Role of PET/CT in Hepatocellular Carcinoma

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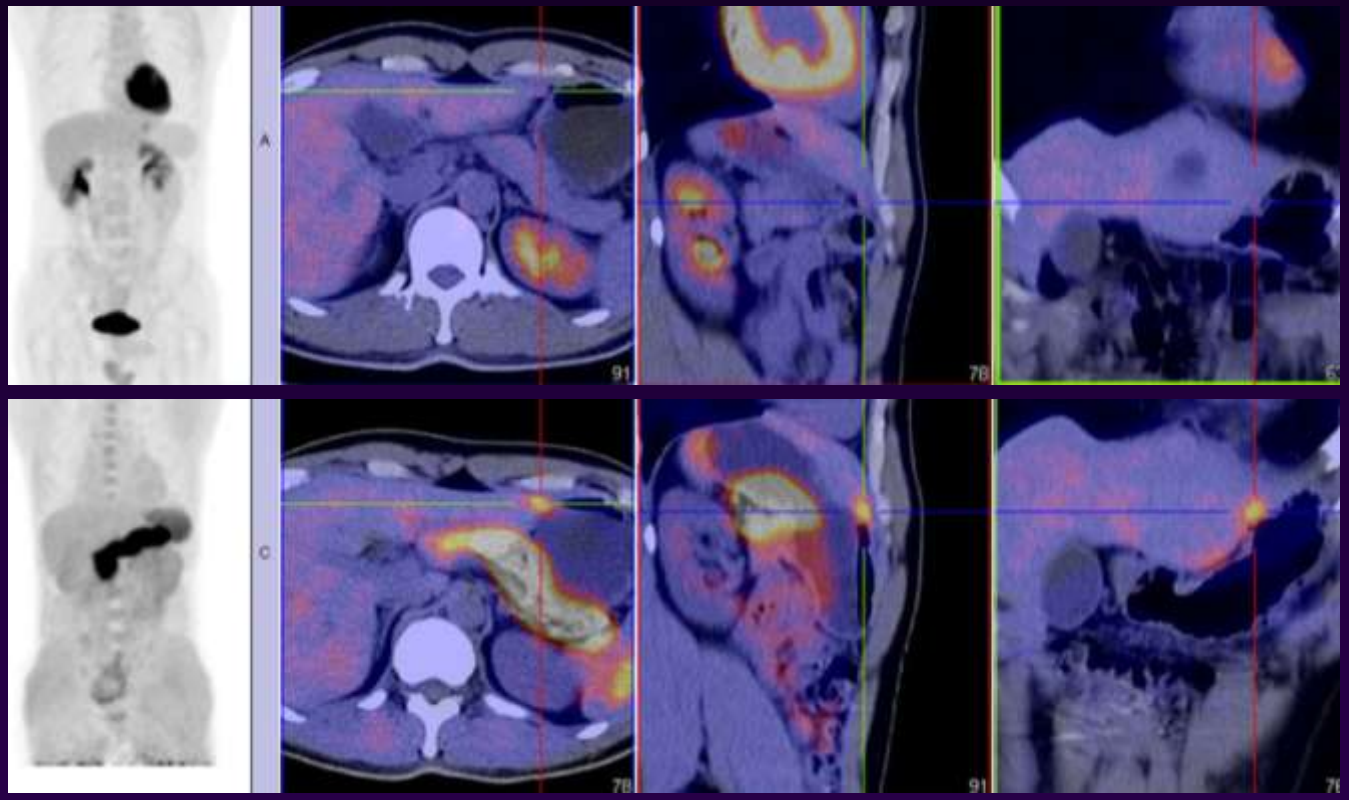
CT / MRI / USG…

Why PET/CT?

Case 1

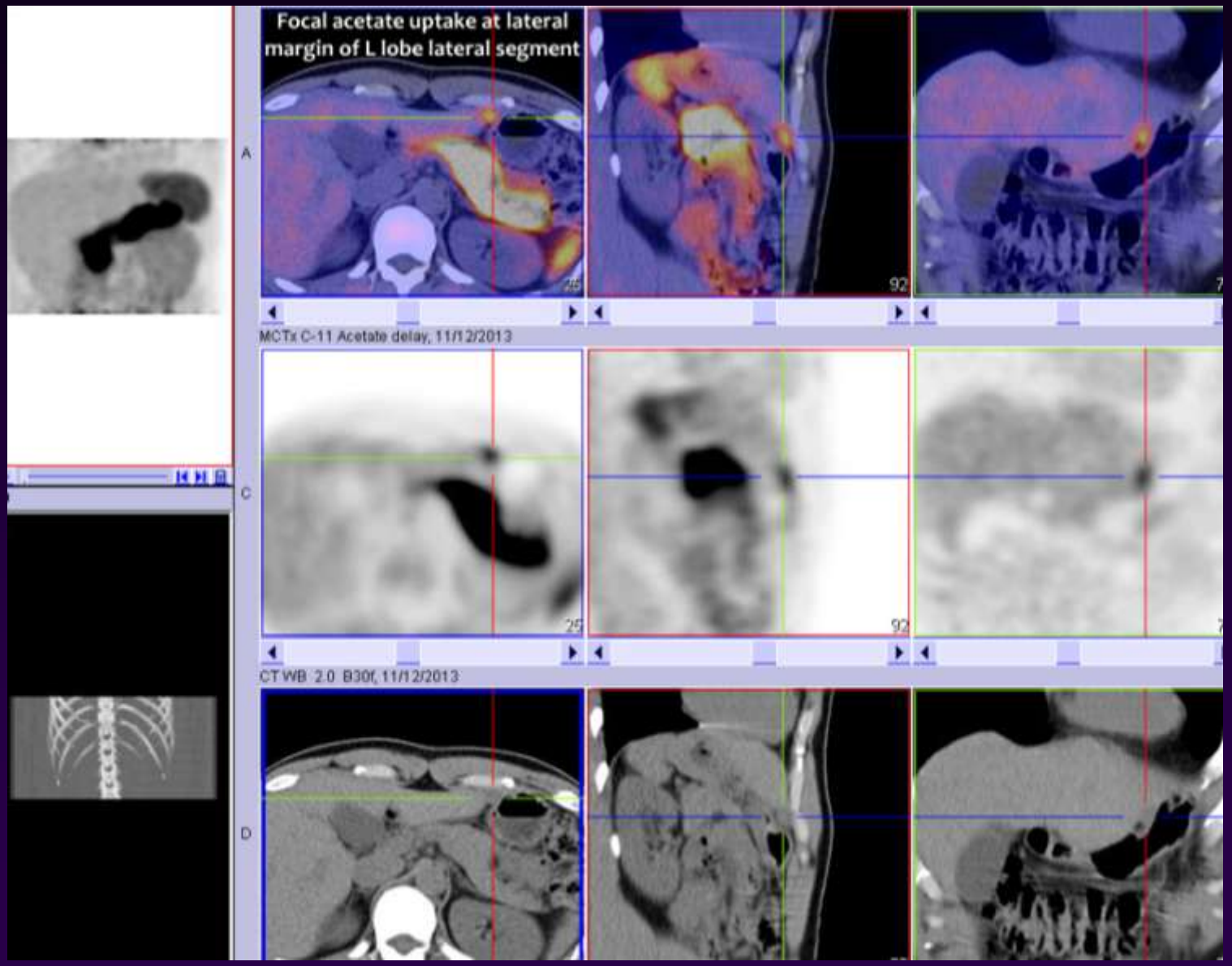
- M/46
- HBsAg carrier
- elevated AFP 200 ng/ml
- MRI liver normal

Well differentiated hepatocellular carcinoma



^{18}F-FDG

^{11}C-Acetate



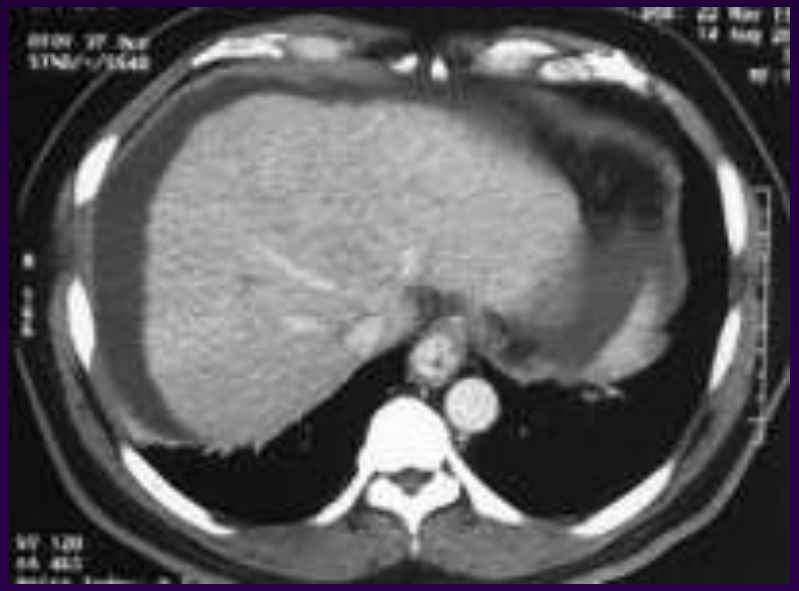
Fusion Image of PET & CT

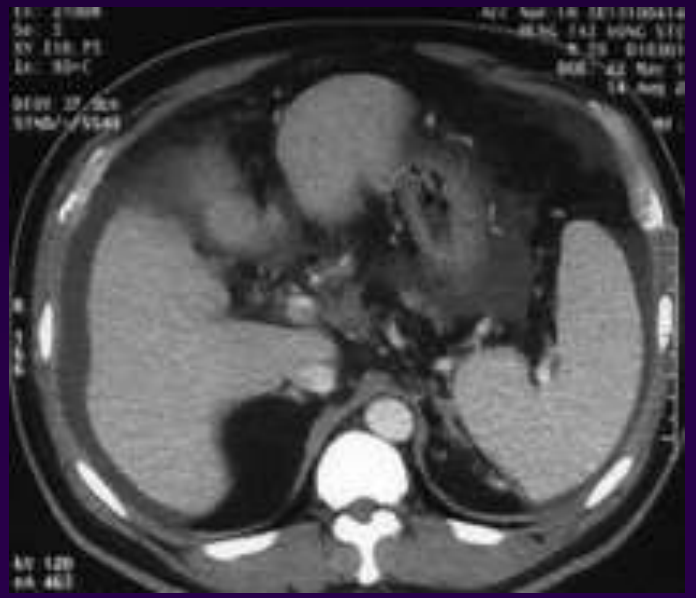
^{11}C-Acetate

CT

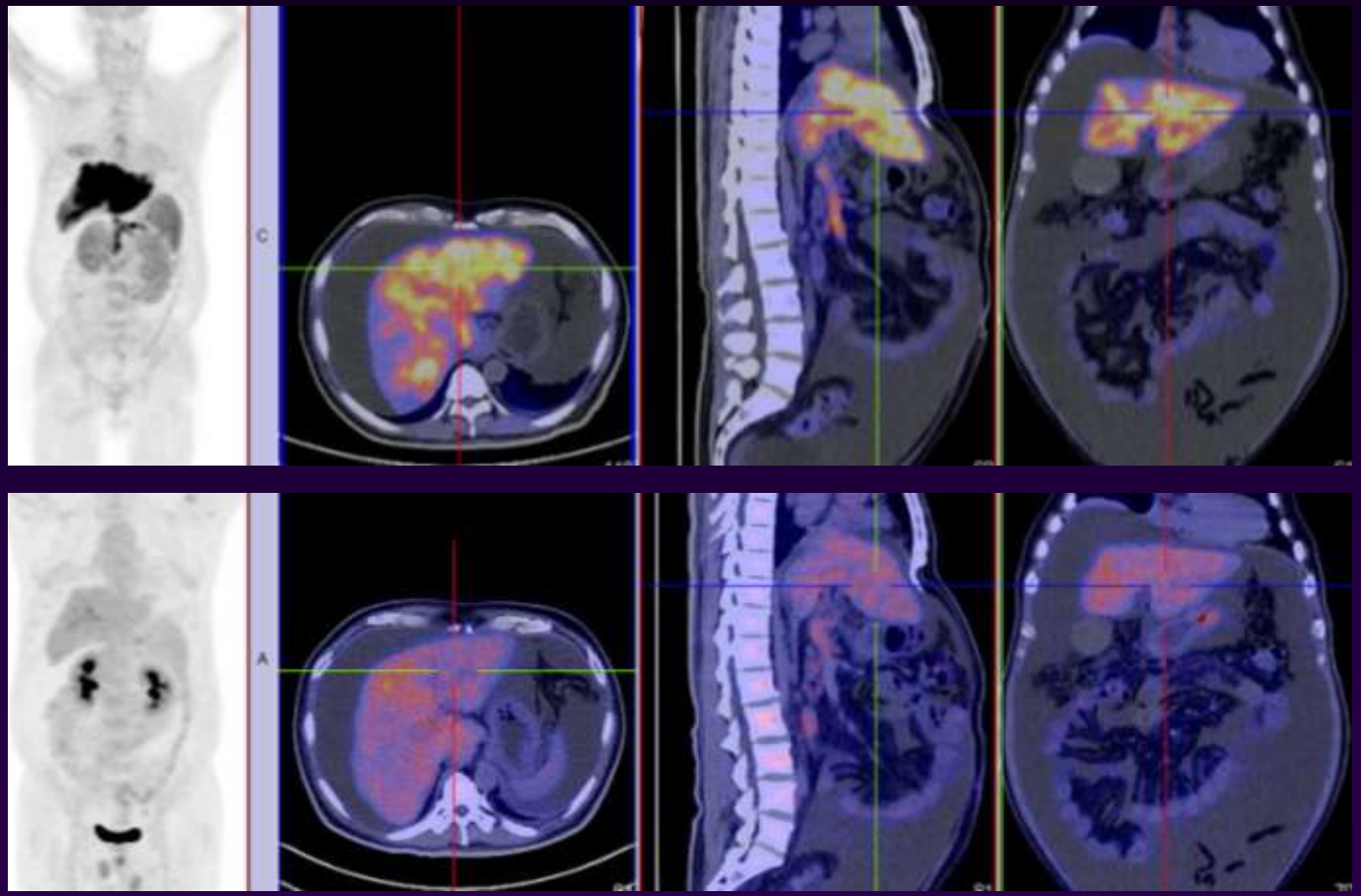
Case 2

- M/59 presented with abdominal distension
- No hepatitis B/C
- Tumor marker including CEA and AFP normal.
- CT and MRI showed liver cirrhosis, ascites, and portal vein thrombus
- Radiology meeting reviewed no definite hepatocellular carcinoma or carcinoma of colon





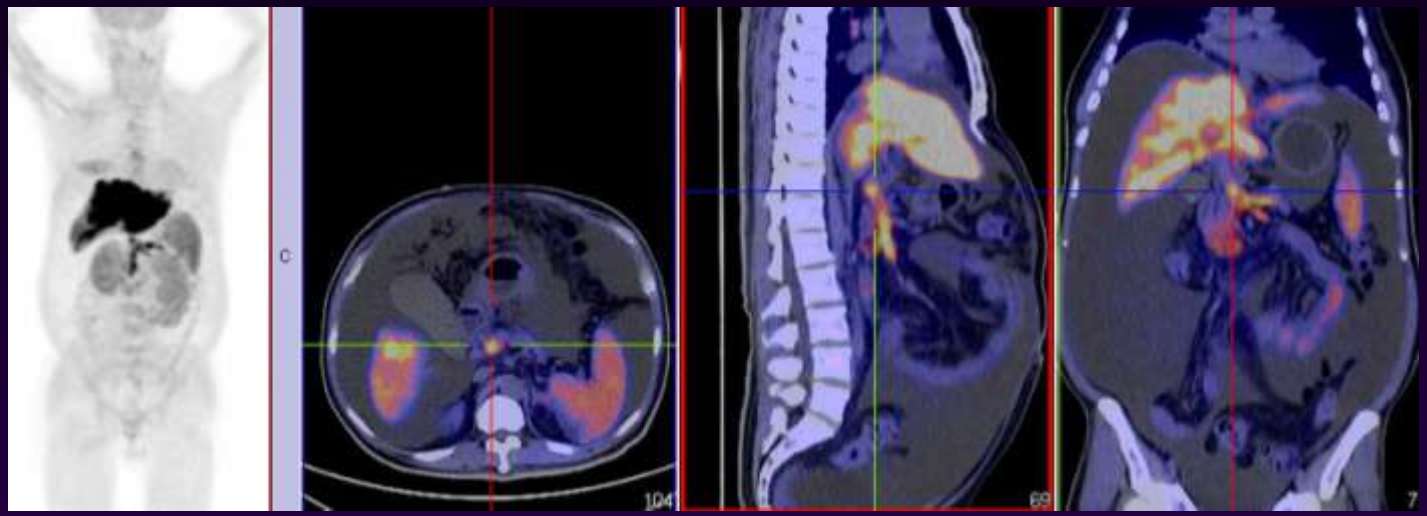
Piecemeal-type hepatocellular carcinoma



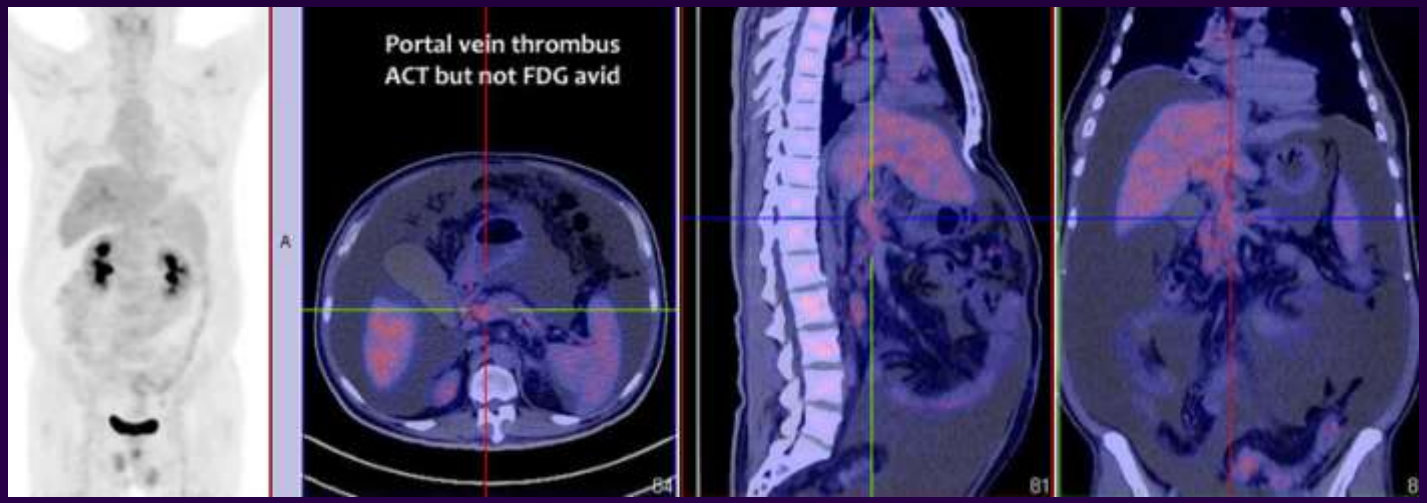
^{11}C-Acetate

FDG

Portal vein tumor thrombus

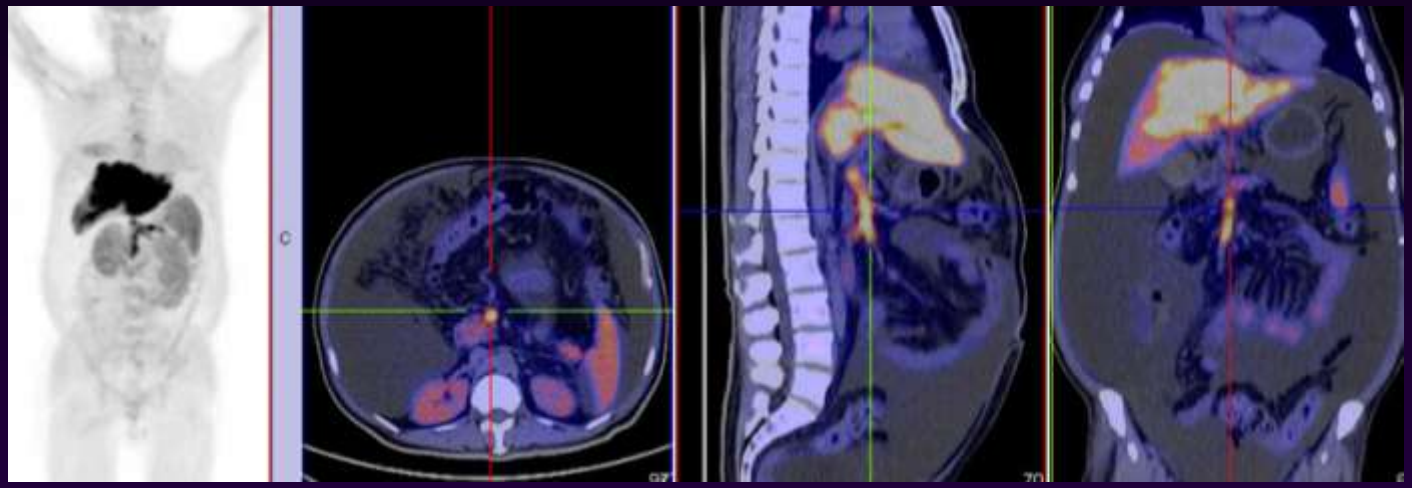


^{11}C-Acetate

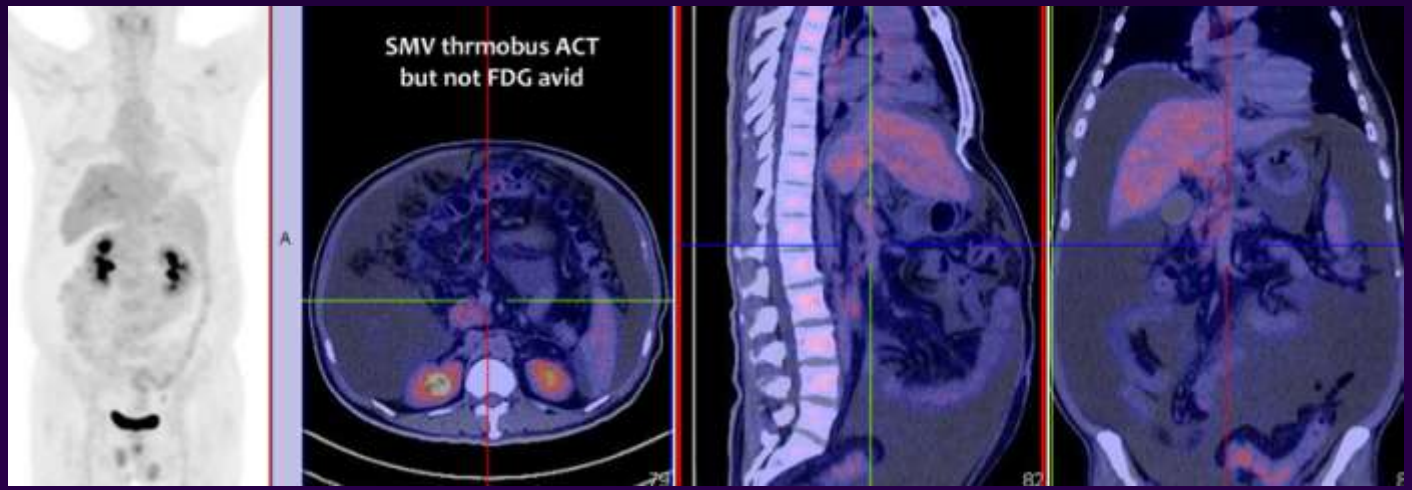


FDG

SMV tumor thrombus

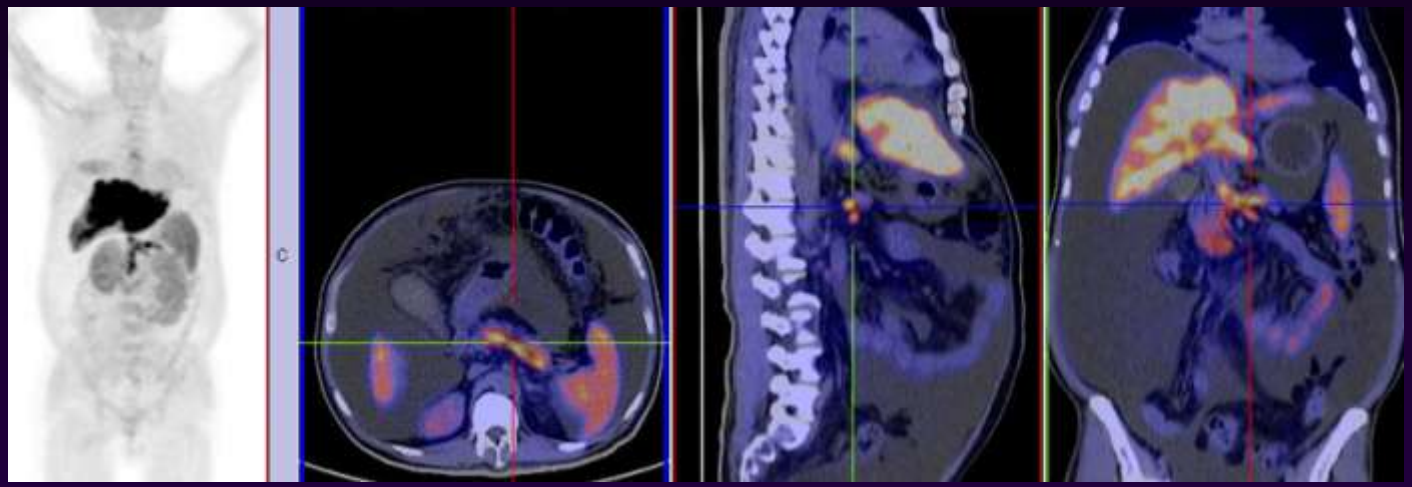


^{11}C-Acetate

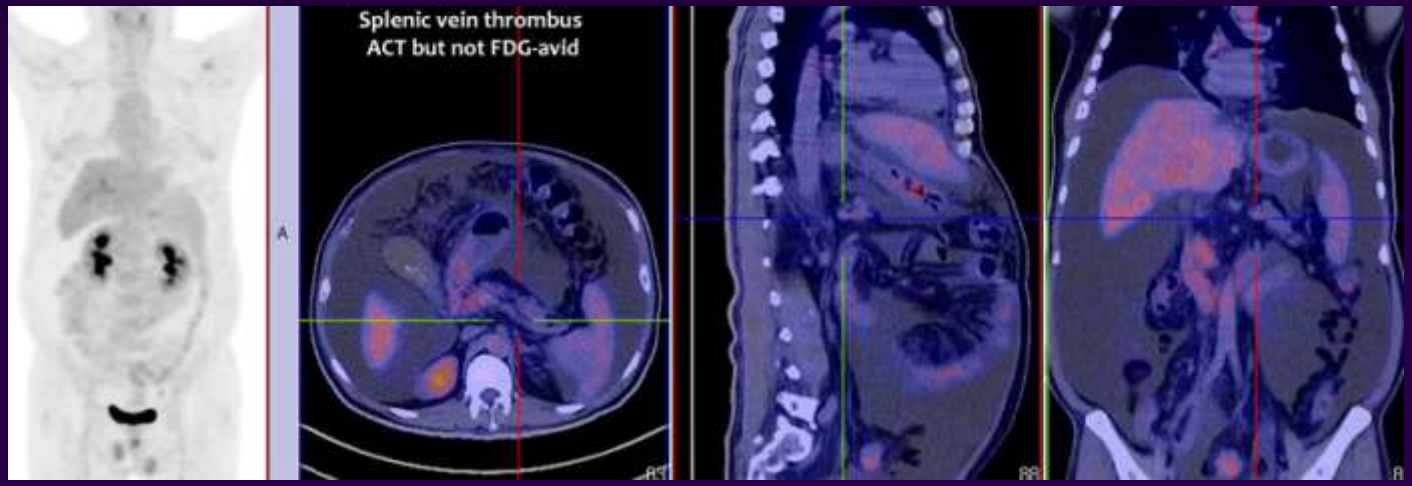


FDG

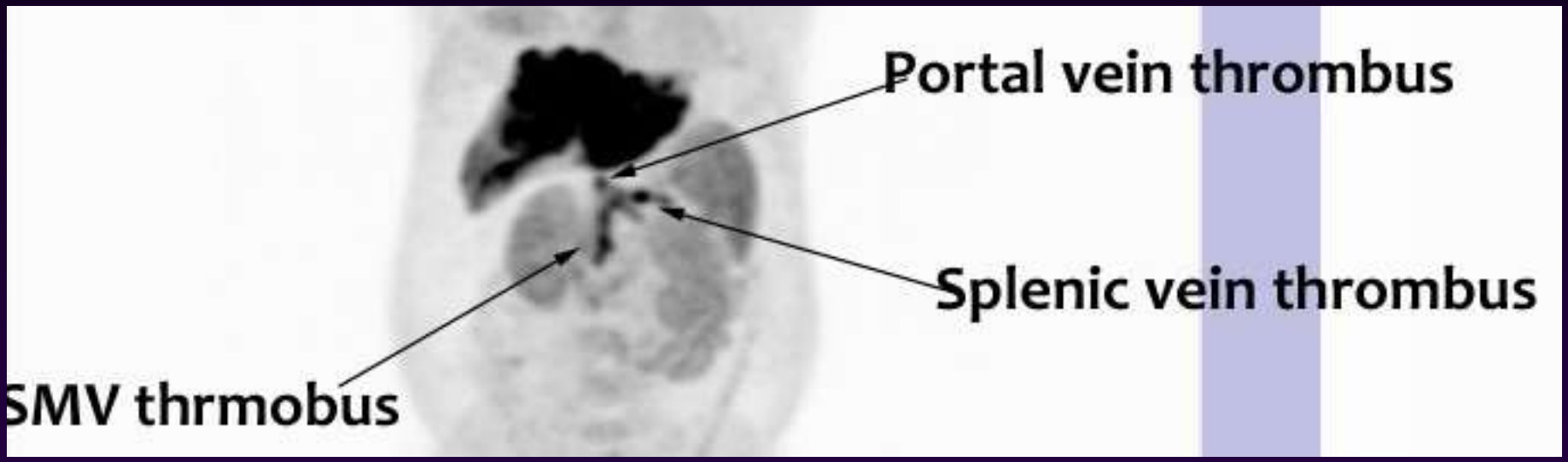
Splenic vein tumor thrombus



^{11}C-Acetate



FDG



^{11}C-Acetate PET/CT
maximum intensity projection image (MIP)

Dual-Tracer PET/CT
- Shift in paradigm of PET/CT in HCC

- Conventional ^{18}F-FDG-PET has a limited role in the evaluation of primary hepatocellular carcinoma (HCC) due to the low sensitivity of 40-50%
- using ^{11}C-acetate and ^{18}F-FDG as complementary biochemical probes of primary HCC
- detection sensitivity is related to the degree of tumor cellular differentiation
- maximize the detection accuracy

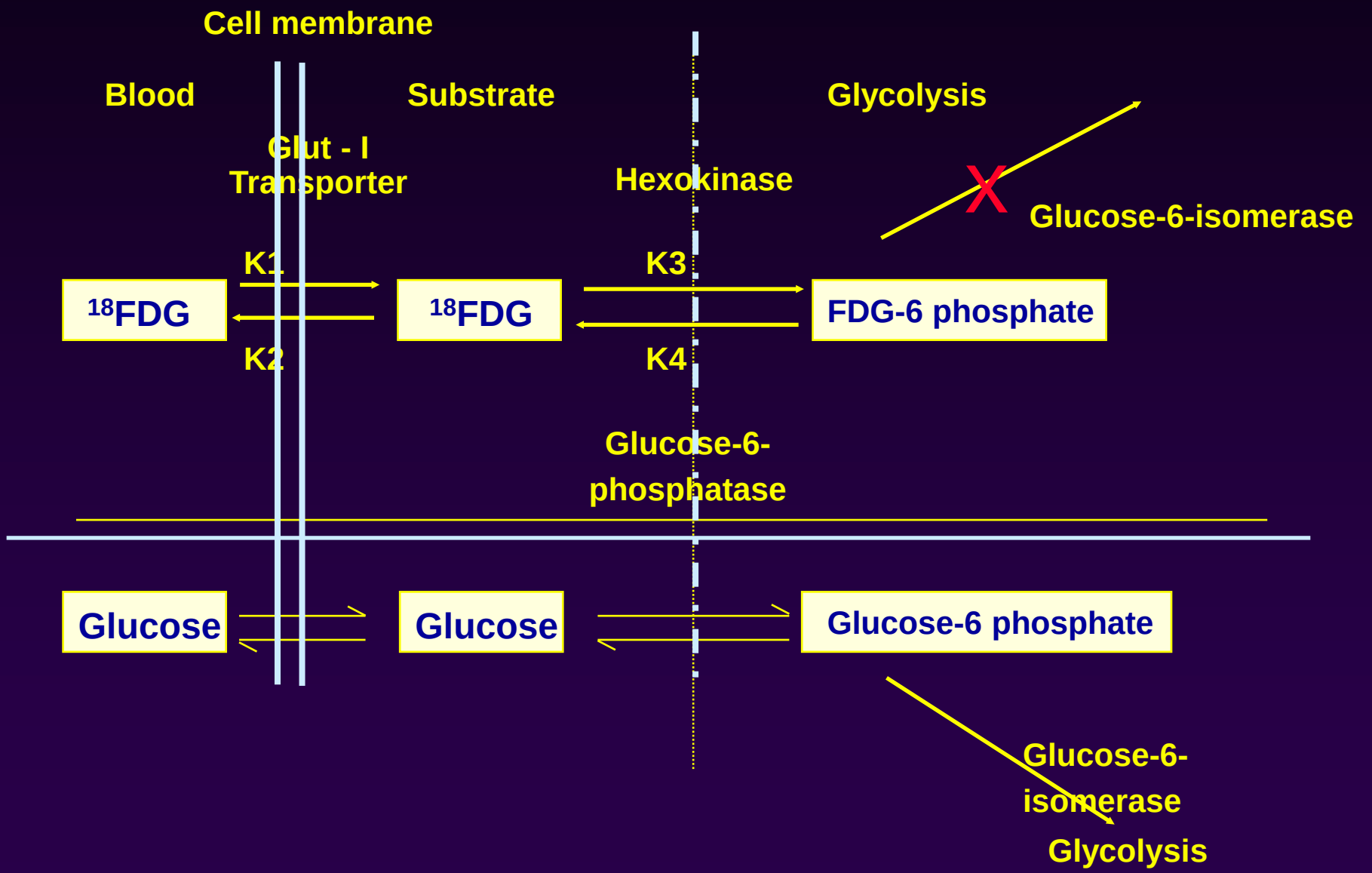
(A) Radiopharmaceuticals

(B) Clinical application

Radiopharmaceuticals

1. ^{18}F-fluorodeoxyglucose ^{18}F-FDG
2. ^{11}C-Acetate

^{18}FDG Metabolism



Limitations of ^{18}FDG in HCC

- HCC may exhibit a net glycolysis similar to or even lower than that of normal liver parenchyma
- abundant amount of the enzyme Glucose-6-phosphatase in the normal liver and certain types of HCC, such as well-differentiated HCC, leading to dephosphorylation of FDG-6-phosphate result in low tracer uptake by a higher k4/k3 level
- ^{18}F-FDG useful in poorly-differentiated HCC with increase uptake by a lower k4/k3 level

Radiopharmaceuticals

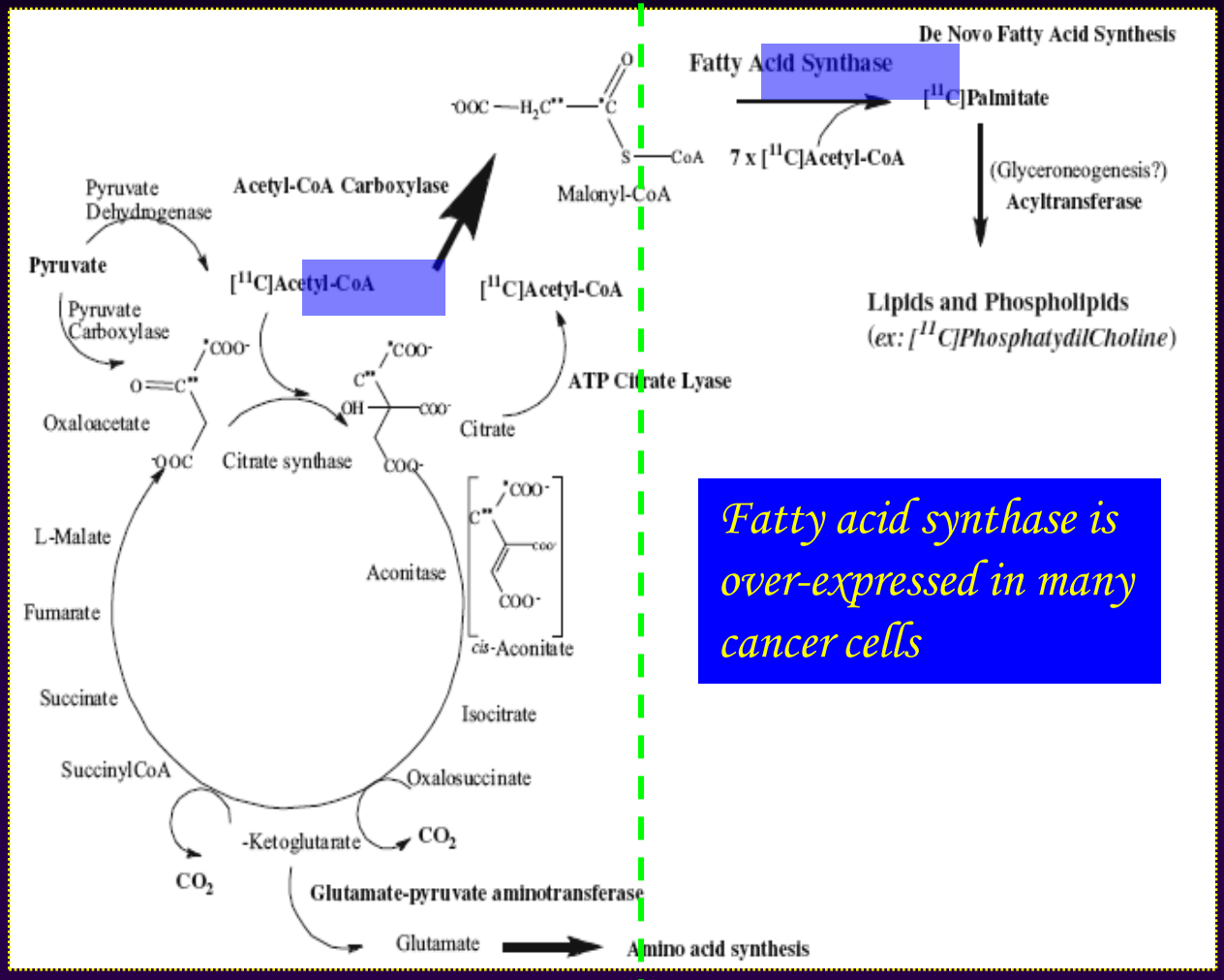
1. ^{18}F-fluorodeoxyglucose ^{18}F-FDG
2. ^{11}C-Acetate

Biochemical rationale of ^{11}C-Acetate uptake in tumor cells

- acetate is a precursor converted into acetyl-coenzyme A for synthesis of fatty acids by fatty acid synthase and distributed into biosynthetic pathways for phospholipid membrane synthesis and maintenance.
- overexpression of fatty acid synthase in tumor cells may increase the accumulation of acetate as a marker of tumor activity

Biochemistry of ^{11}C-Acetate in tumor cells

Acetate: precursor for ^{11}C-acetylCoA



Clinical application of PET/CT in HCC

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Dual tracer PET in HCC

- Ho *et al* in year 2003 reported
  - sensitivity of ^{11}C- acetate 87.3% vs. ^{18}F-FDG 47.3%
- complementary with 100% sensitivity using dual-radiopharmaceuticals protocol
- ^{11}C-acetate highly specific for HCC and negative in hemangioma, cholangiocarcinoma, secondary carcinomas (colon, breast & lung) and carcinoid tumors

Ho et al, JNM vol. 44(2) Feb, 2003

Sensitivity in detection of primary HCC
- results of different centers in 2003-2012

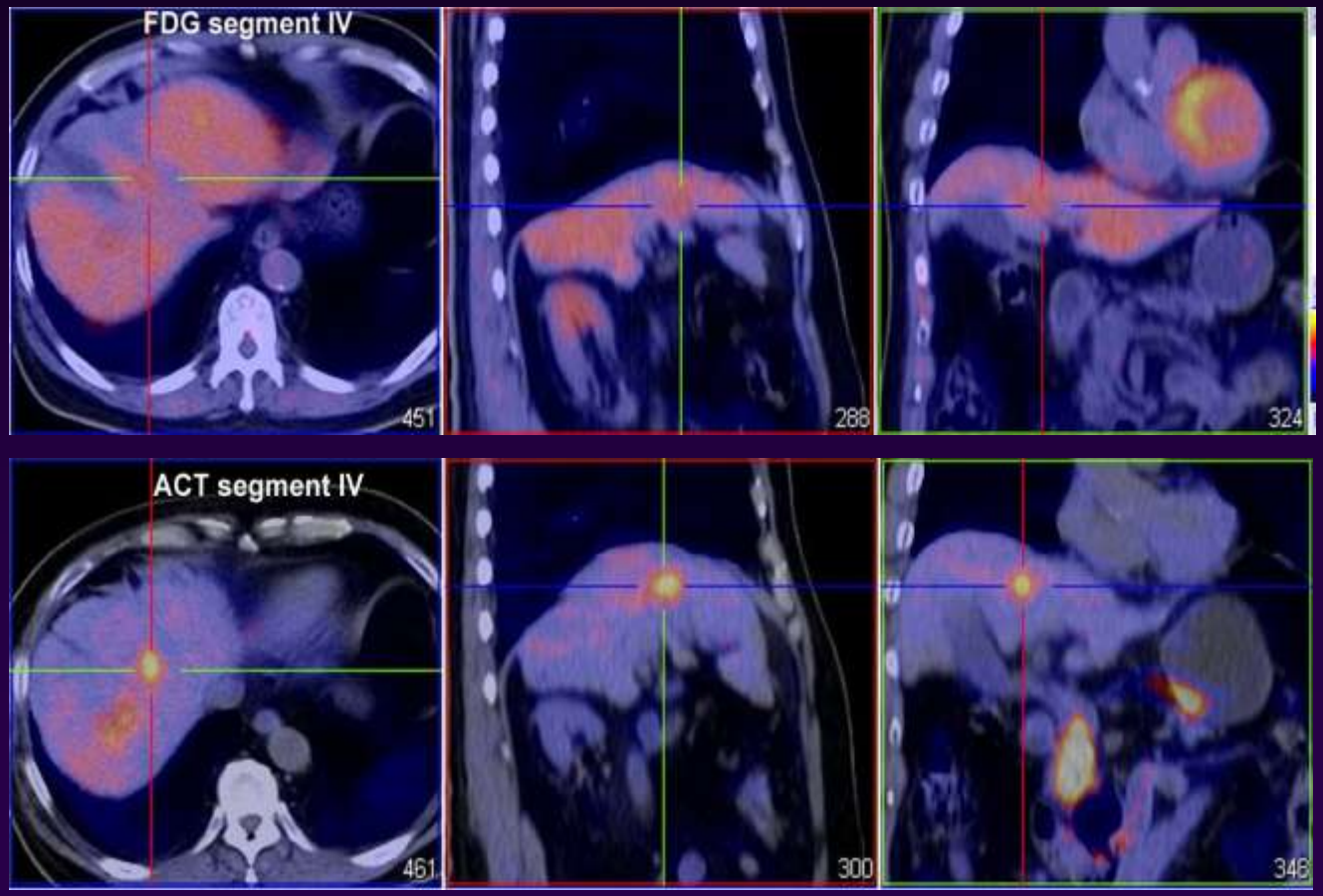
	Ho et al	Park et al	Hwang et al	Cheung et al	Larsson et al
Year	2003	2008	2009	2011	2012
No. of patients	39	99	12	58	44
^{11}C-acetate (%)	87	75	83	97	77
FDG (%)	47	61	40	60	30
Dual tracer (%)	100	83	92	97	89

Dual tracer uptake in HCC

	^{11}C- Acetate	^{18}F- FDG
well differentiated HCC	+++	-/+
moderately differentiated HCC	++	++
poorly differentiated HCC	-/+	+++
non-HCC malignancy	-	+++

Ho et al, JNM vol. 44(2) Feb, 2003

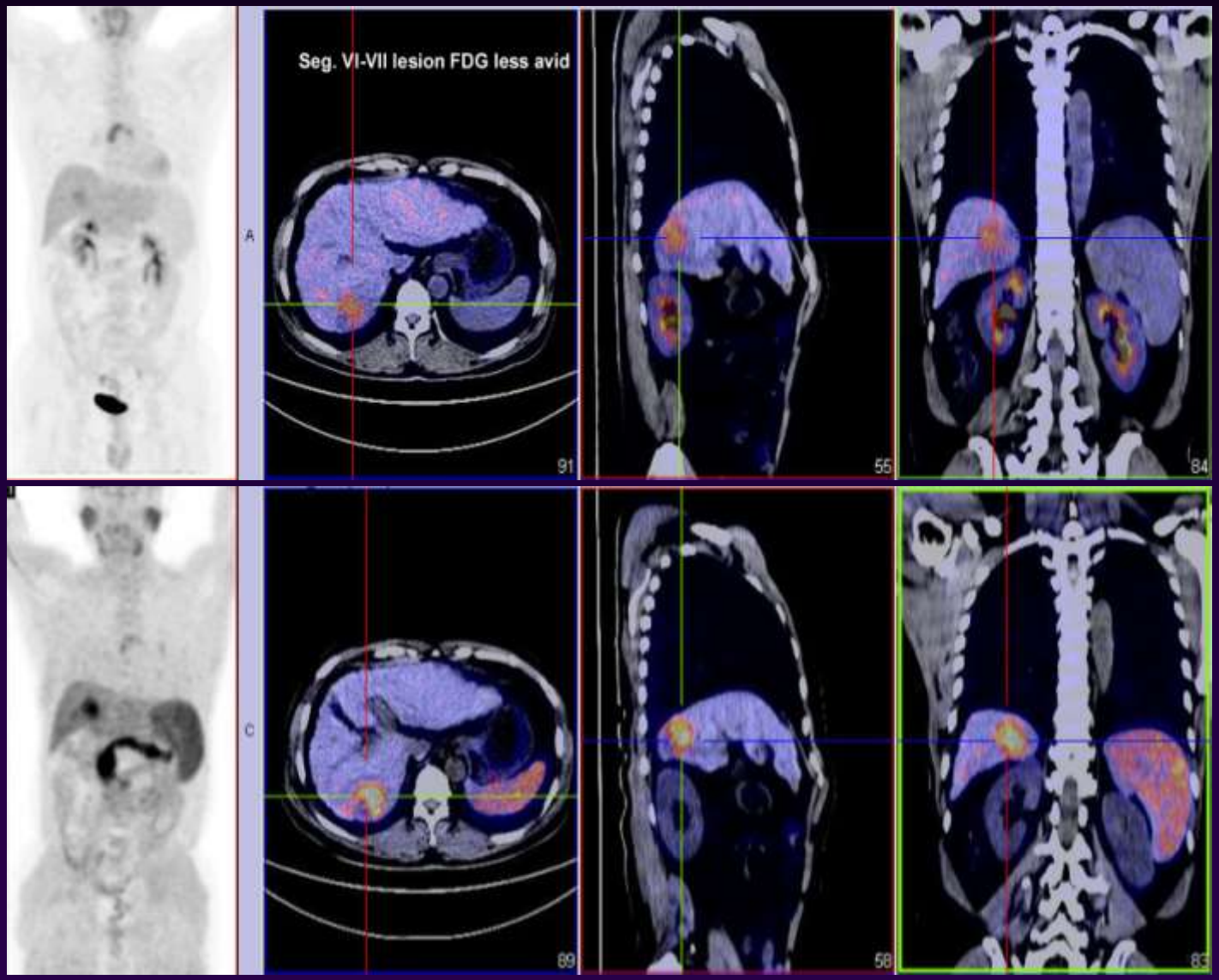
Well-differentiated HCC



FDG

^{11}C-Acetate

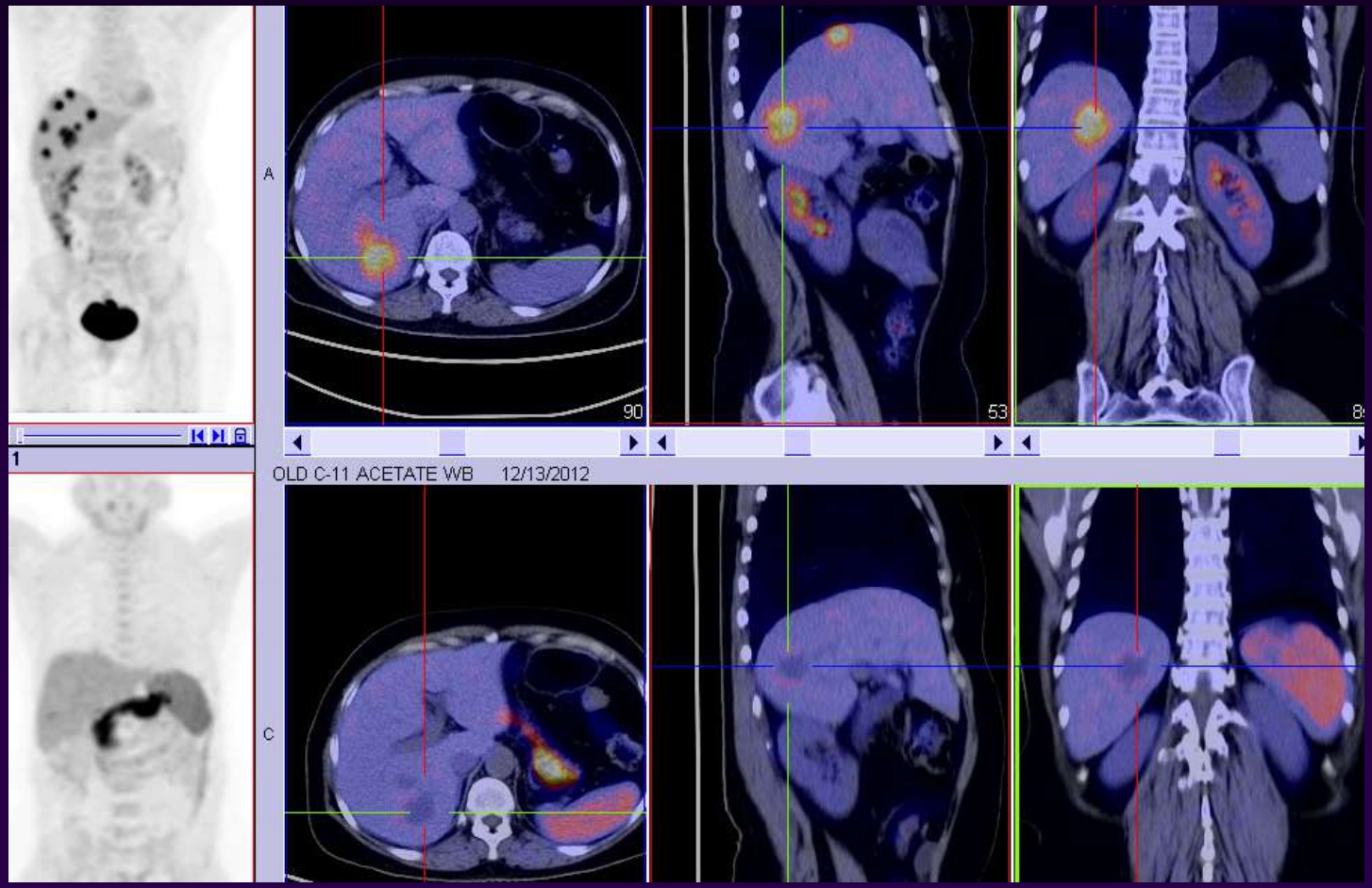
Moderately differentiated HCC



FDG

^{11}C-Acetate

Poorly differentiated HCC

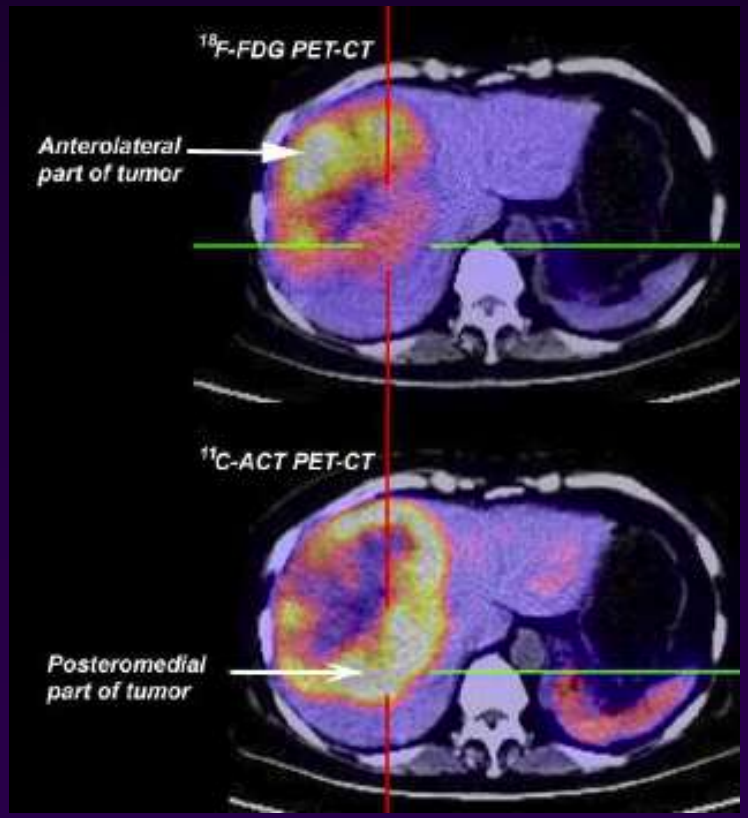


FDG

^{11}C-acetate

“Complementary nature” of dual tracer in HCC

- different stage of development and cellular differentiation within the same tumor



FDG

^{11}C-Acetate

Small hepatocellular carcinoma <2 cm

- Consensus statement from the European Association for the Study of Liver Diseases (EASL)
- Imaging techniques for liver lesions less than 2 cm do not have sufficient accuracy in distinguishing hepatocellular carcinoma from other conditions

Small hepatocellular carcinoma <2 cm

- 38 HCC tumors with mean size of 1.46 cm (0.8 – 2.0 cm)
- sensitivity of ^{11}C-acetate in small HCC 86.8%
  - similar to sensitivity of 87.2% for the HCC lesions of intermediate size (3.5 ±1.9 cm)

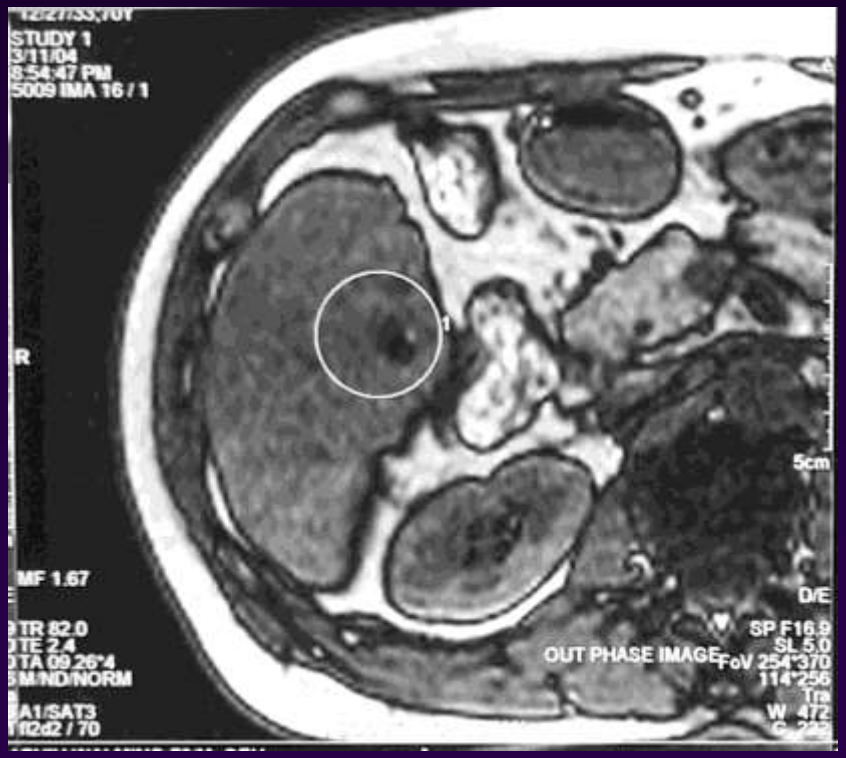
Ho et al, J Nucl Med, 2005. 46(5): p. 46P.

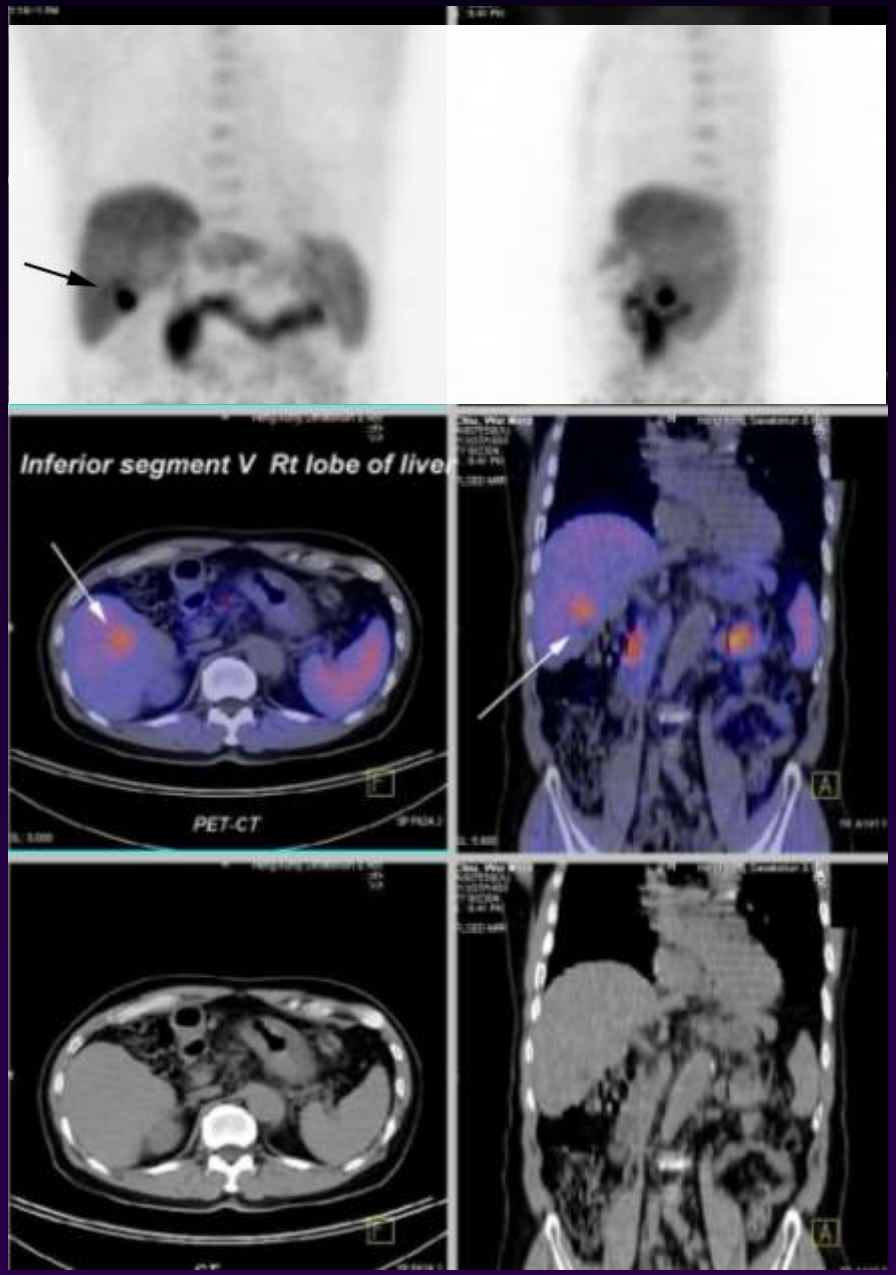
Small hepatocellular carcinoma <2 cm

- shift in proportion of lesions positive for both tracers to a larger proportion of lesions positive for ^{11}C-acetate only
- small tumors usually well differentiated in early stage of development and more often detected by ^{11}C-acetate instead of ^{18}F-FDG

Ho et al, J Nucl Med, 2005. 46(5): p. 46P.

- MRI suggested a 8 x 13 mm fatty nodule and not HCC
- ^{11}C-acetate-avid segment V lesion in PET/CT
- Pathology: well-differentiated hepatocellular carcinoma





Clinical application of PET/CT in HCC

1. Liver lesion detection
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Dual-Tracer PET/CT Imaging in Evaluation of Metastatic Hepatocellular Carcinoma

- 121 patients
- detection of metastatic HCC disease
- 48% (47/97 patients) not known to have metastasis before PET/CT

Ho et al, Journal of Nuclear Medicine, June 2007

Patient-Based Diagnostic Values of Single and Dual-Tracer PET/CT in the detection of HCC metastasis

Tracer	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
^{18}F-FDG*	79 (78/99)	91 (20/22)	98 (78/80)	49 (20/41)	81 (98/121)
^{11}C-ACT*	64 (63/99)	95 (21/22)	98 (63/64)	37 (21/57)	69 (84/121)
Dual-tracer	98 (97/99)	86 (19/22)	97 (97/100)	90 (19/21)	96 (116/121)

- complementary nature of ^{11}C-ACT and ^{18}F-FDG is evident in metastatic lesions
- NPV <50% when using either tracer alone

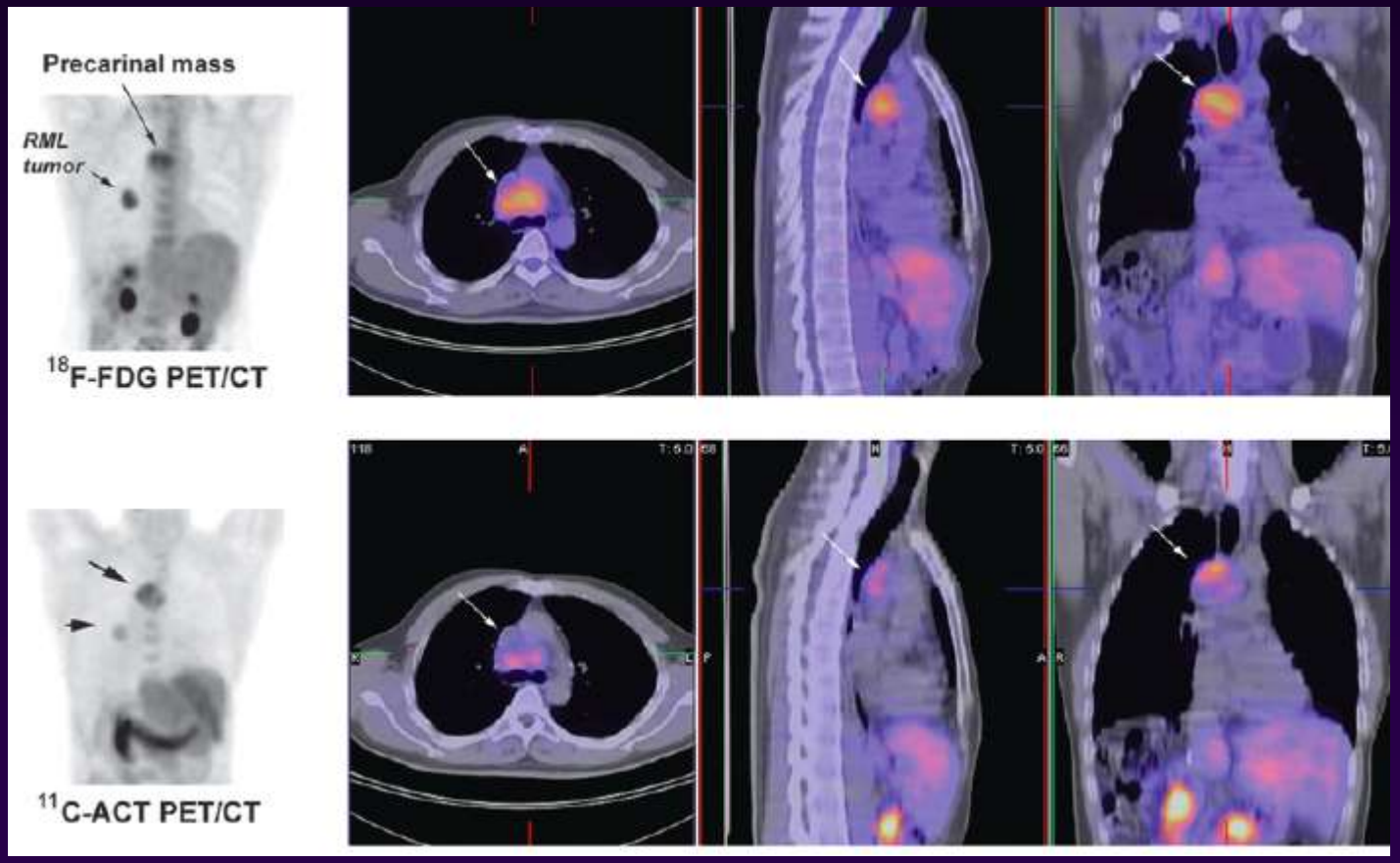
Ho et al, Journal of Nuclear Medicine, June 2007

Primary HCC features affecting likelihood of metastasis

- higher sensitivity by ^{18}F-FDG-PET in detection of metastasis because it is more likely for metastasis to occur in primary HCC tumors with "poor differentiation" than for those with well-differentiated pathology

Ho et al, Journal of Nuclear Medicine, June 2007

HCC metastases in RML mass and large precarinal node



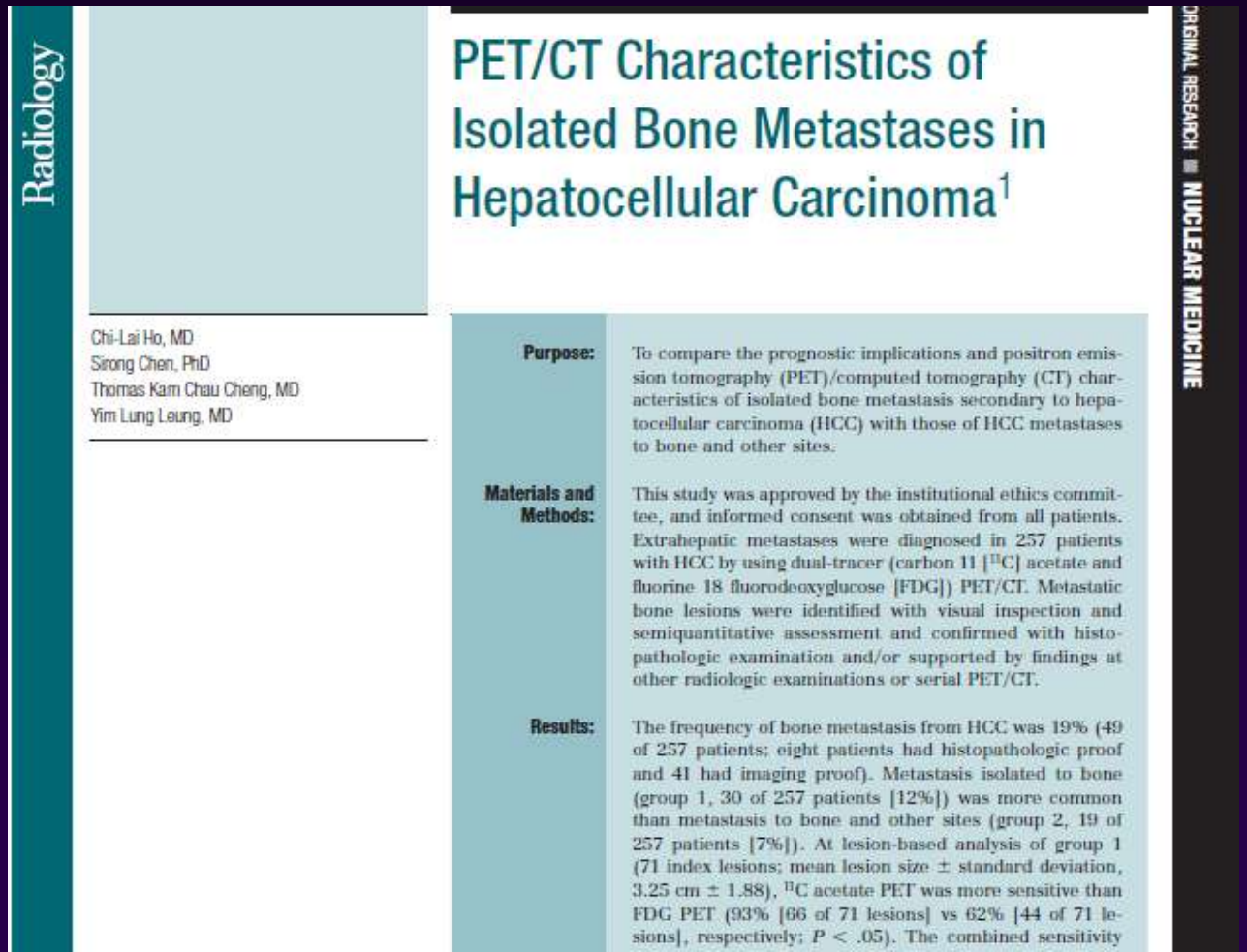
^{18}F-FDG

^{11}C-Acetate

PET/CT Characteristics of Isolated Bone Metastases in Hepatocellular Carcinoma

Chi-Lai Ho, Sirong Chen, Thomas Cheng, Yim Lung Leung

Radiology: Volume 258: Number 2—February 2011



Radiology

ORIGINAL RESEARCH ■ NUCLEAR MEDICINE

PET/CT Characteristics of Isolated Bone Metastases in Hepatocellular Carcinoma[1]

Chi-Lai Ho, MD
Sirong Chen, PhD
Thomas Kam Chau Cheng, MD
Yim Lung Leung, MD

Purpose: To compare the prognostic implications and positron emission tomography (PET)/computed tomography (CT) characteristics of isolated bone metastasis secondary to hepatocellular carcinoma (HCC) with those of HCC metastases to bone and other sites.

Materials and Methods: This study was approved by the institutional ethics committee, and informed consent was obtained from all patients. Extrahepatic metastases were diagnosed in 257 patients with HCC by using dual-tracer (carbon 11 [^{11}C] acetate and fluorine 18 fluorodeoxyglucose [FDG]) PET/CT. Metastatic bone lesions were identified with visual inspection and semiquantitative assessment and confirmed with histopathologic examination and/or supported by findings at other radiologic examinations or serial PET/CT.

Results: The frequency of bone metastasis from HCC was 19% (49 of 257 patients; eight patients had histopathologic proof and 41 had imaging proof). Metastasis isolated to bone (group 1, 30 of 257 patients [12%]) was more common than metastasis to bone and other sites (group 2, 19 of 257 patients [7%]). At lesion-based analysis of group 1 (71 index lesions; mean lesion size ± standard deviation, 3.25 cm ± 1.88), ^{11}C acetate PET was more sensitive than FDG PET (93% [66 of 71 lesions] vs 62% [44 of 71 lesions], respectively; $P < .05$). The combined sensitivity

PET/CT scan in HCC with bone metastases

- 257 patients with HCC
- frequency of bone metastasis from HCC 19%
  - (49 of 257 patients)
- Group I - metastasis isolated to bone
  - (30 of 257 patients [12%])
- Group II - metastasis to bone and other sites
  - (19 of 257 patients [7%])
- detection of bone metastases significantly enhanced with ^{11}C-acetate PET compared with ^{18}F-FDG PET alone

Ho et al, Radiology. 2011;258:515–523.

SUVmax of FDG and ^{11}C-acetate in bone metastases

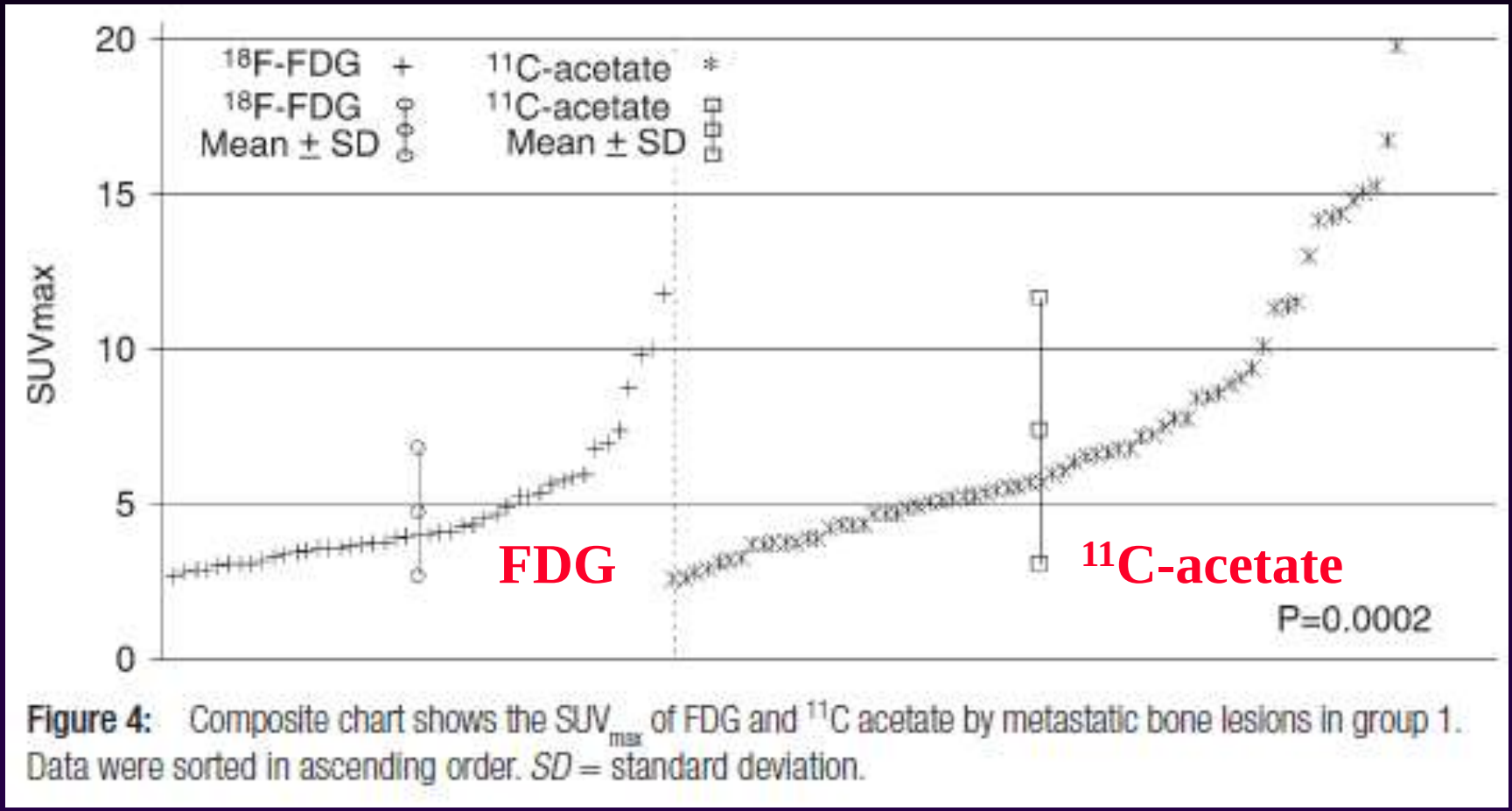
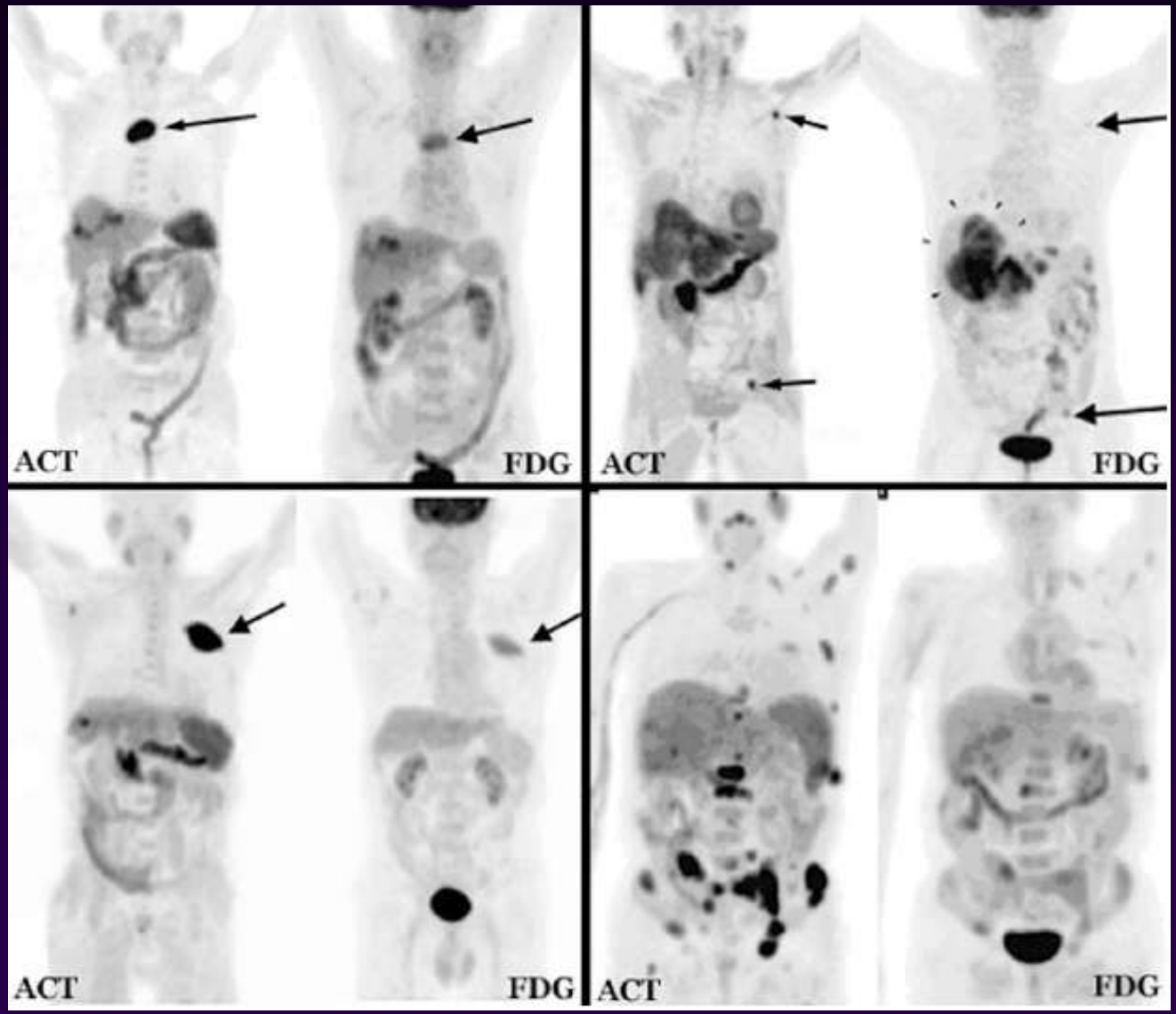


Figure 4: Composite chart shows the SUV_{max} of FDG and ^{11}C acetate by metastatic bone lesions in group 1. Data were sorted in ascending order. *SD* = standard deviation.

- uptake intensity of ^{11}C-acetate significantly higher than FDG
- (mean SUV max , 7.42 vs 4.81; *P* = .0002)

Ho et al, Radiology. 2011;258:515–523.

4 patients with HCC and isolated bone metastases
more intense avidity for ^{11}C-acetate than for FDG

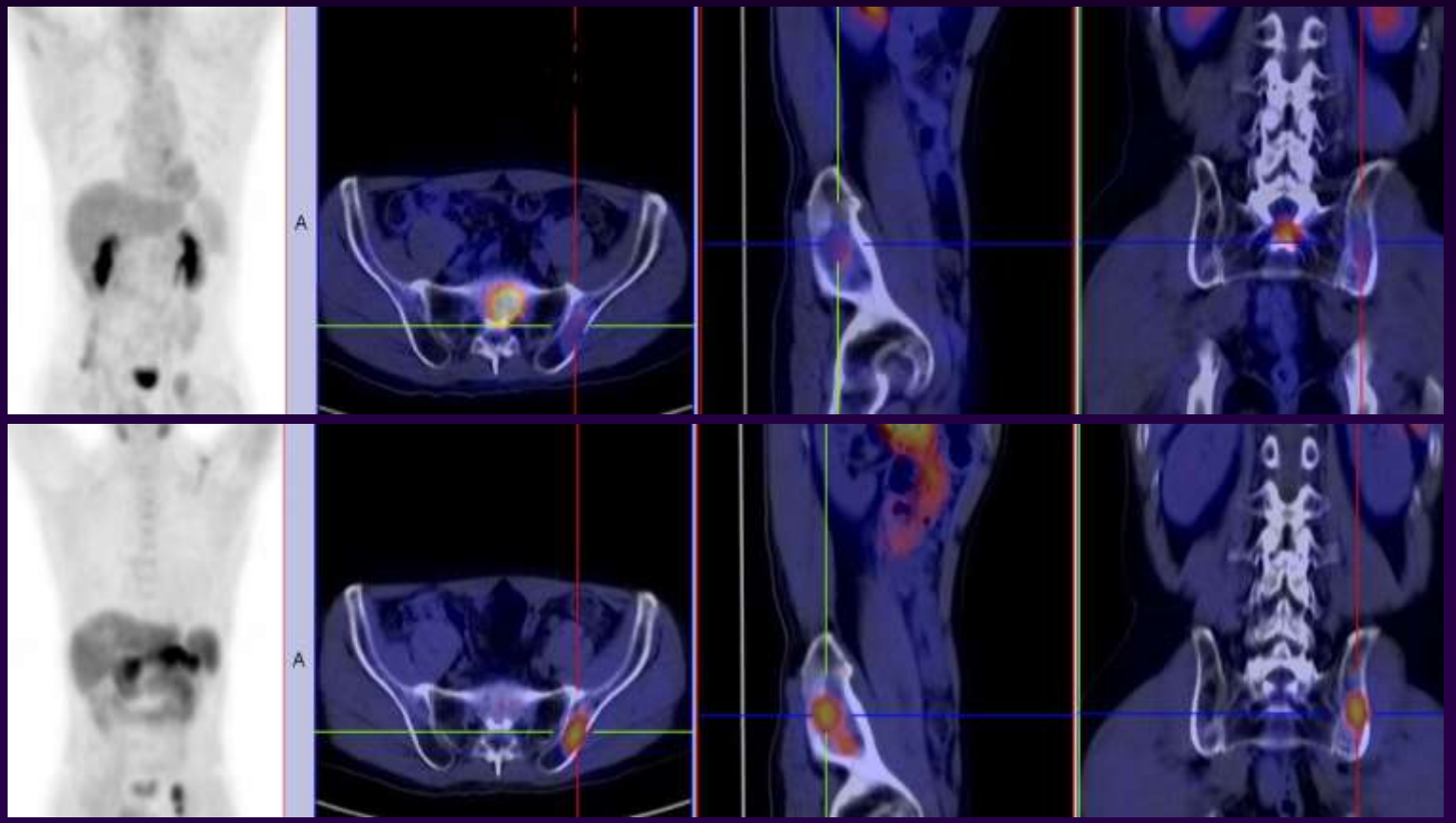


Dual tracer “complementary in bone metastases” in same patient

M/55 hepatitis B carrier, S/P resection of segment VIII HCC

Lytic bone metastases in sacrum and left posterior ilium

L ilium	FDG -ve,	C11-Acetate +ve
Sacrum	FDG +ve,	C11-Acetate –ve



FDG

^{11}C-Acetate

Clinical application of PET/CT in HCC

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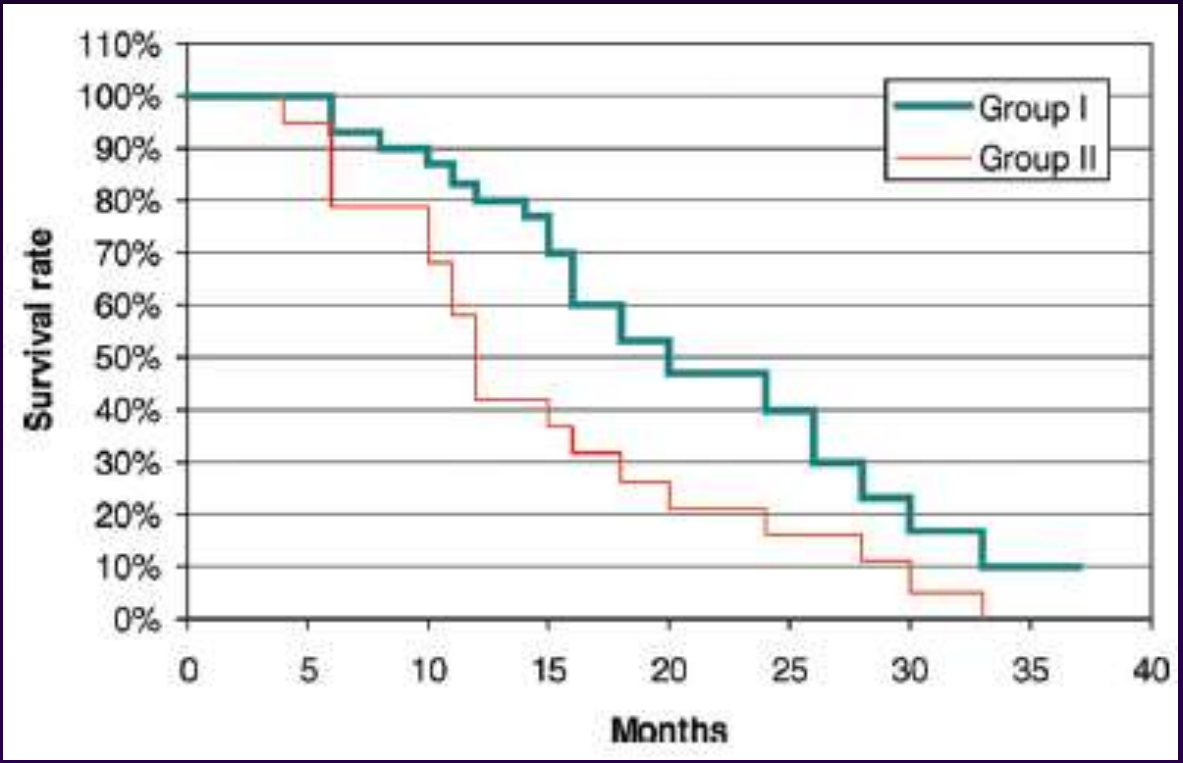
Survival curves

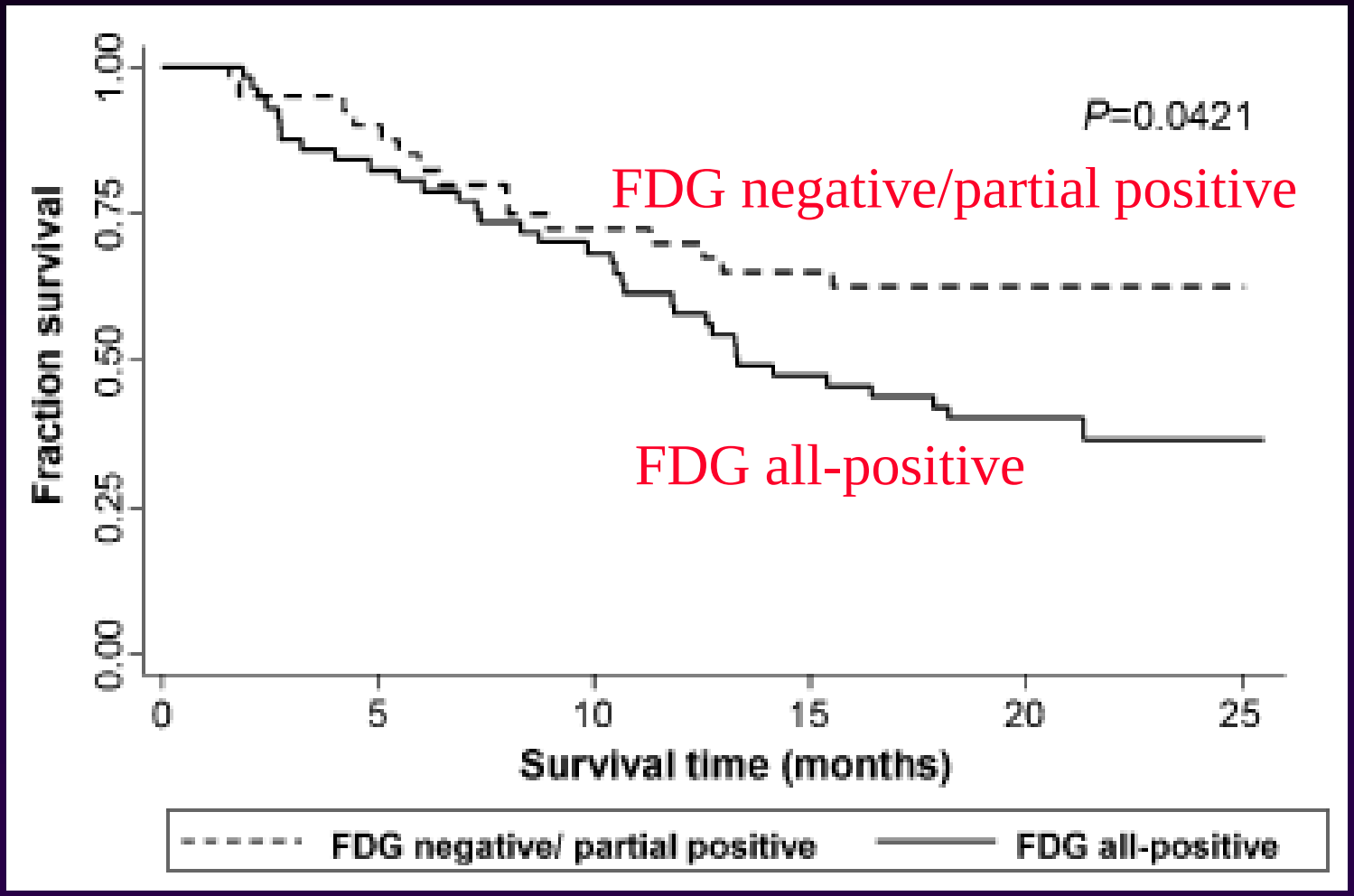
Group I – HCC and isolated bone metastases
: better survival

Group II – HCC and metastases to bone and other organs
: poorer survival



Ho et al, Radiology. 2011;258:515–523.

Overall survival after diagnosis of HCC



Park el al, J Nucl Med 2008; 49:1912–1921

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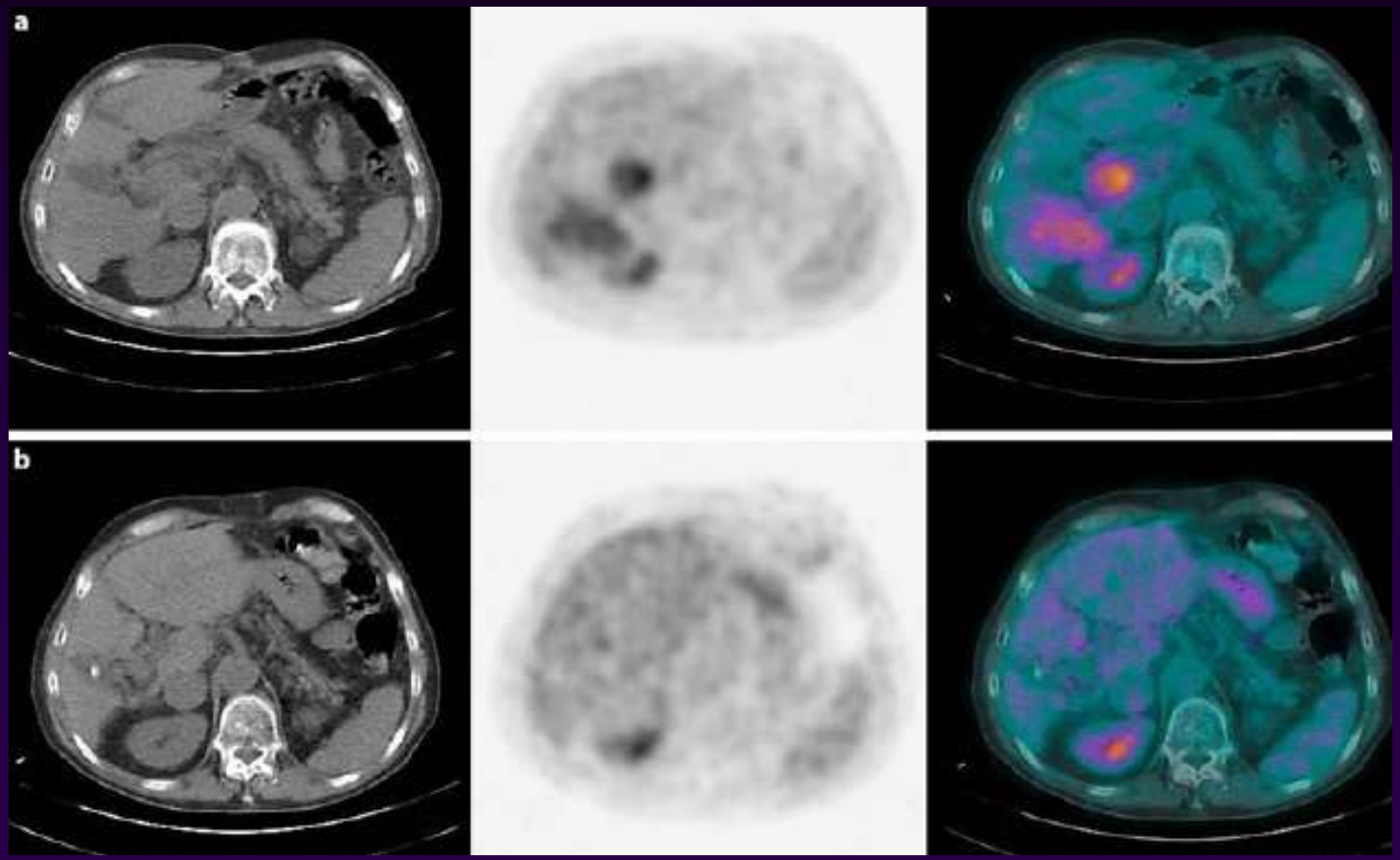
FDG PET/CT in evaluation of early treatment response after interventional therapy for HCC

- 31 patients 1 month after interventional therapy
  - Transcatheter arterial chemoembolization (TACE)
  - Radiofrequency ablation (RFA)
  - Percutaneous ethanol injection therapy (PEIT)
- Sensitivity 87.5%, specificity 71.4%
- PPV 77.8%, NPV 83.3%

Sung et al, NMMI, 2012, 46 (2), 102-110

Recanalization of portal vein tumor thrombosis after Sunitinib in HCC



Baseline FDG-PET

1-year later

Basso et al, Case Rep Oncol 2010; 3:391-396

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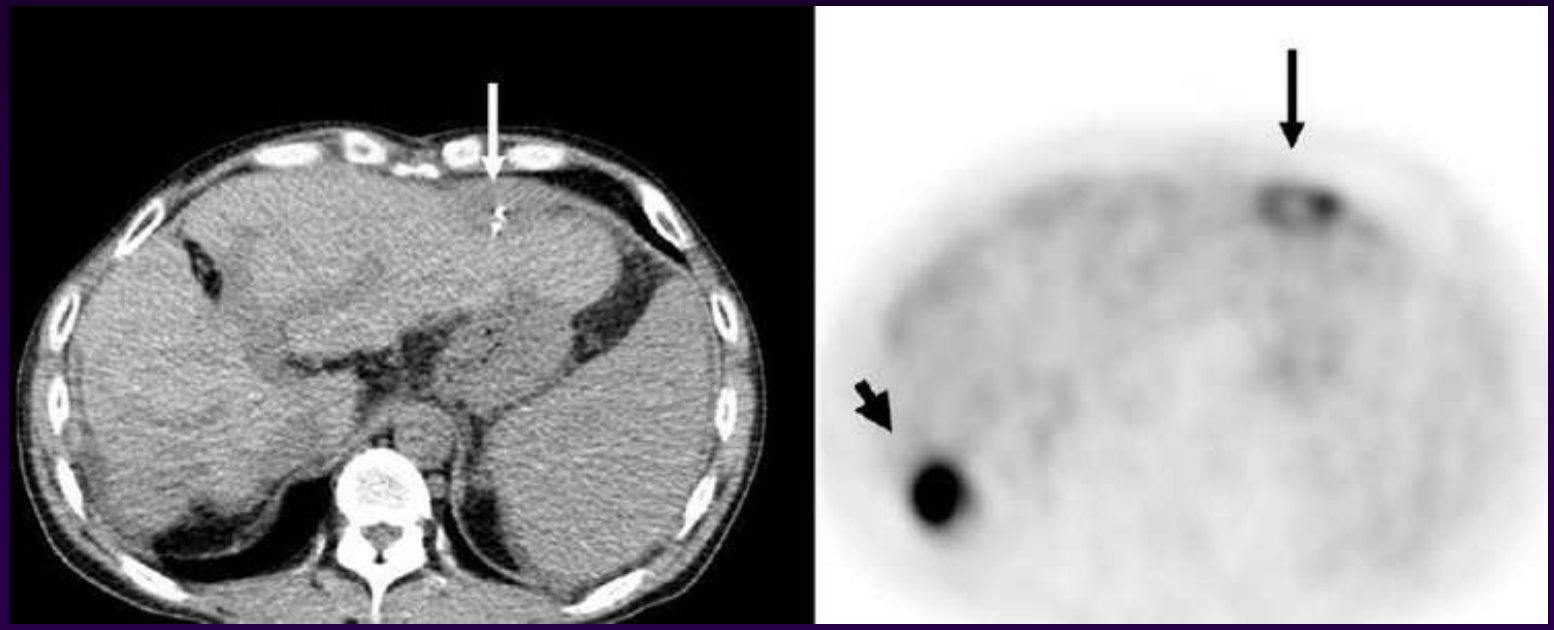
^{18}F-FDG in unexplained rising serum AFP levels after treatment of HCC

- 26 patients undergone either surgical resection or interventional therapy for HCC
- subsequently high serum AFP level
- *normal anatomical imaging studies*
- Abnormal FDG PET in 71% (22/31 studies)
  - 10 studies 1 intrahepatic lesion
  - 3 studies >1 intrahepatic lesion
  - 9 studies extrahepatic metastases
- Sentitivity 73.3%, specificity 100%, accuracy 74.2%

Chen et al, Anticancer Research, 2005 25: 4719-4726

- M/45 HCC post-hepatectomy
- AFP>5000 ng/ml
- US & CT normal

^{18}F-FDG PET



Chen et al, Anticancer Research, 2005 25: 4719-4726

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Partial hepatectomy vs Liver transplantation

- Surgery offers the best chance of cure
- Tumor recurrence rate at 5 years after "partial hepatectomy" (PH) can be as high as 80%
- "Liver transplantation" (LT) is regarded as the ultimate solution
  - low success rates attributed to inappropriate patient selection and a long waiting time

Milan Criteria for liver transplantation

- a single HCC lesion of ≦ 5 cm
- a maximum of 3 HCC lesions of ≦ 3 cm each
- no macroscopic vascular invasion
- no extrahepatic metastasis

Mazzaferro et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med. 1996; 334:693–699.

Staging and selection for Liver Transplantation on the Basis of Milan Criteria

- a set of selection criteria on the basis of the relationship between small HCCs and better patient survival after LT
- tumor number and size are the key factors that affect patient survival
- results of orthotopic LT improved substantially through careful patient selection
- the Milan group achieved a patient survival rate of over 70%

Journal of Nuclear Medicine, published on January 15, 2013 as doi:10.2967/jnumed.112.107516

^{11}C-Acetate and ^{18}F-FDG PET/CT for Clinical Staging and Selection of Patients with Hepatocellular Carcinoma for Liver Transplantation on the Basis of Milan Criteria: Surgeon's Perspective

Tan To Cheung[1], Chi Lai Ho[2], Chung Mau Lo[1,3], Sirong Chen[2], See Ching Chan[1,3], Kenneth S.H. Chok[1], James Y. Fung[1], Albert Chi Yan Chan[1], William Sharr[1], Thomas Yau[1], Ronnie T.P. Poon[1,3], and Sheung Tat Fan[1,3]

[1]Department of Surgery, Queen Mary Hospital, The University of Hong Kong, Hong Kong, China; [2]Department of Nuclear Medicine and PET, Hong Kong Sanatorium and Hospital, Hong Kong, China; and [3]State Key Laboratory for Liver Research, The University of Hong Kong, Hong Kong, China

Cheung TT, Ho CL et al, J Nucl Med. 2013; 54:192–200.

Sensitivities of PET/CT and Contrast CT for Detection of Malignant Lesions

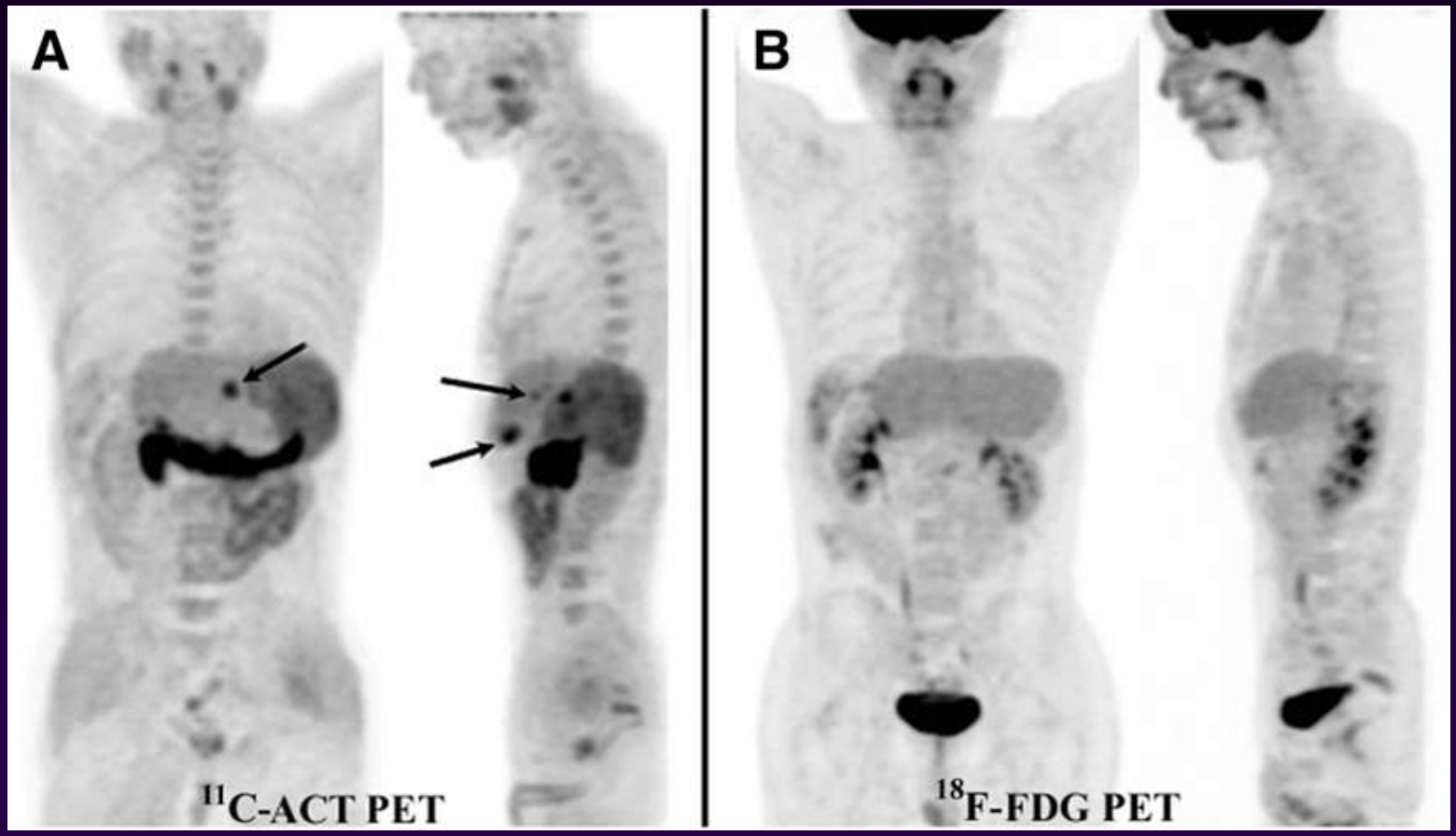
- 43 patients
- 22 liver transplantation (LT)
- 21 partial hepatectomy (PH)

Imaging	All lesions	Small HCCs
Contrast CT	55.2% (32/58)	43.5% (10/23)
^{18}F-FDG PET/CT	32.8% (19/58)	17.4% (4/23)
^{11}C-ACT PET/CT	93.1% (54/58)	87.0% (20/23)
Dual-tracer PET/CT	94.8% (55/58)	91.3% (21/23)

Cheung et al, J Nucl Med. 2013;54:192–200.

HCC patient met Milan criteria

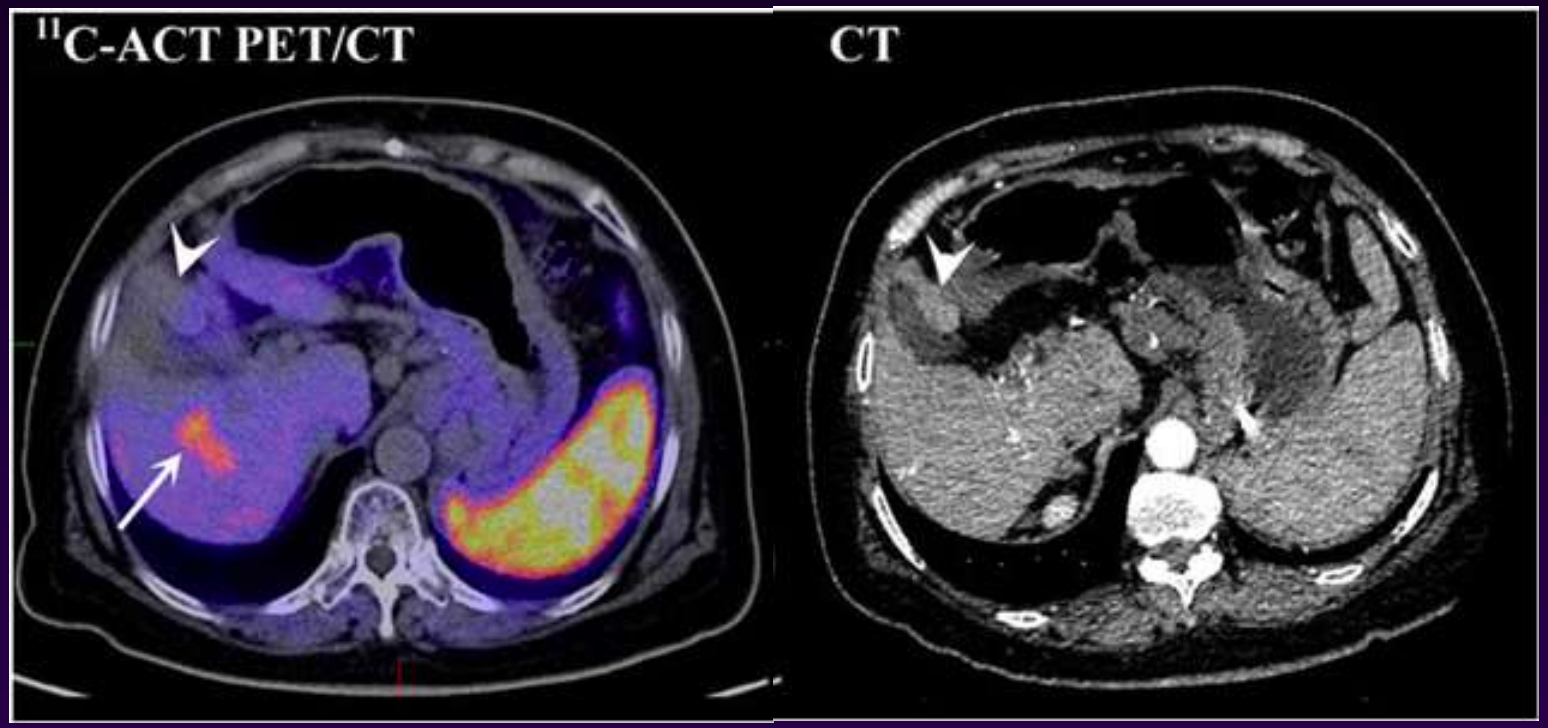
- 3 tumors <3cm, avid for ^{11}C-ACT but not ^{18}F-FDG
- no vascular invasion and no extrahepatic metastasis



Cheung et al, J Nucl Med. 2013;54:192–200.

CT showed mildly contrast-enhanced nodule in segment IVb impinging on gallbladder, suggestive of HCC, with no abnormal metabolism on PET/CT

Pathology - dysplastic nodule (2.0 cm) in left lobe (segment IVb) adjacent to gallbladder

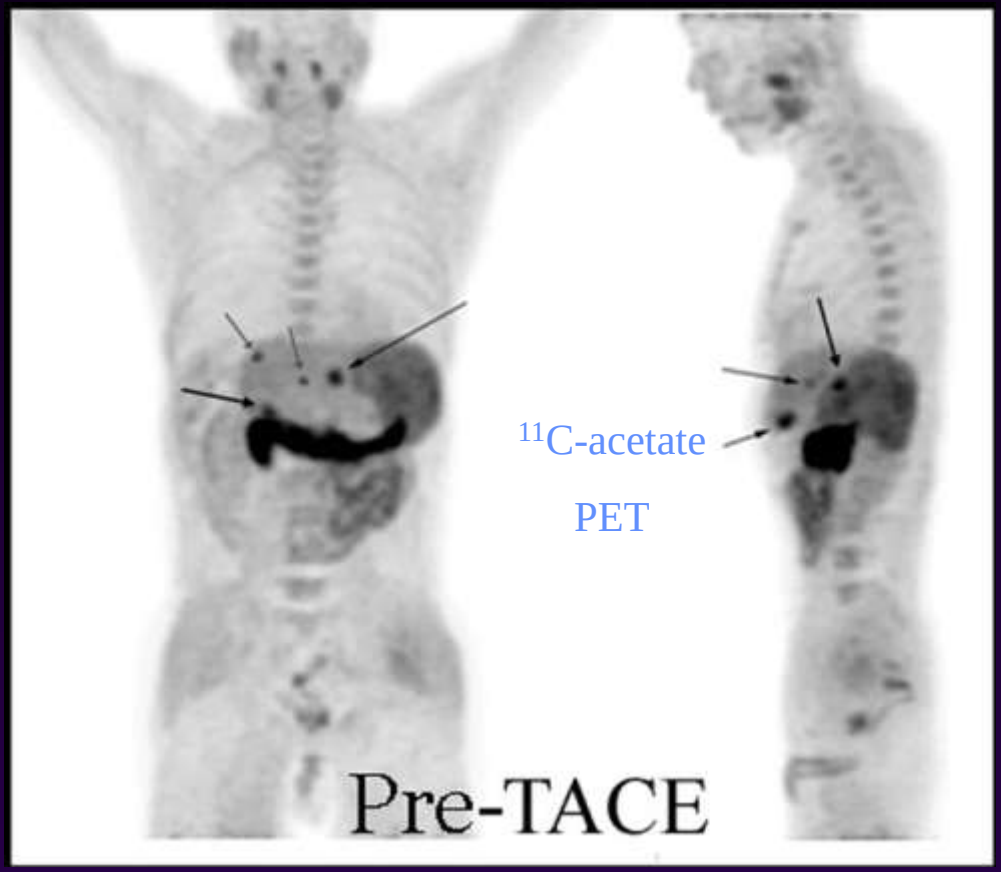


^{11}C-ACT–avid lesion found in segment V

Pathology - well-differentiated HCC (3.6 cm) in right lobe (segments V and VI)

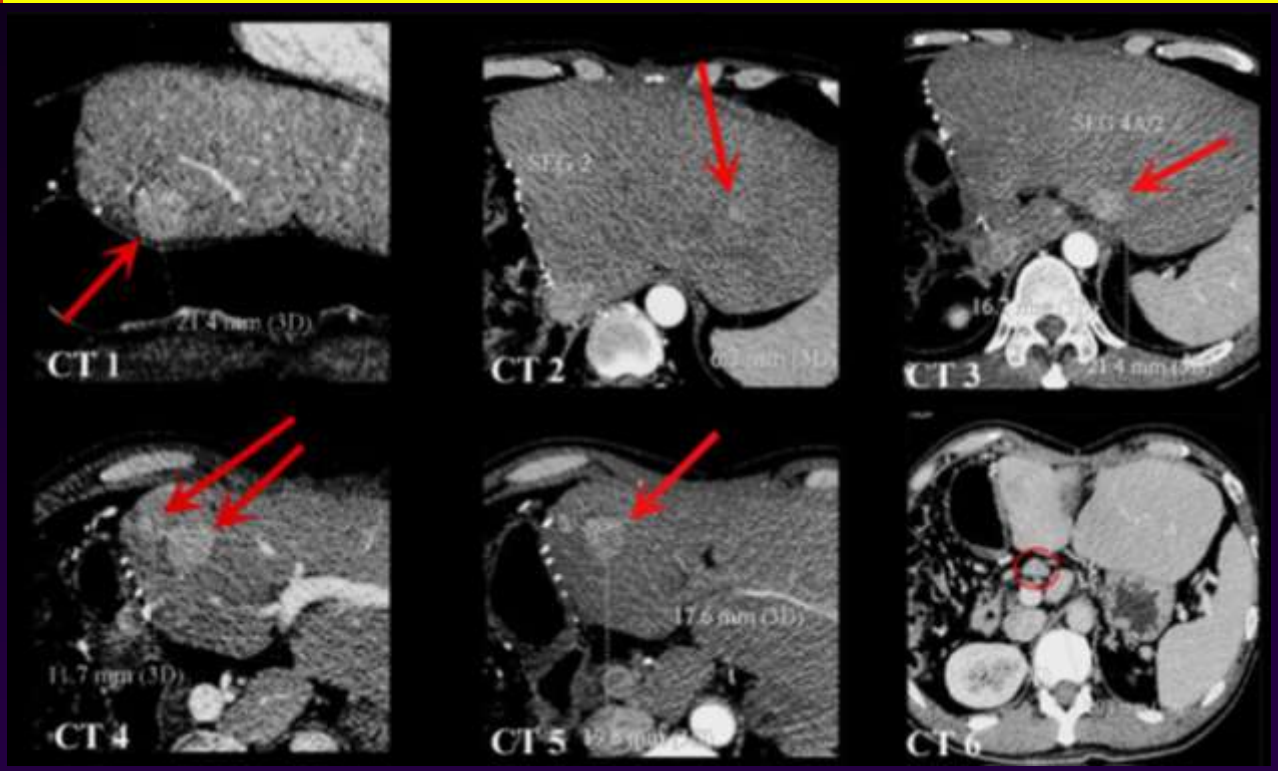
Cheung et al, J Nucl Med. 2013;54:192–200.

Pre-TACE assessment



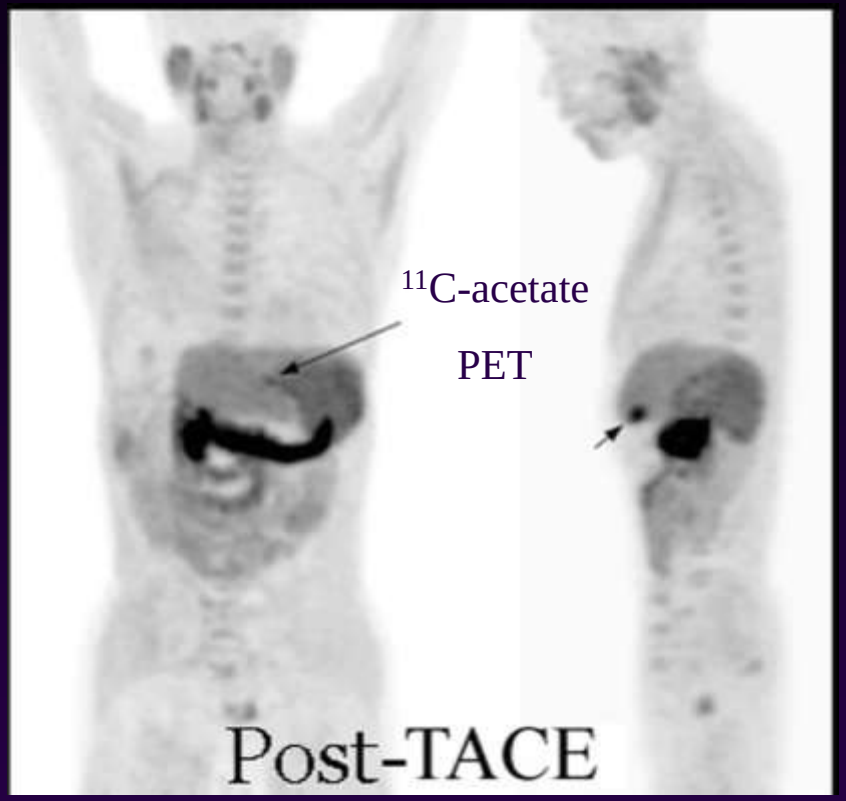
A 46 y gentleman after right hepatectomy had multicentric HCC recurrence detected by both ^{11}C-acetate PET/CT and contrast CT.

Post-TACE, pre-transplant assessment - Contrast CT



CT showed 6-7 contrast-enhanced lesions (red arrows, CT 1-5) and an enlarged portal node (red circle, CT 6). CT impression: TACE is **not effective**; the patient is **not a candidate** for liver transplant based on Milan criteria.

Post-TACE, pre-transplant assessment ^{11}C-acetate PET



^{11}C-acetate PET impression:

1. **Successful downstage** to 2 lesions (black arrows): 2.1 & 2.2 cm; no metastatic portal node
2. TACE is **effective.**
3. Patient **satisfies** Milan criteria for liver transplant.

Final pathology of explanted liver:

1. Only 2 small HCC lesions (2.4 & 2.7 cm, one in each hepatic lobe)
2. A few necrotic nodules without malignant cells (likely post-treatment)
3. Portal node (22 mm) was **negative** for metastasis
4. Patient is **within Milan criteria**.

Advantages of PET/CT

- PET/CT less affected by cirrhosis and TACE
- detection of osseous metastatic disease as most are osteolytic and evident on CT only as a late manifestation

CONCLUSION

- ^{18}F-FDG PET/CT alone has a reasonable sensitivity in the detection of HCC metastasis, but it is not sensitive enough for the evaluation of HCC primary tumor
- Dual-tracer PET/CT by ^{18}F-FDG and ^{11}C-acetate has a mutual complementary advantage in the detection of both the primary HCC tumors and HCC metastasis
- PET/CT is less affected by cirrhosis and can be used to perform a metastatic survey and better patient selection in candidates for liver transplantation.


Thank you!