The Diagnostic Accuracy of $^{18}$F-FDG-PET/CT for Cancer of the Gallbladder: A Retrospective Study

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Abstract

**Background**  Gallbladder cancer has a poor prognosis and imaging can have variable diagnostic accuracy. We assessed the ability of preoperative $^{18}$F-fluorodeoxyglucose positron emission tomography computed tomography ($^{18}$F-FDG-PET/CT) imaging to predict a postoperative histological diagnosis of gallbladder cancer.

**Method**  A retrospective analysis was undertaken in a cohort of patients, who had suspected gallbladder cancer on cross-sectional imaging and that underwent preoperative FDG-PET/CT scan. The discriminatory power of FDG-PET/CT was determined in receiver operator characteristic (ROC) analysis and diagnostic accuracy parameters were estimated at different thresholds of maximum standard unit value (SUV$_{\text{max}}$).

**Results**  Twenty-two patients were included in the study; 7 had malignant and 15 benign diagnoses. There was no statistically significant difference between the measured SUV$_{\text{max}}$ between the two groups ($p = 0.71$). With an area under the curve of 0.486, the ROC curve did not indicate any discriminatory power of FDG-PET/CT at any potential threshold of SUV$_{\text{max}}$.

**Conclusion**  This study indicates that the diagnosis of primary gallbladder cancer cannot be accurately confirmed with FDG PET/CT scanning.
Carcinoma of the gallbladder (GBC) is the commonest malignancy of the biliary tract with a global incidence of 2.2/100,000 population. In general, GBC is detected upon radiological imaging either as an incidental finding or during investigation of upper abdominal symptoms. The increased use of cross-sectional imaging modalities for investigating abdominal symptoms has meant an increase in reported rates of both benign and malignant gallbladder pathology. Distinguishing between these pathologies has important implications for management and significantly dictates patient outcomes. For instance, patients with advanced GBC have poor 5-year survival rates of 4 to 12%. Conversely, patients diagnosed at early stages of the disease, that is amenable to surgical resection, have an improved 5-year survival of 63%. Resection surgery offers the best opportunity for long-term survival following a diagnosis of GBC. However, abnormalities of the gallbladder are frequently identified on radiological imaging and the differential diagnosis can include acute and chronic cholecystitis, xanthogranulomatous cholecystitis, adenomyomatosis, as well as GBC. The appearance of GBC on radiological imaging can range from subtle findings such as gallbladder wall thickening to mass occupying lesions with liver infiltration, although the latter findings is only present in 40 to 65% of patients. Biopsy is not recommended for the diagnosis of GBC, although recent studies appear to suggest that this is a feasible approach. Thus, patient management is primarily determined by radiological features and in those patients where features are concerning for GBC, radical surgical resection must be considered as it offers the best form of long-term survival.

Patient staging in the form of cross-sectional imaging includes computed tomography (CT) and/or magnetic resonance imaging (MRI). However, many of the aforementioned radiological changes will be present and the diagnosis of GBC may not be excluded. Clearly, if benign pathology is confirmed a simple cholecystectomy, if deemed appropriate, would be the preferred intervention. However, if GBC remains a differential, then radical cholecystectomy with intraoperative frozen section of surgical margins is advocated. However, radical cholecystectomy has a reported morbidity of 29% and thus needs careful patient selection and preoperative counselling.

Fluorodeoxyglucose-positron emission tomography (FDG-PET) scanning has been suggested to have superior sensitivity and specificity in being able to differentiate between benign and malignant disease when compared with CT, MRI, and ultrasound (US). by means of measuring the maximum standard unit value (SUVmax) level of the primary gallbladder lesion, thereby potentially allowing patient to be counselled and offered appropriate surgical management.

The aim of this study was to evaluate the ability of preoperative 18F-FGD-PET/CT (FDG PET/CT) imaging to predict a postoperative histological diagnosis of gallbladder cancer.

We conducted a retrospective study from January 2013 to December 2019 inclusive. We identified all patients at The Royal Marsden Hospital, who had undergone a cholecystectomy during this time period.

All patients included in the study were adults. To be included in the study, patients were required to have a CT and/or MRI scan that was reported as consistent with GBC by a specialist hepatopancreatobiliary (HPB) radiologist. In addition, all included patients had to have undergone a preoperative FDG-PET/CT scan and had formal histology report of the resected gallbladder and/or liver by a dedicated HPB histopathologist. Only patients who had an FDG-PET/CT within 120 days prior to cholecystectomy were included. Clinical and radiological information were scrutinized on electronic patient records and all FDG-PET/CT scans were re-evaluated with measurements of SUVmax levels in conjunction with a nuclear medicine radiologist.

Our population was examined with an integrated PET/CT system (Siemens Biograph Horizon, Erlangen, Germany). The PET/CT was performed according to a standardized protocol. Each patient was fasted for at least 6 hours, rested and hydrated and blood glucose level was checked. 18F-FDG was injected into a peripheral vein (dose calculated according to body weight – scaling base on the EANM guidelines on FDG imaging). Image acquisition was performed 60 minutes following FDG injection with the patient in a supine position. The imaging protocol considered half body examination of each patient from the supraorbital region to mid-thigh. Acquisition duration was determined by the patient’s body weight and activity administered. The study protocol began with the acquisition of a topogram (50mA, 120kV), and a helical CT examination (150mA, 120kV) followed by positron emission imaging. The CT scan images were used for the identification of the lesion and attenuation correction of the PET/CT imaging. Images were processed on a Hermes imaging processing program. – Fig. 3 illustrates examples of benign and malignant cases.

Demographic (gender, age), clinical (days between scan to operation), and descriptive statistics for SUVmax (mean, median, standard deviation, and interquartile range) were calculated according to histopathological result. Differences in SUVmax between patient with malignant and benign diagnoses on histology were determined using a Student’s t-test for independent samples and the nonparametric Mann–Whitney U test. The discriminatory power of PET/CT-CT was determined in a receiver operator characteristic (ROC) analysis. The area under the curve (AUC) of the ROC was used to visualize its diagnostic ability and diagnostic accuracy parameters (S: sensitivity, Sp: specificity, PPV: positive predictive value, NPV: negative predictive value and
Results

Three hundred and seventy-eight patients had cholecystectomies during the study period. There was no FGD-PET/CT scan prior to surgery for 178 patients. We note that in many of these cases cholecystectomy had been undertaken as part of another surgical procedure (e.g., pancreaticoduodenectomy or liver resection). In a further 177 patients, GBC was not suspected on the reported cross-sectional imaging. One patient had histology confirming a metastatic mucinous tumor of gynecological origin and was also excluded. Hence, 22 patients were identified for inclusion in the study as a GBC was suspected upon preoperative imaging (see Fig. 1).

Patient breakdown and their summative characteristics are presented in Tables 1 and 2. The patients have been classified based upon postoperative histology in benign and malignant groups. There was no statistical difference between the groups for age and gender. In addition, there was no difference in the time period between the FDG-PET/CT scan and the patient having cholecystectomy performed.

All 22 included patients had preoperative cross-sectional imaging in the form of an MRI abdomen and/or CT thorax/abdomen/pelvis (TAP) scan. Twelve patients had both MRI abdomen and CT TAP, 6 patients had CT TAP only, while 4 patients had MRI abdomen alone. Sixteen overall accuracy) were estimated at different values of SUV<sub>max</sub>. Analyses were performed using Stata SE 11.
|   | Age | M/F | PET to Op (days) | CT findings          | MRI findings          | Ca 19–9 | Histology                                      | SUV max |
|---|-----|-----|------------------|----------------------|----------------------|---------|-----------------------------------------------|---------|
| 1 | 55  | M   | 67               | No CT                | GB wall thickening   | 35      | Xanthogranulomatous cholecystis               | 5.8     |
| 2 | 65  | M   | 16               | No CT                | GB wall thickening   | 211     | Xanthogranulomatous cholecystis               | 11.8    |
| 3 | 74  | F   | 109              | GB mass              | GB mass              | 863     | Chronic cholecystitis and fibrosis            | 3.7     |
| 4 | 73  | F   | 28               | GB mass              | GB wall thickening   | 21      | Chronic cholecystitis with mucosa ulceration | 7.0     |
| 5 | 73  | F   | 28               | GB wall thickening   | GB mass              | 27      | Chronic cholecystitis with mucosa ulceration | 10.7    |
| 6 | 57  | F   | 67               | GB wall thickening   | No MRI               | N/A     | Chronic cholecystitis with localized perforation | 14.6    |
| 7 | 58  | F   | 71               | GB wall thickening   | No MRI               | N/A     | Chronic cholecystitis with abscess           | 21.9    |
| 8 | 55  | M   | 40               | GB mass              | GB wall thickening   | N/A     | Chronic cholecystitis and fibrosis            | 9.7     |
| 9 | 70  | F   | 80               | GB wall thickening   | GB wall thickening   | 44      | Chronic cholecystitis and fibrosis            | 7.4     |
| 10| 61  | F   | 33               | GB wall thickening   | No MRI               | 2       | Chronic cholecystitis                        | 6.7     |
| 11| 63  | M   | 84               | GB wall thickening   | GB wall thickening   | < 2     | Chronic cholecystitis                        | 2.9     |
| 12| 67  | M   | 49               | GB wall thickening   | GB wall thickening   | 23      | Chronic cholecystitis                        | 7.6     |
| 13| 79  | M   | 75               | GB wall thickening   | GB wall thickening   | N/A     | Chronic cholecystitis                        | 11.5    |
| 14| 84  | F   | 101              | GB wall thickening   | No MRI               | N/A     | Chronic cholecystitis                        | 7.1     |
| 15| 58  | F   | 103              | GB wall thickening   | No MRI               | < 2     | Adenomyosis                                   | 1.0     |
| 16| 56  | M   | 6                | GB mass              | No MRI               | 59      | Adenocarcinoma (well/moderate differentiation)| 6.0     |
| 17| 77  | F   | 109              | GB wall thickening   | GB mass              | < 2     | Adenocarcinoma (moderate/poor differentiation)| 3.7     |
| 18| 81  | M   | 45               | No CT                | GB wall thickening   | 248     | Adenocarcinoma (moderate/poor differentiation)| 15.3    |
| 19| 65  | F   | 19               | No CT                | GB mass              | 2,082   | Adenocarcinoma (moderate differentiation)     | 11.4    |
| 20| 68  | F   | 73               | GB mass              | GB mass              | N/A     | Adenocarcinoma (moderate differentiation)     | 4.0     |
| 21| 74  | M   | 24               | GB mass              | GB wall thickening   | 31,783  | Adenocarcinoma (moderate differentiation)     | 13.2    |
| 22| 78  | M   | 14               | GB mass              | GB mass              | 91      | Adenocarcinoma (moderate differentiation)     | 3.7     |

Abbreviations: CT, computed tomography; GB, gallbladder; MRI, magnetic resonance imaging; N/A, not available; SUV max, maximum standard unit value.
patients had preoperative CA19–9 levels, six in whom postoperative histology was consistent with malignancy and 10 patients with benign pathology. There was no statistical difference in Ca19–9 levels between these two groups ($p = 0.33$).

Based upon cross-sectional imaging and FDG-PET/CT, all patients underwent radical cholecystectomy with intraoperative frozen section and selective lymphadenectomy. Histopathological data was available for all 22 patients included in the study. Seven (32%) patients had malignant pathology, while fifteen (68%) patients had benign pathology. All seven patients with malignancy had histopathology consistent with GBC of varying differentiation. Of the 15 cases with benign pathology, 12 had features of chronic cholecystitis, 2 had xanthogranulomatous cholecystitis, and 1 reported case of adenomyosis.

| Table 2 Patient demographics | Malignant | Benign | p-Value |
|------------------------------|-----------|--------|---------|
| Female gender                | 3         | 9      |         |
| Male gender                  | 4         | 6      |         |
| Mean age (range)             | 71.29 (56–81) | 66.13 (55–84) | 0.23    |
| Scan to operation interval (days) | 41.4 (6–109) | 63.4 (16–109) | 0.20    |
| GB wall thickening           | 2         | 9      |         |
| Discreet GB mass or polyp    | 4         | 3      |         |
| GB wall thickening           | 2         | 8      |         |
| Discreet GB mass or polyp    | 4         | 2      |         |
| Median Ca 19–9 ($n = 16$)    | 169.5     | 25     | 0.33    |

Abbreviations: Ca, cancer; CT, computed tomography; GB, gallbladder; MRI, magnetic resonance imaging.

Fig. 2 Receiver operator characteristic (ROC) curve of fluorodeoxyglucose-positron emission tomography-computed tomography (FDG-PET/CT) maximum standard unit value (SUV$_{max}$).
The frequency of reported gallbladder abnormalities continues to increase in the modern era in tandem with the increased use of cross-sectional imaging. This poses a particular dilemma for the surgical community. If imaging is consistent with malignancy, the patient should be offered a radical cholecystectomy with frozen sections of the liver and cystic duct margins. The patient may then progress to more substantial liver resections, lymphadenectomy, and/or extrahepatic bile duct resection, respectively, dependent upon these results. While in the setting of a known GBC this is the optimal surgical intervention, radical resection is associated with a morbidity 29 to 53% and mortality 5 to 8%.4,14 Furthermore, when benign biliary pathology is diagnosed, simple cholecystectomy can be considered where appropriate without the need for radical resection.

Thus, the surgical approach to an abnormal gallbladder is dependent upon the likelihood of GBC and the absence of metastatic disease. FDG-PET has been reported as having a high sensitivity and specificity in differentiating between benign and malignant diseases compared with conventional US, CT, and MRI.11,15,16 Most studies have utilized FDG-PET in advanced stage GBC,17,18 whereas Ramos-Font et al reported the use of FDG-PET/CT in 49 patients with suspected GBC and reported a diagnostic accuracy of 95.9% of the primary lesion with a threshold SUV$_{\text{max}}$ value of 3.62 for malignancy.12 At this SUV$_{\text{max}}$ threshold, our data demonstrated a sensitivity and negative predictive value of 100%; however, the specificity was 13.3% with a positive predictive value of 35.0% (95% CI: 15.1–54.9%).

**Table 3** FDG-PET/CT SUV$_{\text{max}}$ values for patient with benign pathology and gallbladder cancer

|                | Mean (SD) | Median | Range | IQR range | Student’s t-test | Mann–Whitney U test |
|----------------|-----------|--------|-------|-----------|-----------------|---------------------|
| All            | 8.23 (4.97) | 7.0    | (1.0, 21.9) | (4.0, 11.5) |                 |         |
| Malignant (n = 7) | 8.18 (4.98) | 6.0    | (3.7, 15.3) | (3.7, 13.2) | 0.89             | 0.92    |
| Benign (n = 15)  | 8.52 (5.19) | 7.1    | (1.0, 21.9) | (5.8, 11.5) |                 |         |

Reported SUV$_{\text{max}}$ were 8.18 ± 4.98 for patient cases with GBC versus 8.52 ± 5.19 for patients with benign disease (independent samples $t$-test $p$-value = 0.89). The ROC analysis gave AUC 0.486 (95% confidence interval [CI]: 0.192, 0.779) suggesting limited ability for preoperative PET/CT-CT to discriminate between benign gallbladder pathology and GBC (►Fig. 2). For completeness, the diagnostic accuracy parameters for PET/CT-CT at different values of SUV$_{\text{max}}$ are shown in ►Tables 3 and 4. These demonstrate a poor global accuracy of 30 to 68% at different SUV$_{\text{max}}$ levels. At SUV$_{\text{max}}$ 3.7, sensitivity and negative predictive value was 100%, but specificity was 13.3% (95% CI: 0.0–27.5%) with a positive predictive value of 35.0% (95% CI: 15.1–54.9%).

**Table 4** Sensitivity and specificity at different values of FDG-PET/CT SUV$_{\text{max}}$

| Sn (95% CI) | Sp (95% CI) | PPV (95% CI) | NPV (95% CI) | Accuracy |
|-------------|-------------|--------------|--------------|-----------|
| ≥ 2.9       | 100.00% (100.00%, 100.00%) | 6.67% (0.00%, 17.09%) | 33.33% (13.63%, 53.03%) | 100.00% (100.00%, 100.00%) | 36.4% |
| ≥ 3.7       | 100.00% (100.00%, 100.00%) | 13.33% (0.00%, 27.54%) | 35.00% (15.07%, 54.93%) | 100.00% (100.00%, 100.00%) | 40.9% |
| ≥ 4.0       | 71.43% (52.55%, 90.31%) | 20.00% (3.29%, 36.71%) | 29.41% (10.37%, 48.45%) | 60.00% (39.53%, 80.47%) | 36.4% |
| ≥ 5.8       | 57.14% (36.46%, 77.82%) | 20.00% (3.29%, 36.71%) | 25.00% (6.91%, 43.09%) | 50.00% (29.11%, 70.89%) | 31.8% |
| ≥ 6.7       | 42.86% (22.18%, 63.54%) | 40.00% (19.53%, 60.47%) | 25.00% (6.91%, 43.09%) | 60.00% (39.53%, 80.47%) | 41.0% |
| ≥ 7.6       | 42.86% (22.18%, 63.54%) | 60.00% (39.53%, 80.47%) | 33.33% (13.63%, 53.03%) | 69.23% (49.94%, 88.52%) | 50.0% |
| ≥ 10.7      | 42.86% (22.18%, 63.54%) | 73.33% (54.85%, 91.81%) | 42.86% (22.18%, 63.54%) | 73.33% (54.85%, 91.81%) | 59.1% |
| ≥ 13.2      | 14.29% (0.00%, 28.91%) | 86.67% (72.46%, 100.00%) | 33.33% (13.63%, 53.03%) | 68.42% (49.00%, 88.84%) | 68.2% |

Abbreviations: CI, confidence interval; FDG-PET/CT, fluorodeoxyglucose-positron emission tomography/computed tomography; IQR, interquartile range; SD, standard deviation; SUV$_{\text{max}}$, maximum standard unit value.
value of 35% giving an overall diagnostic accuracy of 41%. One explanation for these discordant results may be the precise radiological protocol utilized or potentially all biliary tract cancers being classified together without a distinction being made between GBC and cholangiocarcinoma.19,20

Based upon the FDG-PET/CT and CT and/or MRI, the 22 patients in our series underwent radical cholecystectomy with only 32% of patients having malignancy confirmed on histopathology. Therefore, FDG-PET/CT appears not to discriminate between benign gallbladder pathology and GBC in our series. In addition to Ramos-Font et al and our series, Oe et al reported 12 patients with gallbladder wall thickening identified on imaging that underwent FDG PET.18 GBC was diagnosed based on high uptake in four patients. On histopathology, three patients had GBC, while one had chronic cholecystitis. Lee et al reported FDG-PET/CT had no significant advantage over CT for diagnosis of GBC.19 However, a significantly higher positive predictive value (94 vs. 78%) was recorded for FDG-PET/CT compared with CT for the detection of regional lymph node metastasis. A significantly higher sensitivity (95 vs. 63%) was also reported for the detection of distant metastases compared with CT. Indeed, in this setting FDG-PET/CT may have utility in patients with potential GBC. While FDG-PET/CT may not predict primary pathology within the gallbladder, its ability to detect metastatic disease in addition to predicting resectability21 may aid in surgical decision-making pathways.

Overall, the role of FGD-PET/CT in the investigation of GBC remains controversial with European and American guidelines not recommending its routine use in disease staging,22,23 while The Royal College of Radiologists of England recommends FDG-PET/CT use for staging potentially GBC where cross-sectional imaging is equivocal for metastatic disease.24 Certainly, our study would not support the use of FDG-PET/CT as a diagnostic tool to discriminate between benign and malignant gallbladder pathology and we would advocate all patients in whom CT and/or MRI suggest GBC the patient should be considered for radical surgery as suggested by previous authors.4,9,14

There are limitations to our study. Given the low incidence of GBC, only 22 patients were included in the study cohort and the analysis was performed in retrospect. We have not included patient survival in our analysis as this was not the primary aim of the study.

In summary, this study does not support the findings of some previous studies where FDG PET/CT was used as a diagnostic tool for discriminating between benign and malignant gallbladder pathology. More research is necessary to improve preoperative diagnosis of GBC.

Authors’ Contributions
SP and RHB conceptualized the manuscript. SP and SLFD were involved in data curation. SP and RHB were involved in methodology. SP and NM did formal analysis. AW, MT, AR, GB, JS, SC, and NH validated the data. SP, SLFD, and RHB were involved in write up of original data. SP, AW, MT, AR, GB, JS, SC, NH, DC, SK, and RHB were involved in write-up, review, and editing.
Conflicts of Interest
None declared.

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