

artery occlusion : MCAO) ラット] での脳酸素代謝機能を測定した⁷⁾。

その結果 (図④), 障害側である右脳は, 閉塞 1 時間後において CBF 減少と代償的な OEF 上昇を示したが, 24 時間後では著しい CBF 減少とともに OEF の代償的上昇は消失していた。CMRO₂ は, 非障害側である左脳において 1 時間後, 24 時間後で変化しなかった。一方, 右脳の CMRO₂ は左脳とくらべて有意に小さく, さらに, 24 時間後では 1 時間後とくらべて有意に低下していた。なお正常側 CMRO₂ は, 閉塞 1 時間後, 24 時間後とも, 外科的手法により求めたラット正常脳の値⁸⁾と同等であった。

臨床において, 慢性的な脳循環障害によって脳還流圧が低下し CBF が減少すると, CMRO₂ を維持するため代償的に OEF が上昇するが, 還流圧低下が顕著になると代償性 OEF 上昇機構は破綻し著しい CMRO₂ 減少に至

ることが知られている。上記の結果は, 急性モデルではあるが, ラットにおいても酸素代謝に関する代償機構が存在し機能することを示したものである。

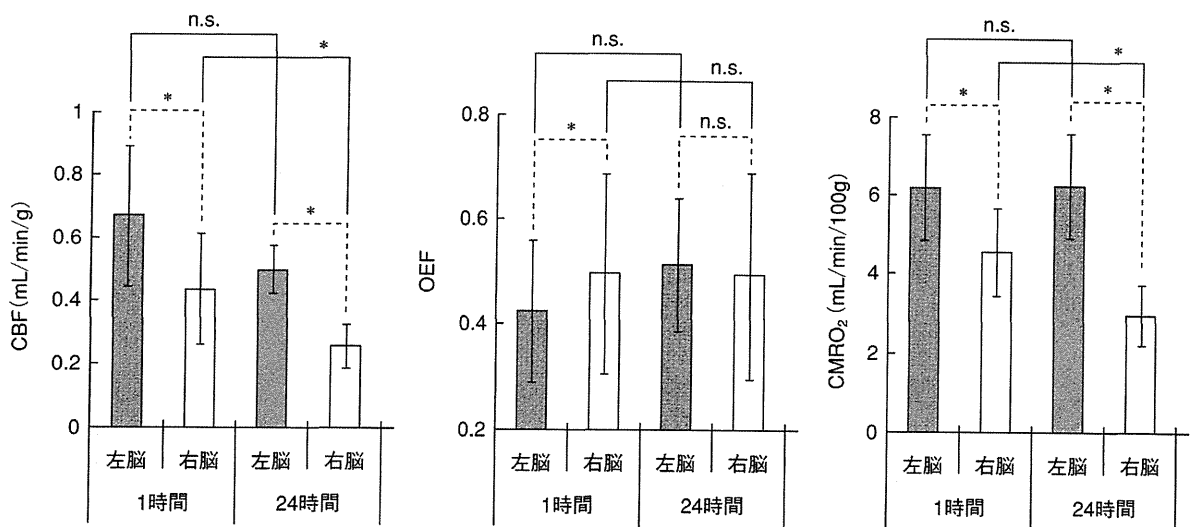
4 脳卒中発症後超急性期の脳循環代謝機能に与える高血圧の影響について

高血圧は疫学的に脳卒中と関連が強く, 脳卒中罹患率・死亡率の間には正の相関がある。最近では, 高血圧は脳卒中発症後の治療成績にも影響を及ぼし, 高血圧を有する脳卒中患者では予後が悪いことが報告されてきている⁹⁾。

慢性高血圧は, 脳血管や周囲組織に長期にわたり負荷を与えることから, CBF, OEF, CMRO₂ の障害応答性を変化しうる¹⁰⁾。しかしながら, これらの脳循環代謝パラメータを脳卒中発症後超急性期の患者で評価することは,

表① 正常ラット脳循環代謝パラメータ (Magata Y *et al*, 2003⁴⁾より引用)

	Injectable ¹⁵ O-C ₂ -PET	Surgical
CBF (mL/min/g)	44±4.5	—
OEF	0.54±0.11	0.57±0.13
CMRO ₂ (mL/min/100g)	4.3±1.3	—



図④ MCAO 処置ラット (閉塞 1 時間, 24 時間) の左右脳での脳循環代謝パラメータ (Temma T *et al*, 2006⁷⁾より引用)

MCAO 障害側は右脳

有意差検定は, Wilcoxon signed rank test (左脳 vs 右脳), Mann-Whitney U test (1 時間 vs 24 時間) によりおこなった。

*P<0.05, n.s. not significant.

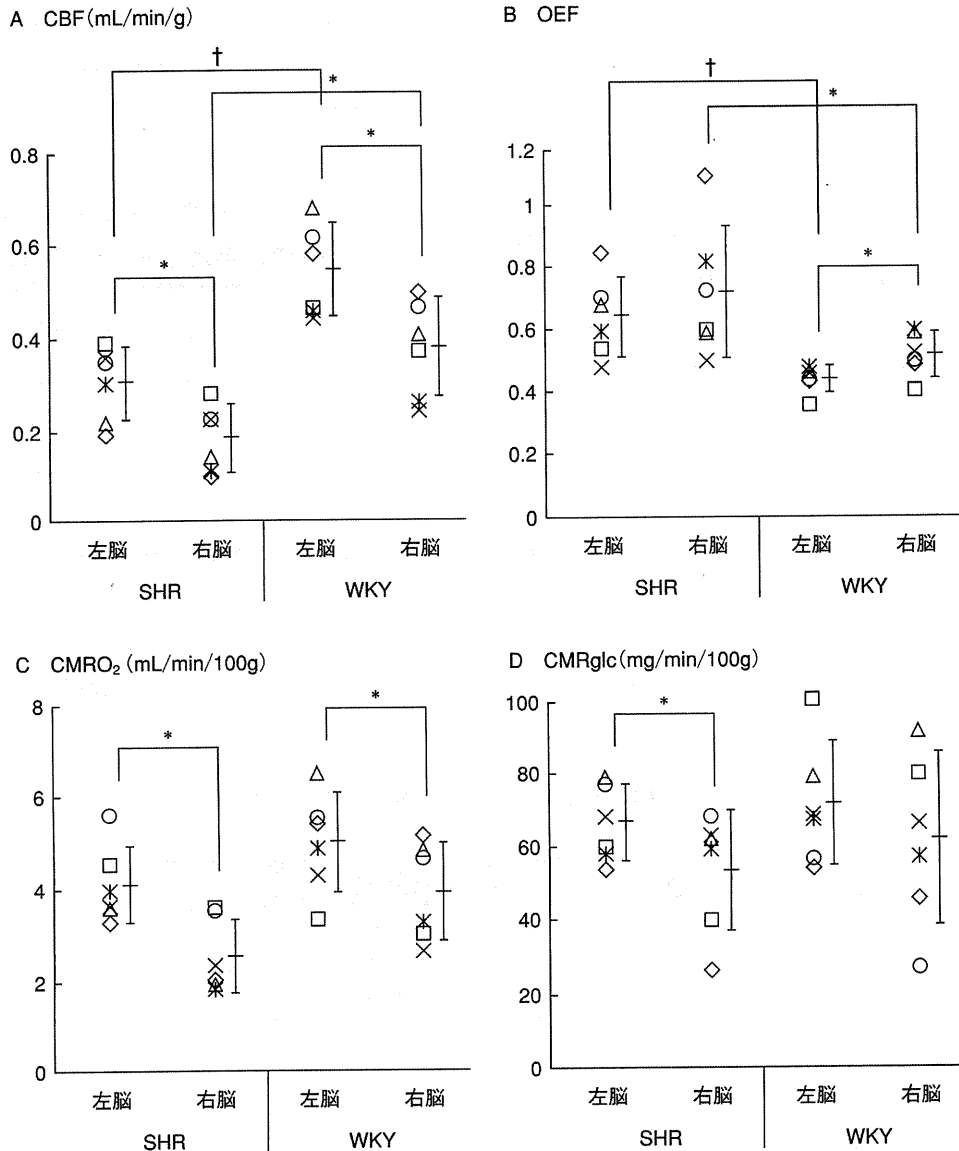


図5 MCAO (閉塞 1 時間) 処置 SHR・WKY ラットの左右脳での脳循環代謝パラメータ (Temma T *et al*, 2008¹³)より引用
 MCAO 障害側は右脳
 有意差検定は, Wilcoxon signed rank test (左脳 vs 右脳), Mann-Whitney U test (SHR vs WKY) によりおこなった.
 *P<0.05, †P<0.01

治療可能時間域 (発症後 3 時間) の制限のため現実的でない。これまでに、高血圧モデル動物として自然発症高血圧ラット (Spontaneously Hypertensive Rat : SHR) を用いた検討がなされているが、手技的な限界により CBF と脳梗塞体積のみが評価されているだけで¹¹⁾¹²⁾、高血圧が脳卒中発症後急性期の脳循環代謝機能障害に及ぼす影響についてはいまだ明らかではない。そこで、脳卒中発症後超急性期の脳循環代謝パラメータ変化に与える

高血圧の影響を明らかにすることを目的として、SHR に 1 時間の右 MCAO を処置し¹⁵O-H₂O, injectable ¹⁵O-O₂を用いて CBF, OEF, CMRO₂の定量測定をおこなった¹³⁾。

その結果(図5), SHR では対照の Wistar Kyoto ラット (WKY) とくらべ、両側 CBF の低下¹⁴⁾と両側 OEF の上昇が認められたが、CMRO₂では明らかな系統差は消失していたことから、SHR では代謝性の代償機構が有効に機能

していることが示された。しかしながら、SHR 右脳では WKY 右脳とくらべて CMRO₂低下傾向が認められ、OEF が個体により大きくなることから、SHR 右脳の代償機構は不完全であり、WKY とくらべて虚血障害の進行が速やかであることが示唆された。さらに、エネルギー代謝機能を詳細に調べるため、2-¹⁸F-fluoro-2-deoxy-D-glucose (¹⁸F-FDG) を用いた脳グルコース代謝率 (Cerebral Metabolic Rate for Glucose : CMRglc) 定量測定をあわせて実施したところ、SHR においてのみ左右差が認められた。これは、WKY 障害側では虚血コア周辺領域における嫌氣的解糖系の亢進を起因とする¹⁸F-FDG の集積増加が起こり¹⁴⁾、半球ベースの解析では左右差が生じなかったためと考えられる。また、MCAO7 時間後に梗塞面積を調べたところ SHR において WKY と比較して有意に広い結果となった。

以上、injectable ¹⁵O-O₂-PET 法を MCAO 処置 SHR に適用することで、慢性的な高血圧が脳卒中の発症だけでなく発症後の脳虚血障害の進行にも影響を及ぼすことを見出した。この結果は、基礎疾患の有無（程度）によって脳卒中発症後の虚血障害進行が発症ごく早期から異なることを形態変化が現れる以前に酸素代謝の観点からはじめて明らかにしたものである。今後、これを発展させることで、t-PA が真に効果的な発症後時間域のテラーメイド評価など、臨床ではきわめて困難な研究を、ラットを用いた injectable ¹⁵O-O₂-PET 法により推進できる可能性を有するものと期待される。

おわりに

今回開発した静脈内投与可能な O-15 標識 O₂剤を用いる injectable ¹⁵O-O₂-PET 法は、従来不可能であった小動物での OEF、CMRO₂の非侵襲的局所定量測定を可能にし、高血圧が脳卒中発症後急性期の脳循環代謝機能障害に関与することを明らかにした。これらの知見は、今後の脳循環疾患の病態解明および診断・治療法開発に有益な情報を提供するものと考えられる。

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てんま・たかし

天満 敬 京都大学大学院薬学研究科病態機能分析学分野

1977 年、滋賀県生まれ。

2000 年、京都大学薬学部薬学科卒業。2002 年、京都大学大学院薬学研究科医療薬科学専攻修士課程修了。2004 年、京都大学大学院薬学研究科医療薬科学専攻博士後期課程中退、京都大学大学院薬学研究科助手。2007 年、同助教。2008 年、京都大学博士（薬学）。専門は、放射性医薬品学、分子イメージング学。研究テーマは、脳卒中・がん・動脈硬化を標的とした分子プローブ開発と分子イメージング法にもとづく病態解析。趣味は音楽活動（吹奏楽、ピアノ、歌、ドラム）と水泳。

FDG PET as a prognostic predictor in the early post-therapeutic evaluation for unresectable hepatocellular carcinoma

Tatsuya Higashi · Etsuro Hatano · Iwao Ikai ·
Ryuichi Nishii · Yuji Nakamoto · Koichi Ishizu ·
Tsuyoshi Suga · Hidekazu Kawashima · Kaori Togashi ·
Satoru Seo · Koji Kitamura · Yasuji Takada ·
Shinji Kamimoto

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Abstract

Purpose To elucidate the prognostic role of post-therapeutic ^{18}F -fluorodeoxyglucose (^{18}F -FDG) positron emission tomography (PET), we conducted a retrospective cohort study analysing the clinical factors that affect overall survival after non-operative therapy for unresectable hepatocellular carcinoma (HCC).

Methods Sixty-seven cases with unresectable HCC who received non-operative therapy (transcatheter arterial chemo-embolization: $n=24$, transcatheter arterial infusion chemotherapy: $n=31$, radiofrequency ablation: $n=5$ or systemic chemotherapy: $n=7$) and had received FDG PET for the evaluation of the therapeutic effect within 1 month after the end of the therapy were evaluated. Overall survival rate was evaluated using the univariate and multivariate analyses of relevant clinical and laboratory parameters before and after

therapy, including visual PET analysis and quantitative analysis using maximum standardized uptake value (SUV). **Results** Visual PET diagnosis of post-therapeutic lesions was a good predictor of overall survival of unresectable HCC patients. The low FDG group showed significantly longer survival (average: 608 days) than that (average: 328 days) of the high FDG group ($p<0.0001$). Multivariate analysis showed four significant prognostic factors for the survival: post-therapeutic alpha-fetoprotein (αFP) level (≥ 400 ng/ml, $p=0.004$), post-therapeutic visual PET diagnosis ($p=0.006$), post-therapeutic clinical stage (UICC stage IV, $p=0.04$) and post-therapeutic Milan criteria ($p=0.03$), while pre-therapeutic clinical factors, SUV by post-therapeutic FDG PET (5.0 or more) or others did not show significance.

Conclusion The present study suggests that post-therapeutic PET performed within 1 month after non-operative therapy can be a good predictor of overall survival in unresectable HCC patients, while pre-therapeutic evaluation including PET, tumour markers and clinical staging may not be useful.

T. Higashi (✉) · R. Nishii
Shiga Medical Center Research Institute,
5-4-30, Moriyama,
Moriyama City, Shiga 524-8524, Japan
e-mail: higashi@shigamed.jp

E. Hatano · I. Ikai · S. Seo · K. Kitamura · Y. Takada ·
S. Kamimoto
Department of Gastroenterological Surgery,
Kyoto University Graduate School of Medicine,
54 Kawahara-cho, Shogoin,
Sakyo-ku, Kyoto 606-8507, Japan

Y. Nakamoto · K. Ishizu · T. Suga · H. Kawashima · K. Togashi
Department of Diagnostic Imaging and Nuclear Medicine,
Kyoto University Graduate School of Medicine,
54 Kawahara-cho, Shogoin,
Sakyo-ku, Kyoto 606-8507, Japan

Keyword FDG · Hepatocellular carcinoma · PET ·
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Introduction

Hepatocellular carcinoma (HCC) is one of the most frequently occurring tumours worldwide and ranks fifth in frequency in the world [1, 2]. Resection and transplantation achieve the best outcomes in well-selected candidates; however, the 5-year survival rate is only 60–70% [3, 4].

Therefore, a large proportion of patients with HCC were treated with non-operative therapy, because of high risk factors, such as non-localized multiple intrahepatic lesions, extensive vascular invasion or extrahepatic metastasis or because of the shortage of donor livers for transplantation. At the present time, transcatheter arterial chemoembolization (TACE) and transcatheter arterial infusion chemotherapy (TAI) are the main non-operative therapies for relatively large or advanced intrahepatic HCC, while radiofrequency ablation (RFA) and percutaneous ethanol injection therapy (PEIT) are the main non-operative therapies for relatively small HCCs which present in small quantities [5]. For patients with distant metastasis, systemic chemotherapy is supposed to be the best choice. Recently, sorafenib, a multi-targeted tyrosine kinase inhibitor, was found to improve survival of patients with advanced stage HCC [6]. The clinical role of non-operative therapies will become more important in the near future.

In general, the therapeutic response of HCC to non-operative therapy is assessed by conventional radiological imaging modalities, based on the Response Evaluation Criteria in Solid Tumors [7]. However, such criteria using conventional imaging modalities have shown their limitations because therapeutic response and tumour viability are not appropriately reflected in patients with HCC [8]. It was reported in post-operative HCC patients that intrahepatic recurrence could be predicted by several factors, such as the presence of microvascular invasion, poor histological differentiation and satellite lesions [9, 10]. However, these factors based on pathological evaluation cannot be utilized for the evaluation of patients with unresectable HCC treated with non-operative therapy. There is really a call for an appropriate indicator of tumour viability and a predictor of prognosis in patients after non-operative therapy, especially one using a non-invasive imaging modality.

The uptake of ^{18}F fluorodeoxyglucose (^{18}F -FDG), based on the enhanced glucose metabolism in cancer cells, is supposed to be a sensitive marker of tumour viability. Tumour detection using increased ^{18}F -FDG uptake by positron emission tomography (PET) has therefore been applied in diagnostic imaging for a variety of tumours, including HCC [11, 12]. Several studies in liver tumours have shown that FDG PET is useful for tumour characterization, assessment of therapeutic response and outcome [13–15]. On the other hand, other reports showed that the sensitivity of FDG PET is not sufficiently high (50–55%) in HCC patients [16–19]. Recently, concerning resectable HCC, our group reported that FDG uptake evaluated by pre-operative PET is associated with tumour differentiation and post-operative survival in HCC patients treated with partial hepatectomy [20, 21]. However, there has been no report regarding the relationship between prognosis and FDG uptake evaluated by post-therapeutic PET after non-operative therapy in patients with unresectable HCC.

The purpose of this study is to investigate retrospectively the efficacy of FDG PET as an *in vivo* marker for tumour viability of HCC after non-operative therapy and as a prognostic predictor for post-treatment overall survival in patients with unresectable HCC.

Materials and methods

Study population

From May 2003 to April 2008, 465 cases with HCC were admitted to our unit in Kyoto University Hospital for the wish to receive a radical operation or non-operative therapy. By computed tomography (CT) scan, magnetic resonance imaging (MRI) and other imaging modalities, 320 cases were diagnosed to be candidates for a curative operation and underwent surgery. Another 23 cases were diagnosed as having far-advanced HCC and only received palliative treatment. The other 122 cases were diagnosed as having unresectable HCC and treated by non-operative therapy. Inclusion criteria in the present study were as follows: (1) diagnosed as unresectable HCC by CT scan and MRI in pre-therapeutic evaluation, (2) treated with non-operative therapy (TACE, TAI, RFA, PEIT or systemic chemotherapy) and completed a single course of a therapeutic regimen, (3) diagnosed by FDG PET within 1 month after the end of non-operative therapy and (4) clinical follow-up more than 6 months after non-operative therapy. Exclusion criteria were as follows: (1) patients who received FDG PET only before non-operative therapy and (2) patients who received FDG PET more than 1 month after the end of non-operative therapy.

Of 122 cases with unresectable HCC, 67 were included in the present study, where 67 consecutive post-therapeutic FDG PET studies were performed in 58 patients within 1 month after the end of non-operative therapy (ranging from 0 to 28 days, mean interval of days: 10.9 ± 10.9 days). In 29 patients, pre-therapeutic FDG PET was also performed within 3 months before the start of the therapy. Nine patients received non-operative therapies two times, with an interval of more than 1 month between each therapy (ranging from 32 to 1,960 days, mean interval of days: 328.5 days). Therefore, the patient who received non-operative therapies twice was counted as two cases for diagnosis of lesion viability and counted as a single patient at the time of the last post-therapeutic PET for analysis of survival. Finally, in this retrospective analysis, 67 cases (55 men and 12 women, mean age: 59.3 ± 12.6 years) were analysed for diagnosis of lesion viability and 58 patients (46 men and 12 women, mean age: 60.8 ± 12.1 years) were analysed for prediction of survival.

Before admission to Kyoto University Hospital, each patient gave written informed consent to becoming a possible candidate for retrospective clinical research (except for gene-

related researches), as required by the Kyoto University Human Study Committee.

Patient characteristics

Patient characteristics of 67 cases are shown in Table 1. The chemotherapeutic agents used in TACE, TAI and systemic chemotherapy were as follows: fluorouracil (5-FU) and 5-FU with cisplatin (CDDP) for TACE; 5-FU with CDDP and 5-FU with interferon for TAI; 5-FU, Farmorubicin (Farm) and gemcitabine (GEM) for systemic chemotherapy. The clinical stage of HCC was analysed at first before the treatment based on the criteria of the International Union

Against Cancer (UICC) using several imaging modalities (CT, MRI and/or angiography and/or PET if available) [22]. The clinical stage of HCC was re-analysed at the time of post-therapeutic PET based on UICC criteria using PET results and other imaging modalities. Analyses using Milan criteria for the selection of liver transplantation were evaluated before the treatment based on the size and the number of tumours determined from imaging modalities using CT or MRI (single tumour: 5 cm or less in size; or three or less tumours: each 3 cm or less in size; and no macrovascular invasion) [23]. Analyses using Milan criteria were also re-evaluated at the time of post-therapeutic PET based on imaging modalities including PET. Thirty-seven patients

Table 1 Patient characteristics of 67 cases (58 patients)

Characteristic	Value	Characteristic	Value
Age (years)		Past history of therapy ^a , <i>n</i> (%)	
Mean±SD	59.3±12.6	Partial resection	33 (49)
Range	32–80	LDLT	2 (3)
Gender, <i>n</i> (%)		TACE	51 (76)
Male	55 (82)	TAI	38 (57)
Female	12 (18)	RFA	31 (46)
Tumour differentiation, <i>n</i> (%)		PEIT	12 (18)
Well	3 (4)	Child-Pugh classification at pre-treatment, <i>n</i> (%)	
Moderately	16 (24)	A	38 (57)
Poorly	20 (30)	B	29 (43)
Unknown	28 (42)	Child-Pugh classification at PET study, <i>n</i> (%)	
Target therapy in the present study, <i>n</i> (%)		A	38 (57)
TACE	23 (34)	B	26 (39)
TAI	30 (45)	C	3 (4)
RFA	5 (7)	Child-Pugh score at PET study	
TACE+PEIT	1 (1)	Mean±SD	6.4±1.4
TAI+RFA	1 (1)	Aetiology of hepatitis, <i>n</i> (%)	
Systemic chemotherapy	7 (10)	HBV	19 (28)
Clinical stage at pre-treatment, <i>n</i> (%)		HCV	40 (60)
UICC, 6th edition		HBV+HCV	4 (6)
Stage II–III	47 (70)	Alcoholic	2 (3)
Stage IV	20 (30)	Unknown	2 (3)
Milan criteria at pre-treatment, <i>n</i> (%)		Pathological evaluation of hepatic parenchyma	
Fulfilled	21 (31)	Grade of hepatitis, <i>n</i> (%)	
Beyond	46 (69)	None	2 (3)
Clinical stage at post-PET evaluation, <i>n</i> (%)		Low	22 (38)
UICC, 6th edition		Moderate	12 (21)
Stage II–III	39 (58)	High	1 (2)
Stage IV	28 (42)	Not available	30 (36)
Milan criteria at post-PET evaluation, <i>n</i> (%)		Grade of fibrosis, <i>n</i> (%)	
Fulfilled	18 (27)	None	3 (5)
Beyond	49 (73)	Low	9 (16)
		Moderate	7 (12)
		High	18 (31)
		Not available	30 (36)

UICC International Union Against Cancer, TNM classification, PET positron emission tomography, TACE transcatheter arterial chemoembolization therapy, TAI transcatheter arterial infusion chemotherapy, RFA radiofrequency ablation therapy, PEIT percutaneous ethanol injection therapy, LDLT living donor liver transplantation, HBV hepatitis B virus, HCV hepatitis C virus

^a Including overlapping therapy

received pathological evaluation of lesions and surrounding liver parenchyma by biopsy at the time of RFA or PEIT (at the present therapy or at the previous one within 6 months before the present therapy, $n=27$) or by surgical resection (within 2 weeks after the post-therapeutic PET, $n=10$). Activity grades of hepatitis and fibrosis were also evaluated in surrounding liver parenchyma by well-experienced pathologists using four-grade scales.

Tumour markers, including serum alpha-fetoprotein (α FP), lens culinaris agglutinin-reactive fraction of serum α FP (α FP-L3 fraction) and protein induced by vitamin K absence or antagonist II (PIVKA-II), were evaluated before the non-operative therapy and at the time of post-therapeutic PET. The presence of positive results in all these three tumour markers (α FP=400 or more, α FP-L3=15 or more and PIVKA-II=400 or more) was defined as “triple plus”.

PET study

^{18}F was produced by $^{18}\text{O}(\text{p}, \text{n})\ ^{18}\text{F}$ reaction. ^{18}F -FDG was synthesized by the nucleophilic substitution method using an ^{18}F -FDG-synthesizing instrument F-100 (Sumitomo Heavy Industries, Co. Ltd., Tokyo, Japan) and a cyclotron, CYPRIS-325R (Sumitomo Heavy Industries, Co. Ltd., Tokyo, Japan). All patients were examined with a whole-body PET scanner with an 18-ring detector arrangement (Advance, General Electric Medical Systems, Milwaukee, WI, USA).

The patients fasted for more than 4 h before the injection of ^{18}F -FDG. All subjects received an intravenous injection of ^{18}F -FDG (296 ± 74 MBq), and the acquisition of whole-body PET images started 50 min later. Data acquisition (emission and transmission scan) was performed in two-dimensional imaging mode with septae in place. Emission images were acquired for 3 min per bed position and each post-emission transmission scan was obtained for 1 min per position. Whole-body scanning (from head to upper thigh) was performed in each patient using five or six bed positions according to the height of each patient. The data were reconstructed using the ordered subsets expectation maximization method (OSEM) using 16 subsets, 3 iterations and 128×128 array size.

Image analysis

PET images were interpreted and analysed visually by two or three experienced nuclear medicine physicians (TH, YN, KI, TS) with all available clinical information. Next, these physicians had a discussion and made a final diagnosis. Diagnosis of lesion viability was performed separately in liver lesions and metastatic lesions with a two-category system, positive or negative. In the diagnosis of liver lesions, FDG uptake of a lesion was compared with background uptake of liver parenchyma. If a nodule showed

remarkably higher uptake than the liver parenchyma, PET diagnosis was defined as positive. If a nodule showed similar or lower uptake than the surrounding liver parenchyma, PET diagnosis was defined as negative. In the diagnosis of metastatic lesions, FDG uptake of each lesion was compared with background uptake of surrounding normal tissue or with the contralateral normal tissue (when the lesion was located in the lung field). All PET diagnostic results were based on the diagnostic reports described in patient charts at the time of the clinical course, and the whole results were again confirmed by nuclear medicine physicians (TH, RN) with 100% concordance rate, retrospectively. When visual PET analysis was negative in the whole body and then known lesions or newly discovered metastatic lesions were confirmed as alive within 6 months after PET study, visual PET diagnosis on lesion viability was defined as false-negative. On the contrary, when visual PET analysis was positive in a lesion and the lesion was confirmed as necrotic or nonexistent within 6 months after PET study, visual PET diagnosis on lesion viability was defined as false-positive. For univariate and multivariate analysis of prognostic factors, a positive PET finding in any lesion in the body (hepatic or metastatic, known or unexpected) was defined as positive for the patient.

In addition, semi-quantitative analysis of ^{18}F -FDG uptake was also performed for univariate and multivariate analysis of prognostic factors. Regions of interest (ROIs) were defined on the target lesions in the transaxial tomograms of PET images by the PET-to-CT co-registration method using the automatic rigid/non-rigid body-deformable fusion software: Quantiva/BodyGuide (Tomographix IP Ltd., Toronto, Canada). The maximum standardized uptake value (SUV) was calculated for quantitative analysis of tumour ^{18}F -FDG uptake as follows:

$$\text{SUV} = \frac{C(\text{kBq/ml})}{\text{ID}(\text{kBq})/\text{body weight}(\text{g})}$$

where C represents tissue activity concentration measured by PET and ID represents the injected dose. The highest maximum SUV of the lesion in the whole body (hepatic or metastatic) was defined as the SUV of the patient.

Clinical confirmation

Lesion viability after treatment was confirmed by surgical resection in ten cases (surgery could be performed later because of the therapeutic effect of non-operative therapy) and by clinical follow-up at least more than 6 months in 57 cases. Overall survival was confirmed in patient records by clinical follow-up at least more than 6 months, in which patients received at least one of several imaging modalities as follow-up study every 3 months, including CT, MRI, angiography

and PET. The starting point and the end-point of survival were defined as the date of post-therapeutic PET study and the date of death, respectively. Overall cumulative survival rates were obtained using the Kaplan-Meier method.

Statistics

All values are expressed as mean±SD. All of the statistical analysis was performed using statistical software, JMP 4 J version (SAS Institute, Cary, NC, USA), in which *p* values <0.05 were considered statistically significant. Patients were stratified and analysed by univariate analysis using the log-rank test according to the following factors: age, gender, histological grade of tumour differentiation, type of non-operative target therapy in the present study, clinical stage at pre-treatment evaluation (UICC), Milan criteria at pre-treatment evaluation, clinical stage at post-PET evaluation (UICC), Milan criteria at post-PET evaluation, past history of therapy, Child-Pugh classification, aetiology of hepatitis, pathological grade of hepatitis, pathological grade of fibrosis as well as pre-therapeutic and post-therapeutic tumour markers, including serum α FP level, serum α FP-L3 fraction, PIVKA-II level and triple plus, and pre-therapeutic and post-therapeutic FDG PET-related factors [SUV and visual PET diagnosis (positive or negative)]. Cut-off values, such as α FP=400 ng/ml, α FP-L3=15%, PIVKA-II=400 AU/ml and SUV=5.0, were defined based on the previous reports [21, 24, 25]. According to the univariate analysis, eight significant factors [clinical stage at post-PET evaluation (UICC), Milan criteria at post-PET evaluation, Child-Pugh classification, pathological grade of hepatitis, α FP level, presence of triple plus, SUV and visual PET diagnosis] were selected for the multivariate analysis using the stratified Cox proportional hazards model. A comparison between high FDG and low FDG groups was analysed by Wilcoxon score or chi-square test for unpaired data. Survival curves were calculated by Kaplan-Meier analysis and the differences between high FDG and low FDG

groups and the differences between L-L, L-H, H-L and H-H groups were compared using the log-rank test.

Results

Patient characteristics

Table 1 summarizes the patient characteristics. The average follow-up of living patients (*n*=35) was 483±413 days (range: 202–1,565 days), while the average follow-up of dead patients (*n*=23) was 253±162 days (range: 22–644 days). The clinical stage at pre-treatment was evaluated as stage II–III (*n*=47, 70%) vs stage IV (*n*=20, 30%) by UICC. However, the clinical stage at post-PET was stage II–III (*n*=39, 58%) vs stage IV (*n*=28, 42%) by UICC. This is because an unexpected distant metastasis was detected by post-therapeutic PET study in 13% of patients (*n*=9) and PET refuted the presence of a distant metastasis in 1% of patients (*n*=1). Similar results were observed in Milan criteria.

Diagnosis of lesion viability

Table 2 shows the results of clinical values of post-therapeutic FDG PET as the diagnosis of lesion viability and as the survival prediction in unresectable HCC patients.

As for visual diagnosis of lesion viability of post-therapeutic hepatic lesions, sensitivity was relatively low with the value of 62.8% (27/43 cases), while positive predictive value was high with the value of 96.4% (27/28 cases). Sixteen false-negative PET cases (37.2%) were confirmed as having residual liver tumours within 6 months by several procedures, such as surgical resection (*n*=5), biopsy at the time of follow-up RFA (*n*=1) and other imaging modalities (contrast-enhanced CT: *n*=6, angiography: *n*=3, MRI: *n*=1). In these cases, however, the course of disease progression was slow and controllable because these lesions tended to respond to the subsequent repeated therapies.

Table 2 Post-therapeutic FDG PET: visual diagnosis of lesion viability and survival prediction

	Viability of hepatic lesions (based on pathological evaluation and clinical follow-up of 6months)	Viability of metastasis (based on clinical follow-up of 6months)	Survival prediction ^a (death within 12months)	Survival prediction ^b (death within 24months)
Sensitivity	62.8% (27/43 cases)	78.6% (22/28 cases)	96.0% (24/25 cases)	92.5% (37/40 cases)
Specificity	95.8% (23/24 cases)	92.3% (36/39 cases)	68.0% (17/25 cases)	100% (7/7 cases)
Positive predictive Value	96.4% (27/28 cases)	88.0% (22/25 cases)	75.0% (24/32 cases)	100% (37/37 cases)
Negative predictive Value	59.0% (23/39 cases)	85.7% (36/42 cases)	94.4% (17/18 cases)	70.0% (7/10 cases)
Accuracy	74.6% (50/67 cases)	86.6% (58/67 cases)	82.0% (41/50 cases)	93.6% (44/47 cases)

^a Excluding patients who are alive within 12 months

^b Excluding patients who are alive within 24 months

As for the diagnosis of viability of metastatic lesions, the sensitivity (78.6%, 22/28 cases) was higher than that of hepatic lesions. The positive predictive value in metastatic lesions (88.0%, 22/25 cases) was lower than that in hepatic lesions (96.4%, 27/28 cases). Three false-positive cases for metastatic lesions were as follows: remnant stomach after distal gastrectomy mimicking peritoneal dissemination, sarcoid nodules mimicking mediastinal lymph nodes metastases and faint thoracic vertebral uptake mimicking bone metastasis. Ultimately, the visual diagnostic accuracy of post-therapeutic lesion viability was higher in the metastatic lesions (86.6%, 58/67 cases) than that in hepatic lesions (74.6%, 50/67 cases).

Survival prediction by FDG PET

Survival prediction by visual FDG PET in unresectable HCC patients treated by non-operative therapy is also summarized in Table 2. Of 18 patients diagnosed as negative by post-therapeutic PET, 17 survived more than 12 months (negative predictive value: 94.4%). All 37 patients diagnosed as positive by post-therapeutic PET died within 24 months (positive predictive value: 100%). Survival prediction in 24 months by FDG PET was quite accurate with the value of 93.6% (44/47 cases).

Univariate analysis of each prognostic factor

Table 3 shows the results of univariate analysis of each prognostic factor in 58 patients. Clinical stage (UICC) and Milan criteria at pre-treatment evaluation did not show significant prognostic value, while those at post-PET evaluation showed statistically significant prognostic values ($p=0.001$ – 0.0001). Pathological grade of hepatitis showed significance, while that of fibrosis did not. All of the pre-therapeutic tumour markers were not significant factors. As for the post-therapeutic tumour markers, α FP (=400 ng/ml) showed significance ($p=0.001$). Post-therapeutic triple plus was also significant in prognostic value ($p=0.005$), although only six patients were positive.

FDG PET as a prognostic factor

Table 3 also shows prognostic values of FDG PET analysis before and after the non-operative therapy. The factors “post-therapeutic visual PET diagnosis (positive or negative)” and “post-therapeutic SUV=5.0” showed significance ($p=0.001$). In contrast, pre-therapeutic FDG PET analysis did not show any significant value.

The results of multivariate analysis of prognostic factors for overall survival in unresectable HCC patients treated by non-operative therapy are shown in Table 4. The independent prognostic factor with highest statistical value was

“post-therapeutic α FP (= 400 ng/ml)” (risk ratio=0.277, $p=0.004$), followed by post-therapeutic visual PET diagnosis (risk ratio=0.212, $p=0.0056$). On the other hand, the factor “SUV=5.0” was not significant as a predictor (risk ratio=0.889, $p=0.810$). “Clinical stage at post-PET evaluation (UICC stage IV)” and “Milan criteria at post-PET evaluation” also showed significant value (risk ratio=0.335 and 0.001, $p=0.041$ and 0.033, respectively). The other factors did not show any significance in the prediction of overall survival.

Based on the results of multivariate analysis, we classified the patients into two groups: high FDG group (diagnosed as positive at the post-therapeutic PET) and low FDG group (diagnosed as negative at the post-therapeutic PET). Figure 1a shows the survival curve of these two groups. The low FDG group showed higher survival (average survival: 607.9 ± 29.7 days) than the high FDG group (average survival: 327.5 ± 40.1 days). The log-rank test showed a statistically significant difference in survival between these two groups ($p < 0.001$). Table 5 reveals the characteristics of the two groups. Among the pre-treatment factors evaluated, UICC stage was the only significantly different one between the two groups. However, the other pre-treatment factors (age, gender, tumour differentiation, Milan criteria, target non-operative therapy, past history of therapy and pathological grade of hepatitis) were not different between the two groups. The other factors (clinical stages and Milan criteria at post-PET evaluation) showed significant differences between the two groups, but these differences were based on the PET results, where an unexpected distant metastasis was detected by post-therapeutic PET study in 13% of patients ($n=9$) and PET refuted the presence of a distant metastasis in 1% of patients ($n=1$). Therefore, clinical stages and Milan criteria at post-PET evaluation turned out to be different between the two groups as a result of FDG PET study. Pre-therapeutic tumour markers were not different in both groups. Post-therapeutic tumour markers were lower in the low FDG group because of the response to the target non-operative therapy. Although there was a significant difference in the factors of post-therapeutic FDG PET, there was no difference in the factors of pre-therapeutic PET (SUV and diagnosis). Thus, it may be said that there was no significant bias between the two groups before the target treatment.

Analysis using FDG uptake pattern

In the present study, 29 patients received pre-therapeutic FDG PET studies. According to pre- and post-therapeutic PET results, we classified these patients ($n=29$) into four groups by the pattern of FDG uptake as follows (Fig. 1b): low-low uptake group (L-L group) which consisted of patients who were diagnosed as negative in pre- and post-therapeutic PET studies ($n=3$); high-high uptake group (H-H group) which

Table 3 Univariate analysis of prognostic factors for overall survival in 58 patients

	n	Mean survival			n	Mean survival		
		days	p			days	p	
Age (years)				Grade of fibrosis				
<60	26	438	0.76	None	3	158	0.77	
≥60	32	465		Low	9	518		
Gender				Moderate	7	283		
Male	48	450	0.62	High	18	308		
Female	10	327						
Tumour differentiation				Pre-therapeutic tumour markers				
Well	3	22	0.88	αFP (ng/ml)				
Moderately	16	487		<400	34	489	0.12	
Poorly	14	310		400 or higher	20	286		
Unknown	25	462						
Target therapy in the present study				αFP-L3 fraction (%)				
TACE ^a	22	498	0.13	<15	11	305	0.18	
TAI ^b	26	318		15 or higher	18	287		
RFA	4	133						
Systemic chemotherapy	6	339						
Clinical stage at pre-treatment				PIVKA-II (AU/ml)				
UICC, 6th edition				<400	35	433	0.65	
Stage II–III	42	475	0.30	400 or higher	16	301		
Stage IV	16	276		Triple plus (αFP=400 or higher & αFP-L3=15 or higher & PIVKA-II=400 or higher)	6	317		
				Triple plus	6	317		
				Negative	44	421		
Milan criteria at pre-treatment				Post-therapeutic tumour markers				
Fulfilled	20	495	0.25	αFP (ng/ml)				
Beyond	38	431			<400	39	516	0.001 ^c
Clinical stage at post-PET evaluation				400 or higher	19	262		
UICC, 6th edition				αFP-L3 fraction (%)				
Stage II–III	36	532	0.001 ^c	<15	32	488	0.16	
Stage IV	22	259		15 or higher	23	302		
Milan criteria at post-PET evaluation				PIVKA-II (AU/ml)				
Fulfilled	17	all alive	0.0001 ^c	<400	37	481	0.11	
Beyond	41	376			400 or higher	17		389
Past history of therapy				Triple plus (αFP=400 or higher & αFP-L3=15 or higher & PIVKA-II=400 or higher)				
Partial resection ±	29/29	398/502	0.13	Triple plus	6	218	0.005 ^c	
LDLT ±	1/57	-			Negative	46		474
TACE ±	43/15	458/290	0.90					
TAI ±	31/27	445/452	0.98	Pre-therapeutic FDG PET				
RFA ±	28/30	317/471	0.88	Visual PET diagnosis				
PEIT ±	12/46	167/457	0.84	Positive	18	294	0.78	
				Negative	11	399		
Child-Pugh classification at PET study				SUV				
A	33	438	0.0001 ^c	<5.0	15	419	0.73	
B	22	322			5.0 or higher	13		278
C	3	84						
Aetiology of hepatitis				Post-therapeutic FDG PET				
HBV	15	421	0.14	Visual PET diagnosis				
HCV	37	490			Positive	32	327	0.0001 ^c
Others	6	142			Negative	26	608	
Pathological grade of hepatitis				SUV				
None	2	-	0.01 ^c	<5.0	40	523	0.0001 ^c	
Low	22	487			5.0 or higher	18		227
Moderate	12	268						
High	1	131						

αFP alpha-fetoprotein, αFP-L3 lens culinaris agglutinin-reactive fraction of αFP, PIVKA-II protein induced by vitamin K absence or antagonist II, FDG fluorodeoxyglucose, SUV standardized uptake value

^aIncluding PEIT

^bIncluding overlapping therapy

^cSignificant by log-rank test

Table 4 Multivariate analysis of prognostic factors for overall survival

Prognostic factors	Risk ratio	(95% confidence interval)	<i>p</i>
Clinical stage at post-PET evaluation			
UICC, 6th edition, stage IV	0.335	(0.094–0.959)	0.041 ^a
Milan criteria at post-PET evaluation			
Fulfilled	0.001	(–0.891)	0.033 ^a
Child-Pugh classification at PET study			
B or C	0.482	(0.136–0.482)	0.218
Pathological grade of hepatitis			
Moderate or high	1.155	(0.159–9.122)	0.887
Post-therapeutic tumour markers			
α FP (ng/ml)=400	0.277	(0.089–0.680)	0.004 ^a
Triple plus (α FP=400 & α FP-L3=15 & PIVKA-II=400)	3.964	(0.869–25.039)	0.077
Post-therapeutic FDG PET			
Visual PET diagnosis: positive	0.212	(0.042–0.661)	0.0056 ^a
SUV=5	0.889	(0.337–2.451)	0.810

^a Significant in Cox proportional hazards model

consisted of patients who were diagnosed as positive in pre- and post-therapeutic PET studies ($n=10$); low-high group (L-H group) which consisted of patients who were diagnosed as negative before the treatment and then showed positive uptake in the post-therapeutic PET study ($n=8$) (Fig. 2); and high-low group (H-L group) which consisted of patients who were diagnosed as positive before the treatment and then showed negative uptake in the post-therapeutic PET study ($n=8$) (Fig. 3). Figure 1b shows the survival curve of these four groups. The H-L group showed the highest survival rate in these four groups and all of them ($n=8$) still survived in the follow-up period. The H-H group showed the lowest survival curve. There was no difference in survival between the L-L group and L-H group. The log-rank test showed a significant difference between these groups.

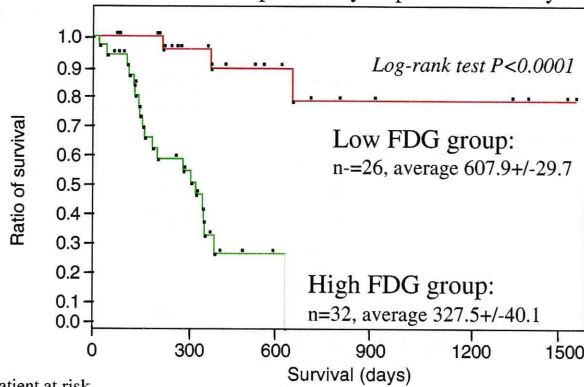
Discussion

FDG PET is considered as a well-established non-invasive diagnostic tool for the detection of malignant tumours [26, 27], staging and monitoring of chemotherapeutic response [28, 29] in several cancers. Shiomi et al. reported that FDG PET is useful not only for the evaluation of the malignancy but also for the prediction of outcome in patients with HCC [15]. For HCC, however, several investigators have reported that the sensitivity of FDG PET is low in the detection of HCC [17–19]. Relatively low FDG accumulation in HCC can be explained by the activity of enzymes involved in glucose metabolism. The activity of glucose-6-phosphatase (G-6-Pase), which converts FDG-6-P to FDG, is reported to be high in normal liver and nearly zero in the vast majority of tumours, including metastatic liver tumours [14, 30]. In

contrast, the enzyme activity has been reported to vary widely in individual HCC; well-differentiated HCC cells exhibit an FDG metabolism similar to that of normal liver tissue, whereas undifferentiated HCC cells do not [21]. Therefore, well-differentiated HCC tends to accumulate similar amounts of FDG as normal liver, which results in relatively lower SUV. However, this enzymatic theory for FDG uptake can only be applicable in pre-operative, non-treated HCCs. As an imaging modality for the early evaluation of treatment response after non-operative therapy for HCC, the role of FDG PET has not been established, nor reported so far.

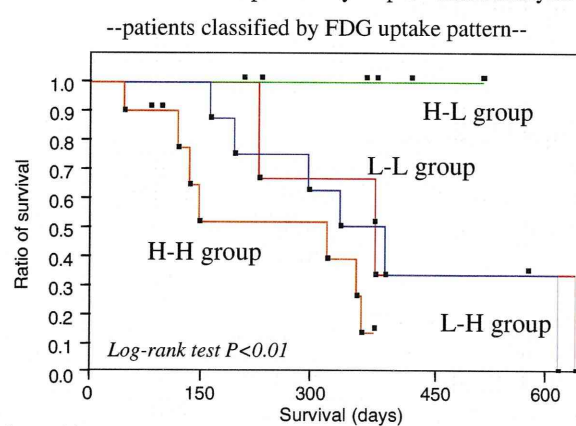
Interventional therapy, such as TACE or TAI, is considered to be an effective palliative treatment in patients with HCC [31, 32]. However, a meta-analysis of randomized clinical trials showed that a survival advantage associated with therapeutic chemoembolization versus supportive care alone has not been clearly proven so far [33]. Therefore, it is clinically important to analyse the therapeutic effect of non-operative therapy as soon as possible, because inefficacious palliative treatment may be not only useless but also harmful for patients with advanced HCC. Conventional imaging modalities, such as CT or MRI, cannot satisfy clinicians in that context, because therapy evaluation by these anatomical imaging modalities requires sufficient time to confirm tumour shrinkage [34, 35]. Herein, PET, as a metabolic imaging modality, is expected to be useful in electing to proceed or terminate therapy. Our data in the present study showed that FDG PET could evaluate therapeutic effect and prognostic value in patients with unresectable HCC. To our knowledge, the present study is the first report evaluating the effectiveness of FDG PET in the early therapeutic response evaluation in unresectable HCC patients treated by non-operative therapies.

a Survival Curve of HCC patients by Kaplan-Meier analysis



Patient at risk					
Low UV	26	16	9	5	4
High UV	32	13	1	0	0

b Survival Curve of HCC patients by Kaplan-Meier analysis



Patient at risk					
H-L group	8	8	8	8	8
L-L group	3	3	2	2	1
L-H group	8	8	4	4	2
H-H group	10	6	4	1	0

Fig. 1 Survival curve of HCC patients by Kaplan-Meier analysis. **a** The overall survival rate in HCC patients treated by non-operative therapy was significantly higher in the low FDG group than that in the high FDG group ($p < 0.0001$). **b** The overall survival rate in four groups of patients classified by the FDG uptake pattern (see exact definition in the text) is shown. The H-H group showed poor survival. On the other hand, the H-L group showed the best survival with 100% survival rate in the follow-up period. There was no difference between the L-H group and L-L group. The log-rank test showed that there was a significant difference between the four groups ($p < 0.01$)

Our principal finding is that visual FDG PET diagnosis after non-operative therapy is an independent predictor of survival in unresectable HCC patients. This is compatible with a variety of previous studies performed in other malignancies [36–38]. Table 2 also clearly reveals the advantage of FDG PET diagnosis in early post-therapeutic evaluation with respect to the prediction of patient survival. High negative predictive value (94.4%) means that patients with negative post-therapeutic PET result are supposed to survive at least

12 months, while high positive predictive value (100%) means that patients with positive post-therapeutic PET result are supposed to die within 24 months. We believe that post-therapeutic FDG PET after non-operative therapy would make a great contribution in the clinical management of patients with unresectable HCCs, such as in electing to proceed or terminate therapy, altering the chemotherapeutic regimen, choosing treatment modalities or in other decisions.

On the other hand, FDG PET within 1 month after non-operative therapy is not sensitive in the diagnosis of lesion viability. Table 2 shows the limitation of FDG PET diagnosis in early post-therapeutic evaluation of HCC. Relatively low sensitivity (62.8%) and low negative predictive value (59%) in the analysis of viability of hepatic lesions suggest that negative FDG PET findings cannot ensure the complete remission of HCC after therapy. At the current moment, it is not clear what the cellular or tissue condition of the tumour is when FDG PET is negative after the non-operative therapy. It is implied, however, that they lie dormant with temporary enzymatic or other dysfunction, but can survive.

Our result shown in Fig. 2 suggests that even if FDG uptake shows a partial reduction after non-operative treatment, as observed in the H-H group, HCCs with constant positive PET finding tend to have more aggressive malignant potential. Long survival may not be expected, and continued treatment or a newly introduced therapeutic procedure would be required. On the contrary, the result of the H-L group suggests that prognostic improvement can be expected when FDG uptake disappeared. These observations provide helpful information for the management of patients with unresectable HCCs.

Bibliographically, a number of reports have been published as for the prognostic factors in patients with HCC treated by surgical procedures. Imamura et al. showed that non-anatomical resection, presence of microscopic vascular invasion and serum α FP were significant risk factors contributing to early recurrence of HCC after hepatectomy [10]. Miyaaki et al. also showed that α FP-L3 and PIVKA-II levels are potential indicators of a poor prognosis in surgically resected HCC [39]. For patients treated with liver transplantation, presence of capsule, α FP levels and viral cirrhosis were independent factors for survival [40]. Above all, the Milan criteria (single tumour: 5 cm or less in size; or three or less tumours: each 3 cm or less in size; and no macrovascular invasion) are known for their excellent outcome in the prediction of survival in patients treated with liver transplantation [24]. All these data in patients treated by surgical procedures seem to be consistent with our results. In the present study, multivariate analysis revealed that the post-therapeutic tumor marker α FP, clinical staging and Milan criteria at post-PET and visual PET diagnosis are significant prognostic factors (Table 4). This is also basically compatible (except for PET diagnosis) with the previous report using multivariate analysis

Table 5 Comparison of high FDG and low FDG groups

	High FDG group (n=32)	Low FDG group (n=26)	<i>p</i>		High FDG group (n=32)	Low FDG group (n=26)	<i>p</i>
Age (years)				Past history of therapy ^a , <i>n</i> (%)			
Mean±SD	59.5±13.3	62.4±10.4	n.s.	Partial resection	17 (53)	12 (46)	n.s.
Range	34–80	42–78		LDLT	1 (3)	0 (0)	
Gender, <i>n</i> (%)				TACE	24 (75)	19 (73)	
Male	26 (81)	20 (77)	n.s.	TAI	17 (53)	14 (54)	
Female	6 (19)	6 (23)		RFA	16 (50)	12 (46)	
Tumour differentiation, <i>n</i> (%)				PEIT	5 (16)	7 (27)	
Well	2 (6)	1 (4)	n.s.	Child-Pugh classification at PET study, <i>n</i> (%)			
Moderately	10 (31)	6 (23)		A	21 (66)	12 (46)	0.02 ^c
Poorly	8 (25)	6 (23)		B	8 (25)	14 (54)	
Unknown	12 (38)	13 (50)		C	3 (9)	0 (0)	
Target therapy in the present study, <i>n</i> (%)				Child-Pugh score at PET study			
TACE	9 (28)	12 (46)	n.s.	Mean±SD	6.3±1.6	6.6±1.1	n.s.
TAI ^a	17 (53)	9 (35)		Pathological grade of hepatitis			
RFA	1 (3)	3 (12)		None or low	14 (44)	10 (38)	n.s.
TACE+PEIT	0 (0)	1 (4)		Moderate or high	8 (25)	5 (19)	
Systemic chemotherapy	5 (16)	1 (4)			(n=22)	(n=15)	
Clinical stage at pre-treatment, <i>n</i> (%)				Pre-therapeutic tumour markers			
UICC, 6th edition				αFP (ng/ml)	12,926±37,934	6,734±30,440	n.s.
Stage II–III	19 (59)	23 (88)	0.01 ^c	αFP-L3 fraction (%)	37.2±29.9	42.6±33.8	n.s.
Stage IV	13 (41)	3 (12)		PIVKA-II (AU/ml)	8,666±25,900	10,093±43,296	n.s.
Milan criteria at pre-treatment, <i>n</i> (%)					(n=32)	(n=23)	
Fulfilled	10 (31)	10 (38)	n.s.	Post-therapeutic tumour markers			
Beyond	22 (69)	16 (62)		αFP (ng/ml)	14,532±35,462	306±796	0.001 ^b
Clinical stage at post-PET evaluation, <i>n</i> (%)				αFP-L3 fraction (%)	38.5±28.6	35.1±31.9	n.s.
UICC, 6th edition				PIVKA-II (AU/ml)	9,206±34,433	531±1,938	0.005 ^b
Stage II–III	13 (41)	23 (88)	0.0001 ^c	Pre-therapeutic FDG PET			
Stage IV	19 (59)	3 (12)		SUV	4.9±2.5	5.8±3.6	n.s.
Milan criteria at post-PET evaluation, <i>n</i> (%)				Diagnosis: positive vs negative	10 vs 8	8 vs 3	n.s.
Fulfilled	4 (13)	13 (50)	0.002 ^c		(n=18)	(n=11)	
Beyond	28 (88)	13 (50)		Post-therapeutic FDG PET			
				SUV	7.0±4.6	2.6±0.9	0.0001 ^b

^a Including overlapping therapy

^b Significant by Wilcoxon score

^c Significant by chi-square

in TACE patients, in which αFP level, unilobar tumours and/or Child-Pugh score are the prognostic factors in HCC patients treated with TACE [41, 42]. Based on the evidence reported, it seems reasonable to suppose that our results in prognostic factor analysis have considerable validity. Although αFP level was the strongest, the most convenient and the less expensive prognostic factor in the present study, FDG PET has an advantage in the detection of active lesions. In addition, PET results would be helpful when the post-therapeutic αFP response was controversial. For example, in

Fig. 3 post-therapeutic αFP showed a rise while PET diagnosis showed negative result. Thus, we believe that FDG PET has important clinical value in the prognostic prediction and in the decision-making process of patient management. It is to be noted that clinical staging and Milan criteria at post-PET were significant prognostic factors, while those at pre-treatment were not. It again emphasizes the importance of FDG PET diagnosis, not only for the prognostic value of its own, but also in the sense of detection of unknown metastases and the resultant renewed clinical

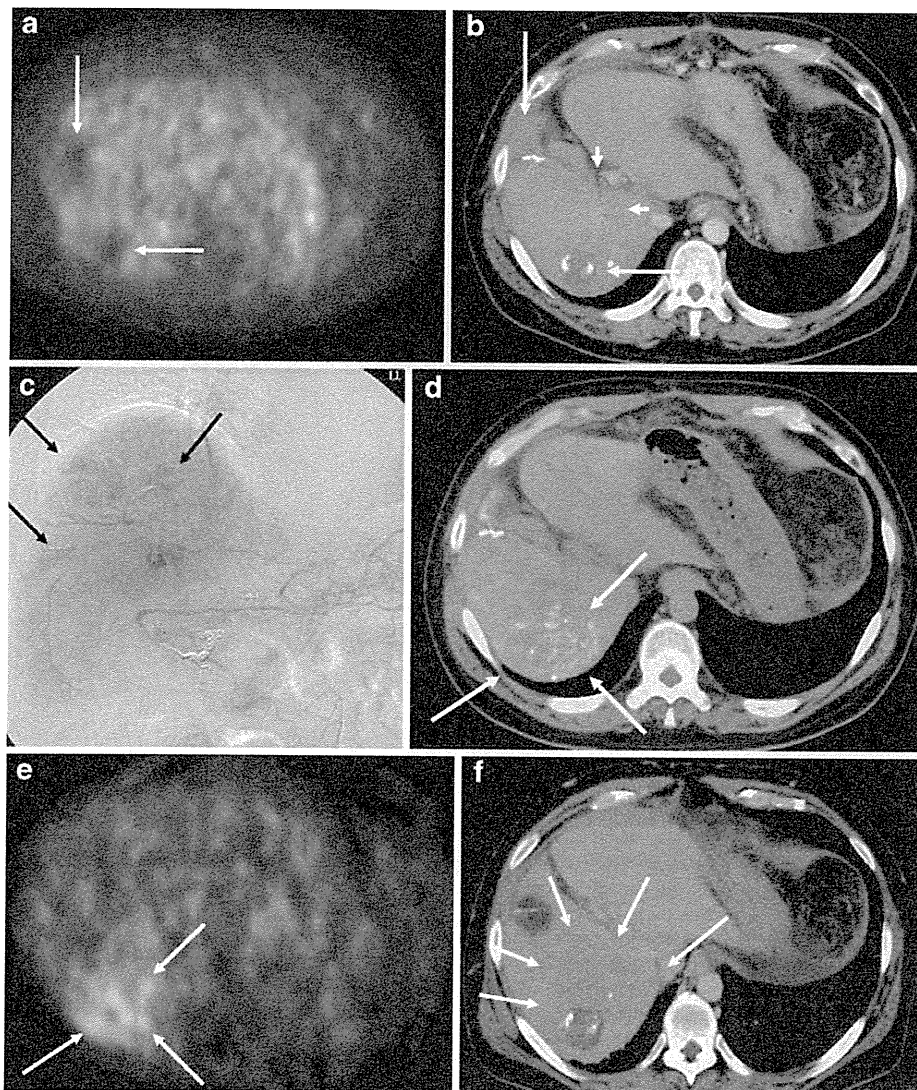


Fig. 2 A case of the L-H group: a 50-year-old man with unresectable moderately differentiated HCC, based on hepatitis type C. Past history: HCC was detected 2 years ago, and partial hepatectomy (S5) with splenectomy, TACE and RFA had been already performed. Present history: multiple recurrent nodules in bilateral lobes were detected with increased tumour markers. Then, an arterial catheter was inserted in the proper hepatic artery and TAI using biweekly infusion of CDDP and 5-FU had been performed via an indwelling arterial port. However, the arterial port was decannulated 80 days before the target TAI therapy because of the complication in the local subcutaneous tissue. **a** FDG PET was performed at 73 days before the TAI therapy. Defects of FDG uptake (*arrows*) were observed in the right lobe of the liver; therefore, visual PET diagnosis was negative at this time (SUV: 3.76 in the right posterior section). Tumour markers at this time were as follows: α FP: 632 ng/ml, α FP-L3: 53.4%, PIVKA-II: 193. **b** Follow-up contrast-enhanced CT scan was performed at 23 days before the TAI therapy. Faint enhancement at arterial phase was observed in the right posterior section (*arrowheads*) and lateral lobe (not shown). Therefore, the TAI therapy was scheduled because

of these multiple nodules. Low-density areas corresponding to the defects in PET are also shown (*arrows*). **c** Angiography at the time of the non-operative therapy. Vague and faint multiple tumour stains were observed in the whole liver (*arrows*). Arterial infusion chemotherapy using one shot of water-soluble CDDP (50 mg) and lipiodol (5CC) was performed via the proper hepatic artery. **d** Follow-up plain CT scan was performed at 7 days after the TAI therapy. Scattered lipiodol deposition was observed in the right posterior section (*arrows*), which corresponded to the tumour stain at angiography. **e** FDG PET was performed at 14 days after the TAI therapy. Increased FDG uptake was observed in the right posterior section corresponding to the lipiodol deposition (SUV: 5.99) (*arrows*). Tumour markers showed a rise despite the therapy: α FP: 1860 ng/ml; α FP-L3: 46.4%; PIVKA-II: 1670. **f** Follow-up contrast-enhanced CT scan was performed at 35 days after the TAI therapy. Widespread low enhancement in the right posterior section at portal phase was clearly revealed at this CT scan (*arrows*). Since then, the recurrent HCC showed a rapid increase with portal vein tumor thrombus, and this patient died 187 days after the TAI therapy because of liver failure

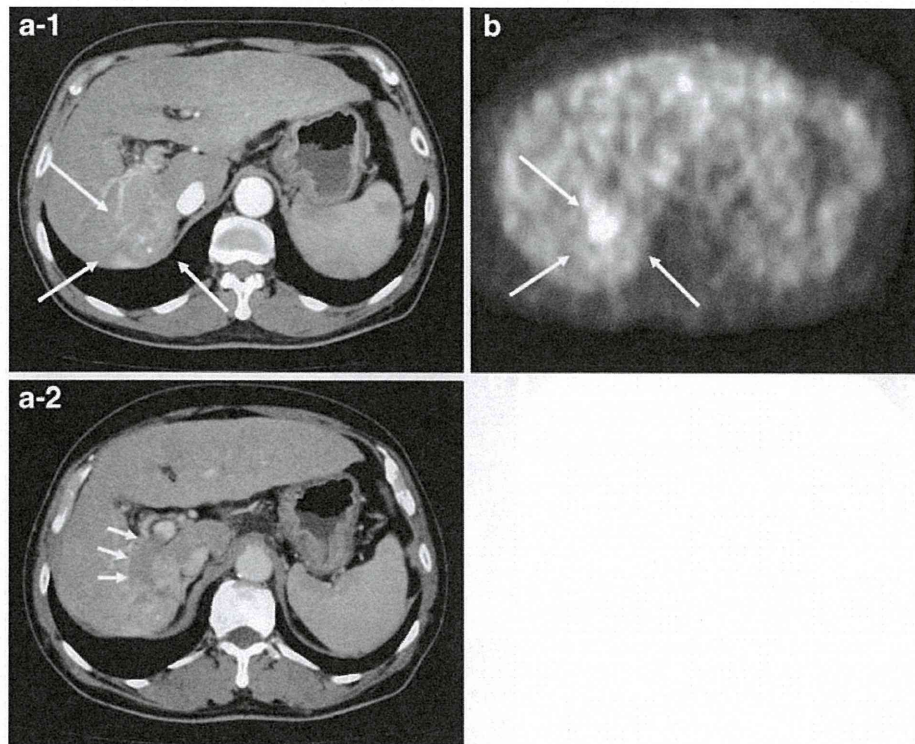


Fig. 3 A case of the H-L group: a 73-year-old man with unresectable poorly differentiated HCC, based on hepatitis type C. Past history: solitary HCC was detected 4 years ago, and RFA and TACE (twice) had been performed. Present history: post-operative HCC in the right posterior section showed local re-growth with portal vein tumour thrombus. **a** Contrast-enhanced CT scan was performed at 90 days before the start of the target TAI therapy. Solitary nodule in the right posterior section was observed with irregular hypervascularity at arterial phase (A-1) (*arrows*). CT scan at portal phase revealed that tumour thrombus reached the right main branch of the portal vein (A-2) (*arrowhead*). **b** FDG PET was performed at 88 days before the start of TAI therapy. Increased FDG uptake (*arrows*) were observed in the right posterior section of the liver; therefore, visual PET diagnosis was positive at this time (SUV: 4.89). Then, right lobectomy with resection of the portal vein tumour thrombus was performed 85 days before the TAI therapy. **c** Follow-up contrast-enhanced CT scan was performed at 40 days before the start of TAI therapy. Irregular hypervascular lesions were observed in the middle lobe and in the lateral lobe at arterial phase (C-1) (*arrows*). These lesions also showed low enhancement in the portal phase (C-2) (*arrows*). Coronal image of CT scan at portal phase revealed tumour thrombus in the left main branch of the portal vein (C-3) (*arrowhead*). Tumour markers were not so high at this time: α FP: 17 ng/ml; α FP-L3: 80.6%; PIVKA-II: 20. **d** Angiography at the time of the non-operative therapy. Multiple tumour stains were

observed in the whole liver (*arrows*). An arterial catheter was inserted in the left hepatic artery and then transarterial infusion chemotherapy (TAI) was started via an indwelling arterial port using continuous infusion of low-dose CDDP and 5-FU for 3 weeks (5 days infusion with 2 days rest). **e** Contrast-enhanced CT scan was performed at 1 day after the end of the TAI therapy. An irregular hypervascular lesion in arterial phase with low enhancement in portal phase was observed almost the same area in the middle lobe (E-1, E-2) (*arrows*). Coronal image of CT scan at portal phase showed enlarged tumour thrombus in the left main branch of the portal vein (E-3) (*arrowhead*). CT diagnosis implied that TAI therapy was not effective. Tumour markers at this time also showed a rise despite the therapy: α FP: 50.9 ng/ml, α FP-L3: 78.6%, PIVKA-II: 399. **f** FDG PET was performed at 2 days after the end of the TAI therapy. No increased FDG uptake was observed in the corresponding area (SUV: 3.84 in the middle lobe), which suggested positive therapeutic effect despite the results of CT scan and tumour markers. **g** Contrast-enhanced CT scan was performed at 309 days after the end of the TAI therapy. There was no hypervascular lesion in the liver. After the TAI therapy, several TAI therapies had been continued intermittently and the multiple hepatic lesions disappeared as shown in this CT image. This patient was disease-free for 420 days after the TAI therapy, and then local recurrence was detected. He was still alive at 519 days after the TAI therapy

staging. In the present study, PET showed positive results and upgraded clinical stages in around 10% of patients.

Quantitative analysis of FDG PET using SUV was not significantly useful for the prognostic prediction in multivariate analysis. This is not compatible with the previous reports from our group [20, 21]. The reason is probably because of the difference in patient population, resectable

HCC vs unresectable HCC. In the present study, not only the cases with hepatic lesions, but also the cases with distant metastasis were included for the analysis. For example, metastatic lung nodules with SUV=3.5 can be detected easily by FDG PET, while intrahepatic nodules with SUV=3.5 cannot be detected easily because of relatively higher background uptake of liver parenchyma.

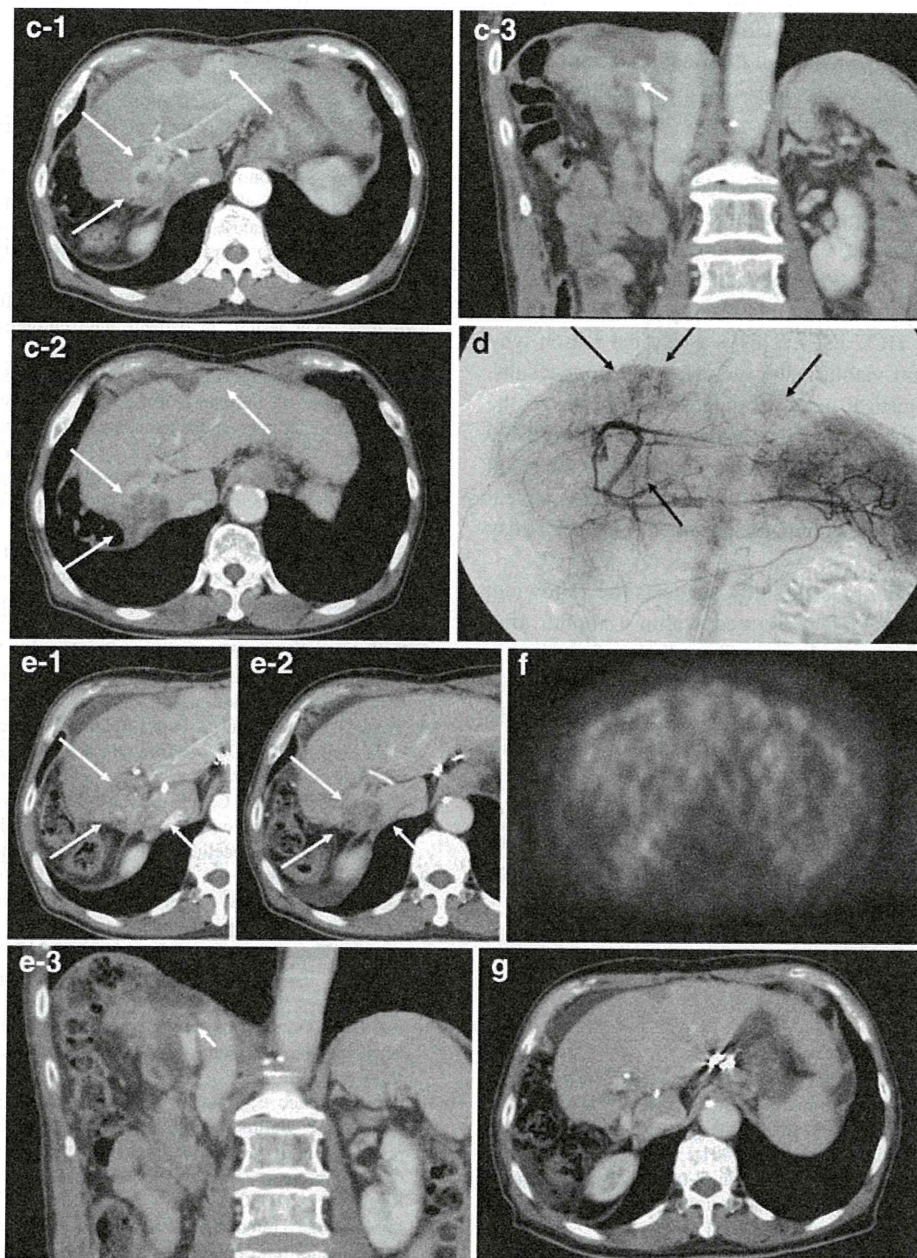


Fig. 3 (continued)

Therefore, only the factor “post-therapeutic visual PET diagnosis (positive or negative)” was statistically significant in the present study.

Limitations of the study should be discussed. First of all, there was a potential bias in the study population. Of 122 cases with unresectable HCC, only 67 cases were included in the present study. Some of the excluded cases received FDG PET 1 month after the end of non-operative therapy, while others did not receive post-therapeutic PET at all. In most cases, however, the reason why these patients did not receive PET

within 1 month after the therapy was unknown. This is a limitation in a retrospective study. Secondly, the timing of post-therapeutic FDG PET might have been too early after the non-operative therapy. This was the reason why the diagnosis of lesion viability showed relatively poor results. Typically, post-therapeutic FDG PET study is supposed to be performed more than 2 weeks after the end of the chemotherapy cycle and 6–8 weeks after radiotherapy [43, 44]. Post-therapeutic PET performed more than 4 weeks after the end of non-operative therapy might be better for the diagnostic value in

the diagnosis of lesion viability. However, it can be said from our data that early performance of PET is more useful from a prognostic point of view. Post-therapeutic PET within 1 month after the end of therapy may help in making a prompt decision in patient management. Thirdly, pre-treatment FDG PET was performed in only 29 cases (50%). It means that post-therapeutic PET did not always reflect the therapeutic effect of non-operative therapy. Negative results of post-therapeutic PET can be explained not only by therapeutic effect, but also by lack of the FDG-avid character of HCC itself. This is partly the reason why diagnosis of lesion viability showed relatively poor results. However, the statistical analysis suggested that one of the most important factors for the prognosis of unresectable HCC patients treated by non-operative therapy was the result of post-therapeutic FDG uptake, not that of the pre-treatment one. From a clinical viewpoint, pre-treatment FDG PET may be omitted.

In conclusion, the present study suggests the following: (1) post-therapeutic PET performed within 1 month after non-operative therapy can be a good predictor of survival in unresectable HCC patients, (2) patients with unresectable HCC diagnosed as positive by post-therapeutic FDG PET study are highly supposed to die within 24 months, while patients diagnosed as negative are highly supposed to survive more than 12 months and (3) a negative result of post-therapeutic FDG PET study may not always mean tumour cell death, and further treatment or further clinical follow-up would be needed.

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TOPIX post-FDG : 放射性薬剤の未来

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京都大学大学院薬学研究科 病態機能分析学分野 河嶋 秀和

1. はじめに

2002年に ^{18}F FDGが保険適用の認可を受けて以降、FDG-PETは臨床画像診断の分野で拡大を続け、現在、脳や心臓、腫瘍を対象とした各種疾患の描出において中心的な役割を担っている。さらに、近年では、PETは臨床診断だけでなく、生命現象や病態の分子レベルでの解明、あるいは医薬品開発におけるトランスレーショナル研究での活用も注目されるようになった。こうした現状を受け、細分化されたPETの使用目的に符合する、テイラーメイド的な新規PET薬剤の開発推進が強く望まれている。

一般に、放射性分子プローブは以下の性質を満たすことが必要である。

① 選択的に標的分子と結合、あるいは組織内環境と相互作用すると同時に、非標的組織成分との結合性は低い。すなわち、Signal-to-Noise比が高く、プローブの挙動が標的分子（環境）の変化を高感度に反映する。

② 代謝的に安定である。また、放射性核種の半減期に相応した体内動態を示すことにより、数学的モデル解析が実行可能である。これにより、定量的に優れた生体情報を抽出できる。

③ 高比放射能、高収量を達成するため、プローブに対応した放射性核種で、迅速かつ効率的に標識合成できる。

④ 薬剤としての有効性、安全性を担保

する製造システムを確立できる。

以上を踏まえ、本稿では、post-FDGとして現在開発、臨床への展開が試みられている新たなPETプローブについて、幾つかを紹介する。

2. 腫瘍イメージングプローブ

腫瘍診断を目的とする臨床では、現在、FDG-PETが最も有用な手段となっている。しかし、 ^{18}F FDGは生理的に解糖系が活発な組織（脳、心臓）や炎症性組織、排泄に伴う腎尿路系に対しても集積性を示すため、しばしば使用に制限が生じる。また、高分化型腫瘍には集積が低くなるなど、偽陰性が問題となる場合もある。そこで、 ^{18}F FDGを補完するための放射性分子プローブの開発が精力的に進められている。

腫瘍への集積機序からこれらのプローブを分類すると、① 組織における代謝機能（アミノ酸代謝、核酸代謝、脂質代謝）の亢進を利用したものと、② 組織の病理変化（低酸素、アポトーシス、血管新生等）を利用したものとに大別される。前者は腫瘍細胞が普遍的に有している性質であることから、スクリーニングを中心とした今後の臨床腫瘍診断の主流となる可能性が期待される。一方、後者は腫瘍の生物学的組織特性に基づくものであり、個別化治療戦略の設計あるいは治療効果判定を行う上で極めて重要になる。