Can Positron Emission Tomography with the Dual Tracers \( ^{11}C \)Acetate and \( ^{18}F \)Fludeoxyglucose Predict Microvascular Invasion in Hepatocellular Carcinoma?

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Microvascular invasion is a poor prognostic indicator of the recurrence of hepatocellular carcinoma (HCC) after surgical treatment. Positron emission tomography (PET) with \( ^{18}F \)fludeoxyglucose (\( ^{18}F \)FDG) as a tracer has been employed to predict the prognosis before surgery for various kinds of tumors, but it has not been found to be sensitive enough for HCC. Thus, \( ^{11}C \)acetate has been adopted as an additional tracer. This study was designed to evaluate the ability of dual-tracer PET (\( ^{18}F \)FDG and \( ^{11}C \)acetate) to predict microvascular invasion before liver resection or transplantation. Fifty-eight HCC patients who were preoperatively examined with whole-body dual-tracer PET were studied. Twenty-five patients were \( ^{18}F \)FDG-positive, and 56 were \( ^{11}C \)acetate-positive. The sensitivity of \( ^{18}F \)FDG in detecting primary HCC was 43%, and the sensitivity of \( ^{11}C \)acetate was 93%. Twenty-nine patients had HCC with microvascular invasion according to the final pathological examination. The sensitivity, specificity, positive predictive value, and negative predictive value of \( ^{18}F \)FDG PET in predicting microvascular invasion were 55.2%, 69%, 64%, and 60.6%, respectively; the corresponding rates for \( ^{11}C \)acetate PET were 93.1%, 0%, 48.2%, and 0%. The factors associated with HCC recurrence, which included multifocal involvement, a large tumor size, microsatellite lesions, poor HCC differentiation, and an advanced stage of disease, were analyzed and compared with positive PET results. A tumor size greater than 5 cm was significantly associated with positive \( ^{18}F \)FDG PET results; \( ^{11}C \)acetate was not associated with poor prognostic indicators. Preoperative \( ^{18}F \)FDG PET may predict microvascular invasion. The addition of \( ^{11}C \)acetate improves the overall sensitivity of PET, but it has no incremental value in predicting microvascular invasion. Liver Transpl 17:1218-1225, 2011. © 2011 AASLD.
nodules with individual diameters ≤ 3 cm. Patients with major vascular involvement or extrahepatic metastases are excluded. By adopting these selection criteria, the Milan group has achieved a survival rate greater than 70% for 300 LT procedures in 10 years. Equally good results have been observed in the rest of the world when the same principles have been followed.3,6-10

In recent years, studies have shown that the outcomes of LT can be affected by the tumor biology. High-grade tumors and microvascular invasion are known risk factors for high recurrence rates and poor survival.11,12 Preoperative computed tomography can reveal obvious macrovascular invasion but not microvascular invasion. A postoperative tissue diagnosis can provide the most accurate prognosis, but it is often too late for decision making. Positron emission tomography (PET) with the tracer [18F]fludeoxyglucose ([18F]FDG) is one of the noninvasive diagnostic tools used for the detection of various malignancies, including colonic, pancreatic, and lung tumors. It has been demonstrated that [18F]FDG PET can predict microvascular tumor invasion in candidates for LT.13-15 However, the sensitivity of [18F]FDG PET for the detection of HCC remains controversial. To improve the sensitivity of PET to HCC, [11C]acetate has been used as an additional tracer. It has been reported to be quite specific for primary liver cancers in the evaluation of liver lesions and has been shown to be negative for hemangiomas, cholangiocarcinomas, secondary cancers from the colon, breast, or lungs, and carcinoid tumors. For the evaluation of HCC and its metastases, PET with [11C]acetate and [18F]FDG PET as dual tracers has been shown to be incrementally better than single-tracer PET and to have a complementary advantage.16,17

In this study, we performed a retrospective analysis to determine the prognostic value of preoperative dual-tracer PET ([11C]acetate and [18F]FDG) for HCC patients. Specifically, we sought to determine whether dual-tracer PET has adequate power to differentiate tumor aggressiveness in terms of microvascular invasion so that better outcomes can be achieved with hepatectomy and LT.

PATIENTS AND METHODS

From January 2004 to September 2009, 551 HCC patients underwent liver resection (459) or LT (92) at the Department of Surgery of Queen Mary Hospital (Hong Kong, China). Fifty-eight patients (49 males and 9 females) who were examined with dual-tracer PET during the preoperative assessment were included in this study. Contrast computed tomography scanning was used as a baseline reevaluation tool for HCC. Dual-tracer PET scanning, which was an additional workup procedure, was offered to patients who were willing to pay for it. The 58 patients had a median age of 60.5 years (range = 30-83 years). Dual-tracer PET CT scan is a standard and accepted practice at our institution. As the investigation was not performed on a clinical trial setting, IRC approval was not required. Three patients were hepatitis C carriers, and 47 were hepatitis B carriers. The remaining 8 patients had neither the hepatitis B surface antigen nor the hepatitis C antibody. One patient underwent deceased donor LT, 15 patients underwent living donor LT, 25 patients underwent major hepatectomy, and 17 patients underwent minor hepatectomy. Two LT patients underwent transarterial chemoembolization as a neoadjuvant treatment before transplantation because their liver function was good enough.

All the dual-tracer PET scans were performed at the Department of Nuclear Medicine and Positron Emission Tomography of Hong Kong Sanatorium and Hospital (Hong Kong, China). The [11C]acetate tracer was prepared with a modification of the method and setup reported by Norenberg et al.18 It was administered intravenously (550-740 MBq), and whole-body imaging was performed 20 minutes afterwards. Approximately 15 minutes after the imaging, [18F]FDG was injected intravenously (370-550 MBq). The scanning of the whole body with the same imaging positions and acquisition settings began 60 minutes after the administration of [18F]FDG. This allowed approximately 105 minutes for interpretation after the initial injection of [11C]acetate (more than 5 decay half-lives of [11C]acetate).

The details of the examination method can be found in published articles.17,19 A lesion was determined to be HCC-positive on the basis of a visual judgment of increased metabolism by 3 independent and experienced interpreters, and this was supported by a semiquantitative evaluation based on the calculation of the standard uptake value (SUV) for both sets of scans. The maximum and average SUVs were calculated. A lesion was considered negative for a PET tracer if it was found by a visual inspection to be isodense with nontumorous tissue (and this was supported by a lesion-to-liver ratio < 1.20).

Patient demographics and tumor characteristics, including the tumor size and number, were recorded. When there were multiple tumors in 1 cluster, the diameter of the largest tumor was measured. Pathological specimens from paraffin-embedded liver sections were examined by at least 2 experienced pathologists who were unaware of the results of the radiological examinations. Microvascular invasion was recorded when tumor emboli were found inside the liver’s venous system, which included the portal vein and its lobar and segmental branches, the hepatic vein, the capsular vein, and the inferior vena cava. Histological grading was assessed according to the Edmondson criteria.20

Statistical Analysis

The baseline characteristics of the patients were expressed as medians and ranges. The Mann-Whitney U test was used to compare continuous variables, and a chi-square test was used to compare discrete
variables. Significance was defined as \( P < 0.05 \). All statistical calculations were made with SPSS/PC+ software (SPSS, Inc., Chicago, IL).

**RESULTS**

In this study, all patients were confirmed to have at least 1 tumor during the final pathological examination. There were 82 tumors in the liver resection specimens of the 58 patients. According to the results of the pathological examination, 4 patients (6.9%) had more than 3 tumors, and 54 (93.1%) had 3 or fewer. The median tumor size was 5.2 cm (range = 1-19 cm). Twenty-nine patients (50%) had tumors with diameters \(<5\) cm, and 29 (50%) had tumors with diameters \(\geq5\) cm. During the final pathological examination, 29 patients were found to have microvascular invasion, 5 were found to have microsatellite lesions, and 12 had poorly differentiated HCC according to the Edmondson criteria. According to the tumor-node-metastasis staging system of the International Union Against Cancer (1997), 6 patients (10.3%) had stage I disease, 17 (29.3%) had stage II disease, 17 (29.3%) had stage III disease, and 18 (31.0%) had stage IV disease (Table 1).

The sensitivity of \([18F]FDG\) PET for HCC was 60\%, and the sensitivity of \([11C]Acetate\) PET was 93\%. On the other hand, \([11C]Acetate\) PET had a sensitivity of 55.2\% [confidence interval (CI) = 36\%-73\%] and a specificity of 69\% (CI = 49\%-84\%). The positive predictive value was 64\% (CI = 42.6\%-81.2\%), and the negative predictive value was 60.6\% (CI = 42.2\%-76.5\%). On the other hand, \([11C]Acetate\) PET had a sensitivity of 93.1\% (CI = 75.8\%-98.8\%) and a specificity of 0\% (CI = 0\%-14.56\%). The positive predictive value was

| Table 1. Pathological Characteristics of HCCs |
|---------------------------------------------|
| \(\leq3\) nodules (n) | 54 |
| >3 nodules (n) | 4 |
| Tumor size (cm; median (range)) | 5.2 (1-19) |
| Tumor size \(<5\) cm (n) | 29 |
| Tumor size \(\geq5\) cm (n) | 29 |
| Vascular permeation (n) | 29 |
| Microsatellite lesions (n) | 5 |
| Poorly differentiated HCC (n) | 12 |
| Stage I HCC (n) | 6 |
| Stage II HCC (n) | 17 |
| Stage III HCC (n) | 17 |
| Stage IV HCC (n) | 18 |

| Table 2. Detection of HCC by Dual-Tracer PET |
|---------------------------------------------|
| Nodules (n) | \([18F]FDG\) Tracer (n) | \([11C]Acetate\) Tracer (n) | Pathology (n) |
| 0 | 22 | 2 | 0 |
| 1 | 30 | 35 | 41 |
| 2 | 5 | 14 | 8 |
| 3 | 1 | 5 | 5 |
| 4 | 0 | 1 | 1 |
| 5 | 0 | 0 | 0 |
| >5 | 0 | 0 | 3 |

Two of the 4 patients with more than 3 tumors were \([18F]FDG\)-avid, and 2 were \([18F]FDG\)-negative. Seven of the 29 patients who had tumors with diameters \(\leq5\) cm were \([18F]FDG\)-avid, and 22 were \([18F]FDG\)-negative. Eighteen of the 29 patients who had tumors with diameters \(>5\) cm were \([18F]FDG\)-avid, and 11 were \([18F]FDG\)-negative. Nineteen of the 29 patients who had microvascular invasion according to the final pathological examination were \([18F]FDG\)-avid, and 16 were \([18F]FDG\)-negative. Sixteen of the 29 patients who had no microvascular invasion according to the final pathological examination were \([18F]FDG\)-avid, and 13 were \([18F]FDG\)-negative. Five patients were found to have microsatellite lesions, and only 3 of these patients were \([18F]FDG\)-avid. Twelve patients were found to have poorly differentiated HCC, and 8 of these patients were \([18F]FDG\)-avid.

**Assessment With \([11C]Acetate\) PET**

Fifty-two of the 54 patients with 3 or fewer tumors were \([11C]Acetate\)-avid, and 2 were \([11C]Acetate\)-negative. All 4 patients who had more than 3 tumors were \([11C]Acetate\)-avid. Twenty-eight of the 29 patients who had tumors with diameters \(\leq5\) cm were \([11C]Acetate\)-avid, and 1 was \([11C]Acetate\)-negative. Twenty-eight of the 29 patients who had tumors with diameters \(>5\) cm were \([11C]Acetate\)-avid, and 1 was \([11C]Acetate\)-negative. All 29 patients who had no microvascular invasion according to the final pathological examination were \([11C]Acetate\)-avid. Twenty-seven of the 29 patients who were positive for microvascular invasion according to the final pathological examination were \([11C]Acetate\)-avid, and 2 were \([11C]Acetate\)-negative. Five patients were found to have microsatellite lesions, and only 4 of these patients were \([11C]Acetate\)-avid. Twelve patients were found to have poorly differentiated HCC, and 11 of these patients were \([11C]Acetate\)-avid (Table 3).

For the prediction of HCC with microvascular invasion, \([18F]FDG\) PET had a sensitivity of 55.2\% [confidence interval (CI) = 36\%-73\%] and a specificity of 69\% (CI = 49\%-84\%). The positive predictive value was 64\% (CI = 42.6\%-81.2\%), and the negative predictive value was 60.6\% (CI = 42.2\%-76.5\%). On the other hand, \([11C]Acetate\) PET had a sensitivity of 93.1\% (CI = 75.8\%-98.8\%) and a specificity of 0\% (CI = 0\%-14.56\%). The positive predictive value was
48.2% (CI = 34.8%-61.8%), and the negative predictive value was 0% (CI = 0%-80.2%).

The survival analysis was based on the PET tracer uptake. For the [18F]FDG-avid patients (n = 25), the overall survival rates were 84% at 1 year, 61.9% at 3 years, and 46.4% at 5 years. For the [18F]FDG-negative patients (n = 33), the corresponding rates were 97%, 81.6%, and 81.6%. On the other hand, the [11C]acetate-avid patients (n = 56) had the following overall survival rates: 92.9% at 1 year, 73.6% at 3 years, and 65.4% at 5 years. The [11C]acetate-negative patients (n = 2) had a 1-year rate of 50% and a 3-year rate of 50%; their 5-year overall survival rate is not available yet (Fig. 1).

Table 3. Results of PET With the [18F]FDG and [11C]Acetate Tracers

| Characteristic                        | [18F]FDG Tracer |           | [11C]Acetate Tracer |           |
|--------------------------------------|-----------------|-----------|---------------------|-----------|
|                                      | Positive | Negative | P Value  | Positive | Negative | P Value  |
| ≤3 nodules (n)                       | 23       | 31       | 0.99     | 52       | 2        | 0.99     |
| >3 nodules (n)                       | 2        | 2        |          | 4        | 0        |          |
| Tumor size ≤ 5 cm (n)                | 7        | 22       | 0.008    | 28       | 1        | 0.99     |
| Tumor size > 5 cm (n)                | 18       | 11       |          | 28       | 1        |          |
| Negative for microvascular invasion (n) | 9        | 20       | 0.06     | 29       | 0        | 0.47     |
| Positive for microvascular invasion (n) | 16       | 13       | 0.75     | 27       | 2        | 0.40     |
| Microsatellite lesions (n)           | 3        | 2        | 0.16     | 4        | 1        | 0.51     |
| Poorly differentiated HCC (n)        | 8        | 4        |          | 11       | 1        |          |

The [18F]FDG-avid patients (n = 25) had the following disease-free survival rates: 62.5% at 1 year, 49.2% at 3 years, and 49.2% at 5 years. For the [18F]FDG-negative patients (n = 33), the corresponding rates were 72.7%, 65.5%, and 39.3%. On the other hand, the [11C]acetate-avid patients (n = 56) had the following disease-free survival rates: 69.1% at 1 year, 58.6% at 3 years, and 52.1% at 5 years. The [11C]acetate-negative patients (n = 2) had a 1-year rate of 50% and a 3-year rate of 50% (Fig. 2).

Six of the 16 LT patients were [18F]FDG-avid, and they had the following overall survival rates: 100% at 1 year, 60% at 3 years, and 60% at 5 years. The [18F]FDG-negative patients (n = 10) had a 1-year rate of 100% and a 3-year rate of 100%. On the other hand, the [11C]acetate-avid patients (n = 15) had the following overall survival rates: 100% at 1 year, 77.8% at 3 years, and 77.8% at 5 years. The 1- and 3-year overall survival rates for the [11C]acetate-negative patient were both 100% (Fig. 3).

The disease-free survival rates for the [18F]FDG-avid patients who underwent LT (n = 6) were as follows: 83.3% at 1 year, 66.7% at 3 years, and 66.7% at 5 years. The [18F]FDG-negative patients (n = 10) had a 1-year rate of 100% and a 3-year rate of 100%. On the other hand, the [11C]acetate-avid patients (n = 15) had the following rates: 93.3% at 1 year, 86.7% at 3 years, and 86.7% at 5 years. The 1- and 3-year rates for the [11C]acetate-negative patient were both 100% (Fig. 4).

DISCUSSION

HCC is one of the commonest cancers in the world, especially in populations in which hepatitis B or C is prevalent. Multidisciplinary approaches to the diagnosis of HCC include the use of contrast

**Figure 1.** Overall survival of all patients.

**Figure 2.** Disease-free survival of all patients.
ultrasonography, high-resolution contrast computed tomography, and magnetic resonance imaging. These tools enable better detection of HCC.\textsuperscript{21-24} Early detection of the disease allows more patients to undergo curative treatments such as ablation surgery, hepatectomy, and LT and to obtain better survival results.

LT, the ultimate solution to HCC and cirrhosis, has significant risks for recipients and involves complicated calculations for organ allocation. Because of the serious scarcity of liver grafts, no effort is spared in ensuring that grafts are allocated in the fairest and most beneficial way possible. The Milan criteria are a good model for patient selection. In addition to a large tumor size and a large number of tumors, major vascular invasion is also considered a risk factor for poor surgical outcomes.\textsuperscript{25,26} Macrovascular invasion, which can easily be revealed by computed tomography, magnetic resonance imaging, or even ultrasonography, has been associated with a median survival period of less than 3 months. Microvascular invasion is also associated with poor survival outcomes. It has been shown to be an independent factor for HCC recurrence and to affect patient survival after hepatectomy.\textsuperscript{11,12,26} Although a histopathological examination of the whole HCC specimen is most accurate for diagnosing microvascular invasion, an accurate model for preoperative predictions is crucially important.

The use of fine-needle biopsy is always debatable. It is not widely recommended as a routine practice for predicting microvascular invasion for 2 reasons. First, it poses the risks of tumor seeding and hemorrhaging for patients with severe cirrhosis, who have compromised immunity. Second, its diagnostic accuracy is poor, especially for patients with a heterogeneous pattern of HCC differentiation.\textsuperscript{27,28} \textsuperscript{\textsuperscript{\textsuperscript{\textsuperscript{[18F]FDG PET}}}\textsuperscript{\textsuperscript{is also used for preoperative predictions. As a noninvasive tool, it makes use of the specific cellular glucose mechanism of HCC. Normal liver cells contain a large amount of glucose-6-phosphatase and a lower level of hexokinase, but this enzyme ratio is reversed for tumor cells in general. This disparity enables the accumulation of \textsuperscript{[18F]FDG inside HCC and other metastatic liver tumors but not inside normal liver parenchymal cells. This makes \textsuperscript{[18F]FDG PET a useful noninvasive tool for the diagnosis of HCC. It is part of the preoperative workup protocol for LT in Asia.\textsuperscript{29} However, it is not an ideal investigation modality because of its low sensitivity. Its sensitivity for HCC ranges from 50% to 55%.\textsuperscript{29-33} The low detection rate is due to the differences in the differentiation of assorted HCCs. Well-differentiated HCC cells demonstrate an \textsuperscript{[18F]FDG pattern similar to that displayed by normal liver parenchymal cells, whereas poorly differentiated HCC cells do not. The fact that well-differentiated HCC is not \textsuperscript{[18F]FDG-avid makes the detection of tumor cells difficult. Hence, a method capable of detecting a wide spectrum of HCCs is desirable.

In this study, we tried to overcome the problem of the low sensitivity of \textsuperscript{[18F]FDG PET by using \textsuperscript{[11C]Acetate as an additional tracer. According to a study by Yoshimoto et al.,\textsuperscript{34} \textsuperscript{[11C]Acetate is incorporated into membrane lipids in tumor cells, and this makes tumor detection possible. A recent study by Yun et al.\textsuperscript{35} found that acetyl coenzyme A synthetase, an enzyme involved in the conversion of acetate to acetyl coenzyme A, is elevated in well-differentiated HCC during acetate-dependent lipid synthesis. In our study, \textsuperscript{[11C]Acetate PET detected nearly the whole population of HCCs (56 of 58 patients). The sensitivity of single-tracer PET (\textsuperscript{[18F]FDG) was 43%, whereas the sensitivity of dual-tracer PET (\textsuperscript{[18F]FDG and \textsuperscript{[11C]Acetate) was 93%; a considerable increase was observed. However, \textsuperscript{[11C]Acetate was too sensitive to HCC for differentiating between poor prognostic factors because HCCs were also found to be \textsuperscript{[11C]Acetate-avid in patients with less aggressive tumor biology. Two patients had \textsuperscript{[11C]Acetate-negative HCCs. One underwent transarterial chemoembolization as a neoadjuvant treatment.
before surgery, and the other had a lesion smaller than 1 cm. The effect of neoadjuvant treatments on \[^{11}C\]acetate uptake requires further investigation, and the detection of tumors smaller than 1 cm remains a problem for clinicians. Dual-tracer PET may not solve the problem of the detection of very small tumors.

\[^{18}F\]FDG PET has been demonstrated to be useful for the prediction of microvascular permeation, which is a condition reflecting the aggressiveness of a tumor and predicting a poor surgical outcome.\(^{13,29}\) In this study, the tracers \[^{18}F\]FDG and \[^{11}C\]acetate were used to determine poor prognostic indicators for HCC recurrence; these included large tumors, a large number of tumors, an advanced stage of disease, the presence of microsatellite lesion, and the presence of microvascular invasion. Although no statistical significance was found in terms of tumor grade differentiation or microsatellite lesions, \[^{18}F\]FDG PET was effective in the prediction of microvascular invasion. However, our sample size was very small when we divided our patients into resection and transplant cases, and when we considered \[^{18}F\]FDG-avid cases versus \[^{18}F\]FDG-negative cases, the statistical significance was only marginal for predicting microvascular invasion with \[^{18}F\]FDG PET. A large sample size is needed for a better demonstration. In comparison with \[^{11}C\]acetate PET, \[^{18}F\]FDG PET demonstrated a higher SUV when there was microvascular invasion (Fig. 5). Sixteen of the 29 patients who had microvascular invasion were \[^{18}F\]FDG-avid, and this led to a sensitivity of 55.2% and a specificity of 69%. 27 patients were \[^{11}C\]acetate-avid, and this led to a sensitivity of 93.1% and a specificity of 0%. In addition to microvascular invasion, \[^{18}F\]FDG PET was also good at predicting advanced-stage HCC. Its sensitivity for stage IV HCC was 45%.

Only 2 patients were \[^{11}C\]acetate-negative (1 underwent partial hepatectomy, and 1 underwent LT), and this makes the interpretation of their poor survival difficult. The \[^{11}C\]acetate-negative patient who underwent partial hepatectomy died of bleeding esophageal varices. The \[^{18}F\]FDG-avid patients appeared to have poorer overall survival and disease-free survival in comparison with the \[^{18}F\]FDG-negative patients, and this may coincide with the prediction of microvascular invasion; however, the difference in survival was not statistically significant.

PET with \[^{18}F\]FDG and \[^{11}C\]acetate as dual tracers is a useful tool in the pre-LT workup: it provides an accurate prediction of the pathological staging of HCC in

![Figure 5. \[^{18}F\]FDG PET demonstrates a higher SUV than \[^{11}C\]acetate PET when there is microvascular invasion.](image)
terms of the Milan criteria because of the high sensitivity of $[^{11}C]$acetate and detects microvascular invasion with $[^{18}F]$FDG. It also provides more information about the number of tumors, the tumor behavior, and the probability of microvascular invasion before LT. This information is particularly important for patients with an HCC status beyond the Milan criteria. Kornberg et al. reported a 3-year disease-free survival rate of 80% for such patients who also had PET scan results that were not $[^{18}F]$FDG-avid, whereas those with $[^{18}F]$FDG-avid results had a 3-year disease-free survival rate of only 35%. LT for advanced HCC is feasible for a particular subgroup of patients, and PET scanning with suitable tracers enables better patient selection for LT.

This study has shown that $[^{18}F]$FDG PET before LT can be used to predict HCC with microvascular invasion, and the addition of $[^{11}C]$acetate improves the overall sensitivity of PET but does not improve the prediction of microvascular invasion. These findings are consistent with the previous observation that a more aggressive pathology tends to be more dedifferentiated and is more often detected by $[^{18}F]$FDG. The use of dual-tracer PET deserves to be considered, especially when patients with an HCC status beyond the Milan criteria are being selected for LT.

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