# $^{11}$C-acetate and $^{18}$F-fluorodeoxyglucose positron emission tomography/computed tomography dual imaging for the prediction of response and prognosis after transarterial chemoembolization

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## Abstract

The aim of the present study was to evaluate the clinical significance of dual radiotracer studies, $^{11}$C-acetate and $^{18}$F-fluoro-D-glucose positron emission tomography/computed tomography ($^{18}$F-FDG PET/CT), for the prediction of response and recurrence after transarterial chemoembolization (TACE).

This study retrospectively included a total 42 hepatoceullar carcinoma (HCC) patients (median age, 59; range, 34–85 years old) who underwent $^{11}$C-acetate and $^{18}$F-FDG PET/CT concurrently. Tumor uptake normalized by liver uptake (TNR; maximum tumor SUV to mean normal liver SUV ratio) was obtained first. Then, FAratio, which is the ratio of $^{18}$F-FDG TNR (TNR_FDG) to $^{11}$C-acetate TNR, was obtained and correlated with response after TACE and recurrence-free survival (RFS), using a Cox multivariate proportional-hazard model.

Among clinical factors, including the Hepatoma Arterial Embolization Prognostic score and positron emission tomography (PET) parameters, multiple regression analysis revealed FAratio and tumor size to be the only significant factors. As a PET parameter, FAratio exhibited the largest area under the curve in the prediction of response after TACE. In the Cox multivariate proportional-hazard model, TNR_FDG was the only significant predictive factor for RFS. In subgroup analysis, TNR_FDG was the only significant predictive factor for recurrence in intermediate stage patients. However, FAratio was the only significant predictive factor for recurrence in advanced stage patients.

Dual radiotracer use of $^{11}$C-acetate and $^{18}$F-FDG PET/CT contributed to the prediction of response and recurrence after TACE. Used in addition to $^{18}$F-FDG, $^{11}$C-acetate PET/CT could give additional information in advanced stage patients. Based on the characteristics of tumor metabolism assessed by dual radiotracer PET/CT, treatment plans could be more personalized and optimized.

**Abbreviations:** $^{18}$F-FDG = $^{18}$F-fluoro-D-glucose, AUC = area under the curve, BCLC = Barcelona Clinic Liver Cancer, CoA = acetyl coenzyme A, FAratio = ratio of TNR_FDG and TNR_Ace, HAP score = hepatoma arterial-embolization prognostic score, HCC = hepatoceullar carcinoma, HR = hazard ratio, mHAP score = modified hepatoma arterial-embolization prognostic score, mRECIST = modified response evaluation criteria in solid tumors, PET/CT = positron emission tomography/computed tomography, RFS = recurrence-free survival, ROC = receiver-operating-characteristic, SUV = standardized uptake value, SUVmax = maximum standardized uptake value, SUVmean = mean standardized uptake value, TACE = transarterial chemoembolization, TNR = maximum tumor SUV to mean normal liver SUV ratio, TNR_Ace = maximum tumor SUV to mean normal liver SUV ratio of $^{11}$C-acetate, TNR_FDG = maximum tumor SUV to mean normal liver SUV ratio of $^{18}$F-FDG.

**Keywords:** acetate, fluoro-D-glucose, hepatoma, positron emission tomography/computed tomography, prognosis, transarterial chemoembolization

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## 1. Introduction

Hepatocellular carcinoma (HCC) is the sixth leading cause of cancer-related deaths in men, and its incidence has been increasing in developed countries.[1] Curative resection of the tumor and liver transplantation are the treatments of choice in early stage HCC patients. However, most patients have intermediate to advanced stage HCC at diagnosis, and transarterial chemoembolization (TACE) is performed as the initial treatment in these patients.[2–4] TACE plays a significant role in the control of HCC by inducing ischemic necrosis due to arterial embolization and due to its chemotherapeutic effects, but recurrence is inevitable.[5,6]

The response and prognosis of hepatoma after TACE are variable. Recently, the hepatoma arterial-embolization prognostic score (HAP score) was introduced based on clinical variables, such as serum albumin level, bilirubin level, and tumor size.[7] Computed tomography (CT) imaging features, such as the completeness of lipiodol uptake by the tumor, are also considered,[8] but there are no reliable prognostic tools.

In addition to tumor phenotype and impairment of hepatic reserve, the metabolic features of hepatomas could predict the response to or prognosis after TACE, especially using imaging tools such as positron emission tomography/computed tomography (PET/CT).[9] 2-deoxy-2-^{18}F-fluoro-D-glucose (^{18}F-FDG) PET/CT is widely used for noninvasive cancer imaging. It is also widely used in the diagnosis of poorly differentiated HCC, extrahepatic metastasis, and prediction of recurrence after liver transplantation.[10–13] Based on these results, ^{18}F-FDG PET/CT plays in significant role in the management of HCC. At the same time, ^{11}C-acetate is useful in the detection of low grade HCC and the differentiation between HCC and benign lesions.[14,15][11]C-acetate uptake is known to be related to acetyl coenzyme A (CoA) expression in well-differentiated HCC.[16] Therefore, ^{11}C-acetate has the potential to play a complementary role to ^{18}F-FDG PET/CT in the diagnosis of HCC.[17]

In the aspects of tumor metabolism and prognosis, ^{18}F-FDG uptake is correlated with poorly differentiated HCC, and it is known to have aggressive characteristics.[9] Since ^{11}C-acetate uptake is related to well-differentiated HCC and could be expected with less aggressiveness or a fair prognosis, there have been a lack of studies of prognosis after TACE regarding the aspect of ^{11}C-acetate metabolism.

In our previous study, we performed ^{11}C-acetate and ^{18}F-FDG dual radiotracer PET/CT for the characterization of HCC.[14] Based on our previous work, we attempted to evaluate the role of ^{18}F-FDG and ^{11}C-acetate dual tracer PET/CT in the prediction of treatment response in HCC patients who underwent TACE. Second, we attempted to evaluate whether it could predict recurrence after TACE.

## 2. Materials and methods

### 2.1. Ethics statement

Institutional Review Board at National Cancer Center approved the study design and waived informed consent (NCC2017-0149).

### 2.2. Patients

Forty-two patients diagnosed with HCC between June 2006 and April 2007 were enrolled retrospectively. All of the patients were part of our previous prospective study: among them, patients who received TACE were selected.[14] All of the patients had newly diagnosed HCC and the diagnosis of HCC was based on the guidelines of the Korean Liver Cancer Study Group and National Cancer Center of Korea.[18] All of the patients underwent ^{18}F-FDG, ^{11}C-acetate PET/CT, and dynamic spiral CT before treatment. All tumors were pathologically confirmed 1 week before or after PET/CT by percutaneous core biopsies in the aid of ultrasonography. The inclusion criteria for the subjects were as follows: age between 18 and 80 years old; adequate liver function (Child–Pugh classification A or B); Eastern Cooperative Oncology Group performance status of 0 to 2; and adequate renal function (serum creatinine <1.4 mg/dL). The exclusion criteria for subjects were whether they had any other malignancy or distant metastasis.

### 2.3. Imaging studies

Synthesis of radiopharmaceutical and acquisition of PET/CT images were performed in the same manner as in our previous study.[14] In brief, 2 dedicated PET/CT scanners were used (Biograph LSO; Siemens Healthcare, Erlangen, Germanyand

Discovery LS; GE Healthcare, Milwaukee, WI). Noncontrast CT images were acquired in the range of the skull base to upper thigh, and subsequent PET images were acquired 20 minutes after injection of ^{11}C-acetate and 60 minutes after injection of ^{18}F-FDG. Image acquisition was performed 4 minutes per bed in the 2-dimensional acquisition mode. ^{11}C-acetate PET/CT and ^{18}F-FDG PET/CT were performed on the same day: ^{11}C-acetate PET/CT was performed first, and ^{18}F-FDG PET/CT was performed at least 4 hours later, after >5 half-lives later. PET images were reconstructed using ordered-subset expectation maximization with 2 iterations and 8 subsets and with attenuation correction. The standardized uptake value (SUV) was calculated as (decay-corrected activity [kBq] per milliliter of tissue volume)/(injected ^{18}F-FDG or ^{11}C-acetate activity [kBq]/body mass [g]). The SUVs of lesions were obtained by manually placing of a volume of interest (VOI) around the lesion. PET/CT images were interpreted by 2 nuclear medicine physicians, who were unaware of the clinical information about these patients.

Acquisition of dynamic spiral CT imaging was performed using a multidetector CT scanner (Lightspeed pro-16, GE Healthcare) with contrast enhancement. Images were acquired in the noncontrast phase, hepatic artery phase (25 second after contrast injection), portal vein phase (70 second after contrast injection), and equilibrium phase (180 second after contrast injection). Final agreement of 2 experienced radiologists was used in the interpretation of the images.

### 2.4. TACE methodology

TACE was performed for the treatment of HCC according to National Cancer Center protocol.[19] Briefly, an arterial catheter was placed in the hepatic artery via the femoral artery by the Seldinger technique. Tumor feeding vessels were superselected—segmental arteries, subsegmental arteries, or lobar branches when possible—and infusion of solution containing 20 to 60 mg of doxorubicin hydrochloride (ADM; Dong-a Pharmacy, Seoul, South Korea) and 2 to 20 mL of iodized oil (Lipiodol; Guerbet, Aulnay-sous-Bois, France) was performed. The infusion was ended when the lipiodol mixture in the feeding arteries was in stasis as indicated by the appearance of iodized oil in the portal vein nearest the tumor. Subsequent embolization was performed using absorbable gelatin sponge particles (Gelfoam; Upjohn, MI).

### 2.5. Clinical features and image analysis

Clinical features, which show tumor phenotype, stage, and functional reserve, were collected, including serum albumin level, bilirubin level, and tumor size. For the assessment of prognosis after TACE, the modified Hepatoma Arterial Embolization Prognostic (mHAP) score was investigated.[20]

Tumor lipiodol uptake after TACE was evaluated by dynamic spiral CT as complete or partial, representing the technical success of TACE, and it is potentially correlated with response after TACE. PET/CT images were reviewed using a dedicated workstation (GE Healthcare). Intrahepatic primary lesions were interpreted visually by comparing data with tracer uptake by the normal liver parenchyma for ^{11}C-acetate and ^{18}F-FDG PET. The hypermetabolic lesion for each radiopharmaceutical was defined as positive in the diagnosis of the tumor, compared with normal liver uptake of each radiopharmaceutical.

For semiquantitive analysis, the tumor to normal liver ratio (TNR) was obtained. To evaluate tumor uptake, a VOI was placed to cover the highest activity of each tumor on CT images

from PET/CT scans with the guidance of contrast-enhanced dynamic CT. The maximum SUV (SUVmax) of the tumor VOI was used for further analysis. To evaluate normal liver uptake, 3 $1 cm^3$-sized VOIs were placed where the tumor was not detected, and the mean SUV (SUVmean) was obtained. Among 3 VOIs, the median of the SUVmeans of the normal liver VOIs was used. Then, TNR was obtained SUVmax of tumor normalized by selected SUVmean of normal liver in each radiotracer. Finally, the ratio of TNR in each radiotracer was obtained and was used for the analysis (FAratio; ratio of TNR_FDG [$^{18}$F-FDG TNR] and TNR_Ace [$^{11}$C-Acetate TNR]).

### 2.6. Endpoints

Patients' data were obtained from electronic medical record review. First, response assessment after TACE was conducted 4 to 6 weeks after TACE by dynamic spiral CT, using the modified Response Evaluation Criteria in Solid Tumors (mRECIST).[21] Based on the mRECIST criteria, the patients were divided into a responder group (complete and partial remission) and a nonresponder group (stable disease and progressive disease). After complete remission, the patients were evaluated 3 months later with dynamic CT scans and alpha-fetoprotein (AFP). Response after TACE according to the clinical factors was primary endpoint.

Second, the recurrence-free survival (RFS) period was determined when recurrence was detected. Recurrence was defined as the appearance of a viable tumor in contact with or inside the treated area or the appearance of a new lesion. Evaluation of RFS according to TNR in each radiotracer and FAratio was secondary endpoint.

### 2.7. Statistical analysis

The data were analyzed using MedCalc software (version 17.5; Broekostraat, Mariakerke, Belgium). Quantitative values are expressed as the median and range. The chi-square test was performed for the comparison of clinicopathologic factors in the responder and non-responder groups. Student's $t$ test and the Mann–Whitney $U$ test were used for the evaluation of differences in TNR between the complete lipiodol uptake and partial lipiodol uptake groups. Receiver-operating-characteristic (ROC) curve analysis was performed for the prediction of response after TACE in each parameter and acquisition of optimal cutoffs. Multivariate analysis using logistic regression was performed for the prediction of response after TACE. RFS was evaluated by Kaplan–Meier survival analysis. For the comparison with optimal the cutoff, the log-rank test was performed. Using significant factors in the univariate analysis, Cox stepwise proportional hazard regression analysis was performed. $P$ values <.05 were considered significant.

## 3. Results

### 3.1. Patient characteristics

Forty-two patients were included in the present study (34 men and 8 women). The ages of the patients ranged from 34 to 85 years old (median 59.0 year old). All of the patients had Child–Pugh classification A or B liver function (A: 36, B: 6 patients). According to the Barcelona Clinic Liver Cancer (BCLC) staging classification, 4 patients were very early stages, 3 patients were in early stages, 23 patients were in intermediate stages, and 12

patients were in advanced stages. Twenty-six patients showed a tumor size <5 cm, and 16 patients showed a tumor size >5 cm. Eighteen patients had a single lesion, and 24 patients had >2 lesions. Fifteen patients had HAP score A, 17 patients had HAP score B, 7 patients had HAP score C, and 3 patients had HAP score D.

### 3.2. Prediction of response after TACE

After TACE, patients with complete response numbered 9 (21.4%), those with partial response numbered 16 (38.1%), those with stable disease numbered 10 (23.8%), and those with progressive disease numbered 7 (16.7%). Clinical characteristics of the patients according to the objective response are summarized in Table 1. Among TNR_FDG, TNR_Ace, and FAratio, only TNR_FDG and FAratio were significant parameters between responders and nonresponders (Table 2). Comparison of TNR_FDG and TNR_Ace between responders and nonresponders was performed (Fig. 1). Using ROC curve analysis, the optimal cutoff of each parameter was determined. FAratio with a cutoff value of 1.67 exhibited the largest area under the curve (AUC). Representative cases are presented in Figs. 2 and 3.

In univariate analysis, FAratio (cutoff, 1.67), number of tumors (single or multiple), vascular invasion (present or absent), tumor size (cutoff, 5 cm), lipiodol uptake (complete or incomplete), and mHAP score (A, B, or C) were significant factors. However, in multivariate analysis, FAratio and tumor size were significant factors in the prediction of response (Table 3).

### 3.3. Relationships between lipiodol uptake and metabolic features

$^{11}$C-acetate and $^{18}$F-FDG uptake were compared according to lipiodol uptake. TNR_Ace was higher in the complete lipiodol uptake group than in the partial lipiodol uptake group, although statistical significance was not attained ($P = .1808$, Student $t$ test), while TNR_FDG was significantly higher ($P = .0022$, Mann–Whitney $U$ test) in the partial lipiodol uptake group than in the complete lipiodol uptake group (Fig. 4).

### 3.4. Predictors of recurrence after TACE

In the follow-up of patients after TACE (median, 30.1 months; range, 1.0–126.0 months), recurrence was observed in 36 patients (86%). The median value and range of RFS was 5.98 month (1.0–27.0 month). Visual analysis revealed significant differences in RFS (Fig. 5, Kaplan–Meier analysis, $P = .0217$) among $^{18}$F-FDG positive $^{11}$C-acetate positive, $^{18}$F-FDG positive $^{11}$C-acetate negative, $^{18}$F-FDG negative $^{11}$C-acetate positive, and $^{18}$F-FDG negative and $^{11}$C-Acetate negative patients (see Table S1, Supplemental Content, http://links.lww.com/MD/C483, which demonstrates number of patients in each group). In univariate analysis, BCLC stage, TNR_FDG, FAratio, vascular invasion, and tumor size were significant factors, but in multivariate analysis, TNR_FDG was the only significant factor in the prediction of recurrence (Table 4). Patients with TNR_FDG >2.41, which was the cutoff value derived from response after TACE, exhibited shorter RFS based on the log-rank test (median, RFS 7.40; range, 0.8–14.9 months, $P < .001$).

## Table 1

**Patients' characteristics classified by response after TACE.**

| Characteristic | | Responder (N = 25) | Non-responder (N = 17) | P value |
|---|---|---|---|---|
| Age | | 59 (34–75) | 61 (41–85) | .5585 |
| Sex | | | | .8339 |
| | Male | 20 | 14 | |
| | Female | 5 | 3 | |
| Tumor number | | | | .0162 |
| | Single | 15 | 3 | |
| | Multiple | 10 | 14 | |
| Tumor size | | | | .0066 |
| | <5 cm | 21 | 5 | |
| | >5 cm | 4 | 12 | |
| Vascular invasion | | | | .0659 |
| | No | 21 | 9 | |
| | Yes | 4 | 8 | |
| α-fetoprotein, ng/mL | | 28.8 (2.5–3573.1) | 106.9 (5.8–158526) | .0279 |
| Child–Pugh class | | | | .9488 |
| | I | 22 | 14 | |
| | II | 3 | 3 | |
| mHAP score | | | | .0362 |
| | A | 13 | 2 | |
| | B | 8 | 9 | |
| | C | 2 | 5 | |
| | D | 2 | 1 | |
| Lipiodol uptake on CT | | | | .0072 |
| | Complete | 18 | 5 | |
| | Partial | 7 | 12 | |
| PET parameter | | | | |
| | TNR_Ace | 2.01 (1.10–4.11) | 1.86 (0.79–3.49) | .3550 |
| | TNR_FDG | 1.71 (1.28–5.11) | 3.59 (1.31–9.26) | .0038 |
| | FAratio | 0.92 (0.38–2.16) | 1.89 (0.89–9.34) | .0011 |

CT = computed tomography, FAratio = ratio of TNR_FDG to TNR_Ace, mHAP = modified Hepatoma Arterial Embolization Prognostic, PET = positron emission tomography, TNR_Ace = maximum tumor SUV to mean normal liver SUV ratio of ^{11}C-acetate, TNR_FDG = maximum tumor SUV to mean normal liver SUV ratio of ^{18}F-FDG.

### 3.5. Subgroup analysis according to BCLC stage: intermediate stage and advanced stage patients

Patients with intermediate and advanced BCLC stages were divided into subgroups, and subgroup analysis was performed. In each group, RFS was 4.03 months (range, 0.37–9.20 months) in intermediate BCLC stages and 1.40 months (0.8–3.06 months) in advanced BCLC stages (see Table S2, Supplemental Content, http://links.lww.com/MD/C483, which shows patients' demographics in each stages). In patients in the intermediate BCLC stage group, multivariate analysis revealed that TNR_FDG was the only significant factor among Child–Pugh class, mHAP score, number, size, vascular invasion, AFP and FAratio (HR [harzard ratio] 1.37, P = .0099). In contrast, for patients in the advanced BCLC stage group, multivariate analysis revealed that FAratio was the only significant factor among Child–Pugh class, mHAP score, number, size, vascular invasion, AFP and TNR_FDG (HR 1.57, P = .0181). Kaplan–Meier survival curves in each stage are depicted in Fig. 6.

## 4. Discussion

TACE is widely performed in intermediate to advanced HCC.[4] Since TACE is a palliative treatment, meticulous follow-up is needed to manage recurrence.[22] There are known tools for the prediction of recurrence, such as the mHAP score. It is based on clinical factors and the size of the tumor using data-driven approach. However, there has been a lack of studies correlating tumor recurrence with aspects of tumor metabolism, which could be evaluated by ^{18}F-FDG and ^{11}C-acetate PET/CT.

In the present study, FAratio, which is the ratio of TNR_FDG to TNR_Ace, exhibited the largest AUC when correlated with the response after TACE. FAratio was a significant factor for the prediction of response after TACE among various factors. However, FAratio could predict recurrence after TACE in univariate analysis but not in multivariate analysis. As reported in the previous study, TNR_FDG was the only significant factor in the prediction of tumor progression after TACE.[9] ^{18}F-FDG uptake of tumors is well known as a poor prognostic factor for

## Table 2

**Receiver-operating characteristic curve analysis of PET parameters in predicting response after TACE.**

| Index | Area under curve | Sensitivity (%) | Specificity (%) | Cutoff | P value |
|---|---|---|---|---|---|
| TNR_Ace | 0.579 (0.417–0.729) | 23.5 | 100 | 1.02 | .4010 |
| TNR_FDG | 0.772 (0.616–0.887) | 92.0 | 70.6 | 2.41 | .0019 |
| FAratio | 0.814 (0.664–0.917) | 96.0 | 58.8 | 1.67 | <.001 |

FAratio = ratio of TNR_FDG to TNR_Ace, TNR_Ace = maximum tumor SUV to mean normal liver SUV ratio of ^{11}C-acetate, TNR_FDG = maximum tumor SUV to mean normal liver SUV ratio of ^{18}F-FDG.
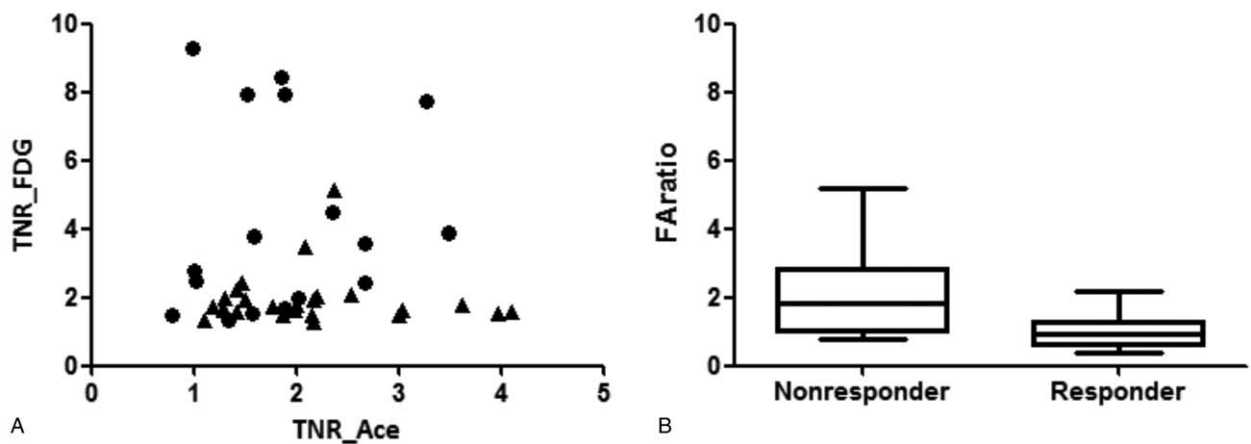
**Figure 1.** Values of TNR_FDG, TNR_Ace, FAratio in the patients, divided into responders and nonresponders after TACE. (A) Patients with high TNR_FDG and low TNR_Ace corresponded to the nonresponder group, and patients with low TNR_FDG and high TNR_Ace corresponded to the responder group. (B) Box plot of FAratio between the nonresponder and responder groups. Larger values of FAratio were observed in the nonresponder group compared with the responder group after TACE, with significant differences ($P = .0006$, Mann–Whitney $U$ test). FAratio = ratio of TNR_FDG and TNR_Ace, TACE = transarterial chemoembolization, TNR_Ace = maximum tumor SUV to mean normal liver SUV ratio of $^{11}$C-acetate, TNR_FDG = maximum tumor SUV to mean normal liver SUV ratio of $^{18}$F-FDG.
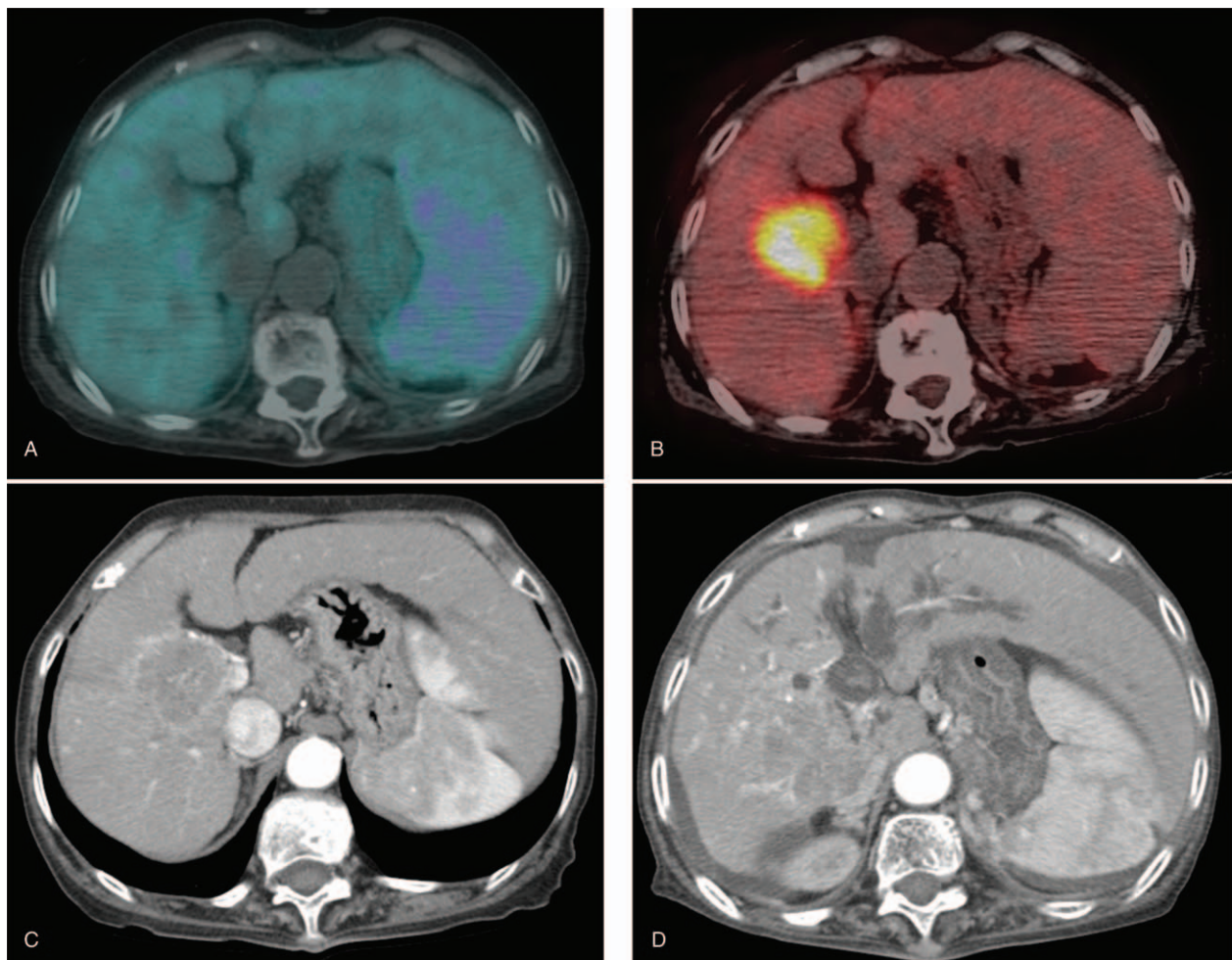


**Figure 2.** Eighty-four-year-old woman with right hepatic lobe mass. (A) Tumor did not exhibit definite $^{11}$C-acetate uptake (TNR_Ace: 0.99). (B) In contrast, high $^{18}$F-FDG uptake was shown (TNR_FDG: 6.73). FAratio was 6.80. (C) Initial arterial phase image of dynamic CT. (D) She was a nonresponder after TACE. Three months after TACE, the size of the tumor was increased, and right portal vein invasion was observed. CT = computed tomography, $^{18}$F-FDG = $^{18}$F-fluoro-D-glucose, FAratio = ratio of TNR_FDG and TNR_Ace, TACE = transarterial chemoembolization, TNR_Ace = maximum tumor SUV to mean normal liver SUV ratio of $^{11}$C-acetate, TNR_FDG = maximum tumor SUV to mean normal liver SUV ratio of $^{18}$F-FDG.
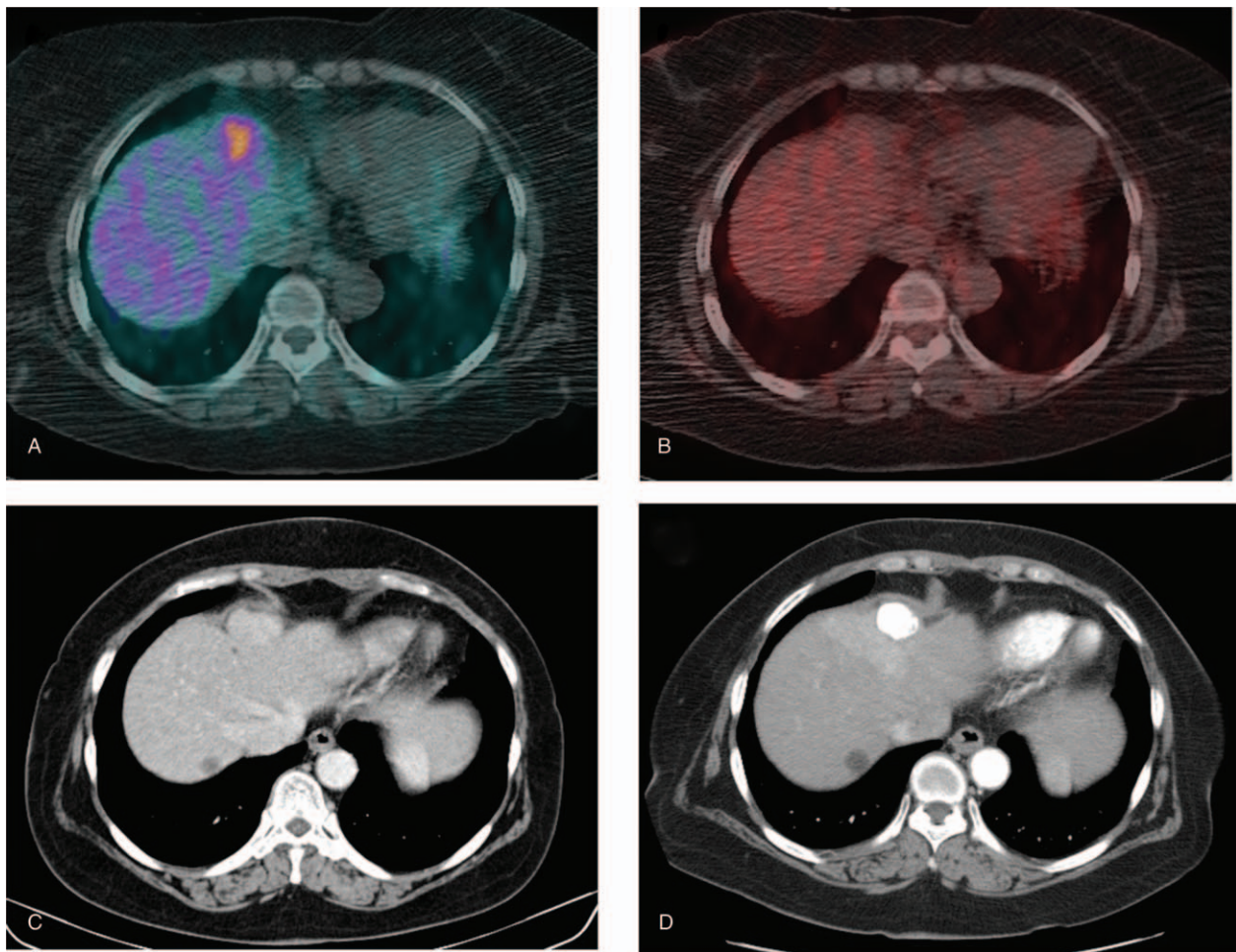
**Figure 3.** Seventy-year-old woman with a nodule in liver segment 4. (A) Tumor exhibited increased ^{11}C-acetate uptake (TNR_Ace: 2.17). (B) In contrast, subtle ^{18}F-FDG uptake was shown (TNR_FDG 1.92). (C) Initial arterial phase image of dynamic CT. (D) She was a responder after TACE. Three months after TACE, compact lipiodol retention was observed without an arterial enhancement lesion. A benign hepatic cyst is observed in liver segment 8. CT = computed tomography, ^{18}F-FDG = ^{18}F-fluoro-D-glucose, TACE = transarterial chemoembolization, TNR_Ace = maximum tumor SUV to mean normal liver SUV ratio of ^{11}C-acetate, TNR_FDG = maximum tumor SUV to mean normal liver SUV ratio of ^{18}F-FDG.

recurrence.[9–11] ^{18}F-FDG uptake is related to poorly differentiated HCC and the aggressiveness of the tumor.[23–25] However, in the subgroup analysis of patients with advanced BCLC stage, FAratio was the only significant factor in the prediction of RFS in multivariate analysis.

TNR_Ace is the denominator of FAratio, and it is closely related to ^{11}C-acetate uptake, in addition to ^{18}F-FDG uptake. ^{11}C-acetate uptake itself was not significant factor in the prediction of response or prognosis after TACE. However, significant differences in RFS were observed among ^{18}F-FDG

**Table 3**

**Multivariate logistic regression for prediction of response after TACE.**

| | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| **Factor** | **Hazard ratio** | **P value** | **Hazard ratio** | **P value** |
| Tumor size | 12.60 (2.83–56.17) | .0003 | 5.8264 (1.05–32.22) | .0434 |
| Tumor number | 7.00 (1.59–30.80) | .0100 | | NS |
| α-fetoprotein, ng/mL | 2.83 (0.66–12.34) | .1525 | | NS |
| Vascular invasion | 4.67 (1.11–19.54) | .0291 | | NS |
| mHAP score | 2.12 (1.00–4.51) | .0402 | | NS |
| Lipiodol uptake on CT | 6.17 (1.58–24.06) | .0087 | | NS |
| TNR_Ace | 0.68 (0.31–1.52) | .3362 | | NS |
| TNR_FDG | 16.43 (2.89–93.42) | .0016 | | NS |
| FAratio | 34.29 (3.72–316.12) | <.0001 | 17.27 (1.67–178.49) | .0168 |

CT = computed tomography, FAratio = ratio of TNR_FDG to TNR_Ace, mHAP = modified Hepatoma Arterial Embolization Prognostic, NS = not selected as a significant factor, TNR_Ace = TNR_Ace, maximum tumor SUV to mean normal liver SUV ratio of ^{11}C-acetate, TNR_FDG = maximum tumor SUV to mean normal liver SUV ratio of ^{18}F-FDG.
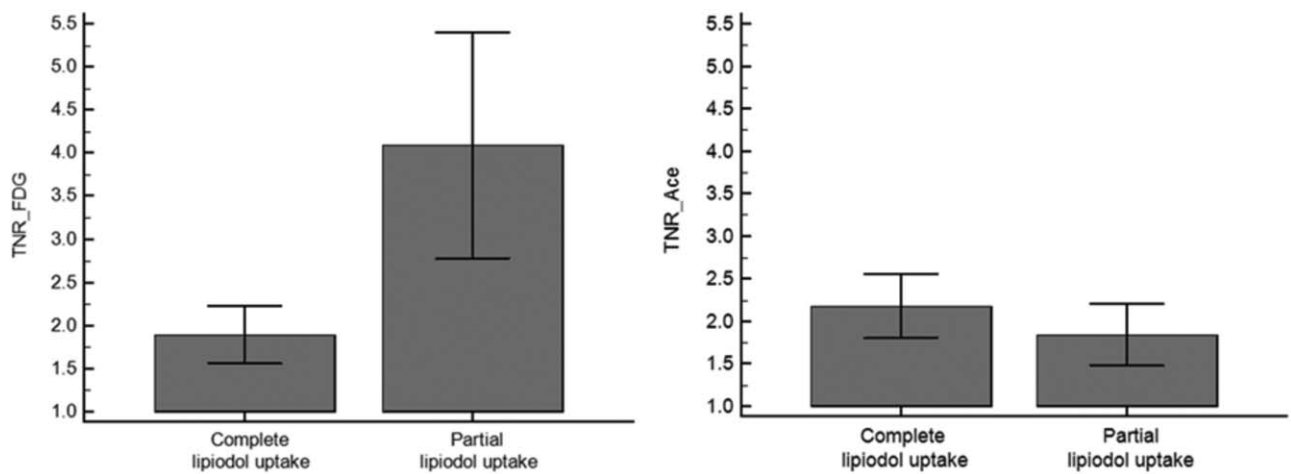
**Figure 4.** Comparison of TNR_FDG and TNR_ace in the complete lipiodol uptake and partial lipiodol uptake groups. (TNR_FDG: $1.89 \pm 0.77$ in the complete lipiodol uptake group, $4.09 \pm 2.72$ in the partial lipiodol uptake group, $P = .0022$; and TNR_Ace: $2.18 \pm 0.88$ in the complete lipiodol uptake group, $1.84 \pm 0.75$ in the partial lipiodol uptake group, $P = .1885$). TNR_Ace = maximum tumor SUV to mean normal liver SUV ratio of ^{11}C-acetate, TNR_FDG = maximum tumor SUV to mean normal liver SUV ratio of ^{18}F-FDG.

positive ^{11}C-acetate positive, ^{18}F-FDG positive ^{11}C-acetate negative, ^{18}F-FDG negative ^{11}C-acetate positive, and ^{18}F-FDG negative and ^{11}C-acetate negative patients using Kaplan–Meier analysis (Fig. 5). In particular, longer RFS was observed in acetate positive patients in the ^{18}F-FDG positive group, compared with acetate negative patients. The reason for the fair outcomes of patients with ^{11}C-acetate in the ^{18}F-FDG avid group was related to lipiodol uptake after TACE. Heterogeneous or non-compact lipiodol uptake is known to be related to recurrence after

TACE.[8,26,27] Lipiodol uptake of the tumor could be affected by the vascularity of the tumor, and ^{11}C-acetate uptake increases under a hypervascular environment.[28–30] In contrast, hypovascularity and severe hypoxia are less favorable for ^{11}C-acetate uptake and could be related to poor differentiation of the tumor and could potentially explain ^{18}F-FDG uptake.[31] TNR_Ace was higher in the complete lipiodol uptake group than in the partial lipiodol uptake group. In contrast, ^{18}F-FDG uptake was significantly higher in the partial lipiodol uptake group, as
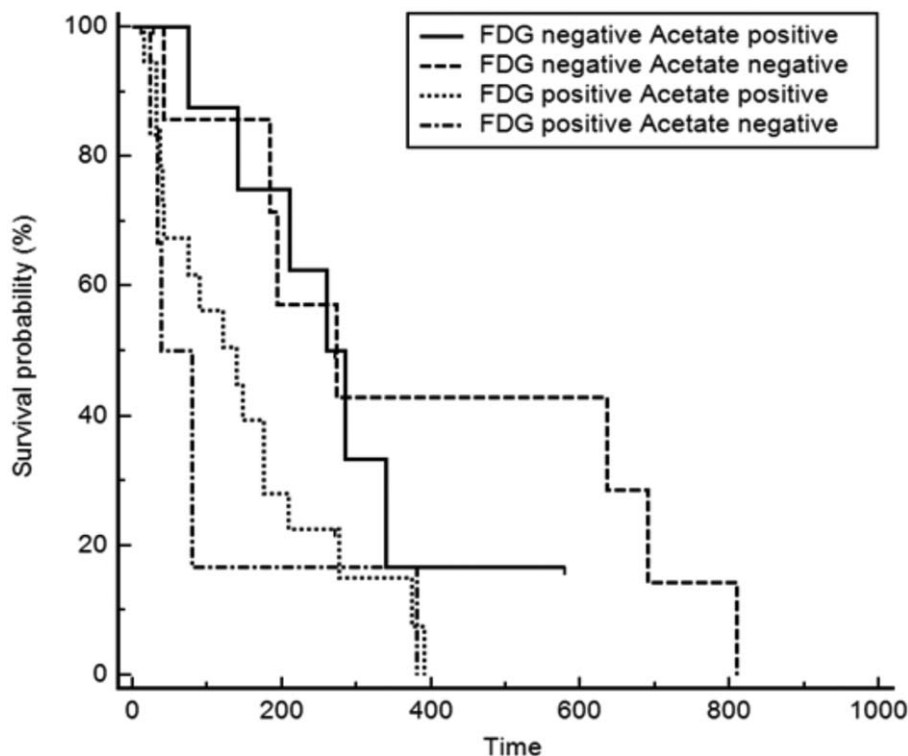


**Figure 5.** Kaplan–Meier survival analysis with regard to ^{11}C-acetate and ^{18}F-FDG avidity. Significant differences in RFS were observed among the 4 groups according to the ^{18}F-FDG and ^{11}C-acetate uptake. ^{18}F-FDG = ^{18}F-fluoro-D-glucose, RFS = recurrence-free survival.

**Multivariate analysis for the prediction of recurrence after TACE.**

| Factor | Univariate analysis | | Multivariate analysis | |
| --- | --- | --- | --- | --- |
| | Hazard ratio | P value | Hazard ratio | P value |
| BCLC stage | 7.19 (1.50–34.51) | .0090 | | NS |
| Tumor size | 2.72 (1.34–5.53) | .0079 | | NS |
| Vascular invasion | 2.25 (1.05–4.82) | .0487 | | NS |
| TNR_FDG | 1.45 (1.23–1.71) | <.0001 | 1.45 (1.23–1.71) | <.0001 |
| FAratio | 1.44 (1.16–1.78) | .0324 | | NS |

BCLC = Barcelona Clinic Liver Cancer staging classification, FAratio = ratio of TNR_FDG to TNR_Ace, NS = not selected as a significant factor, TNR_FDG = maximum tumor SUV to mean normal liver SUV ratio of ^{18}F-FDG PET/CT.

expected. Thus, when tumors exhibit ^{11}C-acetate and ^{18}F-FDG uptake both, tumor characteristics are more hypervascular, compared with tumors with ^{18}F-FDG uptake alone, which could lead to fair outcomes after TACE. Uptake patterns of ^{11}C-acetate and ^{18}F-FDG could be heterogeneous in the same tumor (Fig. 7). Metabolic features related to ^{11}C-acetate uptake might partially incorporate the CT features related to lipiodol uptake.

However, FAratio was a significant factor only in the BCLC advanced group in the prediction of tumor progression and not in all of the patients. In the intermediate stage patients, TNR_FDG was sufficient in the prediction of tumor progression, but in cases of advanced patients, the majority of patients exhibited ^{18}F-FDG uptake. Tumor differentiation using the Edmonson–Steiner grade of these patients was III in 7 patients and II in 2 patients, and relatively poor differentiation likely resulted in ^{18}F-FDG uptake. Therefore, in advanced patients, ^{18}F-FDG uptake was common, and ^{11}C-acetate uptake was more critical, compared with in the intermediate stage patients. In the intermediate stage patients, relative heterogenous differentiation was observed, which had an impact on ^{18}F-FDG uptake. Since advanced BCLC stage patients generally exhibited poor overall survival with heterogenous clinical characteristics, precise and personalized approaches are needed.[32] Additionally, ^{11}C-acetate PET/CT could help in the management of advanced stage patients.

There were some limitations of the present study. The study was performed in a retrospective manner, and it could influence patient selection. However, our patients were from our previous prospective study, and the image acquisition of PET/CT was uniform.[14] This condition could offset the retrospective nature of the study. Second, although ^{11}C-acetate uptake was related to fair outcomes after TACE, it did not contribute greatly. The TNR_Ace was not a significant factor for the prediction of response or recurrence independently. The small number of patients probably resulted in the marginally significant difference in TNR_Ace between the complete lipiodol uptake and partial lipiodol uptake groups. In addition to response after TACE, low TNR_Ace was potentially related to recurrence after TACE. Good differentiation of the tumor itself was related to relatively longer RFS, but more studies of cancer metabolomics in terms of utilization of acetate are needed. Third, the value of FAratio is a ratio that emphasizes the value of each TNR. FAratio was a significant factor for the prediction of response and recurrence after TACE in the advanced patients, likely emphasizing TNR_FDG. However, since TNR could be affected by various PET/CT conditions, such as reconstruction method, the ratio of ^{18}F-FDG uptake to ^{11}C-acetate uptake was affected by technical problems more than uptake itself. Fourth, small number of patients with various BCLC stage was included in the study, and that could lead to false positive results. We could find significant factors for the prediction of response and recurrence after TACE with quite low P-values, but large prospective studies are needed for the validation of the present study.
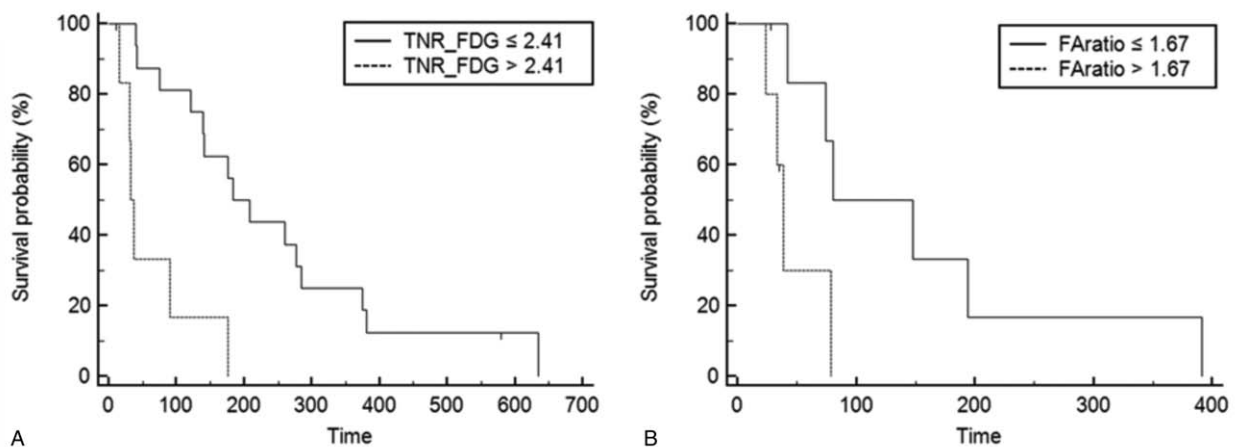


Figure 6. Kaplan–Meier survival analysis of subgroup analysis with regard to BCLC stage. (A) In intermediate stage patients, significantly longer RFS was observed in low TNR_FDG. (B) In advanced stage patients, significantly longer RFS was observed in low FAratio. Multivariate analysis revealed in intermediate stage patients that TNR_FDG was the only significant factor and in advanced stage patients, and FAratio was the only significant factor in the prediction of tumor progression after TACE. BCLC = Barcelona Clinic Liver Cancer, FAratio = ratio of TNR_FDG and TNR_Ace, TACE = transarterial chemoembolization, TNR_FDG = maximum tumor SUV to mean normal liver SUV ratio of ^{18}F-FDG, RFS = recurrence-free survival.
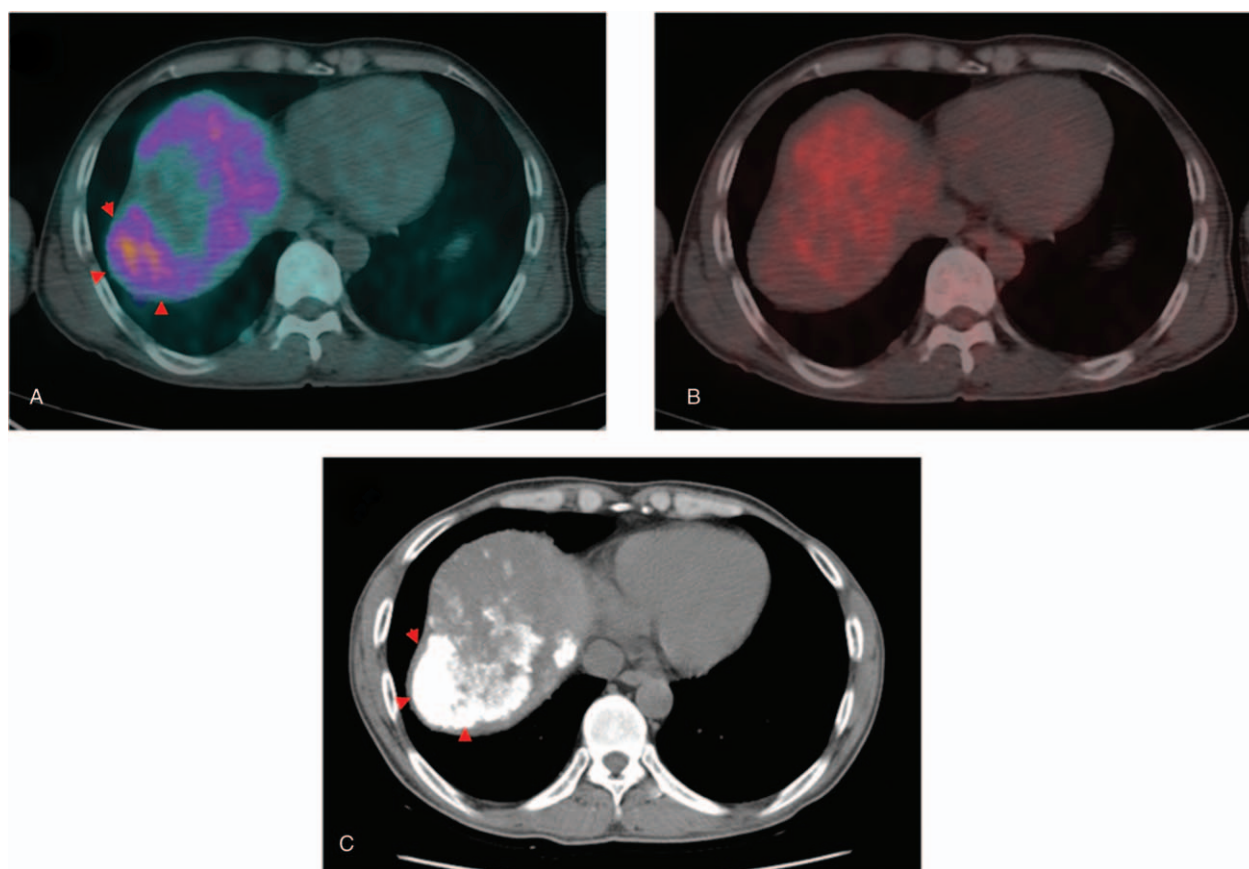
**Figure 7.** Forty-eight-year-old man with huge infiltrative HCC in the right hepatic lobe. (A) $^{11}$C-acetate uptake is shown in the lateral side of the right hepatic lobe tumor (arrowhead). (B) In contrast, $^{18}$F-FDG uptake is shown in the medial side of the right hepatic lobe tumor. (C) Lipiodol uptake is shown in the lateral side of the tumor, concordant with the $^{11}$C-acetate uptake portion (arrowhead). $^{18}$F-FDG = $^{18}$F-fluoro-D-glucose, HCC = hepatoceullar carcinoma.

## 5. Conclusion

$^{11}$C-acetate and $^{18}$F-FDG dual tracer PET/CT assisted in the characterization of the tumor nature and in the prediction of response and recurrence after TACE. For the prediction of prognosis, dual radiotracer PET/CT could be beneficial in the management of advanced stage patients.

## Author contributions

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