Journal of Gastrointestinal Cancer (2019) 50:901–906
https://doi.org/10.1007/s12029-018-0176-2

ORIGINAL RESEARCH

Radio-pathological Correlation of 18F-FDG PET in Characterizing Gallbladder Wall Thickening

Vikas Gupta[1] · K. S. Vishnu[1] · Thakur D. Yadav[1] · Yashwant R. Sakaray[1] · Santosh Irrinki[1] · B. R. Mittal[2] · N. Kalra[3] · K. Vaiphei[4]

Published online: 6 November 2018

Abstract

Aim Thick-walled gallbladder is difficult to characterize on conventional imaging. 18F-FDG PET was used to differentiate benign and malignant wall thickness and compared with histopathology.

Methods Thirty patients with gallbladder (GB) wall thickening (focal > 4 mm and diffuse > 7 mm), underwents uspected on ultrasound, or CT scan, and underwent 18F-FDG PET. Histopathology of the specimen was compared with imaging findings.

Results The mean age was 48.22 ± 31.33 years with a M:F 1:4 ratio. Twenty patients had diffuse and 10 had focal thickening. On 18F-FDG PET, lesion was benign in 12, malignant in 13, and indeterminate in 5. Histopathology was malignancy in 12; benign in 18-chronic cholecystitis in 11, xanthogranulomatous in 4, IgG4 related in 2, and polyp in 1. The mean GB wall thickness was 7.79 ± 3.59 mm (10.34 malignant and 6.10 in benign, $p = 0.001$). At a cutoff of 8.5 mm, the sensitivity and specificity of detecting malignancy was 94% and 67%. The mean SUV uptake was 7.46 (benign 4.51, malignant 14.26, $p = 0.0102$). At a cutoff of 5.95, the sensitivity and specificity of detecting malignancy was 92% and 79%. For 18F-FDG PET, overall sensitivity was 91%, specificity 79%, PPV 77%, NPV 92%, and diagnostic accuracy was 84%.

Conclusion 18F-FDG PET is a reliable method of differentiation between benign and malignant thickening of the gallbladder particularly when wall thickness and SUV value is taken into account.

Keywords Gall badder · PET CT · Xanthogranulomatous · Cholecystitis · Cancer · Thickening

Introduction

North India is one of the highest incidence regions of carcinoma gallbladder (GB) worldwide [1]. Early diagnosis and curative surgery is the only hope for cure [2]. It is difficult to pick up early lesions on conventional imaging. Commonly, early GB cancer can present as wall thickening on imaging without any invasion into the adjacent viscera [3]. Such wall thickness may also be observed in acute or chronic cholecystitis, xanthogranulomatous cholecystitis [4–7]. It is imperative to differentiate aforementioned conditions from malignancy as the surgical management will entirely be different in both the situations. Till date, there is no modality which can reliably differentiate between early GB malignancy from benign thickening [3–10]. Contrast-enhanced computerized tomogram (CECT) has been widely used in evaluation of GB mass for staging the tumor [5, 6, 9]. GB thickening, focal or diffuse as seen on CT, is sometimes difficult to characterize particularly in the absence of associated findings [4–8]. More so, tumor with underlying chronic cholecystitis, can further make this differentiation even difficult [5–9].

The use of 18F-FDG PET, a functional study, has been found useful for preoperative assessment of patients with biliary tract cancer [11, 12]. The poor anatomic localization by 18F-FDG PET has been overcome by combining 18F-FDG PET with CECT. There are a few studies regarding the role of 18F-FDG PET-CT scan in staging of gallbladder carcinoma [13]. However, there is paucity of literature regarding the use of 18F-FDG PET-CT as a diagnostic modality in evaluation of GB thickening [14, 15].

✉ Vikas Gupta
vikaspgi@gmail.com

[1] Department of General Surgery, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India

[2] Department of Nuclear Medicine, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India

[3] Department of Radiodiagnosis, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India

[4] Department of Histopathology, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India

So the present study was planned to discern the role of 18F-FDG PET-CT to resolve the diagnostic dilemma of thick-walled gallbladder.

Methodology

From July 2014 to December 2015, 30 adult patients with gallbladder (GB) wall thickening (less than 20 mm) were prospectively evaluated at Postgraduate Institute of Medical Education and Research, a tertiary care center in India. GB wall thickening was defined as diffuse wall thickness of more than 7 mm or focal thickness of more than 4 mm as seen on abdominal ultrasonogram (USG) or computerized tomogram (CT). Patients with definite evidence of malignancy or metastasis on USG or CT were excluded from the study. GB thickening beyond 20 mm was excluded from the study. The study was approved by the Institute ethics committee. Informed consent was taken from all the patients prior to enrollment.

Clinical examination, complete hemogram, coagulation profile, and liver and renal function tests were carried out in all the patients. Subsequently, whole body scanning was done in all the patients by acquiring images from base of skull to mid-thigh using a dedicated 18F-FDG PET-CT scanner (Discovery 710). 18F-FDG PET-CT was performed in diabetic patients only after the blood glucose level was below 150 mg/dl on the day of study. Patients with acute cholecystitis underwent PET-CT 8 weeks after the resolution of acute episode.

All patients underwent surgery within 8 weeks of PET-CT. Surgery was tailored as per the PET-CT and operative findings (Fig. 1). Patients with clear cut evidence of benign disease underwent cholecystectomy, while those with definite malignancy underwent extended cholecystectomy. Patients with indeterminate lesion underwent anticipatory extended cholecystectomy wherein a 2-cm liver wedge was resected en-bloc with gallbladder and was sent for frozen section. The need for systemic lymphadenectomy was governed by the findings on the frozen section. The excised specimen was sent for histopathology using standard hematoxylin and eosin staining. Special stains were performed as per the requirement. Pathological diagnosis was corroborated with imaging findings.

Statistical Analysis

All the data collected through this study were statistically analyzed and the degree of co relation between 18F-FDG PET-CT findings and histopathological report was ascertained. Sensitivity, specificity, accuracy, and positive and negative predictive value were calculated for 18F-FDG PET scan findings keeping histopathological diagnosis as gold standard. SUV uptake values and GB wall thickness were analyzed to determine a cutoff value to distinguish between benign and malignant GB lesions. For all analysis, P value of less than 0.05 will be considered statistically significant. All the statistical analyses were done using SPSS (Statistical Package for Social Sciences) software version 20.

Results

The mean age of the patients was 48.22 ± 31.33 (15–76) years with male to female ratio of 1:4. Clinical presentation was abdominal pain in all, anorexia and weight loss in 10 (33.3%), and jaundice in 3 (10%).

Imaging Findings

Diffuse wall thickening was observed in 20 (66.7%) and focal in 10 (33.3%) patients. The mean wall thickness was 7.79 ±

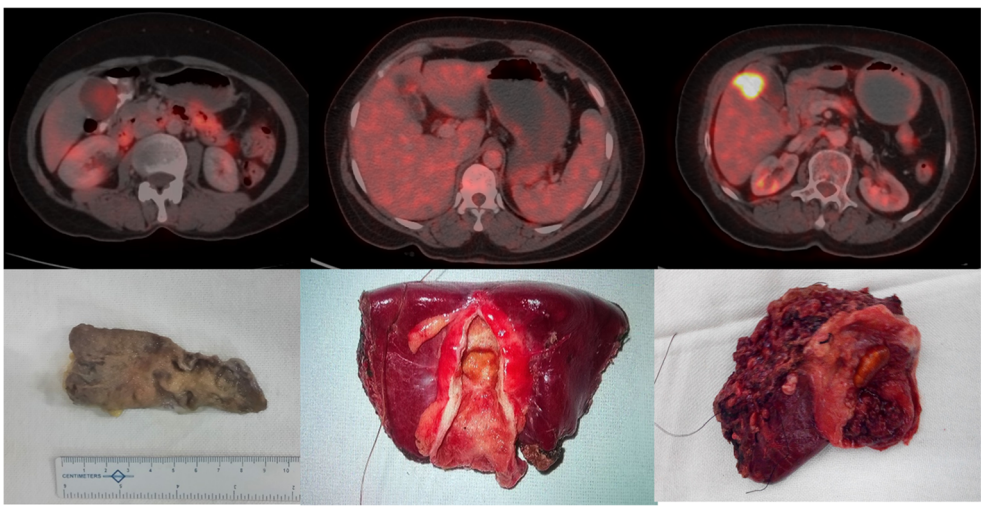

Fig. 1 PET CT and specimen photograph for simple cholecystitis (left), xanthogranulomatous cholecystitis (middle), and carcinoma gallbladder (right)

3.59 (3–17) mm. The mean of diffuse thickening was 6.47 ± 1.61 mm, while that of focal thickening was 10.59 ± 4.16 mm.

The mean SUV uptake was found to be 7.46 ± 6.81 (0–22.1). The mean SUV uptake of diffuse wall thickening was 5.98 ± 6.52 (0–17.4) while that of focal wall thickening was 10.44 ± 6.70 (3.8–22.1).

Lymph node enlargement was seen in 6 (23%) patients on conventional imaging. However, a total of 16 (53%) patients showed uptake in the lymph nodes on 18F-FDG PET.

On conventional imaging, the lesion was characterized as benign in 13 (43%), malignant in 15 (50%), and indeterminate in 2 (7%). On PET-CT, it was benign in 12 (40%), malignant in 13(43%), and indeterminate in 5 (17%).

Operative Details

Seven patients had benign disease and underwent cholecystectomy. Eighteen patients had operative suspicion of malignancy; out of which 16 underwent extended cholecystectomy and two were not resectable due to locally advanced disease at the time of surgery. Five patients with diagnostic dilemma at operation underwent en bloc GB resection with 2-cm liver wedge as per the protocol described above. Frozen section in all these patients turned out to be benign.

Pathological Findings

Histopathology confirmed gallbladder cancer in 12 (40%) patients (including biopsy of 2 who could not be resected) and benign lesion in 18 (60%). Among the benign lesions, chronic cholecystitis was seen in 11 (37%), xanthogranulomatous cholecystitis in 4 (13%), IgG_4-related cholecystitis in 2 (7%), and polyp in 1 (3%).

Wall Thickness and Pathological Diagnosis

Among the 18 benign lesions, 17 had diffuse and 1 had focal (patient had polyp) thickening. Of the 12 malignant lesions, 9 had focal and 3 had diffuse thickening.

The mean wall thickness for benign lesions 6.1 ± 1.78 mm and that of the malignant lesions was 10.34 $\pm$ 4.17 mm and the difference was statistically significant ($p = 0.001$).

A receiver operator characteristic (ROC) curve was plotted between wall thickness on CT scan and the histopathological diagnosis. The area under the curve was 0.796 ($p = 0.042$). At a cutoff value of 8.5 mm, the sensitivity and specificity are 94.4% and 66.7% respectively to characterize the lesion (Fig. 2a).

ROC curves separately for focal and diffuse thickening failed to show any correlation with the type of the lesion.

18F-FDG Uptake and Pathological Diagnosis

The mean SUV uptake was 7.46 ± 6.81 (0–22.1). Mean SUV uptake of diffuse wall thickening was 5.98 ± 6.52 (0–17.4) and that of focal wall thickening was 10.44 ± 6.70 (3.8–22.1) and the difference was statistically not significant ($p = 0.92$).

The SUV max was high for patients with complicated cholecystitis. Three patients with xanthogranulomatous cholecystitis had SUV max values of 3.95, 7.6, and 17.4 while two patients with IgG4-related disease had SUV max values of 10.8 and16.9.

Area under ROC curve, plotted for SUV max and the nature of lesion, was 0.857 ($p = 0.031$). At a SUV max value of 5.95, the sensitivity and specificity to characterize the lesion was 91.7% and 77.8% respectively (Fig. 2b). For diffuse GB thickening, area under ROC curve was 0.882 ($p = 0.039$). At a SUV cutoff of 8.35, the sensitivity was 100% and specificity was 82% (Fig. 2c). ROC curves for focal thickening failed to show any correlation with the type of the lesion.

Five (16.7%) lesions were not characterized on PET-CT and were labeled as indeterminate. However, four (80%) of the indeterminate lesions were confirmed to be benign on histopathology. After censoring indeterminate cases, 18F-FDG PET-CT had sensitivity of 90.91% (CI 58.72%–99.97%), specificity of 78.57% (CI 49.20%–95.34%), positive predictive value 76.92% (CI 46.19%–94.96%), negative predictive value 91.67% (CI 61.52%–99.79%), and diagnostic accuracy of 84%. There was good degree of agreement between PET-CT and histopathological diagnosis (kappa value 0.682; 95% CI 0.399–0.964).

On inclusion of indeterminate lesions into the benign category, the sensitivity, specificity, and positive and negative predictive values were 83.33% (CI 50.88–97.05), 94.44% (CI 70.62–99.70), 90.90% (CI 57.11–99.50), and 89.47% (CI 64.46–98.15) respectively. The accuracy was 90%. There was good degree of agreement between the PET CT findings and pathological diagnosis (Kappa value 0.658, SE 0.139, CI 0.563–1.0, $p = 0.000$).

When the cutoff of both wall thickness of 8.5 mm and SUV max 5.98 are taken together into account then, the sensitivity, specificity, and positive and negative predictive values were 58.33% (CI 28.59–83.50), 94.44% (CI 70.62–99.70), 87.50% (CI 46.67–99.34), and 77.27% (CI 54.17–91.31) respectively. The accuracy was 84 %. There was moderate degree of agreement between the PET CT findings and pathological diagnosis (Kappa value 0.559, SE 0.153, $p = 0.001$).

Lymph Node Positivity

Without the use of metabolic imaging, only 6 out of 13 pathologically positive lymph nodes were identified however with the addition of uptake value 12 lymph nodes could be correctly identified in 16 patients who underwent oncological resection.

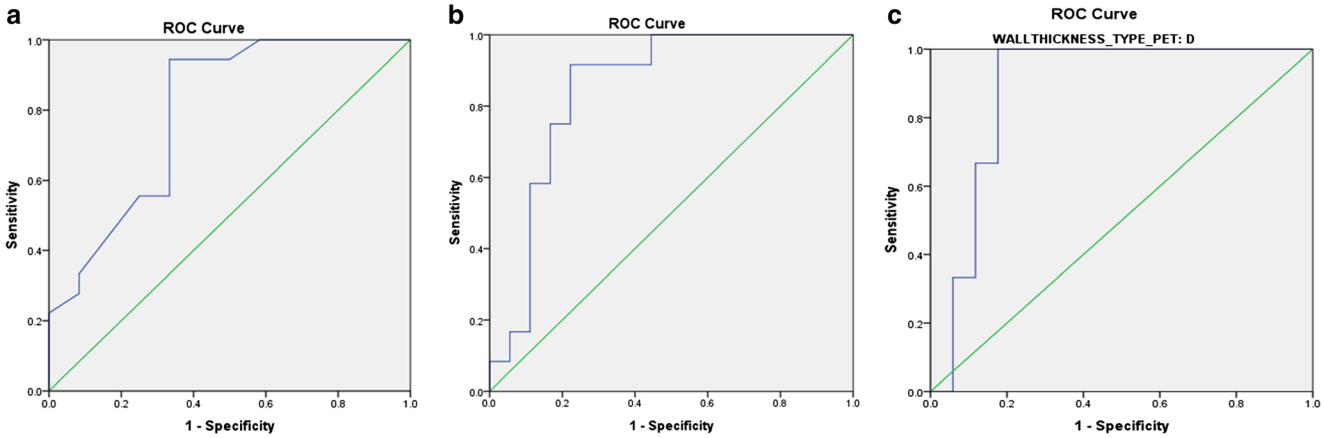

Fig. 2 Receiver operating characteristic curve for **a** GB wall thickening, **b** SUV max value, and **c** SUV max value for diffuse wall thickness

Discussion

The present study has shown the diagnostic potential of PET-CT in characterizing the GB wall thickening. The strength of present study is the stringent inclusion criteria; particularly of only those cases with GB thickening which were difficult to characterize on conventional imaging. We excluded all the cases with GB thickening beyond 20 mm, as those are more likely to harbor malignancy. The diagnostic dilemma is greatest in patients who have 4–20-mm wall thickening, which forms only a small fraction of patients with benign or malignant GB lesions [3–6]. This limited enrollment in the present study to 30 cases. Contrary to the present study, other studies have included a wide variety of benign and malignant lesions of GB [12, 15–17].

Surgery is the only curative treatment for early GB cancer. There are no specific symptoms of early GB cancer [1–3]. It is suspected only when GB wall appears thickened on conventional imaging [4–6]. Mere presence of wall thickening is difficult to characterize with certainty as benign or malignant [5–9]. However, it is imperative to have the exact knowledge of the diagnosis prior to surgery so as to offer appropriate treatment of the underlying condition. India being a high incidence area for GB cancer [1], all suspicious lesions should be thoroughly evaluated to ascertain the diagnosis. With conventional imaging, it is at times difficult to establish the exact nature of the lesion [3–10].

A recent study on evaluation of GB wall thickening to differentiate malignancy from XGC and acute cholecystitis using multidetector CT has found it to have moderate sensitivity, poor specificity, and moderate-to-substantial inter-rater repeatability. They identified disrupted gallbladder mucosa, gall stones, and wall thickness as the only significant factors [5]. All these are non-specific and can be found in benign disease as well. Another recent series has demonstrated the role of contrast enhanced ultrasonogram in detecting gallbladder cancer. Wall thickness more than 16 mm was one of the predictors of malignancy in addition to early arterial enhancement, interrupted inner layer, and early washout [6]. Another recent study has found GB wall thickening as the second commonest presentation of GB carcinoma [18]. To exactly define the thick-walled GB with uncertain pathology, we excluded all the patients with more than 20 mm thickness.

Role of PET-CT in staging of GB cancer is well established [12, 13, 19]. The diagnostic potential of this modality in patients with GB cancer is emerging. Ramos-Font et al. [15] in a study of 49 patients found PET-CT to be 95.9%, 85.7%, and 95.9% accurate in the detection of primary lesion, lymph node involvement, and metastatic disease. They concluded that SUV max has a complementary role in addition to visual analysis. Koh et al. [20] in a small series reported 75% sensitivity and 87% specificity to detect GB cancer in protuberant lesion of the gallbladder. Anderson et al. have reported 78% sensitivity of PET-CT to detect GB carcinoma.

Nishiyama et al. [17] reported that sensitivity and specificity of PET-CT to detect GB cancer can be improved by addition of delayed phase imaging. Furukawa et al. [21] have demonstrated the prognostic significance of preoperative PET-CT by defining the cutoff of uptake value. A meta-analysis of 13 studies including 495 patients reported 87% sensitivity and 78% specificity in evaluation of cancer GB [13]. Most of the studies have suggested the reasons for false-positive results due to inflammatory conditions of GB while false negative due to small size tumor and a low-grade malignancy [13–17, 19–22]. In the present study, we have specifically looked into this subset of the patients where the lesions were likely to give erroneous result on imaging.

A study of 12 patients by Oe et al. [14] on defining the role of PET-CT on GB thickening found FDG uptake in 4 patients out of which 3 were malignant while those without any uptake were benign. They did not report any case with complicated cholecystitis, unlike those observed in the present series. Moreover, they did not exactly define thick-walled GB. In the present study, we have defined and classified GB thickening into diffuse and focal. We did not observe any difference of diffuse thickening between benign and malignant cases.

With addition of uptake value to diffuse thickening, benign and malignant lesions could be differentiated. On the contrary, only one case with focal thickening without any uptake was benign while the rest had uptake and were malignant.

In the present study, we observed 16% patients who could not be classified on PET-CT and were labeled as indeterminate. The high incidence of indeterminate lesions was due to strict inclusion criteria. Although majority of the indeterminate cases turned out to be benign, we still advocate anticipatory en bloc surgery in such a situation. Others have also proposed similar approach in such a situation [23]. En bloc removal of GB with liver wedge gives an advantage of not breaching the tumor plane and need for lymphadenectomy is guided by frozen section.

The uptake value in PET-CT is helpful in differentiating benign and malignant lesions. However, there is no consensus regarding the absolute cutoff value. The major problem is due to intense uptake in inflammatory conditions. In the present study, we observed intense uptake in xanthogranulomatous cholecystitis and IgG4-related cholecystitis, despite taking due precautions while performing PET-CT. Rodrigues et al. [22] in a study of 16 patients found mean SUV of 4.1 in patients harboring tumor. Another study on 49 patients defined a cutoff value of 3.62 to determine malignant lesions [15]. Nishiyama et al. [17] described the use of delayed phase imaging and calculating retention index to determine malignancy. They arbitrarily defined SUV cutoff for early PET to be 4.5 and for delayed to be 2.9. In the present study, we found higher cutoff values in the entire group and also those with diffuse thickening probably due to more number of patients with complicated cholecystitis.

Concluding, PET-CT is a useful tool to characterize between less than 20-mm lesions of GB. Focal thickening with uptake in PET is suggestive of malignancy. For diffuse thickening, SUV value should be taken into account to differentiate between benign and malignant disease.

Authors' Contributions VG, TDY: concept and idea; KSV: clinical data collection; NK: Radiological data, BRM: PET-CT data; KV: Pathological data, VG, YRS, SI: drafting and correction.

Compliance with Ethical Standards

Ethical Clearance Obtained.

References

1. Malhotra RK, Manoharan N, Shukla NK, Rath GK. Gallbladder cancer incidence in Delhi urban: a 25-year trend analysis. Ind J Cancer. 2017;54:673–7.
2. Köhn N, Maubach J, Warschkow R, Tsai C, Nussbaum DP, Candinas D, et al. High rate of positive lymph nodes in T1a gallbladder cancer does not translate to decreased survival: a population-based, propensity score adjusted analysis. HPB (Oxford). 2018 Jun 8 S1365-182X(18)30819-0. https://doi.org/10.1016/j.hpb.2018.05.007.
3. Goussous N, Maqsood H, Patel K, Ferdosi H, Muhammad N, Sill AM, et al. Clues to predict incidental gallbladder cancer. Hepatobiliary Pancreat Dis Int. 2018;17:149–57.
4. Mitchell CH, Johnson PT, Fishman EK, Hruban RH, Raman SP. Features suggestive of gallbladder malignancy: analysis of T1, T2, and T3 tumors on cross-sectional imaging. J Comput Assist Tomogr. 2014;38:235–41.
5. Wasnik AP, Davenport MS, Kaza RK, Weadock WJ, Udager A, Keshavarzi N, et al. Diagnostic accuracy of MDCT in differentiating gallbladder cancer from acute and xanthogranulomatous cholecystitis. Clin Imag. 2018;50:223–8.
6. Chen LD, Huang Y, Xie XH, Chen W, Shan QY, Xu M, et al. Diagnostic nomogram for gallbladder wall thickening mimicking malignancy: using contrast-enhanced ultrasonography or multidetector computed tomography? Abdom Radiol. 2017;42:2436–46. https://doi.org/10.1007/s00261-017-1162-z.
7. Kishore R, Nundy S, Mehrotra S, Mehta N, Mangla V, Lalwani S. Strategies for differentiating gallbladder carcinoma from xanthogranuomatous cholecystitis – a tertiary care centre experience. Ind J Surg Oncol. 2017;8:554–9.
8. Rao RV, Kumar A, Sikora SS, Saxena R, Kapoor VK. Xanthogranulomatous cholecystitis: differentiation from associated gall bladder carcinoma. Trop Gastroenterol. 2005;26:31–3.
9. Kim SJ, Lee JM, Lee JY, Kim SH, Han JK, Choi BI, et al. Analysis of enhancement pattern of flat gallbladder wall thickening on MDCT to differentiate gallbladder cancer from cholecystitis. Am J Roentgenol. 2008;191:765–71.
10. Sureka B, Singh VP, Rajesh SR, Laroia S, Bansa K, Rastogi A, et al. Computed tomography (CT) and magnetic resonance (MR) findings in xanthogranulomatous cholecystitis: retrospective analysis of pathologically proven 30 cases – tertiary care experience. Pol J Radiol. 2017;82:327–32.
11. Sacks A, Peller PJ, Surasi DS, Chatburn L, Mercier G, Subramaniam RM. Value of PET/CT in the management of primary hepatobiliary tumors, part 2. AJR Am J Roentgenol. 2011;197:260–5.
12. Covera CU, Blumgart LH, Akhurst T, DeMatteo RP, D'Angelica M, Fong Y, et al. 18 F-fluorodeoxyglucose positron emission tomography influences management decisions in patients with biliary cancer. J Am Coll Surg. 2007;206:57–65.
13. Annunziata S, Pizzuto AP, Caldarella C, Galiandro F, sadeghi R, Treglia G. Diagnostic accuracy of fluorine-18-fluorodeoxyglucose positron emission tomography in gallbladder cancer: a meta-analysis. World J Gastroenterol. 2015;21:11481–8.
14. Oe A, Kawabe J, Toril K, Higashiyama S, Kotani J, Hayashi T, et al. Distinguishing between benign from malignant gallbladder wall thickening using FDG-PET. Ann Nucl Med. 2006;20:699–703.
15. Roms-Font C, Gomez-Rio M, Rodriguez-Fernandez A, Jimenez-Haffernan A, Sanchez RS, Llamas-Elvira JM. Ability of FDG-PET/CT in the detection of gallbladder cancer. J Surg Oncol. 2014;109:218–24.
16. Anderson CD, Rice MH, Pinson W, Chapman WC, Chari RS, Delbeke D. Fluorodeoxyglucose pet imaging in the evaluation of gallbladder carcinoma and cholangiocarcinoma. J Gastrointest Surg. 2004;8:90–7.
17. Nishiyama Y, Yamamoto Y, Fukunaga K, Kimura N, Miki A, Sasakawa Y, et al. Dual-time –point ^{18}F-FDG PET for evaluation of gallbladder carcinoma. J Nucl Med. 2006;47:633–8.
18. Jindal G, Singal S, Nagi B, Mittal A, Mittal S, Singal R. Role of multidetector computed tomography (MDCT) in evaluation of gallbladder malignancy and its pathological correlation in an indian rural center. Maedica – J Clin Med. 2018;13:55–60.
19. Hwang JP, Lim I, Cho EH, Kim BI, Choi CW, Lim SM. Prognostic value of SUV max measured by Fluorine-18 fluorodeoxyglucose

positron emission tomography with computed tomography in patients with gallbladder cancer. Nucl Med Mol Imag. 2014;48:114–20.
20. 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.
21. Furukawa H, Ikuma H, Assakura K, Uesaka K. Prognostic importance of standardized uptake value on F-18 fluorodeoxyglucose-positron emission tomography in biliary tract carcinoma. J Surg Oncol. 2009;100:494–9.
22. 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-Dglucose for gallbladder cancer diagnosis. Am J Surg. 2004;188:171–5.
23. Kapoor VK, Singh R, Behari A, Sharma S, Kumar A, Prakash A, et al. Anticipatory extended cholecystectomy: the 'Lucknow' approach for thick walled gall bladder with low suspicion of cancer. Chin Clin Oncol. 2016;5:8. https://doi.org/10.3978/j.issn.2304-3865.2016.02.07.