

## Distinguishing benign from malignant gallbladder wall thickening using FDG-PET

Ai OE,\* Joji KAWABE,\* Kenji TORII,\* Etsushi KAWAMURA,\* Shigeaki HIGASHIYAMA,\*\*  
Jin KOTANI,\* Takehiro HAYASHI,\* Hiroko KUROOKA,\* Chikako TSUMOTO,\*\*  
Shoji KUBO\*\*\*\* and Susumu SHIOMI\*

\*Department of Nuclear Medicine, \*\*Department of Gastroenterology,  
\*\*\*Department of Radiology, and \*\*\*\*Department of Hepato-Biliary-Pancreatic Surgery,  
Graduate School of Medicine, Osaka City University

**Objective:** Because thickening of the gallbladder wall is observed not only in patients with gallbladder cancer but also in those with benign diseases such as chronic cholecystitis and gallbladder adenomyosis, it is difficult to distinguish between benign and malignant gallbladder wall thickening by conventional techniques of diagnostic imaging such as computed tomography (CT), magnetic resonance imaging (MRI), and abdominal ultrasonography (US). In the present study, we attempted to distinguish between benign and malignant gallbladder wall thickening by means of fluorine-18-fluorodeoxyglucose (FDG)- Positron emission tomography (PET). **Methods:** FDG-PET was performed in 12 patients with gallbladder wall thickening detected by CT or US, to determine whether it was benign or malignant. Emission scans were taken, beginning 45 minutes after intravenous administration of FDG, and SUV was calculated as an indicator of glucose metabolism. **Results:** Of the 12 patients, 4 showed positive uptake of FDG in the gallbladder wall. Of these 4 patients, 3 had gallbladder cancer. The remaining one, who had chronic cholecystitis, had false-positive findings. The other 8 patients had negative uptake of FDG in the gallbladder wall. Two of these 8 underwent surgical resection, which yielded a diagnosis of chronic cholecystitis. The other 6 patients exhibited no sign of gallbladder malignancy and have been followed without active treatment. **Conclusions:** FDG-PET appears able to distinguish between benign and malignant gallbladder wall thickening.

**Key words:** gallbladder cancer, wall thickening, FDG-PET

### INTRODUCTION

INCREASED GLUCOSE METABOLISM is one of the biochemical characteristics of cancer cells. Making use of this feature, attempts have recently been made to diagnose cancer by PET with FDG, a glucose analogue.<sup>1–8</sup>

PET is known to have higher sensitivity and specificity in distinguishing between benign and malignant tumors than other conventional techniques of diagnostic imaging, including CT, MRI, and US.<sup>2,4,9</sup> It has also been

reported that PET is useful in diagnosing gallbladder cancer.<sup>10–19</sup>

Gallbladder cancer can be divided into two types: (1) that presenting as an protuberant lesion and permitting distinction from benign disease on the basis of size and other factors; and (2) that presenting with gallbladder wall thickening, which is difficult to distinguish from benign disease preoperatively.<sup>20</sup> Although attempts at using PET to distinguish the former type of gallbladder cancer from benign gallbladder tumors have been reported, very few reports have been published concerning the distinction of the latter type of gallbladder cancer from benign gallbladder disease using PET.<sup>10</sup> We recently performed FDG-PET in patients exhibiting gallbladder wall thickening, and correlated the findings of FDG-PET with the course of these patients.

Received August 21, 2006, revision accepted October 2, 2006.

For reprint contact: Ai Oe, M.D., Department of Nuclear Medicine, Graduate School of Medicine, Osaka City University, 1–4–3 Asahimachi, Abeno-ku, Osaka 545–8585, JAPAN.

**Table 1** Patient characteristics

Patient no.	Age (yrs)	Sex	Diagnosis	FDG	SUV
1	74	M	GBC	+	5.1
2	84	F	GBC	+	9.1
3	57	F	GBC	+	5.5
4	60	F	Chronic cholecystitis	+	4.7
5	69	M	Chronic cholecystitis	-	ND
6	64	M	Chronic cholecystitis	-	ND
7	60	M	ND	-	ND
8	83	F	ND	-	ND
9	67	M	ND	-	ND
10	65	M	ND	-	ND
11	64	M	ND	-	ND
12	64	M	ND	-	ND

Sex; M = Male, F = Female GBC = Gallbladder cancer ND = Not Done SUV = standardized uptake value

## MATERIALS AND METHODS

### *Patients*

This was a retrospective study involving 12 patients with gallbladder wall thickening who underwent FDG-PET between November 2001 and August 2006 (Table 1). In all of these patients, gallbladder wall thickening was revealed by abdominal ultrasonography (US) or CT scans prior to PET. There were 8 males and 4 females, with ages ranging from 57 to 83 years (mean: 67.6 years).

### *PET imaging protocol*

FDG was produced with the NKK-Oxford superconducting cyclotron and NKK synthesis system. A HEADTOME IV SET-1400W-10 (Shimadzu Corp., Japan), which has 4 detector rings providing 7 contiguous slices at 13 mm intervals, was employed for the PET studies. The effective spatial resolution was 14 mm at full width at half maximum (FWHM). Before emission scanning, transmission scans were performed with a  $^{68}\text{Ge}/^{68}\text{Ga}$  ring source for attenuation correction. Images were obtained from 40 to 55 minutes after intravenous injection of 185–370 MBq FDG while fasting.<sup>9</sup>

### *Data analysis*

Patients exhibiting higher FDG uptake by the gallbladder in regions with wall thickening than in normal liver were considered positive. For quantitative evaluation of FDG accumulation in tumor, we designated regions of interest (ROIs: circles 8 mm in diameter) in the regions of gallbladder wall exhibiting thickening compared to other images. The mean of the standardized uptake values (SUV = tissue concentration/activity injected per body weight) of the ROIs were determined. Disease was rated benign or malignant on the basis of the findings of histopathologic examination of surgical specimens and the clinical course of individual patients.

## RESULTS

Of the 12 patients, 4 were rated as FDG-positive (SUV 4.7–9.4). Of these 4, 3 had gallbladder cancer (Fig. 1) and 1 had chronic cholecystitis (Fig. 2). Eight patients were FDG-negative. Of these 8, 2 underwent surgery and were diagnosed with chronic cholecystitis (Fig. 3). The other 6 were diagnosed with chronic cholecystitis on the basis of a combination of FDG-PET findings and other test results, and have been followed without active treatment (Table 1).

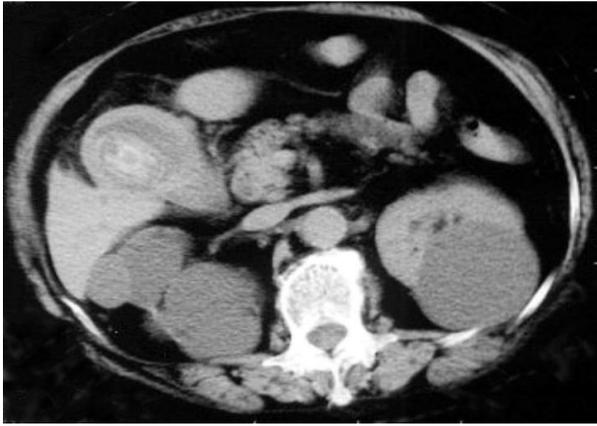
When used for the diagnosis of gallbladder cancer, FDG had a sensitivity of 75%, a specificity of 100%, and an accuracy of 93%.

## DISCUSSION

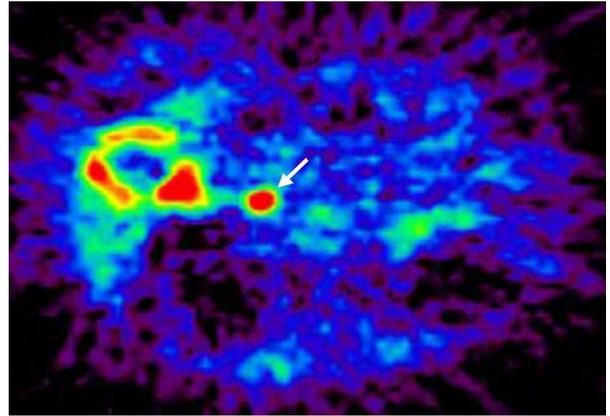
Gallbladder cancer is a relatively rare disease. At present, surgical resection is the only means available to treat it.<sup>21</sup> However, since this disease lacks specific symptoms and is often detected in advanced stages, the five-year survival rate for patients with inoperable gallbladder cancer is below 10%, and the mean duration of survival of these patients is 6 months.<sup>13</sup> Although early diagnosis and treatment are desirable when dealing with this cancer, there are few characteristic clinical symptoms, and it is difficult at present to detect this cancer in the early stage with diagnostic imaging.<sup>13</sup>

FDG-PET has recently been used frequently for the detection and evaluation of tumors. PET itself has been used to distinguish between benign and malignant tumors, for staging of tumors, and to follow patients with tumors. In the past, US, CT, MRI, ERCP, and other imaging modalities were used for the diagnosis of gallbladder cancer. It has recently begun to be reported that PET is also useful in the diagnosis of gallbladder cancer.<sup>18</sup>

Rodriguez-Frenandez et al. reported that PET had a sensitivity of 75% and a specificity of 82% in a study of 16 cases of gallbladder disease (with gallbladder wall



a

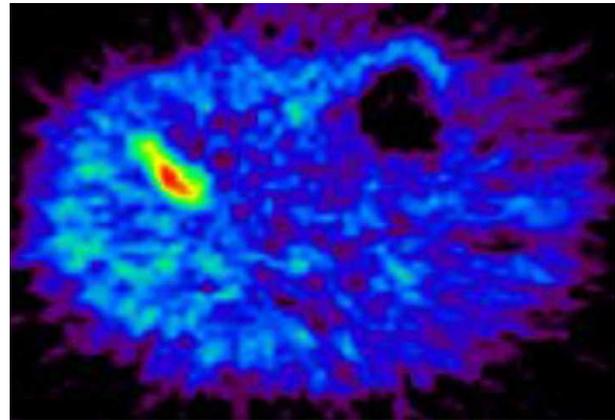


b

**Fig. 1** Case 2. (a) Abdominal CT scan shows whole wall thickening of the gallbladder and gallstone. (b) FDG-PET shows increased uptake (SUV 9.1) around the whole wall and at the neck of the gallbladder. Also a part of the duodenum (*arrow*) showed increased uptake. This case was diagnosed as advanced gallbladder carcinoma with duodenal invasion.

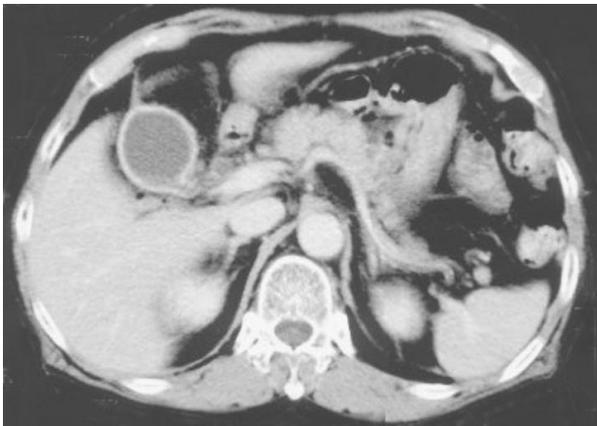


a

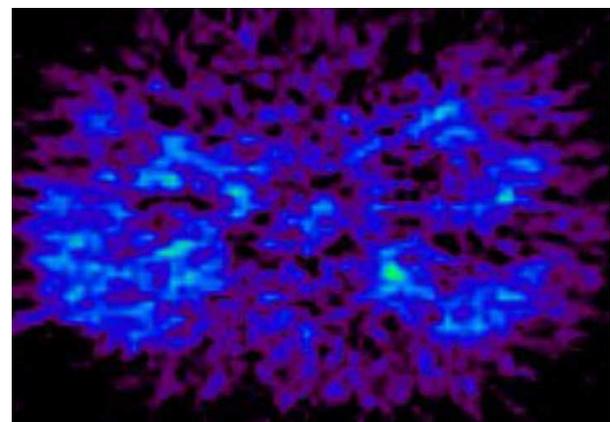


b

**Fig. 2** Case 4. (a) Abdominal CT scan shows whole wall thickening of the gallbladder and gallstones. (b) FDG-PET shows increased uptake (SUV 4.7) at the bed of the gallbladder. This case was diagnosed as cholecystitis with an excision specimen. The gallbladder wall adhered to the liver due to severe inflammation.



a



b

**Fig. 3** Case 5. (a) Abdominal CT scan shows whole wall thickening of the gallbladder. (b) FDG-PET does not show increased uptake at the gallbladder. This case was diagnosed as chronic cholecystitis.

thickening observed in 7 cases).<sup>10</sup> Anderson et al. evaluated the usefulness of PET in cases of gallbladder carcinoma and cholangiocarcinoma, as well as in 14 cases of gallbladder disease, and reported that the sensitivity of PET in detecting gallbladder cancer was 78%.<sup>11</sup> Koh et al. performed PET on 16 patients with protuberant lesions of the gallbladder, and reported that PET was superior to CT in diagnosing gallbladder cancer, with a sensitivity of 75% and specificity of 87.5%.<sup>12</sup>

Gallbladder cancer can be divided into two types, that presenting as an protuberant lesion and that characterized by gallbladder wall thickening. It has been thought that a protuberant lesion in the gallbladder over 15 mm in size is very likely to be malignant.<sup>22</sup> The protuberant type can be distinguished between benign and malignant tumors with the conventional imaging techniques, CT, MRI, US, and so on. The latter type of gallbladder cancer is more difficult to distinguish preoperatively from benign gallbladder disease, since wall thickening is also noted in cases of cholecystitis, adenomyomatosis, and other conditions.

In the present study, we performed PET on patients found only by CT or US to have gallbladder wall thickening. When used to distinguish between malignant and benign gallbladder wall thickening, PET had a sensitivity of 75% and specificity of 100%. There was one case (Case 4) in which the results of PET examination were false-positive. Acute/chronic cholecystitis and xanthogranulomatous cholecystitis are reported to be sometimes false-positive in the gallbladder wall thickening type,<sup>12,14,16,17</sup> because FDG is taken up by activated inflammatory cells. Nishiyama et al. stated that false-positive findings are likely in cases in which CRP > 1, that CRP is a good predictor of the specificity of PET, and that not only CRP but also other clinical or laboratory data emphasizing the existence of acute inflammatory conditions might be helpful.<sup>16</sup> In our study the false-positive case had developed acute cholecystitis one year previously. At the time of PET, this patient had neither clinical symptoms nor hematological findings of acute inflammation, with a CRP of 0.2. But the postoperative pathologic examination revealed intense inflammation and adhesion of the gallbladder wall to the liver, where there was abnormal FDG accumulation. FDG was thought to be taken up because there were severe inflammatory lesions at the cell level even though CRP was negative.

The results of the present study indicate that preoperative distinction between benign and malignant gallbladder wall thickening is possible with PET. If PET is used for this purpose, it may be possible to avoid unnecessary surgery. Because the number of cases evaluated in this study was very small, and because very few reports have been published on this topic, further evaluation is needed in a larger number of cases.

## REFERENCES

1. Van den Abbeele AD, Badawi RD. Use of positron emission tomography in oncology and its potential role to assess response to imatinib mesylate therapy in gastrointestinal stromal tumors (GISTs). *Eur J Cancer* 2002; 38 (Suppl 5): S60–65.
2. Kitagawa Y, Nishizawa S, Sano K, Ogasawara T, Nakamura M, Sadato N, et al. Prospective comparison of <sup>18</sup>F-FDG PET with conventional imaging modalities (MRI, CT, and <sup>67</sup>Ga scintigraphy) in assessment of combined intraarterial chemotherapy and radiotherapy for head and neck carcinoma. *J Nucl Med* 2003; 44: 198–206.
3. Hoh CK, Hawkins RA, Glaspy JA, Dahlbom M, Tse NY, Hoffman EJ, et al. Cancer detection with whole-body PET using 2-[<sup>18</sup>F]fluoro-2-deoxy-D-glucose. *J Comput Assist Tomogr* 1993; 17: 582–589.
4. Kubota K, Yokoyama J, Yamaguchi K, Ono S, Qureshy A, Itoh M, et al. FDG-PET delayed imaging for the detection of head and neck cancer recurrence after radio-chemotherapy: comparison with MRI/CT. *Eur J Nucl Med Mol Imaging* 2004; 31: 590–595.
5. Kubota K. From tumor biology to clinical PET: A review of positron emission tomography (PET) in oncology. *Ann Nucl Med* 2001; 15: 471–486.
6. Kelloff GJ, Hoffman JM, Johnson B, Scher HI, Siegel BA, Cheng EY, et al. Progress and promise of FDG-PET imaging for cancer patient management and oncologic drug development. *Clin Cancer Res* 2005; 11: 2785–2808.
7. Strauss LG, Conti PS. The applications of PET in clinical oncology. *J Nucl Med* 1991; 32: 623–648.
8. Strauss LG. Positron Emission Tomography: Current Role for Diagnosis and Therapy Monitoring in Oncology. *Oncologist* 1997; 2: 381–388.
9. Kunishima S, Taniguchi H, Yamaguchi A, Koh T, Yamagishi H. Evaluation of Abdominal Tumors with [<sup>18</sup>F]fluoro-deoxyglucose positron emission tomography. *Clin Positron Imaging* 2000; 3: 91–96.
10. Rodriguez-Fernandez A, Gomez-Rio M, Llamas-Elvira JM, Ortega-Lozano S, Ferron-Orihuela JA, Ramia-Angel JM, et al. Positron-emission tomography with fluorine-18-fluoro-2-deoxy-D-glucose for gallbladder cancer diagnosis. *Am J Surg* 2004; 188: 171–175.
11. Anderson CD, Rice MH, Pinson CW, Chapman WC, Chari RS, Delbeke D. Fluorodeoxyglucose PET imaging in the evaluation of gallbladder carcinoma and cholangiocarcinoma. *J Gastrointest Surg* 2004; 8: 90–97.
12. Koh T, Taniguchi H, Yamaguchi A, Kunishima S, Yamagishi H. Differential diagnosis of gallbladder cancer using positron emission tomography with fluorine-18-labeled fluoro-deoxyglucose (FDG-PET). *J Surg Oncol* 2003; 84: 74–81.
13. Shukla HS. Gallbladder cancer. *J Surg Oncol* 2006; 93: 604–606.
14. Rodriguez-Fernandez A, Gomez-Rio M, Medina-Benitez A, Moral JV, Ramos-Font C, Ramia-Angel JM. Application of modern imaging methods in diagnosis of gallbladder cancer. *J Surg Oncol* 2006; 93: 650–664.
15. Petrowsky H, Wildbrett P, Husarik DB, Hany TF, Tam S, Jochum W, et al. Impact of integrated positron emission tomography and computed tomography on staging and management of gallbladder cancer and cholangiocarcinoma.

- J Hepatol* 2006; 45: 43–50.
16. Nishiyama Y, Yamamoto Y, Fukunaga K, Kimura N, Miki A, Sasakawa Y, et al. Dual-time-point <sup>18</sup>F-FDG PET for the evaluation of gallbladder carcinoma. *J Nucl Med* 2006; 47: 633–638.
  17. Rosenbaum SJ, Stergar H, Antoch G, Veit P, Bockisch A, Kuhl H. Staging and follow-up of gastrointestinal tumors with PET/CT. *Abdom Imaging* 2006; 31: 25–35.
  18. Chander S, Lee P, Zingas AP, Joyrich RN, Zak IT, Bloom DA. PET imaging of gallbladder carcinoma. *Clin Nucl Med* 2005; 30: 804–805.
  19. Wakabayashi H, Akamoto S, Yachida S, Okano K, Izuishi K, Nishiyama Y. Significance of fluorodeoxyglucose PET imaging in the diagnosis of malignancies in patients with biliary stricture. *Eur J Surg Oncol* 2005; 31: 1175–1179.
  20. Yoshimitsu K, Honda H, Jimi M, Kuroiwa T, Hanada K, Irie H. MR diagnosis of adenomyomatosis of the gallbladder and differentiation from gallbladder carcinoma: importance of showing Rokitansky-Aschoff sinuses. *AJR* 1999; 172: 1541–1546.
  21. Hirooka Y, Naitoh Y, Goto H, Furukawa T, Ito A, Hayakawa T. Differential diagnosis of gall-bladder masses using colour Doppler ultrasonography. *J Gastroenterol Hepatol* 1996; 11: 840–846.
  22. Yang HL, Sun YG, Wang Z. Polypoid lesions of the gallbladder: Diagnosis and indications for surgery. *Br J Surg* 1992; 229: 498–504.