

December 13, 2018

RE: WJCC-42973

Dear editor,

We appreciate you and the reviewers for the time and efforts in evaluating/reviewing our manuscript " Surgical treatment of malignant biliary papillomatosis invading adjacent organs: a case report" to be considered for publication in World Journal of Clinical Cases.

We are grateful for the opportunity to revise the paper and for the constructive comments in order to improve the overall content and presentation. In this response letter, we have addressed each of the reviewer's comments, provided additional content as suggested, and modified the manuscript accordingly with the modified text highlighted.

We hope the newly revised manuscript will be acceptable for publication in your respected journal and look forward to your response.

Sincerely,

Yange Zhang, M.D.
Associate Professor
Department of Plastic and Burn Surgery
West China Hospital of Sichuan University

Reviewers' Comments to Author:

Reviewer #1 (code: 02732296)

Comments to the Author

This article represents a very interesting case of a rare condition that was treated successfully. In my opinion this case is a valuable contribution to the common scientific knowledge. However, the authors needs to elucidate some points: 1. How did the previous attending physicians justified leaving a t tube in its place for two years? What was the rationale behind it? 2. How did the authors decide to undertake a radical resection of a locally advanced tumor

which was proven to be an adenocarcinoma of biliary origin (with a skin biopsy) considering the very poor prognosis of locally advanced cholangiocarcinomas. Also the article needs heavy language editing. Some parts of the case report section are barely comprehensible.

Response

Thank you for the insightful comments. The patient visited the local hospital two years ago because of obstructive jaundice with right epigastric pain for 3 months. She received cholecystectomy at local hospital, which revealed a gallbladder filled with tumour-like tissue, leading to the diagnosis of gallbladder adenocarcinoma. Cholangioscopy revealed blockage of the common bile duct by tumor-like tissue. Tumor tissue was totally removed and a T-tube was retained in the common bile duct. Two months later, she came back to hospital to pull out the T-tube. The choledochoscopy showed that common bile duct was filled with adenomatoid tissue and biopsy showed severe dysplasia of the biliary papilloma. The patient and her family members felt hopeless and decided not to pursue any further treatment. However, the patient still survived 2 years later and she came to us for help. This is why she kept the T-tube for 2 years. It seems that the local hospital had misdiagnosed the lesion as gallbladder adenocarcinoma which may actually be malignant transformation of biliary papillomatosis. When she came to us, we considered that her illness was malignant transformation of biliary papillomatosis which was less aggressive than gallbladder adenocarcinoma and had a chance to be resected.

We put these additional content in the section of Case Report and we revised the text as follows:

Page5, Paragraph 2, Line 7-14

“The choledochoscope showed a common bile duct filled with adenomatoid

tissue. After removing the tumor tissue, T-tube drainage was performed. Two months later, she came back to hospital to pull out the T-tube. The choledochoscopy showed that common bile duct was filled with adenomatoid tissue and biopsy showed severe dysplasia of the biliary papilloma. The patient and her family members felt hopeless and decided not to pursue any further treatment. However, the patient still survived 2 years later and she came to us for help."

Page6, Paragraph 3, Line 1-5

"It seems that the local hospital had misdiagnosed her illness as gallbladder adenocarcinoma which may actually be malignant transformation of biliary papillomatosis. When she came to us, we considered that her illness was malignant transformation of biliary papillomatosis which was less aggressive than gallbladder adenocarcinoma and had a chance to be resected."

We have revised this manuscript by AJE and corrected the errors of grammatical mistakes and we attached the revised certificate in attach files. Please see attached the revision certification.

Reviewer #2 (code: 02541859)

Comments to the Author

This is a nice case report. Minor language revision required. In the discussion, any case of obstructive jaundice, ERCP should be tried first. ERCP with cholangioscopy with biopsy could give early diagnosis.

Response: Thank you for your comments and for raising this important point. We agree with your point that ERCP with cholangioscopy with biopsy could give early diagnosis.

This part had been added to our manuscript in the section of Discussion and we revised the text as follows:

Page9, Paragraph 1, Line 5-6

“ERCP with cholangioscopy with biopsy could give early diagnosis.”

We have revised this manuscript by AJE and corrected the errors of grammatical mistakes and we attached the revised certificate in attach files. Please see the attached revision certification.

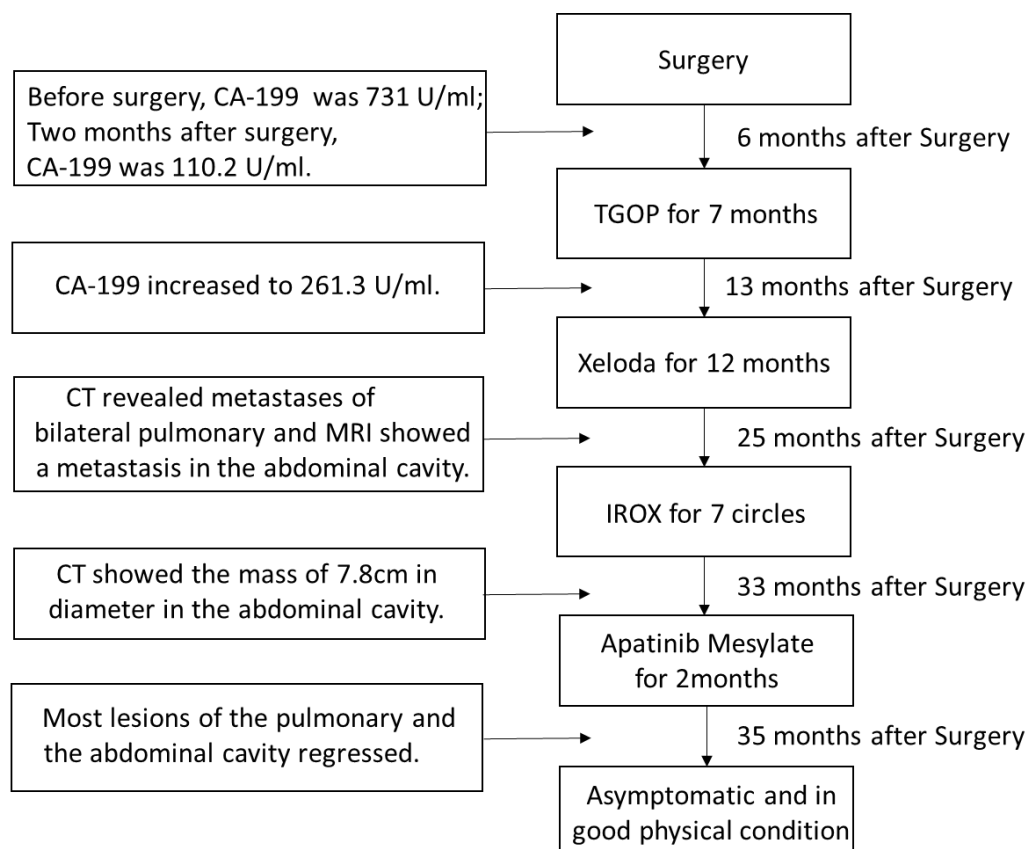
Reviewer #3 (code: 00069423)

Comments to the Author

This case report is well written and surgical procedure is clearly illustrated. The discussion was good. If this patient who underwent such an extensive surgery could survive with restored nutrition for 2 years, authors are congratulated. It will be worthwhile to continue observation and if long term survival would be possible, authors should report the long term survival. Comment: The consent form signing should be included under the case report section than in the introduction. Hb 37 g/L, should also be expressed as 3.7 g/dL as most readers are familiar with in other countries.

Response: Thank you for your comments. As we revised the paper, we contacted the patient again. We updated the patient's survival as follows: She received adjuvant chemotherapy by oral administration of 40mg tegafur, gimeracil, and oteracil potassium capsules (TGOP; Weikangda; Lunan Pharmaceutical Co., China) twice daily on days 1-28, every 2 weeks for 7 months after half a year of radical surgery. However, with this treatment, the level of CA-199 still increased to 261.3 U/ml, which was considered to be a sign of disease progression, even though there is no evidence from CT scan. The oncologist began to treat her with oral administration of 1000mg Capecitabine Tablets (Xeloda; Luoshi Pharmaceutical Co., China) twice daily on days 1-14, every 3 weeks for 12 months. After 25 months of the surgery, CT

scan revealed metastases of bilateral pulmonary and MRI showed a metastasis in the abdominal cavity.. She began to receive IROX regimen (intravenous injection of 100 mg Oxaliplatin on day 1 and 160mg Irinotecan on day 1 followed by oral administration of 1000mg Capecitabine Tablets once daily on days 1, every 4 weeks) every 3 weeks. After 7 cycles of IROX regimen, there was no change of the metastases as showed on the CT of the chest. However, the abdomen CT showed the mass of abdominal cavity increased to 7.8cm in diameter. At 33 months after the operation, she took 0.25g Apatinib Mesylate Tablets (Aitan; Hengrui Pharmaceutical Co., China) once daily. At 35 months after operation, most lesions of the pulmonary regressed. The abdominal mass decreased to 5.1cm in diameter. She was asymptomatic and in good physical condition at 35 months postoperatively.



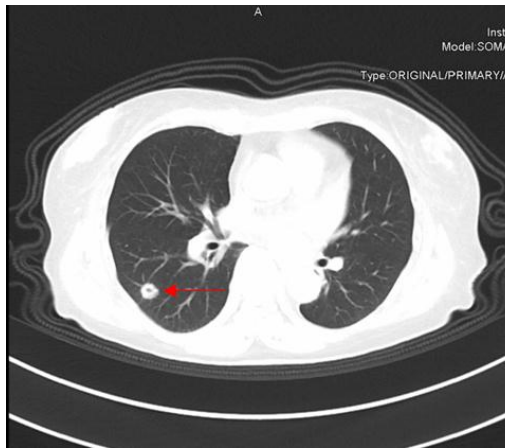


Figure 1. **25 months after surgery.** CT revealed metastases of bilateral pulmonary (red arrow) and MRI showed a metastasis in the abdominal cavity (white arrow).



Figure 2. **33 months after surgery.** There was no change of the metastases as showed on the CT of the chest (red arrow)). However, the abdomen CT showed the mass of abdominal cavity increased to 7.8cm in diameter (white arrow).

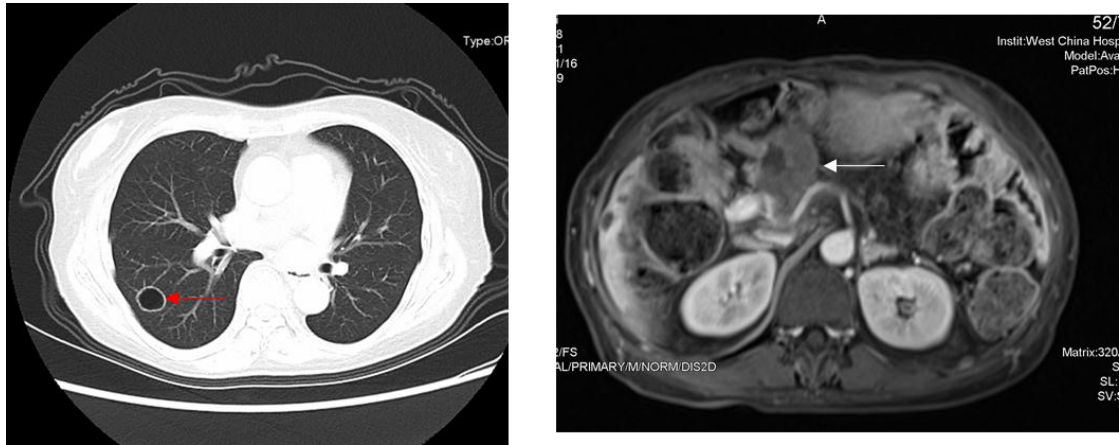


Figure 3. **35 months after surgery.** The lesions of the pulmonary regressed (red arrow). The abdominal mass decreased to 5.1cm in diameter (white arrow).

We had put these additional content to the section of Case Report and we revised the text as follows:

Page6, Paragraph 1, Line 8-28

“She received adjuvant chemotherapy by oral administration of 40mg tegafur, gimeracil, and oteracil potassium capsules (TGOP; Weikangda; Lunan Pharmaceutical Co., China) twice daily on days 1-28, every 2 weeks for 7 months after half a year of radical surgery. However, with this treatment, the level of CA-199 still increased to 261.3 U/ml, which was considered to be a sign of disease progression, even though there is no evidence from CT scan. The oncologist began to treat her with oral administration of 1000mg Capecitabine Tablets (Xeloda; Luoshi Pharmaceutical Co., China) twice daily on days 1-14, every 3 weeks for 12 months. After 25 months of the surgery, CT scan revealed metastases of bilateral pulmonary and MRI showed a metastasis in the abdominal cavity.. She began to receive IROX regimen (intravenous injection of 100 mg Oxaliplatin on day 1 and 160mg Irinotecan on day 1 followed by oral administration of 1000mg Capecitabine Tablets once daily on days 1, every 4 weeks) every 3 weeks. After 7 cycles of IROX

regimen, there was no change of the metastases as showed on the CT of the chest. However, the abdomen CT showed the mass of abdominal cavity increased to 7.8cm in diameter. At 33 months after the operation, she took 0.25g Apatinib Mesylate Tablets (Aitan; Hengrui Pharmaceutical Co., China) once daily. At 35 months after operation, most lesions of the pulmonary regressed. The abdominal mass decreased to 5.1cm in diameter. She was asymptomatic and in good physical condition at 35 months postoperatively."

We had put the Consent Form Signing in the section of Case Report and we revised the text as follows:

Page6, Paragraph 3, Line 5-7

"After the patient signed a consent form, exploratory laparotomy using a left reverse L-shaped incision was performed."

We had expressed Hb 37 g/L as 3.7 g/dL in the manuscript and we revised the text as follows:

Page5, Paragraph 2, Line 14-16

"She presented with severe malnutrition and recurrent infection with minimum haemoglobin and albumin of 3.7 g/dL and 2.8 g/dL, respectively."

Reviewer #4 (code: 02742751)

Comment: Dear Associate Editor, Thank you for sending me the case report for review. It reported a case of biliary papilomatosis with malignant transformation. The tumor extended outside the biliary tract and involved the adjacent organs. There is no data regarding chemoradiation in this case. Moreover, There is no data regarding post operative recurrence using PET scan or any other imaging modality. Considering the grade of tumor differentiation and tumor behavior he time of follow up is rather short.

Response: Thank you for your comments. During the time we revised the paper, we contacted the patient again. We updated the chemotherapy and survival as follows: She received adjuvant chemotherapy by oral administration of 40mg tegafur, gimeracil, and oteracil potassium capsules (TGOP; Weikangda; Lunan Pharmaceutical Co., China) twice daily on days 1-28, every 2 weeks for 7 months after half a year of radical surgery. However, with this treatment, the level of CA-199 still increased to 261.3 U/ml, which was considered to be a sign of disease progression, even though there is no evidence from CT scan. The oncologist began to treat her with oral administration of 1000mg Capecitabine Tablets (Xeloda; Luoshi Pharmaceutical Co., China) twice daily on days 1-14, every 3 weeks for 12 months. After 25 months of the surgery, CT scan revealed metastases of bilateral pulmonary and MRI showed a metastasis in the abdominal cavity.. She began to receive IROX regimen (intravenous injection of 100 mg Oxaliplatin on day 1 and 160mg Irinotecan on day 1 followed by oral administration of 1000mg Capecitabine Tablets once daily on days 1, every 4 weeks) every 3 weeks. After 7 cycles of IROX regimen, there was no change of the metastases as showed on the CT of the chest. However, the abdomen CT showed the mass of abdominal cavity increased to 7.8cm in diameter. At 33 months after the operation, she took 0.25g Apatinib Mesylate Tablets (Aitan; Hengrui Pharmaceutical Co., China) once daily. At 35 months after operation, most lesions of the pulmonary regressed. The abdominal mass decreased to 5.1cm in diameter. She was asymptomatic and in good physical condition at 35 months postoperatively.

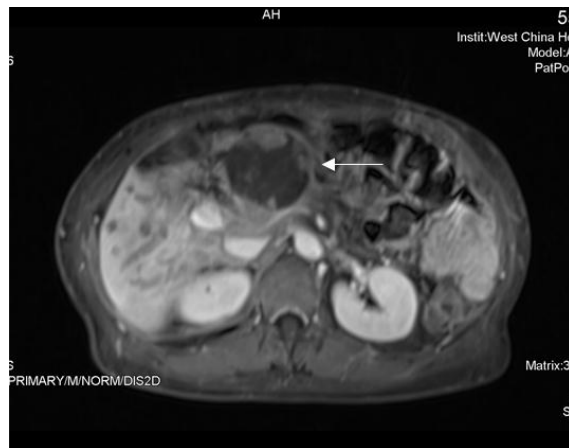
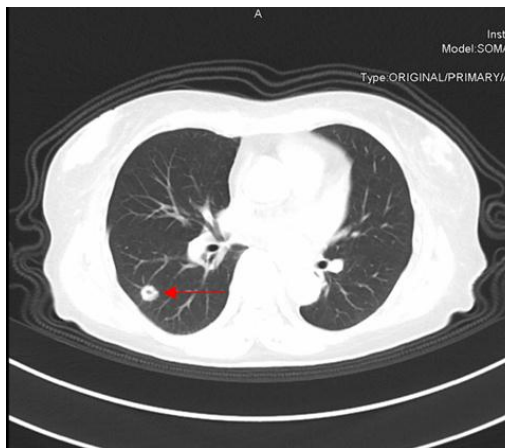
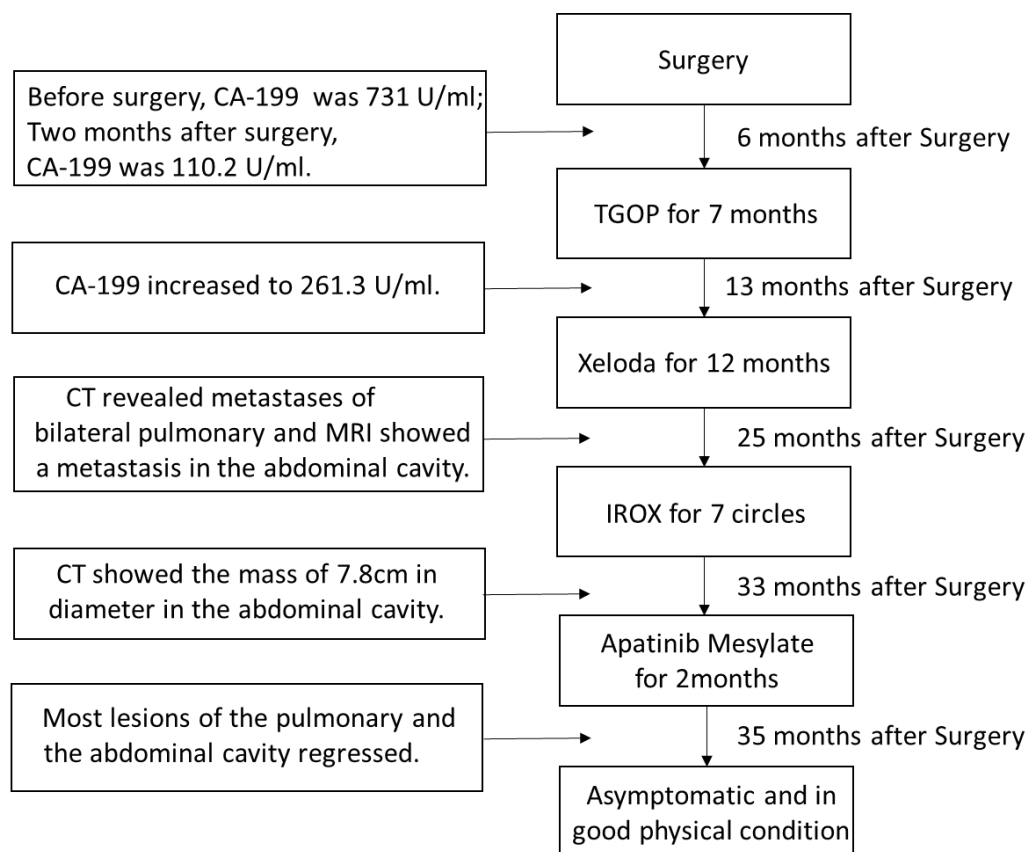


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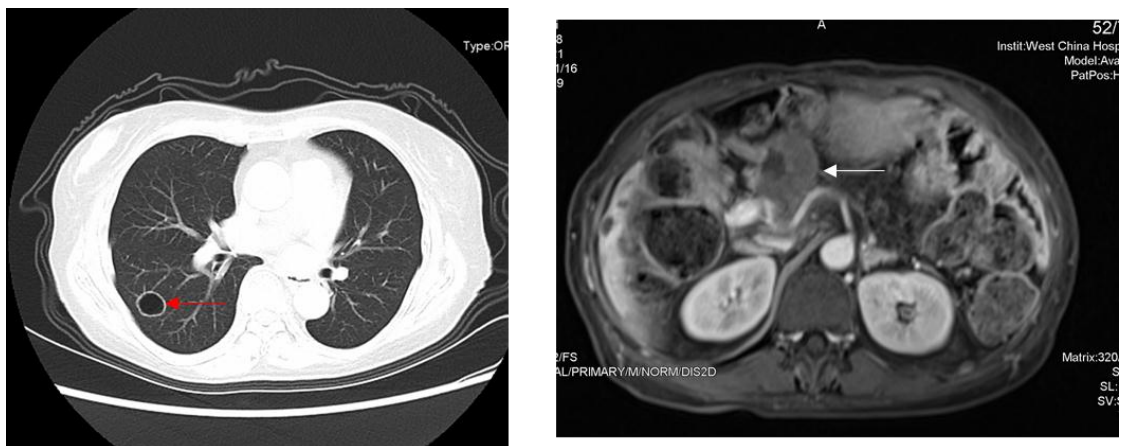


Figure 3. **35 months after surgery.** The lesions of the pulmonary regressed (red arrow). The abdominal mass decreased to 5.1cm in diameter (white arrow).

We had put these additional content to the section of Case Report and we revised the text as follows:

Page6, Paragraph 1, Line 8-28

“She received adjuvant chemotherapy by oral administration of 40mg tegafur, gimeracil, and oteracil potassium capsules (TGOP; Weikangda; Lunan

Pharmaceutical Co., China) twice daily on days 1-28, every 2 weeks for 7 months after half a year of radical surgery. However, with this treatment, the level of CA-199 still increased to 261.3 U/ml, which was considered to be a sign of disease progression, even though there is no evidence from CT scan. The oncologist began to treat her with oral administration of 1000mg Capecitabine Tablets (Xeloda; Luoshi Pharmaceutical Co., China) twice daily on days 1-14, every 3 weeks for 12 months. After 25 months of the surgery, CT scan revealed metastases of bilateral pulmonary and MRI showed a metastasis in the abdominal cavity.. She began to receive IROX regimen (intravenous injection of 100 mg Oxaliplatin on day 1 and 160mg Irinotecan on day 1 followed by oral administration of 1000mg Capecitabine Tablets once daily on days 1, every 4 weeks) every 3 weeks. After 7 cycles of IROX regimen, there was no change of the metastases as showed on the CT of the chest. However, the abdomen CT showed the mass of abdominal cavity increased to 7.8cm in diameter. At 33 months after the operation, she took 0.25g Apatinib Mesylate Tablets (Aitan; Hengrui Pharmaceutical Co., China) once daily. At 35 months after operation, most lesions of the pulmonary regressed. The abdominal mass decreased to 5.1cm in diameter. She was asymptomatic and in good physical condition at 35 months postoperatively."