Feasibility of ^{18}F-Fluorodeoxyglucose Positron-emission Tomography for Preoperative Evaluation of Biliary Tract Cancer

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Abstract. *^{18}F-Labeled fluorodeoxyglucose positron-emission tomography (FDG-PET), a rapidly evolving functional imaging modality, has recently been shown to be useful in the diagnosis and staging of various malignant tumors due to focal uptake of FDG-labeled glucose in malignant cell populations. However, the role of FDG-PET in the diagnosis and staging of biliary tract cancer is still controversial and has not yet been fully evaluated. The aim of this study was to determine the clinical importance of FDG-PET in the preoperative evaluation of biliary tract cancer and retrospectively clarify the characteristics of false-negative and false-positive cases. We retrospectively analyzed data for 73 consecutive patients diagnosed with cancer of the biliary tract and were admitted to the Department of Hepato-Biliary-Pancreatic Surgery at Kobe University Hospital for treatment, from January 2007 to August 2009. Since the sensitivity, specificity and positive predictive value (PPV) of FDG-PET in the diagnosis of bile duct carcinoma are usually relatively high, FDG-PET is considered to be a useful tool in diagnosing biliary tract cancer. FDG-PET also seems to be useful in clinical decision-making, regarding treatment strategy, including surgery. Our results showed that FDG-PET is highly sensitive in delineating the primary focus of biliary cancer and is a useful tool in preoperative examination. A disadvantage of FDG-PET is its inability to indicate small metastases and false-positive findings of inflamed gallbladder and bile duct lesions.*

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Biliary tract cancer, which includes intrahepatic cholangiocellular carcinoma, extrahepatic bile duct carcinoma, gallbladder carcinoma, and papilla of Vater carcinoma, arises from the bile duct epithelium of the biliary tree; more than 90% of these lesions are adenocarcinomata. Since most bile duct carcinomata are asymptomatic until diagnosed at advanced stages with distant metastases or local invasion, the prognosis for bile duct cancer is relatively poor (1).

Optimal treatment plan and overall prognosis are critically dependent on accurate assessment of local invasion, tumor size, lymph node involvement, and the presence or absence of distant metastasis. Endoscopic procedures such as endoscopic retrograde cholangiopancreatography (ERCP) and intraductal ultrasonography have been used in conventional diagnosis of malignancy in biliary tract disease. The most recent and best imaging modalities, such as multi-detector computed tomography (MDCT) and magnetic resonance imaging (MRI), play a crucial role in the diagnosis and staging of biliary tract cancer, as well as in the evaluation of the local extent of the disease and its relationship with vascular structures. Limitations of anatomic imaging with CT and MRI for detection of tumor recurrence or metastases are well known and are often related to size criteria for determination of lymph node involvement. In addition, these imaging tools cannot reliably differentiate residual or recurrent tumor from scans taken after therapy. Therefore, the focus has shifted to the development of functional imaging for evaluation.

^{18}F-Labeled fluorodeoxyglucose positron-emission tomography (FDG-PET), a rapidly evolving functional imaging modality, has recently been shown to be useful in the diagnosis and staging of various malignant tumors due to focal uptake of FDG-labeled glucose in malignant cell populations. FDG-PET is highly sensitive and specific for the detection and localization of primary cancer lesions and distant metastases of malignancies. However, the role of

FDG-PET in the diagnosis and staging of biliary tract cancer is still controversial and has not yet been fully evaluated (2-9). The aim of this study was to determine the clinical importance of FDG-PET in evaluating preoperative biliary tract cancer and retrospectively clarify the characteristics of false-negative and false-positive cases.

Patients and Methods

Patients. We retrospectively analyzed data for 73 consecutive patients that were diagnosed with cancer of the biliary tract and were admitted to the Department of Hepato-Biliary-Pancreatic Surgery at Kobe University Hospital for treatment from January 2007 to August 2009. All patients included in the analysis underwent FDG-PET to determine therapeutic strategy with preoperative staging. Patients' data were reviewed by hepato-biliary-pancreatic surgeons, medical oncologists, and interventional radiologists during a conference to determine treatment strategies for each patient.

Tumor staging. The American Joint Committee on Cancer (AJCC) "TNM" system, approved by the International Union against Cancer (UICC), is the most widely accepted method for staging bile duct cancer. This system bases staging criteria on the evaluation of three primary factors: tumor (T), which describes the number and size of the original tumor; lymph node (N), which indicates whether the cancer is present in the regional lymph nodes; and metastasis (M), which refers to whether cancer has spread to distant parts of the body. Tumor staging was performed according to the TNM classification of the International Union against Cancer (6th edition) (10). All images were used for staging. At least two radiologists and surgeons staged the disease preoperatively, according to preoperative radiological examination and gross findings in surgery.

FDG-PET study. ^{18}F-FDG (FDGscan Injectable, generic name: fluorodeoxyglucose injection) was purchased from Nihon-mediphysics Co., Ltd. (Tokyo, Japan). All patients were examined with a high-resolution, whole-body PET scanner (ALLEGRO; Philips/ADAC Laboratories, Milpitas, CA, USA). All patients fasted for at least 6 h before intravenous administration of approximately 4.5 MBq/kg of FDG. PET examination started one hour after FDG injection. Three-dimensional emission scanning from the groin to the base of the skull (9-10 bed positions) was performed with gadolinium oxyorthosilicate (GSO)[$GD_2(SiO_4)O$:Ce] scintillator, lasting 2.5 min per bed position, in combination with a transmission scan lasting 30 s per bed position (the transmission scanning time was corrected to allow for the decay of the transmission sources). The data acquired were reconstructed by iterative ordered-subset expectation maximization (21 subsets, two iterations).

Image analysis. FDG-PET images were viewed by Centricity PACS (GE Healthcare Japan, Tokyo, Japan). Positive lesions were identified as the FDG uptake being higher than that in the background organs. These images were interpreted by at least two experienced radiology-nuclear medicine physicians using all available clinical information, correlative conventional imaging such as MDCT, MRI, or ERCP and maximum standardized uptake value (SUV) as a reference.

Data analysis. The diagnostic accuracy of FDP-PET was compared to the histopathological study of the surgical specimen. The diagnosis of malignancy in each case was confirmed by pathological analysis of surgical specimens in resected cases, biopsy, or cytological analysis. Sensitivity was calculated as true positives/(true positives + false negatives). Accuracy was calculated as (true positives + true negatives)/total cases. Positive predictive value (PPV) was calculated as true positives/(true positives + false positives).

Statistics. Statistical analysis was performed using SPSS v. 11.0.1 (SPSS, Chicago, IL, USA). All *p*-values were two-tailed; a *p*-value of less than 0.05 was considered significant. The statistical analyses of the sensitivity, accuracy, and PPV were performed for each tumor site and cancer stage in all 73 patients with biliary tract cancer. The characteristics of false-negative diagnosis of metastatic lesions and false-positive cases were also clarified in the subgroup of 55 patients who underwent laparotomy.

Results

Patients' characteristics. The study group comprised 46 men and 27 women, with a mean age of 68±10.5 years, ranging from 30 to 83 years old. Clinical diagnoses of these patients were intrahepatic cholangiocarcinoma (16), hilar cholangiocarcinoma (18), extrahepatic bile duct cancer (20), gallbladder cancer (14), and ampulla cancer (5). Eighteen patients were excluded from indication for surgery due to liver metastasis (n=7), multiple lymph node metastasis (n=3), locally advanced primary tumor (n=3), and comorbidity (n=5), as determined by CT scan. Surgical treatment was planned for the remaining 55 patients; 42 patients underwent surgical curative resection, including hepatectomy in 21 patients, pancreatoduodenectomy in 18 patients, bile duct resection in two patients, and cholecystectomy in one patient. Thirteen patients were found to be incurable at laparotomy; nine patients underwent explorative laparotomies and four underwent palliative operations because liver metastasis, peritoneal dissemination, and paraaortic lymph node metastasis were detected and confirmed by pathology during surgery. Table I shows the clinicopathological features of these patients.

Sensitivity accuracy and PPV for final diagnosis of bilary duct cancer using FDG-PET. The overall sensitivity of FDG-PET was 81% for all biliary carcinomas. FDG-PET was highly sensitive (100%) and accurate (93.8%) for intrahepatic cholangiocarcinoma, with a PPV of 92.9%. The sensitivity and accuracy for hilar cholangiocarcinoma were 77.7% and 77.7%, respectively. The sensitivity, accuracy, and PPV for extrahepatic bile duct cancer were similar to those for hilar cholangiocarcinoma. Sensitivity and accuracy for residual gallbladder carcinoma and papilliary cancer were lower than those of cholangiocarcinoma. The PPV of the FDG-PET was 95% for all biliary cancer; 92.9% for intrahepatic cholangiocarcinoma, 100% for hilar cholangiocarcinoma, 94.1% for extrahepatic bile duct cancer, 90% for gallbladder cancer, and 100% for papilliary cancer (Table II).

Table I. *Patients' characteristics.*

Item	n
Gender	
Male	46
Female	27
Age, year Mean: 68±10.5 (range: 30-83)	
≤69	35
70≤	38
Final diagnosis	
Intrahepatic cholangiocarcinoma	16
Hilar cholangiocarcinoma	18
Extrahepatic bile duct cancer	20
Gallbladder cancer	14
Ampullary cancer	5
Stage*	
I 4	
II 8	
III	6
IV	50
Treatment	
Surgical resection (+)	
Hepatectomy	21
Bile duct resection	2
Pancreatoduodenectomy	18
Cholecystectomy	1
Surgical resection (–)	
No surgery	18
Exploratory laparotomy	9
Palliative operation	4

*Excluding false-positive cases.

Table II. *Sensitivity (%), accuracy (%), and Positive predictive value (PPV) (%) of primary tumor (preoperative diagnosis).*

Tumor site	Sensitivity	Accuracy	PPV
Intrahepatic cholangiocarcinoma	100.0	93.8	92.9
Hilar cholangiocarcinoma	77.7	77.7	100
Extrahepatic bile duct cancer	84.2	80.0	94.1
Gallbladder cancer	69.2	64.3	90.0
Papilliary cancer	71.4	71.4	100

PPV: Positive predictive value, NS: not significant.

Table III. *Sensitivity (%), accuracy (%), and PPV (%) for final staging.*

Stage	Sensitivity	Accuracy	PPV
I	25.0*	25.0	100
II	75.0	75.0	100
III	100.0	100	100
IV	90.0	90.0	100

*p-Value<0.01.

Sensitivity, accuracy, and PPV for final staging of biliary duct cancer using FDG-PET. The sensitivity and accuracy of FDG-PET for stage I cancer was remarkably lower than those for other stages. Sensitivity and accuracy at stage II, III, and IV ranged between 75% and 100%, with 100% PPV. These results indicate that the sensitivity and accuracy vary according to the stage of the primary tumor, and that FDG-PET was a reliable diagnostic tool when biliary tract cancer was at the advanced stage (Table III).

False-positive cases. There were 5 false-positive results in this study: four patients had chronic inflammation of the biliary tract and one had hepatic granuloma. In these patients, FDG-PET yielded incorrect diagnoses. Histopathological examinations of these lesions indicated inflammatory cell infiltrate and fibrosis (Table IV).

Analysis of unresectable cases at exploration. Although surgery was performed, surgical resection of primary tumors was not performed in nine patients at exploration because of locally advanced tumor with vascular invasion in one patient, multiple liver metastases in 4 patients, and distant lymph node metastases in 2 patients. All of these lesions were unsuspected based on FDG-PET. Peritoneal disseminations in 2 patients with carcinomatosis were found at exploration. The summary of unresectable cases is shown in Table V.

Discussion

Our study demonstrated that FDG-PET is a useful tool for diagnosing biliary tract cancer. However, FDG-PET has limitations in detecting peritoneal dissemination and small liver metastases. Approximately 60% to 70% of cholangiocarcinomata occur at the hepatic bile duct bifurcation, and the remainder occur in the distal common bile duct (20% to 30%) or in the liver (5% to 15%). Gallbladder carcinoma, which is more common than cholangiocarcinoma, is discovered in approximately 1% of cholecystectomy specimens and is the fifth most common gastrointestinal malignancy. Bile duct carcinoma can metastasize in lymphatic chains, including the hepatoduodenum ligament, and often invades adjacent organs or metastasizes to other visceral organs such as the lungs, bones, and brain. Since biliary tract cancer is often asymptomatic, surgery remains the only curative therapy, with a five-year survival rate of approximately 30-50%, despite the development of treatment modalities. The response rates for systemic chemotherapy and/or radiation therapy regimens for biliary cancer are limited; thus, surgical resection offers the best chance for curative therapy (1).

Table IV. *False-positive cases*.

Age (years)	Gender	Preoperative diagnosis	Pathological diagnosis
79	F	Intrahepatic cholangiocarcinoma	Hepatic granuloma
65	M	Intrahepatic cholangiocarcinoma	Intrahepatic cholangitis
73	M	Intrahepatic cholangiocarcinoma	Intrahepatic cholangitis
77	M	Gallbladder cancer	Chronic cholecystitis
78	M	Extrahepatic bile duct cancer	Cholangitis with bile duct stone

Table V. *Summary of data regarding patients who underwent exploratory laparotomy.*

	Age (years), gender	Tumor origin	Unresectable factor	FDP-PET	
				Primary	Metastatic
1	37 M	Gallbladder cancer	Multiple liver metastases	Negative	Negative
2	67 F	Intrahepatic bile duct cancer	Multiple liver metastases	Positive	Negative
3	59 M	Extrahepatic bile duct cancer	Multiple liver metastases	Positive	Negative
4	55 M	Extrahepatic bile duct cancer	Multiple liver metastases	Positive	Negative
5	79 M	Intrahepatic cholangiocarcinoma	Distant lymph node metastases	Positive	Negative
6	60 M	Intrahepatic cholangiocarcinoma	Distant lymph node metastases	Positive	Negative
7	60 M	Hilar cholangiocarcinoma	Peritoneal carcinomatoses	Positive	Negative
8	70 M	Hilar cholangiocarcinoma	Peritoneal carcinomatoses	Positive	Negative
9	74 F	Extrahepatic bile duct cancer	Direct vessel invasion	Positive	NA

NA: Not applicable.

PET using glucose analog FDG is rapidly developing the fields of primary tumor detection, planning and monitoring therapy, and the detection of metastasis and recurrence. Thus, PET has become an established, essential imaging tool in oncology. PET scan use has been markedly increased in many institutes in Japan, since the medical costs for PET examinations for various types of cancer are currently covered by Japanese government insurance. Radiopharmaceutical FDG is a glucose analoge suitable for assessing *in vivo* glucose utilization of vital tumor tissue. Most malignant tumors show increased uptake of FDG because of malignant formation of glucose transporters and increased hexokinase activity (11, 12).

Since FDG-PET imaging is a whole-body scanning technique, it allows detection of unsuspected distant metastases that may lead to major changes in the surgical management of patients with biliary tract cancer. Kluge *et al*. demonstrated that PET may be useful in the detection of distant metastatic disease (5), but other investigators questioned its usefulness in detecting regional lymph node metastases. Kobayashi *et al*. reported that FDG-PET is useful for detection of para-aortic lymph node metastases of biliary tract cancer, since they are far from the primary tumor. Accurate and specific detection of lymph nodes near the primary tumors is difficult, since it is challenging to distinguish accumulation of lymph nodes from the primary tumor. However, these regional lymph nodes would be included within the area of the dissection in standard surgery for biliary cancer, so it would not be important to determine the surgical procedure except in cases of invasion of major vessels (13, 14). An accurate estimation of lesion sizes in PET studies is compromised due to influence of the activity concentration, the object-to-background ratio, and physical properties of the transmitted media (15).

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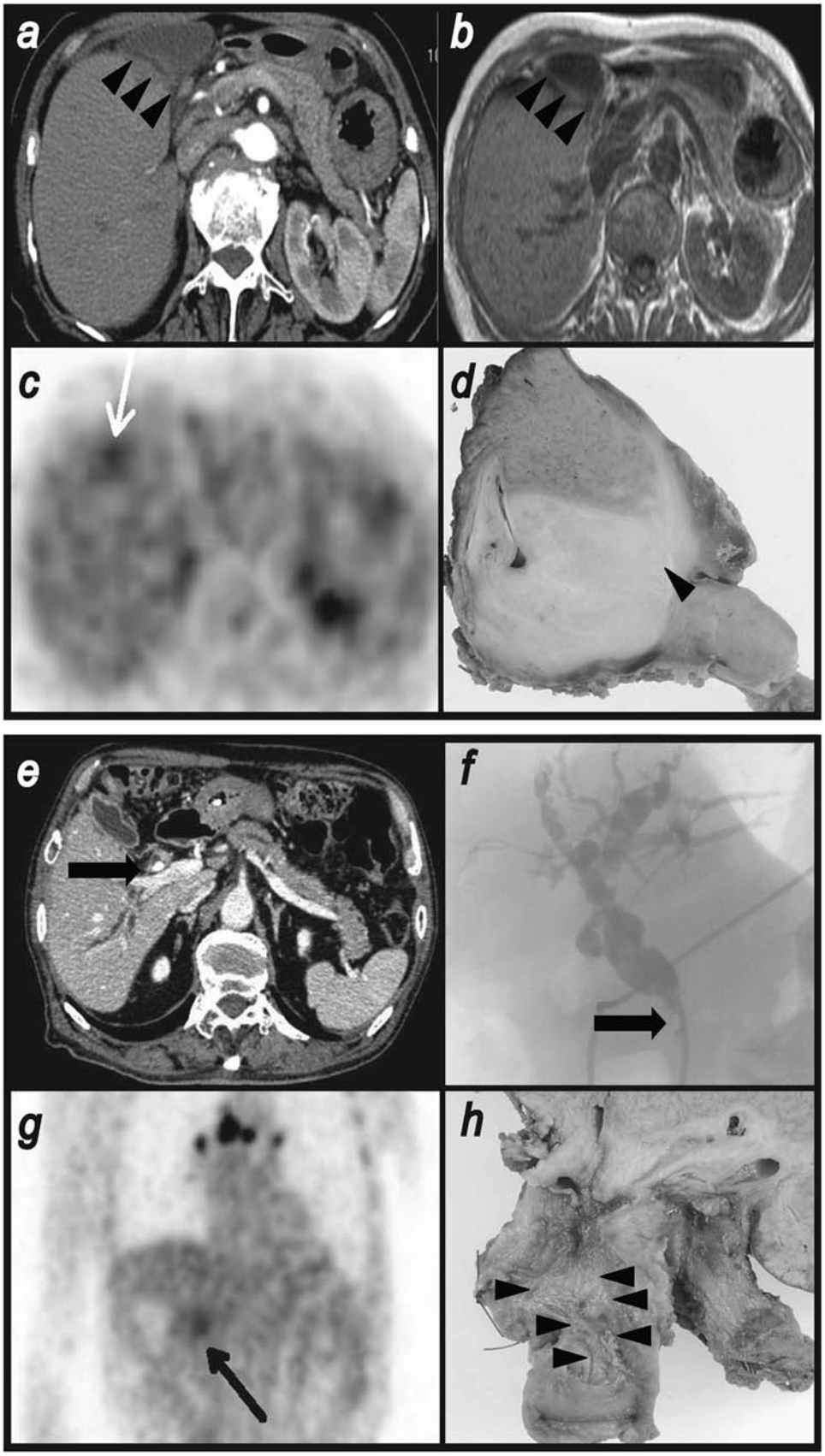
Figure 1. *Representative images of the false-positive cases detected by ^{18}F-Labeled fluorodeoxyglucose positron-emission tomography (FDG-PET). Upper panels are images of a 79-year-old woman with hepatic granuloma. Computed tomography (CT) (a), magnetic resonance imaging (MRI) (b), positron-emission tomography (PET) (c), and gross finding of the resected specimen (d). Images show an intense focus of [^{18}F]-FDG uptake in the left lobe of the liver. Lower panels are images of a 78-year-old man with extrahepatic cholangitis with common bile duct stone. CT (e), cholangiography (f), PET (g), and gross finding of the resected specimen (h). Images show an intense focus of [^{18}F]-FDG uptake in the hilum of the liver.*


a
b
c
d
e
f
g
h

It is important to consider that morphology of the different types of biliary duct cancer influence their detection with FDG-PET imaging. Lesion detection with imaging modalities is dependent on the resolution of the modality and the degree of contrast enhancement of FDG uptake compared to background. Lesions with a size of less than twice the resolution of the imaging system suffer from partial volume-averaging artifact. The intrinsic resolution of state-of-the-art PET scanners is in the 4 to 5 mm range, meaning that lesions less than 8 mm will suffer from partial volume-averaging artifact and may not be detectable even if the degree of FDG uptake is higher than in the normal liver. Previous studies reported the discrepancies that may occur between the size of the lesions and the size of the hypermetabolic foci in PET studies (5). Cholangiocarcinoma with infiltrating morphology may not have the cellular density required to form a lesion larger than 8 mm, and therefore may not be detected by PET.

In our study, FDG-PET was found to be a useful modality to diagnose every type of bile duct cancer, especially intrahepatic bile duct cancer. The relatively high false-negative rate was attributed to limited spatial resolution, which was a disadvantage for detecting micrometastases and discriminating between the primary tumor and FDG-accumulating lymph nodes. In addition, the reason that sensitivity in early stage is lower than in other cancer stages is due to the low spatial resolution on FDG-PET. In our series of patients, we retrospectively clarified the characteristics of false-negative and false-positive cases, proposing suitable therapy decision-making for all patients. Therefore, FDG-PET may not be suitable for early diagnosis of early-stage biliary duct cancer, or for a screening method in higher risk patients.

In conclusion, FDG-PET is considered as useful diagnostic tool for biliary tract cancer. However, FDG-PET imaging seems to have a certain false-negative rate for infiltrating biliary tract cancer and for the detection of carcinomatosis. Foci of inflammation with cholangitis may accumulate FDG, and early postoperative changes may interfere with the accurate interpretation of FDG imaging for residual or recurrent biliary duct cancer.

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