

Part 1: PET Radiopharmaceuticals: An Overview

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1. A PET radiopharmaceutical is composed of a biologically active molecule and a positron-emitting radionuclide. The most commonly used radionuclides for PET imaging include ^{11}C , ^{15}O , ^{13}N , ^{18}F , ^{68}Ga and ^{82}Rb (Table 1). In addition to radiation issues, short half-lives of these positron emitters (78 sec~110 min) result in unavoidable limitations on production, quality control and clinical use of PET radiopharmaceuticals.

2. PET Radionuclides and their Properties

Nuclide	Half-life	β^+ (%)	Max E_{β^+} (MeV)	Max β^+ range (mm)	Production route
^{11}C	20 min	99	0.96	4.1	Cyclotron
^{15}O	123 sec	100	1.19	5.1	Cyclotron
^{13}N	10 min	100	1.72	7.3	Cyclotron
^{18}F	110 min	97	0.635	2.4	Cyclotron
^{68}Ga	68 min	95	3.35	14.1	^{68}Ge Generator
^{82}Rb	75 sec	99	1.534	6.5	^{82}Sr Generator

3. What is PET?

"PET" stands for Positron Emission Tomography. This technique allows us to measure organ function while the patient is comfortable, conscious and alert.

PET represents a step forward in evaluating function of internal organs and in diagnosing malignant tumors. Unlike X-rays or a CT scan, which show only structural details within the body, PET excels at determining organ function.

We are very interested in organ function because functional change often predates structural change in tissues, such as tissue metabolism and physiologic functions.

4. In oncology, PET is the only modality that can accurately image many organs of the body with a single pass to allow determination of malignancy.

PET helps determine whether a primary cancer has metastasized to other parts of the body.

5. Value of PET

- permits cost effective, whole-body metastatic surveys
- avoids biopsies for low grade tumors
- permits non-invasive differentiation of tumors from radiation necrosis
- permits early change in course of ineffective chemotherapy
- avoids unnecessary diagnostic and therapeutic surgeries.

6. PET Radiopharmaceuticals

PET radiopharmaceuticals commonly incorporate short-lived radionuclides of elements encountered in nature; these compounds are generally chemically equivalent to or close analogs of naturally occurring compounds; e.g.,

^{15}O ($t_{1/2} = 2$ min), ^{13}N ($t_{1/2} = 10$ min),

^{11}C ($t_{1/2} = 20$ min), ^{18}F ($t_{1/2} = 110$ min).

produce no physiological or pharmacological effects; inherently have a high degree of safety.

No documented adverse reactions of clinical significance after millions of studies performed in humans worldwide

7. PET Radiopharmaceuticals: Radiation Exposure

radiation exposure from a PET imaging procedure is comparable to that of some Nuclear Medicine diagnostic procedures using gamma-emitting radiopharmaceuticals, many of which have been in use for decades.

8. PET Radiopharmaceuticals: Underlying Principle

the radioactive substance used to evaluate the metabolic or physiologic process must participate in, but not alter, the process it is attempting to measure.

They provide functional images of the human body.

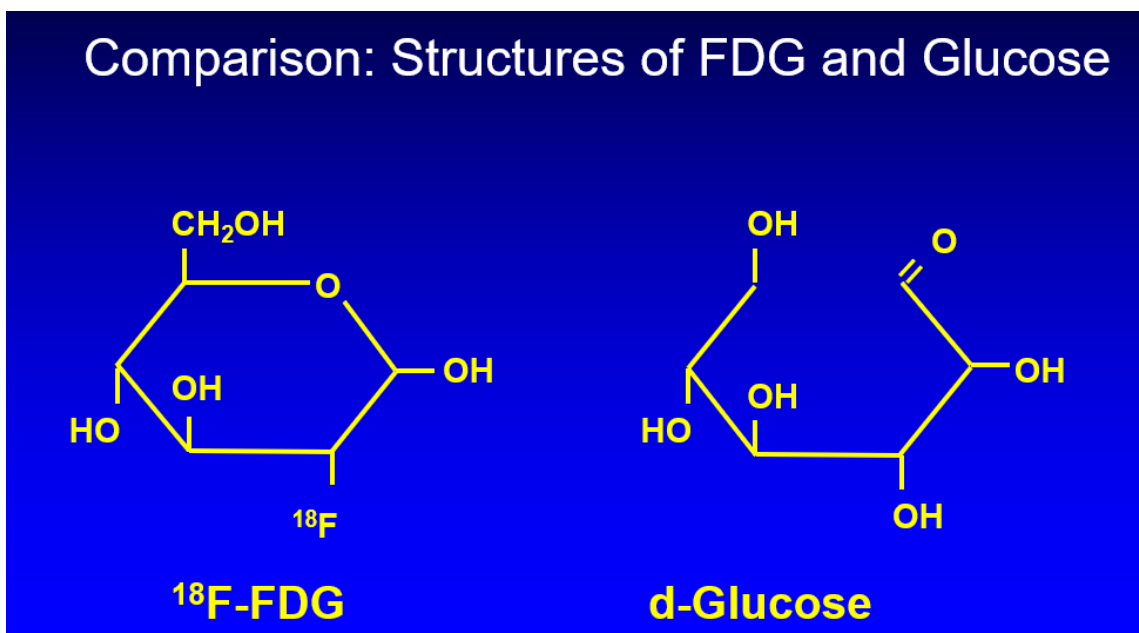
9. Many PET radiopharmaceuticals are radiolabeled versions of substances commonly present in the body, e.g., ^{13}N -ammonia, ^{15}O -water, ^{11}C -acetate, ^{11}C -methionine, ^{18}F -fluoride.

The most widely used radiopharmaceutical worldwide is ^{18}F -FDG. Similar in structure to glucose, this compound is used in PET due to the ubiquitous use of glucose by the human body.

10. Production of F-18 FDG

FDG is labeled with ^{18}F , a cyclotron produced radioisotope with a half life of approximately 110 minutes.

11. Comparison: Structures of FDG and Glucose



12. ^{18}F -FDG: Mechanism of Uptake

Called **metabolic trapping**, based on the fact that tumors have higher metabolic rate than normal tissue.

Structures of FDG and glucose are similar enough for there to be uptake, but different enough that metabolism cannot take place.

13. Examples of: ^{11}C PET Radiopharmaceuticals

- CO
- Raclopride
- N-methylspiroperidol
- hydroxyephedrine
- acetate
- L-deprenyl
- L-methionine
- thymidine
- flumazenil

14. Examples of: ^{13}N , ^{15}O PET Radiopharmaceuticals

- ^{13}N -ammonia
- ^{15}O -water
- ^{15}O -butanol

15. Examples of F-18 PET Radiopharmaceuticals:

- fluoride
- FDG
- 6-fluoroDOPA
- fluoromethane
- N-methylspiroperidol
- 6-fluoronorepinephrine
- 14-fluoro-6-thiaheptadecanoate
- 16-fluoro-17 β -estradiol
- fluoroethyl-oubain
- fluoromisonidazole

16. Examples of PET Radiopharmaceuticals using other radionuclides

- $^{82}\text{Rb}^+$ ion
- ^{68}Ga -EDTA
- ^{62}Cu -PTSM
- ^{76}Br -bromolisuride
- ^{124}I -monoclonal antibody

17. PET Reimbursement Issues

FDA and Medicare approval of the radiopharmaceuticals used in PET has always been a prerequisite for public-sector reimbursement.

18. PET Pharmaceuticals: Clinical Utility

- Most commonly used in oncology to detect and evaluate tumors
- useful in cardiology to assess myocardial viability
- also useful in the brain for diagnosis of a variety of neurological conditions

19. General Tumor Imaging with FDG

FDG-PET is effective in the diagnosis and staging of the following cancers: brain tumor, breast cancer, colorectal cancer, head and neck cancer, lung cancer, lymphoma, melanoma, musculoskeletal tumors, ovarian cancer, pancreatic cancer, and thyroid cancer.

20. Approved indications for whole-body ^{18}F -FDG PET scans

- evaluation of recurrent colorectal Ca in patients with rising CEA levels
- staging and characterization of lymphoma (both Hodgkin's and non-Hodgkin's lymphoma, when performed as an alternative to a gallium scan)
- detection of recurrent or metastatic melanoma prior to surgery
- Characterization of solitary pulmonary nodules
- Initial staging of non-small cell lung cancer

21. PET in Cardiology

Cardiology enables physicians to:

- screen for coronary artery disease
- assess flow rates and flow reserve
- distinguish viable from nonviable myocardium for bypass and transplant candidates.

22. PET in Neurology

- PET enables assessment of Alzheimer's and other dementias, Parkinson's, and Huntington's
- Localizes epileptic foci for qualifying and identifying the site for surgical intervention
- Permits characterization, grading, and assessment of possible brain tumor recurrence

PART 2: Specific PET Radiopharmaceuticals: Clinical Utility

23. **^{11}C -Sodium Acetate**

- Acetate is a molecule rapidly taken up by cells and converted into acetyl-CoA and participates in cytoplasmic lipid synthesis, which is believed to be increased in tumors.
- ^{11}C -Sodium Acetate has been proved to be clinically useful in prostate cancer, hepatocellular carcinoma, lung cancer, nasopharyngeal carcinoma, renal cell carcinoma, bladder carcinoma and brain tumors.
- has been used to clinically measure myocardial oxygen consumption

24. **^{13}N -ammonia (NH_3)**

- a useful ^{13}N -labeled PET imaging agent for assessing regional blood flow in tissues
- a well-validated radiotracer for clinical management of patients with coronary artery disease
- recently ^{13}N - NH_3 has been used in prostate cancer patients, because the up-regulation of NH_3 during *de novo* glutamine synthesis was known in tumors.
- ^{13}N - NH_3 is also used for elucidation of NH_3 metabolism in patients with hepatic encephalopathy

25. **^{15}O -CO (Carbon Monoxide)**

- For institutions with a cyclotron, ^{15}O -CO is one of the most common tracers used for noninvasively measuring oxygen consumption and blood volume to clarify the relationship between Mean Blood Flow and oxygen extraction fraction (OEF), because both OEF and MBF are important indicators in describing myocardial function
- ^{15}O -CO is valuable for the evaluation of acute stroke patients.

26. ^{15}O - H_2O

- Although the short half-life (123 sec) of ^{15}O creates challenges in clinical use, ^{15}O - H_2O is still the preferred tracer because of its ease of production from a generator, its effectiveness, and safety for patient use.
- Particularly, PET with ^{15}O - H_2O has been a standard method and most reliable approach for quantitative measurement of cerebral blood flow (CBF).
- ^{15}O - H_2O has been used to clinically investigate cerebral and myocardial perfusion as well as tumor perfusion.

27. ^{18}F -fluorodeoxyglucose (FDG)

- Since its synthesis in 1976, ^{18}F -FDG has been the most widely used radiotracer for PET studies in neuroscience, cardiology and oncology.
- After FDA approval in 1997, ^{18}F -FDG with PET or PET/CT scanner became an established imaging tool in the clinical assessment of many neoplasms, as well as the nonmalignant diseases including dementia, myocardial ischaemia, inflammation and infection

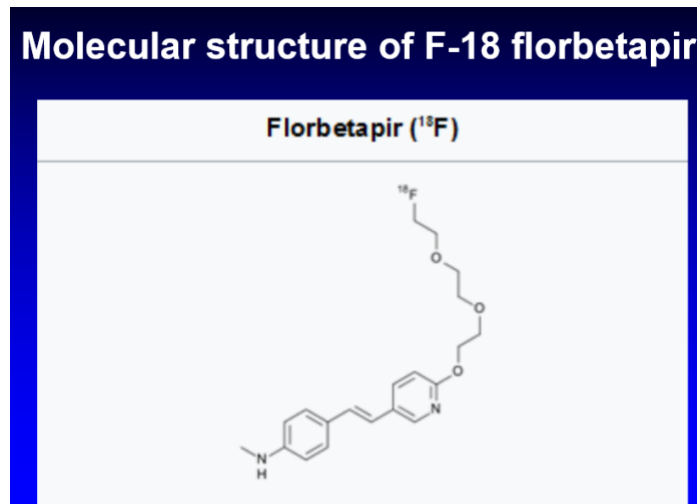
28. Clinical Utility of ^{18}F -fluorodeoxyglucose (FDG)

- **Neurology:** Alzheimer's Disease, pre-surgical evaluation for epileptogenic foci (85–90% accuracy).
- **Cardiology:** Assessment of myocardial viability prior to cardiac surgery to identify high-risk patients and to select patients who will benefit from bypass
- **Oncology:** Tumor Evaluation; differentiate tumor from necrosis; tumor staging; determining malignant vs benign; Lung nodules, primary breast and colon cancers; tumor monitoring and response to therapy.
- **Infection and Inflammation:** Orthopedic infections
- **Psychiatry:** Evaluation of schizophrenia, depression

29. ^{18}F Florbetapir

- Indication: to estimate β -amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer's disease (AD) and other causes of cognitive decline.

- A positive Amyvid scan does not establish a diagnosis of AD or other cognitive disorder.
- Typical injected dose: 10 mCi
- **Molecular structure of F-18 florbetapir**



Imaging: Obtain 10-min PET images starting approximately 30 to 50 minutes after IV injection

Radiation absorbed whole body dose from a 10 mCi dose of Amyvid is 7 mSv = 700 mRem

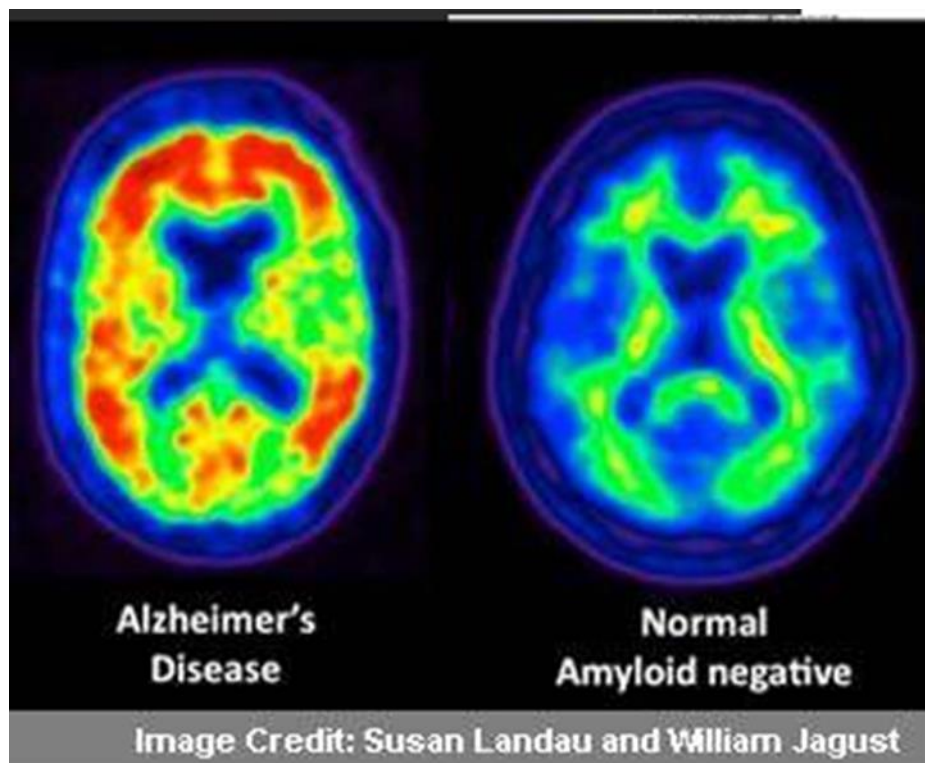
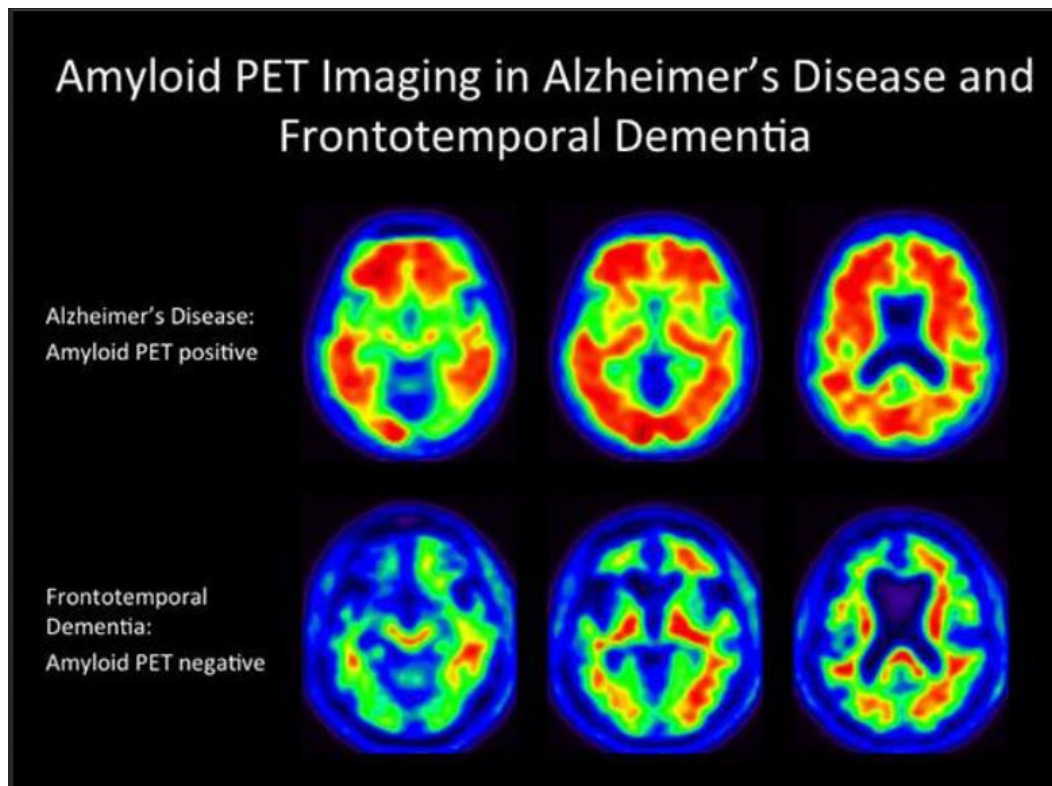
Mechanism of Action: F-18 Florbetapir binds to β -amyloid plaques and the annihilation photons produce a signal that is detected by a PET scanner.

Pharmacodynamics: Following intravenous injection, F-18 Florbetapir diffuses across the human blood-brain barrier and produces a radioactivity signal detectable throughout the brain.

Interpretation

A negative Amyvid scan indicates sparse to no neuritic plaques, and is inconsistent with a neuropathological diagnosis of AD at the time of image acquisition; a negative scan result reduces the likelihood that a patient's cognitive impairment is due to AD. A positive Amyvid scan indicates moderate to frequent amyloid neuritic plaques; neuropathological examination has shown this amount of amyloid neuritic plaque is present in patients with AD but may also be present in patients with other types of neurologic conditions as well as older people with normal cognition.

Images of F-18 Florbetapir



30. **^{18}F -FDOPA (fluorodopamine)**

- Dopamine is an intermediate in the catecholamine synthesis pathway. One of the ^{18}F -radiolabeled analogs, ^{18}F -FDOPA, was first reported as a PET tracer for imaging pre-synaptic dopaminergic functions in 1983.
- Subsequent studies revealed the utility of ^{18}F -FDOPA for the visualization of various peripheral tumors using PET, e.g., neuroendocrine cell-related malignancies like neuroendocrine tumors, pheochromocytoma, pancreatic adenocarcinoma and neuroblastoma with good diagnostic efficiency and sensitivity.

31. **^{18}F -FMISO (fluoromisonidazole)**

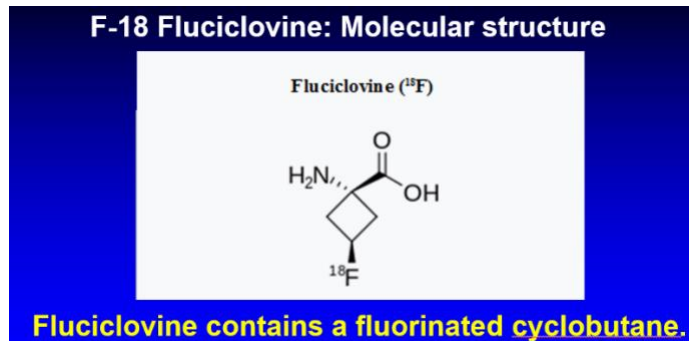
- Hypoxia (insufficient oxygen availability) is an important prognostic indicator of response to either chemotherapy or radiation therapy; it is also an independent factor for predicting the metastases tendency of a tumor cell.
- ^{18}F -FMISO is the most established agent for assessing hypoxia and has been used for cancer imaging over the past 30 y for glioblastoma multiforme, non-small-cell lung Ca, & head and neck tumors.
- In addition, high accuracy of ^{18}F -FMISO PET imaging for determining the duration of survival without relapses and for predicting the radiotherapy efficiency in patients with malignant tumors of various localizations has been reported

32. **^{18}F -NaF (Na fluoride)**

- The bone is the most common site of tumor metastases next to the lung and liver. Therefore, early and accurate diagnosis of metastatic bone disease plays an important role in developing an appropriate therapeutic strategy.
- ^{18}F -NaF was introduced in 1962 and approved by FDA in 1972. It is a high sensitivity bone-seeking PET agent and is considered an excellent substitute for traditionally used $^{99\text{m}}\text{Tc}$ -labeled tracers, because of its negligible protein binding, rapid blood pool clearance, and high tumor to background ratio.
- Additionally, uptake of ^{18}F -NaF reflects blood flow and bone remodeling and use of ^{18}F -NaF has been proposed for detection of benign and malignant osseous abnormalities that allows the regional characterization of lesions in metabolic bone diseases.

33. PET Scan with F-18 Fluciclovine

Molecular Structure:



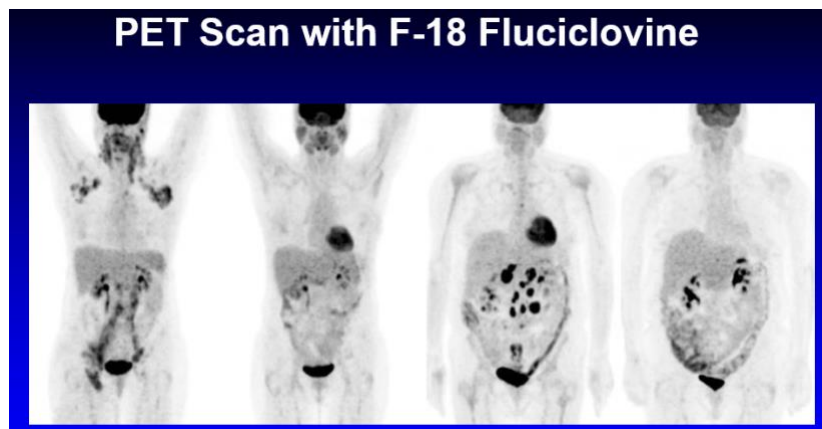
Indications:

F-18 Fluciclovine is a radioactive diagnostic agent indicated for positron emission tomography (PET) imaging in men with suspected prostate cancer recurrence based on elevated blood prostate specific antigen (PSA) levels following prior treatment.

Mechanism of Uptake:

Fluciclovine F-18 is a synthetic amino acid transported across mammalian cell membranes by amino acid transporters, such as LAT-1 and ASCT2, which are upregulated in prostate cancer cells. Fluciclovine F-18 is taken up to a greater extent in prostate cancer cells compared with surrounding normal tissues.

PET Scan with F-18 Fluciclovine



34. ⁶⁸Ga-citrate

- Bacterial infection is still one of the major worldwide causes for human morbidity and mortality. Because of the trapping of gallium in the extravascular compartment of inflammatory or infectious sites with the increased capillary permeability, and the iron-like binding characteristics in bacterial siderophores and activated lactoferrin in neutrophils, gallium is thought to be indirectly taken up by macrophages or directly taken up by bacteria.
- ⁶⁷Ga-Citrate has been used for clinical imaging of infection and inflammation since 1967 and ⁶⁸Ga-Citrate since 1984.
- The utility of ⁶⁸Ga-Citrate includes the monitoring of osteomyelitis, diskitis, intra-abdominal infection, tuberculosis and interstitial nephritis, as well as the localization of infection in patients with cellulitis and abscesses.

35. ⁶⁸Ga-DOTA-TOC

- NETs arise from neuroendocrine cells and are slow-growing tumors with 75% of overall 5-y survival, which is strongly dependent on stage and grade of the tumor. Because NETs have been known for their unique overexpression of somatostatin receptors on the tumor cells, PET radiopharmaceuticals targeting these receptors provide a promising and useful approach for both diagnostic imaging and further peptide receptor radionuclide therapy (PRRT), such as DOTA-TOC).
- ⁶⁸Ga-DOTA-TOC has been recognized for its affinity toward both the type 2 somatostatin receptor (SSTR2) and the type 5 somatostatin receptor (SSTR5). ⁶⁸Ga-DOTA-TOC was the first PET radiopharmaceutical to clinically localize in NETs in 2001 and has been widely used to assist in therapy planning and accurate diagnosis of NETs patients.
- In addition, this drug is valuable for neuroectodermal tumors, Hurthle cell thyroid carcinoma, prostate cancer patients with bone metastases and autoimmune thyroid disease like Graves' disease and Hashimoto's disease.

36. ⁸²Rb-chloride

- Just like ¹³N-NH₃ and ¹⁵O-H₂O, ⁸²Rb-chloride has a directly proportional relationship between its uptake and MBF. In addition, several studies have demonstrated the good diagnostic accuracy of ⁸²RbCl in monitoring of cardiac flow.
- The ⁸²Sr/⁸²Rb generator (CardioGen-82®) has been approved by FDA for clinical cardiac imaging since 1989. Therefore, production and administration of ⁸²RbCl can be easily coordinated clinically. Rubidium chloride Rb-82 injection is

a myocardial perfusion agent that is useful in distinguishing normal from abnormal myocardium in patients with suspected myocardial infarction.

- Rubidium chloride Rb-82 injection obtained from Cardiogen-82 Generator) is intended only for intravenous administration utilizing an appropriate infusion system that is labeled for use with the generator. The usual adult (70 kg) dose (single injection) is 1480 MBq (40 mCi) with a range of 1110-2220 MBq (30-60 mCi). The dose must be administered at a rate of 50 mL/minute not to exceed a cumulative volume of 200 mL.
- The estimated absorbed radiation doses to an average adult patient (70 kg) from an intravenous injection of a recommended dose of 2220 MBq (60 mCi) of rubidium Rb 82 are shown in Table 5.
- The advantages of $^{82}\text{RbCl}$ cardiac imaging include its ability to accurately quantify MBF while delivering a low radiation dose for a rest/stress test due to its very short half-life of 75 sec.

37. Sr-82/Rb-82 Generator

- Cardiogen-82 (Rb-82 generator) is a diagnostic aid used for PET imaging of the myocardium under rest or pharmacologic stress conditions to evaluate regional myocardial perfusion in adult patients with suspected or existing coronary artery disease.



- Cardiogen-82® Generator is supplied in the form of strontium Sr 82 adsorbed on a hydrous stannic oxide column with an activity of 90-150 millicuries Sr-82 at calibration time. The generator is encased in a lead shield surrounded by a labeled plastic container and is intended for use only with an appropriate, properly calibrated infusion system labeled for use with the generator.
- CardioGen-82 provides a means for obtaining sterile nonpyrogenic solutions of rubidium Rb-82 chloride injection.

QC Testing of the Sr-82/Rb-82 Generator

- Record each generator eluate volume, including waste and test volumes, and keep a record of the cumulative eluate volume.
- Determine Rb-82, Sr-82, Sr-85 in the generator eluate once a day, prior to any drug administration

QC Specifications: Sr-82/Rb-82 Generator

- When eluted at a rate of 50 mL/minute, each generator eluate at the end of elution should not contain more than 0.02 mCi of Sr-82 and not more than 0.2 mCi of Sr-85 per mCi of Rb-82 chloride injection, and not more than 1 mg of tin per mL of eluate.

Physical Characteristics of Rb-82

- Rb-82 decays by β^+ emission (95.5%) and EC (4.5%) It has a half-life of 75 sec. β^+ emission produces annihilation radiation. Both decay modes result in formation of stable Kr-82.
- The first half-value layer is 0.7 cm of lead. The first tenth value layer is 2.3 cm.

Clinical Utility of the Sr-82/Rb-82 Generator

For rest imaging:

- Administer a single (“rest”) Rb-82 chloride dose; start imaging 60-90 sec after completion of the infusion of the rest dose and acquire images for 5 minutes.

For stress imaging:

- Begin the study 10 min after completion of the resting dose infusion, to allow for sufficient Rb-82 decay;
- Administer a pharmacologic stress agent in accordance with its prescribing information;
- After an interval of 3 min, infuse a single stress Rb-82 chloride dose; start imaging 60-90 sec after completion of the stress Rb-82 chloride dose infusion and acquire images for 5 min.

To correct for physical decay of strontium Sr-82: the fractions that remain at selected intervals after the time of calibration are shown in Table 3.

TABLE 3

Physical Decay Chart: Sr-82 half-life 25 days					
Days	Fraction Remaining	Days	Fraction Remaining	Days	Fraction Remaining
0*	1.000	11	0.737	21	0.559
1	0.973	12	0.717	22	0.543
2	0.946	13	0.697	23	0.529
3	0.920	14	0.678	24	0.514
4	0.895	15	0.660	25	0.500
5	0.871	16	0.642	26	0.486
6	0.847	17	0.624	27	0.473
7	0.824	18	0.607	28	0.460
8	0.801	19	0.591	29	0.448
9	0.779	20	0.574	30	0.435
10	0.758				

*Calibration time

To correct for physical decay of rubidium Rb-82

- the fraction of rubidium chloride Rb-82 injection remaining in all 15 second intervals up to 300 seconds after time of calibration are shown in Table 4.

TABLE 4

Physical Decay Chart: Rb-82 half-life 75 seconds			
Seconds	Fraction Remaining	Seconds	Fraction Remaining
0*	1.000	165	.218
15	.871	180	.190
30	.758	195	.165
45	.660	210	.144
60	.574	225	.125
75	.500	240	.109
90	.435	255	.095
105	.379	270	.083
120	.330	285	.072
135	.287	300	.063
150	.250		

*Elution time

Pharmacology

- Following intravenous administration, rubidium Rb-82 rapidly clears the blood and is extracted by myocardial tissue in a manner analogous to potassium. In human studies, myocardial activity was noted within the first minute after injection. When areas of myocardial infarction are detected with rubidium chloride Rb-82 injection, they are visualized within two to seven minutes after injection as photon-deficient or "cold areas" on the myocardial scan. Uptake is also observed in kidney, liver, spleen, and lung.

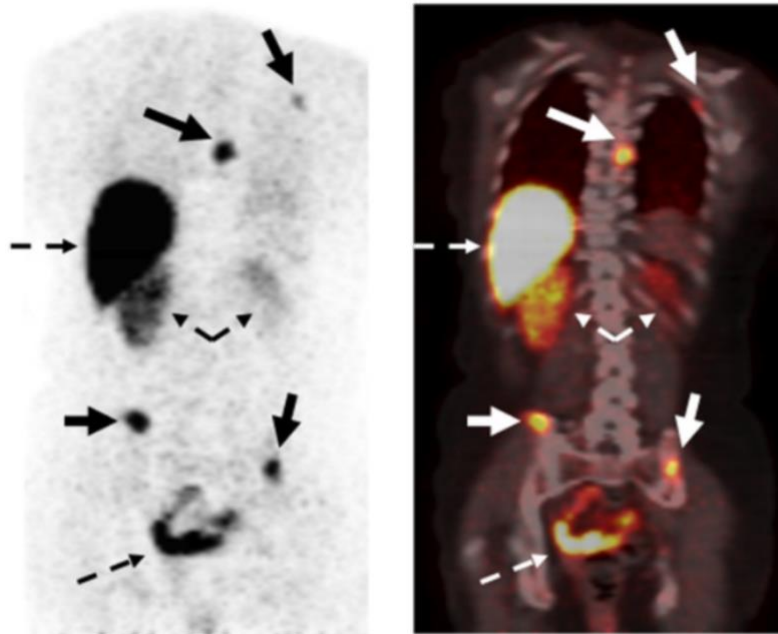
38. ¹⁸F-fluorothymidine (¹⁸F-FLT)

- Cellular proliferation plays an important role in cancer and is a prime imaging target of PET radiopharmaceuticals, with the aim of targeting of DNA synthesis. This drug has been designed to trap its phosphorylated metabolite within cells. Up to now, ¹⁸F-FLT has been widely investigated in an oncologic setting comprising tumor detection, staging, restaging, & response assessment to treatment. ¹⁸F-FLT imaging has several clinical advantages: it is noninvasive, produces 3D tumor images and simultaneously detects multiple tumor sites. Also, ¹⁸F-FLT can evaluate tumor heterogeneity in day-to-day practice.

39. F-18 Fluoroestradiol

- F-18 Fluoroestradiol, also known as 16 α -fluoroestradiol and sold under the brand name Cerianna, is a radioactive diagnostic agent indicated for use with positron emission tomography imaging. It is a chemical analog of estrogen and is used to detect estrogen receptor-positive breast cancer lesions.

Image of F-18 Estradiol in Breast Cancer Patient

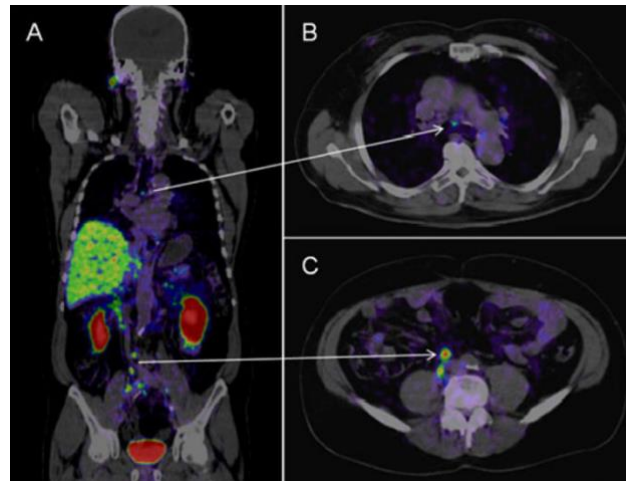


Example of 16 α -[18F]-fluoro-17 β -estradiol (FES) positron emission tomography (PET) imaging with 18F-fluoroestradiol. (Left) PET emission image. (Right) PET-computed tomography fusion image. In the emission image, increased tracer uptake appears dark, whereas in the fusion image, increased uptake appears white/yellow. Images show multiple sites of estrogen receptor-expressing bone metastases along with normal uptake and excretion of FES into the liver, kidneys, and bowel (dashed arrows).

40. Ga-68 PSMA-11

- On December 1, 2020, the Food and Drug Administration (FDA) approved the radioactive tracer Gallium (Ga) 68 PSMA-11 for use in PET imaging of men with prostate cancer. Under the approval, the tracer can be used in PET imaging for prostate cancer that is suspected of having spread to other parts of the body. Ga 68 PSMA-11 can also be used in men who have been treated successfully for prostate cancer but, because of elevated PSA levels, their disease is suspected of having returned.
- PSMA stands for **P**rostate **S**pecific **M**embrane **A**ntigen

Images from a Ga-68 PSMA PET-CT in a man with prostate cancer shows tumors in lymph nodes in the chest and abdomen. Credit: Adapted from Int J Mol Sci. July 2013.



41. ¹⁸F-Flutemetamol

- Flutemetamol is a PET scanning radiopharmaceutical containing the radionuclide fluorine-18 that binds to β -amyloid aggregates and is intended for use with PET imaging of the brain as a diagnostic tool for Alzheimer's disease.
- The U.S. FDA has approved of Vizamyl (flutemetamol F-18 injection), a radioactive diagnostic agent indicated for Positron Emission Tomography (PET) imaging of the brain to estimate beta amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer's disease (AD) or other causes of cognitive decline.
- Positive/Negative Scans

