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RESEARCH

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Impact of 18F FDG PET/CT on management of incidental gallbladder carcinoma

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Abstract

Background Incidental gallbladder carcinoma (IGBC) is identified after cholecystectomy being performed for a presumed to be benign disease, and histopathology turns out as malignant disease. For optimal management planning, it is crucial to know the actual disease status. 18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) provides local, regional as well as distant disease, i.e., restaging and identifying true burden of disease for optimal treatment planning. The aim of this study was to restage the IGBC patients on 18F FDG PET/CT and find out any change in treatment plan.

Methods This retrospective descriptive study was performed between November 2021 and February 2023. All PET/CT scans were analyzed which came for restaging in IGBC.

Results PET/CT was performed at a median time of 9 weeks (range 6–12 weeks) from the date of surgery. This study included 17 patients (6 males and 11 females), with a median age of 55 years (range 38–76 years). From total of 17 PET/CT scans, 10 (58.8%) patients were positive and 7 (41.1%) patients were negative on PET/CT. Among the PET/CT positive patients, disease pattern was seen in the form of local/residual disease/liver infiltration, regional lymph nodes and distant metastases. Among the 17 patients, treatment plan in 5 patients (having PET/CT negative) was changed from surgical intervention to no treatment, and in 2 patients (having PET/CT positive), treatment plan was changed to chemotherapy, i.e., total 7 (5 + 2, 41% of total 17 patients) patients' treatment plans were changed. By reducing the number of patients undergoing re-resection, we can say that it reduces the burden on already overburdened health infrastructure, especially in developing countries like India where incident is high.

Conclusions PET/CT provides the actual stage of IGBC. It changes treatment plan and reduces the number of patients undergoing re-resection. It also decreases burden on overburdened health infrastructure.

Keywords 18F FDG PET-CT, Incidental gallbladder carcinoma, Restaging, Neuroendocrine gallbladder carcinoma, Cholelithiasis, Cholecystitis

Background

Primary carcinoma of gall bladder is an uncommon malignancy, and it is one of the most common malignancies of the biliary tract [1]. Cholelithiasis is the most common risk factor for development of gallbladder carcinoma worldwide with a variable incidence of gallbladder carcinoma among different geographic areas because it depends on prevalence of cholelithiasis [2]. Gallbladder cancer is one of the commonest carcinomas of Gangetic and Brahmaputra belt in Northern and Eastern India [3, 4]. Gallbladder carcinoma cases are diagnosed preoperatively in less than 20%, and remaining cases are diagnosed intraoperatively or after laparoscopic cholecystectomy which constitutes 74–92% [5].

Gallbladder carcinoma is one of the most aggressive malignancies among gastrointestinal tract neoplasms, and it is associated with poor prognosis. Patients with

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early-stage gall bladder carcinaoma have a better prognosis. They are usually diagnosed incidentally after a cholecystectomy for a presumed to be benign disease like gallstone disease and chronic cholecystitits, either during surgery or on final histopathological report of the specimen. It is recommended to do histopathological examination after all cholecystectomies [6].

Early diagnosis is difficult because it is clinically silent in early stage and many gallbladder carcinomas are not diagnosed preoperatively. Pathological staging of gallbladder carcinoma is according to their depth of invasion into wall of gall bladder, tumor spread toward peritoneal side or hepatic side of the gallbladder and involvement of the lymph nodes. Direct tumor spread into the liver and other adjacent organs like common bile duct, colon, stomach, duodenum, diaphragm and abdominal wall is not considered distant metastasis (according to AJCC 8th edition) [7].

In T1a gallbladder carcinoma, there is low probability of lymphatic metastasis, and hence, a simple cholecystectomy can contribute a high cure rate. For T1b cancer, either simple or an extended cholecystectomy is appropriate, but extended cholecystectomy is recommended for cancer at stage T2 or above [8]. In spite of much advancement in cross-sectional imaging and new minimally invasive techniques, accurate staging of incidental gallbladder cancer may be challenging. PET/CT may be useful for assessment of suspected residual, local extent of disease and distant metastatic disease as compared to CT and/or MRI [9]. Fused PET/CT scan is more accurate in staging of malignant disease as well as restaging [10]. The most pivotal and crucial step is accurate staging of IGBC patients. Thus, staging should be performed for each patient. Gallbladder cancer stage directly affects management and prognosis of disease [5]. There are few studies which show the role of PET/CT in patients of IGBC. They showed that PET/CT reduces the number of patients who undergo resection of liver in pT1b stage, while there may be role of giving chemotherapy in case of pT2 stage [11, 12]. In our study, additionally we found that adjuvant treatment was not needed even in higher pathological stage (pT3) if PET/CT was negative.

The main aim of the present study was restaging of the incidentally detected gallbladder carcinoma patients on whole-body PET/CT and any change in treatment plan.

Methods

Study design, patient inclusion

This retrospective and descriptive study was performed on 17 patients of incidentally detected gallbladder cancer, diagnosed after simple cholecystectomy, who underwent 18F FDG PET/CT scan in nuclear medicine department between November 2020 and February 2023. Patients who received any intervention during preoperative, perioperative and post-operative period were excluded from the study. All patients were followed-up after PET/CT. The study was approved by the institutional ethical committee, and informed written consent to publish was received from all participants.

Imaging protocol

After fasting for at least 6 h, all patients were injected 18F FDG intravenously as a dose of 5–9 mCi (185–333 MBq), 0.1 mCi/Kg (3.7 MBq/Kg), followed by PET/CT scan after 45–60 min. The patients were administered with 100 ml of negative contrast orally, i.e., 5% mannitol diluted in 1 L drinking water before the scan. Blood glucose level of each patient was equal or less than 150 mg/dl.

PET/CT acquisition and image evaluation

Combined PET/CT images were acquired using Ingenuity TF PET/CT (Koninklijke Philips N.V, United States) scanner. Images were acquired from vertex to mid-thigh region. The serum creatinine levels were within the normal range for all patients. The CT scans with intravenous contrast were carried out prior to PET scan. The PET acquisition was done at a rate of 1.5 min/bed. On the PET/CT system, BLOB-OS-TF reconstruction algorithm was applied for PET reconstruction. PET, CT and also fused PET/CT images were carefully reviewed on the three major projections including axial, coronal and sagittal. Standardized uptake values (SUVs) were calculated using standard formula. All 18F FDG PET/CT images were reviewed by two independent nuclear medicine specialists with consensus, having experience of more than 10 years. The nuclear medicine specialists were blinded to the clinical and prognostic characteristics at the time of image interpretation.

PET/CT negative finding

Apart from physiological areas of FDG uptake, there was no abnormal or suspicious lesion suggestive of disease.

PET/CT positive finding

Apart from physiological distribution of the radiotracer, any suspicious area of disease showing FDG uptake higher than the background activity on visual observation was considered as pathological. Maximum standardized uptake value (SUVmax) was measured for all abnormal lesions for semiquantitative analysis. These lesions were categorized as local, regional or distant disease. Regional lymph nodes were included along the common bile duct, portal vein, hepatic artery and cystic duct.

Statistical analysis

We recorded the clinical, histopathological, PET/CT data and hospital records for treatment detail. We did follow-up of all patients to assess the current status of the patients till February 2023. The Kaplan–Meier analysis was used to estimate the survival.

Results

A total of 17 patients, 11 female (64.7%) and 6 male (35.2%) with a median age of 55 years (range, 38–76 years), were included in this study. On histopathology, 16 patients had adenocarcinoma and 1 patient had poorly differentiated neuroendocrine carcinoma (Fig. 1). Among 17 patients, three had pT1 (one patient had pT1a and two had pT1b stage), eleven patients had pT2 stage (2 had T2a, 5 had T2b and in 4 patients, the histopathology did not mention clearly whether it was T2a or T2b) and three patients had pT3 stage. The characteristics of the patients are shown in Table 1.

All patients were restaged on 18F FDG PET/CT. The burden of disease was analyzed in terms of tumor size and metabolic activity, i.e., SUVmax. The median time between surgery and PET/CT was about 9.3 weeks (range 6–12 weeks). Out of 17 PET/CT scans, 10 patients (58.8%) were positive and 7 patients (41.1%) were negative on PET/CT. These findings, i.e., anatomical distribution, size and SUVmax of malignant lesions, are shown in Table 2. Out of total ten PET/CT positive patients, five patients had only local/residual disease/liver infiltration, two patients had local and distant metastases, one patient had regional, and distant metastases without evidence of local disease and two patients had disseminated disease in the form of local, regional as well as distant metastases. The summary of PET/CT positive patients is shown in Table 3.

Follow-up data of all 17 patients after 18F FDG PET/CT are summarized in Table 4. Kaplan–Meier survival analysis was used of patients with IGBC (Fig. 2). The median follow-up in our study group was 12.6 months (range 3–26), and median overall survival was 11.0 months [95% confidence interval 7.8–14.1]. On follow-up, treatment plan was changed in 7 patients (41.1%, i.e., 7/17). Among these 7 patients, in five patients who had PET/CT negative, treatment plan was changed from surgical intervention to no treatment (Figs. 3, 4), and in 2 patients having PET/CT positive, treatment plan was changed to chemotherapy (Figs. 5, 6, 7). The change in treatment plan for these 7 patients is summarized in Table 5. Among the remaining 10 patients, four patients lost to follow-up, one patient expired, and the remaining 5 patients underwent treatment according to recommended guidelines. By reducing the number of patients undergoing

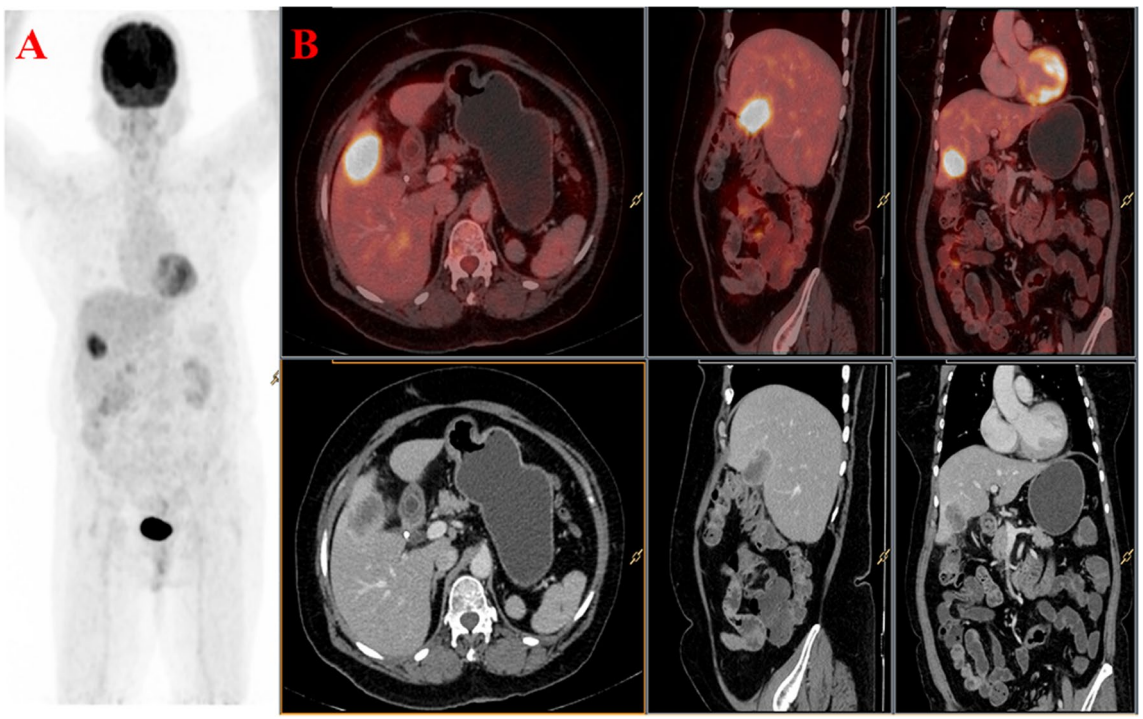

Fig. 1 18F FDG PET/CT scan of patient a 63-year-old women was having right hypochondriac pain, neuroendocrine carcinoma stage pT2a, G3 grade and positive on PET/CT **A**, Maximum intensity projection image (MIP) shows abnormal focal area of FDG avidity in segment V of right hepatic lobe, **B**, PET/CT and corresponding CT show FDG avid liver infiltration

Table 1 Patients characteristics

Patient No	Age (years)	Sex	Histological type	Grade	Margin	Pathological staging
1	42	F	Adenocarcinoma	Not available	Not available	T2bNx
2	57	M	Adenocarcinoma	G1	R0	T1bNx
3	61	F	Adenocarcinoma	Not available	Not available	T3NxMx
4	59	F	Adenocarcinoma	Not available	Not available	T2bNx
5	38	M	Adenocarcinoma	G1	R0	T2Nx
6	63	F	Neuroendocrine	G3	Not available	T2aNx
7	50	F	Adenocarcinoma	Not available	Not available	T2aNx
8	55	F	Adenocarcinoma	G1	R1	T1bNx
9	61	M	Adenocarcinoma	G1	R0	T3Nx
10	61	F	Adenocarcinoma	G2	R0	T2Nx
11	55	F	Adenocarcinoma	G2	Not available	T1aNx
12	54	M	Adenocarcinoma	Not available	Not available	T3Nx
13	76	M	Adenocarcinoma	G2	Not available	T2N0
14	47	F	Adenocarcinoma	G1	Not available	T2bN0
15	66	M	Adenocarcinoma	G1	Not available	T2bNx
16	42	F	Adenocarcinoma	G1	Not available	T2bNx
17	50	F	Adenocarcinoma	G1	Not available	T2N0

re-resection/radical cholecystectomy, it reduces the burden on already overburdened health infrastructure, especially in developing countries like India where incidence is high. Also it might be helpful in determining improvement in overall survival in case if there is an available control group.

In our sample, there were 5 patients having pT2b stage. Among these, 3 patients had infiltration into liver (3/5, i.e., 60%). In our study, PET/CT had predictive value in pT2b stage and it is recommended that all histopathological reports having T2 disease must contain the stage as either T2a or T2b.

Discussion

In our study, all patients were restaged on 18F FDG PET/CT. On follow-up, treatment plan was changed in 7 patients (41.1%, i.e., 7/17) on the basis of PET/CT, i.e., changed from surgical intervention to no treatment or chemotherapy. Thus, it reduces the burden on already overburdened health infra-structure.

Re-resection is indicated in patients with pathologically confirmed T1b, T2 or T3 disease without evidence of metastatic disease. R0 resection is the goal and to achieve it, often repeated operations are done as R1 or R2 margin status is accompanied with significantly worse immediate-, medium- and long-term outcome. But extensive resections to achieve R0 resection margin status in gallbladder carcinomas are also associated with increased morbidity, but not survival [13]. Re-resection is generally accepted for T2 and T3 disease, while the role of resection in patients with T1b disease is more controversial. However, there is significant improvement in overall survival in well-selected patients with T1b disease who undergo re-resection compared to those who do not [14, 15]. Thus, current standard of care is to recommend re-resection for incidental T1b, T2 and T3 gallbladder carcinoma.

In our study, we had aimed to restage the IGBC patients on 18F FDG PET/CT and find out any change in treatment plan.

Staging laparoscopy is performed prior to performing a laparotomy to rule out the possibility of distant metastasis in the abdomen. Disseminated disease is relatively uncommon among IGBC, and staging laparoscopy provides a very low yield. However, patients with poorly/undifferentiated, i.e., high grade carcinomas, T3 or positive-margin gallbladder carcinomas, are at high risk of disseminated disease, and selecting these patients for staging laparoscopy may increase its yield [16]. In any suspicious patient for distant metastasis, PET/CT restages the patient and staging laparoscopy can be avoided in such type of patients as seen in one of our patient (patient no. 3) of stage pT3NxMx, and in this patient treatment plan was changed to chemotherapy.

PET/CT is the most advanced technology for structural, functional and molecular phenotyping of carcinoma at the whole-body level. PET/CT scan provides the information about local as well as distant disease involvement and is routinely used. Its applications in

Table 2 Restaging of patients on PET/CT and burden of disease (in terms of size and metabolic activity, i.e., SUVmax)

Patient no.	Time between surgery and PET/CT scan (in weeks)	PET/CT findings (positive/negative)	Local/residual disease/liver infiltration	Size (cm)	SUVmax	Regional lymph nodes	Number of regional lymph nodes (1–3/≥4)	Size of largest (cm)	SUVmax	Distant site of metastases	Location (largest)	Size	SUVmax
1	8	+	–	–	–	Peripancreatic, celiac	≥4	1.4×1.0	7.7	Abdominal, retroperitoneal, left supraclavicular lymph nodes and pulmonary nodules	Gastrohepatic lymph node	1.4×0.8	10.8
2	6	–	–			–	–	–		–	–	–	–
3	7	+	Infiltration into liver	2.7×3.1	12.1	Periportal	2	1.1×1.0	5.3	Right cervical level Vb, mediastinum & periportal lymph nodes, port site, peritoneal, mesenteric deposits	Port site	3.5×2.8	12.0
4	12	+	Infiltration into liver	3.1×2.0	6.1	–	–	–	–	–	–	–	–
5	8	+	Infiltration into liver	2.8×2.6	8.5	–	–	–	–	–	–	–	–
6	10	+	Infiltration into liver	3.2×2.1	9.3	–	–	–	–		–	–	–
7	7	–	–	–		–	–	–	–	–	–	–	–
8	10	–	–	–		–	–	–	–	–	–	–	–
9	10	+	Infiltration into liver	2.7×2.6	8.1	–	–	–	–	–	–	–	–
10	8	–	–	–	–	–	–	–	–	–	–	–	–
11	9	–	–	–	–	–	–	–	–	–	–	–	–
12	12	–	–	–	–	–	–	–	–	–	–	–	–
13	12	+	Infiltration into liver	2.6×2.5	11.5	–	–	–	–	Abdominal, mesenteric and retroperitonal lymph nodes, bilateral adrenal deposits	Portocaval lymph node & left adrenal	1.1×1.0 & 1.4×1.3	4.1 & 4.9
14	12	+	Infiltration into liver	4.7×5.2	11.3	Cystic, portal	3	1.3×1.1	4.2	Omental deposits	–	2.5×2.3	5.6
15	10	–	–			–	–	–		–	–	–	–
16	10	+	Infiltration into liver	3.1×2.7	10.2	–	–	–	–	Aortocaval lymph node	Aortocaval lymph node	1.1×1.0	10.2
17	8	+	Infiltration into liver	2.3×28	8.4	–	–	–	–	–	–	–	–

Table 3 Summary of PET/CT positive patients

Patient No	local/residual disease/ liver infiltration	Regional lymph nodes	Distant metastases
1	−	+	+
3	+	+	+
4	+	−	−
5	+	−	−
6	+	−	−
9	+	−	−
13	+	−	+
14	+	+	+
16	+	−	+
17	+	−	−

Table 4 Summary of follow-up patients after PET/CT

Patient No	Follow-up time (months) after PET/ CT	Therapy given
1	3 (Expired)	–
2	26	No
3	16	Radical cholecystectomy
4	3 (lost to follow-up)	–
5	4 (lost to follow-up)	–
6	10	Radical cholecystectomy + chemotherapy
7	10	No
8	11	No
9	4	Radical cholecystectomy
10	4	Radical cholecystectomy + chemotherapy
11	12	No
12	12	No
13	8	Chemotherapy
14	5 (lost to follow-up)	–
15	4 (lost to follow-up)	–
16	36	Chemotherapy
17	3	Radical cholecystectomy

oncology include diagnosis, staging, therapy monitoring and treatment stratification [17].

FDG PET-CT has high diagnostic performance in detecting residual/recurrent disease as well as metastases in IGBC. Thus, FDG PET/CT plays a major impact on clinical decision-making in re-resection [11] and staging laparoscopy. PET/CT helps in reducing the number of patients undergoing nontherapeutic re-exploration in patients with T1b or greater disease [11, 12]. In one of our patient (patient no. 8, Fig. 3) having pT1bNx, treatment plan was changed from radical cholecystectomy to no treatment. Our study supports the same as PET/CT reduces re-resection and also staging laparoscopy.

In our study, two patients (patient no. 13 and 16) had pT2 stage, local liver infiltration and distant metastases on PET/CT. These patients received chemotherapy. Overtreatment can also be avoided, as one of our patient who was negative on PET/CT (patient no. 10, Fig. 4) having pT2 stage, G2 grade and R0 margin underwent radical cholecystectomy and chemotherapy.

There is paucity of literature on utility of PET/CT in gallbladder carcinoma specially in IGBC restaging [11, 12]. Butte et al. [12] described the role of PET/CT in incidental gallbladder cancer patients and concluded that in stage T1b or greater IGBC, 18F FDG PET/CT helps to reduce the number of patients undergoing nontherapeutic re-exploration, determines prognosis and selection of patients for potentially curative treatment. Our study supports the same and reduces the number of patients undergoing radical cholecystectomy in pT1b and pT2 stages. In these patients, no treatment was given as they were negative on 18F FDG PET/CT. Also one of the patients of pT3 stage did not receive any adjuvant treatment, since he had negative PET/CT finding and he is on follow-up.

Depth of tumor is a strong predictor of survival after curative resection of gallbladder cancer. In T2 tumor, location, i.e., peritoneal side versus hepatic side, predicts the pattern of recurrence and survival [18]. Our study supports this study and does not support the study of Lafaro et al. [19] which failed to demonstrate the independent prognostic value of primary tumor location in patients with T2 gallbladder carcinoma. In our study, PET/CT was positive in those patients having T2b stage (3/5, i.e., 60%), in the form of infiltration into liver.

Patients with incidental T2 gallbladder carcinoma, often have residual liver disease, which reduces survival. Consideration should be given to reclassify such patients to reflect the adverse survival [20]. PET/CT helps to detect the residual tumor in resected liver. We have classified these patients on PET/CT in our study, as FDG PET/CT has high diagnostic performance in detecting residual tumor [11]. Histopathological reports must mention about T2 stage, either it is T2a or T2b stage. In our study sample, this was missing in 4 out of total 11 patients having T2 disease (36.3%). The patients having T2b stage have more chances of having liver infiltration as seen in our study (60%). One out of two patients was positive on PET/CT having T2a stage.

Histopathological grade is an independent prognostic factor for overall survival and disease free survival in gallbladder carcinoma. Histopathological reports must contain detailed grade of the tumor, which was missing in few of our patients (5/17 patients, 29.4%).

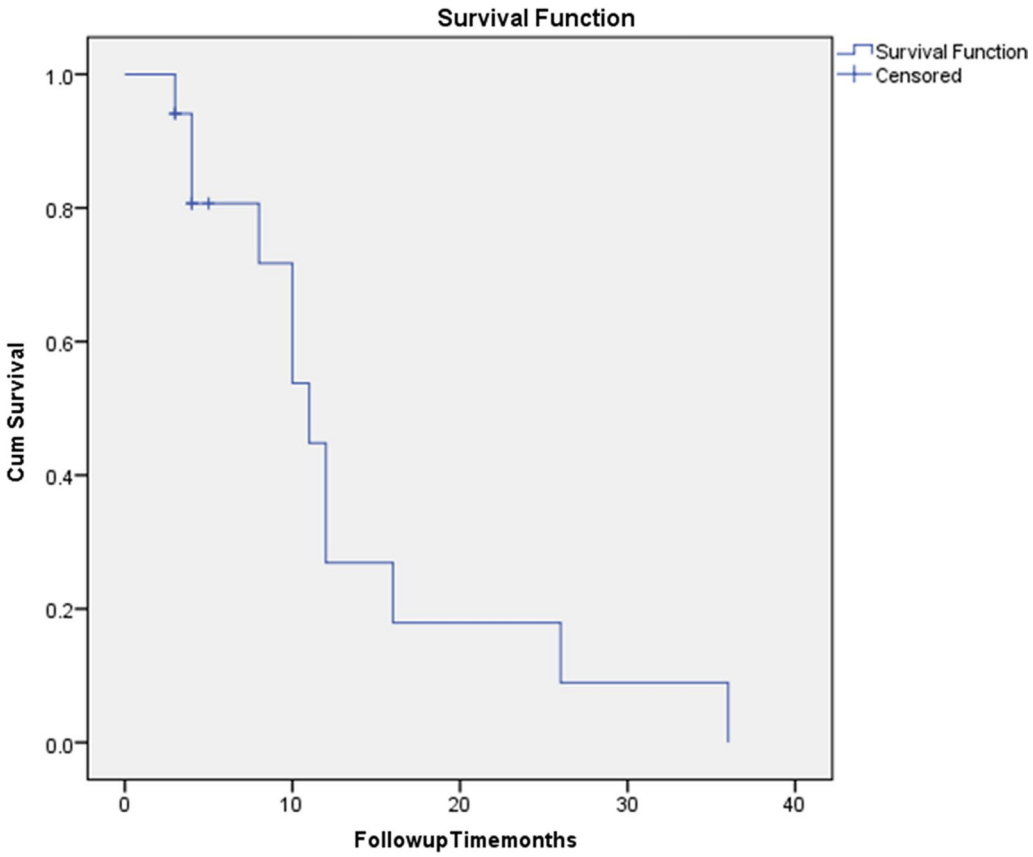

Fig. 2 Kaplan–Meier survival analysis of patients with IGBC

In our study, one patient was of high-grade neuroendocrine carcinoma. This histopathological type of cancer is staged according to the gallbladder carcinoma staging system (according to AJCC 8th edition) [6]. Neuroendocrine gallbladder carcinoma is relatively rare and in terms of treatment available. Surgical treatment is the best choice and active multi-mode comprehensive treatment significantly prolongs survival times in these patients [21]. This patient had pT2a stage and had residual disease in liver detected on PET/CT. Among all the neuroendocrine tumors, prevalence in gallbladder is 0.5%, which accounts for approximately 2.1% of all gallbladder carcinoma [21]. As most of these patients do not have any manifestations of carcinoid syndrome [22], our patient also did not have any such manifestations. Neuroendocrine gallbladder carcinoma patients have lower survival rate compared with other types of gallbladder cancer [23]. Due to the low incidence and limited availability of studies, there is no uniform standard treatment for neuroendocrine gallbladder carcinoma [21, 24]. In these patients, we can perform somatostatin receptor (SSTR) PET/CT like Ga68 DOTANOC/DOTATATE PET/CT and can provide Lu177 DOTATATE peptide receptor radionuclide therapy (PRRT) if SSTR uptake is present. Lu177 DOTATATE PRRT leads to both clinical and biochemical improvement and provides superior progression-free survival and overall survival rates substantially in most of the neuroendocrine tumors patients [25, 26].

Limitations of the study

It is single-center and retrospective study with small sample size. As a result of the relatively low incidence of carcinoma gallbladder, this may require a multi-center, prospective study. Several patients' pathology reports had no mention about the status of resected margin. Finally, survival analyses of these small numbers of patients were carried out on short period of follow-up which may under estimate the survival. Almost all of our study patients were from outside and were operated for a presumed to be benign disease; hence, we had limited preoperative clinical data to categorize cTNM.

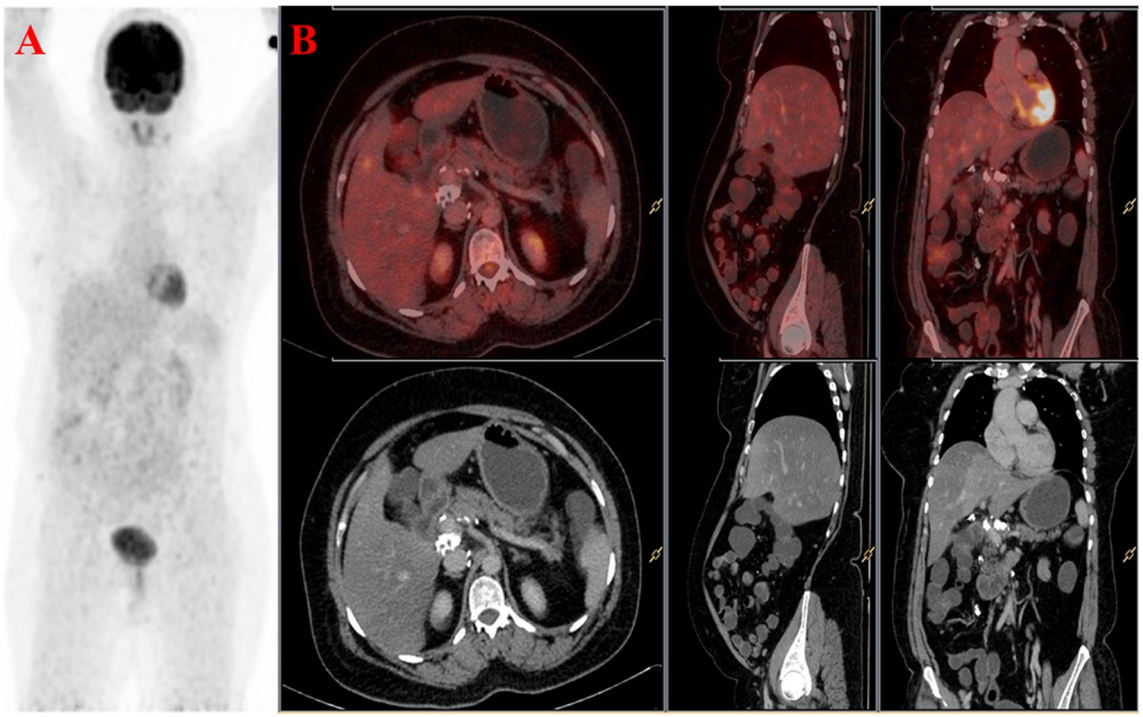

Fig. 3 18F FDG PET/CT scan of a 55-year-old women was having right hypochondriac pain and pT1b stage and negative on PET/CT **A**, Maximum intensity projection image (MIP) **B**, PET/CT and corresponding CT at the gallbladder fossa region

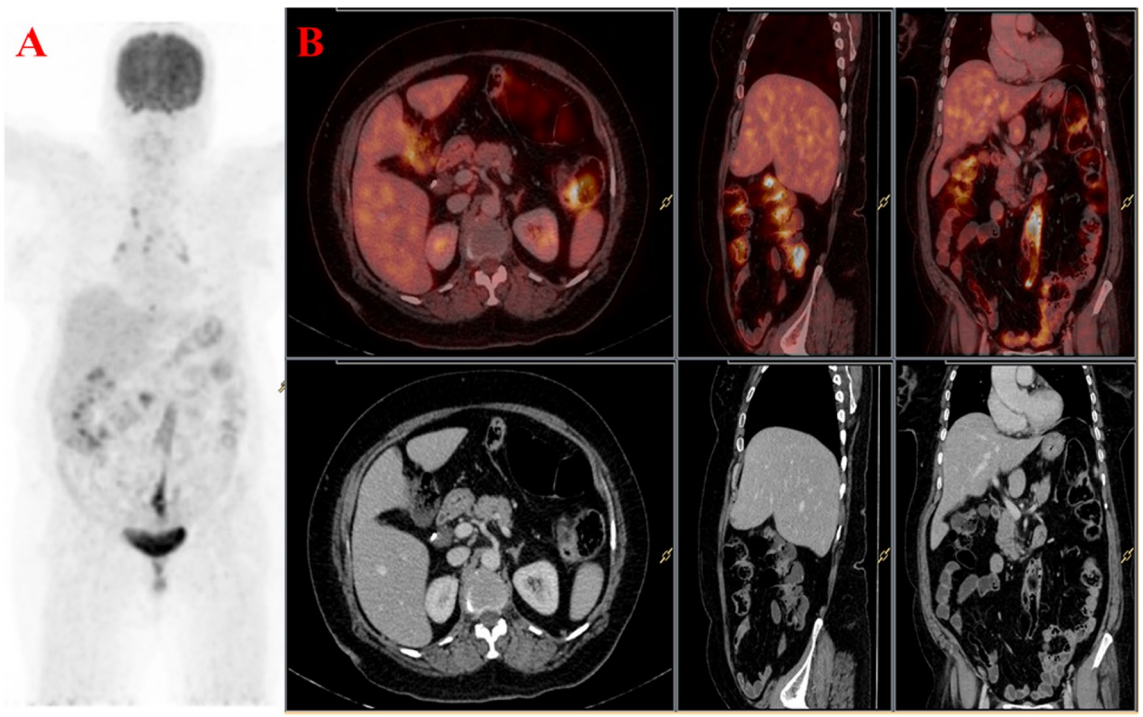

Fig. 4 18F FDG PET/CT scan of a 61-year-old women was having right hypochondriac pain and pT2 stage and negative on PET/CT **A**, Maximum intensity projection image (MIP) **B**, PET/CT and corresponding CT at the gallbladder fossa region

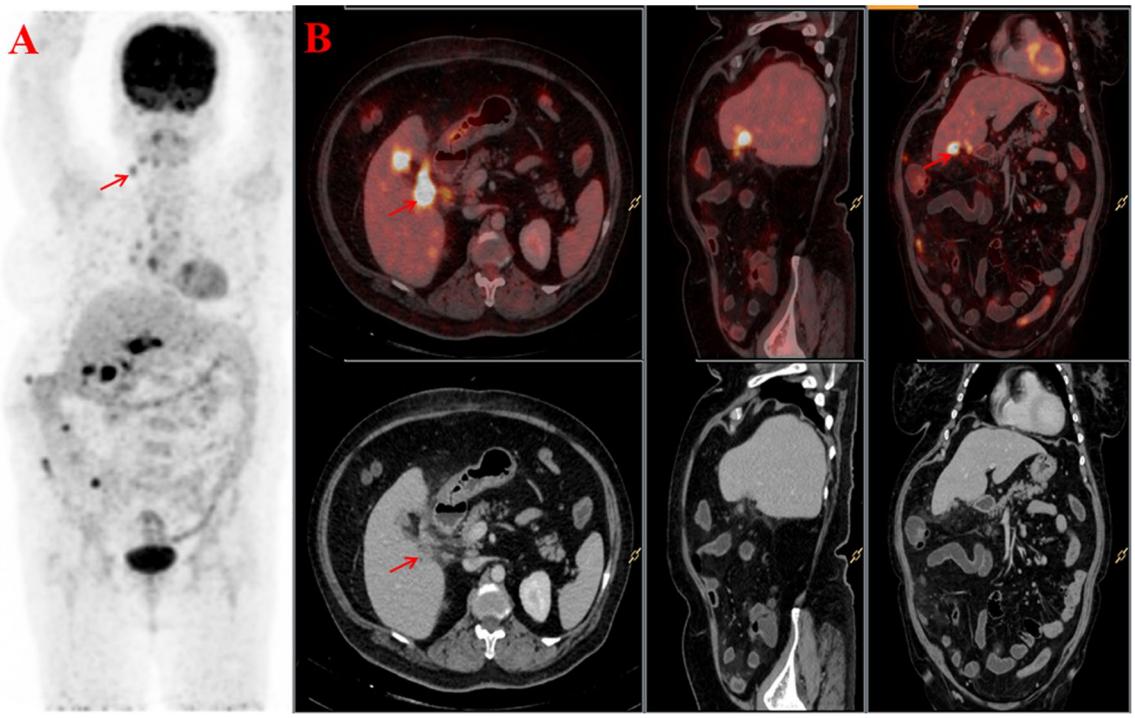

Fig. 5 18F FDG PET/CT scan of a 61-year-old women was having right hypochondriac pain and pT3Nx stage and positive on PET/CT **A**, Maximum intensity projection image (MIP) shows abnormal foci of FDG avidity in neck, mediastinum and abdominal region **B**, PET/CT and corresponding CT show FDG avid liver infiltration and periportal lymph node (arrow)

Table 5 Patients underwent change in treatment plan

S. No	Patients no	Pathological stage	Expected treatment plan	PET/CT positive/ negative	Therapy given
1	2, 8	pT1b	Re-resection/radical cholecystectomy	–	No
2	7, 11	pT2	Re-resection/radical cholecystectomy	–	No
2	13, 16	pT2	Re-resection/radical cholecystectomy	+	Chemotherapy
3	12	pT3	Re-resection/radical cholecystectomy	–	No

Conclusions

Gallbladder carcinoma is rare in western countries but common in India with female preponderance. It is very aggressive and has very poor prognosis. Most of the cases are diagnosed incidentally while treating a presumed to be benign disease. In IGBC patients, restaging guides for optimal disease management in terms of proper and accurate patient selection for available treatment multimodalities. FDG PET/CT is useful for post-operative assessment of disease extent in patients coming for restaging and scheduled to undergo further treatment. FDG PET/CT helps to reduce the number of patients who undergo re-resection and re-exploration in IGBC and also helps in prognostication.

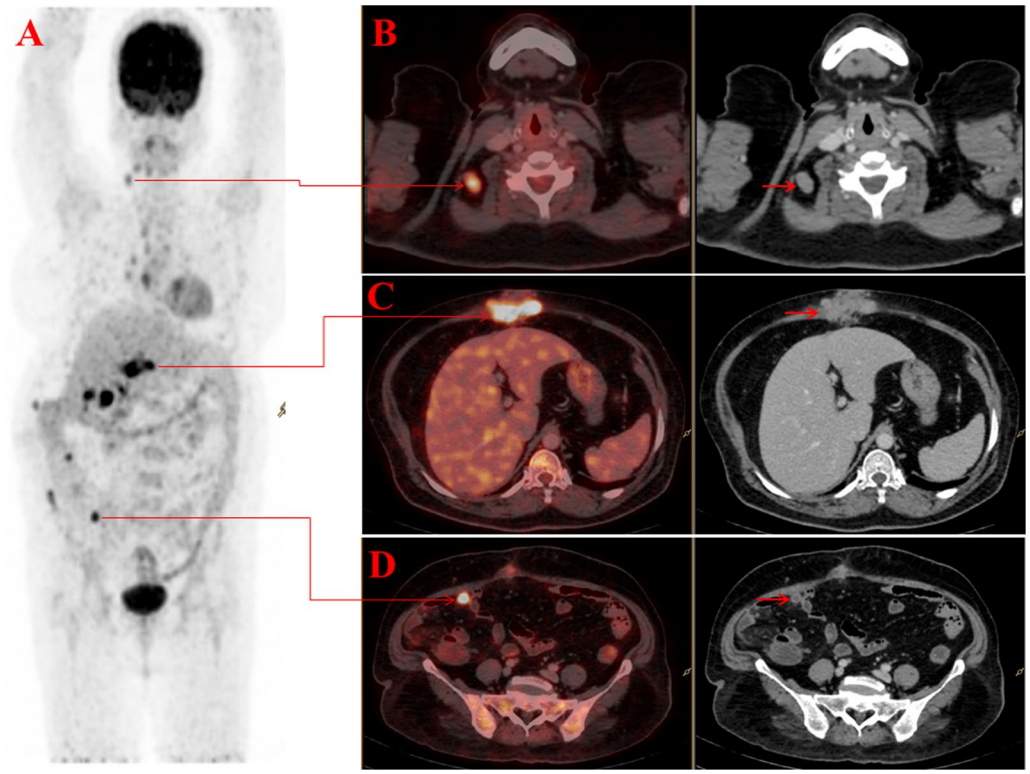

Fig. 6 18F FDG PET/CT scan of a 61-year-old women was having right hypochondriac pain and **A**, Maximum intensity projection image (MIP) shows abnormal foci of FDG avidity in neck, mediastinum and abdominal region **B**, corresponding regions on PET/CT and corresponding CT show B FDG avid right cervical level Vb lymph node, **C**, port site deposit and **D**, peritoneal deposit

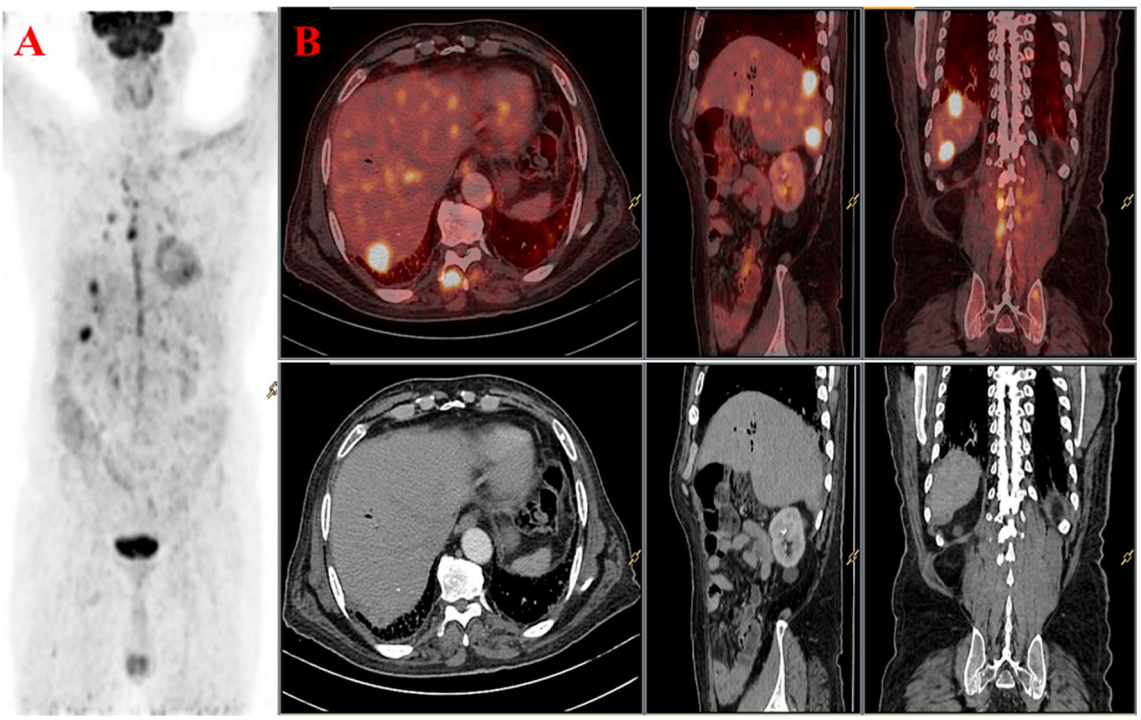

Fig. 7 18F FDG PET/CT scan of a 76-year-old man was having right hypochondriac pain and pT2No stage and positive on PET/CT **A**, Maximum intensity projection image (MIP) shows abnormal foci of FDG avidity in thoracic and abdominal regions **B**, PET/CT and corresponding CT show FDG avid lesion in segment VII of liver

Abbreviations

IGBC	Incidental gallbladder carcinoma
FDG	Fluorodeoxyglucose
PET/CT	Positron emission tomography/computed tomography

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Author contributions
All authors have read and approved the manuscript.

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Availability of data and materials
The dataset used and/or analyzed during the current study is available from the corresponding author on the reasonable request.

Declarations

Ethics approval and consent to participate
Written consent to participate.

Consent for publication
Written consent for publication from study participant.

Competing interests
The authors declare that they have no competing interests.

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