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Title: Port-site metastasis of unsuspected gallbladder carcinoma with ossification after laparoscopic cholecystectomy: A case report and literature review

Authors: Kai-Jun Gao, et al

Dear Professor Lian-Sheng Ma,

Thank you very much for your decision letter and advice, regarding our manuscript (Manuscript NO.: 58762). We are pleased you will consider a revised version of our manuscript for publication in *World Journal of Clinical Cases*. We also thank the reviewers for their constructive and positive comments and suggestions. Accordingly, we have revised the manuscript and submitted the revised manuscript. All the major amendments are highlighted in red in the revised manuscript. In addition, our point-by-point responses to the editors' and reviewers' comments and explanation of the changes in our paper are listed in the following pages.

We hope that our responses and revisions meet the editors' and reviewers' expectation and that the revised manuscript is acceptable for publication in your journal. I look forward to hearing from you soon.

Yours sincerely,

Mou-Cheng Zhang, Professor

Responses to Comments from the Editors and Reviewers

First and foremost, we would like to express our sincere gratitude to the editors and reviewers for their constructive and positive comments that help improve our manuscript tremendously.

Responses to the Comments from Reviewer

- 1 *Case report, History of present illness, page 4, lines 11-12* – it would be clearer if you could provide more information about the methods used for patients re-examination and follow-up after the first occurrence of adenocarcinoma. When was the last ultrasound or CT performed before the second hospitalization? Did the mass occur in a short time? Was the patient followed-up every 6 months after the first surgery? (clarify the word “regularly”) Was the follow-up discontinued for some time?

Response: We are very sorry for the unclear report in the follow-up information. (1) Because of the patient underwent surgery at a community hospital 10 years ago, we can only obtain the follow-up information from the patient. He said that abdominal CT and tests of cancer-associated tumor markers were re-examined after surgery. (2) The patient visited our hospital one day after a mixed mass was found in the upper abdominal wall by ultrasound. He then was admitted to our hospital for further treatment. (3) The mass occurred 10 years after surgery, not in a short time. (4) The patient re-examined every 3 mo in the first year after surgery. After that, he followed-up every 6 mo without interruption. We have now added the information above into the revised manuscript.

- 2 *Case report, History of present illness, page 4, line 11* - To my opinion, the sentence “During the operation, abdominal wall tissue (2 cm) around the trocar hole was not removed” from Abstract, Case summary, page 2, line 3, fits better or is missing in the case presentation part (page 4, line 11).

Response: We appreciate very much for your suggestion. We have now revised the manuscript, and described the sentence “During the operation, abdominal

wall tissue (2 cm) around the trocar hole was not removed" in the "Case Presentation- History of present illness" section.

- 3 *Follow up and outcome, page 6, line 14* – What methods and how often were used to follow up the patient after the second operation? What are your recommendations for further follow-up in this case (regularity, methods)?

Response: We are so sorry for the missing information in the original submission. We have now revised the follow up and outcome as follows : “The patient was followed up every 3 mo with abdominal ultrasonography and tests of cancer-associated tumor markers. No recurrence was found by abdominal enhanced CT 1 year after the latest surgery (Figure 1F). The patient has been followed up for 31 mo, and in good condition.”. We recommend the follow-up strategies for these patients as follows: (1) abdominal ultrasound and tests of cancer-associated tumor markers should be performed every 3 mo within 1 year after surgery; (2) an enhanced CT should be performed within one year; and (3) if there is evidence of recurrence, the patient should be followed up every 6 mo. We have added this part in the " DISCUSSION" section.

- 4 *Treatment, page 10, line 6* – To my opinion, the last sentence of this paragraph needs clarification – why was the treatment refused? Did the patient himself refuse the treatment? You mentioned that in the discussion, but this part of the manuscript could also be written more clearly.

Response: We are very sorry for the unclear explanation for this part. The patient refused our recommendation to do further chemotherapy. We have now revised this part clearly in the revised manuscript.

- 5 *Discussion, page 9, line 13* - You stated that the data about the need for chemotherapy after the surgical removal is limited. Why was it suggested in this particular case?

Response: We are so sorry for the confusion in the understanding of this section in the original submission. Due to PSM of UGC after laparoscopic cholecystectomy is extremely rare, so the data is limited. Vinuela reported that the gemcitabine, capecitabine, and radiation therapy for patients with residual cancer may be effective. After consultation with the Department of Radiotherapy and Chemotherapy further chemotherapy was recommended.

- 6 The discussion part could provide some basic information about the recommended follow-up (methods, regularity) of such patients in order to prevent cancer re-occurrence.

Response: Once again, you have raised an important point related to follow-up strategies. We have added the follow-up strategies into the revised manuscript as follows :“We recommend the follow-up strategies for these patients as follows: (1) abdominal ultrasound and tests of cancer-associated tumor markers should be performed every 3 mo within 1 year after surgery; (2) an enhanced CT should be performed within one year; and (3) if there is evidence of recurrence, the patient should be followed up every 6 mo.”

- 7 There are some spelling issues:

- *Abstract, page 2, line 10* - please correct the spelling of the word “immunohistochemistry”;
- *Abstract, page 3, line 26* - “summarize” - past tense missing;
- *Discussion, page 6, line 19* - “anually” - letter “n” missing;
- *Discussion, page 9, line 9* - please correct the unnecessary capitalization “In the current patient, No recurrence was found”;
- *Discussion page 9, line 14* - please correct the [20] citation according to the manuscript preparation guidelines.

Response: We apologize for the these spelling issues. We have corrected these issues in the revised manuscript.

- 8 Some language polishing needed: articles and commas are missing throughout the manuscript.

Response: Thank you very much for the suggestion. We have submitted our manuscript to MedE for language polishing again.

- 9 Table 1 – in the manuscript, you stated that there is no recurrence of cancer after 31 mo follow-up. In Table 1 – the patient is alive 22 months. Which one is correct?

Response: We are very sorry for the unclear report in follow-up time. We have corrected in Table 1- the patient is alive 31 mo.

- 10 Table 1 does not fill in the page margins.

Response: Thank you very much for the suggestion. We have now revised the manuscript.

- 11 Please clarify the TNM stage of the second occurrence of the gallbladder adenocarcinoma in the text (pT1b is stated only in table 1).

Response: We appreciate very much your suggestion. We have now added T stage in the CASE SUMMARY part as: Histological analysis revealed unexpected papillary adenocarcinoma of the gallbladder with gallstones, which indicated that the tumor had spread to the muscular space (pT1b).

- 12 Please correct the manuscript according to the provided guidelines for manuscript writing (running title, author contributions etc. are missing, inconsistent amount of words (case report -“no more than 150 words”, conclusion -“no more than 20 words”, core tip - “no more than 100 words” – please check <https://www.wjgnet.com/bpg/GerInfo/187>).

Response: Thank you very much for the suggestion. We have now revised this in the revised manuscript.

- 13 Care checklist does not contain lines and pages. Some points are marked as provided in the manuscript, however, are not provided – e.g. case report timeline.

Response: We apologize for the missing information in the Care checklist. We have now corrected in the revised Care checklist.

Port-site metastasis of unsuspected gallbladder carcinoma with ossification after laparoscopic cholecystectomy: A case report and literature review

Gao KJ *et al.* Port-site metastasis after gallbladder carcinoma

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Author contributions: Gao KJ and Zhang MC designed the report; Zhang MC and Yan ZL performed the surgery; Yu Y reviewed the literature and contributed to drafting the manuscript; Guo LQ analyzed and interpreted the imaging findings; Hang C performed the pathology analyses; Yang JB was responsible for the revision of the manuscript for important content; Gao KJ wrote the manuscript; all authors have read and approved the final manuscript.

Informed consent statement: Informed written consent was obtained from the patient for publication of this report and any accompanying images.

Conflict-of-interest statement: The authors declare that they have no conflict of interest.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

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Abstract

BACKGROUND

Unsuspected gallbladder carcinoma (UGC) refers to cholecystectomy due to benign gallbladder disease, which is pathologically confirmed as gallbladder cancer during or after surgery. Port-site metastasis (PSM) of UGC following laparoscopic cholecystectomy is rare, especially after several years.

CASE SUMMARY

A 55-year-old man presenting with acute cholecystitis and gallstones was treated by laparoscopic cholecystectomy in July 2008. **Histological analysis revealed unexpected papillary adenocarcinoma of the gallbladder with gallstones, which indicated that the tumor had spread to the muscular space (pT1b).** Radical resection of gallbladder carcinoma was performed 10 d later. In January 2018, the patient was admitted to our hospital for a mass in the upper abdominal wall after surgery for gallbladder cancer 10 years ago. Laparoscopic exploration and complete resection of the abdominal wall tumor were successfully performed. Pathological

diagnosis showed metastatic or invasive, moderately differentiated adenocarcinoma in fibrous tissue with massive ossification. **Immunohistochemistry** and medical history were consistent with invasion or metastasis of gallbladder carcinoma. His general condition was well at follow-up of 31 mo. No recurrence was found by ultrasound and epigastric enhanced computed tomography.

CONCLUSION

PSM of gallbladder cancer is often accompanied by peritoneal metastasis, which indicates poor prognosis. Once PSM occurs after surgery, laparoscopic exploration is recommended to rule out abdominal metastasis to avoid unnecessary surgery.

Key words: Port-site metastasis; Unsuspected gallbladder carcinoma; Heterotopic ossification; Laparoscopic cholecystectomy; Case report; Literature review

Core tip: Port-site metastasis of unsuspected gallbladder carcinoma occurring several years after laparoscopic cholecystectomy is extremely rare. It is often accompanied by peritoneal metastasis, with poor prognosis. We report a case of 55-year-old man with port-site metastasis after surgery for gallbladder cancer 10 years ago. Complete resection of an abdominal wall tumor was successfully performed and no recurrence was found at follow-up of 31 mo. Although recurrence of unsuspected gallbladder carcinoma is rare, physicians should remain vigilant for this possibility. Once port-site metastasis occurs after surgery, laparoscopic exploration or positron emission tomography/computed tomography (PET/CT) is recommended to rule out abdominal metastasis. Complete tumor resection can improve prognosis.

INTRODUCTION

Unsuspected gallbladder carcinoma (UGC) is referred to as a carcinoma found during cholecystectomy due to benign gallbladder disease, which is pathologically confirmed as gallbladder cancer during or after surgery^[1]. Port-site metastasis (PSM) of UGC following laparoscopic cholecystectomy (LC) is rare, with an incidence of 10.3%^[2]. PSM of UGC occurring several years after surgery is even rarer, with only a few cases reported. The mechanism of the PSM is unknown and many researchers have focused on bile overflow and pneumoperitoneum. We report a case of a 55-year-old man who was diagnosed with PSM after surgery for UGC 10 years ago. Laparoscopic exploration and complete resection of abdominal wall tumor were successfully performed. PSM with obvious ossification was found. Some studies have confirmed that ossification often indicates good prognosis. Our patient had no recurrence after follow-up of 31 mo, so good prognosis of this patient may be related to ossification. We also reviewed the literature and retrieved seven relevant papers, which included 8 cases of late-type PSM of UGC. We analyzed the clinical and pathological features of those cases, and summarized the treatment strategy based on our observations.

CASE PRESENTATION

Chief complaints

A 55-year-old man was admitted to our hospital for a mass in the upper abdominal wall after surgery for unsuspected gallbladder cancer 10 years ago.

History of present illness

The patient underwent LC at a community hospital due to acute cholecystitis and gallstones 10 years ago. Histological analysis revealed unexpected papillary adenocarcinoma of the gallbladder with gallstones,

which indicated that the tumor had spread to the muscular space (pT1b). Radical resection of gallbladder carcinoma was performed 10 d later. During the operation, abdominal wall tissue (2 cm) around the trocar hole was not removed. The patient recovered well and followed up every 3 mo in the first year after surgery, and then every 6 mo or 1 year with abdominal CT and tests of cancer-associated tumor markers, such as serum carcinoembryonic antigen (CEA) and serum carcinoembryonic antigen 19-9 (CA19-9). During the follow-up period, the patient experienced no obvious discomfort. The patient visited our hospital one day after a mixed mass was found in the upper abdominal wall by ultrasound. He then was admitted to our hospital for further treatment. Enhanced magnetic resonance imaging (MRI) of the upper abdomen showed a space-occupying mass in the anterior wall of the upper abdomen.

History of past illness and Family history

The patient denied a history of hypertension, diabetes, and other relevant illnesses. No other surgery was performed during this period. He did not have a family history of cancer.

Physical examination upon admission

Old surgical scars of 20 cm were seen on the abdomen, and a hard mass was felt under the xiphoid process. No other abnormalities were found in the physical examination.

Laboratory examinations

Blood analysis revealed that complete blood count, blood biochemistry, and CEA, alpha fetoprotein, CA19-9, cancer antigen 125 (CA125), and CA153 were within normal limits, except for CA724 which was 7.98 U/mL (normal range 0-6.9 U/mL).

Imaging examinations

Ultrasound and enhanced MRI of the upper abdomen showed a space-occupying mass in the anterior wall of the upper abdomen (Figure 1A, 1B). No recurrence was found in other parts of the body by positron emission tomography/computed tomography (PET/CT).

Pathology

Postoperative pathology showed that a gray-red mass had partial cystic degeneration, and hard calcification of the cyst wall. Microscopic examination showed atypical ethmoid hyperplasia (Figure 2A) protruding to the cystic cavity with massive necrosis and hemorrhage and interstitial ossification around multifocal carcinoma (Figure 2B), with infiltration into the fibrous stroma (Figure 2A, 2B). There was no neurovascular invasion, and several foci of cancer cells produced bone-like matrix (Figure 2C). Partial cyst wall thickening and fibrosis with previous hemorrhage with hemosiderin deposition, and interstitial fibrous bone were observed (Figure 2D). Pathological diagnosis was metastatic or invasive, moderately differentiated adenocarcinoma in the fibrous tissue with massive ossification. After consultation with the Department of Radiotherapy and Chemotherapy in our hospital, immunohistochemical staining was recommended to determine whether the metastasis was originated from gallbladder. Immunohistochemistry showed cytokeratin (CK)7(+++), CK20(++), carcinoembryonic antigen(+), villin(+++), p53(-), Ki-67(+)40%, CK19(+++), MC (HBME1)(-) and Wilms tumor (-).

FINAL DIAGNOSIS

Immunohistochemistry and medical history were consistent with the invasion or metastasis of gallbladder carcinoma. The final diagnosis was PSM of gallbladder cancer.

TREATMENT

Laparoscopic exploration and abdominal wall tumor resection were performed after excluding surgical contraindications. No ascites or metastatic nodules were found in the peritoneum and greater omentum during the operation. After the abdominal adhesion was separated, the mass located outside the peritoneum was observed, with a size about 5 × 3 × 3 cm (Figure 1C). An incision of ~5 cm was made above the mass in the right upper abdomen. After incision of the skin and subcutaneous tissue, the mass was found located in the muscular layer of the abdominal wall. The mass was completely removed (Figure 1D, 1E). After consultation with the Department of Radiotherapy and Chemotherapy further chemotherapy was recommended, but was refused by the patient.

OUTCOME AND FOLLOW-UP

The patient was followed up every 3 mo with abdominal ultrasonography and tests of cancer-associated tumor markers. No recurrence was found by abdominal enhanced CT 1 year after the latest surgery (Figure 1F). The patient has been followed up for 31 mo, and in good condition.

DISCUSSION

In recent years, the incidence of UGC has increased annually with the widespread use of LC. About 0.25–3.0% of patients were diagnosed with UGC after surgery, accounting for 50% of all patients with gallbladder cancer^[3]. The overall prognosis of patients with gallbladder cancer is poor, and more than a third have metastasis at the time of diagnosis. In contrast, the pathological stage of UGC patients is relatively early, with a pT2 of 50% and pT1 of 33.3%, and they have a relatively good prognosis^[4]. Papillary adenocarcinoma of the gallbladder accounts for ~5% of all gallbladder cancers, and prognosis of these patients is significantly better than that of patients with other types of gallbladder carcinoma. This may be due to the

late infiltration of the gallbladder wall and growth into the cavity, so it is easy to show the symptoms of obstruction and early diagnosis can be made^[5]. PSM after UGC is rare, and mostly occurs at 4–10 mo after surgery, with a median time of 7 mo. It is often associated with poor prognosis such as peritoneal metastasis, and the median survival time after recurrence is only 10 mo^[6]. Bergerrichardson^[2] reported that the incidence of PSM in gallbladder cancer after LC decreased from 18.6% before 2000 to 10.3% after 2000, but it was still higher than that of other primary malignant tumors.

Cases of late-type PSM of UGC after surgery are even rarer, and only a few cases have been reported in the literature, with only 8 cases being identified over the past 3 years^[7-13] as shown in Table 1. So far, the longest time to recurrence is 12 years^[13]. It has been reported that late recurrence is more common in other primary tumors such as breast cancer and melanoma. This may be related to the lack of angiogenesis in micrometastasis, cell autophagy and tumor inhibition by the immune system^[14]. Ninety percent of PSM occurs in the trocar hole from where the gallbladder specimen is extracted, which is higher than that in non-gallbladder extraction sites (19%)^[2]. The possible mechanisms of PSM are as follows. (1) The outer wall of the gallbladder is contaminated by tumor cells. When the gallbladder specimen is removed, the tumor cells are directly planted on the resected specimen. Microperforation of the gallbladder wall and bile overflow caused by intraoperative clamping or improper surgical procedure are also involved. No incision protection is given during the operation, and the gallbladder specimen is not removed with an extraction bag. (2) Artificial pneumoperitoneum (CO₂) affects tumor cell implantation. Under the condition of artificial pneumoperitoneum, the pressure of gas in the abdominal cavity is higher than that of atmospheric pressure and some gas leaks along the trocar, which is called chimney effect^[15]. In addition, when the gas is filled into

the abdominal cavity, the tumor cells may be atomized, which may cause incision metastasis of tumor cells^[16]. (3) Postoperative incision trauma, blood osmosis, low immunity and other factors provide favorable conditions for tumor cell implantation and growth. Pathological examination in our patient showed metastatic or invasive adenocarcinoma with massive ossification, but gallbladder carcinoma with ossification is not reported in the literature. Ossification is generally considered to be an adaptive mechanism that limits the spread of inflammation to control the spread of harmful processes and protect adjacent tissues^[17]. Some studies have confirmed that ossification of breast cancer often indicates good prognosis^[18], so the good prognosis in the current patient may be related to ossification.

Although recurrence several years after UGC resection is rare, it is still necessary to be vigilant. Therefore, attention must be paid to specimen handling and incision protection during cholecystectomy to avoid bile spillover. In particular, for patients with suspected gallbladder cancer, it is recommended to use extraction bags to reduce the possibility of tumor cell spread. The gallbladder specimen should be routinely dissected during the operation, and suspected cases must be examined by frozen section. It is suggested that the gallbladder should be exposed along the long axis, the adventitia or serosa of the gallbladder should be cut along the maximum diameter in the suspected lesions, and the specimens of suitable parts should be selected for frozen section examination^[19]. Although the removal of abdominal wall tissue around the trocar hole after laparoscopic two-stage radical UGC has nothing to do with recurrence and prognosis^[6], the prognosis is poor if the PSM occurs at trocar sites. Therefore, tissue resection should be performed on the trocar holes with clear contamination in order to reduce the possibility of implant recurrence. If PSM occurs after surgery, the patient's condition should be comprehensively evaluated. When local recurrence was found, PET/CT was used to check whether there

were other sites of metastasis. The main treatment of PSM after gallbladder cancer is complete resection. If radical surgery is feasible, the tumor should be resected as soon as possible. As shown in Table 1, surgery was performed in all previous cases. Since PSM of gallbladder cancer is often accompanied by peritoneal metastasis, laparoscopic exploration is recommended to exclude abdominal metastasis in order to avoid unnecessary surgery. To improve prognosis, the tumor should be removed completely during the operation. In the current patient, no recurrence was found in other parts of the body by PET/CT. The abdominal wall mass was isolated outside the peritoneum and there was no peritoneal metastasis through laparoscopic exploration, so resection of the abdominal wall tumor was performed. Limited data support combined gemcitabine, capecitabine, and radiation therapy for patients with residual cancer^[20], but there is no clear guideline. As shown in Table 1, only three patients received postoperative chemotherapy, but one of them had peritoneal and pulmonary metastases at 3 mo after surgery. Our patient refused further chemotherapy treatment after operation, and there was no recurrence at follow-up of 31 mo. We recommend the follow-up strategies for these patients as follows: (1) abdominal ultrasound and tests of cancer-associated tumor markers should be performed every 3 mo within 1 year after surgery; (2) an enhanced CT should be performed within one year; and (3) if there is evidence of recurrence, the patient should be followed up every 6 mo.

CONCLUSION

We report a case of PSM 10 years after resection of UGC, and postoperative pathology showed papillary adenocarcinoma complicated with massive ossification. The patient was followed up for 31 mo after surgery, and his condition is good. Although this late type of PSM is rare, we must pay

attention to it. For such patients, we recommend that PET/CT should be performed before surgery to exclude metastases at other sites. Laparoscopic exploration should be performed to avoid unnecessary excessive surgery. The final diagnosis should be made based on postoperative pathology combined with medical history and immunohistochemistry to determine whether the metastasis is originated from gallbladder. We hope to find more tumor patients with PSM to determine whether further treatment is needed after surgery, in an attempt to provide experience in PSM of UGC.

ACKNOWLEDGMENTS

We thank the patient for permitting us to use his data to complete this article.

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Table 1. Cases of late-type port-site metastasis of unsuspected gallbladder carcinoma after surgery from PubMed (including the present case)

Ref.	Age/sex	1 st pathology	T stage	Interval	2nd pathology	IHC	Rt or Cmt	Follow-up
Ciulla et al [7]	72/F	ADC	pT1	3 yr	ADC	Not performed	N	2 yr, alive
Wettstein et al [8]	74/F	ADC	PT1a	40 mo	ADC	Not performed	N	3 mo, died
Nakagawa et al [9]	73/F	ADC	pT2	44 mo	ADC	Not performed	Unknown Y	Unknown
Sharma et al [10]	58/M	Unknown	Unknown	4 yr	ADC	CK19(+) CK20(+)	Gemcitabine and Cisplatin	Unknown
Sultania et al [11]	35/F	Unknown	Unknown	5 yr	ADC	Not performed	N	3 yr, alive
Sultania et al [11]	60/F	Unknown	Unknown	6 yr	ADC	CK7(+) CK19(+)	Y Gemcitabine	3 mo, died

						CK20 (–)	and Oxaliplatin		
Tsujita et al ^[12]	55/M	ADC	pT2	139 mo	ADC	Not performed	Unknown	20 mo, alive	
Carboni et al ^[13]	78/F	P-ADC	pT ₂	12 yr	ADC	CK7 (++) CK20 (+) CK7 (+++)	Y Capecitabine	6 mo, alive	
This case	59/M	P-ADC	pT1b	10 yr	ADC	CK19 (+++)) CK20 (++)	N	31 mo, alive	

ADC: adenocarcinoma; P-ADC: papillary adenocarcinoma; IHC: immunohistochemistry; Rt: radiotherapy; Cmt: chemotherapy

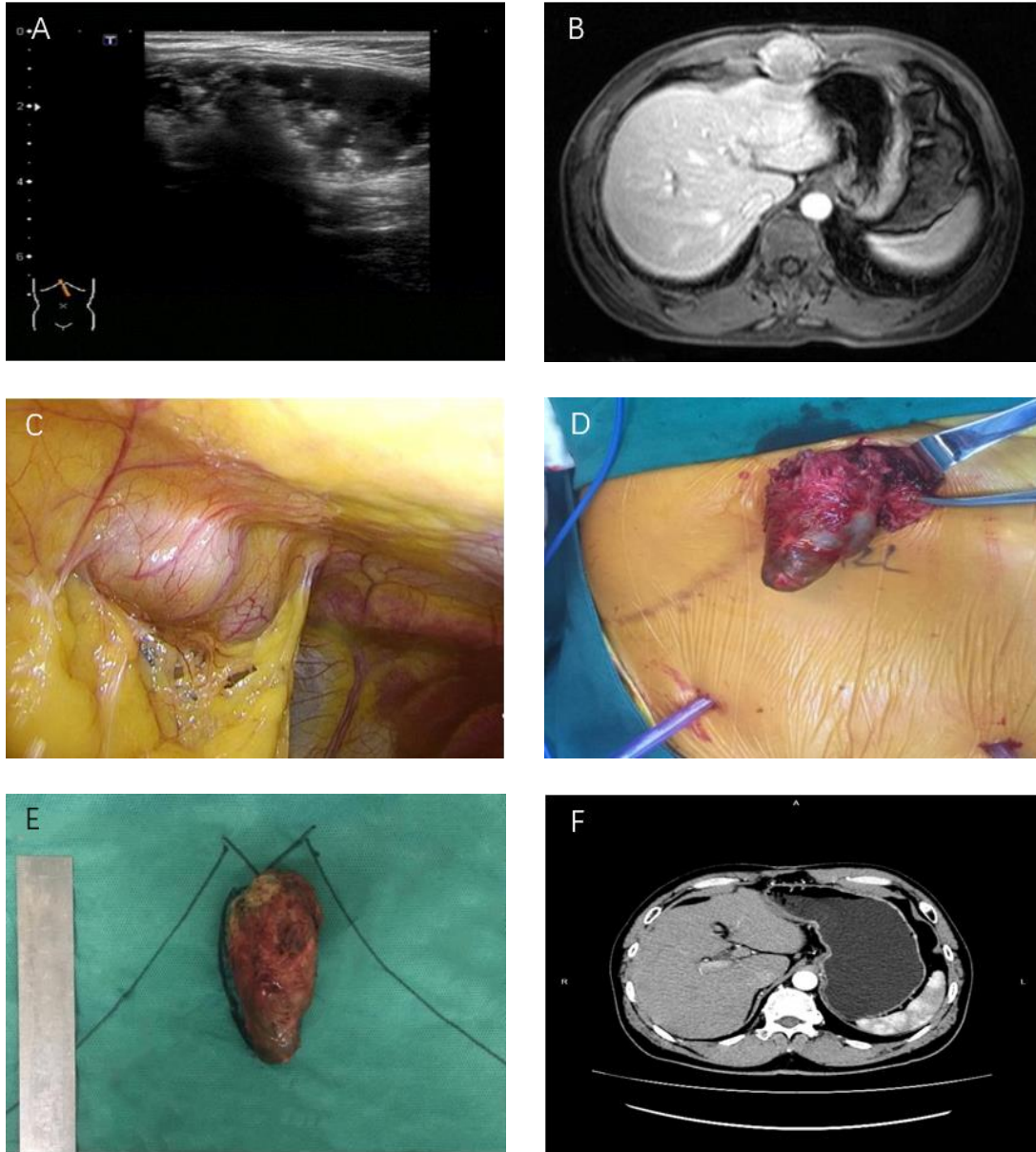


Figure 1. Imaging examinations of the upper abdomen and the specimens seen during and after surgery. A: A mixed mass in the upper abdomen was found by ultrasound; B: A mass under the xiphoid process showed by enhanced MRI; C: Laparoscopic exploration of the mass located outside the peritoneum; D: The mass was located between the muscles of the upper abdominal wall; E: The mass was about $5 \times 3 \times 3$ cm; F: No obvious recurrence was found by abdomen enhanced CT 1 year after the latest surgery.

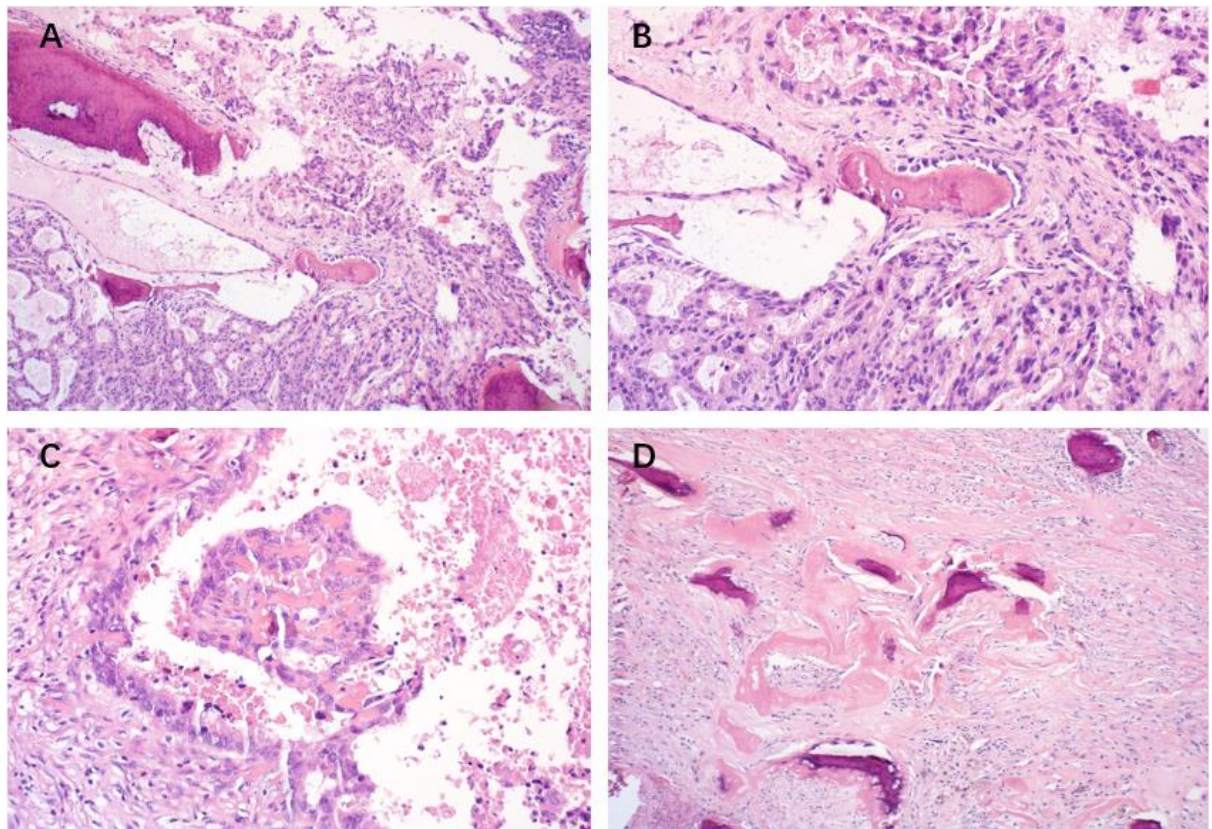


Figure 2. Postoperative pathological examination. A: Atypical epithelial cribriform hyperplasia was seen in some areas [hematoxylin and eosin (HE) 100×]; B: Protrusion into the cystic cavity, with massive necrosis and hemorrhage; multifocal pericancerous interstitial ossification and infiltration into the fibrous stroma (HE 200×); C: Several foci of cancer cells produced bone-like matrix (HE 200×); D: Part of the cyst wall thickening and fibrosis with previous hemorrhage and hemosiderin deposition, and interstitial mass of fibrous bone (HE 100×).