 90% of diagnoses occurring at the age of 55 and above.
2. Race is a major risk factor for prostate cancer. African-Americans have the highest incidence of prostate cancer than any other race or ethnicity elsewhere in the world.
3. The two faulty genes - BRCA 1 and BRCA 2 - which are important risk factors for breast cancer and ovarian cancer, have also been implicated in prostate cancer risk.
4. Lack of vitamin D, a diet high in red meat may raise a person's chances of developing prostate cancer.
5. There is a link between obesity and raised prostate cancer risk, as well as a higher risk of metastasis and death among obese people who develop prostate cancer.
6. Men who have had gonorrhea have a higher chance of developing prostate cancer [2-5].

Tests for Prostate Cancer

Most prostate cancers are first found during screening with a prostate-specific antigen (PSA) blood test or a digital rectal exam (DRE). If cancer is suspected based on results of screening tests or symptoms, tests will be needed to confirm the diagnosis [13, 14].

1. PSA blood test: Most men without prostate cancer have PSA levels under 4 nanograms per milliliter (ng/mL) of blood. The chance of having prostate cancer goes up as the PSA level goes up. When prostate cancer develops, the PSA level usually goes above 4. Still, a level below 4 does not guarantee that a man doesn't have cancer. About 15% of men with a PSA below 4 will have prostate cancer on a biopsy. Men with a PSA level between 4 and 10 have about a 1 in 4 chance of having prostate cancer. If the PSA is more than 10, the chance of having prostate cancer is over 50% [13, 14].

2. Transrectal ultrasound (TRUS): For this test, a small probe about the width of a finger is lubricated and placed in your rectum. The probe gives off sound waves that enter the prostate and create echoes. The probe picks up the echoes, and a computer turns them into a black and white image of the prostate [13, 14].

3. Prostate biopsy A biopsy is a procedure in which small samples of the prostate are removed and then looked at under a microscope. A core needle biopsy is the main method used to diagnose prostate cancer [13, 14].

4. Grade (Gleason score) of prostate cancer Prostate cancers are graded according to the Gleason system. This system assigns a Gleason grade based on how much the cancer looks like normal prostate tissue.
If the cancer looks a lot like normal prostate tissue, a grade of 1 is assigned.
If the cancer looks very abnormal, it is given a grade of 5.
Grades 2 through 4 have features in between these extremes [13, 14].

Imaging Tests for Prostate Cancer

Bone scan: For this test, you are injected with a small amount of low-level radioactive material, which settles in damaged areas of bone throughout the body. A special camera detects the radioactivity and creates a picture of your skeleton. A bone scan may suggest cancer in the bone [15].
Computed tomography (CT) scan: A CT scan uses x-rays to make detailed, cross-sectional images of your body. The CT scan can often tell if the tumor is growing into other organs or structures in your pelvis [15].
Magnetic resonance imaging (MRI): MRI scans use radio waves and strong magnets instead of x-rays. A contrast material called gadolinium may be injected into a vein before the scan to better see details. MRI scans can give a very clear picture of the prostate and show if the cancer has spread outside the prostate into the seminal vesicles or other nearby structures. This can be very important in determining your treatment options [16].
Lymph node biopsy: In this, one or more lymph nodes are removed to see if they have cancer cells. This isn't done very often for prostate cancer, but can be used to find out if the cancer has spread from the prostate to nearby lymph nodes [16].

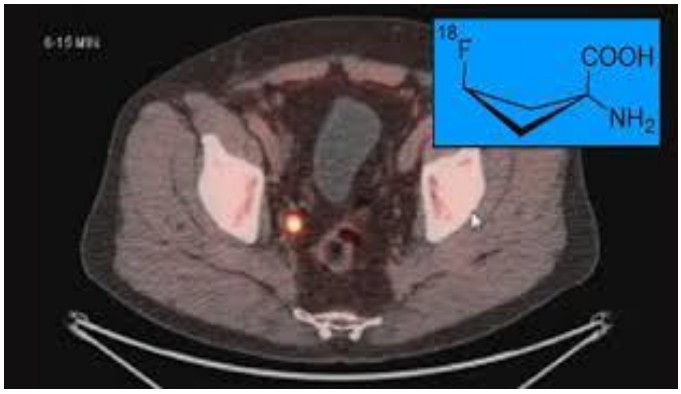


Figure 2. Axumin imaging via CT scan, showing areas of cancer in red. Blue inset is the FACBC-fluciclovine compound structure.

Axumin As A Diagnostic Agent

Regulatory History

The following is a summary of the regulatory history for NDA 208054, Risk Assessment and Risk Mitigation Reviews:

- 4/30/2010: IND 107707 active
- 6/26/14: Type C meeting to discuss clinical program
- 2/2/15: Type C Meeting to discuss statistical plan for Blue Earth Diagnostics(BED)-001
- 2/26/15: Type C Meeting to discuss statistical plan for Blue Earth Diagnostics(BED)-002
- 09/28/2015: New Drug Application (NDA) 208054 submission received for positron emission tomography (PET) imaging of men with suspected prostate cancer recurrence
- 10/9/2015: Agreed Initial Pediatric Study Plan
- 1/6/2016: Mid-cycle Meeting.

Table 1. Summary of Treatment Options Relevant to Proposed Indication

Product Trade Name (Generic)	Year of Approval	Indication	Dosing/ Administ-ration	Important Safety and Tolerability Issues	Risk Management Approaches/ Boxed Warning, Medication Guide
^{111}Indium capromab pendetide (Prostascint)	1996	For newly diagnosed patients with biopsy-proven prostate cancer, thought to be clinically localized after standard diagnostic evaluation who are at high-risk for pelvic lymph node metastases; also indicated as a diagnostic imaging agent in postatecto-my patients with a rising PSA and a negative or equivocal standard metastatic evaluation in whom there is a high clinical of occult metastatic disease.	0.5mg radiolabeled with 5mCi of Indium In 111 chloride by intravenous injection	Allergic hypersensitivity reactions	None
Fludeoxyglu cose F 18 (FDG)5	1994	Indicated in PET imaging for assessment of abnormal glucose metabolism to assist in the evaluation of malignancy in patients with known or suspected abnormalities found by other testing modalities or in patients with an existing diagnoses of cancer.	185-370 MBq (5-10 mCi)	None	None
Choline C 11	2012	For PET imaging of patients with suspected prostate cancer recurrence and non-informative bone scintigraphy, computerized tomography (CT) or magnetic resonance imaging.	370 to 740 MBq (10 to 20 mCi) as a bolus IV injection	Mild indication site reactions (no numbers).	None

Of these agents listed in Table 1, Choline C 11 is the most similar to fluciclovine, since its indication is for those with suspected prostate cancer recurrence. Limiting factors with the use of Choline C 11 include greater patient preparation to take the drug by having to fast 6 hours prior to administration with Choline C 11 versus 4 hours with fluciclovine, higher radiation dose to patients, and possibly poorer image quality. When fluciclovine is added to PET scanning, lesion detectability is enhanced due to improved resolution of the images [18].

Comparison to other imaging tools: Studies comparing the agent to the gamma-emitting agent ProstaScint, and to CT and ^{11}C-choline have been reported, as have descriptions of its use in primary prostate cancer and in therapy planning. In an NIH funded prospective RO1 study at Emory University, 115 patients with BCR and negative ^{99m}Tc bone scans after radical prostatectomy or radiotherapy were imaged with fluciclovine F 18. The majority (n=93) also received ^{111}In capromab pendetide (ProstaScint, a radio-labelled monoclonal antibody that binds to prostate-specific membrane antigen). This study compared the regional sensitivity and specificity of the two agents, relative to histology and clinical follow-up. Sufficient data for truth assessment (histology, response to therapy and clinical follow-up) were available for 91 patients with prostate/bed findings and for 70 patients with extra-prostatic involvement. The following results were found.

Table 2. Diagnostic performance of fluciclovine and 111In capromab pendetide.

Agent	Location	Sensitivity	Specificity	Accuracy	PPV	NPV
Fluciclovine F 18 (n=91)	Prostate/bed	90.2%	40.0%	73.6%	75.3%	66.7%
ProstaScint (n=91)	Prostate/bed	67.2%	56.7%	63.7%	75.9%	45.9%
Fluciclovine F 18 (n=70)	Extra-prostatic sites	55.0%	96.7%	72.9%	95.7%	61.7%
ProstaScint (n=70)	Extra-prostatic sites	10.0%	86.7%	42.9%	50.0%	41.9%

Of the 77 index lesions used to prove positivity, histological proof of PCa was obtained in 74 (96.1%). Fluciclovine F 18 identified 14 more positive prostate bed recurrences (55 vs 41) and 18 more subjects with extra-prostatic involvement (22 vs 4). The agent upstaged 25.7% of the patients. For fluciclovine, imaging was complete within 40 min post-injection (PI), in contrast to ^{111}In capromab pendetide, where images were obtained at 3 days PI [18].

Comparison to 11C-choline:

A prospective study conducted at Bologna University enabled a within-subject comparison of the performance of fluciclovine F 18 PET and 11C-choline PET in patients with BCR post-radical prostatectomy (n=89). Follow-up at 1 year was used as the reference standard. Diagnostic performance was comparable for both agents at PSA values above 1 ng/mL, but fluciclovine F 18 imaging showed higher sensitivity in patients with low PSA levels (<1 ng/mL). 11C-choline has been approved for use in the detection of BCR at selected sites in, but the 20 minute half-life of the 11C isotope limits its use to facilities with a nearby cyclotron. In contrast, the 110 minute half-life of F18 in fluciclovine improves the potential for broad patient access [19, 20].

Up to one third of patients treated with curative intent following a diagnosis of primary prostate cancer will experience recurrent disease within 10-15 years following primary treatment.

Fluciclovine is a synthetic amino acid that is transported into mammalian cells by amino acid transporters (AATs), most notably LAT1 and ASC2 transporters. The indication for fluciclovine is as a radioactive diagnostic agent for positron emission tomography (PET) imaging of men with suspected prostate cancer recurrence. 111Indium capromab pendetide and Choline C 11 are similar FDA approved products for the detection of primary or recurring prostate cancer. All of these products are given as a single IV dose for diagnostic use and have low incidences of adverse effects. The adverse effects that have been reported for both products were mild in intensity and Grade 1 and neither of the product labels have Boxed Warnings. However, the 20 minute half-life of Choline C 11 limits the use of this agent to medical centers with on-site 11C production capability, which prevents this agent from being supplied via the established PET supply chain. The longer half-life (110 minutes) makes fluciclovine more practical for clinical use. Furthermore, fluciclovine appeared to have better sensitivity and specificity for lesion detection and better imaging results compared to indium capromab pendetide or Choline C 11.

As with other diagnostic radiopharmaceuticals, fluciclovine will be restricted to inpatient settings. This product will be prepared and given by nuclear medicine physicians and staff who are required to have specialized training for the handling and management of radionucleotides as part of their daily clinical practice. Past regulatory actions have not required a REMS for approval of these types of products [19, 20].

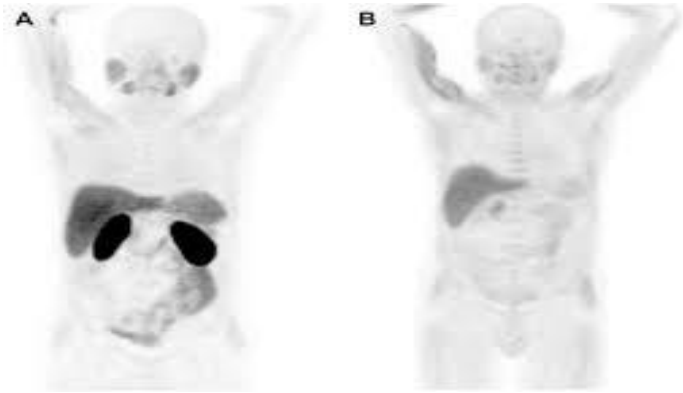


Figure 3. Imaging of Prostate Cancer Using Fluciclovine. Comparison of 11C Choline and 18F Fluciclovine physiologic biodistribution

Chemical Characteristics

Axumin contains the fluorine 18 (F 18) labeled synthetic amino acid analog fluciclovine. Fluciclovine F 18 is a radioactive diagnostic agent used with PET imaging. Chemically, fluciclovine F 18 is (1r, 3r)-1-amino-3[^{18}F] fluorocyclobutane-1-carboxylic acid. The molecular weight is 132.1 and the structural formula is:



Figure 4. Fluciclovine F-18

Axumin is a sterile, non-pyrogenic, clear, colorless, hyperosmolal (approximately 500-540 mOsm/kg)injection for intravenous use. Each milliliter contains up to 2 micrograms of fluciclovine, 335 to 8200 MBq (9 to 221 mCi) fluciclovine F 18 at calibration time and date, and 20 mg trisodium citrate in water for injection. The solution also contains hydrochloric acid, sodium hydroxide and has a pH between 4 and 6 [17].

Physical Characteristics

Fluorine 18 F is a cyclotron produced radionuclide that decays by positron emission (β+ decay, 96.7%) and orbital electron capture (3.3%) to stable oxygen 18 with a physical half-life of 109.7 minutes. The positron can undergo annihilation with an electron to produce two gamma rays; the energy of each gamma ray is 511 keV (Table 1)

Table 3. Principal Radiation Produced from Decay of Fluorine 18 Radiation

	Energy (ke V)	Abundance (%)
Positron	**249.8**	**96.7**
Gamma	**511.0**	**193.5**

External Radiation

The point source air-kerma coefficient for F 18 is 3.7 x 10^{-17} Gy m^2(Bq s). The first half value thickness of lead (Pb) for F 18 gamma rays is approximately 6 mm. The relative reduction of radiation emitted by F 18 that results from various thickness of lead shielding is shown in Table 2. The use of 8 cm of Pb will decrease the radiation transmission (i.e., exposure) by a factor of about 10,000 [17].

Table 4. Radiation Attenuation of 511 keV Gamma Rays by Lead Shielding

Shield Thickness cm of Lead (Pb)	Coefficient of Attenuation
0.6	0.5
2	0.1
4	0.01
6	0.001
8	0.0001

Clinical Pharmacology

Mechanism of Action

Fluciclovine F 18 is a synthetic amino acid which is transported across mammalian cell membranes by amino acid transporters, LAT-1 and ASCT2, which are upregulated in prostate cancer cells, bring amino acids such as glutamine and leucine into cells, where they are used for protein synthesis, cell growth and metabolism. The drug is taken up to a greater extent in prostate cancer cells compared with surrounding normal tissues [17].

Pharmacodynamics

Following intravenous administration, the tumor-to-normal tissue contrast is highest between 4 and 10 minutes after injection, with a 61% reduction in mean tumor uptake at 90 minutes after injection [17].

Pharmacokinetics

Distribution
Liver (14%)
Bone marrow (12%)
Lung (7%)
Myocardium (4%)
Pancreas (3%)
With increasing time, fluciclovine F 18 distributes to skeletal muscle [17].
Excretion
First 4 hr post injection: 3% excreted in urine.
First 24 hr post injection: 5% excreted in urine [17].

Dosage and Administration

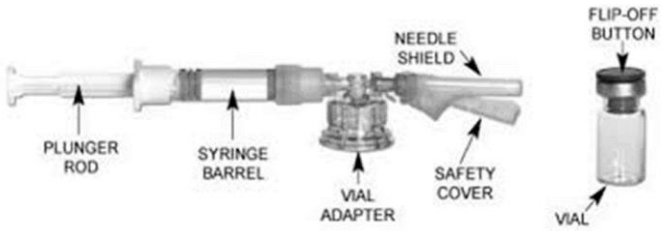


Figure 5. Dosage and Administration of Fluciclovine F18

Patient Preparation

Advise the patient to avoid any significant exercise for at least 1 day before PET imaging and not to eat or drink for at least 4 hr (other than small amounts of water for taking medications) prior to administration [17].

Radiation Safety – Drug Handling

Axumin is a radioactive drug and should be handled with appropriate safety measures to minimize radiation exposure during administration. Precautionary measures like waterproof gloves and effective shielding and syringe shields should be used when handling and administering [17].

Recommended Dose and Administration Instructions

The recommended dose is 370 MBq (10 mCi) administered as an intravenous bolus injection.

1. Inspect solution visually for particulate matter and discoloration before administration; do not use if the solution contains particulate matter or is discolored.
2. Use aseptic technique and radiation shielding when withdrawing and administering.
3. Calculate the necessary volume to administer based on calibration time and date, using a suitably calibrated instrument. The recommended maximum volume of

injection of undiluted drug is 5 mL; may be diluted with NaCl 0.9%.
4. After i.v. bolus injection, administer i.v. flush of sterile NaCl 0.9% to ensure full delivery of the dose.
5. Dispose of any unused drug in a safe manner in compliance with applicable regulations [17].

Image Acquisition Guidelines
- Patient supine should be placed with arms above the head.
- PET scanning should begin 3-5 minutes after completion of the injection.
- It is recommended that image acquisition should start from midthigh and proceed to the base of the skull.
- Patient should be scanned for a time period of 20-30 minutes [17].

Image Display and Interpretation
Localization of prostate cancer recurrence in sites typical for prostate cancer recurrence is based on fluciclovine F 18 uptake in comparison with tissue background.
Small lesions (<1cm in diameter): Focal uptake greater than blood pool should be considered suspicious for prostate cancer recurrence.
Larger lesions: Uptake equal to or greater than bone marrow is considered suspicious for prostate cancer recurrence [17].

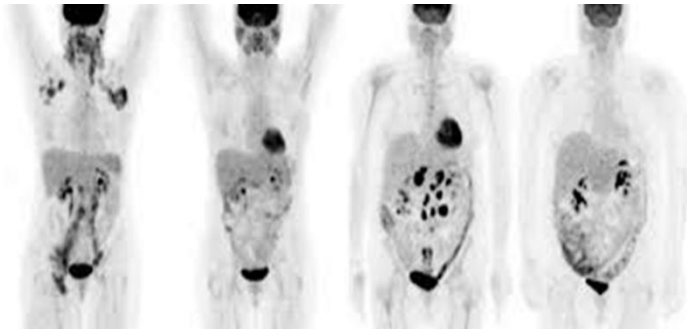


Figure 6. First administered image of Axumin at Northside Hospital Atlanta GA, USA

Radiation Dosimetry
The radiation absorbed doses estimated for adult patients following intravenous injection of Axumin are shown in Table 5. Values were calculated from human biodistribution data using OLINDA/EXM (Organ Level Internal Dose Assessment/Exponential Modeling) software [17].
The (radiation absorbed) effective dose resulting from the administration of the recommended activity of 370 MBq of Axumin is 8 mSv. For an administered activity of 370 MBq (10 mCi), the highest-magnitude radiation doses are delivered to the pancreas, cardiac wall, and uterine wall: 38 mGy, 19 mGy, and 17 mGy, respectively. If a CT scan is simultaneously performed as part of the PET procedure, exposure to ionizing radiation will increase in an amount dependent on the settings used in the CT acquisition [17].

Table 5. Estimated Radiation Absorbed Doses in Various Organs/Tissues in Adults who Received Axumin

Organ/Tissue	Mean Absorbed Dose per Unit Administered Activity (microGyMBq)
Adrenal glands	16
Brain	9
Breasts	14
Gallbladder wall	17
Lower large intestine wall	12
Small intestine wall	13
Stomach wall	14
Upper large intestine wall	13
Heart wall	52
Kidneys	14
Liver	33
Lungs	34
Muscle	11
Ovaries	13
Pancreas	102
Red bone marrow	25
Osteogenic cells	23
Skin	8
Spleen	24
Testes	17
Thymus gland	12
Thyroid	10
Urinary bladder wall	25
Uterus	45
Total body	13
Effective dose	22 (microSv/MBq)

Dosage Forms and Strengths
Injection: supplied as a clear, colorless solution in a 30 mL multiple-dose vial containing 335 to 8200 MBq/mL(9 to 221 mCi/mL) fluciclovine F 18 at calibrated time and date [16].

Contraindications
None [17].

Warnings and Precautions
Risk for Image Misinterpretation
Image interpretation errors can occur with Axumin PET imaging. A negative image does not rule out the presence of recurrent prostate cancer and a positive image des not confirm the presence of recurrent prostate cancer. The performance of Axumin seems to be affected by PSA levels. Fluciclovine F 18 uptake is not specific for prostate cancer hypertrophy in primary prostate cancer. Clinical correlation, which may include histopathological evaluation of the suspected recurrence site, is recommended [17].

Hypersensitivity Reactions
Hypersensitivity reactions including anaphylaxis may occur in patients who receive Axumin.
Emergency resuscitation equipment and personnel should be immediately available [17].

Radiation Risks
Use of Axumin leads to a patient's overall-term cumulative radiation exposure. Long-term cumulative radiation exposure is associated with an increased risk for cancer. Ensure safe handling to minimize radiation exposures to the patient and health care providers [17].

Adverse Reactions

Clinical Trials Experience
Adverse reactions were reported in ≤1% of subjects during clinical studies with Axumin. The most common adverse reactions were pain at the site of injection, erythema and dysgeusia [17].

Use in Specific Populations

Pregnancy
Risk Summary
Axumin is not indicated for use in females and there is no information on the risk of adverse effect [17].

Geriatric Use
The average age of the patient was found to be 66 years with a range of 21 to 90 years. No differences were determined in safety or effectiveness between older subjects and younger subjects [17].

Overdosage
In case of overdose of Axumin, encourage patients to maintain hydration and to void frequently to minimize radiation exposure [17].

How Supplied/Storage and Handling

How Supplied
Axumin is supplied as a clear, colorless injection in a 30 mL multiple-dose glass vial containing approximately 26 mL solution of 335-8200 MBq/mL (9-221 mCi/mL) fluciclovine F 18 at calibration time and date. 30 mL sterile multiple-dose vial: NDC 69932-001-030 [17].

Storage and Handling
Store Axumin at controlled room temperature (USP) 20°C to 25°C (68°F to 77°F). It does not contain a preservative. Store the drug within the original container in radiation shielding.
The preparation is approved for use by persons under license by the Nuclear Regulatory Commission or the relevant regulatory authority of an Agreement State [17].

Patient Counseling Information
Instruct patients to avoid significant exercise for at least a day before the PET scan. Instruct patients not to eat or drink for at least 4 hours before the PET scan (other than small amounts of water for taking medications) [17].

Benefits
1. It is an effective molecular imaging tool to evaluate the patients, provides the extent and location of the tumor and assist clinicians in directing further management.
2. The agent used for Positron Emission Tomography (PET) tend to accumulate in cancer cells, not healthy cells, due to the different cellular metabolism.
3. Clinical trials have demonstrated the effectiveness and safety of fluciclovine F-18 with minimal side effects when compared to standard imaging agents used in PET scans for identification of recurrent prostate cancer.
4. It is cost effective and easy to manufacture.
5. Sufficient dose of the drug remains which can be utilized for diagnosis as minor amount is excreted from the body.
6. Greater convenience for the patient who undergoes the exam when compared to other imaging techniques.
7. Minimizes the probability of error in deciding the treatment options
8. It has the potential to lead to better outcomes in men with recurrent prostate cancer.
1. The diagnostic accuracy of Axumin for the identification of sites of recurrence is high when compared to standard imaging agents
9. It is more sensitive, specific and accurate than other imaging agents.
10. It has a longer half-life of about 110 minutes which helps in getting the detailed image of the region scanned [11, 18].

Commercial Preparation of Axumin
Axumin is manufactured and Marketed by Blue Earth Diagnostics Ltd. Oxford, UK OX4 4GA AxuminTM is a trademark of Blue Earth Diagnostics Ltd.
It is manufactured and distributed by Siemens' PETNET Solutions [17].

Conclusion

Every cancer screening has some harms, even if net beneficial. One should have some perspective of the harm-benefit ratio before using a test. The best way to assess the efficacy of a screening test is a well-designed prospective randomized clinical trial in which subjects volunteer for enrollment and are then randomized to a screening or a control group and followed up over time. Most primary prostate cancers can be successfully treated, recurrence occurs in up to one-third of patients. Recurrent disease is typically detected but often the location and extent of the disease cannot be detected by conventional imaging. There is a need for clinical imaging techniques that can detect and localize suspected recurrent prostate cancer to facilitate the most appropriate patient management. Additionally, many patient care options for men with suspected recurrent

prostate cancer have uncertain benefits that may not justify the risk of side effects.

An imaging agent with sufficient diagnostic performance to adequately detect and localize recurrent prostate cancer can provide referring physicians with actionable information to guide biopsy and inform management decisions for their patients. The discovery of Axumin can solve this problem and furthermore this molecular imaging tool has huge benefits in terms of minimizing the expected and undesirable side effects. It is being investigated for other potential cancer indications, such as glioma.

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