PET : Quantitative imaging technology

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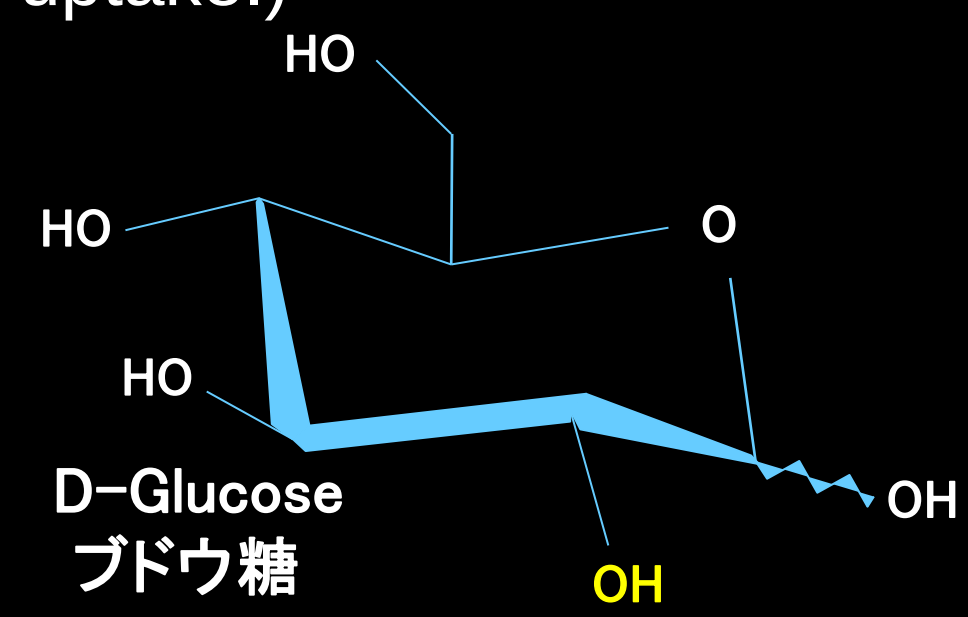
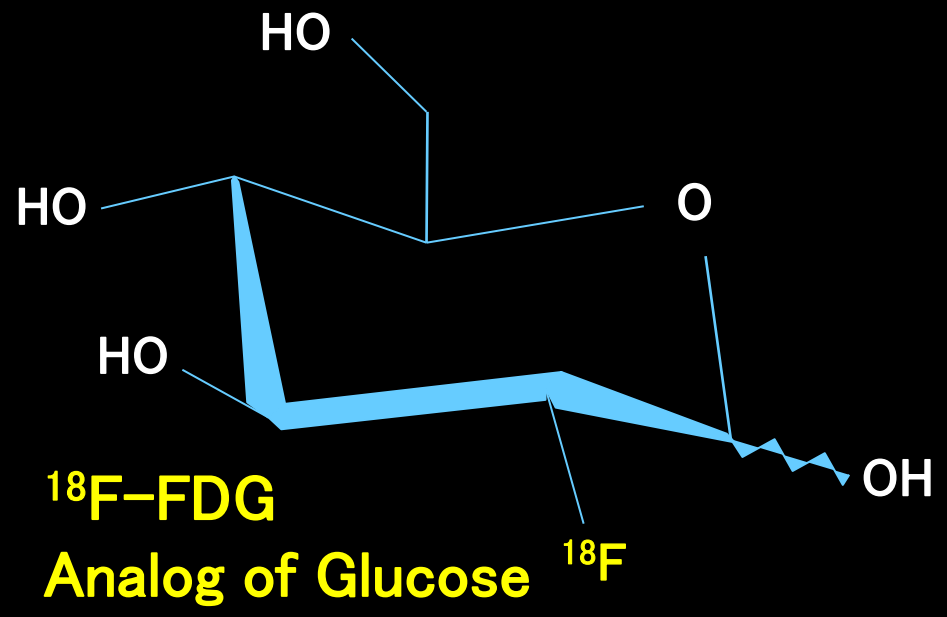
PET（Positron Emission Tomography）:
Radioactivity quantitative measurement device that calculates the distribution of positron emitting nuclides in the body in three dimensions and four dimensions

- High resolution (good image quality)
- High sensitivity
- Excellent quantification

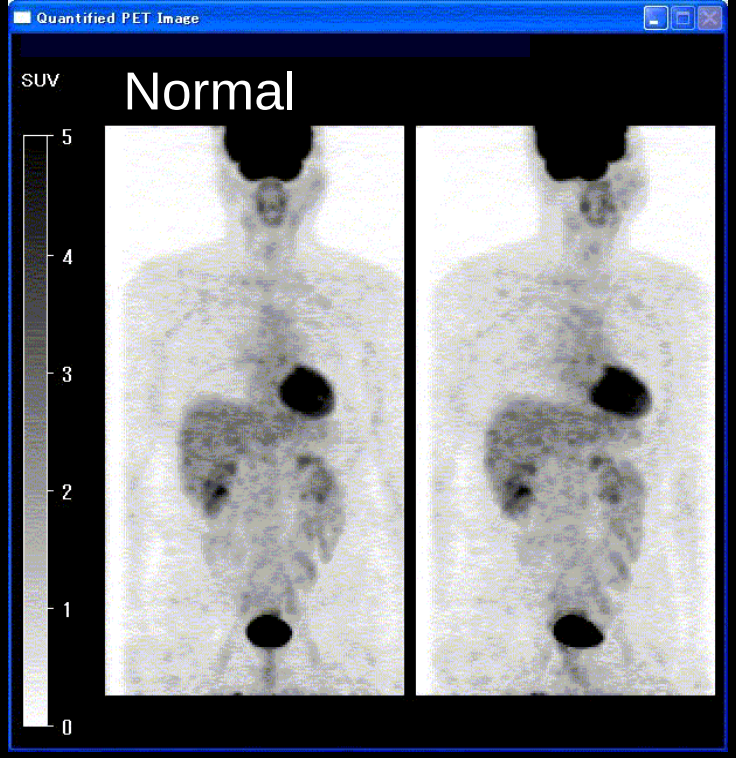
^{18}F-FDG (Fluoro Deoxy Glucose) is a substance similar to glucose, which is taken up by tissues like glucose, but is not metabolized, stays in the tissues for a long time, and is a useful drug for collecting glucose quantitative images of brain and lesions.
(However, it is difficult to be taken into hepatocytes and well-differentiated hepatocellular carcinoma.)
(Renal cancer clear cell carcinoma also has poor FDG uptake.)

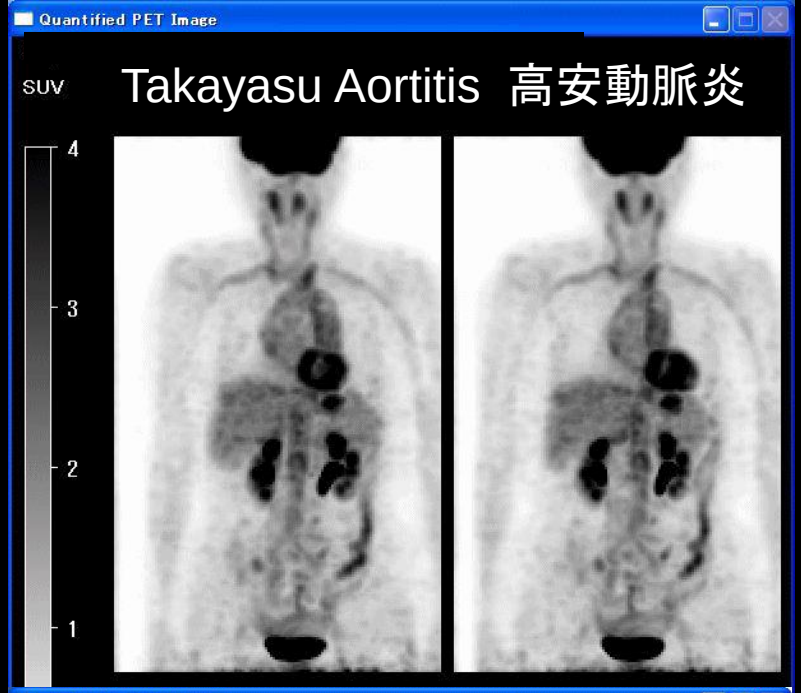


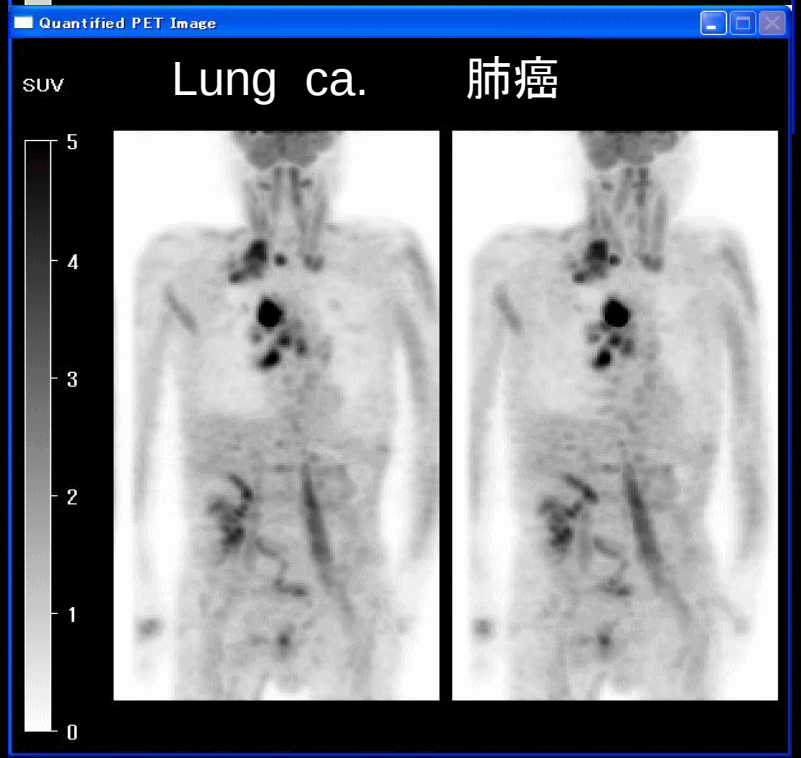
D−Glucose
ブドウ糖



^{18}F−FDG
Analog of Glucose







^{18}F-FDG PET

Normal accumulation in the brain, urine, and sometimes myocardium, in addition to tumors and inflammation.

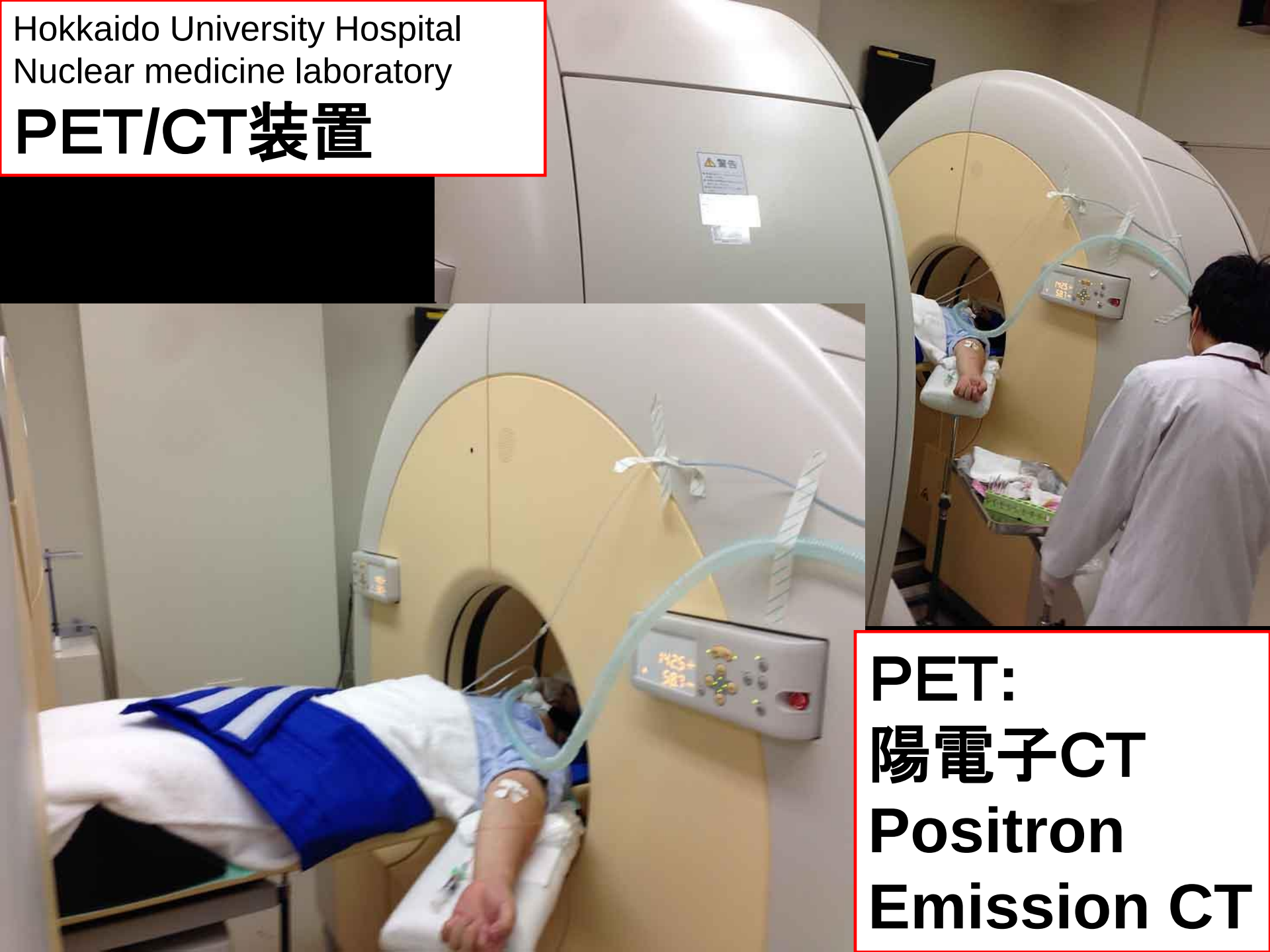
Generally, body tissues ingest fatty acids as an energy source and produce ATP (adenosine triphosphate) from the fatty acids in the beta oxidation cycle in mitochondria.
The beta oxidation cycle produces a lot of ATP but requires a lot of oxygen.

Abnormal tissues with high density of cells, such as cancer cells and inflammatory cells, produce ATP in a glycolytic system that does not require much oxygen because the blood vessels that are the passages of red blood cells that carry oxygen are inadequate.
Glycolysis produces a small amount of ATP, so in normal tissues, glucose is not used very much.

Then, FDG uptake shows the abnormal tissues.

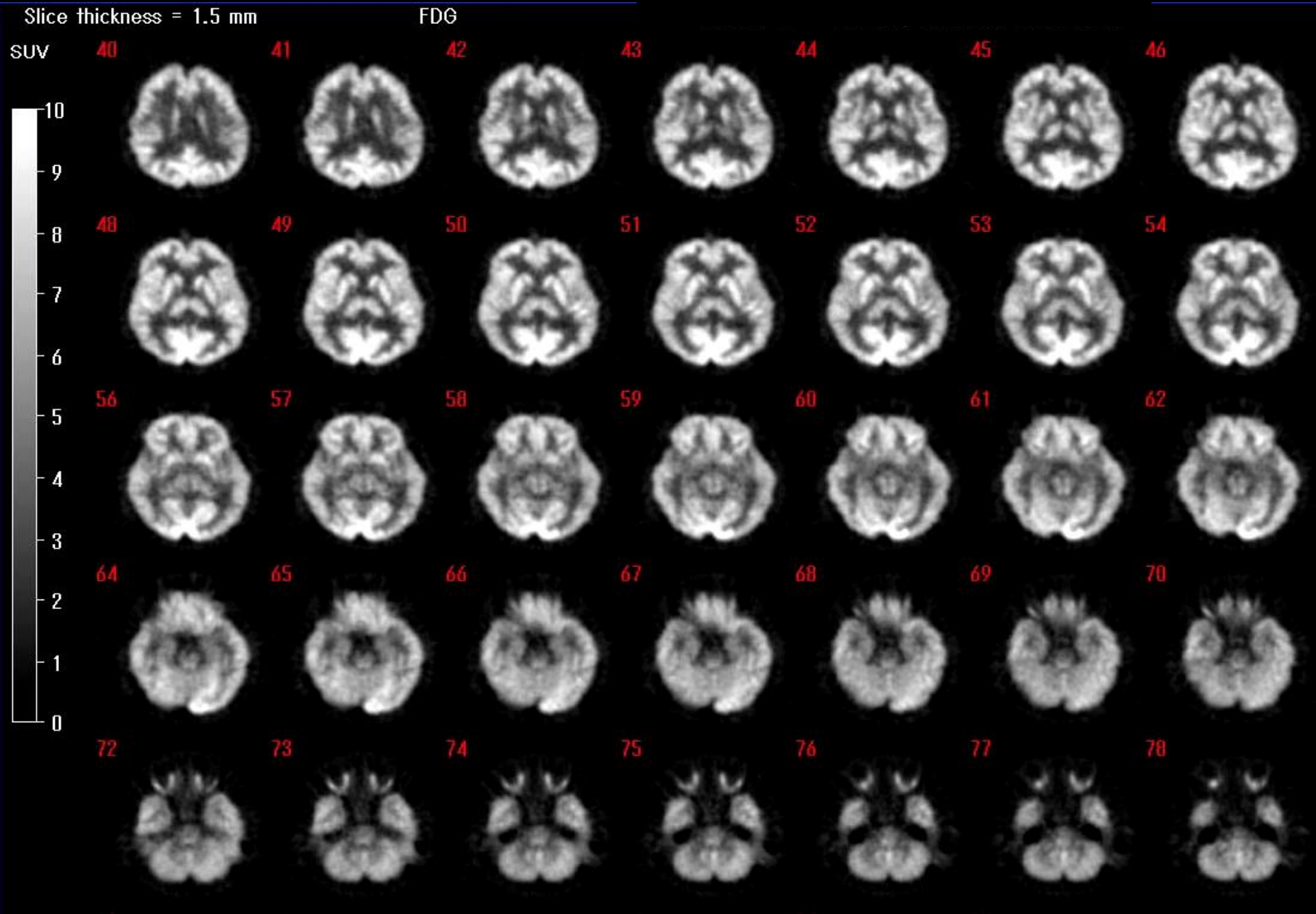
Hokkaido University Hospital
Nuclear medicine laboratory

PET/CT装置



PET:
陽電子CT
Positron
Emission CT

^{18}F-FDG Brain PET 185MBq 1hour after i.v. 5min.



Diseases covered by FDG-PET health insurance

1. Epilepsy (intractable, surgical indication)
2. Ischemic heart disease (diagnosis of viability)
   Cardiac sarcoidosis (fatal arrhythmia)
3. Malignant tumor (excluding early gastric ca.)
   (Cases judged to be malignant by pathological diagnosis, or by other images (CT, MRI, etc.).
   Evaluation of the therapeutic effect of malignant lymphoma.
   Patient with confirmed metastasis.
4. Aortic inflammation
   (Takayasu arteritis, giant cell arteritis)

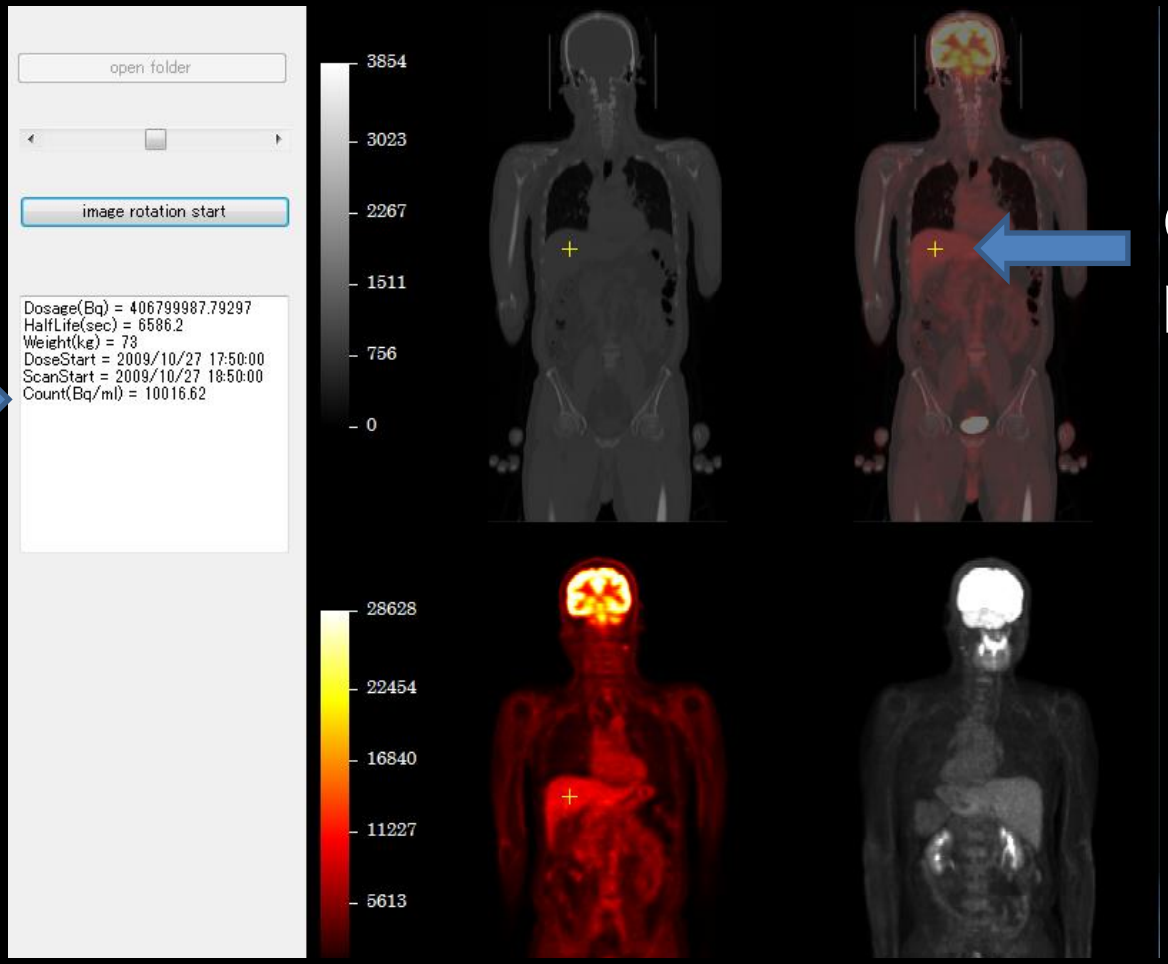
Takayasu arteritis

One of the specified intractable diseases (with 330 diseases). 7,000 registered patients.
90% are women. The most common age is 10 to 30 years old. Young woman.

In a young woman with severe neck pain, headache, stiff shoulder, CT etc., findings such as stenosis in the branch vessels of the aortic arch.
If there is a difference between the left and right upper limb blood pressure measurement values, perform FDG PET / CT. FDG accumulation in inflamed blood vessels.

Treatment is steroids (relapses easily),
Antibody drug (tricizumab (actemra) IL-6R
Originally rheumatoid arthritis. Expensive. 5000 yen /day

Click on any of the CT, PET and fusion images,
The accumulation of the part is displayed.
The clicked point is indicated by a yellow cross.



Clicked point

Clicked part count (radioactivity)

Calculate the SUV of the lesion from the FDG-PET image.

SUV (Standardized Uptake Value)

$$= \frac{\text{Radioactivity concentration of lesion（Bq/ml）}}{\text{Average body radioactivity concentration (Bq / ml)}}$$

(Dosage (Bq) / Weight (g))

The radioactivity of the numerator and denominator must be synchronized (with half-life correction).

Semi-quantitative value indicating how many times the radioactivity concentration of the lesion is higher than the body average. The normal value is 1. 2.5 to 3 or more are considered pathological accumulation.

半減期　Half life $T_{1/2}$

$$N = No \times (1/2)^{(t / T_{1/2})}$$

崩壊定数　Decay constant λ

1秒間に原子核が崩壊する割合

Nuclear decay rate per second

$dN/dt = -\lambda N$

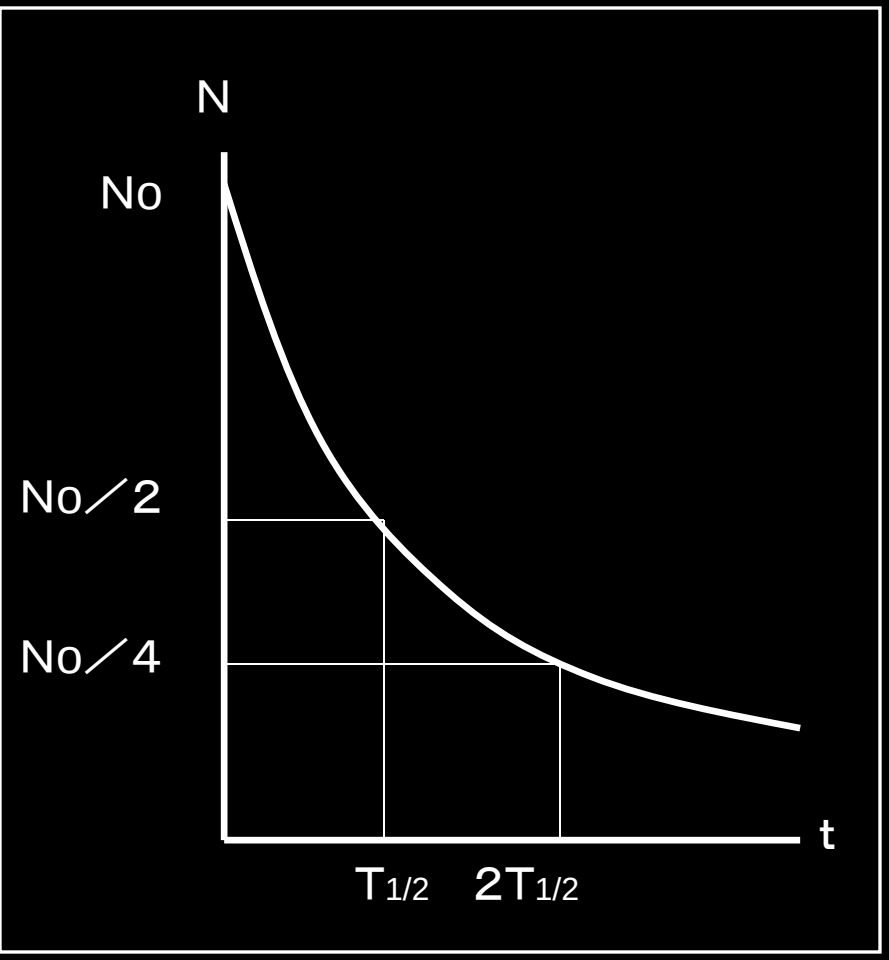
$N = No\ e^{-\lambda t}$

$No/2 = No\ e^{-\lambda T_{1/2}}$

$1/2 = e^{-\lambda T_{1/2}}$

$\mathrm{Log}(1/2) = \mathrm{Log}(e^{-\lambda T_{1/2}})$

$\mathrm{Log}2 = 0.693 = \lambda T_{1/2}$



Clinical Radiologist National Examination

^{18}F-FDG that was 200 MBq at 10:00 was injected to a patient at 10:55. PET scanning was started at 11:50, and image analysis was performed at 13:40.

The radioactivity of the lesion was 12000 Bq/ml. Calculate the SUV of the lesion.

(The patient's weight is 50 kg, height is 150 cm, and half-life of ^{18}F is 110 minutes.)

Calculate the radioactivity at 11:50 of the imaging start time.
The radioactivity in the patient is 200 x (1/2) = 100 MBq
The average concentration in the body is 100 MBq / 50 kg = 2000 Bq / ml

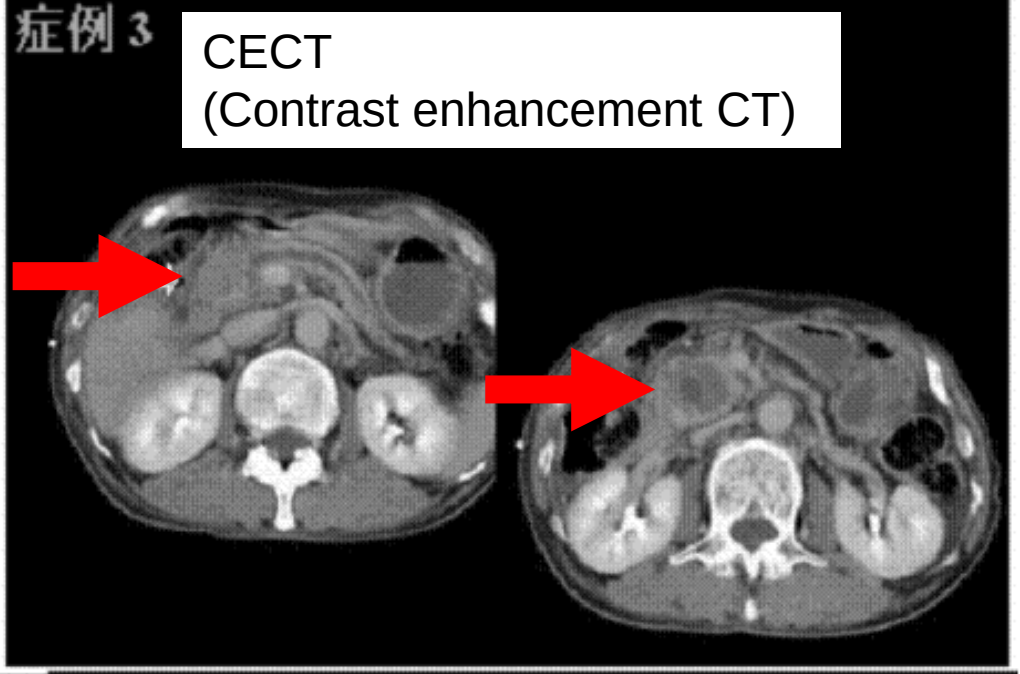
Then, SUV in the lesion is 12000 / 2000 = 6.0

(There is no quantitative unit for SUV. SUV is semi-quantitative.)

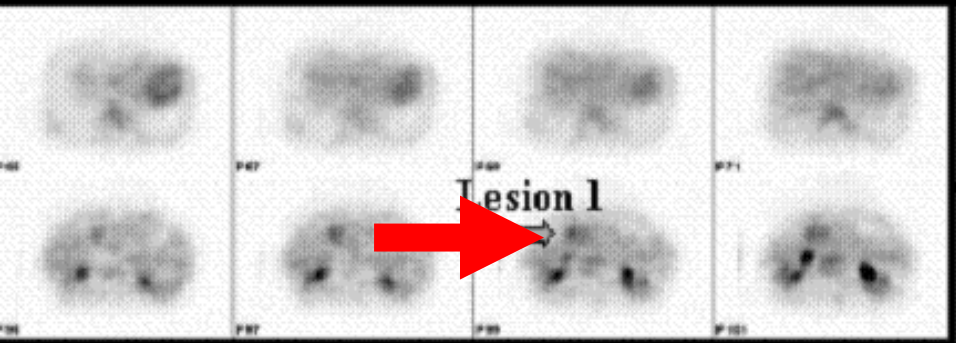
膵頭部癌　Panc. head ca.

FDG-PET after meal showed SUV 2.2 in the lesion.
Re-study was performed on fasting, SUV in the lesion was raised to 3.4

FDG-PET must be performed in the fasting state.



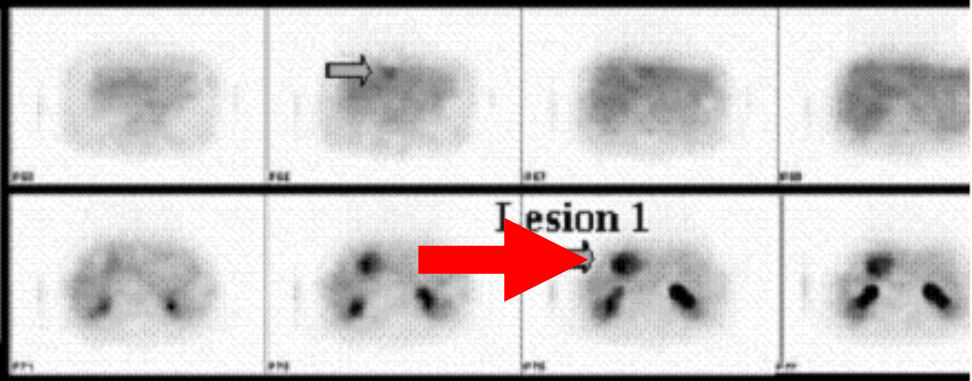
症例3：　FDG-PET（1回目）



SUV 2.2　Lesion1 5029Bq/ml

前処置：検査3時間前に食事(just after meal)。
検査時血糖 BS 167mg/dl

症例3：　FDG-PET（2回目）



SUV 3.4　Lesion1　8251 Bq/ml

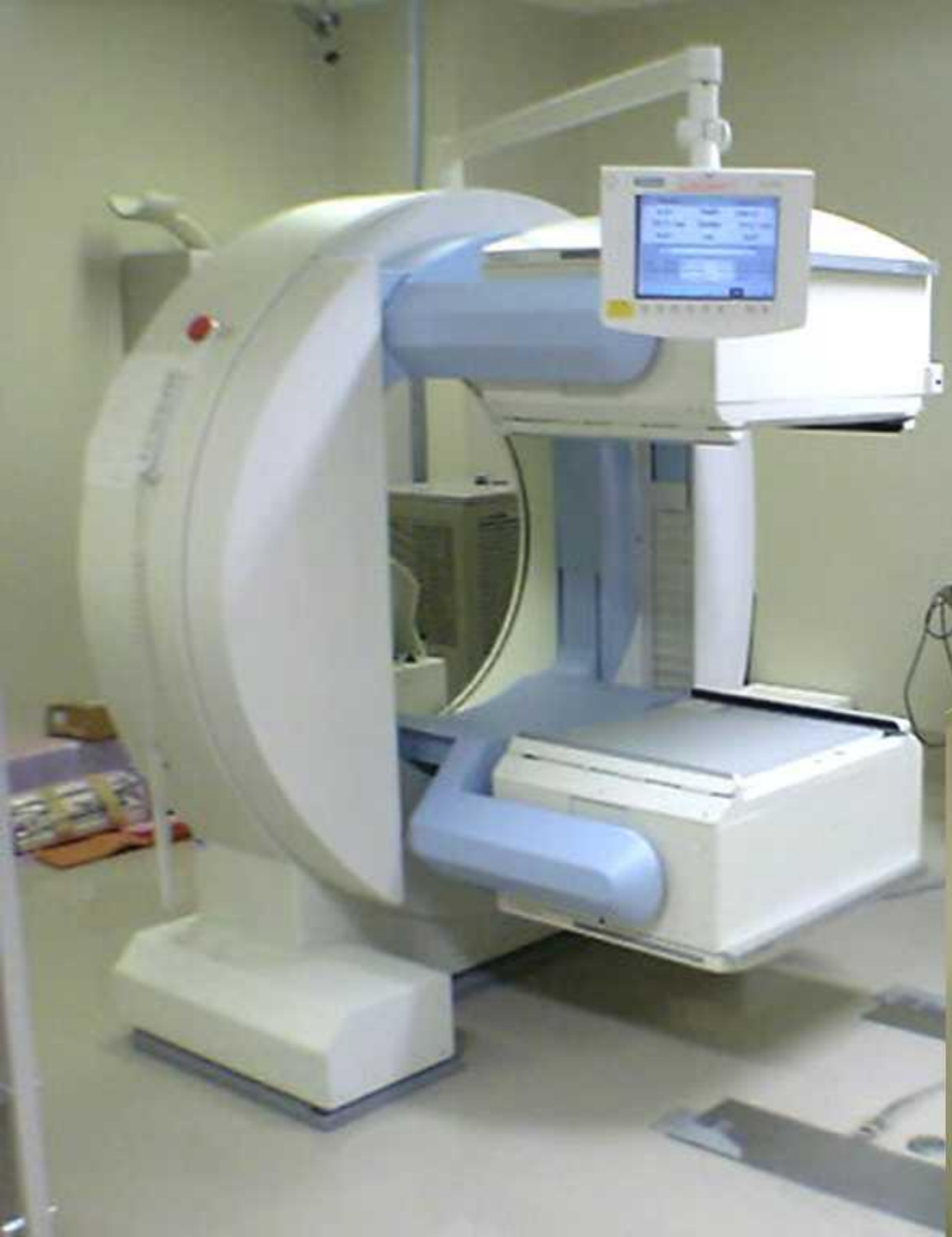
前処置：検査前夜より絶食(fasted all night)。
検査時血糖95mg/dl

In the ^{18}F-FDG PET study, the patient should be fasted and discontinued the sweet drink for 6 hours before. What is the problem with ^{18}F-FDG PET study performed without the pretreatment ?

^{18}F-FDG is an analog of glucose. Since glucose accumulates in tumors and inflammatory lesions, FDG also accumulates. Without fasting pretreatment, the patient's blood glucose level increases.
In hyperglycemic conditions, tumors and inflammatory lesions accumulate much glucose, and FDG accumulation decreases due to the competition.
Therefore, the uptake of the lesion on the PET image is reduced, and the SUV is also reduced.
This makes it difficult to diagnose the lesion.

Gamma camera

Equipment for imaging the distribution (scintigram) of gamma-ray emitting drugs in the body.



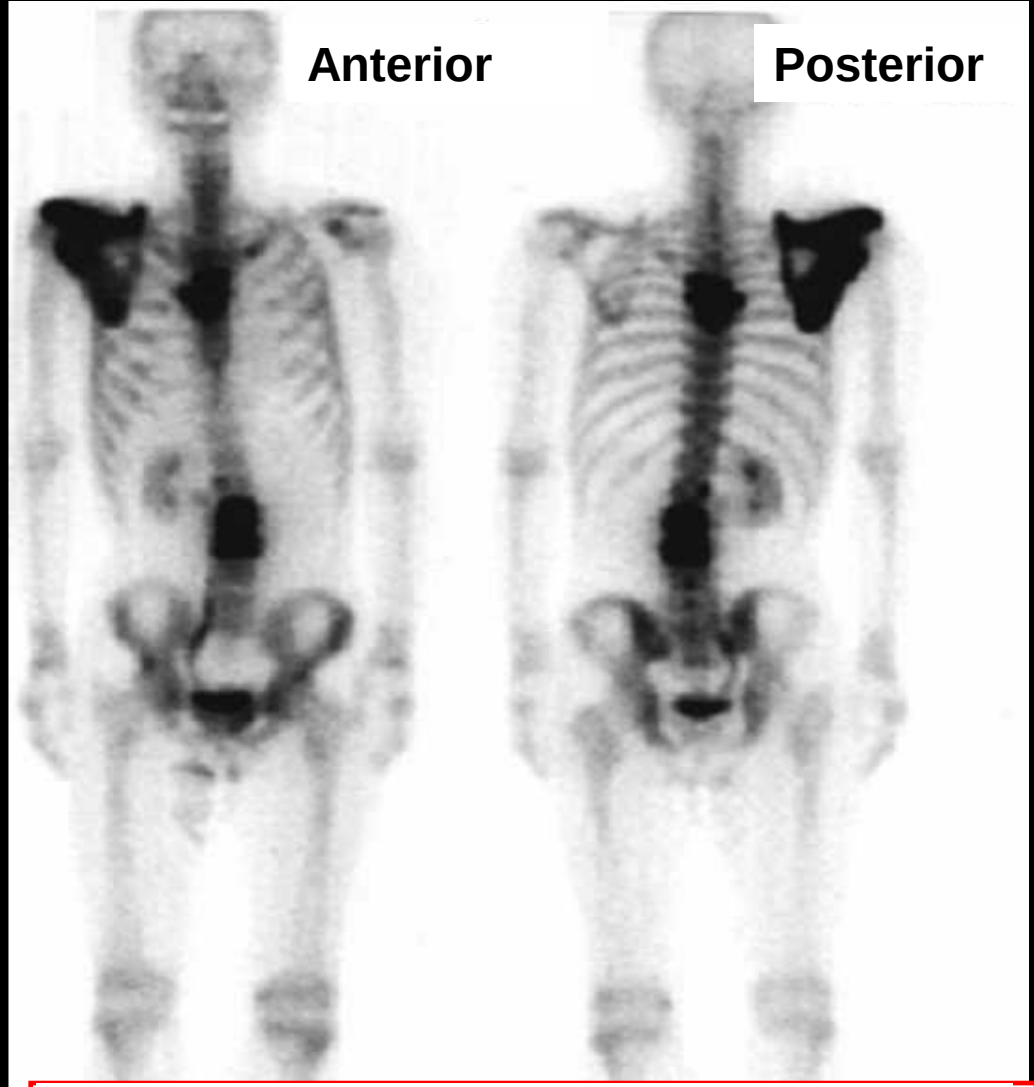
骨シンチグラフィ

Bone scintigraphy

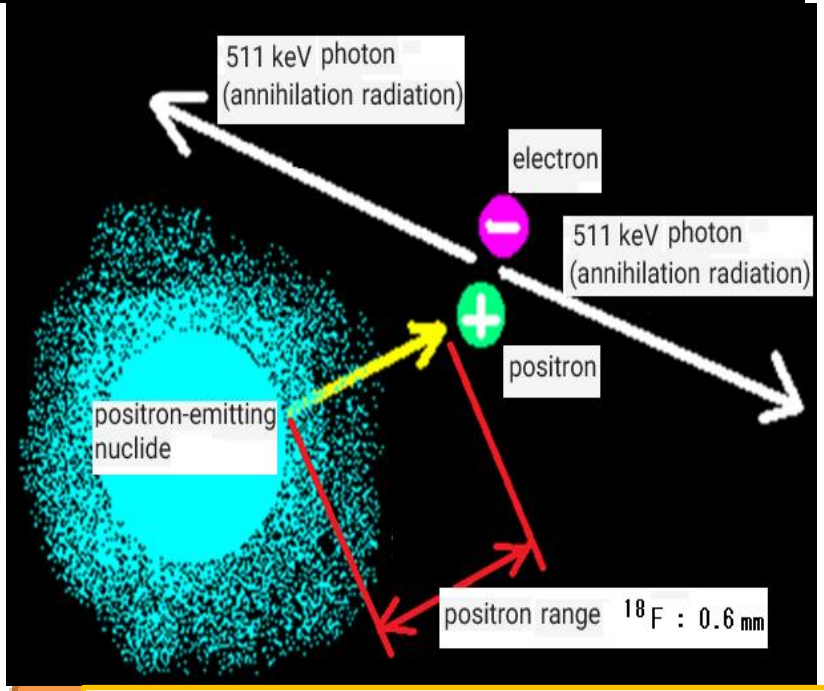
Distribution image of phosphoric acid labeled with gamma-emitting RI.
Strongly distributed in bone metastatic lesions.

A case of lung cancer with bone metastasis in the right scapula, thoracic and lumbar spines.

Since this RI is excreted in urine much, the urinary tract and bladder are depicted.



The reason the images taken by the anterior and posterior cameras are different is that the human body absorbs and scatters gamma rays.
The deeper the part from the body surface, the thinner the depiction.



Annihilation

When a positron is emitted from the positron-emitting nuclide, it collides with the electron over a range of several millimeters and annihilates, and a pair of 511 keV annihilation radiation is emitted in the opposite direction.
The positron and the electron have the same mass, and when they annihilate, a photon (annihilation radiation) with a value of 511 keV is obtained by substituting the electron mass into the equation of $E = mC^2$.

Electromagnetic waves generated from inside the nucleus are called γ-rays, and electromagnetic waves generated by the transition of extranuclear orbital electrons are called X-rays. Annihilation radiation is an electromagnetic wave that does not correspond to either.

Positrons are antiparticles of electrons, having a positive charge and negative energy. When an electron and a positron whose energy and charge are opposite to each other meet, they disappear and are replaced by electromagnetic wave energy equivalent to the disappeared mass. Electromagnetic waves have no mass but energy, so they have momentum. The generated electromagnetic wave flies in the opposite direction according to the law of conservation of momentum. An accurate understanding of this phenomenon requires knowledge of quantum mechanics and relativity.

There are two types of radiation.

1. Electromagnetic waves (X rays, γ rays)
   = Vibration energy of space

2. Particle beam (electron, positron etc.)
   = Particle flying at high speed (with mass) which has greater effect on the human body than X-rays and gamma rays.

Radioactivity is the number of radiations emitted per second.

The unit of radioactivity is Becquerel (Bq).

Electromagnetic wave is the vibration energy of the space (X rays, γ rays, light rays, radio waves).

Space (or Universe) is not nothing.
The space has a physical entity (structure).
The vibration of the spatial structure becomes electromagnetic waves such as X-rays, gamma rays, visible light, etc.

Name and wavelength of electromagnetic wave

X-rays and γ-rays: 10 pico to 10 nano-meters
Visible light : 400 (purple)-800 (red) nano-meters
Microwave: 100 micro to 1 meter

Maxwell's formula : the speed of electromagnetic waves

Speed of electromagnetic waves in vacuum :

$C = 1/\sqrt{\mu o\, \varepsilon o}$ = 300,000 km/s = 3 billion m/s

(μo : Vacuum permeability , εo : Vacuum permittivity)

A vacuum (= space) has a structure having magnetic permeability and permittivity.

= **Space has a physical structure.**

If there is no structure in the space, the magnetic permeability μo in vacuum (probability of magnetic field) and the dielectric constant in vacuum εo (probability of electric field) should be zero.

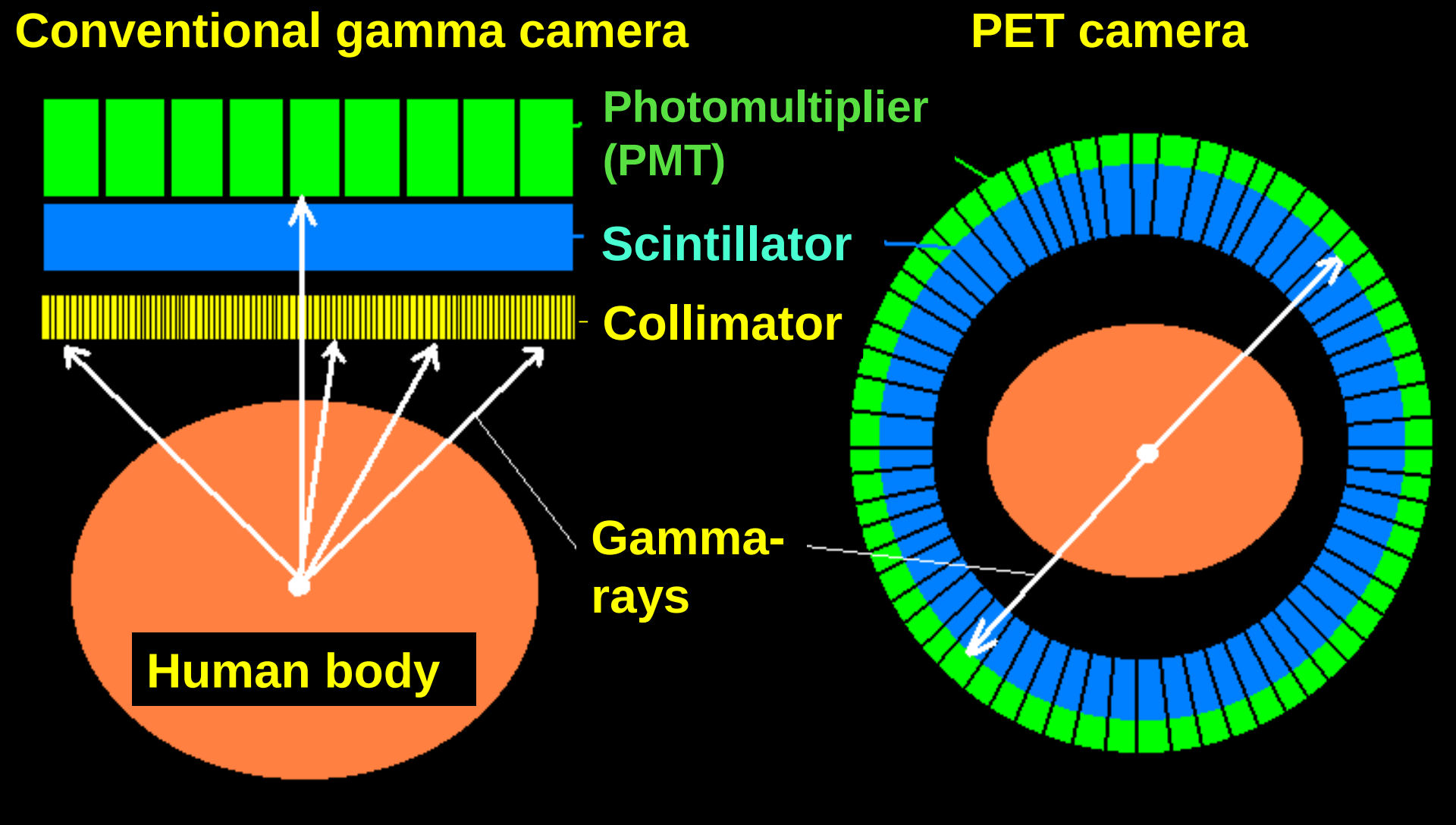
If μo = 0 and εo = 0, the electromagnetic wave velocity in vacuum **$C = 1/\sqrt{\mu o\, \varepsilon o}$** should be infinite, which contradicts reality.

Photon is interpreted as a particle of energy in the space with zero weight. The particle feature of electromagnetic energy such as visible light or X-rays was confirmed by Einstein and Compton.

Even on a daily basis, the phenomenon that stars far from thousands of light years away can be seen in the night sky cannot be explained without recognizing the particle nature of light, that is, the existence of photons. If light is just a wave, the wave of light emitted from the star will spread for thousands of years in outer space, the energy of light reaching the earth will be significantly weakened, and we should not be able to see distant stars.

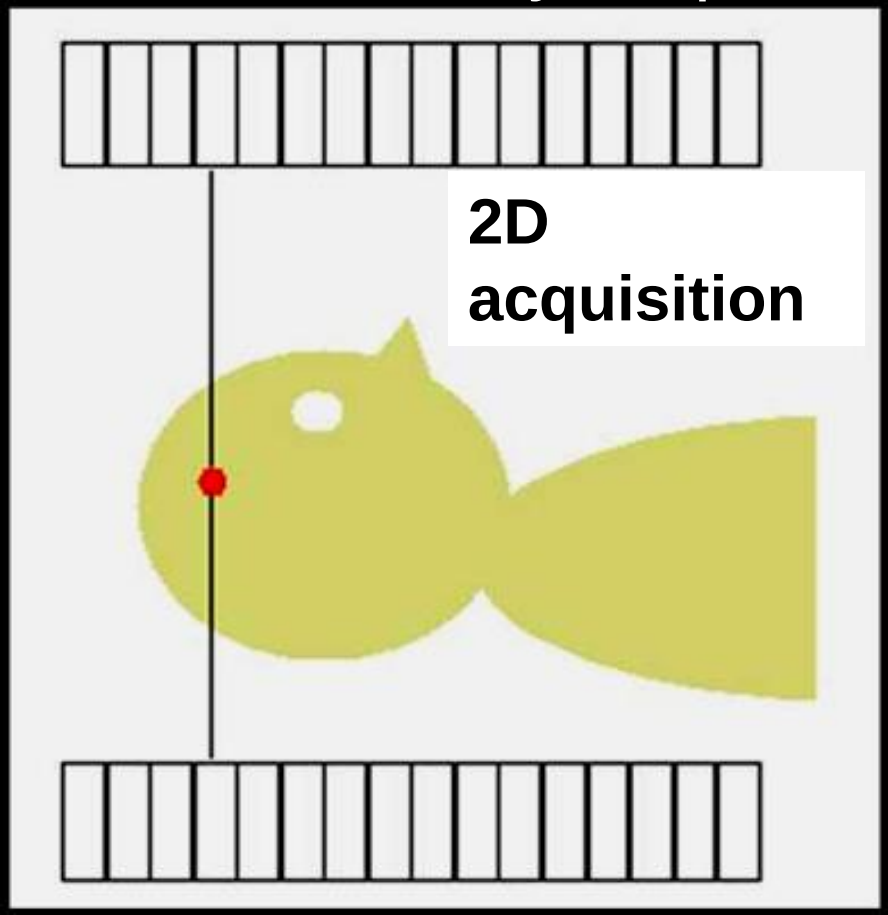
It is difficult to understand the duality that the electromagnetic energy has the feature of both wave and particle. The reason is that it is difficult for us to recognize space as a structure of four dimensions or more. If space has only three-dimensional structure, its duality cannot occur.

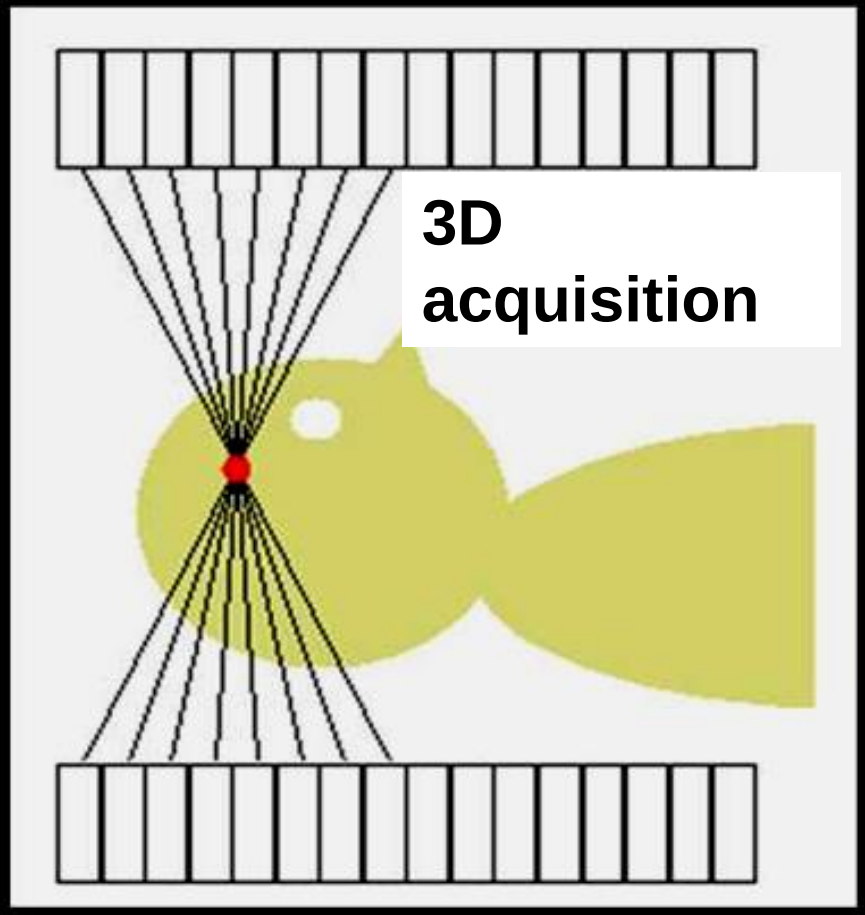
PET camera has high sensitivity because there is no collimator.
The collimator mounted on the conventional gamma camera is a lead plate having many small holes.
The collimator reduces the sensitivity of radioactivity detection.



Currently, most PET is three-dimensional (3D) collection.

Good images can be acquired in a short time compared to two-dimensional (2D) acquisition (The whole body (head to thigh) is collected in about 15 to 20 minutes). But, it is easy to collect Compton scattered radiation, and the accuracy of quantification decreases.

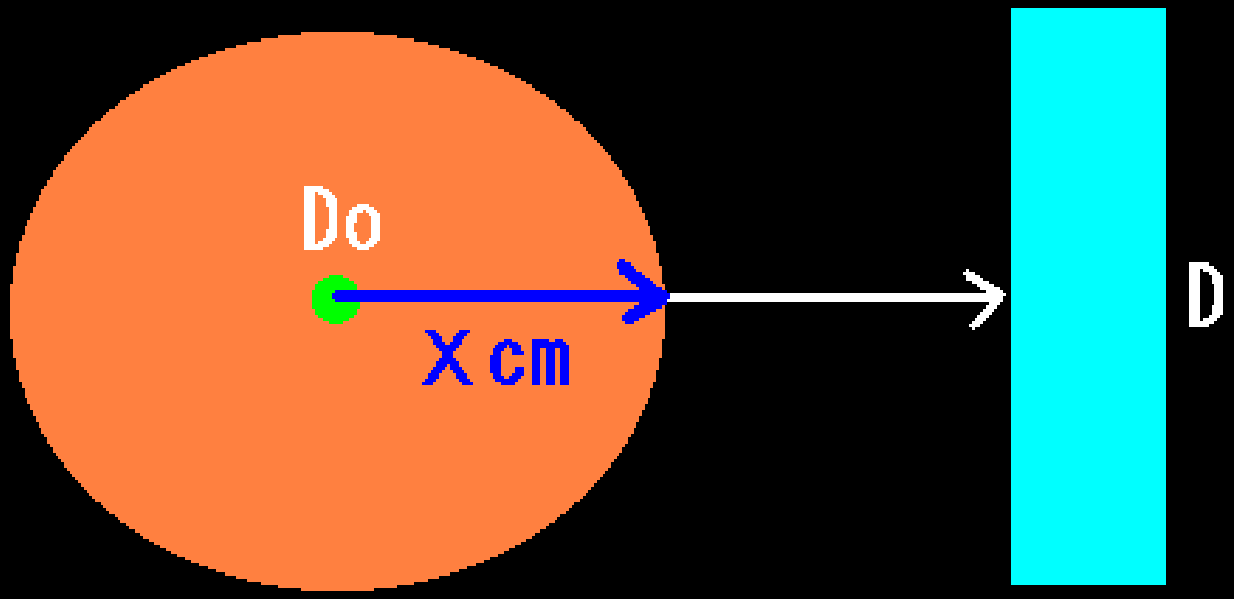




Difficulty quantifying radioactivity distribution in the body with conventional camera

Attenuation of radioactivity Do in the body into D

$$D = Do \exp(-\mu x)$$



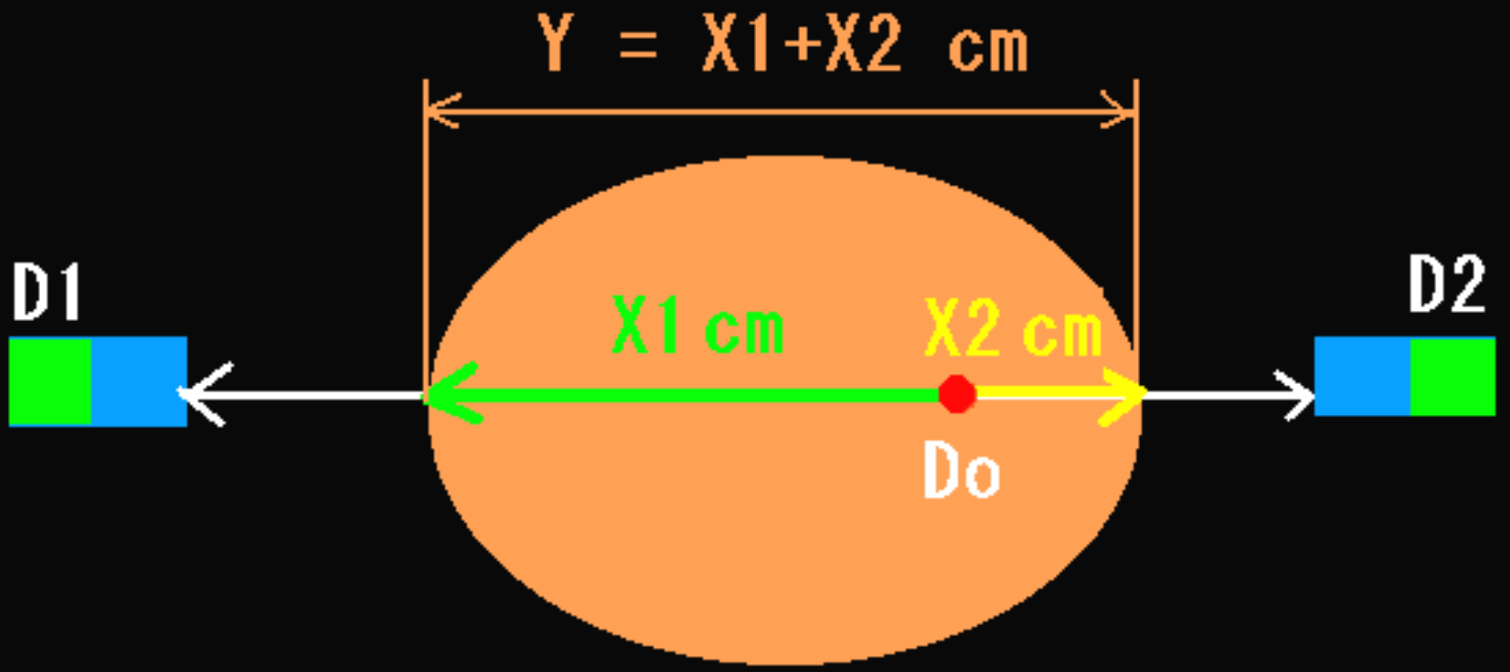
Do : True radioactivity (Bq)

D : Measured radioactivity (Bq)

μ : Linear attenuation coefficient (cm^{-1})

Scintillation camera

PET performs absorption correction on CT images, so it is highly quantitative.



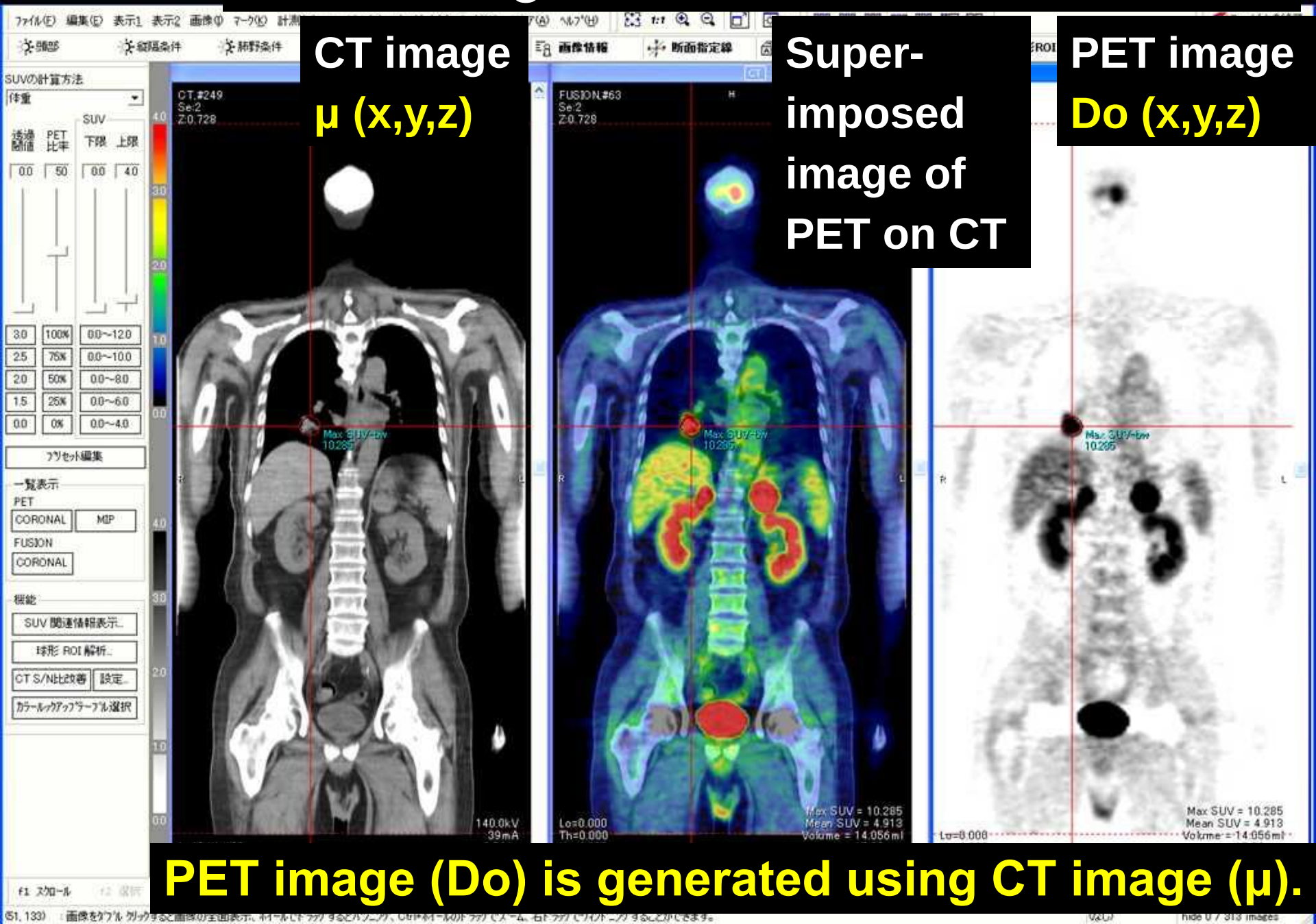
$$D1 = Do \exp(-\mu X1)$$
$$D2 = Do \exp(-\mu X2)$$

$$D1D2 = DoDo \exp(-\mu (X1+X2))$$

$$Do = \sqrt{D1D2 \exp(\mu Y)}$$

PET/CT

Rt. Lung cancer with metastases.



CT value（HU：Hounsfield Unit）

Value proportional to tissue density

The value based on the pixel value of the CT tomogram is the linear attenuation coefficient μt of each tissue in the body, but a value proportional to μt is used for the pixel value of CT to facilitate clinical understanding.

$$\text{CT value} = 1000 \times (\mu_t - \mu_w) / \mu_w$$

μ_w : X-ray absorption coefficient in the water

μ_t : X-ray absorption coefficient in the tissue

CT value in the air is -1000

$1000 \times (\mu_{air} - \mu_w) / \mu_w = -1000$（HU）

Strictly, the linear attenuation coefficient μ_{air} is not 0. But it is extremely small compared to water or body tissue, when calculating the CT value, $\mu_{air} = 0$.

CT Value in the water is 0 (HU).

(Density of specific gravity 1 is 0 (HU))

$1000 \times (\mu_w - \mu_w) / \mu_w = 0$（HU）

The CT value of a substance with a linear attenuation coefficient twice that of water is 1000.

Double density of water is 1000 (HU). (Tooth etc.)

$1000 \times (2\mu_w - \mu_w) / \mu_w = 1000$（HU）

北大医学部 加藤千恵次 北大病院 核医学診療科

大学院医学研究科 PETによる病態の定量化 断層画像再構成の原理

医学科 核医学 PET, SPECTの原理 コンパートメントモデル解析

保健学科

保健学科2年 保健医療概論 原子力発電所事故が人体に与える影響

医療従事者の被曝について

放射線技術科学専攻

核医学総論 核医学検査技術学

核医学検査技術学実習

放射化学基礎

放射線関係法規

医用画像機器工学Ⅱ（CT）

医用画像機器工学実習（FBP, OSEMの原理）

核医学機器工学概論 プログラミング言語C

C#講座 C#講座サンプルプログラム プログラミング言語C#

C言語からVisual C#への移行 DICOMから情報を読み出す

検査技術科学専攻

医療情報科学 医用工学

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Detailed nuclear medicine equipment principles, CT tomographic image creation principle, Slides explaining quantitative analysis theory such as cerebral blood flow, Image analysis programs.

Please refer to those who are interested.

Positron emitting nuclides used in PET

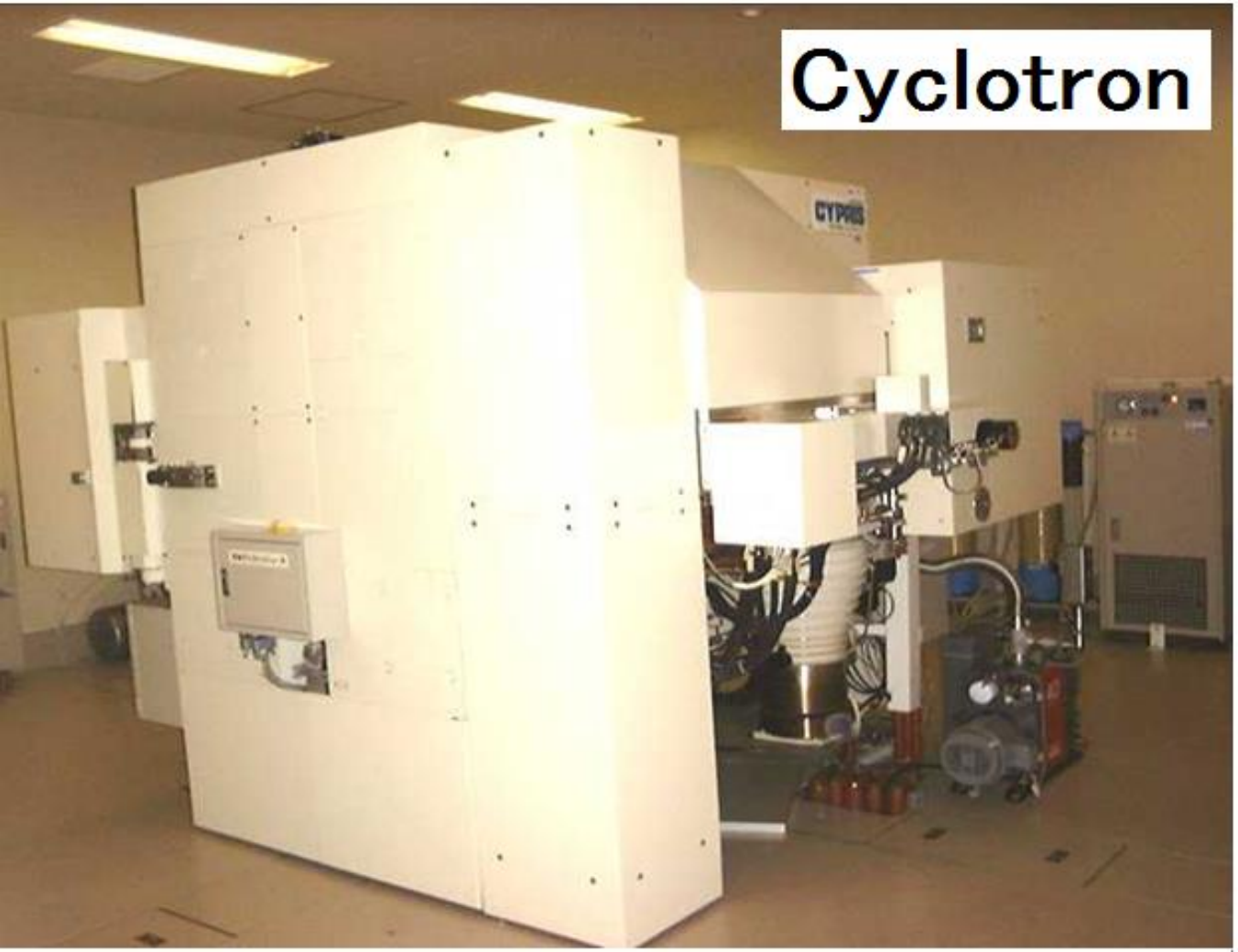
Produced in a cyclotron in a hospital.

		Half-life	Synthetic radiopharmaceutical
酸素15	15-O	2 min.	O2, CO, CO2, H2O
窒素13	13-N	１０ min.	ＮＨ３
炭素11	11-C	２０ min.	^{11}C-Acetate ^{11}C-Methionine
フッ素18	18-F	１１０ min.	ＦＤＧ，ＦＤＯＰＡ

Half-life of radioisotopes used in conventional Nuclear medicine studies

99m-Tc	6	hours (時間)
67Ga	78	hours (時間)（3.2 days 日）
201Tl	73	hours (時間) (3.0 days 日）

^{18}F	110 min	$^{18}O(p,n)\ ^{18}F$
^{15}O	2.04 min	$^{14}N(d,n)\ ^{15}O$, $^{15}N(p,n)\ ^{15}O$
^{11}C	20.4 min	$^{14}N(p,\alpha)\ ^{11}C$
^{13}N	9.97 min	$^{12}C(d,n)\ ^{13}N$, $^{16}O\ (p,\alpha)\ ^{13}N$



A Cyclotron in Hokkaido University hospital.

Huge electromagnet.

Accelerates hydrogen or deuterium nuclei

and collides with elements to create positron emitting nuclides.

被曝 Exposure unit

Absorbed dose : 1 Gy (gray) is the exposure of a 1 kg object absorbing 1 J of radiation energy.

Dose equivalent：The exposure to which the human body receives 1 J of energy per 1 kg of body weight is 1 Sv.

Dose equivalent (Sv) = Absorbed dose (Gy) x Quality factor

Quality factor Q： An index that indicates the energy applied to the human body (the degree of ionization) due to differences in radiation quality.

Q＝1 ： X-rays、γ-rays、β-rays

Q＝10 : Proton beam、neutron beam

Q＝20 : Multiple charged particles

Due to the short half-life of positron emitting nuclides, exposure to PET scans is low.

The unit of exposure is Sv (mSv = 0.001Sv). Exposure to receive 1J of energy per 1kg of body weight is 1Sv. Generally, 100mSv or less is harmless.

^{18}F-FDG (185MBq) 4 mSv (Bladder 20 Heart 10 Fetus 3)

^{11}C-Methionine (370MBq) 2 mSv (Pancreas, Liver 7)

^{15}O-CO2 (3000MBq) 2 mSv (Lung 11)

CT 7mSv ～ 10 ～

Angiography 7 mSv ～ 10 (Skin in 1 minute 0.5)

Stomach, digestive tract X-ray imaging 3 mSv

X-ray photography 0.1 mSv (Chest) 0.2 mSv (Pelvis)

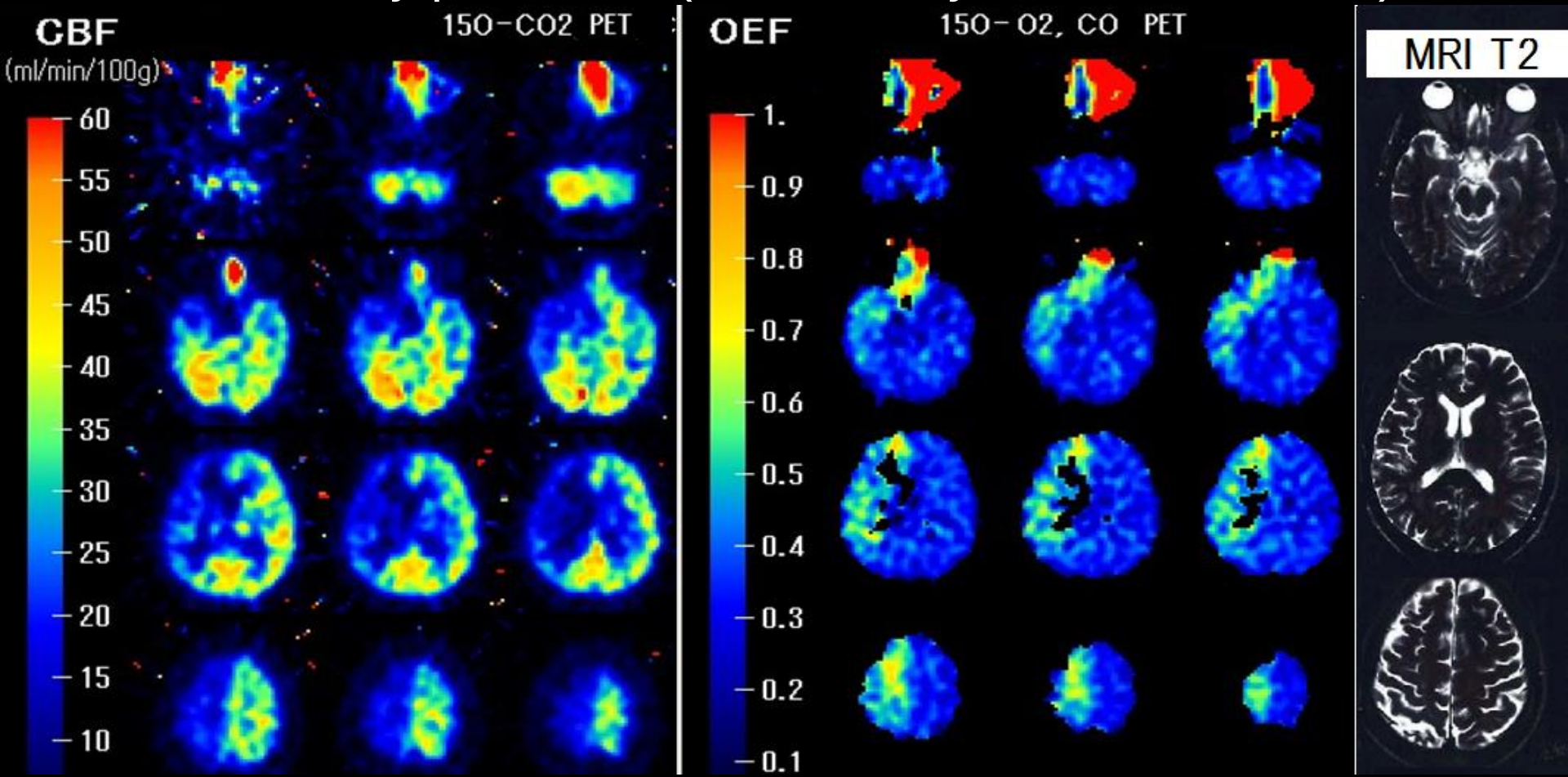
^{15}O-CO2、O2　Brain PET quantifies CBF, OEF.

Cerebral Blood Flow (CBF), Oxygen Extraction Fraction (OEF)。

Case of severe stenosis in the right internal carotid artery.

Although it is not a cerebral infarction (MRI T2 image is normal), severe hypoperfusion, increased oxygen uptake in the Rt. brain.

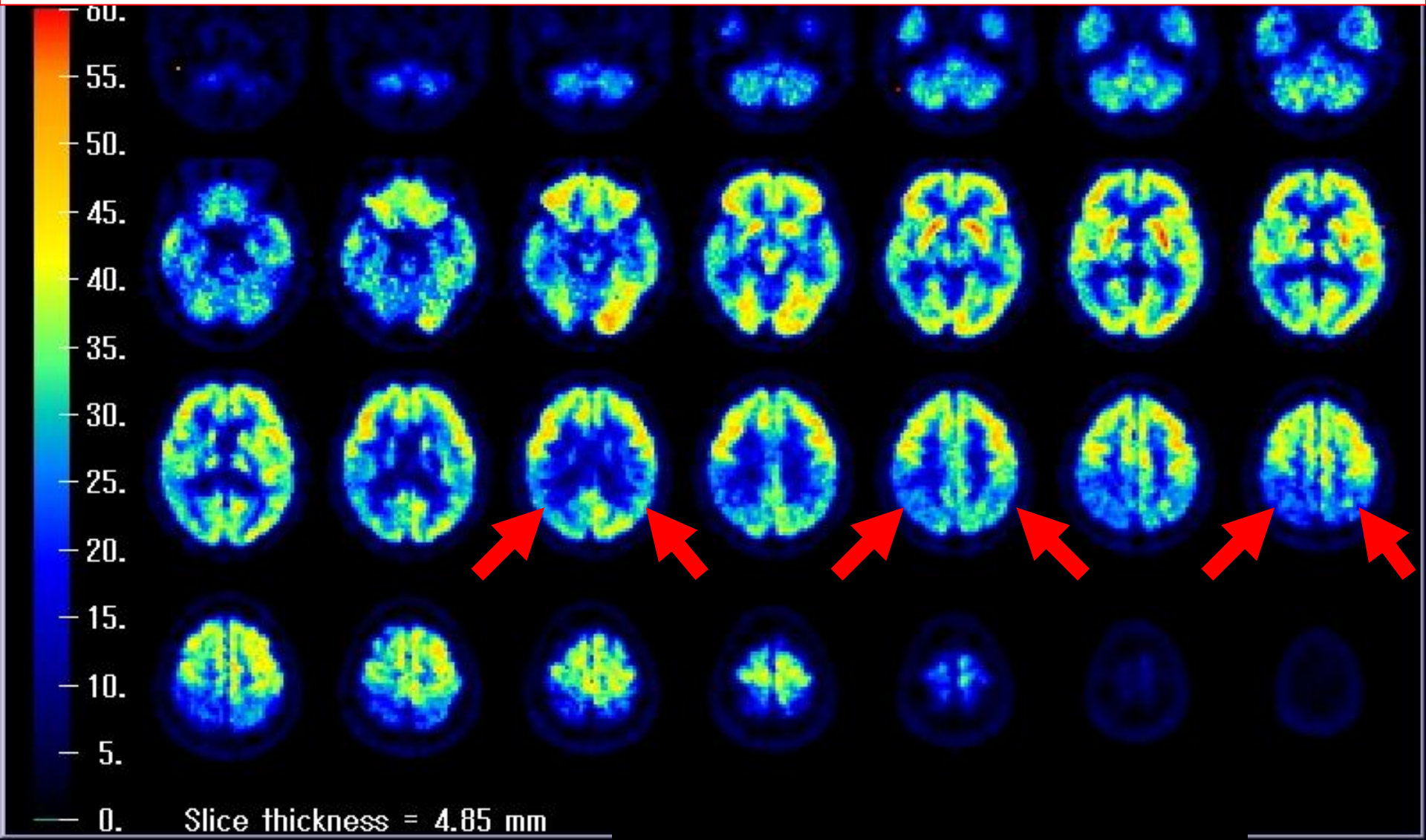
It is called misery perfusion. (Immediately before infarction)



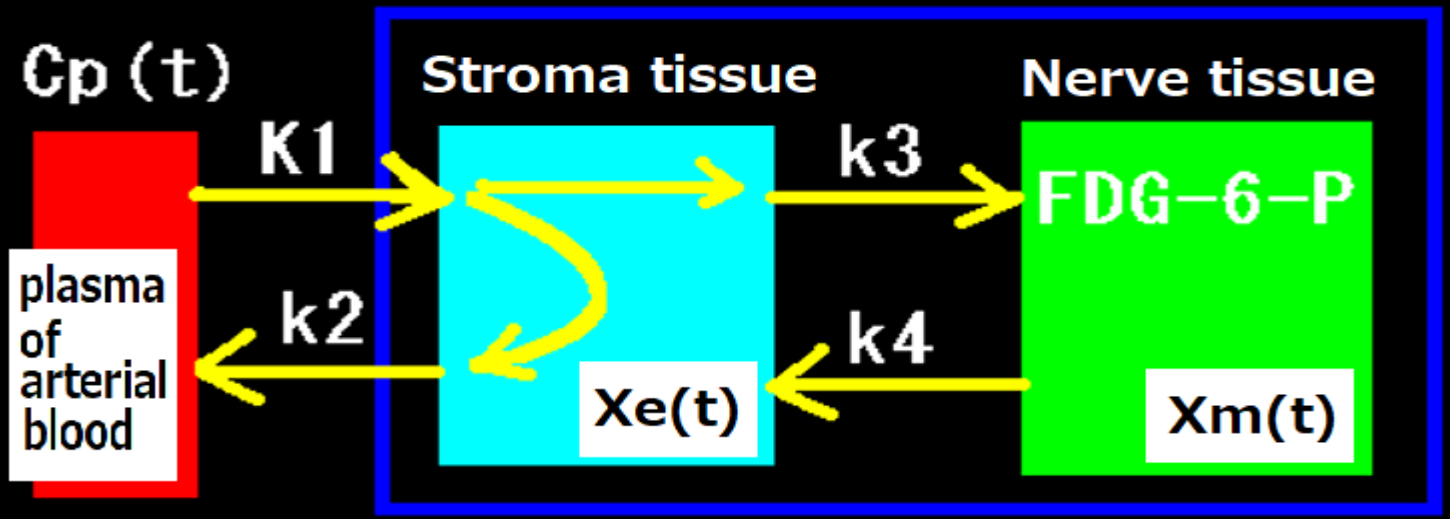
^{18}F-FDG Brain PET Quantify brain glucose consumption.

Alzheimer's disease

Degeneration of bilateral parietal and temporal lobes, decreased glucose metabolism.



Quantitative analysis of dynamic FDG PET with three-compartment model



$$\frac{dCp}{dt} = k2\ Xe - K1\ Cp$$

$$\frac{d\,Xe}{dt} = K1\ Cp + k4\ Xm - (k2+k3)\ Xe$$

$$\frac{dXm}{dt} = k3\ Xe - k4\ Xm$$

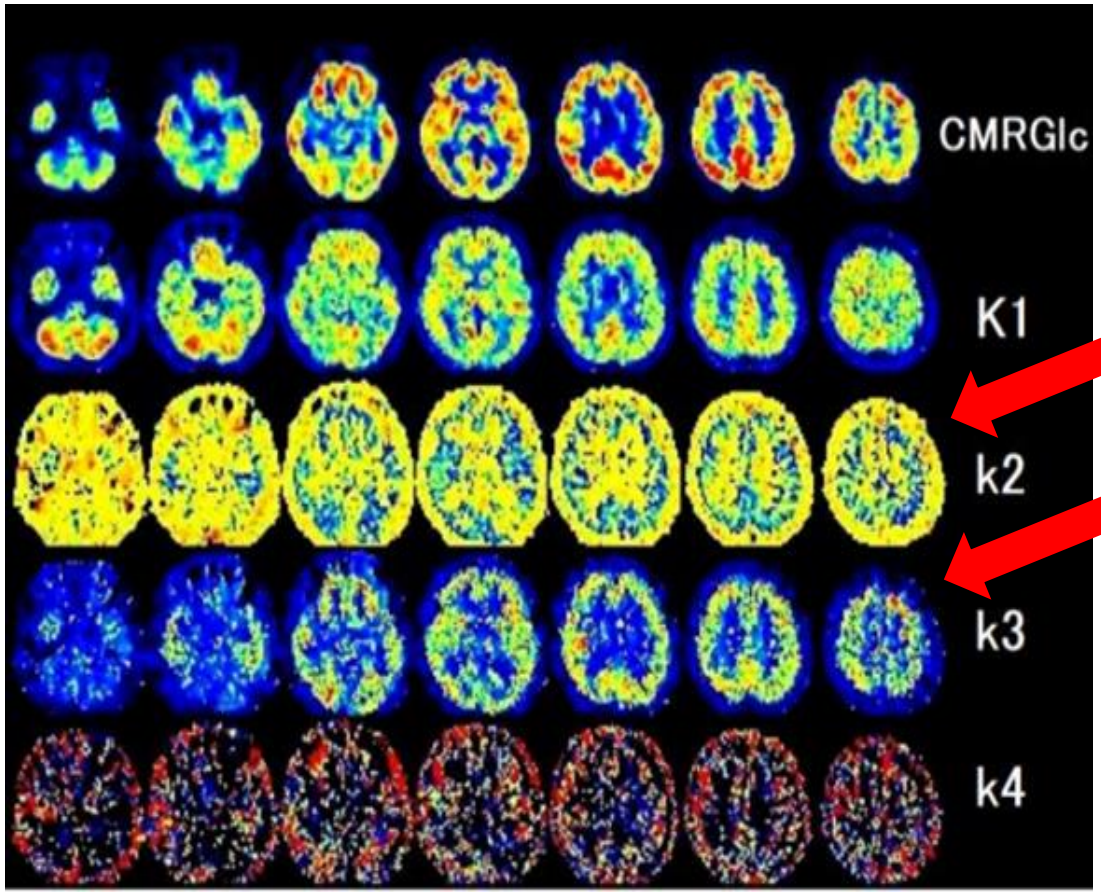
CMRGlc (Cerebral Metabolic Rate of Glucose)

$$= \frac{\text{Blood sugar} \times K1 \times k3/(k2+k3)}{0.42}$$

0.42 is a Lumped constant, uptake ratio of FDG compared with Glucose.

3-compartment model analysis enables to calculate rate constant images of K1 , k2, k3 and k4 from dynamic FDG PET image and arterial blood sampling.

K1 image shows uptate rate of FDG into both stroma and nerve tissues.

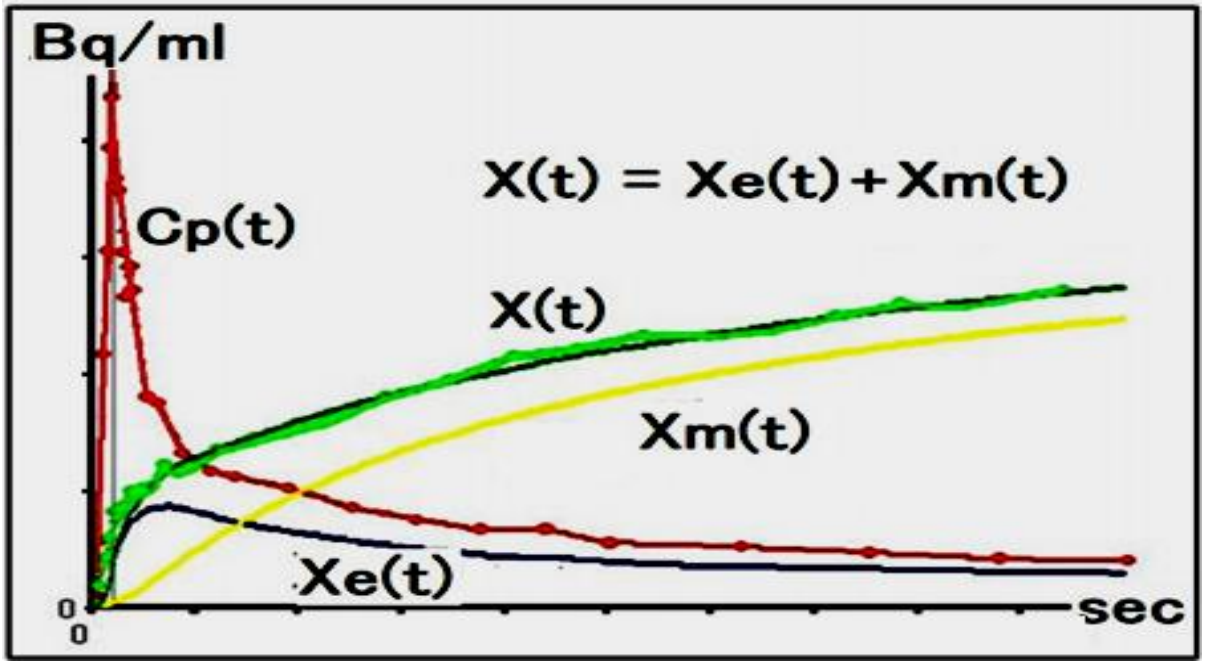


k2 images show release rate of FDG from stroma tissues.
Stroma tissues do not need Glucose, high k2 value is shown.

K3 images presents uptake rate of Glucose into the nerve tissues.
Nerve tissues need Glucose, high k3 value is shown in the brain.

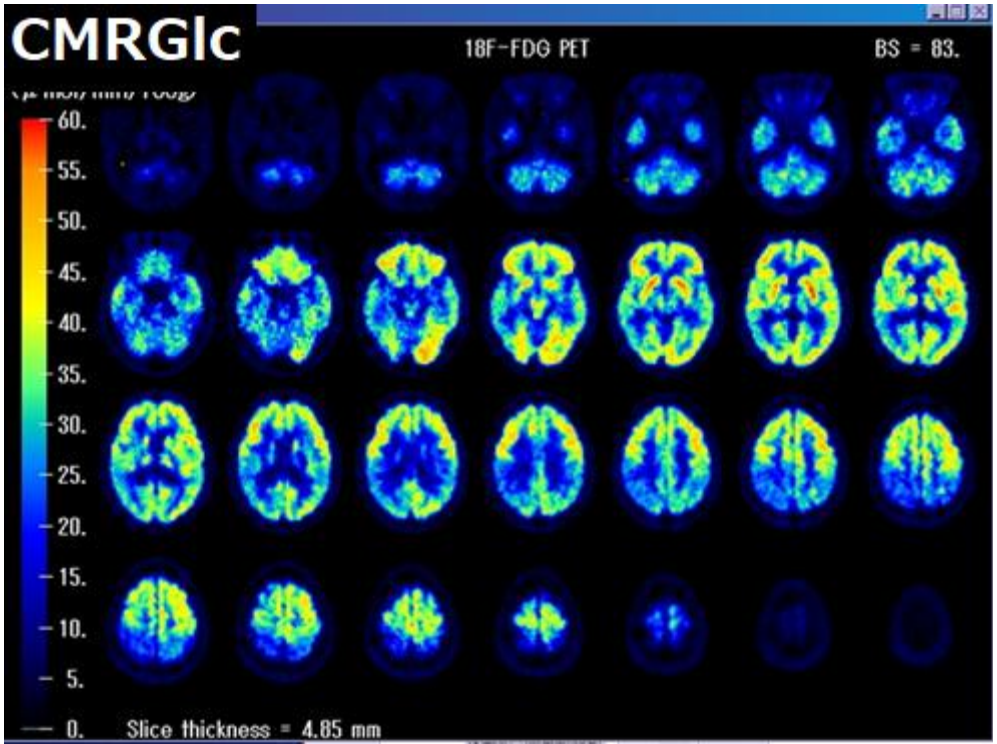
Dynamic brain FDG PET is performed for one hour, time-activity curve X(t) is acquired in every part of the brain.

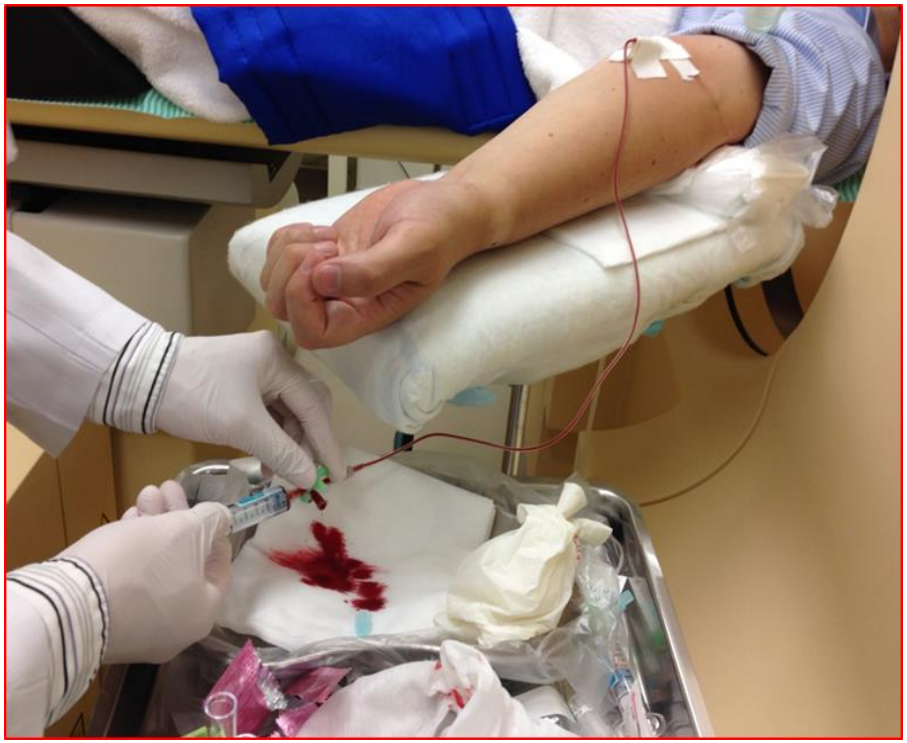
3-compartment model analysis enables to divide the X1 curve into the 2 time-activity curves, Xe(t) (stroma tissue curve) and Xm(t) (brain tissue curve). This technique enables to analyze several pathological uptake rate of brain nerve tissues.



Compartment model analysis is very useful to analyze quantitative evaluation of several diseases. But it sometimes requires arterial blood sampling during the dynamic PET acquisition.

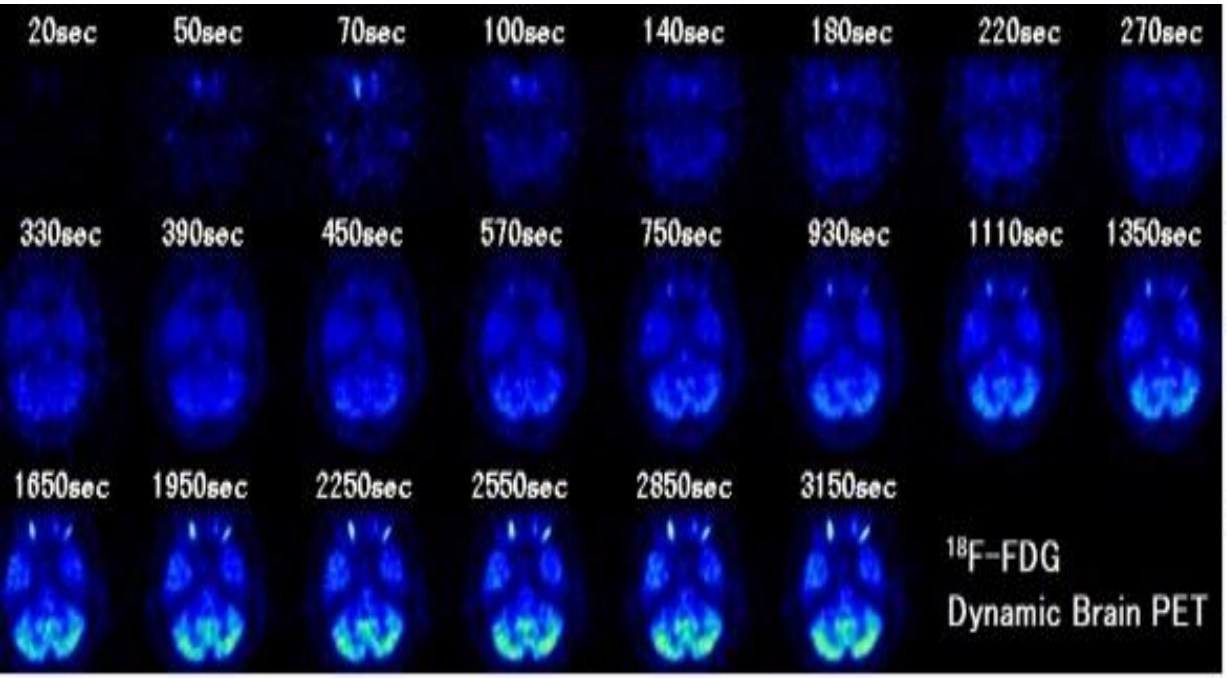
It is invasive and expose high radiation to the doctor who is sampling blood, because he must be nearby a patient who is emitting gamma rays from the body.

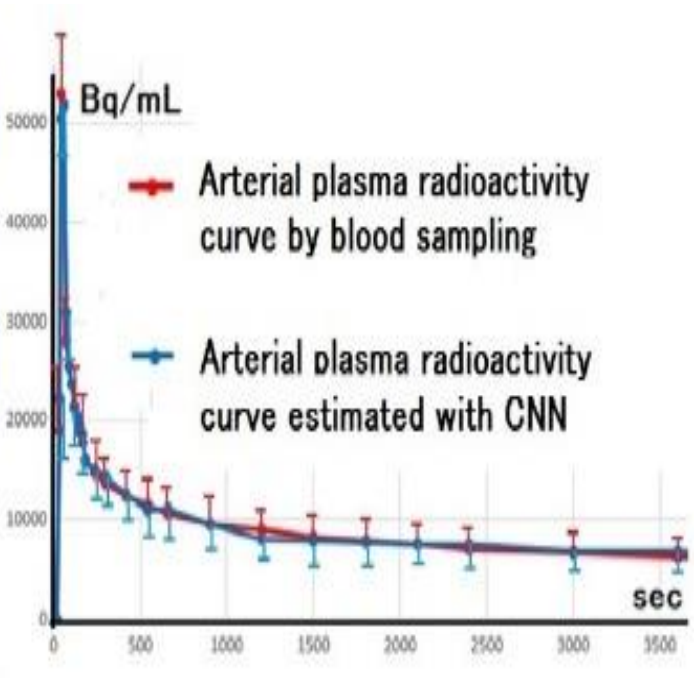




Recently, Deep-Learning is used in the clinical study. Several cases of ^{18}F-FDG dynamic brain PET data and time-activity curves of sampled arterial plasma were used as training data.

Then, the trained Deep-Learning algorithm could estimate the time-activity curve of arterial plasma. It enables non-invasive compartment model analysis.

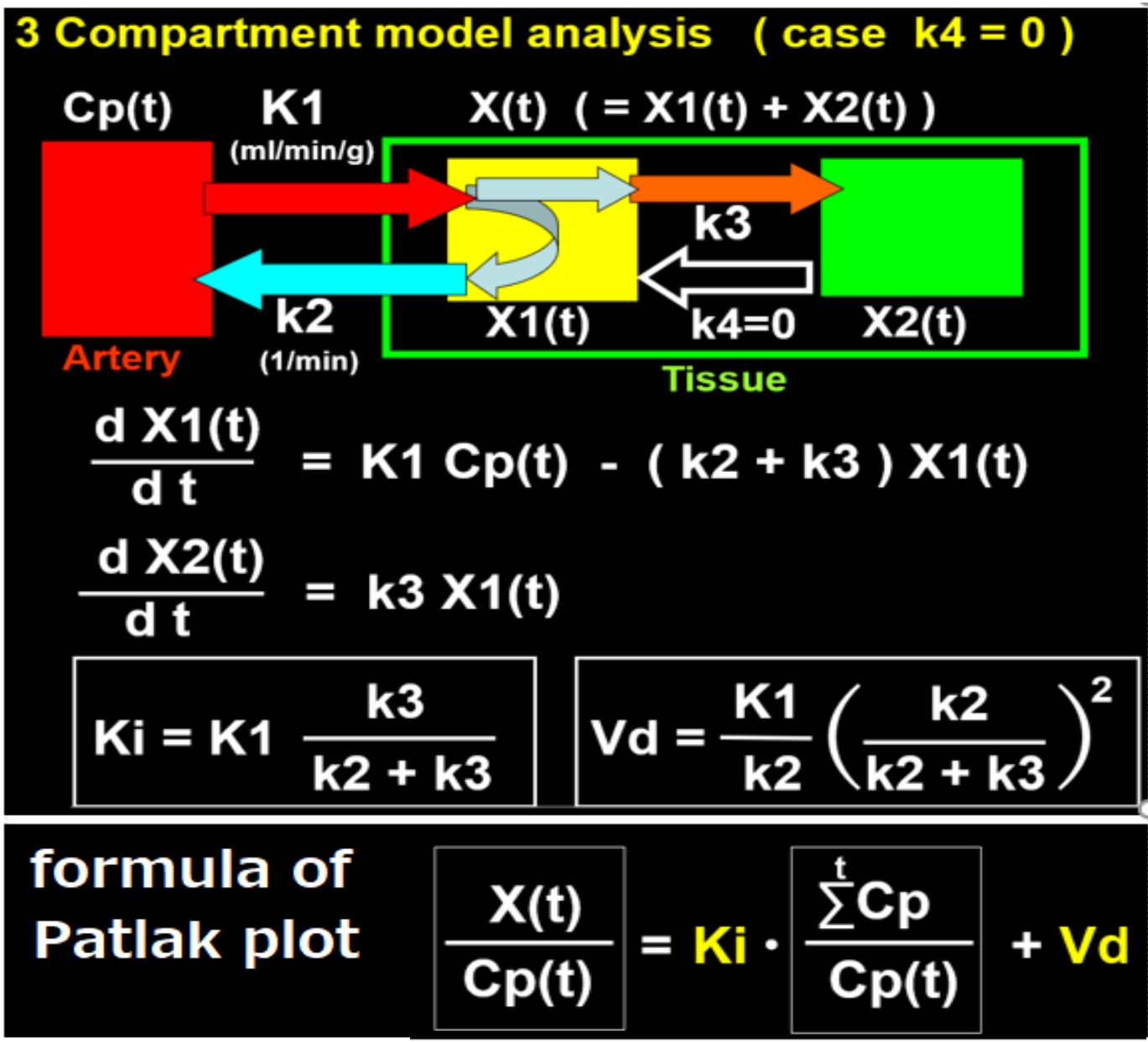




Patlak plot is a 3-compartment model analysis without arterial blood sampling.

This method is used clinically in the ^{99m}Tc-ECD brain dynamic scintigraphy to estimate blood flow in the bilateral cerebral hemisphere.

Simplified model is used, k4 is assumed to be zero, formula of Patlak plot is derived.



Cp(t) is a time-activity curve of the arterial plasma.
But clinically, in the ^{99m}Tc-ECD dynamic brain scintigraphy, the Cp(t) is used the time-activity curve of the Aortic arch.
X(t) is time-activity curve of the bilateral cerebral hemisphere.

Distribution of $\sum Cp(t) / Cp(t)$ and $X(t) / Cp(t)$ are plotted, a fitted line is drawn.

The slope of the line is

Ki（= K1･k3/(k2+k3)）

Ki means the uptake rate of ^{99m}Tc-ECD into the cerebral hemisphere, the value is used as the cerebral blood flow.

formula of Patlak plot

$$\frac{X(t)}{Cp(t)} = Ki \cdot \frac{\sum^{t} Cp}{Cp(t)} + Vd$$

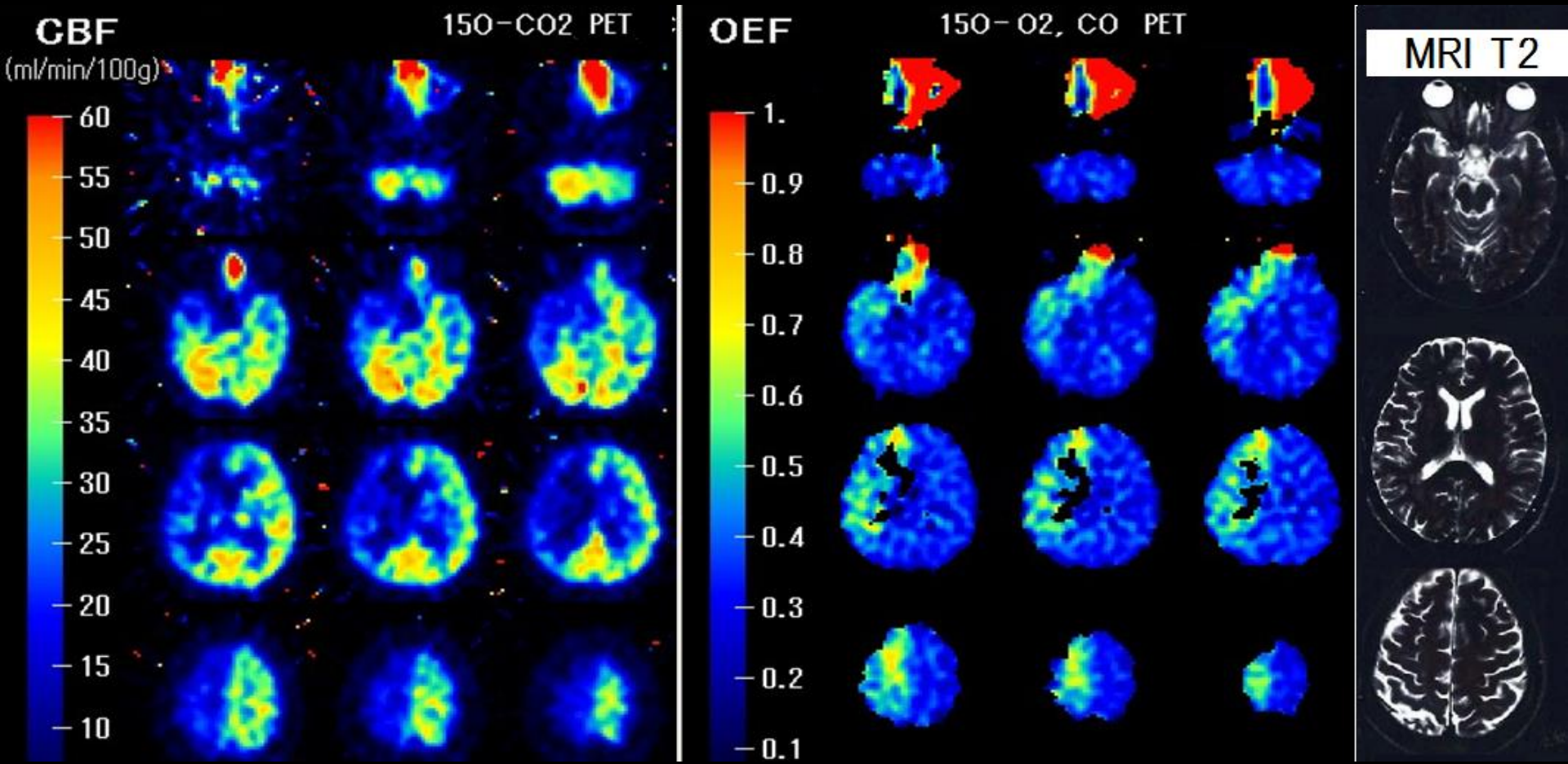
^{15}O-CO2、O2　Brain PET quantifies CBF, OEF.

Cerebral Blood Flow (CBF), Oxygen Extraction Fraction (OEF)。

Case of severe stenosis in the right internal carotid artery.

Although it is not a cerebral infarction (MRI T2 image is normal), severe hypoperfusion, increased oxygen uptake in the Rt. brain.

It is called misery perfusion. (Immediately before infarction)

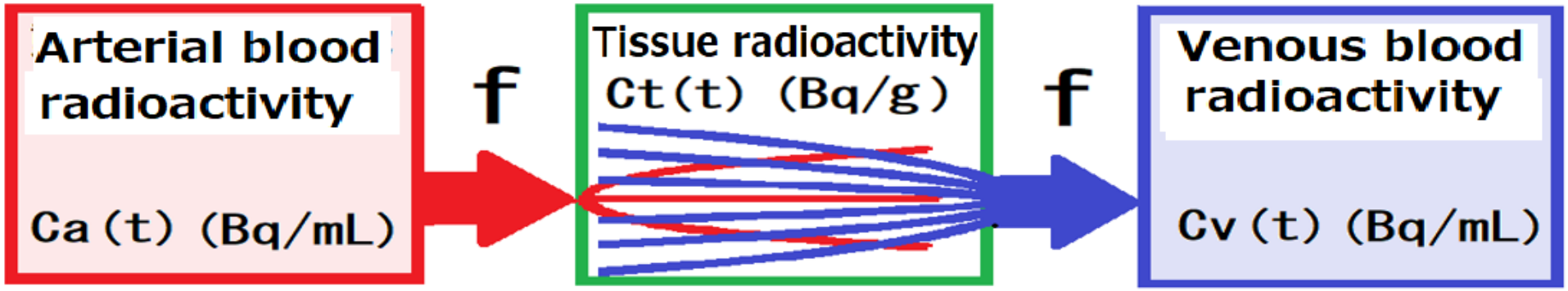


Fick's principle

PET study using ^{15}O-CO_2 or ^{15}O-H_2O, Fick's principle is used to estimate the tissue blood flow.

A micro-tissue uptakes Ct(t) of radioactivity during one second, and radioactivity of the artery and vein nearby the tissue are Ca(t) and Cv(t),
the relationship of Ct, Ca, Cv and blood flow of the micro-tissue f is presented as follows;

$$\frac{dCt}{dt} = f(Ca - Cv)$$



But it is impossible to measure the radioactivity of the vein nearby the micro-tissue Cv(t).

Anatomically, the volume of venous blood is much lager than that of arterial blood in the micro-tissue.

So, radioactivity of the venous blood Cv and nearby microtissue Ct have a linear relationship.

Then the ratio of the Ct and Cv is defined the value p（partition coefficient（= Ct / Cv））.（Cv = Ct / p）.

The Fick's principle is presented as follows;

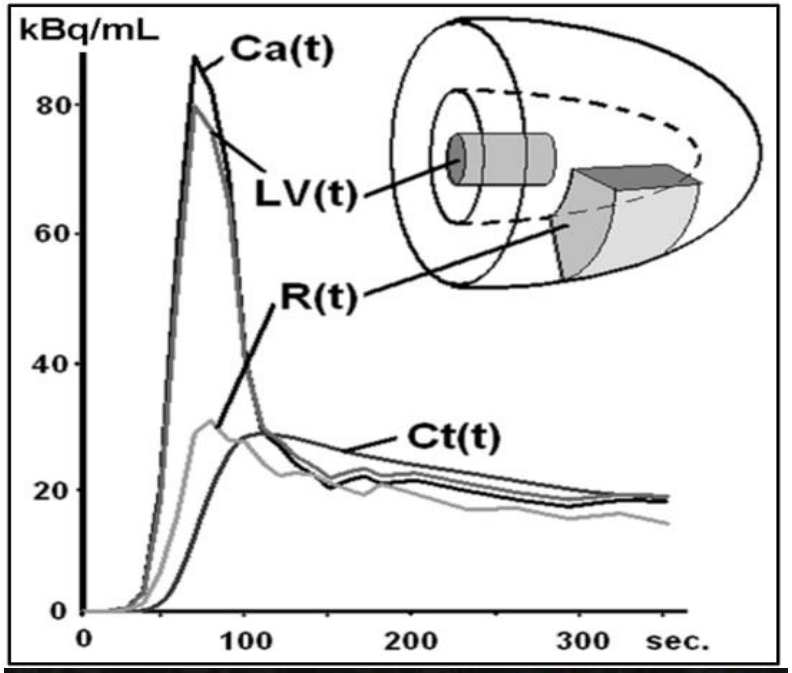
$$\frac{dCt(t)}{dt} = f\,Ca(t) - \left(\frac{f}{p}\right)Ct(t)$$

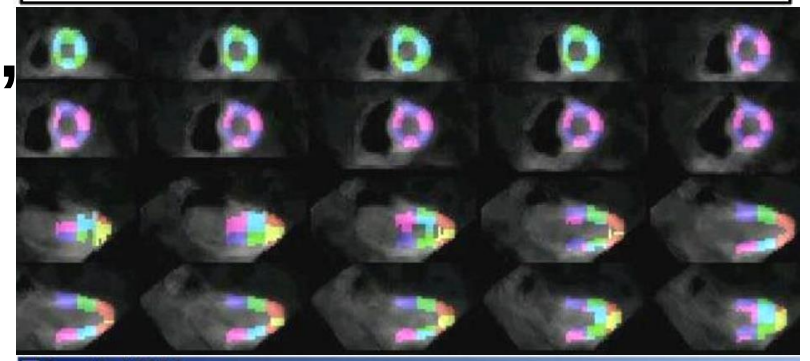
This equation enables to estimate the tissue blood flow f , when Ca(t) and Ct(t) were acquired using dynamic PET study.

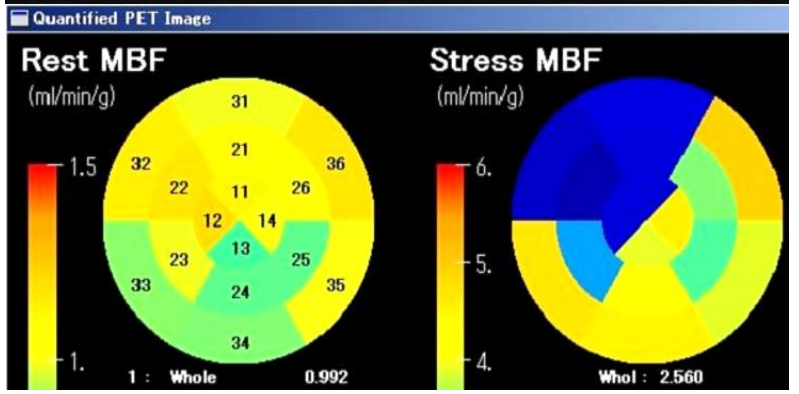
Myocardial PET study with ^{15}O-H_2O, which enables to estimate regional myocardial blood flow (MBF) using Fick's principle.

In the heart study, radio-activity of the artery is derived from the Left ventricular count, blood sampling is not needed.

This case shows normal MBF at resting state, but decreased MBF at the LAD region at stressed state (ATP infusion). Effort Angina at LAD region is diagnosed quantitatively.



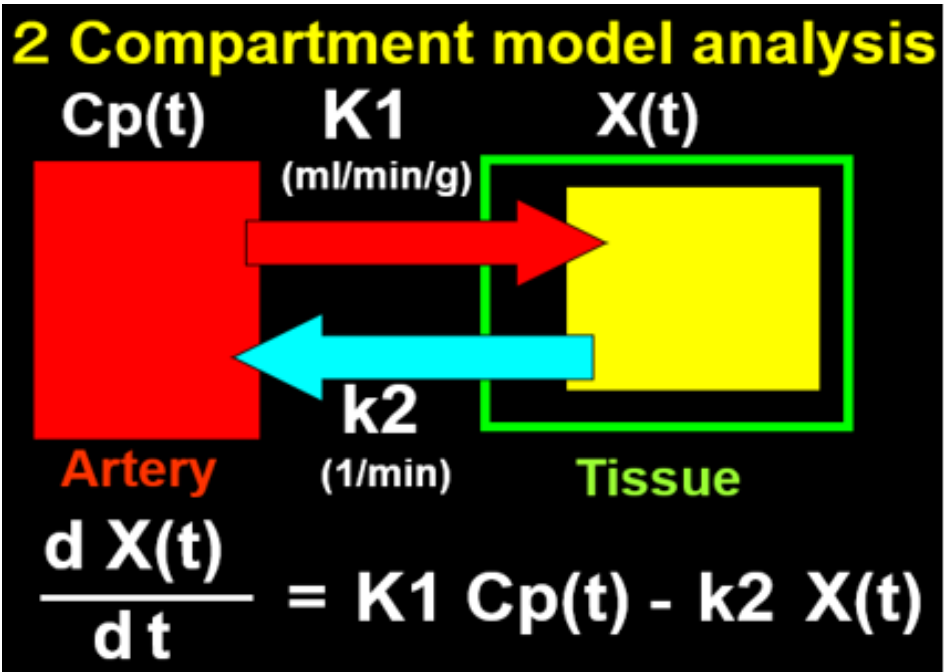


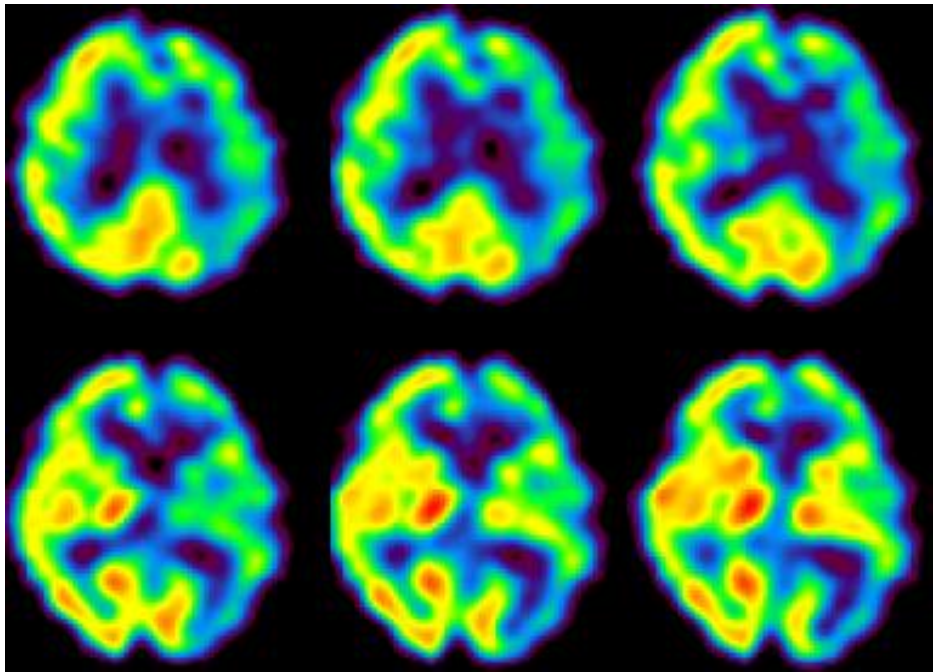


2-compartment model analysis is also useful.
It is used clinically for the ^{123}I-IMP Brain SPECT, myocardial dynamic PET with ^{11}C-acetate, $^{13}NH_3$, ^{82}Rb.

^{123}I-IMP Brain SPECT

IMP is amphetamine, stimulant, highly accumulated into the brain nerve tissue. In the 2-compartment model, k2 (return rate from the brain to the blood) of IMP is assumed to be zero.





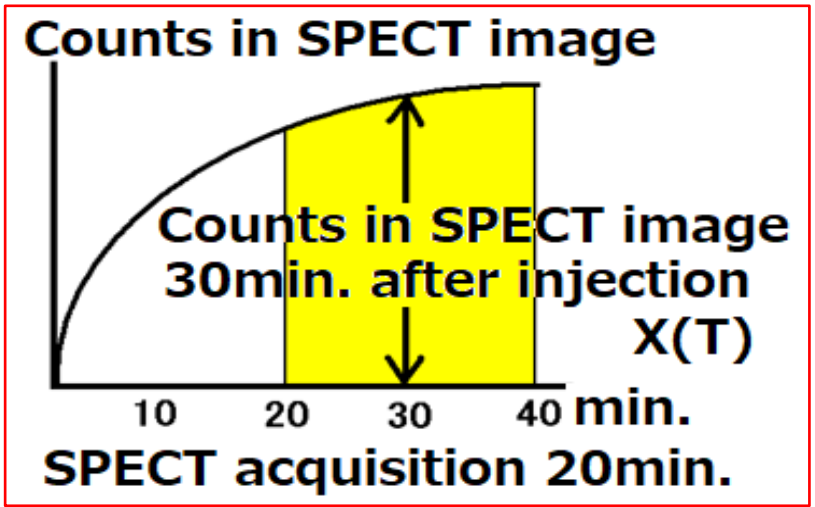
When the k2 value is zero, 2-compartment model to estimate cerebral blood flow (CBF) is solved easily.

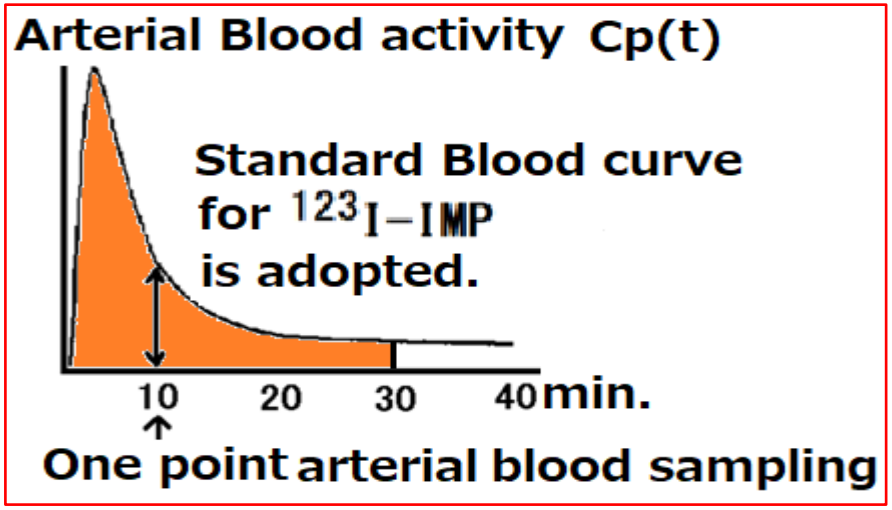
$$\frac{dX(t)}{dt} = K1\,Cp(t) \qquad X(T) = K1 \int_0^T Cp(t)\,dt$$

$$K1 \fallingdotseq CBF = X(T) \Big/ \int_0^T Cp(t)dt \quad (T=30\text{min})$$

$$= \frac{\text{Radioactivity of the brain tissue in the SPECT image}}{\text{Integration of radioactivity of arterial blood for 30min.}}$$

^{123}I-IMP Brain SPECT image is started to scan 20minutes after injection of ^{123}I-IMP, acquisition time is 20mimutes. So,^{123}I-IMP Brain SPECT is assumed to be scanned 30min. after injection.





Q.1

Which is correct about SUV of ^{18}F-FDG PET ?

1. High blood sugar increases in tumors
2. Lower in muscles after exercise
3. Leakage of injection increases in the brain
4. One hour after administration, it becomes constant in the tumor
5. It becomes 1 when ^{18}F-FDG is evenly distributed in the body.

Q.2

Which lesion has low ^{18}F-FDG accumulation ?

1. Colorectal cancer
2. Malignant melanoma
3. Malignant lymphoma
4. Head and neck squamous cell carcinoma
5. Well-differentiated hepatocellular carcinoma

Q.3

Choose two values to calculate SUV of ^{18}F-FDG PET.

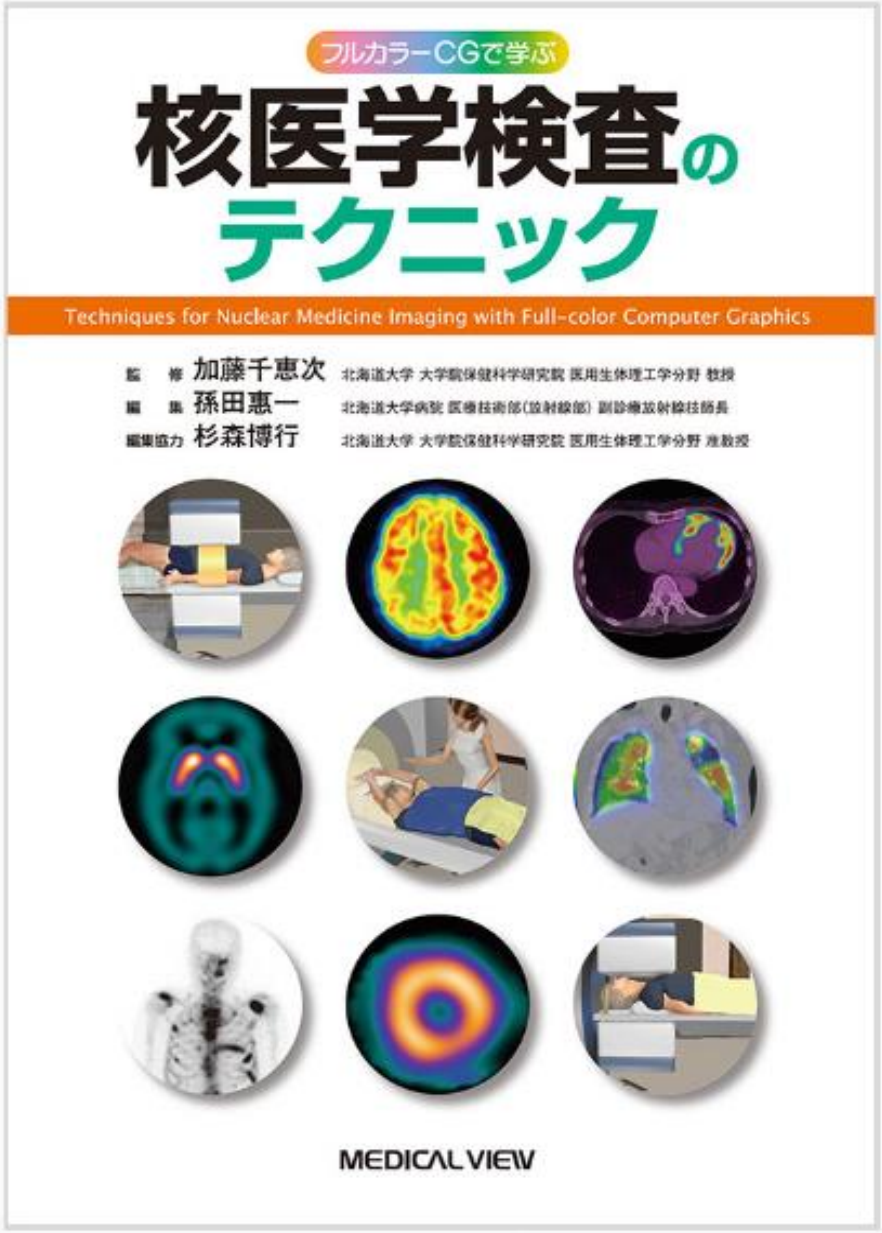
1. Weight
2. Blood glucose level
3. Radioactivity in blood
4. Volume of drug administered
5. Radioactivity of administered drug

Q.4

In the healthy person, which organ has less ^{18}F-FDG accumulation?

1. Brain
2. Liver
3. Gall bladder
4. Kidney
5. Colon

References



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