Nuclear Image Study for High Risk and Locally Advanced Prostate Cancer Before Treatment of Tentative Cure

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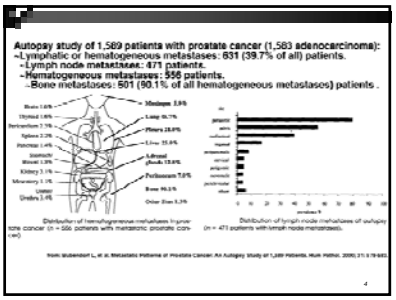
Definition

- High risk group:
  - T category ≧ T3a (or T2c)
  - PSA > 20 ng/mL
  - Gleason score ≧ 8
- Locally advanced disease
  - Clinical T category as T3 or T4.

Characters of Nuclear Medicine Study

- To find clinically metastatic disease (M1 or N1).
- To differentiate the suspicious metastatic disease in other imaging studies.



Bone Scan (Skeletal Scintigraphy)

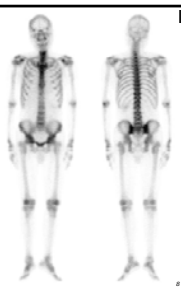
- Radio-labeled compound
  - ^{99m}Tc-labled diphosphonate (MDP, HEDP, HMDP)
  - ^{18}F-Sodium fluoride (NaF)
- High affinity to mineralized bone matrix

^{99m}Tc-MDP Bone Scan

Test	Signs of metastases
Bone scan if you have a:	• T1 tumor and your PSA level is >20 ng/mL, • T2 tumor and your PSA level is >10 ng/mL, • Gleason score of 8 or higher, • T3 or T4 tumor, or • You have symptoms that suggest cancer is in bone

NCCN Guidelines for Patients®: Prostate Cancer Version 1.2014

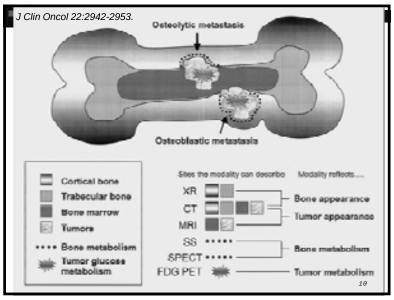
^{99m}Tc-MDP bone scan
Normal pattern of
male adult



Bone Scan

- Increasing uptake ≈ increasing bone turnover
  - ≠ bone metastasis
  - ≠ osteosclerotic change
  - ≠ osteolytic change

J Clin Oncol 22:2942-2953.



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Pattern

- Fundamental of bone scan to diagnose bone metastasis.
- Features:
  - Multifocal
  - Intense
  - Axial skeleton

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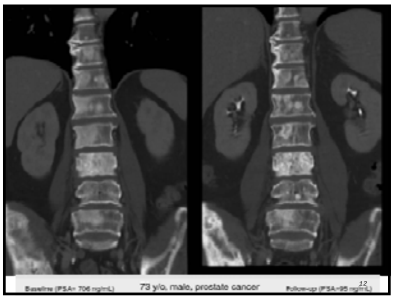

Baseline (PSA= 706 ng/mL) 73 y/o, male, prostate cancer Follow-up (PSA=95 ng/mL)

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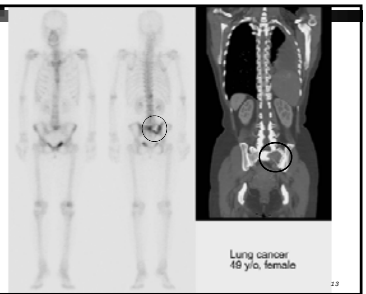

Lung cancer
49 y/o, female

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Positron Emission Tomography (PET)
正子斷層造影

Positron	**β+**	**正電子**
Emission		**射出**
Tomography		**(電腦)斷層造影**

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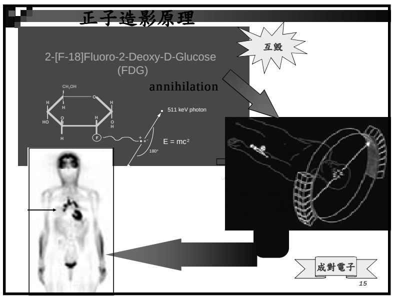
正子造影原理



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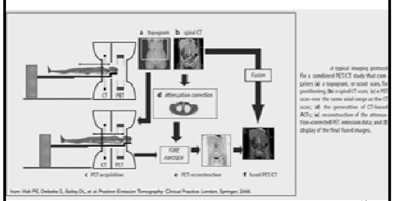
PET/CT擷取影像方式



from: Valk PE, Delbeke D, Bailey DL, et al. Positron Emission Tomography: Clinical Practice. London, Springer, 2006.

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正子射出藥物偵測腫瘤的機制

PET Radiopharmaceuticals: Mechanisms of Uptake and Localization

Biochemical Process	Radiotracer	Mechanism of Uptake or Localization
Blood flow/perfusion	[^{15}O]Water	Freely diffusible across membranes
Glucose metabolism	[^{18}F]FDG	Facilitated diffusion via glucose transporters. Substrate for hexokinase in glucose metabolism
Bone metabolism	[^{18}F]Fluoride	Incorporation in the hydroxyapatite crystals in bone
Membrane synthesis	[^{11}C]Choline, [^{18}F]Fluorocholine (FCH)	Substrates for choline kinase in choline metabolism
Lipid synthesis	[^{18}F]Fluoroacetate	Acetate is activated to acetyl-CoA in both the cytosol and mitochondria by acetyl-CoA synthetase
DNA synthesis	[^{11}C]Thymidine, [^{18}F]Fluorothymidine (FLT)	Substrates for thymidine kinase (TK-1) in DNA synthesis and reflects tumor cell proliferation rate
Hypoxia	[^{18}F]FMISO	Intracellular reduction and binding
Receptor Binding	[^{18}F]FES	Specific binding to estrogen receptors in breast cancer
	^{68}Ga-DOTATOC	Specific binding to somatostatin receptor (SSTR-II)
	^{68}Ga-DOTANOC	Specific binding to somatostatin receptor (SSTR-II, III, V)
AA transport and protein synthesis	[^{18}F]FDOPA	Precursor for the synthesis of dopamine
	[^{11}C]-L-methionine, [^{18}F]FMT, [^{18}F]FCCA	Transport into the cells involves amino acid carrier protein. Intracellular trapping involves protein synthesis or transmethylation
Binding to tumor antigens	^{124}I-, ^{64}Cu-, ^{86}Y-Labeled Antibodies	Specific binding to tumor associated antigenic binding sites (such as CEA, PSMA, CD20 and CD22)
Apoptosis	^{124}I-Annexin V, ^{64}Cu-Annexin V	Specific binding to Phosphatidylserine (PS) on cell membrane
Angiogenesis	RGD peptide, ^{18}F-FB-E[c(RGDyK)]2	Integrin receptors ($\alpha_v\beta_3$) on endothelial cells of neovasculature
Gene expression	[^{18}F]Oligonucleotide	In vivo hybridization with mRNA
	[^{18}F]FHBG	Substrate to herpes virus thymidine kinase

from: Semin Nucl Med 37:400-419

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^{18}F-NaF Bone PET

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氟-18氟化鈉正子造影 健保支付項目

- 限病患需施行全身骨骼掃描時，**無法取得Tc-99m時申報**。
- 不得同時申報26029B (全身骨骼掃描 Whole body bone scan)。
- 申報費用應檢附報告。

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CMS Reimbursement of ^{18}F-NaF PET Bone Scan

(After February 26, 2010)

- Under the Coverage with Evidence Development Program (CED)
- Participating in the approved clinical trial to answer:
  - Change in patient management to more appropriate palliative or curative care?
  - Improved quality of life?
  - Improved survival?

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Hillner BE, et al. Impact of ^{18}F-Fluoride PET in Patients with Known Prostate Cancer: Initial Results from the National Oncologic PET Registry. J Nucl Med. 2014; 55: 1-8.

- Analysis cohort: 3,531 scans in 3,396 patients (from 2011-02 to 2012-12).
  - NOPR (NaF PET) opened on 2011-02-07.
  - Enrolled 25,436 patients (more than 60% with prostate cancer) up to 2013-11-25 (still enrolling).

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Hillner BE, et al. Impact of ^{18}F-Fluoride PET in Patients with Known Prostate Cancer: Initial Results from the National Oncologic PET Registry. J Nucl Med. 2014; 55: 1-8.

- Overall change in intended management ranged from 44% to 52%, and from 12% to 16% if no effect was assumed for those cases with pre-PET plans for other imaging (imaging-adjusted impact).

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Hillner BE, et al. Impact of ^{18}F-Fluoride PET in Patients with Known Prostate Cancer: Initial Results from the National Oncologic PET Registry. J Nucl Med. 2014; 55: 1-8.

- NaF PET has high overall impact, principally related to its **effect on replacing intended use of other advanced imaging.**
- Its imaging-adjusted impact was **similar to that observed with ^{18}F-FDG PET for restaging or suspected recurrence in other cancer types.**

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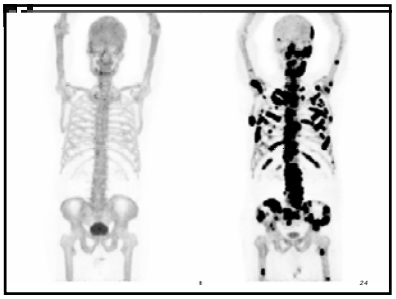

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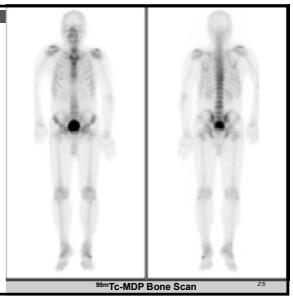
69-year-old male, prostate carcinoma (iT3bN0M0 by MRI of pelvis), Gleason score: 8, PSA: 56.5 ng/mL



^{99m}Tc-MDP Bone Scan

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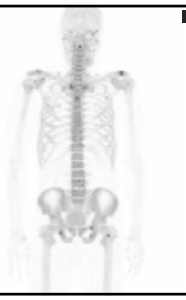
^{18}F-NaF PET



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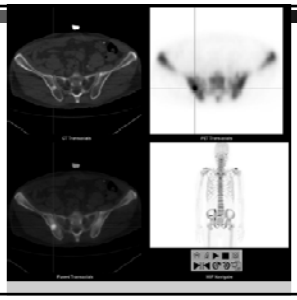

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^{18}F-FDG PET

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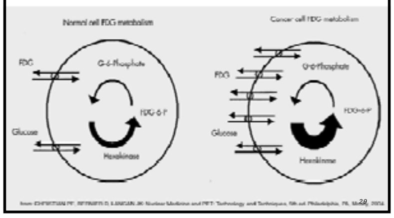
腫瘤細胞與正常細胞吸收FDG的差異



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FDG PET 腫瘤適應症健保支付項目

- 適應症
  - 乳癌、淋巴癌之分期、治療及懷疑復發或再分期。
  - 大腸癌、直腸癌、食道癌、頭頸部癌(不包含腦瘤)、原發性肺癌、黑色素癌、甲狀腺癌及子宮頸癌之分期及懷疑復發或再分期。
    - A.**分期**：評估腫瘤之期別。
    - B.**治療**：評估腫瘤對治療之反應，擬改變治療方式時。
    - C.**懷疑復發或再分期**：使用於患者已接受一階段之正統治療後，偵測疑似有復發或轉移及評估復發之程度(不得用於例行之追蹤檢查)。
    - D.以上各階段須符合：**經電腦斷層、核磁共振、核子醫學掃瞄等檢查仍無法分期者，或認定電腦斷層、核磁共振等檢查不足以提供足夠資訊以供治療所需者**，且**須於病歷中說明施行正子造影之必要性理由**。
    - E.配合腫瘤治療計畫者方得以正子造影作為療效評估項目，未有後續積極處置之計畫者，不得施行。

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CMS Coverage of Oncological FDG PET (After June 11, 2013)

Tumor Type	Initial Treatment Strategy (formerly "diagnosis" and "staging")	Subsequent Treatment Strategy (formerly "restaging" and "monitoring response to treatment")
All solid tumors not listed below	Covered	Covered
All cancers not listed below	Covered	Covered
Cervix	Covered with exceptions*	Covered
Prostate	Not covered	Covered
Breast (male and female)	Covered with exceptions*	Covered
Melanoma	Covered with exceptions*	Covered
Lung*	Covered	Covered

*Cervix: Nationally non-covered for the initial diagnosis of cervical cancer related to initial anti-tumor treatment strategy. All other indications for initial anti-tumor treatment strategy for cervical cancer are nationally covered.

*Breast: Nationally non-covered for initial diagnosis and/or staging of axillary lymph nodes. Nationally covered for initial staging of metastatic disease. All other indications for initial anti-tumor treatment strategy for breast cancer are nationally covered.

*Melanoma: Nationally non-covered for initial staging of regional lymph nodes. All other indications for initial anti-tumor treatment strategy for melanoma are nationally covered.

*Lung: includes solitary pulmonary nodule (SPN).

from: www.siemens.com/mi/o360

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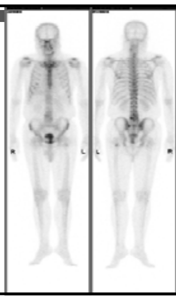
70-year-old male, confirmed prostate carcinoma (after TURP for BPH, iTxN0M1b by MRI of pelvis), Gleason score: 6, PSA: 7.9 ng/mL



^{99m}Tc-MDP Bone Scan

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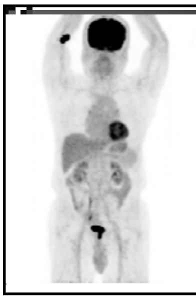
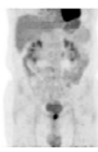


^{18}F-FDG PET



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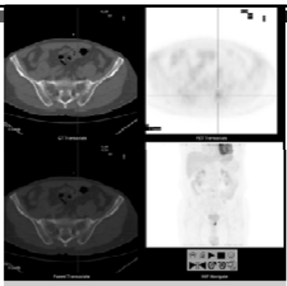

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^{11}C- or ^{18}F-Choline PET

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FDA Approval of ^{11}C-Choline for PET in Prostate Cancer

- In Sep. 2012, the U.S. FDA approved the **manufacture** and **use** (Mayo Clinic PET Radiochemistry Facility, Rochester, Minnesota) of ^{11}C-choline in patients with **suspected prostate cancer recurrence and noninformative bone scintigraphy, CT, or MR imaging** after review of 4 studies (a total of 98 patients).

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FDA Approval

- In each of the studies, **at least half the patients** with positive PET scans also had recurrent prostate cancer confirmed by histopathologic analysis.
- However, false-positive PET scans were observed in 15%–47% of patients in these studies.

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^{11}C-Choline

- Poor performance (both false positive and negative results): PSA < 2 ng/mL
  - False positive: inflammation, prostatic hyperplasia.
  - Colchicine or androgen-deprivation therapeutic drugs: possibly interfere with ^{11}C-choline PET imaging.

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^{11}C-Choline

- Physical half life of ^{11}C: 20.4 minutes.
  - Mayo Clinic PET Radiochemistry Facility is, until now, the first and only site permitted to manufacture ^{11}C-choline by FDA.
- Urinary excretion of ^{11}C-choline: < 2% at 1.5 hours post-injection.

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^{11}C-Choline

- Safety
  - Effective radiation absorbed dose: **3.22 mSv/20 mCi** of ^{11}C-Choline.
  - Adverse reaction: only an uncommon, mild injection site reaction has been reported.

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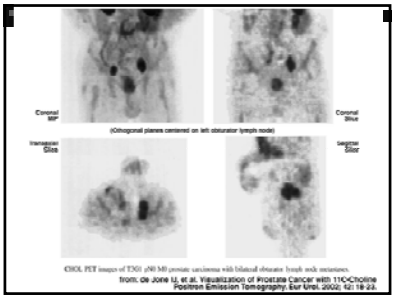
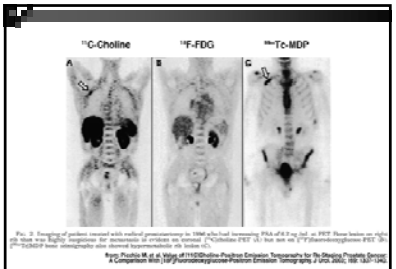


CHOL PET images of T3N1 pM0 MO prostate carcinoma with bilateral obturator lymph node metastases.

from: de Jong IJ, et al. Visualization of Prostate Cancer with 11C-Choline Positron Emission Tomography. Eur Urol. 2002; 42: 18-23.



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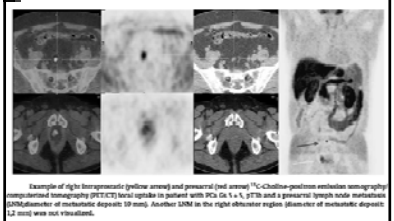

Example of right intraprostatic (yellow arrow) and presacral (red arrow) ^{11}C-Choline-positron emission tomography computerized tomography (PET/CT) focal uptake in patient with PCa (a 5 a 5, pT3b and a presacral lymph node metastasis (LNM)diameter of metastatic deposit: 10 mm). Another LNM in the right obturator region (diameter of metastatic deposit: 1,2 mm) was not visualized.

from: Schiavina R, et al. 11C-Choline Positron Emission Tomography/Computerized Tomography for Preoperative Lymph Node Staging in Intermediate-Risk and High-Risk Prostate Cancer. Comparison with Clinical Staging Nomograms. Eur Urol. 2008; 54: 292-301.

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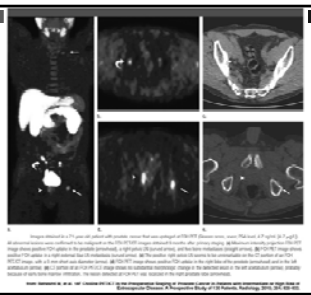

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Bone Metastasis Choline or Fluoride?

Table **Pooled data**

from: Beheshti M, et al. A literature review of 68F-fluoride PET/CT and 18F-choline or 11C-choline PET/CT for detection of bone metastases in patients with prostate cancer. Nucl Med Commun. 2012; 33: 668-676.

Tracer	Analysis	Sensitivity (95% CI interval)	Specificity (95% CI interval)
^{11}C-Choline or ^{18}F-choline	Lesion basis	84.0 (83.5–84.5)	97.7 (97.6–97.8)
^{11}C-Choline or ^{18}F-choline	Patient basis	85.2 (83.8–86.6)	96.5 (95.8–97.1)
^{18}F-Fluoride	Lesion basis	88.6 (88.1–89.1)	90.7 (90.4–91.1)
^{18}F-Fluoride	Patient basis	86.9 (83.7–90.0)	79.9 (78.4–81.4)

Sensitivities and ^{18}F-choline PET prostate cancer. ^{11}C-choline or no metastasis in

No Statistical Difference

CI, confidance interval.

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Current Utility of ^{11}C-Choline

- Initial staging: conflicting results in detecting primary tumor and regional lymph node metastases compared to conventional imaging studies.
- Restaging/detection of recurrence.

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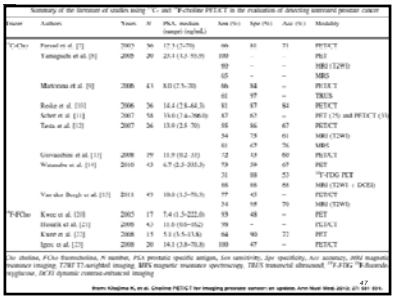

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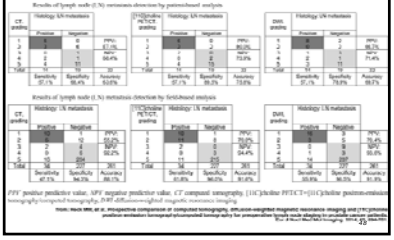
Thirty-three intermediate- and high-risk prostate cancer patients
Preoperative lymph node staging



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Take-Home Message

- 此時此地，若要使用核子醫學掃描偵測攝護腺癌的轉移病灶：
  - ^{99m}Tc-labled diphosphonate bone scan的sensitivity夠好，specificity不足。
  - ^{18}F-NaF PET/CT bone scan的sensitivity非常好，但specificity仍不足，且全民健康保險實質上不給付。
  - ^{18}F-FDG PET/CT的sensitivity不好，specificity相對較好，也許可以當成偵測疑似攝護腺癌復發的第二線輔助檢查，但全民健康保險不給付。
  - ^{11}C- or ^{18}F-choline PET/CT尚未許可合法使用於例行檢查。

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