The role of PET-CT in patients with incidental gallbladder cancer

Jean M. Butte, Francisca Redondo, Enrique Waugh, Manuel Meneses, Rossana Pruzzo, Hugo Parada, Horacio Amaral & Hernán A. De La Fuente

Instituto Oncológico Fundación Arturo López Pérez, Santiago, Chile

Abstract

Introduction: After a cholecystectomy, incidental gallbladder cancer (IGC) requires accurate imaging studies to determine the actual extent of the disease to properly tailor subsequent treatment. The aim of this study was to evaluate the utility of 18F-fluorodeoxyglucose positron emission tomography-computed tomography (18FDG PET-CT) to provide optimal pre-treatment staging in patients with IGC.

Material and Methods: Between January 2006 and August 2008, all patients with IGC and at least muscular layer invasion were studied with 18FDG PET-CT. The examination was considered positive when the standardized uptake values (SUV) were ≥2.5. In all instances patients were offered to undergo definitive exploration and possible radical resection.

Results: The series included 32 patients, 26 women and 6 men, with a median age of 57 years (range 30–81 years). The examination was performed at a median time of 6 weeks after cholecystectomy (range 2–52 weeks). 18FDG PET-CT was negative in 13 patients and positive in 19 patients: 9 with localized potentially resectable disease (PRD) and in 10 with disseminated disease. Of the 13 patients with negative PET-CT, 9 refused surgery and 4 underwent formal exploration: 3 patients were resected with no disease identified in the final pathology report (FPR) and 1 was not resected as a result of peritoneal carcinomatosis. Of the 9 with PRD, 4 patients refused reoperation and 5 underwent exploration: 3 were resected with residual disease noted in the FPR and 2 did not undergo resection because of dissemination. Two patients with disseminated disease were reoperated and in both instances disseminated disease was confirmed. The median survival for the entire group was 20.3 months (range 1.6–32.9 months). The median survival for those patients with negative PET-CT was 13.5 months (range 5.6–32.9 months), 6.2 months (range 1.6–18.7 months) for localized potentially resectable disease and 4.9 months (range 2–14.1 months) for disseminated disease (P < 0.003).

Conclusions: For patients presenting with stage T1b or greater IGC, the use of 18FDG PET-CT will help reduce the number of patients undergoing non-therapeutic re-exploration and may help to determine the likely prognosis. 18FDG PET-CT might be a useful tool for the selection of patients for potentially curative treatment.

Keywords

18FDG PET-CT, incidental gallbladder cancer, pre-operative staging

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Correspondence

Hernán A. De La Fuente, Instituto Oncológico Fundación Arturo López Pérez, Rancagua 878, Santiago, Chile. Tel: 56 2 4457247; Fax: 56 2 4218597; E-mail: delafueh@yahoo.com

Introduction

Gallbladder cancer (GC) is an aggressive and lethal malignancy. Most patients are diagnosed at an advanced stage, with clinically evident disease and when curative surgical resection is not possible. In these patients, the only method of treatment is palliation and the possibility of long-term survival is anecdotal.
Patients diagnosed with incidental gallbladder cancer (IGC) (invasive carcinoma identified in the final pathology report) after cholecystectomy for presumed benign disease, should have a better prognosis than those with overt gallbladder malignancy. Initial pathological study of the gallbladder would permit knowledge of the extent of the disease in the gallbladder wall and permit selection of patients for potentially curative resection. Previous studies have showed that patients with pT1b or pT2 gallbladder cancer may improve their chances of survival with radical resection. However, in spite of the incidental diagnosis, many patients will actually have non-localized disease for which radical resection will have no impact on survival. For this reason, it is appropriate to perform a pre-operative imaging study that might help in the selection of patients for radical resection and likewise avoid laparotomy in patients with disseminated disease.

Multiple studies have been used to evaluate the extent of the disease with computed tomography (CT) and magnetic resonance imaging (MRI) being the most frequently utilized. However, 18F-fluorodeoxyglucose positron emission tomography (18FDG PET) has been demonstrated to have value in properly staging select tumors such as esophageal cancer, melanoma, colorectal cancer and lymphoma. Recently, 18FDG PET plus CT has been reported to improve the sensitivity to detect non-clinically evident metastatic disease. As GC is a malignant tumour with a propensity to early systemic spread, this imaging tool could prove to be useful in identifying and selecting patients with disseminated disease not amenable to curative resection.

The aim of the present study was to evaluate the utility of 18FDG PET-CT in providing optimal pre-treatment staging in patients with incidental gallbladder cancer and to evaluate its role as a prognostic tool.

Patients and methods
Patients
Between January 2006 and August 2008, a prospective study was initiated in which all patients with IGC diagnosed after a laparoscopic or open cholecystectomy, and at least muscular layer invasion, were re-staged with 18FDG PET-CT.

In all patients, a re-review of the pathological tissue of the cholecystectomy specimen was performed to confirm the depth of tumour invasion, the presence or absence of cystic lymph node involvement and to precisely assess the surgical margin in both the gallbladder bed and cystic duct. All patients were staged according to the 2002 The American Joint Commission on Cancer tumour-lymph node-metastasis (AJCC TNM) system.

Definitions
Incidental gallbladder cancer
Cancer diagnosed during final pathologic review (FPR) after an open or laparoscopic cholecystectomy for presumed benign disease. The diagnosis of gallbladder cancer was not suspected at the time of surgery.

Negative 18FDG PET-CT finding
Examination without suspicious lesions and normal 18FDG standardized uptake values (SUV).

Positive 18FDG PET-CT finding
Examination with suspicious lesions and abnormal 18FDG uptake (SUV > 2.5). We categorized FDG/PET findings as demonstrating a local, regional or systemic pattern. Regional and systemic pattern are considered disseminated disease. Local disease confers lymph node compromise at the hepatoduodenal ligament (pericoledochal), gallbladder liver bed and/or cystic duct. Regional disease refers to suspicious lymph nodes located at interaortocaval (IAO), hepatic artery or para aortic bed. Systemic pattern includes the liver, peritoneal and extra abdominal abnormal uptake.

18FDG PET-CT Technique
Beginning the night before examination, patients were not allowed carbohydrates. On the day of the examination, patients fasted for at least 6 h and drank at least 1 liter of water without sugar or saccharin. Diabetic patients had to have a normal blood sugar level (<120 mg/dl).

All studies were performed in a PET-CT Siemens Biograph 6 (PET-CT HiRz, P3D; Siemens Medical System, Erlangen, Germany) with 4-mm crystal detectors and multislice helical CT, 60 min after the intravenous (i.v.) administration of 370 MBq of 18FDG. All patients, unless there was a formal contraindication, received i.v. iodinated contrast media immediately before the acquisition of the CT portion of the study. Studies were considered positive when abnormal focal 18FDG uptake was seen in the PET images, in the absence of inflammatory changes on CT (regardless of the SUV value). The examination was considered positive when the SUV was ≥ 2.5.

Treatment
In all instances of localized and potential resectable disease, patients were offered definitive exploration and possible radical re-resection. In patients with disseminated disease, patients were offered a core biopsy to confirm metastatic disease. All patients were followed until the end of the study or their death.

Surgical treatment
In those patients with non-disseminated disease at surgical exploration treatment included resection of liver segments IVB and V, regional lymph node dissection (cystic, pericoledochal, common hepatic artery and intercavoaortic (IAO) lymph nodes) and common hepatic bile duct resection if there was a positive cystic duct margin.

Statistical analysis
The long-term survival was calculated using the Kaplan–Meier method, log-rank and Cox’s test. A value of P < 0.05 was considered statistically significant. All living patients were censored in the last follow up.

Results
During the study period, 53 patients with gallbladder cancer were evaluated with 18FDG PET-CT. Thirty-two of these patients had
IGC and compromise the study population reported in the present study. The median age was 57 years (range 30–81 years), with 26 women (80%) and 6 men (20%).

Pathological review of the cholecystectomy specimen revealed 31 adenocarcinomas and 1 squamous cell carcinoma. Four patients had invasion of the muscular layer (T1b), 19 patients had invasion of the perimuscular connective tissue (T2), 7 patients had invasion of the serosal layer (T3) and 2 patients had compromise of gallbladder bed (T3). A cystic lymph node was identified in 18 patients (56.2%) and 10 patients were positive for malignancy.

After the cholecystectomy, PET-CT was performed with a median time of 6 weeks (range 2–52 weeks). In 13 patients, the \(^{18}\)FDG PET-CT finding was negative (Fig. 1) and in 19 patients it was positive [localized and potentially resectable disease in 9 patients (Fig. 2) and disseminated disease in 10 patients (Fig. 3)].

The mean and the median SUV in those patients with positive \(^{18}\)FDG PET-CT findings were 7.45 and 7.1 (range 2.6–15.8). The \(^{18}\)FDG PET-CT was positive in the pericoledochal lymph nodes in 11 patients, gallbladder bed in 10 patients, liver (metastases) in 6 patients, IAO lymph nodes in 4 patients, peritoneum (carcinomatosis) in 3 patients, lung (metastases) in 2 patients and the common hepatic artery lymph nodes in 1 patient.

The \(^{18}\)FDG PET-CT findings changed the pre-test stage in 12 out of 32 patients (38%) (Table 1). In those patients with negative FDG-PET-CT findings, nine refused surgery and four underwent laparotomy with three patients resected for cure with no disease identified at FPR and one was not resected because of peritoneal carcinomatosis. This patient had a signet ring cell tumour and localized small volume carcinomatosis.

In those nine patients with potentially resectable disease, four of them refused reoperation and five underwent exploration (three were resected with residual disease noted at the FPR and two did not undergo resection because of carcinomatosis).

Two patients with disseminated disease were reoperated and in both instances disseminated disease was confirmed.

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**Figure 1** An example of a \(^{18}\)F-fluorodeoxyglucose positron emission tomography-computed tomography (\(^{18}\)FDG PET-CT) which showed no evidence of residual disease (negative finding) in a patient who was diagnosed with an incidental gallbladder carcinoma after cholecystectomy.

**Figure 2** An example of a \(^{18}\)F-fluorodeoxyglucose positron emission tomography-computed tomography (\(^{18}\)FDG PET-CT) which showed evidence (positive finding) of localized disease (arrow) in a patient who was diagnosed with an incidental gallbladder carcinoma after cholecystectomy.
The median survival for the entire group was 20.3 months (1.6–32.9 months). The median survival for those patients with negative 18FDG PET-CT (n = 13) was 13.5 months (5.6–32.9 months) and 5.7 months (1.6–18.7 months) for those patients with positive 18FDG PET-CT (n = 19) (P < 0.003) (Fig. 4). The median survival for those patients with localized potentially resectable disease (n = 9) was 6.2 months (1.6–18.7 months) and 4.9 months (2–14.1 months) for those with disseminated disease (n = 10) identified by 18FDG PET-CT (P < 0.003) (Fig. 5).

**Discussion**

GC is the sixth most common gastrointestinal malignancy in the United States and approximately 8500 new cases are diagnosed annually. Patients with GC usually have advanced disease at the time of diagnosis and only 15–47% are candidates for radical resection. In our experience, 80% of the patients have metastatic disease and only 20% have potentially resectable disease at time of the diagnosis. Only half of the second group can be resected when they undergo surgical exploration.

Patients with early gallbladder cancer are usually diagnosed incidentally upon pathological review of the elective

<table>
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<th>18FDG PET-CT findings</th>
<th>N°</th>
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<td>14</td>
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<tr>
<td>IIB or T1bN1M0 or T2N1M0 or T3N1M0</td>
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<td>Negative</td>
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<tr>
<td></td>
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<td>Disseminated*</td>
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*change in stage: 12/32.
cholecystectomy specimen and may have a better prognosis than those patients who present with clinically apparent malignant disease. In those patients with a T1b tumour (muscular layer invasion), there is some controversy about the optimal treatment. However, because this type of tumour is associated with lymph node metastases in 15% of patients and some studies have shown a recurrence rate of 30% with cholecystectomy alone compared with 10% with extended resection, radical resection would appear to be the treatment of choice. In those patients with T2 tumours (perimuscular connective tissue layer invasion), one-third have lymph node metastases and radical resection is considered appropriate in an attempt to optimize long-term survival. In those patients with a T2 tumour and radical resection, Chijiwa et al. showed a 5-year overall survival (OS) of 59% and 17% in those without radical resection. In another study, in those patients with radical resection, Fong et al. showed a 5-year OS of 61% and 19% in those with simple cholecystectomy. In those patients with T3 or T4 tumours, long-term survival might be improved with radical resection in very select cases, as shown by Behari et al. In summary, patients with T1b, T2 and select T3 gallbladder cancer could be suitable for re-exploration and eventual radical resection.

In spite of radical surgical treatment, at least 15% of patients with a T1b tumour, 40% of patients with a T2 tumour and 80% with a T3 tumour will develop recurrent disease and will die in follow-up. Jarnagin et al. showed in 54 patients with IGC, at a median follow-up time of 24 months, a recurrence rate of 65%. In 81% of patients the recurrence was at a distant site. It is important to note that the median time of disease recurrence was 11.5 months, 62% of patients within 12 months of surgery and 88% of patients within 24 months. This relatively short time to recurrence infers that disseminated disease was present at the time of cholecystectomy, becoming evident during the short-term follow-up in the majority of patients. An accurate staging method in IGC is critical to determine resectability, identify disseminated disease and to avoid surgical exploration for those with unresectable and/or disseminated disease.

Recently, CT and MRI have been the most common imaging techniques to evaluate for local or distant extension of this disease and for the relationship between localized tumour and either nearby vascular structures or the biliary tree. However, both CT and MRI have well-recognized limitations for the detection of tumour recurrence or metastases, often related to tumour size, but also including difficulty in differentiating residual/recurrent tumour from surgically induced scarring or inflammatory change. For these reasons, functional imaging with 18F-FDG PET-CT prior to attempted curative intervention could improve the pre-treatment selection of patients who might potentially benefit from such interventions.

18F-FDG PET-CT has been useful as a staging tool in a variety of malignancies such as esophageal, lymphoma, lung, breast, colorectal, melanoma and head and neck cancer. The value of this test is not only in providing information about the spread of the disease,
but in the evaluation of treatment response and in the prediction of long-term survival.\(^{20}\)

There are a paucity of studies utilizing \(^{18}\)FDG PET and \(^{18}\)FDG PET-CT in gallbladder cancer. Anderson et al.\(^{12}\) evaluated 14 patients with a diagnosis of gallbladder cancer with \(^{18}\)FDG PET. In the evaluation of residual gallbladder carcinoma after cholecystectomy, sensitivity and specificity were 78% and 80%, respectively. There was one false-positive result in a patient who underwent \(^{18}\)FDG PET within 1 month of cholecystectomy, and two patients had false-negative findings. These patients had bulky intra-abdominal metastasis and carcinomatosis. Sensitivity for extra hepatic metastases was 56% and \(^{18}\)FDG PET detected carcinomatosis in only one out of six patients. As we demonstrated in this study, one out of four reoperated patients with negative \(^{18}\)FDG PET-CT findings had carcinomatosis at the time of re-exploration. \(^{18}\)FDG PET-CT would be not a good method for identifying carcinomatosis, especially in those patients with small volume carcinomatosis and signet ring cell tumours. In another study, Corvera et al.,\(^{11}\) studied 31 patients with gallbladder cancer diagnosed after cholecystectomy. In seven (23%) of these patients, \(^{18}\)FDG PET changed management by identifying metastatic disease not seen in previous studies. However, in 12 of the other 24 operated patients, the disease could not be curatively resected because of locally advanced or disseminated disease. More recently, Shukla et al.\(^{21}\) studied 80 patients with IGC with \(^{18}\)FDG PET-CT. Fifty-five (70%) of these patients had disseminated disease and 24 (30%) patients had local and potentially resectable disease. Twenty-one of these patients could be resected and in seven (33%) of them, there was residual disease. The sensitivity and positive predictive values of \(^{18}\)FDG PET-CT for residual disease were 28.5% and 20%, respectively.

In this study, \(^{18}\)FDG PET-CT identified 10 (31.3%) patients with disseminated disease and, as with the study of Corvera et al.,\(^{11}\) changed surgical management in eight (25%) of them. Also, after the review of the cholecystectomy FPR, \(^{18}\)FDG PET-CT changed the pre-test stage of the disease in 37.5% patients to identify localized or disseminated disease in those patients without clinically evident disease.

This report is limited because only 9 out of 22 patients with \(^{18}\)FDG PET-CT findings of either no or localized disease underwent surgical re-exploration. However, of these patients who were re-explored, no residual disease was found in patients with a negative \(^{18}\)FDG PET-CT (except by one patient). Conversely, patients with \(^{18}\)FDG PET-CT scans demonstrating either local or disseminated disease were found to have a residual tumour, although sometimes patients with a localized tumour on \(^{18}\)FDG PET-CT were found to have disseminated disease.

Importantly, \(^{18}\)FDG PET-CT accurately identified patients who had a disseminated tumour pre-operatively, in this relatively small study identifying patients who would not benefit from curative attempts. These data suggest that patients with an apparently disseminated tumour would benefit from limited means of verification (e.g. needle biopsy, other imaging, etc.), thereby avoiding futile aggressive attempts at a cure. However, the optimal staging of IGC may be \(^{18}\)FDG PET-CT combined with laparoscopy thus minimizing the risk of missing small volume peritoneal disease.

In patients with a negative \(^{18}\)FDG PET-CT, attempts at surgery with curative intent are warranted as our data demonstrate superior overall survival in this cohort. In patients with apparently localized disease, re-exploration should be attempted, as these patients have intermediate improvements in survival compared with those with no evidence of disease and those with disseminated disease.

Finally, these results should be reproduced by others, particularly in larger series, to confirm our findings. As a result of the relatively low incidence of gallbladder carcinoma, this may require a multi-institutional, prospective investigation.

Conflicts of interest

None declared.

References


