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## Nuclear imaging for functional evaluation and theragnosis in liver malignancy and transplantation

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### Abstract

Currently, nuclear imaging such as positron emission tomography (PET) and single photon emission computed tomography (SPECT) is increasingly used in the management of liver malignancy. <sup>18</sup>F-fluorodeoxyglucose (FDG)-PET is the most widely used nuclear imaging in liver malignancy as in other cancers, and has been reported to be effective in diagnosis, response monitoring, recurrence evaluation, and prognosis prediction. Other PET imaging such as <sup>11</sup>C-acetate PET is also used complementarily to FDG-PET in diagnosis of liver malignancy. Additionally, image-based evaluation of regional hepatic function can be performed using nuclear imaging. Those imaging modalities are also effective for candidate selection, treatment planning, and perioperative evaluation in liver surgery and transplantation. Recently, nuclear imaging has been actively adopted in the transarterial radioembolization therapy of liver malignancy, according to the concept of theragnosis. With the development of new hybrid imaging technologies such as PET/magnetic resonance imaging and SPECT/CT, nuclear imaging is expected to be more useful in the management of liver malignancy, particu-

larly regarding liver surgery and transplantation. In this review, the efficacy and roles of nuclear imaging methods in diagnosis, transplantation and theragnosis are discussed.

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**Key words:** Nuclear imaging; Liver malignancy; Transplantation; Positron emission tomography-computed tomography; Theragnosis

**Core tip:** Nuclear imaging methods including single photon emission computed tomography (SPECT) and positron emission tomography (PET) are increasingly being used in the management of liver malignancy. In this review, the efficacy and clinical role of nuclear imaging methods are discussed with regard to fluorodeoxyglucose PET and other PET or SPECT imaging methods. In particular, the application of nuclear imaging for theragnosis and surgical intervention including transplantation is discussed in detail. This review may be helpful for understanding current trends of nuclear imaging for liver malignancy.

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### INTRODUCTION

Liver cancer is one of the leading causes of cancer death; particularly in men and developing countries. In 2008, the worldwide incidence and the number of deaths from liver cancer were estimated to be 748300 and 695900,

respectively<sup>[1]</sup>. Additionally, the liver is a frequent metastatic site of almost all cancers, and metastatic liver cancer is much more common than primary liver cancer<sup>[2]</sup>.

For primary liver cancer, the curative treatment is surgical resection and/or interventional treatment when the disease is in an early stage. Thus, early diagnosis, accurate staging, and appropriate evaluation of tumor characteristics are of utmost importance to cure the disease. In case of unresectable disease, liver transplantation can be another option for cure if the tumor is confined to the liver. However, because donor organ supply is limited, adequate recipients should be selected meticulously; currently the Milan criteria are most commonly used for candidate selection in liver transplantation<sup>[3]</sup>. In addition to accurate diagnosis and staging, pre- and postoperative functional evaluations are also required for successful transplantation.

In diagnosis and evaluation of liver malignancy, ultrasonography (USG) and computed tomography (CT) have been widely used as conventional imaging modalities, and recently, magnetic resonance imaging (MRI) is increasingly used with a strength of high image contrast in the soft tissue. These imaging methods are based on structural changes, and can show mass lesions in primary or metastatic sites. In contrast, nuclear imaging methods including gamma camera scanning, single photon emission computed tomography (SPECT), and positron emission tomography (PET) target specific physiological or molecular processes, and can show functional and biological features such as hepatobiliary function, viability, and metabolic activity of tumors.

Currently, <sup>18</sup>F-fluorodeoxyglucose (FDG)-PET is the most widely used nuclear imaging for management of liver malignancy. FDG-PET shows cellular glucose metabolism, which is usually enhanced in malignant tissues, and it can be used for sensitive detection and characterization of tumors. Additionally, FDG-PET can cover the whole body with a single scan, therefore, it is valuable in detection of metastatic lesions throughout the body. As well as initial staging and characterization, FDG-PET is now widely used in response evaluation after transarterial chemoembolization (TACE), radiofrequency ablation (RFA) and chemotherapy. In addition to FDG, other imaging radiopharmaceuticals targeting fatty acid metabolism or nucleotide synthesis are also used in recent clinical practice for liver cancer.

Theranosis, another new field of nuclear imaging, is a recently suggested concept that means simultaneous diagnosis and therapy with a common mechanism. In liver cancer, transarterial radioembolization (TARE) or selective internal radiotherapy (SIRT) is an example of theranosis, in which SPECT or PET is directly used for planning treatment and evaluating response.

In this review, the clinical application of FDG and other PET imaging is discussed in terms of diagnostic efficacy in liver malignancy. Additionally, nuclear imaging is reviewed as a tool for candidate selection, and pre- and postoperative functional evaluation in liver surgery and

transplantation. The theragnostic application of nuclear imaging and therapy is also discussed briefly.

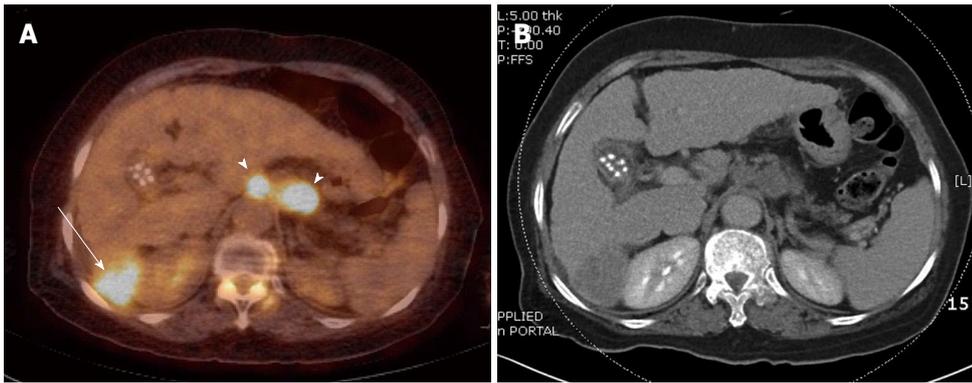
## FDG PET IN EVALUATION OF LIVER MALIGNANCY

### Principles of FDG PET

FDG is an analog of glucose that is labeled with <sup>18</sup>F. In actively growing tumor cells, glucose metabolism is enhanced under various conditions, which is known as the Warburg effect. FDG is taken up by cells with the same mechanism as that of glucose, depending on glucose transporters and hexokinases. FDG that is not taken up by cells is rapidly removed by renal excretion<sup>[4]</sup>. In addition to this biological decay, <sup>18</sup>F decays physically with a half-life of 110 min. Thus, effective radiation doses from routine FDG-PET do not exceed 10 mSv, even with a combined low-dose CT scan. The radiation dose from FDG-PET/CT is usually not higher than that from a single whole-body diagnostic CT scan<sup>[5,6]</sup>. Also, FDG is a safe radiopharmaceutical that has caused no pharmacological adverse reaction in tens of thousands of cases of human administration<sup>[7]</sup>. As a result of the relatively long half-life of <sup>18</sup>F, FDG can be delivered to an imaging center without an on-site cyclotron, within 1 or 2 h distance. Currently, most PET scans are performed using hybrid PET/CT scanners. The combined CT scan can compensate for some weaknesses of isolated PET scans, and faster scan and accurate localization of lesions are available with the CT scan. PET/CT images can provide both functional and anatomical information in a single study.

One of the most important strengths of PET is that it can provide quantitative information on metabolism or molecular processes. Standardized uptake value (SUV) is the most widely used semi-quantitative parameter on FDG-PET. SUV is defined as the ratio of tissue radioactivity concentration and injected dose of radioactivity per kilogram of the patient's body weight. Some researchers adopt corrections for body surface area or serum glucose level. SUV can be easily measured and is commonly used for evaluation of glucose metabolism of normal or cancer tissues. However, some studies have suggested that the tumor-to-normal liver ratio is a more effective parameter than SUV<sup>[8,9]</sup>, because FDG uptake is affected by underlying liver diseases or serum glucose level<sup>[10]</sup> and the ratio can reflect variations in liver glucose metabolism better than tumor SUV itself.

Despite the many advantages, FDG-PET also has some limitations in liver imaging. First of all, the liver is involved in the physiological glucose metabolism and normally shows considerable FDG uptake. The SUV of normal liver on FDG-PET is 2.0-3.0, which may interfere with detection of some tumors that have low glucose metabolism. Additionally, the liver is adjacent to the diaphragm and the liver dome area is prone to motion artifacts caused by breathing or swallowing.



**Figure 1**  $^{18}\text{F}$ -fluorodeoxyglucose-positron emission tomography in hepatocellular carcinoma.  $^{18}\text{F}$ -fluorodeoxyglucose-positron emission tomography/computed tomography (CT) fusion (A) and CT (B) images show hot uptake in the primary lesion (arrow) in the right lobe of the liver and regional lymph node metastases (arrowhead).

### FDG-PET in hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the most common primary liver malignancy. FDG-PET is effective in differential diagnosis between malignant and benign liver lesions such as hepatic adenoma, hamartoma, hemangioma, and nodular hyperplasia<sup>[11,12]</sup>. However, the sensitivity of FDG-PET in diagnosis of primary HCC is relatively limited and has been reported to be 50%-70%; particularly in small tumors<sup>[11,13,14]</sup>. In one of these studies, detection rate was as low as 27.2% for tumors of <2 cm and 47.8% for those of 2-5 cm<sup>[13]</sup>. One probable cause is the relatively high background uptake in the normal liver. Another cause is speculated to be glucose-6-phosphatase, which is highly expressed in HCC cells as well as normal hepatic cells, because dephosphorylation by glucose-6-phosphatase enables FDG to escape from cells. However, FDG uptake depends on malignancy grade of HCC; poorly differentiated HCC showed higher SUV and SUV ratio than moderately or well-differentiated HCC<sup>[9]</sup>. Thus, FDG-PET should be considered not only for lesion detection, but also for characterization or prognosis prediction. FDG-PET is also related to other characteristics of tumor phenotypes such as P-glycoprotein expression or aggressive biological properties<sup>[9,15]</sup>.

Despite relatively low sensitivities for primary liver lesions, FDG-PET plays an important role in finding extrahepatic or distant metastasis (Figure 1). A recent meta-analysis reported that PET or PET/CT has notable performances in diagnosis of extrahepatic metastasis or recurrent lesions of HCC<sup>[16]</sup>. In this meta-analysis, pooled sensitivity and specificity for metastasis were 76.6% and 98.0%, and those for recurrent lesions were 81.7% and 88.9%, respectively. Although PET has a lower sensitivity than CT in detection of small (<1 cm) lung metastasis<sup>[17]</sup>, PET is superior to other imaging modalities in detection of extrahepatic lesions, particularly bone lesions<sup>[18]</sup>.

Selective local treatments are widely performed for unresectable HCCs, along with chemotherapy. In planning of treatment, response evaluation is crucial for adequate selection of treatment methods. Currently used criteria in HCC are the modified Response Evaluation

Criteria in Solid Tumors (RECIST)<sup>[19]</sup>, and the European Association for the Study of the Liver criteria<sup>[20]</sup>, which depend on measurements of size or enhancing portion on contrast CT. However, FDG-PET has advantages in the evaluation of treatment response, in that it can reflect metabolic activity of cancer cells and is less affected by structural distortion after treatment than CT. Torizuka *et al*<sup>[21]</sup> reported that FDG uptake is increased in viable HCC tissue, whereas it is decreased or absent in the necrotic tissue in >90% of cases.

Thus, FDG-PET can be used with high efficacy to detect residual or recurrent lesions. Kim *et al*<sup>[22]</sup> reported that sensitivity, specificity and accuracy of FDG PET/CT were 87.5%, 71.4%, and 80.0%, respectively, in evaluation of residual disease 1 mo after interventional therapy. In another study, diagnostic sensitivity and specificity were 100% and 63%, for residual lesions 3 mo after TACE<sup>[23]</sup>. Paudyal *et al*<sup>[24]</sup> reported that FDG-PET detected recurrence after RFA at least 4 mo earlier than CT in 33% of patients. In their study, overall detection rate of recurrence on FDG-PET was 92%, which was higher than 75% for CT. As a result, FDG-PET could change management plans in 18%-28% of HCC patients<sup>[25,26]</sup>. Additionally, pretreatment FDG-PET *per se* is an effective prognostic predictor for treatment response in HCC. Song *et al*<sup>[8]</sup> have reported that SUV ratio measured on pretreatment FDG-PET/CT is an independent predictor of response to TACE in patient with intermediate-stage HCC. Lee *et al*<sup>[27]</sup> have reported that HCC patients with lower SUV (maximum SUV <5.0) on FDG-PET showed longer overall and progression-free survival than those with higher SUV, after sorafenib treatment. Intriguingly, Kucuk *et al*<sup>[28]</sup> have reported a longer progression-free survival rate in HCC patients with higher FDG uptake, in TARE treatment with  $^{90}\text{Y}$ .

### FDG-PET in cholangiocarcinoma

Cholangiocarcinoma (CCA) is the second most common hepatobiliary malignancy. Prognosis of CCA is generally poor because of difficulty in early diagnosis, delayed clinical manifestation and lack of effective non-surgical therapeutic options.

In diagnosis of bile duct cancer, sensitivity, specificity and accuracy of FDG-PET were reported to be 92.3%, 92.9%, and 92.6%, respectively<sup>[29]</sup>. In another study, a maximum SUV of 3.9 was suggested as a cutoff for differential diagnosis between CCA and primary sclerosing cholangitis, and sensitivity, specificity, and accuracy were reported to be 94%, 83%, and 91%, respectively<sup>[30]</sup>. However, in contrast to intrahepatic CCA, diagnostic sensitivities of FDG-PET were relatively low in extrahepatic CCA, for which MRI or magnetic resonance cholangiopancreatography was more effective than FDG-PET/CT<sup>[31-33]</sup>; probably due to small tumor size and uptake in adjacent organs such as the small bowel. The detection of regional lymph node metastasis in CCA by FDG-PET also depends on size and metastatic tumor burden, thus demonstrating different results according to the stage. The sensitivity of FDG-PET for regional lymph node metastasis was 11.7%-31.6% in the resectable stage and 82.1% in the advanced stage. However, the specificity of FDG-PET was as high as 88.2%-96.4%<sup>[31-33]</sup>.

One strength of FDG-PET/CT is the diagnosis of metastasis in CCA. The accuracy of PET/CT for distant metastasis was reported to be 88.3%-100%, which was superior to that of CT<sup>[31-34]</sup>. With high diagnostic performances, FDG-PET/CT findings changed management plans in 16%-20% of cases deemed resectable after conventional imaging studies<sup>[31,33,35]</sup>.

### FDG-PET in metastatic liver malignancy

Liver metastasis is from many types of malignancies such as colorectal, stomach, breast and lung cancers, and is often found incidentally on FDG-PET during staging work-up. A meta-analysis revealed that FDG-PET is more sensitive than USG and CT for detection of liver metastasis from gastrointestinal cancers<sup>[36]</sup>. Another meta-analysis including 39 studies, in which diagnostic performances of FDG-PET for liver metastasis from colorectal cancers were analyzed, reported sensitivities of CT, MRI and PET as 83.6%, 88.2% and 94.1%, respectively<sup>[37]</sup>. Additionally, PET/CT had a higher sensitivity and specificity (96.5% and 97.2%, respectively) than PET alone.

In colorectal cancers, isolated liver metastasis is a candidate for curative metastasectomy that can benefit long-term prognosis<sup>[38]</sup>. Thus, appropriate selection of resectable liver metastasis is of crucial importance for appropriate treatment and reducing unnecessary surgical procedures. Selzner *et al.*<sup>[39]</sup> have reported that PET/CT is superior to contrast-enhanced CT for detection of local recurrences, and intra- and extrahepatic metastases in colorectal cancer patients who are candidates for liver metastasectomy. It has also been reported that adding FDG-PET/CT to the routine assessment of patients with liver metastases changes therapeutic plans in 28%-34% of cases by changing disease stage<sup>[40,41]</sup>. Eventually, patients with liver metastasis who were preoperatively screened by FDG PET/CT had a longer 5-year

survival rate (58%) than patients who were not screened (30%)<sup>[38]</sup>. Thus, FDG-PET/CT is recommended by several guidelines as an appropriate and necessary imaging tool for initial staging of colorectal cancers<sup>[42,43]</sup>.

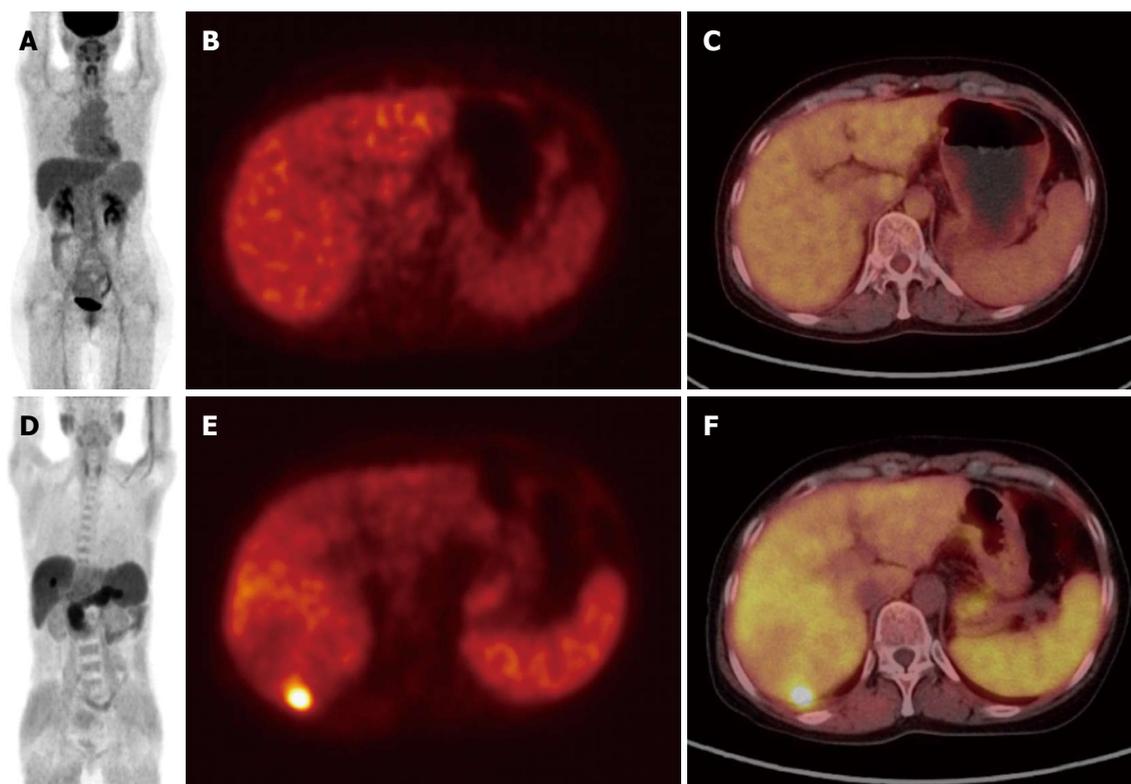
FDG-PET is also effective for early response monitoring and follow-up after selective local treatment of liver metastasis. FDG-PET is reported to be more accurate for evaluation of treatment response and able to detect local relapse earlier than CT in RFA treatment of liver metastases<sup>[44,45]</sup>. Also in TARE, response evaluated by FDG-PET/CT is well correlated with changes in tumor markers and progression-free survival, whereas RECIST and tumor density criteria are not<sup>[46]</sup>. Haug *et al.*<sup>[47]</sup> have reported that the change in maximal SUV at 3 mo after TARE is an independent prognostic factor in patients with liver metastasis from breast cancer. Regarding chemotherapy, Findlay *et al.*<sup>[48]</sup> have reported that FDG-PET can be used for early response evaluation; > 15% reduction in tumor-to-liver ratio at 4-5 wk after chemotherapy was able to discriminate response from non-response with 100% sensitivity and 75% specificity. Parameters on metabolic volume have been widely investigated in evaluation of chemotherapeutic response. In a recent study, metabolic tumor volume and total lesion glycolysis measured on FDG-PET were shown to be effective in response evaluation<sup>[49]</sup>. However, it should be noted that sensitivity of FDG-PET is limited for small lesions with low uptake, particularly within 1 wk after chemotherapy<sup>[50-52]</sup>.

## OTHER PET TRACERS AND NOVEL INSTRUMENTS FOR LIVER MALIGNANCY

Although FDG-PET is widely used in management of liver malignancy, the sensitivity of FDG-PET is limited because of relatively high background uptake in normal liver tissue. Additionally, FDG uptake is often lower in well-differentiated HCC. Thus, several alternative PET imaging agents have been tried in imaging of liver malignancy, including <sup>11</sup>C-acetate, <sup>11</sup>C-choline, <sup>18</sup>F-choline and <sup>18</sup>F-fluorothymidine (FLT).

### PET tracers other than FDG

Acetate is a metabolic substance used for fatty acid synthesis and energy production *via* the Krebs cycle<sup>[53,54]</sup>. <sup>11</sup>C-Acetate PET is approved for human use in many countries including the United States, European Union, and South Korea, and used for tumor imaging in various cancers including HCC, although establishment of an on-site cyclotron is required for use of <sup>11</sup>C that has a short half-life of 20 min. In HCC, the uptake ratio between the lesion and the normal liver is usually much higher on <sup>11</sup>C-acetate PET than on FDG-PET (Figure 2). Ho *et al.*<sup>[55]</sup> have reported that <sup>11</sup>C-acetate PET is more sensitive than FDG-PET for detection of HCC, particularly well-differentiated HCC. Intriguingly, uptake of <sup>11</sup>C-acetate is not as high in CCA and metastatic liver tumors as in HCC, and thus, <sup>11</sup>C-acetate PET is suggested as a



**Figure 2**  $^{18}\text{F}$ -fluorodeoxyglucose and  $^{11}\text{C}$ -acetate positron emission tomography in hepatocellular carcinoma. In a patient with HCC, maximal intensity projection (A), PET (B), and PET/CT fusion (C) images of  $^{18}\text{F}$ -fluorodeoxyglucose-PET does not show a lesion of hot uptake. However, the same image set of  $^{11}\text{C}$ -acetate PET (D-F) shows hot uptake in the S7 segment of the liver. PET: Positron emission tomography; HCC: Hepatocellular carcinoma; CT: Computed tomography.

complementary imaging method to FDG-PET in well-differentiated HCC.  $^{11}\text{C}$ -Acetate PET has also been reported to have a higher sensitivity than FDG-PET in detection of bone metastasis from HCC (93% and 62%, respectively)<sup>[56]</sup>.

As a result of differences between FDG and  $^{11}\text{C}$ -acetate in effective half-life and metabolic characteristics, dual-tracer PET/CT that uses both FDG and  $^{11}\text{C}$ -acetate was suggested to be more accurate in imaging of HCC. A prospective study reported the overall sensitivity of dual-tracer PET/CT was 82.7% in primary HCC<sup>[13]</sup>. Additionally, sensitivity and specificity of dual-tracer PET/CT were significantly higher (96.8% and 91.7%, respectively) than those of contrast CT (41.9% and 33.0%, respectively), in selection of candidates for liver transplantation<sup>[57]</sup>.

Choline is one of the essential components of phospholipids in the cellular membrane, and metabolism and uptake of choline are increased in actively proliferating tumor cells. As well as  $^{11}\text{C}$ -choline, several  $^{18}\text{F}$ -labeled choline analogs such as  $^{18}\text{F}$ -fluorocholine,  $^{18}\text{F}$ -fluoroethylcholine and  $^{18}\text{F}$ -fluoromethylcholine are used for clinical imaging of choline metabolism. These  $^{18}\text{F}$ -labeled tracers have longer half-lives and are more easily accessible in clinical practice<sup>[58]</sup>. A prospective study with  $^{18}\text{F}$ -fluorocholine PET in patients with chronic liver disease reported an overall sensitivity of 84% for HCC (including well-differentiated type), which was significantly higher than that of FDG (67%)<sup>[59]</sup>. Intriguingly, some HCCs presented as a photopenic pattern on choline PET, and

both hyper- and hypometabolic lesions may be regarded as positive results. A pilot study reported that HCC with a photopenic pattern on  $^{18}\text{F}$ -fluorocholine PET was associated with the presence of microvascular invasion, high FDG uptake, and early recurrence after surgical resection, resulting in poor prognosis<sup>[60]</sup>. However, HCC with a photopenic pattern may be an obstacle in differential diagnosis between HCC and benign liver lesions. In a recent study, mean SUV ratios were 1.68 for focal nodular hyperplasia and 0.88 for hepatocellular adenoma<sup>[61]</sup>.

$^{18}\text{F}$ -FLT is an analog of thymidine. FLT-PET is used for imaging of cellular proliferation, reflecting DNA synthesis. Although FLT-PET is effective in many cancers, its efficacy is limited in liver malignancy due to high physiological uptake in the normal liver. A pilot study reported higher FLT uptake than surrounding liver tissue in 11 of 16 HCC cases (69%), which was related to a proliferation marker, MIB-1<sup>[62]</sup>. However, in liver metastases of colorectal cancer, only 11 of 32 cases (34%) were discernible on FLT-PET<sup>[63]</sup>.

#### PET/MRI

PET/MRI is a recently developed hybrid imaging instrument that can provide both PET and MRI images simultaneously. MRI has excellent image contrast in the soft tissue including the liver, and shows a high diagnostic performance for liver malignancy using liver-specific contrast materials and diffusion-weighted imaging, particularly in small lesions<sup>[64,65]</sup>. The hybrid images of

PET/MRI can yield benefits from the strengths of both PET and MRI, which are perfectly co-registered to each other. Thus, PET/MRI has potential for imaging of liver malignancy.

Several studies have investigated the efficacy of software-based image fusion between PET and MRI. One study reported that fusion images of FDG-PET/CT and MRI had a high sensitivity (93%) and specificity (87%-97%) for liver malignancy<sup>[66]</sup>. Recently, some clinical hybrid PET/MRI scanners became commercially available and results of initial studies on PET/MRI have been reported. PET/MRI provided better diagnostic confidence than PET/CT for both benign and malignant liver lesions<sup>[67]</sup>. Additionally, MRI can provide various information using different imaging sequences; diffusion-weighted imaging was reported to be related to histological grade of tumor, and dynamic contrast-enhancement imaging, to tumor viability<sup>[68,69]</sup>. The information from MRI combined with metabolic information from PET could be new imaging biomarker profiles for tumor characterization.

However, attenuation correction is performed by MRI-based methods in PET/MRI scanners, and there is a concern about the difference in SUV between PET/CT and PET/MRI<sup>[70,71]</sup>. Further studies are required to investigate quantitation methods for clinical application of PET/MRI in conjunction with PET/CT.

## IMAGING IN LIVER SURGERY AND TRANSPLANTATION

### FDG-PET in liver transplantation

Liver transplantation is the best curative option in early but unresectable liver malignancy. However, because of limited sources of donor organs, careful candidate selection is of paramount importance. Currently, the Milan or University of California San Francisco criteria are widely used for candidate selection<sup>[3,72]</sup>, in which size and number of tumors are considered. They are based on the concept that a lower tumor burden is related to lower probability of recurrence and better prognosis. However, size and number of tumors are not perfect markers for the tumor burden, and errors may exist in preoperative measurement of tumors on conventional CT.

FDG-PET has been used in pretransplantation evaluation of liver malignancy to detect extrahepatic metastases. Additionally, FDG-PET can show the metabolic activity of the primary liver lesion, which is related to the prognosis and tumor recurrence after transplantation. In a recent study, tumor-to-normal liver SUV ratio on preoperative FDG-PET was reported to be an independent and significant prognostic factor for tumor recurrence and survival in liver transplantation for HCC<sup>[73]</sup>. This agrees with the result that non-FDG-avid HCC showed a significantly lower rate of microvascular invasion, lower recurrence rate, and better 3-year recurrence-free survival (11.5%, 3.8% and 93%, respectively) than FDG-avid HCC (87.5%, 50% and 35%, respectively)<sup>[74]</sup>.

In another study, even in cases exceeding the Milan criteria, the 5-year recurrence-free survival rate of patients with non-FDG-avid HCC was comparable (81%) to that of patients with tumors meeting the Milan criteria (81% and 86.2%, respectively)<sup>[75]</sup>. Pant *et al*<sup>[76]</sup> also have reported that patients with non-FDG-avid HCC largely had lower-stage disease and could be candidates for curative surgical resection and liver transplantation, whereas the majority of patients with FDG-avid HCC had advanced-stage disease, with a higher chance of metastases and vascular invasion. Similar results were reported in hilar CCA; patients with non-FDG-avid CCA had a significantly lower recurrence rate and higher 2-year recurrence-free survival rate after liver transplantation than patients with FDG-avid CCA<sup>[77]</sup>. Thus, FDG-PET can be recommended as an essential imaging modality for preoperative evaluation of liver transplantation.

In postoperative follow-up of liver transplantation, FDG-PET can also be used for detection of recurrence, although there is some limitation in detection of small lesions including intrahepatic and brain metastases<sup>[78]</sup>. Additionally, FDG-PET is effective for diagnosis of post-transplant lymphoproliferative disorder (PTLD). PTLD is the second most common malignancy in adult transplant recipients, and has a very high mortality rate of 50%. Despite a small number of subject cases, several studies reported that FDG-PET/CT may be a useful tool for detection, diagnosis, staging and therapy monitoring of PTLD<sup>[79,80]</sup>.

### Image-based evaluation of hepatic function

In liver malignancy, radical treatment often requires extensive resection, which may impair hepatic function. In liver transplantation, resectability of tumor and feasibility of a living donor should be determined based on hepatic function. Thus, preoperative and postoperative residual hepatic function needs to be meticulously evaluated to prevent postoperative hepatic failure. Nuclear imaging can be used for image-based evaluation of liver function.

<sup>99m</sup>Tc-labeled galactosyl human serum albumin (<sup>99m</sup>Tc-GSA) is a radiopharmaceutical that targets asialoglycoprotein receptor of hepatocytes. <sup>99m</sup>Tc-GSA scanning can provide valuable parameters for determining hepatic functional reserve, which demonstrated a good relationship with other parameters of liver function such as Child-Pugh classification, indocyanine green clearance, serum bilirubin, prothrombin time, and histology<sup>[81,82]</sup>. On <sup>99m</sup>Tc-GSA scanning, the ratio of the heart activities at 15 and 3 min after injection (HH15) is used as a parameter for blood clearance, and the ratio of the liver activity and liver plus heart activity at 15 min after injection (LHL15) is used as a parameter for hepatic uptake. In patients with liver cirrhosis, high LHL15 or low HH15 is related to high survival rate<sup>[82]</sup>.

Preoperatively measured LHL15 is reported to be related to postoperative complications after hepatectomy, with cutoff values of 0.875-0.90<sup>[83,84]</sup>. <sup>99m</sup>Tc-GSA scan-

ning can also be used for postoperative evaluation of hepatic function; LHL15 measured at 2 wk after transplantation is correlated with other functional parameters such as model for end-stage liver disease score and graft-to-recipient weight ratio<sup>[85]</sup>. The modified receptor index, which is calculated as LHL15/HH15, was lower in the partial hepatectomy group than the control group in patients with fatty liver<sup>[86]</sup>, reflecting residual hepatic function. In liver transplantation due to hepatitis, it is suggested that a decrease in the modified receptor index at 3 mo after transplantation could be assumed to be recurrent hepatitis affecting the graft<sup>[87]</sup>.

The most notable advantage of image-based functional evaluation is that it can assess regional function easily. On <sup>99m</sup>Tc-GSA scanning, regional functions can be assessed using separate regions of interest target areas. In a study on auxiliary partial orthotopic liver transplantation, in which the donor liver and residual native liver coexist, <sup>99m</sup>Tc-GSA scanning can be used for monitoring both donor and native liver function after transplantation<sup>[88]</sup>. Additionally, more accurate evaluation of regional function and functional volume is available with SPECT or SPECT/CT imaging. Hwang *et al.*<sup>[89]</sup> have reported that postoperative liver function and complications can be predicted using <sup>99m</sup>Tc-GSA dynamic SPECT in hepatectomy patients. <sup>99m</sup>Tc-GSA SPECT can also show hepatic function-volume relationship; functional recovery was reported to be more rapid than volumetric recovery after portal vein embolization or liver resection, in studies using <sup>99m</sup>Tc-GSA SPECT<sup>[90,91]</sup>.

### Imaging for hepatobiliary function

Hepatobiliary scanning has been used in clinical practice for several decades, using derivatives of <sup>99m</sup>Tc-labeled iminodiacetic acid (IDA) such as <sup>99m</sup>Tc-mebrofenin, <sup>99m</sup>Tc-dimethyl IDA and <sup>99m</sup>Tc-diisopropyl IDA. These radiotracers are transported into hepatocytes and go through the biliary system without being metabolized, and thus, hepatic excretion and biliary drainage can be visualized.

In liver transplantation, hepatobiliary scanning is used for diagnosis of postoperative biliary leakage or stricture, which is a frequent complication with incidences of 5%-32%<sup>[92]</sup>. Hepatobiliary scanning has a high specificity for diagnosis of post-transplantation biliary stricture, because passage of only a small amount of radiotracers can be visualized on the scan. In a study that investigated hepatobiliary scanning with regard to findings of endoscopic or percutaneous cholangiography, positive and negative predictive values were reported to be 92.6% and 22%, respectively<sup>[93]</sup>, which presumably resulted from difference in imaging sensitivities between the modalities. Dynamic hepatobiliary scanning may be useful for diagnosis of complications such as biliary obstruction in liver transplantation<sup>[94]</sup>.

Hepatobiliary scanning can also be used for evaluation of liver parenchymal function. On dynamic <sup>99m</sup>Tc-mebrofenin scanning, hepatic uptake rate expressed as

%/min was well correlated with indocyanine green clearance test and residual liver function after major liver surgery<sup>[95]</sup>. The cutoff value of future remnant liver function to prevent postoperative liver failure was suggested as 2.5-2.7 %/min per m<sup>2</sup> body surface area<sup>[96,97]</sup>.

SPECT and SPECT/CT are also helpful for hepatobiliary scanning. Radiotracers are dynamically excreted through the hepatobiliary system, therefore, SPECT images are acquired at around the peak time of hepatic time-activity curve, when the amount of radioactivity within the liver is relatively stable and well correlated with hepatic function<sup>[98]</sup>. Fusion images of SPECT/CT are expected to be better for regional assessment, with the aid of anatomical reference images of CT.

## THERAGNOSIS USING NUCLEAR IMAGING IN LIVER MALIGNANCY

### TARE as theragnosis

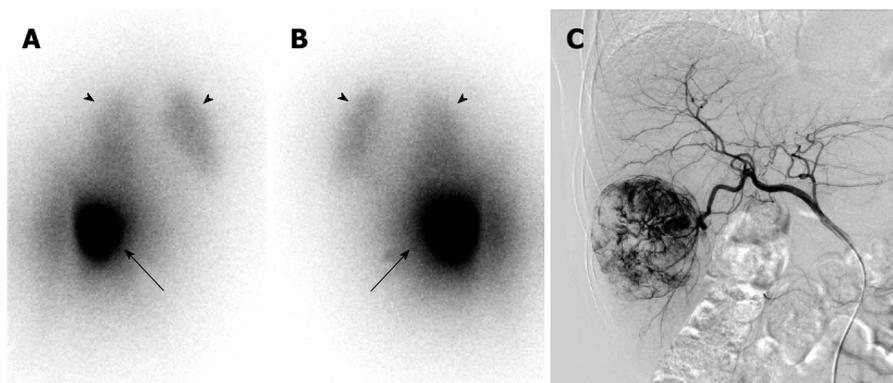
Theragnosis is a term coined from therapy and diagnosis, which means simultaneous diagnosis and therapy sharing a common mechanism. Cancer-targeting tracers that have both imaging and therapeutic moieties are a typical example of theragnosis. In liver malignancy, TARE or SIRT has been investigated for more than a decade, as an effective local treatment. TARE is performed with radiopharmaceuticals emitting therapeutic radiations. Additionally, nuclear imaging can be acquired using the radiations and used as a theragnosis for treatment planning and monitoring.

Currently, <sup>90</sup>Y and <sup>131</sup>I are widely used radioisotopes in TARE. Although <sup>131</sup>I emits  $\gamma$  as well as  $\beta$  rays and can be imaged using a gamma camera, <sup>90</sup>Y, more widely used than <sup>131</sup>I, does not emit  $\gamma$  rays. However, <sup>90</sup>Y can also be imaged using a gamma camera by the Bremsstrahlung X-ray, although image quality is relatively poor with it (Figure 3). Additionally, <sup>90</sup>Y emits a small amount of positrons and can be imaged using a PET scanner. The images acquired from a gamma camera or a PET scanner show distribution of the radiopharmaceuticals, and are used for dosimetry, efficacy monitoring, and planning of next treatment.

### Theragnosis using <sup>90</sup>Y-labeled microspheres

TARE can be considered in a patient with unresectable and hepatic artery-dominant primary or metastatic cancer, who has adequate general condition, preserved liver function, and a life expectancy of at least 3 mo. <sup>90</sup>Y-labeled microspheres are most widely used in clinical trials and practice of TARE. However, several other radiopharmaceuticals are also available for TARE, such as <sup>131</sup>I-lipiodol<sup>[99]</sup>, <sup>166</sup>Ho-chitosan, and <sup>188</sup>Re-lipiodol<sup>[100]</sup>.

<sup>90</sup>Y-labeled microspheres are usually made of resin or glass with sizes of 20-40  $\mu$ m, which enables optimal access into tumor preventing adverse effect by leakage through microcirculation. In addition to embolizing the tumor-feeding artery,  $\beta$  ray irradiation from injected mi-



**Figure 3** A Bremsstrahlung scan of  $^{90}\text{Y}$ -microsphere transarterial radioembolization. Anterior (A) and posterior (B) planar scan images show hot uptake (arrows) in the right lobe of the liver, which is well correlated with findings on angiography (C), in spite of relatively poor image quality with blurring. Some liver-to-lung shunt activities are shown in the lungs (arrowheads).

microspheres destroys tumors. Dosimetry is a great benefit of theragnosis imaging. Radiation doses of the normal liver parenchyme and tumor can be calculated using partition models or body surface area models, based on images that are acquired from pilot or previous treatment. Dosimetry results are used for treatment planning so that the radiation dose for the normal liver parenchyme does not exceed 35 Gy and that of the tumor exceeds 70 Gy<sup>[101]</sup>.

TARE with  $^{90}\text{Y}$ -labeled microspheres can be combined with other treatments. However, surgery immediately after TARE is recommended to be performed carefully considering the radiation safety for surgeons, although the risk of radiation exposure caused by a  $^{90}\text{Y}$  microsphere-administered patient is not high<sup>[102,103]</sup>. Additionally, discontinuation of antiangiogenic drugs such as sorafenib is recommended before pretreatment angiography, in order to avoid vascular complication and to optimize therapy.

Bremsstrahlung scanning and SPECT for  $^{90}\text{Y}$ -labeled microspheres are used for post-treatment imaging and confirmation of dose delivery. However, image quality of the Bremsstrahlung scan and SPECT is relatively poor and insufficient for quantitative analysis, although optimization of reconstruction algorithm has been attempted using a precalculated point-spread function of  $^{90}\text{Y}$ <sup>[104]</sup>. Recently, PET has been performed using positrons produced from minor decay branches of  $^{90}\text{Y}$ , which generate 32 electron-positron pairs per every 1 million decays of  $^{90}\text{Y}$ . As a result of a small branching fraction,  $^{90}\text{Y}$  PET has a limited image quality and requires long imaging time. However, with recent state-of-the-art PET scanners that have high sensitivity, high-quality  $^{90}\text{Y}$  PET images superior to those of Bremsstrahlung SPECT can be acquired<sup>[105]</sup>. More accurate measurements of tumor-absorbed dose and therapeutic response monitoring are provided by  $^{90}\text{Y}$  PET.

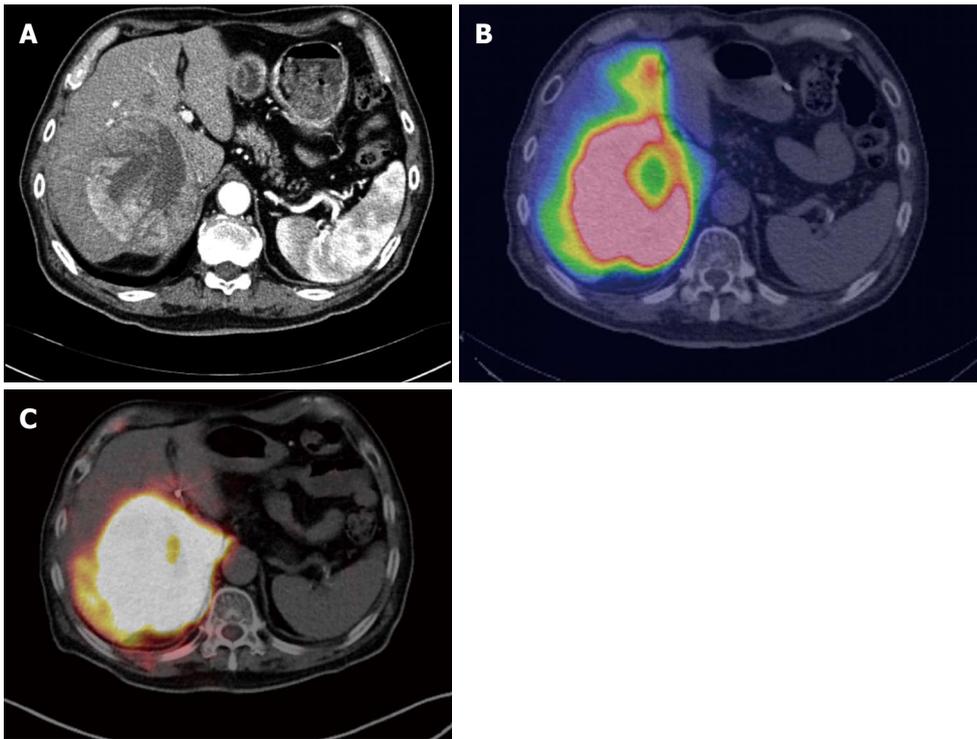
#### **Pretreatment planning and response monitoring in TARE**

In planning treatment with TARE,  $^{99\text{m}}\text{Tc}$ -labeled macro-

aggregated albumin ( $^{99\text{m}}\text{Tc}$ -MAA) scanning is obtained for simulation of microsphere distribution and dosimetry. The estimation from  $^{99\text{m}}\text{Tc}$ -MAA scanning may not always be same as that of therapeutic microspheres, because of differences in particle size, specific gravity, injected particle load, microembolic effects, placement of microcatheter tip, and regional blood flow change from prophylactic coil embolization of non-target arteries<sup>[106,107]</sup>. However,  $^{99\text{m}}\text{Tc}$ -MAA SPECT usually shows accurate registration with  $^{90}\text{Y}$  SPECT images<sup>[108,109]</sup>.

$^{99\text{m}}\text{Tc}$ -MAA scanning is effective for detecting unexpectedly leaked activity in the gastrointestinal tract, measuring the amount of liver-to-lung shunt, and even predicting treatment response and survival<sup>[110]</sup>. In case of abnormally high gastrointestinal activity, changing the position of the microcatheter tip and re-evaluation by  $^{99\text{m}}\text{Tc}$ -MAA scanning should be considered to minimize adverse effects on normal tissue. Furthermore, dose reduction of TARE or other treatment should be considered in patients with a large lung shunt, to prevent toxicity from systemic distribution of microspheres.  $^{99\text{m}}\text{Tc}$ -MAA SPECT or SPECT/CT provides more valuable information than that provided by planar scans because cross-sectional SPECT images can show more accurate regional distribution, particularly with SPECT/CT (Figure 4). Radioactivity measured on SPECT or SPECT/CT can also be used for elaborate calculation of radiation dose, using anatomically correct partition models.

Response to TARE has been variable because of subject heterogeneity, different time points, and different methods of assessment. A recent prospective study including 52 HCC patients reported response, disease control and complete response rates of 40.4%, 78.8% and 9.6%, respectively<sup>[111]</sup>. In another prospective multicenter phase II trial of TARE in chemorefractory liver-dominant metastatic colorectal cancer, disease was controlled in 48% of patients with a median survival of 12.6 mo<sup>[112]</sup>. FDG-PET is also used for monitoring response in TARE, and interval-decreased intrahepatic tumoral uptake on post-treatment FDG-PET suggests better prognosis and longer survival<sup>[146,47,113]</sup>.



**Figure 4** Pretreatment planning and post-treatment evaluation using single photon emission computed tomography and positron emission tomography. In a patient with a large hypervascular tumor in the right lobe of the liver (A; contrast-enhanced CT), pretreatment SPECT/CT using  $^{99m}\text{Tc}$ -labeled macroaggregated albumin shows well-localized accumulation of the radiotracer (B). After treatment evaluation using  $^{90}\text{Y}$ -microsphere,  $^{90}\text{Y}$  PET/CT image shows a similar uptake pattern in the liver (C). SPECT: Single photon emission computed tomography; CT: Computed tomography; PET: Positron emission tomography.

## CONCLUSION

FDG-PET/CT has demonstrated high diagnostic performances in liver malignancy, regarding diagnosis, treatment response monitoring and prognosis prediction.  $^{11}\text{C}$ -Acetate and radiolabeled choline PET is complementary to FDG-PET in liver malignancy with low FDG uptake, such as well-differentiated HCC.  $^{99m}\text{Tc}$ -GSA and hepatobiliary scans can be used for regional evaluation of hepatic function. In liver resection and transplantation, those imaging methods are effectively used for candidate selection, treatment planning and perioperative evaluation of hepatic function. In recently developing treatment of TARE, nuclear imaging is used for planning and evaluation of treatment as theragnosis. With development of new hybrid imaging technologies such as PET/MRI and SPECT/CT, nuclear imaging is expected to be more useful in the management of liver malignancy, particularly regarding liver surgery and transplantation.

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