Dear editor,

Thank you for providing us the opportunity to revise our manuscript entitled “Successful multimodality treatment of metastatic gallbladder cancer: a case report" (No: 70332) to be reconsidered for publication in the World Journal of Clinical Cases. We are glad that the comments from the reviewers and editors are generally positive.

We are grateful to both you and the reviewers for the valuable time as well as the efforts in reviewing and improving our work. We studied each and every comment of the reviewers and editors carefully. Extensive revisions on the original manuscript were made and all the questions were answered ‘point-to-point’ in response to the comments.

Our original manuscript has been substantially strengthened and improved by addressing all the points raised by the reviewers and editors. We feel that amendments meet the requirements for the manuscript to be acceptable for publication in World Journal of Clinical Cases.

We look forward to your favorable response.

Sincerely yours,

Wei Bi, MD, Professor

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Round 1

To Reviewer #1:

We appreciate the reviewer's comments and thank you for the constructive recommendations. As explained below, we have addressed the concerns of this reviewer.

1. The authors need to classify the patient as either stage IVA or IVB and present clear evidence for that, otherwise it is not possible to conclude that "We reported a patient with advanced gallbladder cancer cured by multidisciplinary treatment, which was extremely rare and inspiring".

Reply: We are thankful for the reviewer's valuable comment. We have classified the patient as clinical T4N2M0 and stage IVB gallbladder cancer according to the 8th American Joint Committee on Cancer (AJCC). The diagnosis is based primarily on the patient's abdominal MRI and ^{18}F-FDG PET-CT that depicts gallbladder cancer with multiple liver metastases, peritoneum metastasis, diaphragm metastasis, and more than four regional lymph node metastases. (The first paragraph of FINAL DIAGNOSIS, lines 1-4).

Revised "FINAL DIAGNOSIS" (revisions are highlighted):

Based on all the above examinations and the 8th edition of the American Joint Committee on Cancer (AJCC)[9], the patient was diagnosed with clinical T4N2M0 and stage IVB gallbladder cancer with multiple liver metastases, peritoneum metastasis, diaphragm metastasis and lymph node metastases.

2. Most part of the Discussion is a presentation of results of other studies without directly relating them to the case presented by the authors.

Reply: We have carefully studied the Discussion part and then modify it appropriately to make other studies more relevant to the patient. (The first paragraph of DISCUSSION, lines 3-9; The third paragraph of DISCUSSION, lines 5-10; The fourth paragraph of DISCUSSION, lines 1-6; The sixth paragraph of DISCUSSION, lines 1-3).

Revised "DISCUSSION" (revisions are highlighted):

The prognosis of advanced gallbladder cancer is extremely poor, and many clinicians and even experienced surgeons are uncertain and pessimistic about the treatment of advanced gallbladder cancer. A study from Kayahara et al.[10] found that surgical resection did not improve the prognosis for patients with stage IV gallbladder cancer. However, some studies have shown that surgical resection can provide survival benefits for patients with advanced gallbladder cancer[11, 12]. With the development of adjuvant therapies, such as chemotherapy, radiotherapy, targeted therapy and immunotherapy, a study showed that preoperative adjuvant therapy could increase the resectability and survival time of advanced malignancies[13].

Gemcitabine plus oxaliplatin or gemcitabine plus cisplatin has been shown to significantly increase the survival time of patients with advanced biliary tract cancer (BTC) and is recommended as the first-line chemotherapy for advanced BTC[14-18]. A phase III randomized controlled trial on unresectable gallbladder cancer suggested that, compared with gemcitabine plus cisplatin, gemcitabine plus oxaliplatin could provide a survival improvement, and the survival improvement median overall survival (OS) was 9 months in the gemcitabine plus oxaliplatin group and 8.3 months in the gemcitabine plus cisplatin group (P = 0.057)[19].

Cetuximab is a targeted therapy against epithelial growth factor receptor (EGFR). A phase II study[20] involving 30 patients with unresectable advanced BTC found that cetuximab and gemcitabine plus oxaliplatin had obvious antitumor activity, and nine patients underwent potential radical secondary resection after a major response to treatment. However, a randomized, open-label, noncomparative phase II trial[21] showed that, compared to chemotherapy alone, cetuximab and gemcitabine plus oxaliplatin in patients with advanced biliary tract tumors did not show a survival improvement or a survival advantage. Whether cetuximab can benefit patients with advanced BTC is still a topic that is under research, and we anticipate that a high-quality result will benefit the future of the medical and surgical fields.

Our patient firstly received chemotherapy with gemcitabine plus oxaliplatin and targeted therapy with cetuximab because there was no specific indication for radical surgery. The tumor markers levels of the patient gradually decreased during

chemotherapy and targeted therapy, which suggested that chemotherapy and targeted therapy were beneficial for the patient. After seven cycles of chemotherapy, the patient received ^{125}I seed implantation and immunotherapy.

Radioactive seed implantation can provide continuous therapeutic doses in the tumor target area and rapidly decrease the distance of seeding. Thus, seed implantation can cause tumor cell death and delay tumor growth, and it results in only minor injuries to normal tissues[22, 23]. Studies have shown that biliary stents combined with ^{125}I seed implantation could prolong stent patency and improve survival time for patients with cholangiocarcinoma[22, 24]. Furthermore, studies[25, 26] have shown that compared with transcatheter arterial chemoembolization (TACE) alone, ^{125}I seed implantation combined with TACE can better control the tumor and improve the survival time for liver cancer patients. The treatment of residual liver cancer near complex sites after TACE is challenging, but ^{125}I seed implantation is effective and safe for patients[27].

Immunotherapy based on checkpoint blockers can block the inhibitory pathways of T-cell activation, thereby enabling tumor-reactive T cells to recognize tumor antigens and restore the antitumor immune response[28]. Immunotherapy has been indicated to benefit patients with advanced cancers such as hepatocellular carcinoma, nonsmall cell lung cancer and urothelial carcinoma, but the efficacy of immunotherapy for advanced BTC is still in the exploratory stage[29]. A nonrandomized, multicenter, open-label, phase I study[30] showed that, compared with nivolumab only, nivolumab and cisplatin plus gemcitabine could significantly increase OS from 5.2 months to 15.4 months and increase PFS from 1.4 months to 4.2 months for unresectable or recurrent BTC.

Our patient eventually underwent radical surgery after a series of palliative treatments. Chemotherapy, targeted therapy, ^{125}I seed implantation and immunotherapy certainly played an important role in facilitating radical surgery in this patient. However, the patient underwent a very long and complicated treatment process. It is difficult to identify the specific role of each treatment. More studies are needed to investigate this issue, and we look forward to future studies on

multidisciplinary treatment for advanced gallbladder cancer.

3. "Although the prognosis of advanced gallbladder cancer remains extremely poor in the current medical arena, this successful case demonstrates that the multidisciplinary individualized treatment may be a promising approach and can benefit patients with advanced gallbladder cancer to achieve long-term survival or even disease-free survival." The authors cannot conclude that, as this is a one case report only, not a case series.

Reply: We would like to thank the reviewer for pointing out this issue, and we have revised the conclusion. (The first paragraph of CONCLUSION, lines 2-6).

Revised "CONCLUSION" (revisions are highlighted):

We reported a patient with advanced gallbladder cancer cured by multidisciplinary treatment, which was extremely rare and inspiring. Although the prognosis of metastatic gallbladder cancer remains extremely poor in the current medical field, the presented case highlights the importance of providing aggressive multidisciplinary treatment to appropriately selected patients with metastatic gallbladder cancer to achieve long-term survival.

4. A histopathological microphotograph, Figure 3, with a better resolution will have to be presented. This one is of bad quality. Moreover, please properly identify the histological structures in the photograph with, for example, asterisks, arrows, etc.

Reply: We apologize for the poor quality of the histopathological microphotograph, Figure 3. We have compared the histopathological microphotograph from different visual fields and selected the one with the clearest visual field. Moreover, we have used arrows to properly identify the structure in the photograph. (The first paragraph of Figure Legend, lines 1-3; The second paragraph of Figure Legend, lines 1-3; The fifth paragraph of Figure Legend, lines 1-3; The sixth paragraph of Figure Legend, lines 1-3; The seventh paragraph of Figure Legend, lines 1-3).

Revised "Figure Legend" (revisions are highlighted):

Figure 1 Abdominal MRI in December 2014. Abdominal MRI showed the tumor infiltrated the whole stratum of the gallbladder wall (blue arrow) and metastasized to the left and right liver (red arrow).

Figure 2 ^{18}F-FDG PET-CT in December 2014. ^{18}F-FDG PET-CT depicted gallbladder cancer with multiple liver metastases, peritoneum metastasis, diaphragm metastasis and lymph node metastases.

Figure 3 Pathology of fine needle aspiration of the liver metastases in December 2014. Pathological result indicated that adenocarcinoma. The tumor cells showed a glandular ductal and nest-like infiltrative growth.

Figure 4 The tumor markers levels during chemotherapy and targeted therapy. The levels of CEA, CA19-9 and CA12-5 gradually decreased but remained higher than the normal levels during chemotherapy and targeted therapy.

Figure 5 Abdominal MRI in August 2015. Abdominal MRI showed that the gallbladder was malformed and that the right liver metastasis was larger than the prior scan (red arrow).

Figure 6 ^{18}F-FDG PET-CT in March 2016. ^{18}F-FDG PET-CT showed that ^{125}I seeds were around the gallbladder, but the gallbladder was not clearly visible (blue arrow). The left and right liver metastases still existed (red arrow).

Figure 7 Abdominal CT and ^{18}F-FDG PET-CT in February 2018. A, B and C: Abdominal CT showed that the gallbladder had disappeared and that the liver metastasis was limited to the left liver (red arrow); D: ^{18}F-FDG PET-CT showed that the liver metastasis was limited to the left liver (red arrow).

Figure 8 Surgical specimen, hematoxylin-eosin staining and immunohistochemical examination. A: Surgical specimen; B: Hematoxylin-eosin staining showed tumor cells grew in infiltrating glandular ducts and nests (×200); C: Immunohistochemical examination indicated ARGINASE-1 (-) (×200); D: Immunohistochemical examination indicated CK19 (+) (×200), E: Immunohistochemical examination indicated GPC-3 (partial +) (×200), F: Immunohistochemical examination indicated hep-par (-) (×200), G:

Immunohistochemical examination indicated CEA (partial+) (×200), H: Immunohistochemical examination indicated CK20 (-) (×200); I: Immunohistochemical examination indicated CK7 (+) (×200).

Figure 9 Abdominal CT of follow-up. A: Abdominal CT in October 2019 showed postoperative changes and no signs of tumor recurrence; B: Abdominal CT in March 2021 showed postoperative changes and no signs of tumor recurrence.

5. What was the TNM score of the patient?

Reply: We have added the TNM score of the patient. (The first paragraph of FINAL DIAGNOSIS, lines 1-4).

Revised "FINAL DIAGNOSIS" (revisions are highlighted):

Based on all the above examinations and the 8th edition of the American Joint Committee on Cancer (AJCC)[9], the patient was diagnosed with clinical T4N2M0 and stage IVB gallbladder cancer with multiple liver metastases, peritoneum metastasis, diaphragm metastasis and lymph node metastases.

To Science editor

We thank the science editor for the encouraging comments and constructive suggestions. After carefully studied the comments, we have addressed the questions raised by science editor as follows.

1. Please revise the title as "Successful multimodality treatment of metastatic gallbladder cancer: a case report"

Reply: We agree with this suggestion and have revised the title. (The Title part, line 1).

Revised "Title" (revisions are highlighted):

Successful multimodality treatment of metastatic gallbladder cancer: a case report

2. Introduction: Please expand it to describe the recommended treatment of stage IV or metastatic gallbladder cancer as per NCCN or ESMO guidelines. Also mention the reported median survival of these patients supported by appropriate

references.

Reply: We are thankful for the reviewer's valuable comment. We have added the NCCN guidelines for unresectable or metastatic gallbladder cancer. Furthermore, the median survival is also mentioned. (The first paragraph of Introduction, lines 1-5 and lines 8-12).

Revised "INTRODUCTION" (revisions are highlighted):

Gallbladder cancer is the most common malignant tumor in the biliary system, with a global average incidence of approximately 2.71/100000 and a high incidence in Chile, Japan and India[1, 2]. Gallbladder cancer is characterized by its high aggressiveness and an extremely poor prognosis, and the five-year survival rates of stage I, IVA and IVB gallbladder cancer are only 50%, 12.4% and 2.5% respectively[3-5]. Radical surgery is the only way to cure gallbladder cancer. However, gallbladder cancer has an insidious onset and is difficult to diagnose at an early stage. In fact, some patients are already in the advanced stage when the diagnosis is made[6, 7]. For unresectable or metastatic gallbladder cancer, the National Comprehensive Cancer Network (NCCN) guidelines for hepatobiliary cancers recommend chemotherapy, radiotherapy, immunotherapy and biliary drainage as palliative therapy to prolong patient survival[8]. Here, we report a patient with stage IVB gallbladder cancer who has survived for more than six years and is currently in disease-free survival after multidisciplinary treatment.

3. Case presentation: a. Please mention the baseline complete blood count, liver function and kidney function tests of the patient. Also, add the performance status of the patient. b. Please describe the number, size and location of the lesions on CT at initial presentation in detail. c. Please mention the SUVmax, additional findings other than CT findings about the liver lesions, the location and size of peritoneal and diaphragmmatic lesions on PETCT. d. Please mention that palliative chemotherapy was given and not adjuvant (adjuvant is given after curative surgery). e. Please provide the following details about the surgery:

intraoperative findings, whether gallbladder and common bile duct were excised, operative time, blood loss, postoperative complications, hospital stay. f. Please provide details about how and where the iodine seeds were placed. g. Please mention how was it confirmed that it was gallbladder cancer and not cholangiocarcinoma.

Reply: **a.** The laboratory examinations of the patient showed the following. Blood count: Red blood cell, 4.3×10^{12}/L; Hemoglobin, 129 g/L; Platelet, 201×10^{9}/L; White blood cell, 8.3×10^{9}/L; Neutrophile granulocyte, 7.0×10^{9}/L. Liver function: Alanine aminotransferase, 23 IU/L; Aspartate transaminase, 25 IU/L; Total bilirubin, 9.8 umol/L; Albumin, 38 g/L; Alkaline phosphatase, 69 IU/L; Gamma-glutamyltransferase, 44 IU/L. Kidney function: Creatinine, 67 umol/L; Urea, 6.21 umol/L. Tumor markers: Alpha-fetoprotein (AFP), 1.61 IU/mL (normal, 0-5.8 IU/mL); Carcinoembryonic antigen (CEA), 115.8 ng/mL (normal, 0-5 ng/mL); Carbohydrate antigen19-9 (CA19-9), > 1000 IU/mL (normal, 0-27 IU/mL); CA12-5, 112.3 IU/mL (normal, 0-35 IU/mL). We have stated in the revised manuscript that the blood count, liver function and kidney function tests of the patient were at normal levels. (The Laboratory examinations part of CASE PRESENTATION, lines 5-6). **b.** We have added the number, size and location of the lesions at initial presentation in detail. (The Imaging examinations part of CASE PRESENTATION, lines 1-4). **c.** We have added the SUVmax value of the lesions on PET-CT. (The Imaging examinations part of CASE PRESENTATION, lines 5-9). **d.** We have modified adjuvant chemotherapy to palliative chemotherapy before the curative surgery. (The first paragraph of TREATMENT, lines 1-2). **e.** We have described the surgery, postoperative complications and hospital stay in more detail. (The second paragraph of TREATMENT, lines 4-9 and lines 14-15). **f.** We have added the details about how and where the iodine seeds were placed. (The first paragraph of TREATMENT, lines 11-12). **g.** The patient was diagnosed with gallbladder cancer with multiple liver metastases, peritoneum metastasis, diaphragm metastasis and lymph node metastases based on abdominal MRI and PET-CT. Abdominal MRI indicated gallbladder cancer with a tumor size of approximately 3.2 mm × 4.1 mm, right liver metastasis with a

tumor size of approximately 4.7 mm × 4.7 mm, left liver metastasis with a tumor size of approximately 3.6 mm × 4.2 mm, and peritoneum metastasis. ^{18}F-FDG PET-CT depicted gallbladder cancer (early SUVmax was 9.6, delayed SUVmax was 12.0) with multiple liver metastases (early SUVmax was 12.9, delayed SUVmax was 22.8), lymph nodes metastases (early SUVmax was 4.1, delayed SUVmax was 6.1), peritoneum metastasis and diaphragm metastasis (early SUVmax was 2.1, delayed SUVmax was 3.3).

Revised "CASE PRESENTATION and TREATMENT" (revisions are highlighted):

CASE PRESENTATION

Chief complaints

In December 2014, a 73-year-old male presented to our hospital with right abdominal pain for 3 days.

History of present illness

The patient suffered right abdominal pain for 3 days.

History of past illness

The patient had no other significant medical history.

Personal and family history

The patient had no family history of cancer or hepatobiliary disease.

Physical examination

Physical examination indicated mild tenderness in the right upper quadrant of the abdomen and positive Murphy's sign.

Laboratory examinations

In December 2014, the laboratory examinations showed the following for tumor markers: alpha-fetoprotein (AFP), 1.61 IU/mL (normal, 0-5.8 IU/mL); carcinoembryonic antigen (CEA), 115.8 ng/mL (normal, 0-5 ng/mL); carbohydrate antigen19-9 (CA19-9), > 1000 IU/mL (normal, 0-27 IU/mL); and CA12-5, 112.3 IU/mL (normal, 0-35 IU/mL). The blood count, liver function and kidney function examinations of the patient were at normal levels.

Imaging examinations

In December 2014, abdominal magnetic resonance imaging (MRI) indicated gallbladder cancer with a tumor size of approximately 3.2 cm × 4.1 cm, right liver metastasis with a tumor size of approximately 4.7 cm × 4.7 cm, left liver metastasis with a tumor size of approximately 3.6 cm × 4.2 cm, and peritoneum metastasis (**Figure 1**). ^{18}F-FDG PET-CT depicted gallbladder cancer (early SUVmax was 9.6, delayed SUVmax was 12.0) with multiple liver metastases (early SUVmax was 12.9, delayed SUVmax was 22.8), lymph node metastases (early SUVmax was 4.1, delayed SUVmax was 6.1), peritoneum metastasis and diaphragm metastasis (early SUVmax was 2.1, delayed SUVmax was 3.3) **(Figure 2)**.

Pathologic evaluation

A fine needle aspiration biopsy of the liver metastases indicated adenocarcinoma **(Figure 3)**.

FINAL DIAGNOSIS

Based on all the above examinations and the 8th edition of the American Joint Committee on Cancer (AJCC)[9], the patient was diagnosed with clinical T4N2M0 and stage IVB gallbladder cancer with multiple liver metastases, peritoneum metastasis, diaphragm metastasis and lymph node metastases.

TREATMENT

We recommended that the patient first went to the oncology department to receive palliative therapy, as there were no specific indications for radical surgery. In March 2015, the patient began receiving chemotherapy (gemcitabine 1.4 grams and oxaliplatin 150 milligrams every 21 days, seven cycles) and targeted therapy (cetuximab 400 milligrams every 21 days, continuing to this day). During chemotherapy and targeted therapy, the level of tumor markers gradually decreased but remained higher than the normal level **(Figure 4)**. In August 2015, abdominal MRI after seven cycles of chemotherapy showed that the gallbladder was malformed and that the right liver metastasis was larger than the prior scan **(Figure 5)**. In October 2015, the patient received iodine-125 (^{125}I) seed implantation to treat gallbladder cancer, liver metastases, and lymph node metastases. The ^{125}I seed was implanted

around the gallbladder under the guidance of CT. In January 2016, the patient began receiving immunotherapy (nivolumab 200 milligrams every 21 days, continuing to this day) and targeted therapy (apatinib 250 milligrams every day). Due to the side effects of hypertension, apatinib was in turn replaced with nintedanib and regorafenib. In March 2016, ^{18}F-FDG PET-CT showed that ^{125}I seeds were around the gallbladder, but the gallbladder was not clearly visible. The left and right liver metastases still existed, and the hilar and peripancreatic lymph node metastases had disappeared **(Figure 6)**.

In February 2018, abdominal CT and ^{18}F-FDG PET-CT showed that the gallbladder had disappeared and that liver metastasis was limited to the left liver **(Figure 7)**. We speculated that a series of adjuvant treatments led to the gradual disappearance of the gallbladder. Then the patient underwent surgery because the liver metastasis was limited to the left liver. During surgery, we detected a lesion in the left liver involving the diaphragm, and a hard mass could be palpated in the gallbladder region. Left hepatectomy with radical lymphadenectomy and partial diaphragmatic resection was subsequently conducted. The entire operation lasted approximately 3 hours, and the blood loss was approximately 100mL. The postoperative pathological examination confirmed moderate poorly differentiated cholangiocarcinoma in the left liver with invasion of the liver capsule and diaphragm, and the liver resection margin was negative **(Figure 8)**. The postoperative immunohistochemical examination indicated ARGINASE-1 (-), CK19 (+), GPC-3 (partial +), hep-par (-), CEA (partial+), CK20 (-), and CK7 (+) **(Figure 8)**. There were no postoperative complications, and the patient was discharged 15 days after surgery.

4. Please revise the conclusion as "Although the prognosis of metastatic gallbladder cancer remains extremely poor in the current medical arena, the presented case highlights the importance of providing aggressive multidisciplinary treatment to appropriately selected patients with metastatic gallbladder cancer to achieve long-term survival."

Reply: We thank the science editor for the suggestion, and we have revised the

conclusion. (The first paragraph of CONCLUSION, lines 2-6).

Revised "CONCLUSION" (revisions are highlighted):

We reported a patient with advanced gallbladder cancer cured by multidisciplinary treatment, which was extremely rare and inspiring. Although the prognosis of metastatic gallbladder cancer remains extremely poor in the current medical field, the presented case highlights the importance of providing aggressive multidisciplinary treatment to appropriately selected patients with metastatic gallbladder cancer to achieve long-term survival.

5. The number of references should be at least 30 articles.

Reply: The revised manuscript contains a total of 30 references.

To Company editor-in-chief

We thank the company editor-in-chief for the encouraging comments. After carefully studied the comments, we have addressed the questions raised by science editor as follows.

1. I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Clinical Cases, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Before its final acceptance, the author(s) must provide the Signed Informed Consent Form(s) or Document(s) of treatment. For example, authors from China should upload the Chinese version of the document, authors from Italy should upload the Italian version of the document, authors from Germany should upload the Deutsch version of the document, and authors from the United States and the United Kingdom should upload the English version of the document, etc. The author(s) must provide the English Language Certificate issued by a professional English language editing company. Please visit the following website for the professional English language editing companies we recommend: https://www.wjgnet.com/bpg/gerinfo/240.

Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor. Please upload the approved grant application form(s) or funding agency copy of any approval document(s).

Reply: We have uploaded the Signed Informed Consent Form together with the revised manuscript. We have reedited and polished the manuscript by the professional English language editing company suggested by editor-in-chief, and the English Language Certificate has been uploaded. We have uploaded the original figure documents. We have prepared and arranged the figures using PowerPoint, and the document has been uploaded. We have uploaded the approved grant application forms.

ROUND 2

To editor and reviewer

We appreciate the reviewer and editor for their comments. After carefully studied the comments, we have addressed the questions raised by reviewer and editor as follows.

1. Please further revise the manuscript according to the re-review comments. "Figure 3 is the same as before, the authors only made a cut of the original one. OK, no problem, but the authors still need to properly identify the histological structures the helped to lead to the diagnosis of gallblader cancer in the photograph with, for example, asterisks, arrows, etc. " Please provide point to point answer to all reviewers. Authors should revise their article according to the reviewers' comments/suggestions and provide point-by-point responses to each in a letter that is to accompany their resubmission.

Reply: We are very sorry about the quality of Figure 3. We have compared the histopathological microphotograph from different visual fields and selected the one with the clearest visual field. We are thankful for the reviewer's valuable comment, and we have used arrows to properly identify the histological structure in the photograph. However, it is difficult to prove that the metastasis is from the gallbladder only through pathological

photograph. This requires reference to the patient's imaging examination results and relevant medical history to assist the diagnosis.

Revised "Figure Legend" (revisions are highlighted):

Figure 1 Abdominal MRI in December 2014. Abdominal MRI showed the tumor infiltrated the whole stratum of the gallbladder wall (blue arrow) and metastasized to the left and right liver (red arrow).

Figure 2 ^{18}F-FDG PET-CT in December 2014. ^{18}F-FDG PET-CT depicted gallbladder cancer with multiple liver metastases, peritoneum metastasis, diaphragm metastasis and lymph node metastases.

Figure 3 Pathology of fine needle aspiration of the liver metastases in December 2014. Pathological result indicated that adenocarcinoma, and the tumor cells showed a tubular and nested infiltrating growth (red arrow).

Figure 4 The tumor markers levels during chemotherapy and targeted therapy. The levels of CEA, CA19-9 and CA12-5 gradually decreased but remained higher than the normal levels during chemotherapy and targeted therapy.

Figure 5 Abdominal MRI in August 2015. Abdominal MRI showed that the gallbladder was malformed and that the right liver metastasis was larger than the prior scan (red arrow).

Figure 6 ^{18}F-FDG PET-CT in March 2016. ^{18}F-FDG PET-CT showed that ^{125}I seeds were around the gallbladder, but the gallbladder was not clearly visible (blue arrow). The left and right liver metastases still existed (red arrow).

Figure 7 Abdominal CT and ^{18}F-FDG PET-CT in February 2018. A, B and C: Abdominal CT showed that the gallbladder had disappeared and that the liver metastasis was limited to the left liver (red arrow); D: ^{18}F-FDG PET-CT showed that the liver metastasis was limited to the left liver (red arrow).

Figure 8 Surgical specimen, hematoxylin-eosin staining and immunohistochemical examination. A: Surgical specimen; B: Hematoxylin-eosin staining showed tumor cells grew in infiltrating glandular ducts and

nests (×200); C: Immunohistochemical examination indicated ARGINASE-1 (-) (×200); D: Immunohistochemical examination indicated CK19 (+) (×200), E: Immunohistochemical examination indicated GPC-3 (partial +) (×200), F: Immunohistochemical examination indicated hep-par (-) (×200), G: Immunohistochemical examination indicated CEA (partial+) (×200), H: Immunohistochemical examination indicated CK20 (-) (×200); I: Immunohistochemical examination indicated CK7 (+) (×200).

Figure 9 Abdominal CT of follow-up. A: Abdominal CT in October 2019 showed postoperative changes and no signs of tumor recurrence; B: Abdominal CT in March 2021 showed postoperative changes and no signs of tumor recurrence.

2. Please provide the informed consent of surgical treatment.

Reply: We have uploaded the informed consent of surgical treatment and submit it as ”Informed consent of surgical treatment.pdf” on the system.

3. Regarding the figures: Please provide the decomposable figure of figures, whose parts are all movable and editable, organize them into a PowerPoint file, and submit as “Manuscript No. -Figures.ppt” on the system, we need to edit the words in the figures. All submitted figures, including the text contained within the figures, must be editable. Please provide the text in your figure(s) in text boxes.

Reply: We have uploaded the decomposable figure of figures whose parts are all movable and editable and submit it as "Manuscript No.70332-Figures.pptx" on the system.

4. Please complete all the revisions based on the version of "6802-

70332_Auto_Edited-v1", and upload above mentioned files in a ".zip" file.

Reply: We have completed all the revisions based on the version of "6802-70332_Auto_Edited-v1", and upload above mentioned files in "Re-reviewed Manuscript (No.70332).zip" file.