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Preoperative staging of biliary carcinoma using ^{18}F-fluorodeoxyglucose PET: prospective comparison with PET+CT, MDCT and histopathology

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Abstract The aim of this study was to evaluate the value of positron emission tomography with ^{18}F-labeled fluorodeoxyglucose (FDG-PET) as a preoperative diagnostic investigation in patients with biliary carcinoma. Seventy-two patients with potentially resectable biliary carcinoma underwent preoperative multidetector-row computed tomography (MDCT) and FDG-PET. Both diagnoses were compared with subsequent histopathology and follow-up results. In 64 lesions with biliary carcinoma, 57 (89%) revealed an intense focal accumulation on FDG-PET and were interpreted as malignant. On the other hand, eight benign lesions did not show any specific accumulation. Detection rate of FDG-PET in the nodular type of the tumour (96% or 27/28) was superior to that of the infiltrating type (74% or 17/23) (p=0.037). For the evaluation of lymph node metastasis, the overall accuracy was 69% (35/51) in both FDG-PET and MDCT: FDG-PET had a lower sensitivity (33% vs. 57%) and a higher specificity (97% vs. 79%) than MDCT, although the values were not significantly different. FDG-PET revealed all six lesions of distant metastases in six patients including two lesions missed by MDCT. FDG-PET has high detectability of biliary malignancies. Like MDCT, FDG-PET offers only modest accuracy for regional lymph node staging, but it may reveal distant metastases missed by MDCT.

Keywords Positron emission tomography · Biliary neoplasms · Spiral computed tomography · Neoplasm staging · Biliary surgery

Introduction

The diagnosis, clinical staging and treatment of biliary carcinoma including extrahepatic cholangiocarcinoma and gallbladder carcinoma remain difficult [1]. A variety of diagnostic imaging investigations have been used to evaluate biliary malignancies, including computed tomography (CT), transabdominal or endoscopic ultrasonography, magnetic resonance imaging and endoscopic or transhepatic cholangiography. Although these imaging techniques are often helpful, they do not always provide a definitive diagnosis or detect malignancy at an early stage. Complete resection of the cholangiocarcinoma and gallbladder carcinoma is the most effective and only potentially curative treatment, while operative procedures for these tumours are associated with significant morbidity compared with other gastrointestinal malignancies. The use of imaging studies is therefore important in aiding early diagnosis, identifying patients who are suitable surgical candidates and guiding treatment planning.

CT is the most common diagnostic imaging technique used in the preoperative assessment of biliary carcinoma. The introduction of multidetector-row CT (MDCT) allowed higher-resolution imaging and shorter examination times [2]. This allows the objective organ to be imaged during the bolus phase of contrast enhancement with thin-collimation, resulting in improved multiplanar reconstructions. However, the interpretation of CT images is still sometimes difficult when differentiating carcinoma from benign cho-

lecystitis or cholangitis, and even such sophisticated imaging techniques are still not sufficient for accurate staging [3–9].

Positron emission tomography with glucose analogue ^{18}F-fluoro-2-deoxy-D-glucose (FDG-PET) is a sensitive diagnostic test that images tumours based on the increased utilization of glucose by tumour cells [10, 11]. However, there are few reports of FDG-PET dealing with the primary biliary carcinoma [12–19]. Also, these studies had several limitations: retrospective methods, lack of a valid reference test, high disease prevalence (i.e. advanced-stage disease), small sample size, lack of histopathological verification, comparison with conventional imaging tests with bad sensitivity and inadequate clinical follow-up to confirm negative findings. Thus, the diagnostic role of FDG-PET for primary biliary carcinoma has not yet been fully and fairly investigated.

We therefore prospectively evaluated the accuracy of FDG-PET for the initial staging of biliary carcinoma in comparison with MDCT followed by histopathology of the resected specimen. All studies were performed in one Japanese hospital.

Methods

Patients

Between November 2002 and July 2005, 72 patients (41 men and 31 women; median age 69; range 28–84 years) with suspected extrahepatic cholangiocarcinoma or gall-bladder carcinoma were enrolled in this study after giving written informed consent in accordance with the regulations of the institutional review board. Mass-forming-type intrahepatic cholangiocarcinoma was excluded from this study. Patients were referred to our hospital due to bile duct dilatation and/or mass lesions detected by ultrasonography and CT. Advanced cases with disseminated disease and obvious benign lesions such as acute cholecystitis were excluded in advance. All patients underwent MDCT and FDG-PET for initial staging within 1 month.

MDCT

We used an Aquiline 16 CT system (Toshiba medical systems, Tokyo, Japan). For imaging the whole body, we used 16 high-resolution central detectors. From these detectors we selected a 2-mm slice thickness and reconstructed the data at 2-mm intervals. The other parameters were a 0.5-s helical rotation time, 135 kVp and 300–400 mAs. One hundred and fifty millilitres of iopamidol (Iopamiron; Nihon Schering, Tokyo, Japan) was administered through a peripheral venous line at 4 ml/s by using a power injector (Autoenhance A-50; Nemoto Kyorindo, Tokyo, Japan). Scanning in the arterial and portal venous phase was started at 40 s and 70 s, respectively. The evaluation of primary tumour and regional lymph nodes used these dual-phase images.

CT data acquisition began 120 s after the start of injection of the contrast medium and data were acquired from the neck to the upper femur within one breath hold in approximately 20 s. Multiplanar reformations were reconstructed on a freestanding workstation (ZAIO, Tokyo, Japan). MDCT images, including 3D reconstruction images, were sent to a picture archiving and communication system (SYNAPS; Fuji film medical, Tokyo, Japan) that permits interactive analysis.

FDG-PET

Patients fasted for at least 4 h before the examination. Serum glucose levels were checked in all of the patients before the administration of FDG. Patients received an intravenous injection of 200–250 MBq of FDG and then rested for approximately 60 min before undergoing imaging. Image acquisition was performed with an Advance NXi (GE Medical System, Milwaukee, USA). Two-dimensional emission data from the groin to the base of the skull (6–7 bed positions) were obtained, lasting 5 min per bed position, in combination with a transmission acquisition lasting 1.5 min per bed position (transmission time was corrected to allow for decay of the transmission sources). The data acquired were reconstructed by iterative ordered-subsets expectation maximization (21 subsets, 2 iterations). FDG-PET images were displayed as coronal, sagittal and transaxial slices, and a whole-body image was also displayed as a set of projection images for visual interpretation. These images were sent to a picture archiving and communication system that permits interactive analysis, similar to the arrangement for MDCT images.

Image analysis

At first, MDCT images were prospectively evaluated by two physicians experienced in CT and FDG-PET interpretation in consensus. The MDCT findings were classified malignant when there was apparent thickening and contrast enhancement of the wall and/or intraluminal mass of the bile duct or the gallbladder [3–9]. They were assessed for detectability of the primary tumour, regional lymph node involvement (N factor) and distant metastasis (M factor). Lymph nodes were considered positive when the short axis was greater than 1 cm in diameter. Lesions in the liver not characteristic of a cyst, hemangioma or abscess were considered suspicious of metastases. Also in the lung, pulmonary nodules without calcification were deemed suspicious for metastases.

All PET images were interpreted with knowledge of the patient's medical history and the MDCT findings, and were

evaluated with respect to detectability of primary tumour, lymph node involvement and distant metastases by the same two physicians. Uptake higher than adjacent activity such as liver was considered to be increased. Physicians interpreted the FDG-PET images by visually correlating the FDG-PET and MDCT images. This approach was chosen because it represents the routine practice of combined reading of PET and MDCT images in our hospital. On the basis of their visual correlation, the physicians assigned a TNM stage on FDG-PET. Regarding the N factor, we chose to analyse the imaging studies on a nodal station basis and not on an individual lymph node basis. When the enlarged node on MDCT was negative on FDG-PET, it was considered as negative.

Decision of preoperative staging

Both MDCT and FDG-PET results were presented at a hepatobiliary conference consisting of surgeons, medical oncologists, endoscopists, radiology physicians and radiation oncologists. All conference members confirmed the MDCT and FDG-PET findings. When a clear differentiation between different tumour stages on MDCT and FDG-PET was not possible, both stages were noted and confirmed after surgery. The decisions of diagnosis and treatment plan were recorded and compared with surgical and pathological results.

Data analysis

A radical lymphadenectomy and a detailed histologic examination of a large number of nodes were performed for resected patients. Resected specimens were examined by pathologists without knowledge of the preoperative MDCT and FDG-PET findings. The diagnostic accuracy of MDCT and FDG-PET were assessed using the histopathological findings as the gold standard. The staging criteria were based on the TNM classification. Comparisons of diagnostic and pathological parameters were performed using Fisher's exact test or McNemar test. The level of statistical significance was determined at 5% in all cases.

Results

All 72 patients tolerated both MDCT and FDG-PET examinations without any complications. Eight patients (4 men and 4 women; median age 72; range 28–74 years) presented with nonmalignant biliary disease. Two had primary sclerosing cholangitis, four had benign stricture of the bile duct, and two had chronic cholecystitis (median 20 months follow-up time after FDG-PET scan; range 9–37 months).

Adenocarcinoma of the biliary tract was confirmed in 64 patients (37 men, 27 women) at a median age of 69 years (range 46–84). No patient had any previous biliary malignancy. The final diagnoses of primary tumour were based on the findings of surgery (n=53), cytology of the biliary juice or ascites (n=3), percutaneous or endoscopic biopsy (n=3), and clinical course (n=5). Among the 53 patients who received surgery, 51 underwent resection. The pathological primary tumour stage in the 51 resectable cases was pT1 in six, pT2 in 30, pT3 in 13 and pT4 in two. The histological type in these 51 cases was papillary adenocarcinoma in 11, well-differentiated tubular adenocarcinoma in 23, moderately differentiated tubular adenocarcinoma in 11 and poorly differentiated tubular adenocarcinoma in six. Surgical resection of primary tumours was not performed in 13 patients because of locally advanced tumour (n=5), the presence of distant metastases (n=6), general status (n=1) or patient refusal (n=1).

In all 64 lesions with biliary carcinoma, 57 (89%) revealed an intense focal accumulation and were interpreted as malignant. On the other hand, eight benign lesions did not show any specific accumulation on FDG-PET. The detection rate of FDG-PET for bile duct carcinoma was 84% (40/47) and that for gallbladder carcinoma was 94% (17/18). On MDCT, 62 of 64 (97%) of biliary carcinoma showed equivocal or 'suspicious of malignancy' findings such as wall thickening and/or intraluminal mass. The two cases which were not detected on MDCT were both infiltrating-type adenocarcinomas of the bile duct and ductal wall thickening or enhancement of the wall was absent on CT images. Even upon macroscopic examination of the resected specimens, these tumours were inconspicuous.

Of the 51 resected cases, the positive rates obtained with FDG-PET for the histopathological tumour stages are shown in Table 1. No difference was evident between the positive rate for pT2 and pT3 (p=0.412). According to the macroscopic examination, tumours were divided into two groups: nodular type in which the tumour consisted of a nodule protruding into the bile duct (Fig. 1) or gallbladder

Table 1 Comparisons of PET, MDCT and histopathological tumour staging with resectable biliary carcinoma

Pathologic staging	No.	Detection rate	
		PET	MDCT
pT1	6	6 (100%)	6 (100%)
pT2	30	24 (80%)	28 (93%)
pT3	13	12 (92%)	13 (100%)
pT4	2	2 (100%)	2 (100%)
Total	51	44 (86%)	49 (96%)

MDCT multidetector-row computed tomography, *PET* positron emission tomography

Fig. 1 a Primary bile duct tumour was shown in the intrapancreatic bile duct on computed tomography (arrow). b At the same level of a, an avid uptake was demonstrated on positron emission tomography (arrow). c Of the resected specimen, the nodular type of the tumour was demonstrated. d Histologically, the tumour consisted of papillary adenocarcinoma
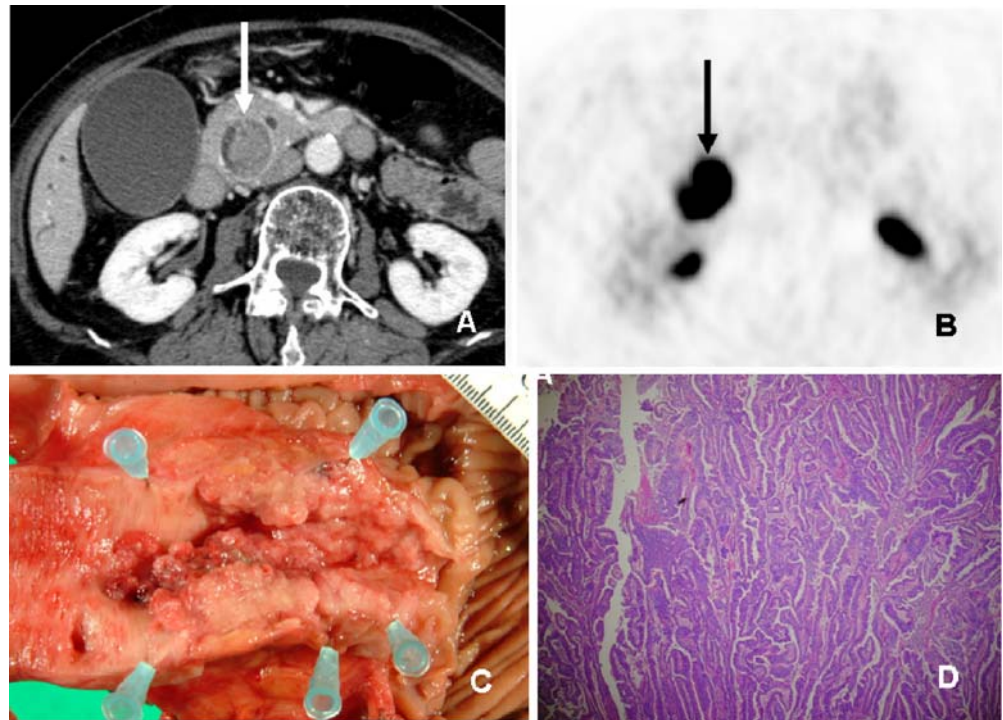
lumen and infiltrating type in which a tumour nodule was absent and the boundary was ill-defined (Fig. 2). The detection rate of FDG-PET in each macroscopic type of tumour was 96% (27/28) in nodular type and 74% (17/23) in infiltrating type. The difference was statistically significant ($p=0.037$). Positive rates obtained with FDG-PET for the histopathological type of the tumour are shown in Table 2. The positive rate of papillary adenocarcinoma was excellent, while those of other histological types were similar to each other.

Fig. 2 a Primary bile duct tumour was shown in the hepatic hilum on computed tomography (arrow). b At the same level of a, any specific uptake was not demonstrated on positron emission tomography (arrow). c Of the resected specimen, the infiltrating type of the tumour was demonstrated. d Histologically, the tumour consisted of poorly differentiated adenocarcinoma with dense connective tissue
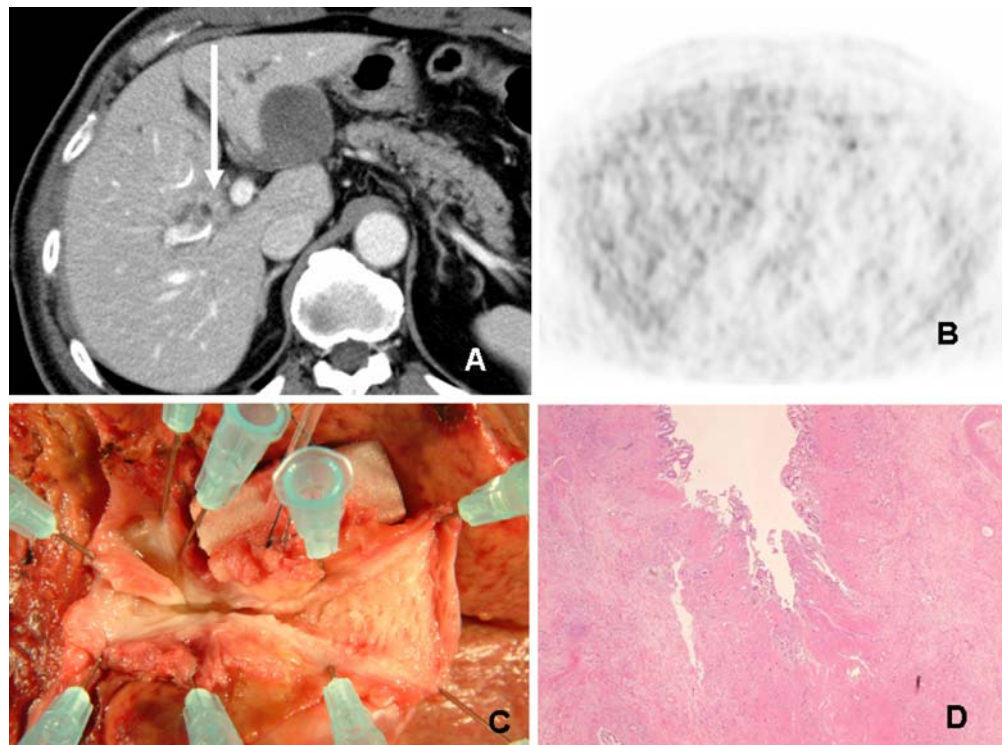
Table 2 Comparisons of PET, MDCT and histopathological tumour type with resectable biliary carcinoma

Histological type	No.	Detection rate	
		PET	MDCT
Papillary	11	11 (100%)	11 (100%)
Well	23	19 (83%)	22 (96%)
Moderate	11	9 (82%)	10 (91%)
Poor	6	5 (83%)	6 (100%)
Total	51	44 (86%)	49 (96%)

MDCT multidetector-row computed tomography, *PET* positron emission tomography

Regarding the N factor, the overall accuracy was 67% (35/51) in both FDG-PET and MDCT (Table 3). The sensitivity, specificity, positive predictive value and negative predictive value were calculated as 33%, 97%, 88% and 67%, respectively, in FDG-PET; and 57%, 79%, 67% and 67%, respectively, in MDCT. FDG-PET showed a lower sensitivity and a higher specificity than MDCT, although the values were not significantly different ($p=0.227$ in sensitivity and $p=0.125$ in specificity).

According to both MDCT and FDG-PET, six lesions of distant metastases were revealed in six patients and defined as unresectable: four distant lymph node metastases and one each of peritoneal dissemination and bone metastases. MDCT showed four out of six lesions and one each of distant lymph node metastases and peritoneal dissemination were missed. FDG-PET revealed all six lesions. These six patients did not receive surgical resection according to these imaging findings.

Discussion

The diagnostic role of FDG-PET for biliary carcinoma has not been fully evaluated in contrast to other gastrointestinal malignancies. CT is the most common diagnostic method for diagnosing and staging biliary carcinoma, and MDCT is expected to improve diagnostic accuracy by providing better anatomical resolution. To evaluate the usefulness of FDG-PET, we compared the diagnostic accuracy of FDG-PET with this up-to-date technology.

The utility of imaging techniques is usually evaluated by radiologists' retrospective reading blinded to the clinical information and other diagnostic imagings. However, this is not a practical situation and many physicians often feel that actual diagnostic results are different from the results reported. We wish to evaluate the usefulness of FDG-PET in clinical setting. Recently, integrated PET-CT has been introduced. Using this technique, PET, CT and integrated PET-CT images are displayed together on the monitor. This type of PET system and reading style is now becoming routine. In this study, FDG-PET images were interpreted with knowledge of the patient's medical history and the MDCT images. We used this type of method for evaluating FDG-PET in the preoperative staging of colorectal cancer [20].

The prospective visual analysis of FDG-PET resulted in a detection rate of 89% for biliary carcinoma. These results confirm that adenocarcinomas located in this region can be detected in FDG-PET studies with similar accuracy as adenocarcinoma of other malignancies such as the pancreas and the colon [21–26]. The injected activity we used was lower than the conventional dose reported. But we confirmed that the image quality of this dose was not deteriorated in our previous study investigating colon cancer [20]. The image quality and the diagnostic results in this study supported its appropriateness. We should try to reduce the radiation exposure while preserving the diagnostic accuracy.

The detection rate of primary tumours by FDG-PET was related to the morphology of the tumour, not to the depth of tumour invasion. Most of the false negative findings were in the group of patients with carcinoma of the infiltrating-type morphology. All six pT1 tumours revealed a high accumulation of FDG, which were nodular type in five and infiltrating type in one. In the infiltrating-type lesions, the metabolically active tumour cells were loosely dispersed forming only small nests of tumour cells disseminated within broad strands of connective tissue. Thus, the tumour cell volume capable of incorporating glucose may be too small to produce a significant PET signal, which itself has a high glucose activity. By comparison, the nodular type of biliary carcinomas that demonstrated a positive PET signal consisted of a high amount of tumour cells. They exhibited much metabolically active cytoplasm per section area. Concerning the histopathological type, all papillary adenocarcinoma revealed an avid accumulation. This type of tumour also had a high amount of tumour cells and less connective tissue.

The detection rate of gallbladder carcinoma was higher than that of bile duct carcinoma. In 39 cases of resected bile duct carcinoma, 19 (49%) were nodular type and 20 (51%) were infiltrating type. Similarly, in 12 cases of resected

Table 3 Comparisons of PET and MDCT in staging lymph node metastasis with biliary carcinoma

	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Accuracy (%)
PET	33 (7/21)	97 (28/29)	88 (7/8)	67 (28/42)	69 (35/51)
MDCT	57 (12/21)	79 (23/29)	67 (12/18)	72 (23/32)	69 (35/51)

The calculation is made on a station basis
MDCT multidetector-row computed tomography, *PET* positron emission tomography

gallbladder carcinoma, nine (75%) were nodular type and three (25%) were infiltrating type. The higher detection rate of gallbladder rather than bile duct carcinoma may depend on the ratio of the morphological type. Endoscopic or percutaneous biopsy is considered to provide conclusive diagnosis for such FDG-PET-negative cases. However, these procedures are invasive and sometimes a sufficient amount of specimen cannot be obtained because of the desmoplastic nature of the lesion [27–29]. Such cases still remain a diagnostic challenge.

CT is an important method of staging biliary carcinoma. However, previous studies showed low accuracy rates in the assessment of lymph node involvement [4, 7]. Also in this study, MDCT did not demonstrate satisfactory results for diagnosis of N factor, even though MDCT allows a large volume to be covered in the same contrast medium phase combined with a better anatomical resolution. Microscopic metastasis or uninvolved enlargement of lymph nodes result in misdiagnosis. As long as the diagnosis is made based on the size of lymph nodes, a certain percentage of false positive and negative lymph nodes are inevitable. These drawbacks cannot be completely overcome by adopting short slice interval or multiplanar reformation. Other criteria, devices or refinements are needed to improve the diagnostic accuracy of the N factor.

In this study, FDG-PET had lower sensitivity (33% vs. 57%) and higher specificity (97% vs. 79%) than MDCT for the evaluation of lymph node metastasis. The high false-negative rate was attributed to limited spatial resolution which was a disadvantage for detecting micrometastases and the difficulty in discriminating between the primary tumour itself and FDG-accumulating lymph nodes. The radical lymphadenectomy and precise histopathological examination might contribute to the detection of micro-metastases. The problem of detection and correct staging of lymph nodes also occurs in other malignancy [20–25].

PET has had the advantage of studying the whole body at one examination and synchronous tumours have been identified on PET. MDCT can examine the whole body in a shorter time than PET. In this study, distant metastases were revealed only six lesions in six patients. While patient numbers are too small to compare the usefulness of both diagnostic techniques, FDG-PET showed two metastatic lesions missed by MDCT. False negative lesions on MDCT were normal-sized paraaortic lymph node metastases and subphrenic small foci of peritoneal dissemination. We think FDG-PET is useful to reveal such ambiguous lesions or unnoted metastases.

Our study has several limitations. Since the enrolled patients were selected and benign lesions were too small, the usefulness of FDG-PET for differential diagnosis of biliary diseases could not be evaluated. For the evaluation of nodal staging, node-by-node correlation between MDCT and FDG-PET was not performed, because it seemed impossible for us to make a precise correlation between individually sampled and mapped lymph nodes on imaging studies. The number of patients with distant metastases was small. Thus, the suitability of FDG-PET for detecting distant metastasis still remains unknown, even though some useful cases were encountered. We did not use SUV in this study because the definition of a standardized cutoff value of the SUV for the differentiation between benign and malignant lesion is complicated and we do not adhere the value of SUV in usual clinical situation. As previously reported [14], we think that visual analysis is the preferred method of assessment. Finally, we could not be use a PET/CT during this research period. A few papers reported the diagnostic value of this technique on management of biliary malignancies [18, 19]. However, their samples were small and included recurrent cases, and technical detail of MDCT compared with PET/CT was not mentioned. As this technology has recently been introduced in our hospital, we are going to investigate its value.

In conclusion, FDG-PET is useful for detecting and confirming possible biliary malignancies, although it is not ideal for detecting the infiltrating type of this tumour. It is not perfect for regional lymph node staging, but may reveal distant metastases missed by MDCT. We think routine evaluation of patients with biliary carcinoma by FDG-PET is not necessary; rather it should be performed on selected patients who have suggestive but inconclusive primary or distant metastatic lesions shown by other imaging techniques.

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