Prostate Cancer Imaging with F-18 Fluciclovine (Axumin)

1. INDICATIONS AND USAGE

a) Axumin is indicated for positron emission tomography (PET) in men with suspected prostate cancer recurrence based on elevated blood prostate specific antigen (PSA) levels following prior treatment.

b) Prostate cancer [PCa] affects 1 man in 7 in the United States, making this the most commonly diagnosed non-cutaneous cancer in males. Although an ever-increasing number of treatment options exist, an estimated 26,100 men will still die of the disease in the US in 2016, generally after primary local and systemic treatments for prostate cancer have failed. One factor contributing to this statistic is the frequent inability of current diagnostic methods to reliably detect the exact location(s) of disease relapse at a time when curative treatment is still possible.

c) Most imaging tests have not been able to localize recurrent prostate cancer when the PSA is mildly increased. Axumin scans were compared to [11C]-tagged choline PET scans, another FDA approved PET scan that can assist in this situation, and to biopsy results. Fluciclovine tagged PET scans appear to be more sensitive than CT scans and to [11C]-tagged choline PET scans.

d) One major problem is that up to a third of men treated for prostate cancer will experience recurrent disease, most often detected only by rising Prostate Specific Antigen [PSA] levels. Conventional imaging tools such as computerized tomography [CT] and bone scintigraphy [BS] frequently fail to identify the site of recurrent disease, presenting a serious challenge to urologists and radiation oncologists charged with the selection of secondary treatment, and causing significant anxiety for these patients.

e) While PCa recurrence may occur locally in the prostate gland or prostate bed, and/or in local lymph nodes in the pelvis, recognition of distant lymph node, bone or other tissue involvement requires different treatment choices. Potentially curative techniques such as salvage lymphadenectomy, radiotherapy or cryotherapy may be used for local recurrences, especially at lower PSA levels,

whereas systemic approaches such as the use of anti-hormonal therapy and/or chemo or immunotherapy may be recommended in the presence of distal metastatic disease.

2. DOSAGE

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

3. ADMINISTRATION PROCEDURES

a) Axumin is a radioactive drug and should be handled with appropriate safety measures to minimize radiation exposure during administration

a) One should use waterproof gloves and effective shielding, including syringe shields, when handling and administering Axumin.

b) Inspect Axumin visually for particulate matter and discoloration before administration. Do not use the drug if the solution contains particulate matter or is discolored. Use aseptic technique and radiation shielding when withdrawing and administering Axumin.

c) 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 Axumin is 5 mL.

d) Axumin may be diluted with Sodium Chloride Injection, 0.9%.

e) After the Axumin injection, administer an intravenous flush of sterile Sodium Chloride Injection, 0.9% to ensure full delivery of the dose.

f) Dispose of any unused drug in a safe manner in compliance with applicable regulations.

4. PATIENT PREPARATION PRIOR TO PET IMAGING

a) Advise the patient to avoid any significant exercise for at least one day prior to PET imaging.

b) Advise patients not to eat or drink for at least 4 hours (other than small amounts of water for taking medications) prior to administration of Axumin.

5. IMAGE ACQUISITION GUIDELINES

Position the patient supine with arms above the head. Begin PET scanning 3 to 5 minutes after completion of the Axumin injection. It is recommended that image acquisition should start from midthigh and proceed to the base of the skull. Typical total scan time is between 20 to 30 minutes.

6. IMAGE DISPLAY AND INTERPRETATION

Localization of prostate cancer recurrence in sites typical for prostate cancer recurrence is based on F-18 fluciclovine uptake in comparison with tissue background. For small lesions (less than 1 cm in diameter) focal uptake greater than blood pool should be considered suspicious for prostate cancer recurrence. For larger lesions, uptake equal to or greater than bone marrow is considered suspicious for prostate cancer recurrence.

7. INTERNAL RADIATION DOSIMETRY

The radiation absorbed doses estimated for adult patients following intravenous injection of Axumin are shown in Table 1. Values were calculated from human biodistribution data using OLINDA/EXM (Organ Level Internal Dose Assessment/Exponential Modeling) software.

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.

Table 1: Estimated Radiation Absorbed Doses in Various Organs/Tissues in Adults who Received Axumin

Organ/Tissue	Mean Absorbed Dose per Unit Administered Activity (microGy/MBq)
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)**

8. DOSAGE FORMS AND STRENGTHS

a) 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) F-18 fluciclovine at calibration time and date.

9. STORAGE AND HANDLING OF AXUMIN

a) Store Axumin at controlled room temperature (USP) 20°C to 25°C (68°F to 77°F). Axumin does not contain a preservative. Store Axumin within the original container in radiation shielding.

b) This preparation is approved for use by persons under license by the Nuclear Regulatory Commission or the relevant regulatory authority of an Agreement State.

10. CONTRAINDICATIONS

a) None

11. RISK FOR IMAGE MISINTERPRETATION

a) 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 does not confirm the presence of recurrent prostate cancer. The performance of Axumin seems to be affected by PSA levels

b) F-18 fluciclovine uptake is not specific for prostate cancer and may occur with other types of cancer and benign prostatic hypertrophy in primary prostate cancer. Clinical correlation, which may include histopathological evaluation of the suspected recurrence site, is recommended.

12. HYPERSENSITIVITY REACTIONS

a) Hypersensitivity reactions including anaphylaxis may occur in patients who receive Axumin. Emergency resuscitation equipment and personnel should be immediately available.

13. RADIATION RISKS

a) Axumin use contributes to a patient's overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure is associated with an increased risk for cancer. Ensure safe handling to minimize radiation exposure to the patient and health care providers

14. ADVERSE REACTIONS

a) Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The clinical trial database for Axumin includes data from 877 subjects

including 797 males diagnosed with prostate cancer. Most patients received a single administration of Axumin, a small number of subjects (n = 50) received up to five administrations of the drug. The mean administered activity was 370 MBq (range, 163 to 485 MBq).

Adverse reactions were reported in ≤1% of subjects during these clinical studies. The most common adverse reactions were injection site pain and/or redness, and dysgeusia (abnormal taste in the mouth). Although not yet observed, hypersensitivity reactions, including anaphylaxis, may occur in patients who receive radiopharmaceuticals, so emergency resuscitation equipment and personnel should be immediately available.

15. USE IN SPECIFIC POPULATIONS

a) Axumin is not indicated for use in females and there is no information on the risk of adverse development outcomes in pregnant women or animals with the use of F-18 fluciclovine. There is also no information regarding the presence of F-18 fluciclovine in human milk.

b) Safety and effectiveness have not been established in pediatric patients.

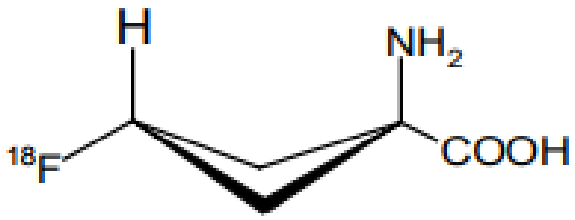
c) Regarding geriatric use, of the total number of patients in clinical studies of Axumin, the average age was 66 years with a range of 21 to 90 years. No overall differences in safety or effectiveness were observed between older subjects and younger subjects.

16. OVERDOSAGE

a) In the unlikely event of an overdose of Axumin, encourage patients to maintain hydration and to void frequently to minimize radiation exposure.

17. CHEMICAL CHARACTERISTICS OF THE DRUG

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



b) 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) F-18 fluciclovine 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.

18. PHYSICAL CHARACTERISTICS

a) Fluorine 18 (F-18) is a cyclotron produced radionuclide that decays by positron emission (ß+ decay, 96.7%) and orbital electron capture (3.3%) to stable oxygen-18 with a physical half-life of 109.7 minutes.

b) The positron can undergo annihilation with an electron to produce two gamma rays; the energy of each gamma ray is 511 keV

Principal Radiation Produced from Decay of Fluorine 18 Radiation

	Energy (keV)	Abundance (%)
Positron	249.8	96.7
Gamma	511.0	193.5

19. EXTERNAL RADIATION

a) The point source air-kerma coefficient for F-18 is 3.75 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 thicknesses of lead shielding is shown in Table 3. The use of 8 cm of Pb will decrease the radiation transmission (i.e., exposure) by a factor of about 10,000.

b) 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

20. CLINICAL PHARMACOLOGY

a) Mechanism of action: Fluciclovine is a [18F]-tagged synthetic analog of the amino acid L-leucine. It is transported across mammalian cell membranes by amino acid transporters, such as LAT-1 and ASCT2, which are upregulated in prostate cancer cells. F-18 Fluciclovine is taken up to a greater extent in prostate cancer cells compared with surrounding normal tissues Although it is handled by the amino acid transporter system, it does not undergo terminally incorporative metabolism within the body. The distribution of the tracer in the body differs from choline and FDG, as kidney uptake of F-18 Fluciclovine is negligible, and no activity is found in the urinary tract. There is low native brain uptake compared to FDG, which may enhance detection of brain metastases or primary brain tumors. The more intense native liver and pancreatic uptake seen with this agent would be expected to limit disease detection in those organs. F-18 Fluciclovine has a short synthesis time and a long half-life, which eliminate the need for an onsite cyclotron.

b) 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.

c) F-18 fluciclovine distributes to the liver (14% of administered activity), pancreas (3%), lung (7%), red bone marrow (12%) and myocardium (4%). With increasing time, F-18 fluciclovine distributes to skeletal muscle.

d) Across the first four hours post-injection, 3% of administered radioactivity was excreted in the urine.

e) Across the first 24 hours post-injection, 5% of administered radioactivity was excreted in the urine.

21. NONCLINICAL TOXICOLOGY

a) No long-term studies in animals have been performed to evaluate the carcinogenic potential of fluciclovine.

b) Fluciclovine was not mutagenic *in vitro* in reverse mutation assay in bacterial cells and in chromosome aberration test in cultured mammalian cells, and was negative in an *in vivo* clastogenicity assay in rats after intravenous injection of doses up to 43 mcg/kg. However, F-18 fluciclovine has the potential to be mutagenic because of the F-18 radioisotope.

c) No studies in animals have been performed to evaluate potential impairment of fertility in males or females.

22. CLINICAL STUDIES

a) The safety and efficacy of Axumin were evaluated in two studies in men with suspected recurrence of prostate cancer based on rising PSA levels following radical prostatectomy and/or radiotherapy.

b) Study 1 evaluated 105 Axumin scans in comparison to histopathology obtained by biopsy of the prostate bed and biopsies of lesions suspicious by imaging. PET/CT imaging generally included the abdomen and pelvic regions. The Axumin images were originally read by on-site readers. The images were subsequently read by three blinded independent readers. Table 4 shows the performance of Axumin in the detection of recurrence in each patient scan and, specifically, within the prostatic bed and extra-prostatic regions, respectively. The results of the independent read were generally consistent with one another and confirmed the results of the on-site reads.

c) The detection rate of Axumin seems to be affected by PSA levels. In general, patients with negative scans had lower PSA values than those with positive scans. The detection rate (number with positive scans/total scanned) for patients with a PSA value of less than or equal to 1.78 ng/mL (1st PSA quartile) was 15/25, of which 11 were histologically confirmed as positive.

d) In the remaining three PSA quartiles, the detection rate was 71/74, of which 58 were histologically confirmed. Among the 25 patients in the first PSA quartile, there were 4 false positive scans and 1 false negative scan. For the 74 patients with

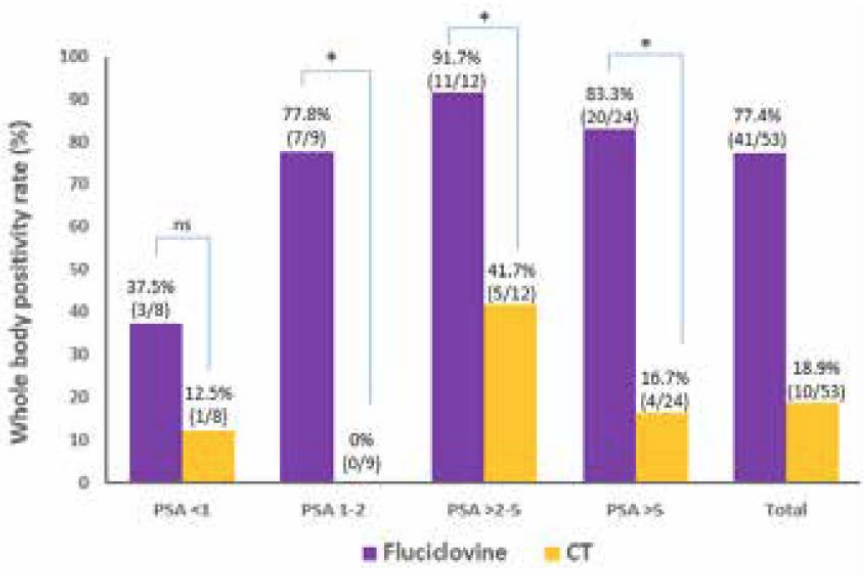
PSA levels greater than1.78 ng/mL, there were 13 false positive scans and no false negative scans.

e) Comparison of ProstaScint and Axumin

Figure 2: Diagnostic performance of fluciclovine and 111In capromab pendetide [11]

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)		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)		10.0%	86.7%	42.9%	50.0%	41.9%

Figure 3: Whole body positivity rate for fluciclovine F 18 and CT in men with biochemically recurrent PCa [11]



f) Comparison of Axumin and CT in men with biochemically recurrent prostate cancer

g) Study 2 evaluated the concordance between 96 Axumin and C11 choline scans in patients with median PSA value of 1.44 ng/mL (interquartile range = 0.78 to 2.8

ng/mL). The C 11 choline scans were read by on-site readers. The Axumin scans were read by the same three blinded independent readers used for Study 1. The agreement values between the Axumin and C11 choline reads were 61%, 67% and 77%, respectively.

23. AXUMIN SCANS

(all scans from Axumin website at www.axumin.com/pdf/AxuminCaseStudies.pdf **)**

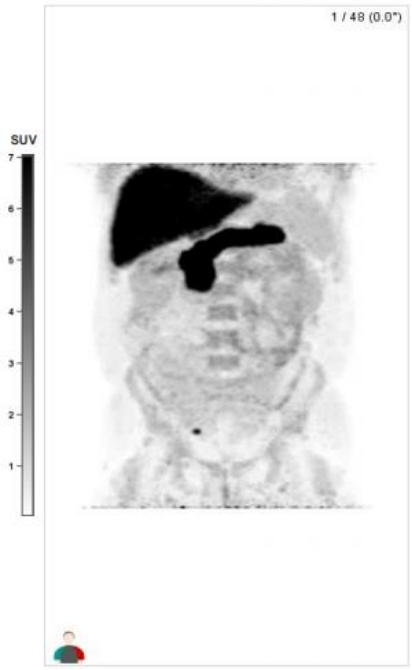
a) Case 1.

Case 1 - Overview

Clinical History	
Age	57
Prior Therapy	Radical prostatectomy and bilateral staging pelvic lymphadenectomy
PSA	0.41 ng/ml
Reason for Scan	Suspected recurrent Prostate Cancer

Acquisition	
PET/CT	GE Discovery 690
Weight	98 kg
Administered Activity	355MBq
Time After Administration	5m 27s
Reconstruction	VPFX

Institution Name: Department of Radiology and Imaging Sciences, Emory University, Atlanta, GA, USA



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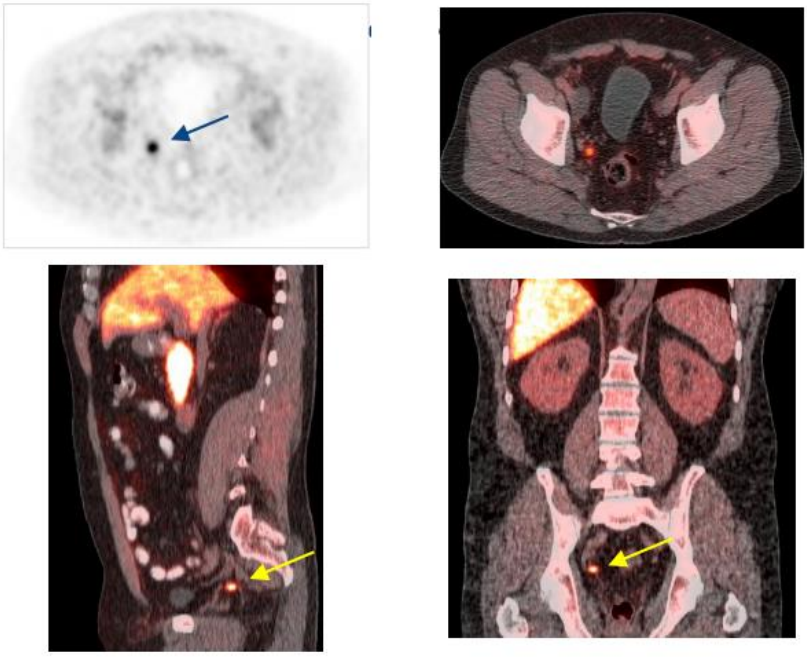


Figure 2: **Internal iliac/pelvic side wall lymph node.**

(PET (Top Left) & PET/CT (Top Right) transaxial and PET/CT (Bottom Left) sagittal and (Bottom Right) coronal)

LN SUV(bw)$_{max}$: *11.9*
Marrow (L3) SUV(bw)$_{mean}$: *3.4*

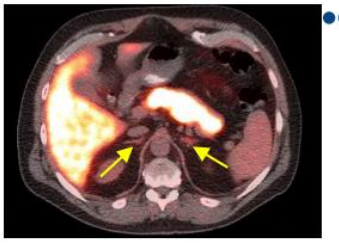


Figure 3: **Adrenal activity - normal variant**

(PET/CT transaxial)

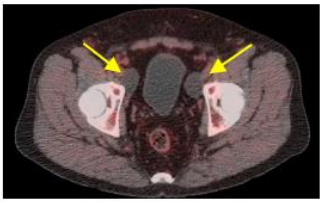


Figure 4: **Benign lymphoceles**

(PET/CT transaxial)

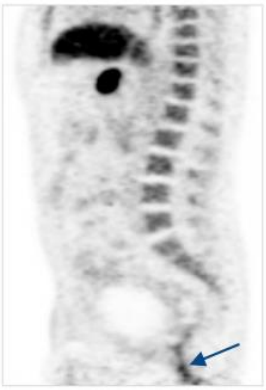
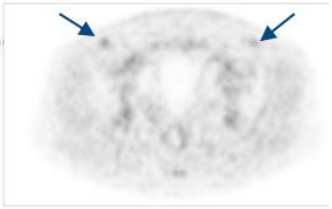


Figure 4: **Rectal activity**

(PET sagittal)



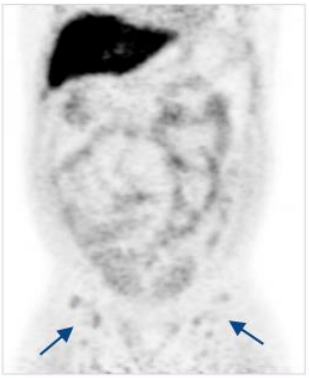


Figure 5: **Benign bilateral inguinal nodes**

(PET (Top) transaxial and (Bottom) coronal)

Case 1 - Results

Imaging Results Summary

- Internal iliac/pelvic side wall lymph node
- Incidental findings
  - Benign bilateral inguinal nodes.
  - Benign bilateral lymphoceles.
  - Adrenal activity - normal variant.
  - Rectal activity.

Case 2 - Overview

Clinical History	
Age	65 y.o.
Primary Stage	T3a N0 M0
Prior Therapy	Radiotherapy (EBRT/IMRT)
PSA	8 ng/ml
Prior Imaging	Planar Bone Scan, CE-CT, Pelvic & Prostate MRI
Reason for Scan	Suspected recurrent Prostate Cancer
Acquisition	
PET/CT	Siemens Biograph Truepoint
Weight	75 kg
Administered Activity	371MBq
Time After Administration	4m 53s
Reconstruction	PSF, ToF, 2i21s

Institution Name: Oslo University Hospital HF, Radiumhospitalet, Oslo

b) Case 2

Case 2

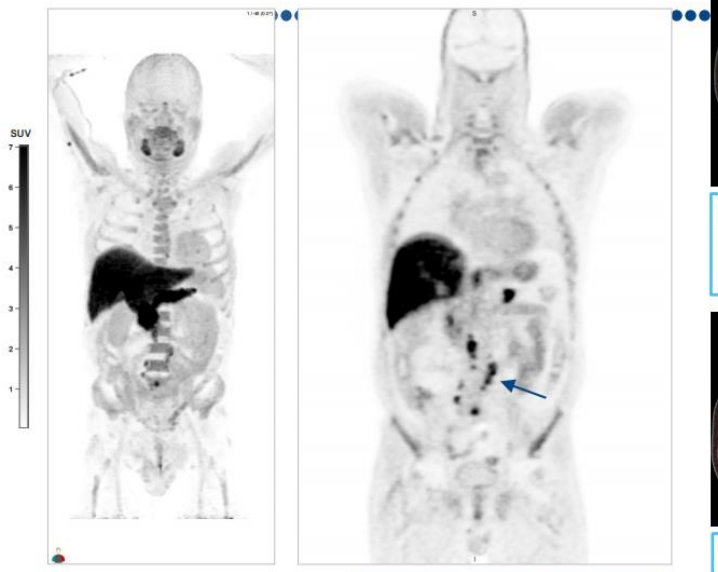


Figure 1:

Figure 2: **Retroperitoneal malignant nodes**
(PET coronal)

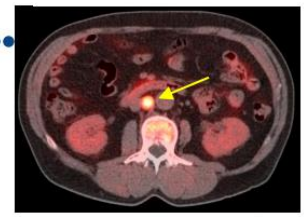


Figure 3: **Retroperitoneal malignant node**
(PET/CT transaxial)

LN SUV(bw)$_{max}$:	*8.3*
LN short axis :	*1.2 cm*
Marrow (L3) SUV(bw)$_{mean}$:	*4.0*

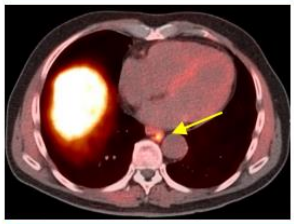
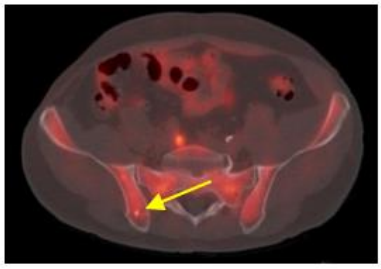
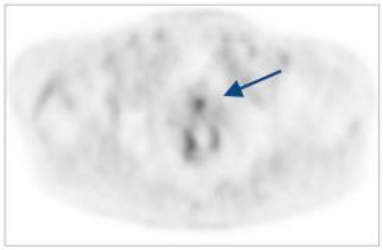


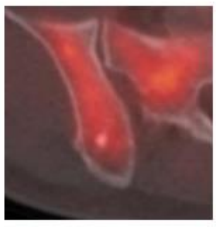
Figure 4: **Thoracic malignant node**
(PET/CT transaxial)

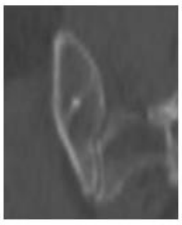
LN SUV(bw)$_{max}$:	*6.0*
LN short axis :	*0.6 cm*
Blood Pool (Aorta) SUV(bw)$_{mean}$:	*1.4*

Case 2









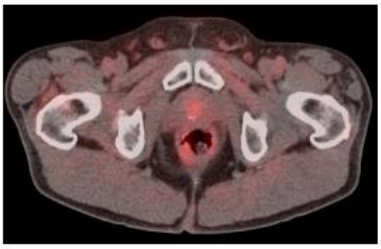


Figure 6: **Benign appearing right iliac sclerosis**

(PET/CT (Top & Bottom Left) transaxials and CT (Bottom Right) coronal)

Figure 7: **Probable benign mild diffuse midline prostate activity**

(PET (Top) and PET-CT (Bottom) transaxials)

Case 2

Figure 8: **Incidental finding: Right arm vein focal activity**

(PET (Top) and PET-CT (Bottom) transaxials)

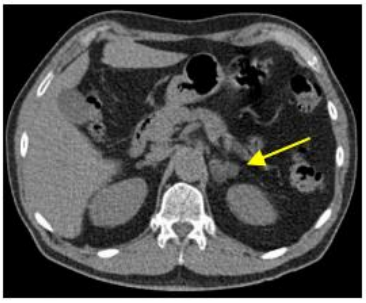


Figure 5: **Incidental finding: Left adrenal low density hyperplasia or adenoma**

(PET (Top) and CT (Bottom) transaxials)

Adrenal $SUV(bw)_{max}$:	*3.5*
Marrow (L3) $SUV(bw)_{mean}$:	*4.0*

Case 2 - Results

Imaging Results Summary

- Extensive retroperitoneal malignant nodes extending into thorax
- Probable benign mild diffuse midline prostate activity.
- Incidental:
  - Left adrenal hyperplasia/adenoma
  - Right arm vein focal activity
  - Benign appearing right iliac sclerosis.

Management Plan

- Intended: Curative
- Revised: Palliative

c) Case 3

Case 3 - Overview

Clinical History	
Age	67 y.o.
Primary Stage	T2c N0 M0
Prior Therapy	Radiotherapy (EBRT/IMRT) and ADT
PSA	3.4 ng/ml
Gleason	3+4 (biopsy)
Prior Imaging	Planar bone scan; pelvic & prostate MRI (Extraprostatic region negative)
Acquisition	
PET/CT	Siemens Biograph Truepoint
Weight	96 kg
Administered Activity	369 MBq
Time After Administration	5m 9s
Reconstruction	PSF, ToF, 2i21s

Institution Name: Oslo University Hospital HF, Radiumhospitalet, Oslo

Case 3

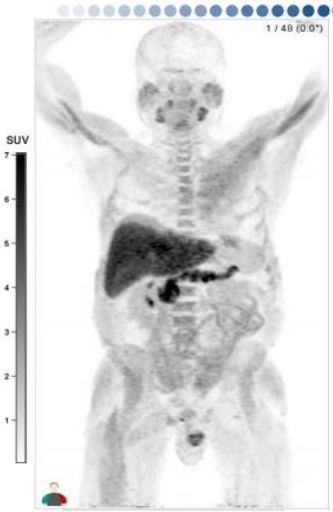
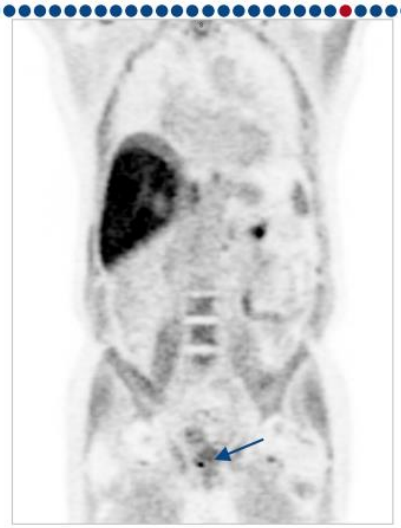
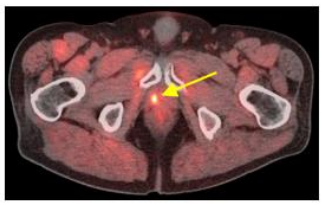


Figure 1: **MIP** *(Click to Play)*





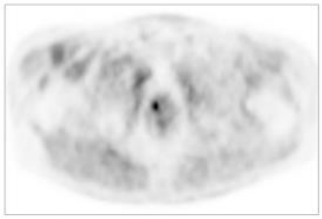


Figure 2: **Prostate (right apex) focal malignant uptake**

(PET (Left) coronal & (Bottom Right) transaxial & PET/CT (Top Right) transaxial)

Prostate $SUV(bw)_{max}$: 7.4
Marrow (L3) $SUV(bw)_{mean}$: 3.7

Case 3 - Results

Imaging Results Summary

- Prostate (right apex) focal uptake

Histopathology

- Biopsy positive right apex

Management Plan

- Intended: Curative – salvage brachytherapy
- Revised: (No revision)
- PSA nadir <0.2 ng/ml

d) Case 4

Case 4

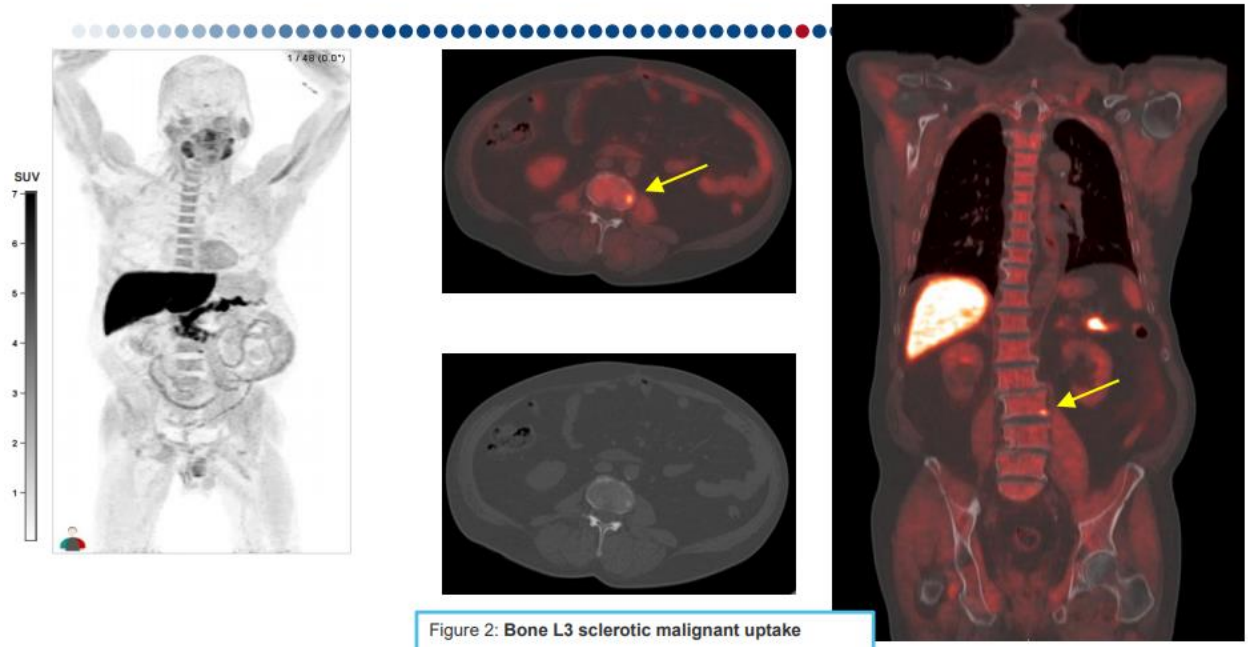


Figure 2: **Bone L3 sclerotic malignant uptake**

(PET/CT (Top Left) transaxial & (Bottom Right) coronal & CT (Bottom Right) transaxial)

L3 focal uptake SUV(bw)$_{max}$: 7.6
Marrow (Normal) SUV(bw)$_{mean}$: 3.8

Figure 1

Case 4 - Overview

Clinical History	
Age	68 y.o.
Primary Stage	T3 (Pathological) N0 M0
Prior Therapy	Radical prostatectomy
PSA	3.9 ng/ml
Gleason	4+5
Prior Imaging	Bone Marrow MRI, Planar Bone Scan
Reason for Scan	Suspected recurrent prostate cancer
Acquisition	
PET/CT	Siemens Biograph Truepoint
Weight	85 kg
Administered Activity	318 MBq
Time After Administration	4m 35s
Reconstruction	PSF, ToF, 2i21s

Institution Name: Oslo University Hospital HF, Radiumhospitalet, Oslo

Case 4 - Results

Imaging Results Summary

- Bone L3 sclerotic malignant uptake
- Post-op bladder tracer activity.
- Incidental mucocele left maxillary sinus, right renal cysts.

Follow-up Imaging

- Bone marrow MRI: Positive at L3 & also at T12

Management Plan

- Intended: Palliative Radiotherapy (EBRT/IMRT) to Prostate & Vesicles
- Revised: No revision

e) Case 5

Case 5 - Overview

Clinical History	
Age	66 y.o.
Primary Stage	T2c (Pathological) N0 M0
Prior Therapy	Radical prostatectomy, negative lymphadenectomy
PSA	0.59 ng/ml
Gleason	4+5
Prior Imaging	Negative MRI (apart from Schwannoma right sacrum); planar bone scan
Acquisition	
PET/CT	Siemens Biograph Truepoint
Weight	122 kg
Administered Activity	370 MBq
Time After Administration	4m 52s
Reconstruction	PSF, ToF, 2i21s

Institution Name: Oslo University Hospital HF, Radiumhospitalet, Oslo

Case 5

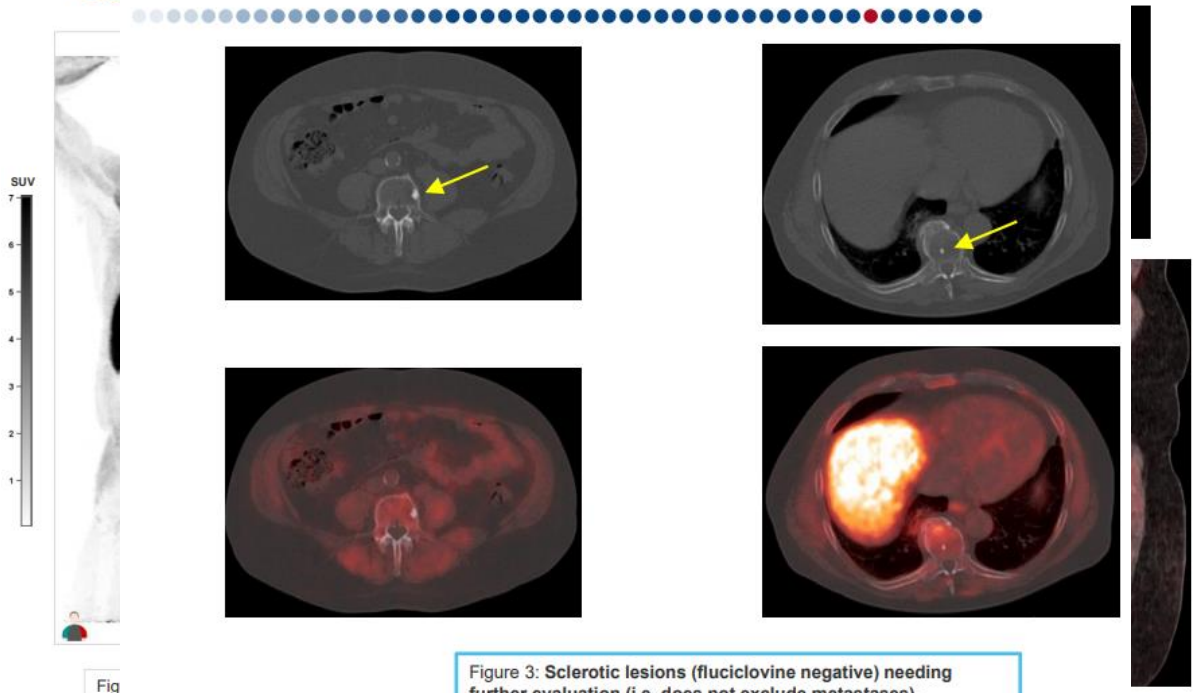


Figure 3: **Sclerotic lesions (fluciclovine negative) needing further evaluation (i.e. does not exclude metastases).**

(CT (Top) & PET/CT (Bottom) transaxials)

Case 5

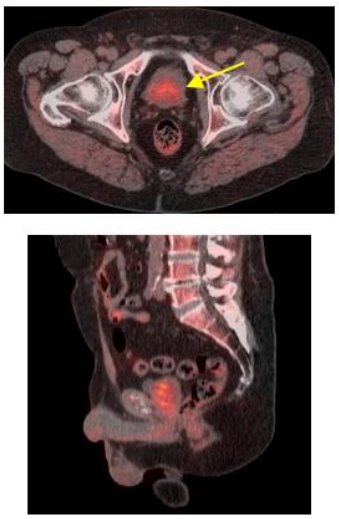


Figure 4: **Bladder activity**

(PET/CT (Top) transaxial & PET/CT (Bottom) sagittal)

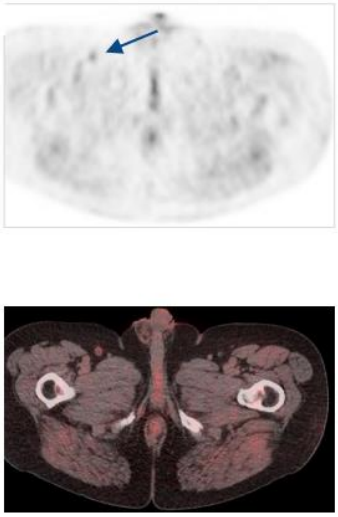


Figure 5: **Mild benign inguinal nodal activity.**

(PET (Top) & PET/CT (Bottom) transaxials)

Case 5 - Results

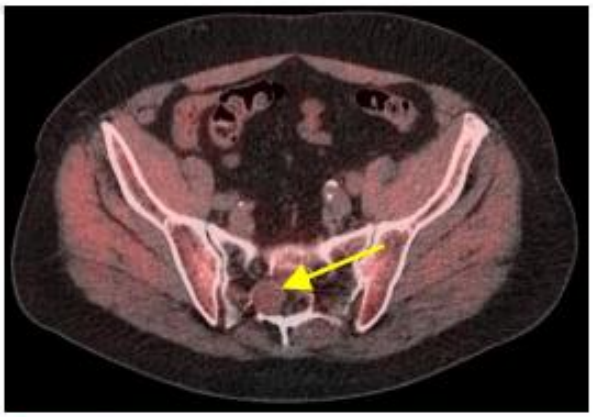


Figure 6: **Benign left lymphocele.**

(PET/CT transaxial)

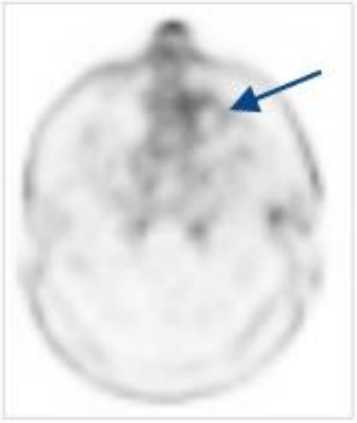


Figure 7: **Sinus disease**

(PET transaxial)

Case 5 - Results

Imaging Results Summary

- Intense small left presacral node (3x4 mm)
- Sclerotic lesions (fluciclovine negative) needing evaluation (i.e. does not exclude metastases).
- Mild symmetric inguinal nodal activity.
- Incidental:
  - Benign left lymphocele.
  - Sinus disease.
  - Bladder activity.

Management Plan

- Intended: Curative - Radiotherapy
- Revised: Palliative - ADT