Clinical Applications of [F-18]FDG and [F-18]FCH PET/CT in Hepatocellular Carcinoma

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Introduction

Hepatocellular carcinoma (HCC) is the sixth most common malignancy worldwide and varies greatly in geographic occurrence. Incidence of HCC in Eastern Asia and Middle Africa is at least 10 times higher as in Europe and the United States.

In a cirrhotic liver, diagnosis of HCC is based on one multiphase CT or dynamic MRI imaging study, if definitively characteristic for HCC.

However, imaging results are complicated by interfering effects of treatment, including necrosis, local inflammation, and fibrosis. This makes detection and distinction of viable tumor tissue difficult and, possibly, unreliable with CT and MRI.

肝癌影像診斷標準

- 2001年European Association for the Study of the Liver對大於2公分的肝臟腫瘤發展出非侵犯性診斷標準。

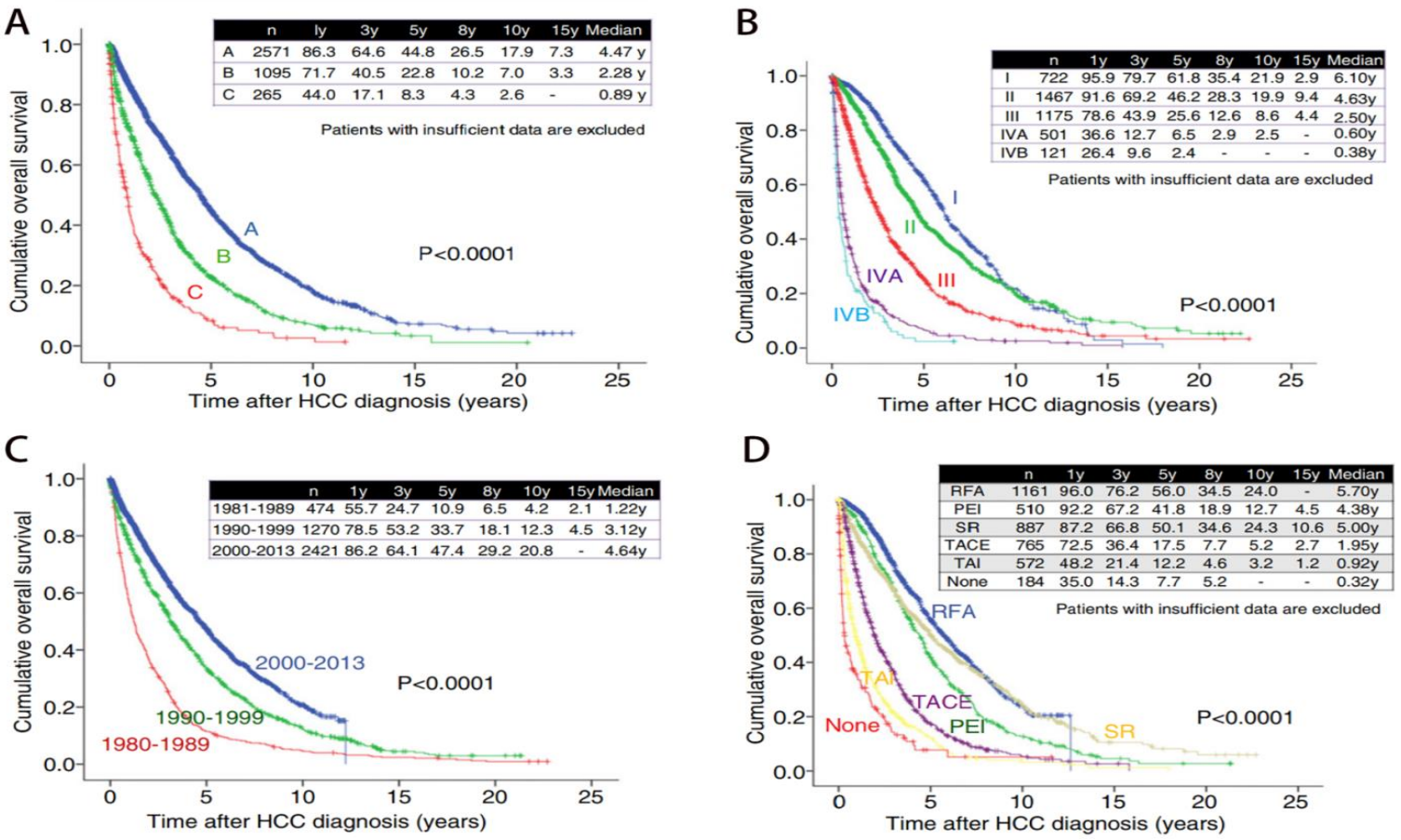
（1）超音波、CT、MRI等影像學檢查，有兩種檢查一致顯示有大於2公分以上且動脈血管豐富(hypervascular)的腫瘤。

（2）一種影像學檢查呈現典型肝癌影像，且合併血清AFP大於400 ng/ml以上。

單一血清AFP或超音波異常並不能確立肝癌診斷。

Bruix J, et al. J Hepatol, 2001, 35: 421-30.

肝癌的治療與預後



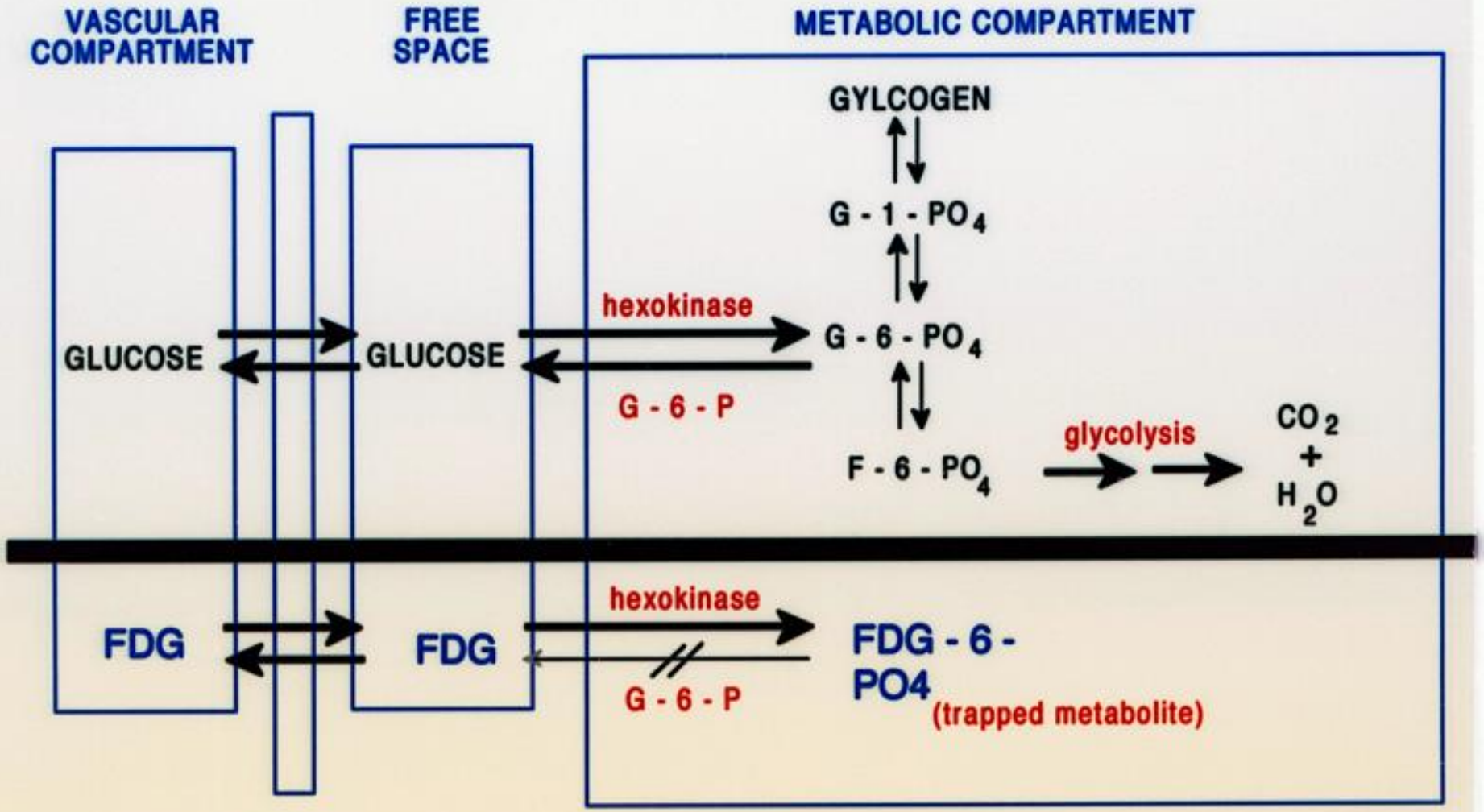
日本1981~2013年間4165位肝癌患者的預後。

Osaki Y, Nishikawa H. Hepatol Res, 2015, 45: 59-74.

Introduction

- The diagnostic work-up for HCC does not include standard ^{18}F-FDG PET/CT imaging, because diagnostic accuracy is limited, especially in well differentiated HCC.
- In a study by Talbot JN, et al., [F-18]methylcholine (^{18}F-FCH) showed a high sensitivity (88%, n=34 Pts), as compared to FDG (68%, p=0.07) , and was found to be useful for detection and follow-up of patients with HCC. (J Nucl Med 2010;51:1699-1706.)

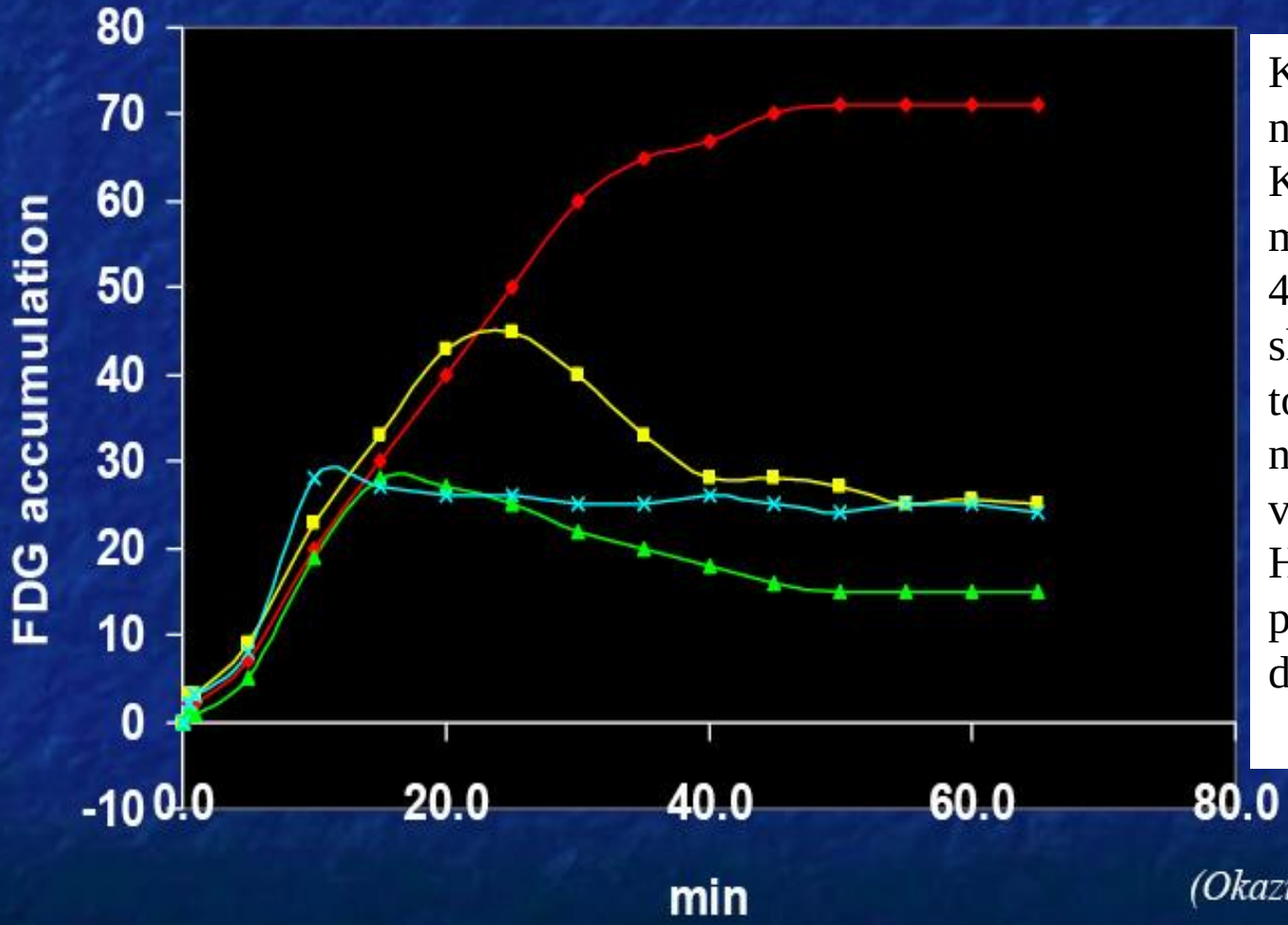
Cellular Uptake of FDG



Phelps ME, et al. *J Nucl Med* . 1978; 92: 1311-1319

UCLA 95

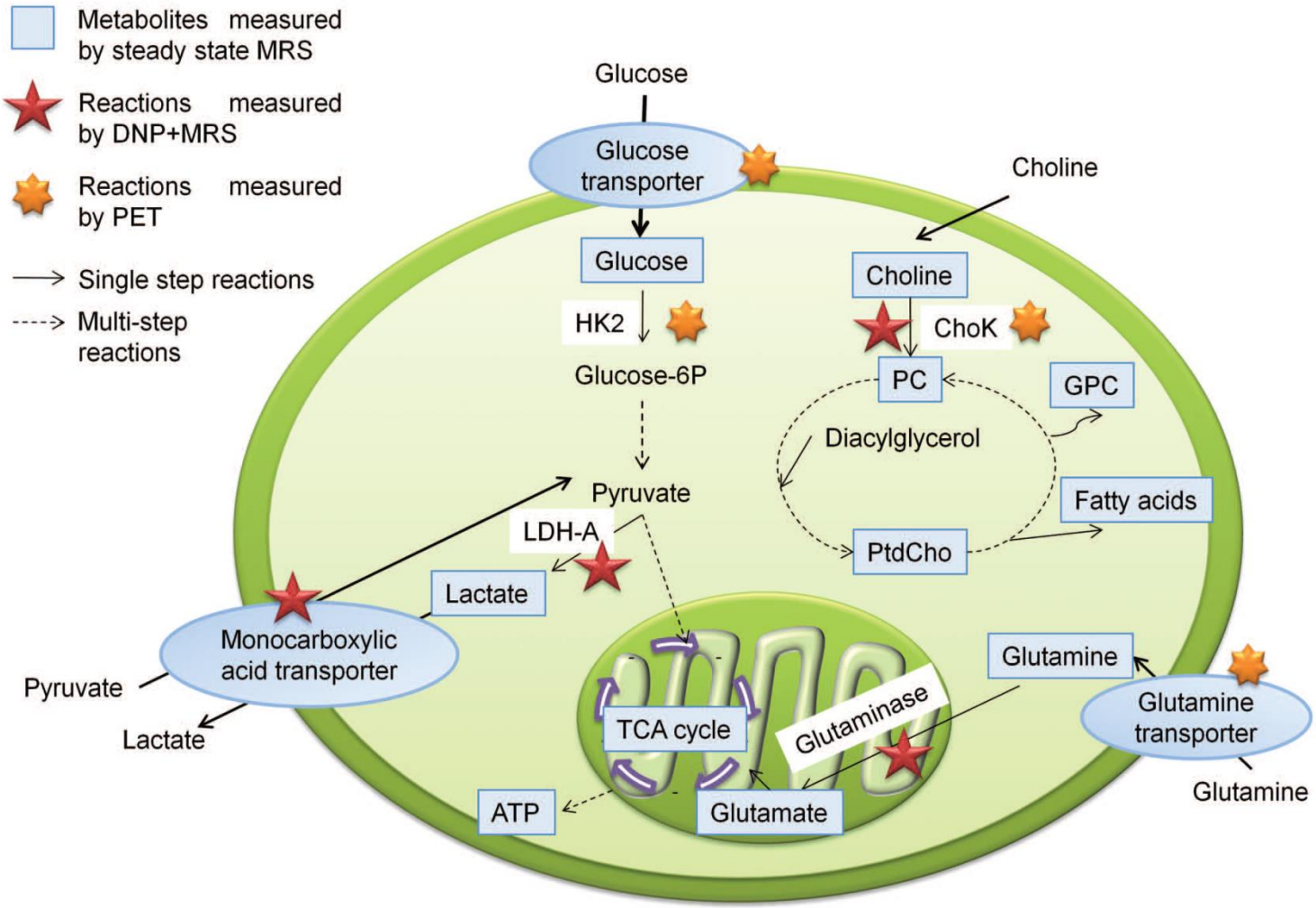
Time activity curve of different types of HCC in FDG accumulation



K1 lower than normal liver tissue; K3 is increased in malignant tumors; 45% of HCC showed similar K4 to surrounding normal liver tissue; visualization of HCC depends on phosphorylation and dephosphorylation.

(Okazumi 1992 JNM)

JNM 1992;33:333



A diagram of some key metabolic pathways and intermediates being used for cancer metabolic imaging by MRS and ^{18}F-FCH and ^{18}F-FDG PET/CT scan. Treatment with molecularly targeted drugs is often associated with alterations in the metabolic profiles of cancer cells and tumors. Cell Cycle 2011;2883-93.

Eur J Nucl Med Mol Imaging (2006) 33:1285-9

PET/CT in patients with hepatocellular carcinoma using [^{18}F] fluorocholine: preliminary comparison with [^{18}F]FDG PET/CT

Jean-Noël Talbot[1], Fabrice Gutman[1], Laetitia Fartoux[2], Jean-Didier Grange[3], Nathalie Ganne[4], Khaldoun Kerrou[1], Dany Grahek[1], Françoise Montravers[1], Raoul Poupon[2], Olivier Rosmorduc[2]

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Results (overall)

	HCC	Non-HCC	Total
FDG (+)	12	10	22
FDG (-)	4	3	7
Total	16	13	29

Sensitivity: 75 %,
specificity:23.1 %,
accuracy: 51.7 %

	HCC	Non-HCC	Total
Fcholine (+)	13	2	15
Fcholine (-)	3	11	14
Total	16	13	29

Sensitivity: 81.3 %,
specificity:84.6 %,
accuracy: 82.8 %

HCC	FDG (+)	FDG (-)	Total
Fcholine (+)	10	3	
Fcholine (-)	2	1	
Total			16

Total detection rate: 93.8 %,
6.3 % missed

Eur J Nucl Med Mol Imaging 2006;1285

J Nucl Med 2010;51:1699-706

TABLE 1
Diagnostic Performance of ^{18}F-Fluorocholine and ^{18}F-FDG PET/CT for Detection of HCC or Other Malignancies in Patients with Liver Nodules on Cirrhosis or Chronic Liver Disease

Parameter	^{18}F-fluorocholine PET/CT		^{18}F-FDG PET/CT		McNemar test
	Value	95% CI	Value	95% CI	
Patient-based sensitivity for HCC or hepatocholangiocarcinoma (n = 34)	88%	73%–97%	68%	50%–83%	NS (P = 0.07)
Detection rate in patients with other malignancies (n = 8)	88%	47%–100%	88%	47%–100%	NS
Patient-based specificity in case of benignity (n = 17)	47%	23%–72%	94%	71%–100%	$P < 0.01$
Overall site-based sensitivity for HCC or hepatocholangiocarcinoma (n = 70)	84%	74%–92% (hot or photopenic site evocative of malignancy)	67%	55%–78% (hot site evocative of malignancy)	P = 0.01
Site-based sensitivity for well-differentiated HCC (n = 32)	94%	79%–99%	59%	41%–76%	P = 0.001
Site-based sensitivity for poorly differentiated HCC or hepatocholangiocarcinoma (n = 38)	76%	60%–89%	74%	57%–87%	NS
Detection rate in other malignant sites (n = 18)	78%	52%–94%	89%	65%–99%	NS
Site-based specificity in case of benignity (n = 34)	62%	44%–78%	91%	76%–98%	$P < 0.01$

NS = nonsignificant.

肝癌正子掃描影像生物標記之研發與多中心臨床試驗－以[18F]fluorocholine 進行肝癌病人的正子電腦斷層掃描

生技醫藥國家型科技計劃

臺大醫院、中山醫大附設醫院、義大醫院、花蓮慈濟醫院

NSC 101-2325-B-040 -001 –

NSC 102-2325-B-040 -001 –

MOST 103- 2325- B- 040- 001-

101年12月 – 104年11月

Study Objectives

Primary study objective :

To evaluate the sensitivity of ^{18}F-FCH and ^{18}F-FDG PET/CT for detecting HCC in patients with cirrhosis or chronic liver disease .

Secondary study objectives :

1. To evaluate the specificity of ^{18}F-FCH and ^{18}F-FDG PET/CT for detecting HCC in patients with cirrhosis or chronic liver disease ,
2. To evaluate the correlation of the uptake of ^{18}F-FCH and ^{18}F-FDG with the differentiation of HCC ;
3. To evaluate safety/tolerability profiles of ^{18}F-FCH .

Inclusion criteria

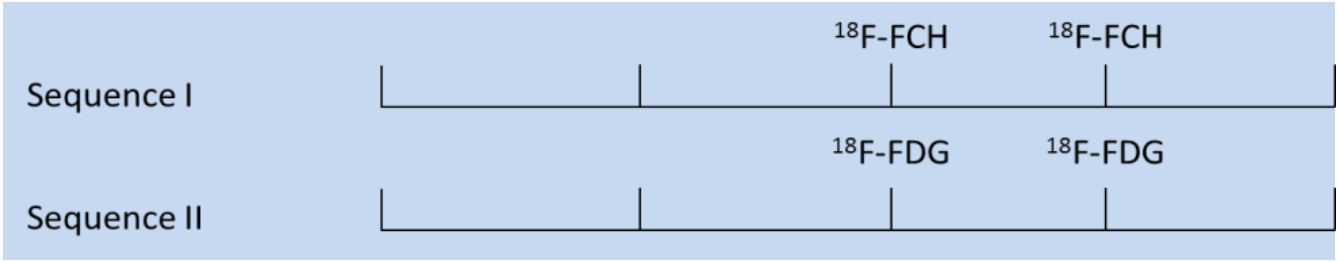
1. Male or female, age ≥ 20 years old.
2. Patient who accepts to enter the study by signing written informed consent.
3. Patient with performance status ≤ 2 Eastern Cooperative Oncology Group (ECOG).
4. Patient with cirrhosis or chronic liver diseases suspected to have at least 1 hepatic nodule larger than 1 cm in diameter detected by conventional image (US, CT, MRI). Patient should not yet receive any therapy relevant to the aforementioned diagnosis.
5. Female patient must take reliable contraception method(s) during the participation of the study.

Exclusion criteria

1. Patient has serious allergic history or known allergy ^{18}F-FCH or ^{18}F-FDG .
2. Patient has been diagnosed of multiple malignancies.
3. Female patient who is pregnant, lactating or planning to become pregnant during the study.
4. Patient has been participated in other investigational trials within 28 days prior to study enrollment.
5. Patient is unable to undergo PET/CT scan.
6. Subjects with active systemic infections, or medical conditions that may significantly affect action, adequate uptake and elimination of radiotracer.
7. Subject with conditions judged by the investigator as unsuitable for the study.

Randomization and Interpretation

Study Period	Screen	Randomization	PET/CT Examinations		Follow-up
Visit	1	2	3	4	N/A
Study time point	**≤ 14 Days prior to Day 1**	**≥ 3 Days prior to Day 1**	**Day 1**	**Day 3~16**	**Day 1 to ≤ 6 Months**



PET/CT reading

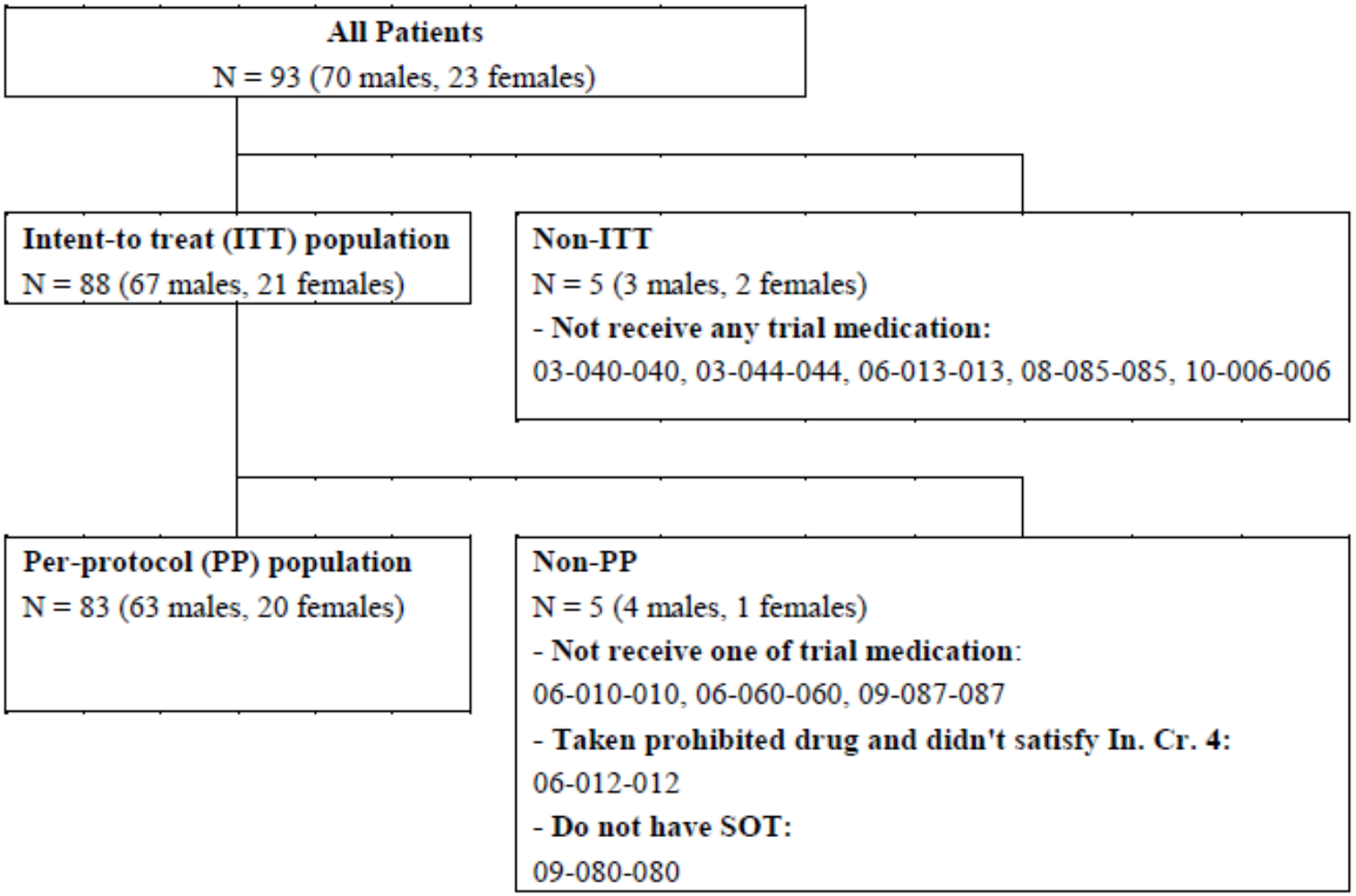
Mask readings were performed for all PET/CT images by 2 nuclear medicine physicians. The evaluation of the likelihood of cancer was reported on a grid according to the following 5-grade scale:

0, no cancer or definitely nonpathologic aspect;
1, probably benign lesion;
2, equivocal lesion;
3, probably cancer;
4, most probably cancer.

Standard of Truth (SOT) Determination

- The SOT determination was on a per-patient basis and per-site basis.
  - On a per-patient basis, the SOT was defined as HCC lesions that was histologically proven or if the arterial hypervascularity and venous or delayed phase washout obtained by dynamic contrast-enhanced MDCT or MRI showed suspected HCC.
  - For the per-site basis, the SOT for liver nodules was based on the histological evidence obtained from the available specimens obtained prior to entering the study or at follow-up.

Deposition of Subjects



Results

Statistical analyses for the sensitivity of ^{18}F-FCH and ^{18}F-FDG (per-patient basis)

Treatment (Patient number)	^{18}F-FCH (N =71)	^{18}F-FDG (N =71)
Negative	14 (19.7%)	31 (43.7%)
Positive	57 (80.3%)	40 (56.3%)
95% CI	[71.03%, 89.54%]	[44.80%, 67.87%]

Statistical analyses for the specificity of 18F-FCH and 18F-FDG (per-patient basis)

Treatment (Patient number)	^{18}F-FCH (N =12)	^{18}F-FDG (N =12)
Negative	6 (50.0%)	6 (50.0%)
Positive	6 (50.0%)	6 (50.0%)
95% CI	[21.71%, 78.29%]	[21.71%, 78.29%]

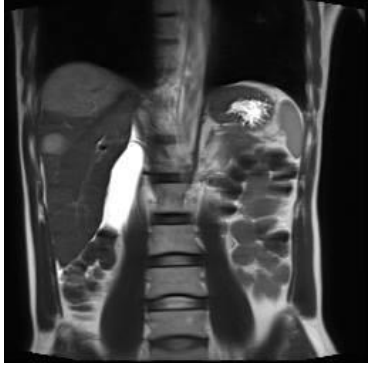
Frequency distribution of the uptake of ^{18}F-FCH, ^{18}F-FDG and differentiated HCC showed no statistical significance in distinguishing the differentiation stages of HCC.

	^{18}F-FCH			^{18}F-FDG		
Standard Of Truth Determination	Poor differentiated (N = 10)	Moderate differentiated (N = 24)	Well differentiated (N = 6)	Poor differentiated (N = 10)	Moderate differentiated (N = 24)	Well differentiated (N = 6)
Likelihood of cancer						
No cancer or nonpathologic aspect	1 (10.0%)	9 (37.5%)	1 (16.7%)	3 (30.0%)	13 (54.2%)	1 (16.7%)
Probably lesion	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Equivocal lesion	1 (10.0%)	4 (16.7%)	1 (16.7%)	0 (0.0%)	0 (0.0%)	1 (16.8%)
Probably cancer	3 (30.0%)	5 (20.8%)	3 (50.0%)	2 (20.0%)	4 (16.67%)	2 (33.3%)
Most probably cancer	5 (50.0%)	6 (25.0%)	1 (16.7%)	5 (50.0%)	7 (29.17%)	2 (33.3%)
p-value	0.4381			0.1578		

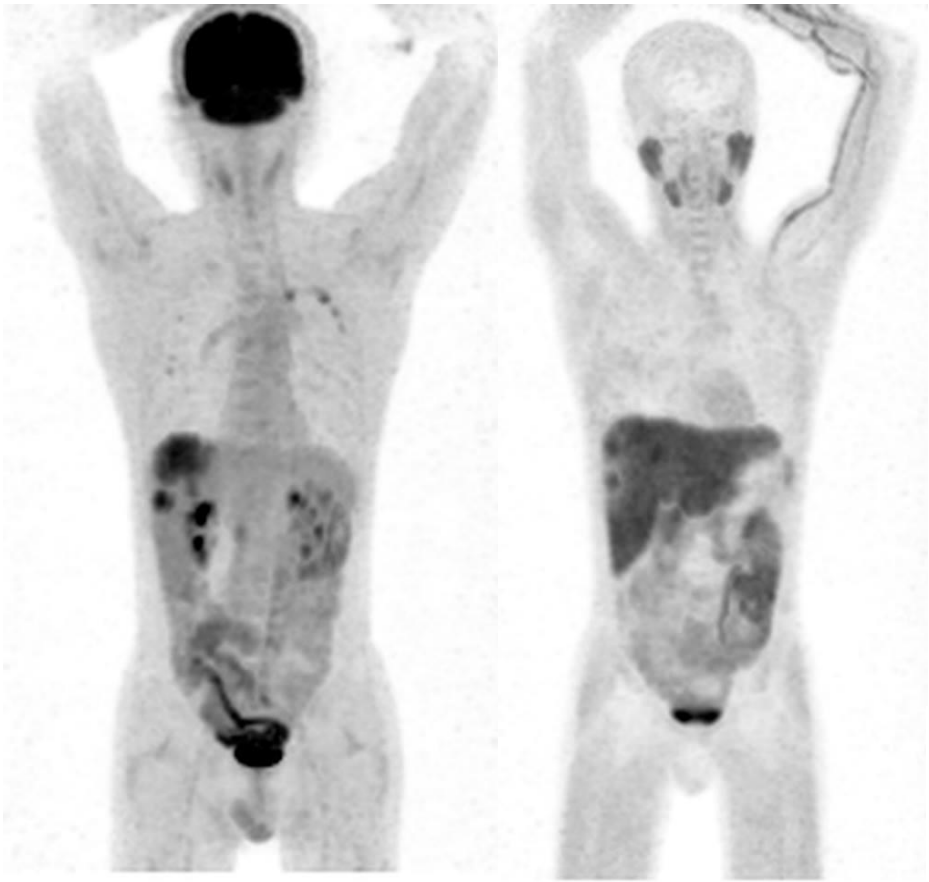
Safety

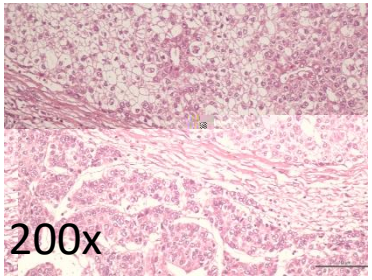
- There was no adverse event reported during the study period.
- The vital signs including blood pressure, pulse rate and body temperature were monitored at the baseline, before and after ^{18}F-FCH and ^{18}F-FDG treatment.
- The changes of vital signs after treatment were not clinically meaningful, and there was no statistically meaningful difference between ^{18}F-FCH and ^{18}F-FDG .

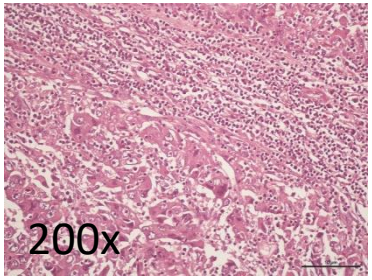
Case 1

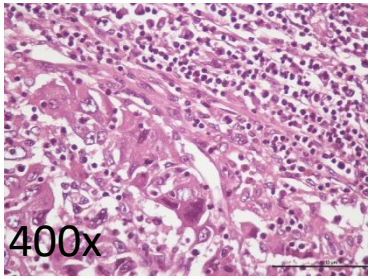


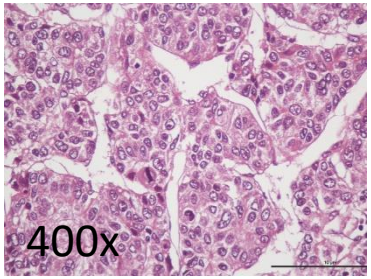
Liver MRI revealed 2 liver tumors in S 7/8 and S6, respectively







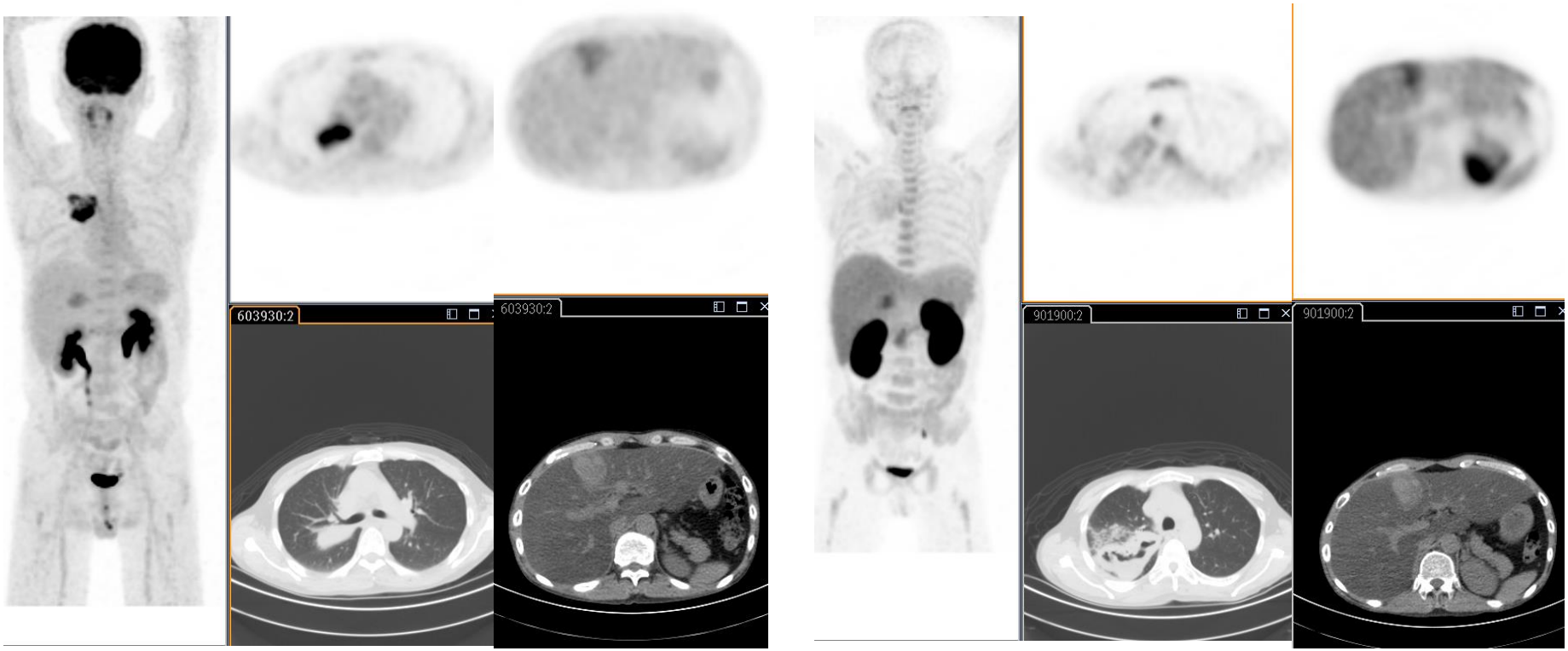




H&E stain: (Lt) S7/8, 6.8 x 5.5 x 4.9 cm, grade Ⅲ-giant cells with pleomorphism; grade III., (Rt) S6, 1.7 x 1.6 x 1.4 cm, grade III.

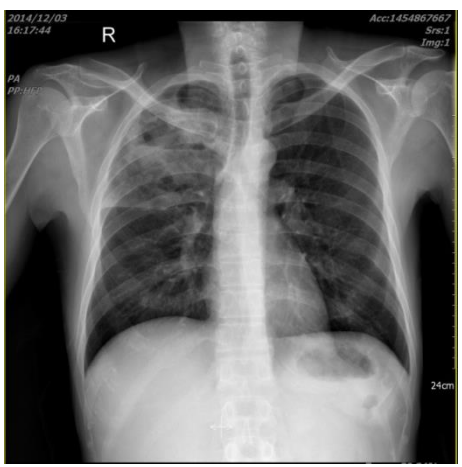
The FDG (Lt) and FCH (Rt) images of a 49y/o male with HBsAg (+), serum AFP 4,766ng/ml. MRI showed a 7.5cm ill-defined hypervascular lesion with contrast washout in S7/8 , and a 2.6cm faint hypervascular lesion with contrast washout and capsular enhancement in S6 liver.

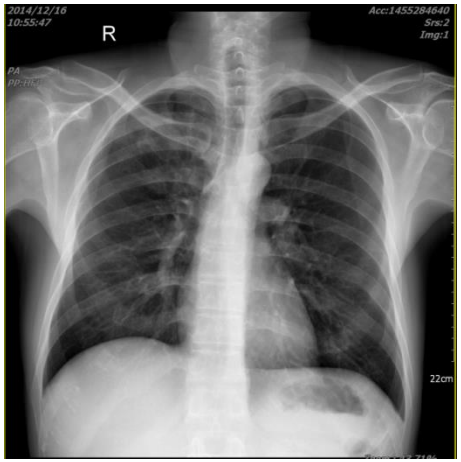
Case 2

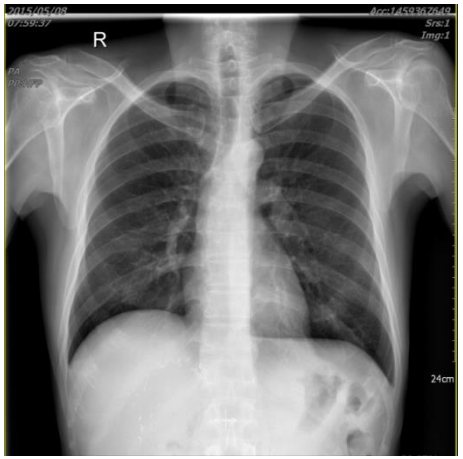


The FDG (Lt) and FCH (Rt) images at the chest and liver levels of a 42 y/o male with HBsAg (+) and serum AFP 4.4ng/ml. The individual lesions expressed both moderate FDG and FCH avidity. Progression of pneumonia during a 7-day interval between these two studies.

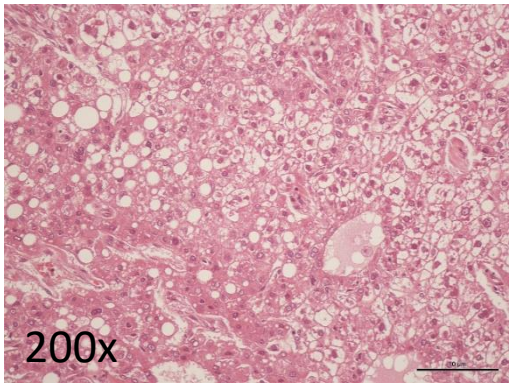
Case 2

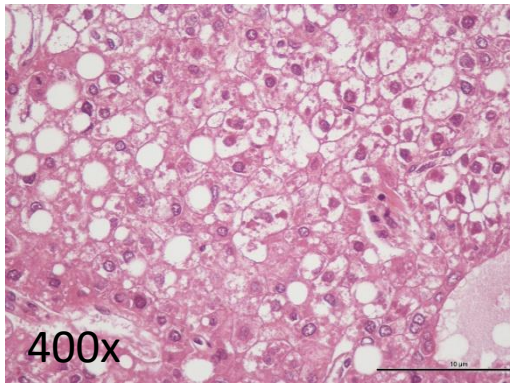






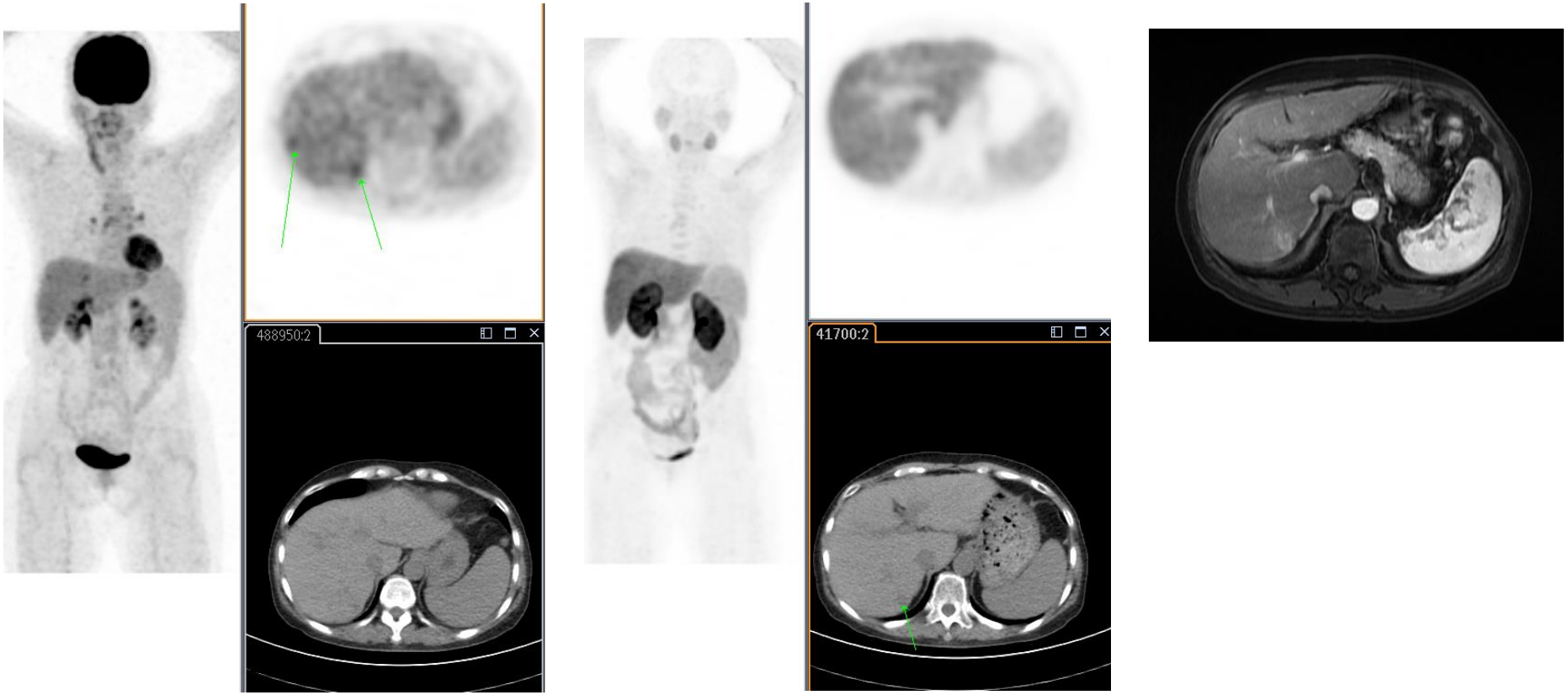
Chest X-ray (Rt) 2014-12-03, (Mid) 2014-12-16, (Lt) 2015-05-08





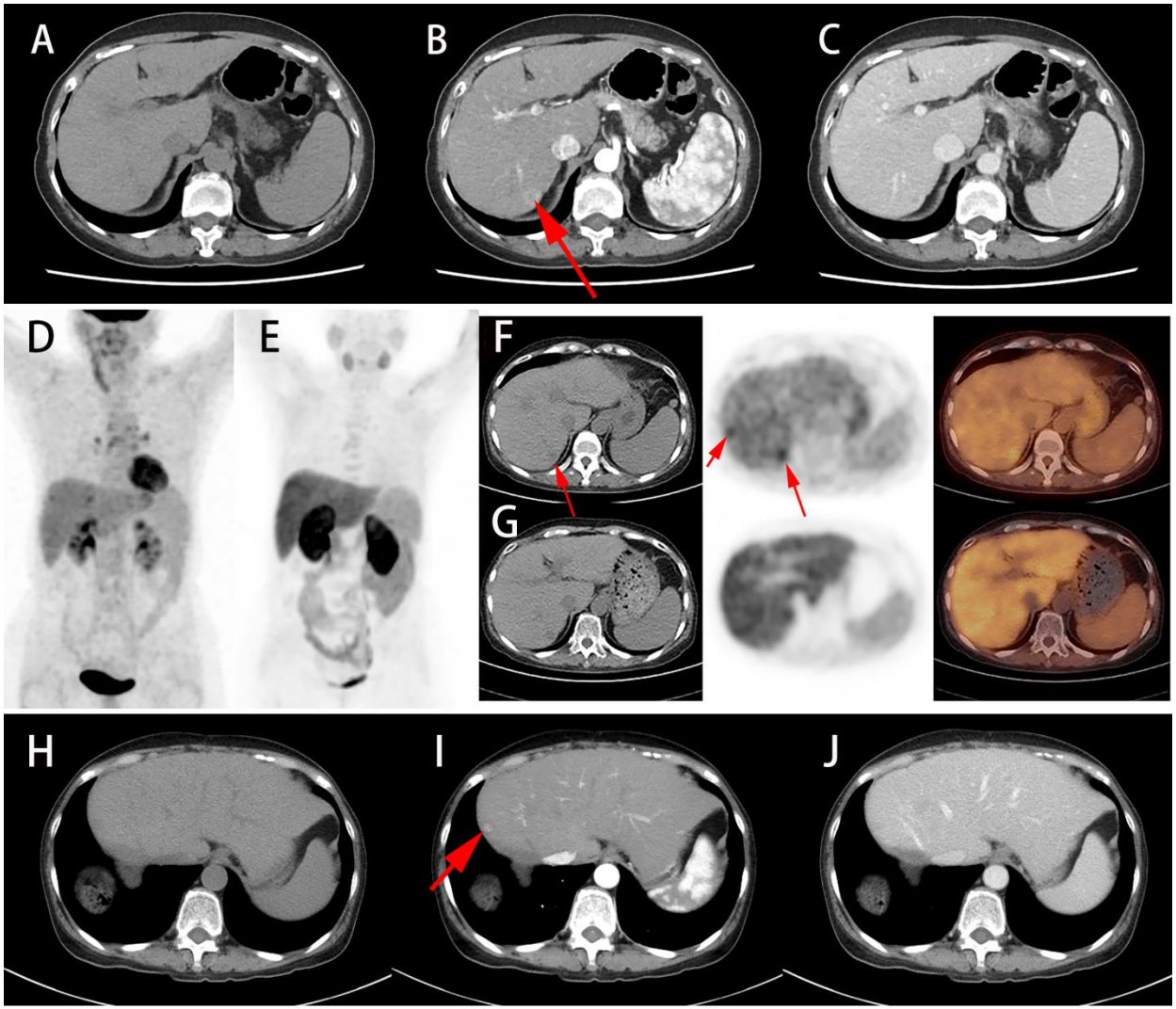
Surgical operation on 2014-12-25. Histopathological results: S4, 3.5 x 3.5 x 3.4 cm HCC, grade III,with some giant cells and nuclear pleomorphism.

Case 3



The FDG (Lt) and FCH (Rt) of a 59-year-old female with serum AFP 5.7 ng/ml, and HCV (+). Abdominal MRI revealed hypervascular lesion over S7/S6 about 1.7cm with early washout and delay capsule enhancement, compatible with hepatocellular carcinoma. Histopathological results: cholangiocarcinoma, poorly differentiated, liver, S6 – 7.

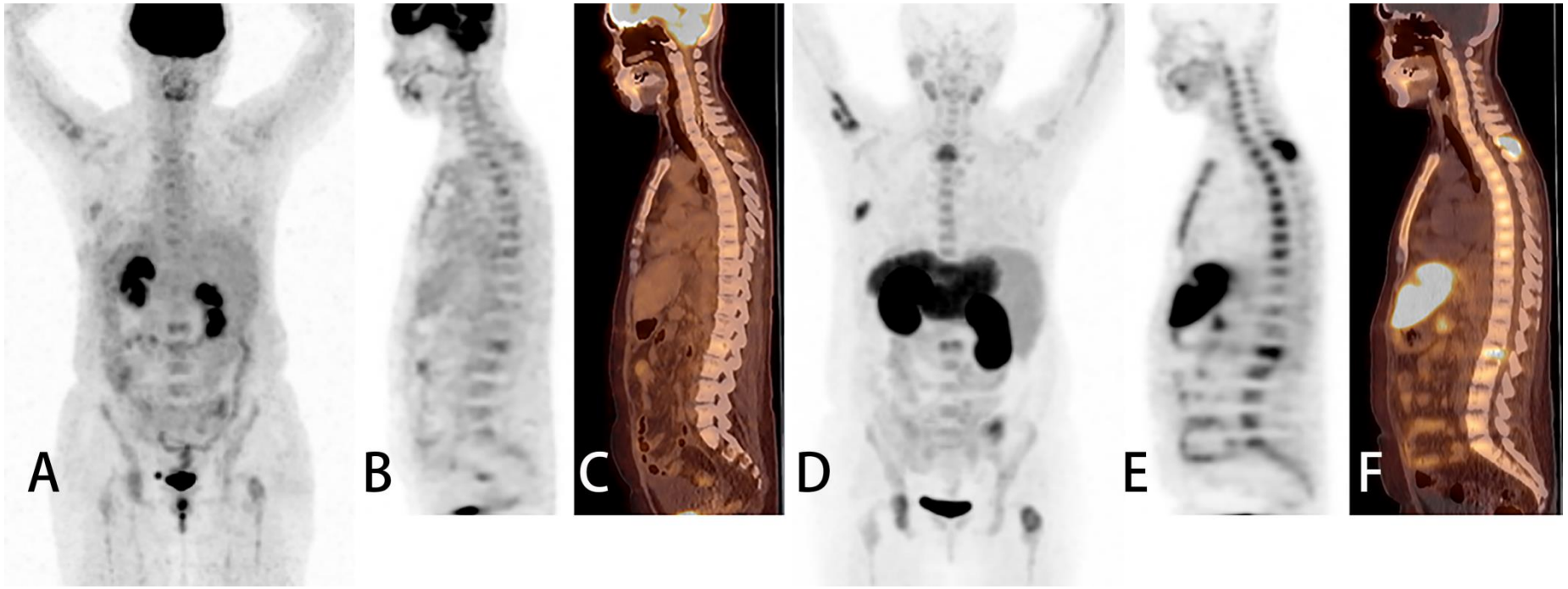
Case 3



59 y/o female, hepatitis C carrier, 1.8 cm nodule in S6/7, Cholangiocarcinoma.
Post-OP AFP 35.8 ng/ml, CT revealed small nodule at S8, S/P RF ablation.

Case 4

[F-18]FDG [F-18]FCH



48 y/o female, HBV (+), Child-Pugh A， BCLC B， S/P TACE x 3, S/P OP Gr 3 HCC. Post-OP 2 months, serum AFP 23,959 ng/ml.

Efficacy Conclusions

- The primary endpoint of this study was to evaluate the superiority of ^{18}F-FCH sensitivity in diagnosing HCC against ^{18}F-FDG by per-patient basis. ^{18}F-FCH (80.3%) showed a 23.94% higher per-patient sensitivity than ^{18}F-FDG (56.3%) (95% confidence interval lower bound = 10.72% and upper bound = 37.16%) in diagnosis HCC with statistical significance (p=0.0011; power=92%).
- The same advantage for ^{18}F-FCH to diagnose HCC in liver against ^{18}F-FDG was found in per-site basis. ^{18}F-FCH (78.2%) had 25.45% higher per-site sensitivity (95% confidence interval lower bound = 10.15% and higher bound = 40.76%) in liver than ^{18}F-FDG (52.7%) with statistical significance (p=0.0028).

Efficacy Conclusions

- Both ^{18}F-FCH and ^{18}F-FDG showed similar specificity in diagnosis HCC. However, due to the small number of sample size to analyzed, the results were not conclusive.
- Both ^{18}F-FCH and ^{18}F-FDG also showed similar efficacy profile in detecting the differentiation stages of HCC.

^{18}F-FDG PET/CT造影的肝癌的診斷結果

作者	發表時間	病例總數	肝癌病例數	研究設計	靈敏度	特異性	註釋
Delbeke[12]	1998	101	23	前瞻性	57 %	-	盲性試驗
Khan[14]	2000	20	20	回溯性	55 %	-	SUV和分化的關聯性
Jeng[16]	2003	48	36	回溯性	55 %	100 %	B型肝炎帶原者
Wudel[17]	2003	67	67	回溯性	64 %	-	
Ho[18]	2007	121	97	回溯性	79 %	91%	雙示蹤劑，比較SUV和轉移的關聯性
Park[38]	2008	112	99	前瞻性	61 %	-	
Yamamoto[19]	2008	12	12	回溯性	50 %	-	低分化的肝癌偵測率75 %
Hwang[20]	2009	10	10	前瞻性	40 %	-	
Sun[21]	2009	25	19	回溯性	89 %	83 %	疑似肝癌復發的病患
Talbot[22]	2010	81	34	前瞻性	68 %	91 %	
Wolfort[23]	2010	20	20	回溯性	70 %	-	
Cheung[24]	2011	58	58	前瞻性	43 %	-	與^{11}C-醋酸鹽PET造影、血管侵犯比較
Larsson[25]	2012	44	44	回溯性	30 %	-	
Cheung[26]	2013	43	43	回溯性	33 %	-	手術或移植前，與TNM分期比較
Ijichi[27]	2013	56	56	回溯性	43 %	-	SUV和變異，腫瘤大小和血管侵犯的關聯性
Schierz[15]	2013	27	27	回溯性	100 %	-	動態PET造影分析動脈灌注
Wang[28]	2013	36	32	回溯性	97 %	83 %	疑似肝癌復發的病患
Cho[29]	2014	457	457	回溯性	-	-	診斷肝外轉移的靈敏度98 %、特異性92 %
Wang[30]	2015	22	22	前瞻性	57 %	-	含動態PET造影的靈敏度78 %
Ferda[31]	2015	65	65	回溯性	-	-	鑑別高低分化的靈敏度84 %、特異性75 %
Castilla-Lievre[32]	2016	33	28	前瞻性	36 %	-	
Kao[33]	2016	83	71	前瞻性	56.3%	50%	與^{18}F-膽鹼PET造影比較
Bailly[34]	2016	34	34	回溯性	29 %	-	SUV與病理分級、血管侵犯的關聯性

^{18}F-FCH PET/CT造影診斷肝癌結果分析

作者	發表時間	病例總數	肝癌病例數	使用放射藥品	研究設計	靈敏度	特異性	註釋
Talbot[57]	2006	12	12	^{18}F-膽鹼	前瞻性	100 %	-	與^{18}F-FDG PET造影比較
Yamamoto[19]	2008	12	12	^{11}C-膽鹼	回溯性	63 %	-	與^{18}F-FDG PET造影比較
Talbot[22]	2010	81	34	^{18}F-膽鹼	前瞻性	88 %	62 %	與^{18}F-FDG PET造影比較
Wu[56]	2011	76	76	^{11}C-膽鹼	前瞻性	71 %	-	與^{18}F-FDG PET造影比較
Bieze[59]	2014	49	49	^{18}F-膽鹼	前瞻性	100 %	97%	評估對治療的意義
Lopci[60]	2015	45	45	^{11}C-膽鹼	回溯性	88 %	90 %	與CT/MRI比較
Kao[33]	2016	83	71	^{18}F-膽鹼	前瞻性	80.3%	50%	與^{18}F-FDG PET造影比較
Castilla-Lievre[32]	2016	33	28	^{11}C-膽鹼	前瞻性	75 %	-	與^{18}F-FDG PET造影比較

Discussion

1. HCC cases detected by at least one PET scan (^{18}F-FDG and ^{18}F-FCH) was high up to 87.3%(62/71) by per-patient basis and 85.5%(47/55) by per-site basis. In the future, ^{18}F-FDG and ^{18}F-FCH may form a “set” of duo-PET scans for the diagnosis of HCC.
2. HCC lesions expressed variable FDG and FCH avidity, current histological grading based on nuclear pleomorphism cannot represent the metabolic change of the tumor.

Detection rate of radiolabelled choline PET or PET/CT in hepatocellular carcinoma: an updated systematic review and meta-analysis

- Nine studies (283 HCC patients) were included in the pooled analysis.
- The pooled detection rate of radiolabelled choline PET or PET/CT on a per patient- and on a per lesion-based analysis was 83% [95% confidence interval (95% CI) 75–89%] and 79% (95% CI 72–86%), respectively. A significant heterogeneity among the studies was found on a per lesion-based analysis only. No significant publication bias was found.
- The subgroup analysis demonstrated a trend towards a higher detection rate when using ^{18}F-choline compared to ^{11}C-choline, without a statistically significant difference.

Signore G, et al. Clinical and Translational Imaging. 2019;7, 237–253.

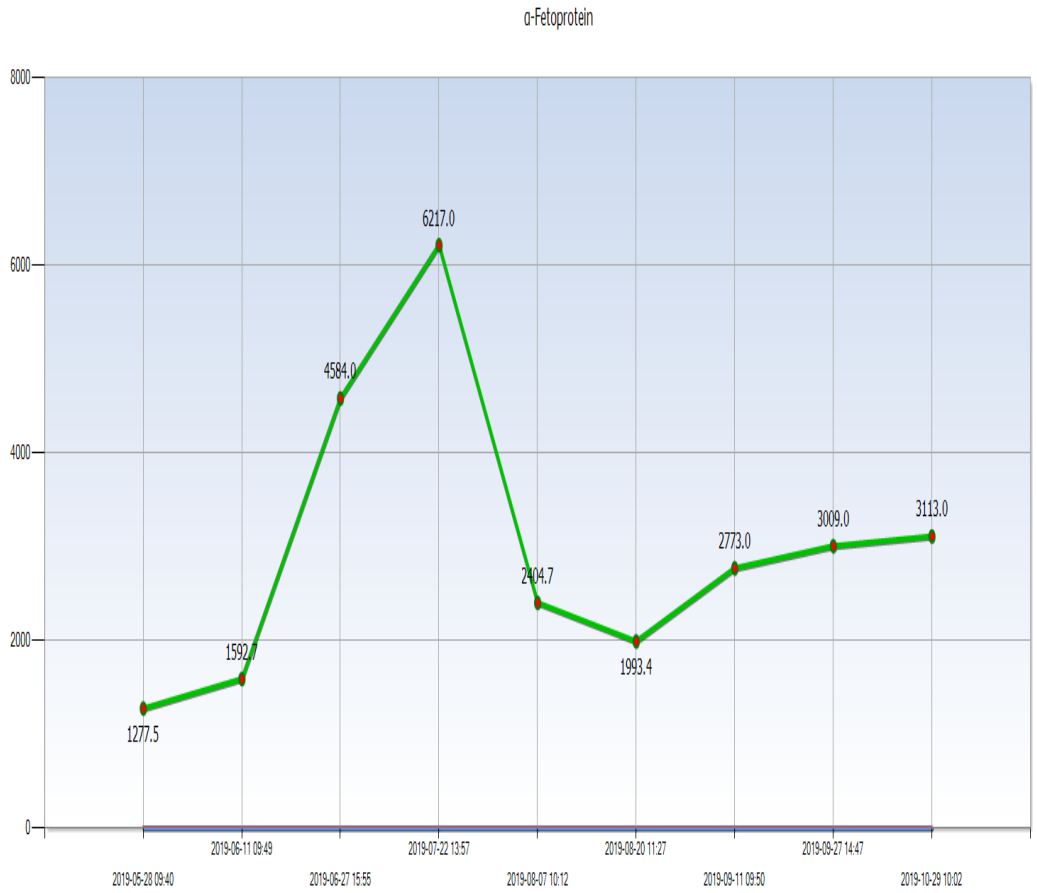
Detection rate of radiolabelled choline PET or PET/CT in hepatocellular carcinoma: an updated systematic review and meta-analysis

- Pooled detection rate of HCC using dual-tracer PET/CT (radiolabelled choline and 18F-FDG) on a per patient- and a per lesion-based analysis was 91% (95% CI 87–95%) and 89% (95% CI 80–95%), respectively, without significant heterogeneity.
- The detection rate increased when dual-tracer PET/CT was performed.

Signore G, et al. Clinical and Translational Imaging. 2019;7, 237–253.

Case 5

History



2019-07-22

2019-10-29

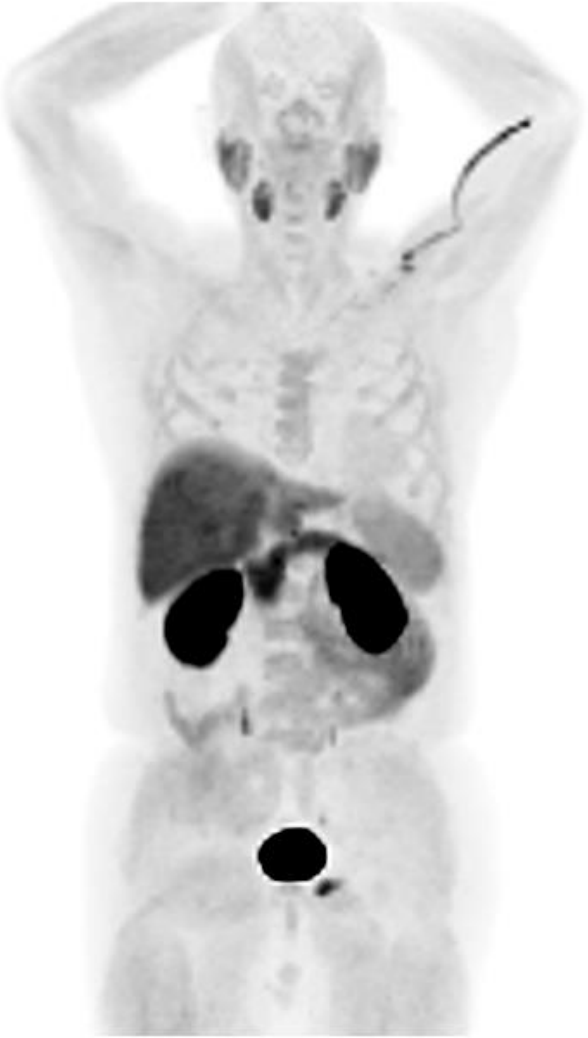
64 y/o, male. HBV Carrier, HCC was proved in 2018-8.
HCC with bone mets s/p Y-90, TACE in liver tumor and XRT to bone metastatic foci, s/p C/T.

Serum AFP level progressive elevation.

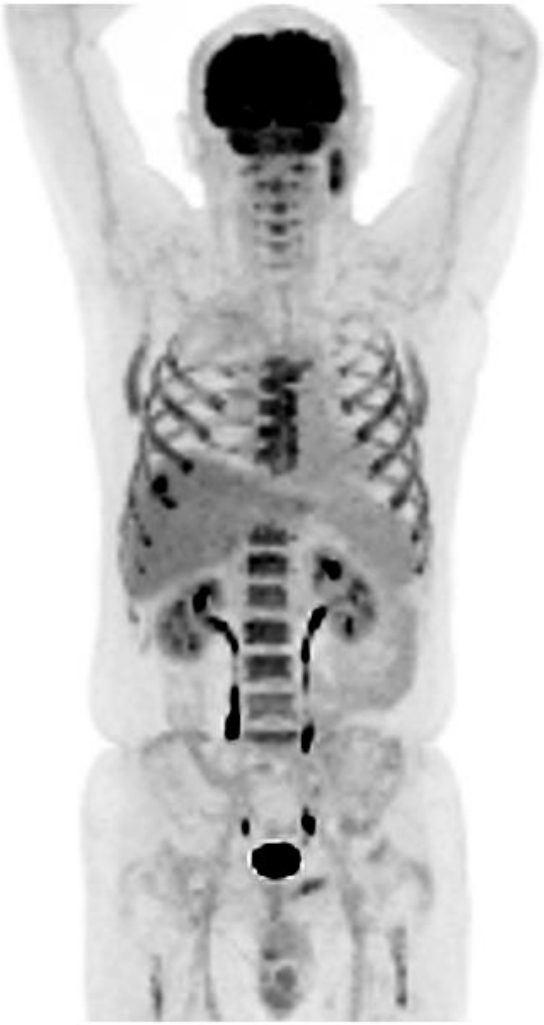
Case 5

First exam

2019-07-08 F-choline



2019-07-11 FDG



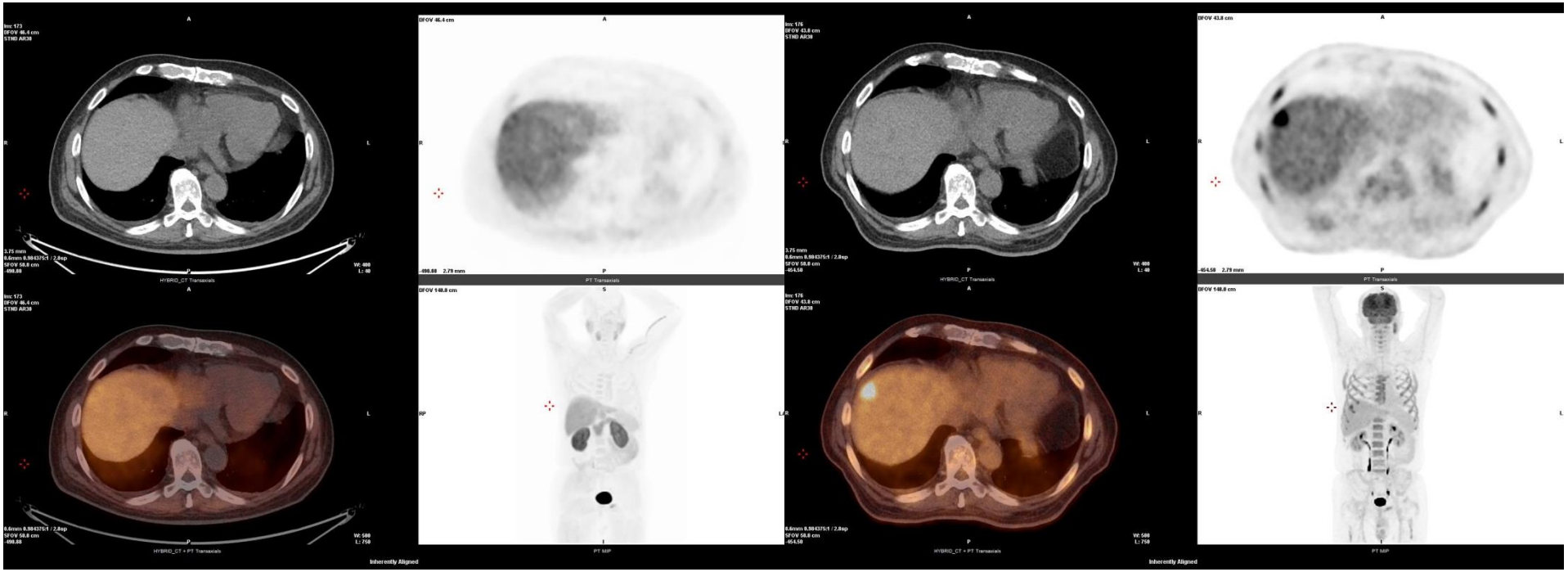
Case 5

First exam- lesion I

 # Right lobe of liver

2019-07-08 F-choline

2019-07-11 FDG



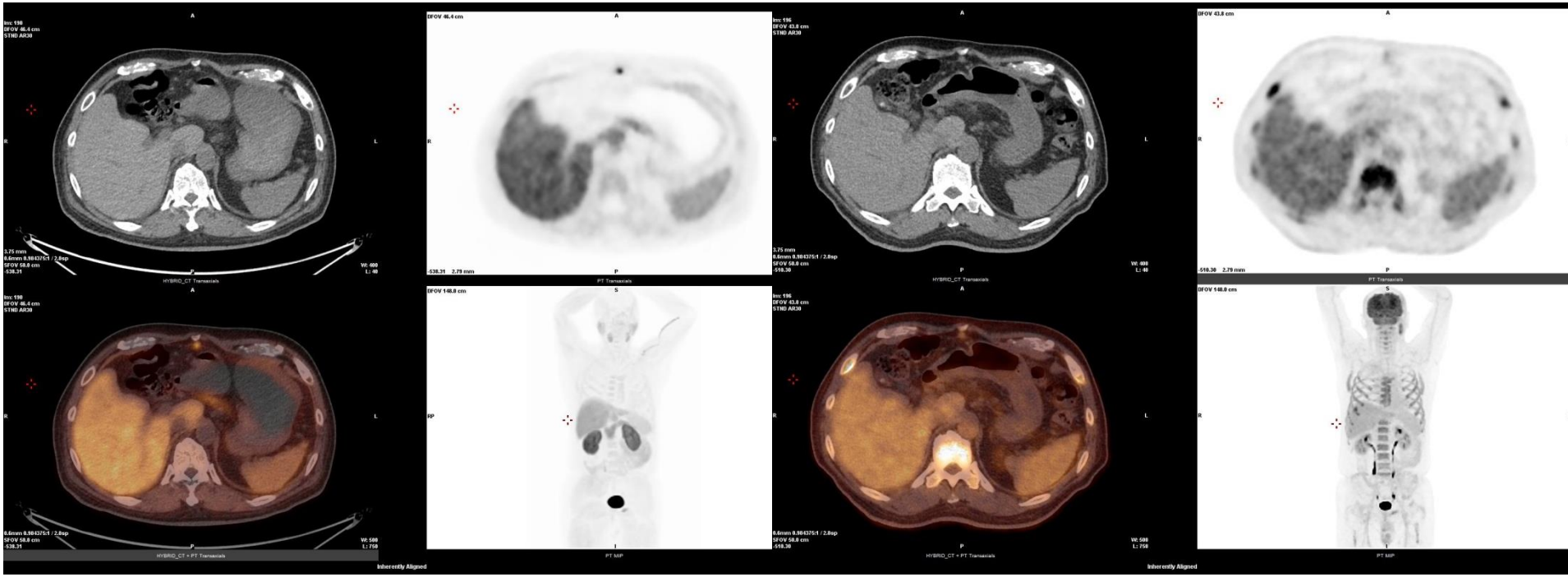
Case 5

First exam- lesion II

 # Lymph node posterior of xiphoid process

2019-07-08 F-choline

2019-07-11 FDG

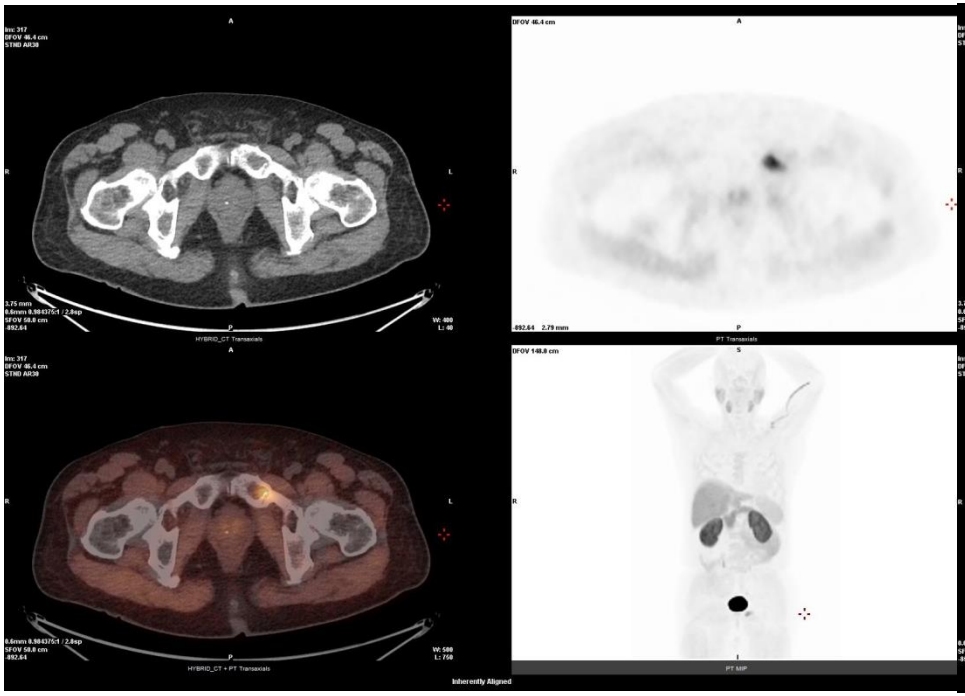


Case 5

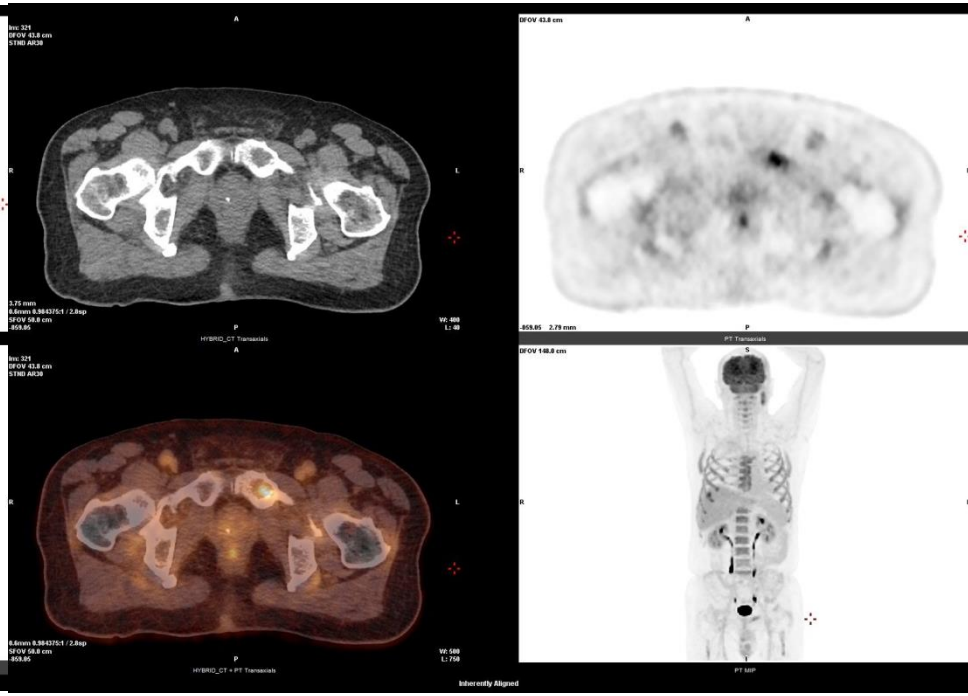
First exam lesion-III

 # Pubic bone

2019-07-08 F-choline

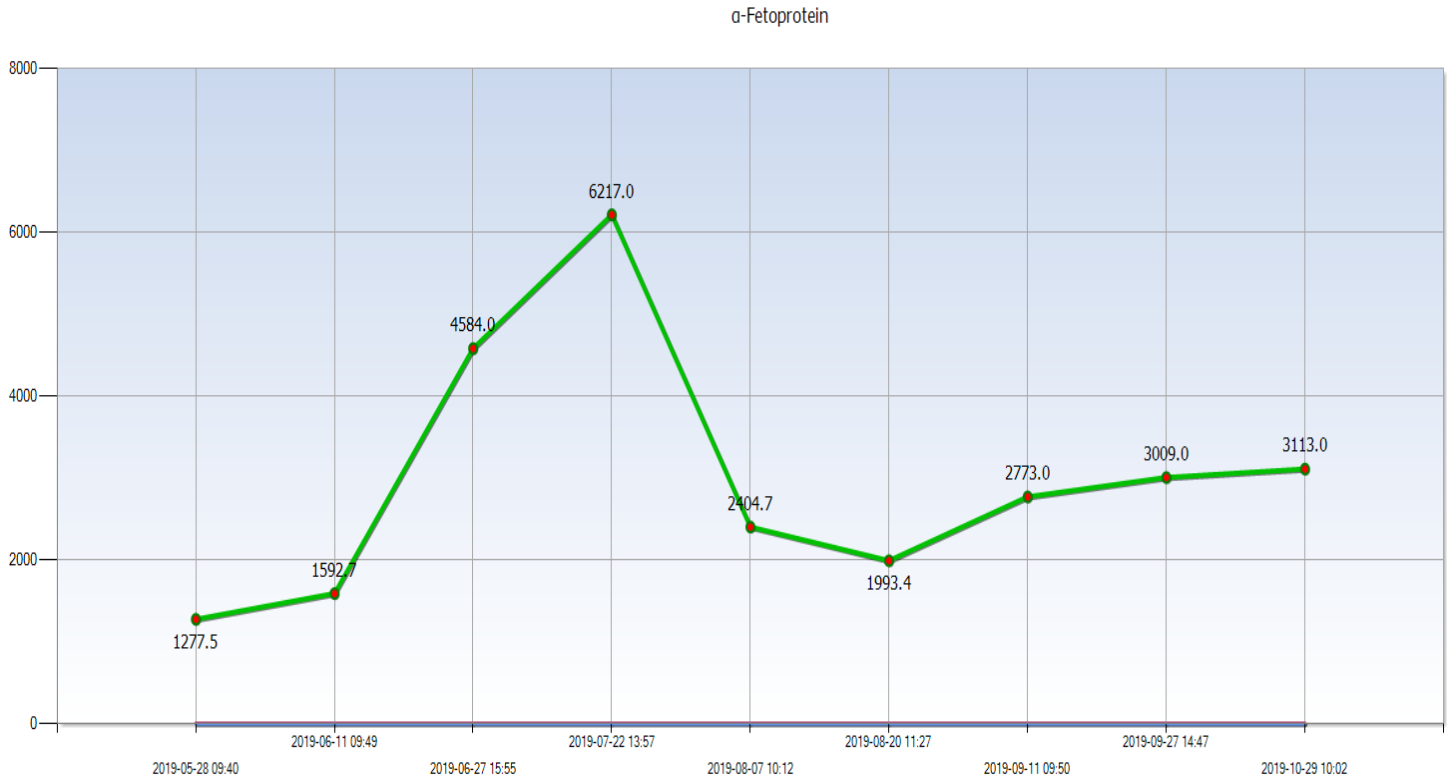


2019-07-11 FDG



Case 5

History



2019-07-22

2019-10-29

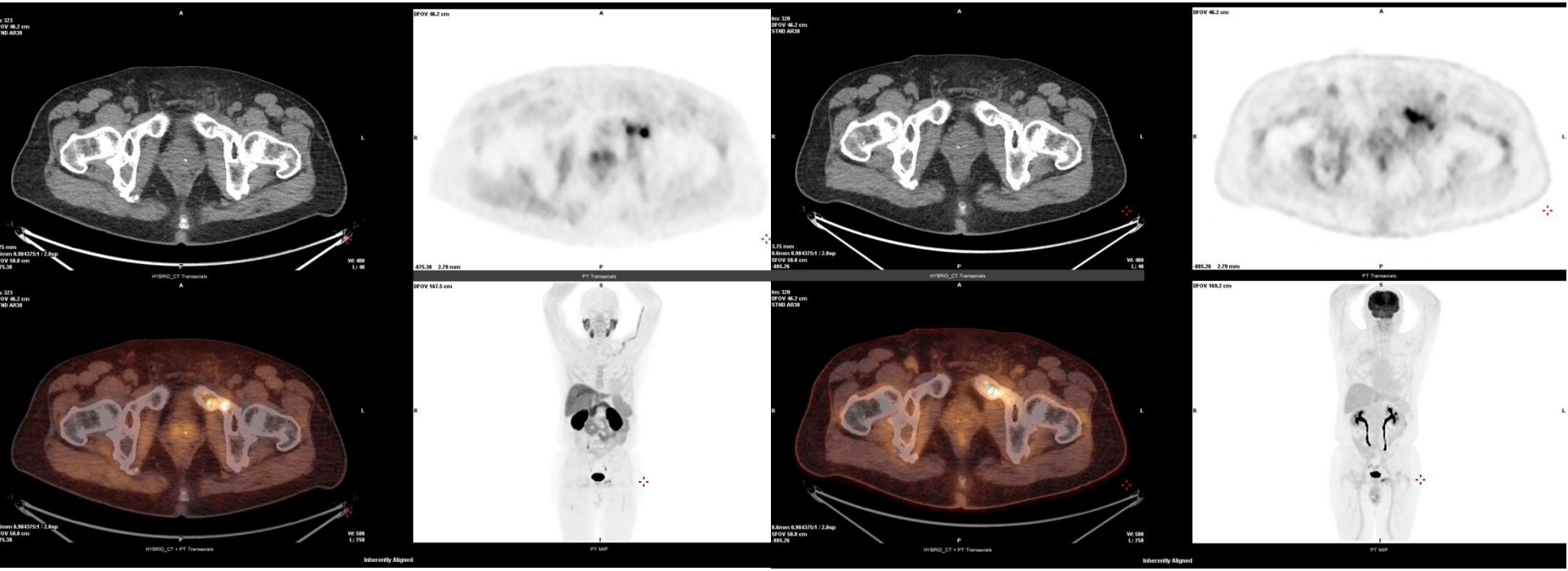
Case 5

Second exam- lesion III

 # Pubic bone

2019-11-01 F-choline

2019-11-06 FDG



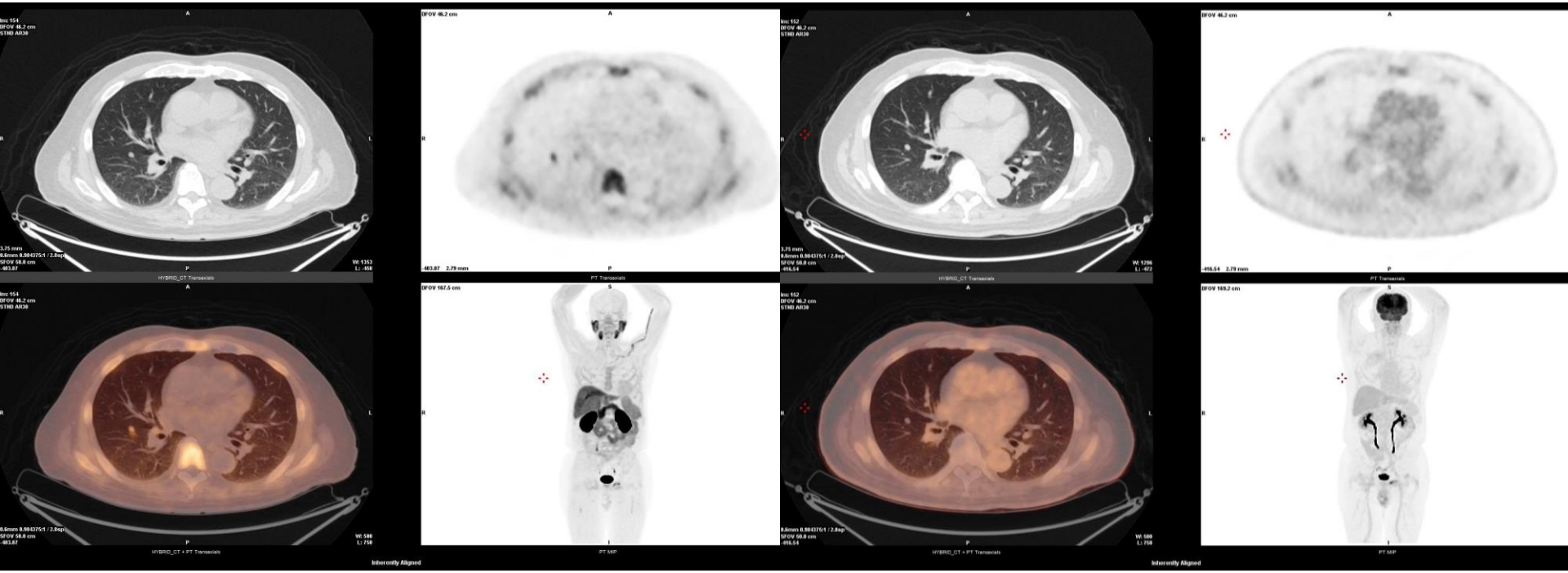
Case 5

Second exam- NEW lesion

 # RLL of lung

2019-11-01 F-choline

2019-11-06 FDG



衛福部食藥署核備醫院調製 PET 藥品品項

F-18 FDG	F-18 FDOPA	F-18 NaF	C-11 Sodium Acetate	N-13 NH3	F-18 FLT	F-18 FCH	Ga-68 DOTATOC
台北榮總			台北榮總	台北榮總			
新光醫院							
臺大醫院		臺大醫院				臺大醫院	臺大醫院
三軍總醫院		三軍總醫院					
林口長庚		林口長庚	林口長庚				
中山附醫		中山附醫			中山附醫		
義大醫院		義大醫院					
阮綜合醫院		阮綜合醫院	阮綜合醫院				
花蓮慈濟	花蓮慈濟	花蓮慈濟	花蓮慈濟				

2019-10-01


今天
2019年6月
農曆四月 ~ 五月
月
週日 週一 週二 週三 週四 週五 週六
26 (廿二) 27 (廿三) 28 (廿四) 29 (廿五) 30 (廿六) 31 (廿七) 6月 1日(廿八)
台大 F-18 choline
台中中山醫 F-18 FLT
花蓮慈濟 NaF
2 (廿九) 3 (五月) 4 (初二) 5 (初三) 6 (芒種) 7 (初五) 8 (初六)
北榮 C-11 acetate
北榮 C-11 acetate
花蓮慈濟 NaF
端午節彈性放假
9 (初七) 10 (初八) 11 (初九) 12 (初十) 13 (十一) 14 (十二) 15 (十三)
台中中山醫 F-18 FLT
花蓮慈濟 NaF
16 (十四) 17 (十五) 18 (十六) 19 (十七) 20 (十八) 21 (夏至) 22 (二十)
花蓮慈濟 NaF
23 (廿一) 24 (廿二) 25 (廿三) 26 (廿四) 27 (廿五) 28 (廿六) 29 (廿七)
台大 F-18 choline
台中中山醫 F-18 FLT
花蓮慈濟 NaF
30 (廿八) 7月 1日(廿九) 2 (三十) 3 (六月) 4 (初二) 5 (初三) 6 (初四)

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Thank you for your attention!