

Laparoscopic Surgery for Gallbladder Neuroendocrine Carcinoma: A Case Series and Literature Review

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Case report

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Abstract

Background: Gallbladder neuroendocrine carcinomas (GB-NECs) are a group of rare and heterogeneous neoplasms. There are few reports regarding laparoscopic surgery for GB-NEC cases diagnosed at advanced stage.

Case presentation: Three patients, two females and one male, were admitted to our hospital. Two patients had the chief complaint of upper quadrant pain and one patient was found to have gallbladder occupation during a routine health checkup. No patient complained jaundice, weight loss, or carcinoid syndrome-related symptoms including diarrhea, edema, flushing and wheezing. Contrast-enhanced computed tomography (CT) examination showed local wall thickening of the gallbladder. In addition, one patient showed focal liver parenchymal invasion, and none of the three patients' preoperative imaging examination revealed lymph nodes (LNs) metastases. All three patients underwent laparoscopic radical cholecystectomy according to intraoperative frozen pathological examination, and they were diagnosed as GB-NEC based on postoperative pathology and immunohistochemistry. TNM stages of these patients were I^{A} (T3N0M0), I^{B} (T3N1M0) and I^{C} (T3N2M0), respectively. Chromogranin A (CgA) and synaptophysin (Syn) were positive in all cases. No patient encountered postoperative bleeding, bile leakage, abdominal abscess, gastrointestinal fistulas or pulmonary complication. Two patients underwent postoperative chemotherapy with two cycles and seven cycles of etoposide plus cisplatin, respectively. Another patient did not receive postoperative chemotherapy due to his poor general condition. The overall survival time of three patients was 4.6 months, 16.8 months and 8.5 months, respectively. All three patients presented with liver and/or bile duct recurrence after surgery with the tumor-free survival time of 2.3 months, 3.3 months and 3.0 months, respectively.

Conclusion: Laparoscopic surgery may be considered as a potential treatment for advanced GB-NEC in selected patients. However, further studies are needed to investigate the tumor-free survival benefit of laparoscopic surgery, and whether expanding the resection scope could reduce postoperative recurrence.

Background

Neuroendocrine neoplasms (NENs) are a type of rare and heterogeneous tumors with the incidence of about 6.98 per 100,000 [1]. They are originated from disseminated neuroendocrine cells and had been found in different organs including lungs, stomach, thyroid, jejunum and ileum. According to the Surveillance, Epidemiology and End result database, the incidence of gallbladder neuroendocrine neoplasms (GB-NENs) was $< 0.74/100,000$ [2]. Based on the 2019 World Health Organization (WHO) classification of tumors of the digestive system, gallbladder neuroendocrine carcinomas (GB-NECs) are defined as a kind of poorly-differentiated NENs with mitotic rate > 20 mitoses/ 2mm^2 and/or Ki-67 index $> 20\%$ [3]. GB-NECs are extremely rare in clinical practice with few reports, and associated with worse prognosis than gallbladder adenocarcinomas. There is no consensus of surgical strategies and guidelines of the GB-NEC, and in clinical practice, the treatment of GB-NEC refers to gallbladder adenocarcinoma. With the improvement of surgical techniques, the clinical application of laparoscopic resection for gallbladder carcinomas is increasing. GB-NEC has high grade malignancy and rapid progress, and is usually diagnosed at advanced stage [4]. There are few reports regarding laparoscopic surgery for GB-NEC, especially for those at advanced stages. We accidentally found three patients who underwent laparoscopic gallbladder surgery with postoperative pathology suggesting GB-NEC and report as follows.

Case Presentation

Three GB-NEC patients, with two female cases and one male case, were admitted into our hospital (Table 1). Two patients complained upper quadrant pain, and one of them showed right upper quadrant tenderness during physical examination. Another one was admitted to our hospital due to an incidental finding of gallbladder occupation during a routine health checkup. No patient complained jaundice, weight loss, or carcinoid syndrome-related symptoms including diarrhea, edema, flushing and wheezing. The preoperative levels of cancer antigen 199 (CA-199) and carcinoembryonic antigen (CEA) for all

patients were normal. All patients underwent ultrasonography, and showed space-occupying lesions of gallbladder wall. Contrast-enhanced computed tomography (CT) examination was performed for three patients, and demonstrated local wall thickening of the gallbladder (Fig. 1). In addition, two patients had gallbladder stones and one patient showed focal liver parenchymal invasion. None of the three patients' preoperative imaging examination revealed lymph nodes (LNs) metastases. Based on these findings, all three patients were diagnosed as gallbladder tumor preoperatively and failed to define the pathological type, and they were scheduled to undergo laparoscopic treatment. Wedge resection of gallbladder bed (≥ 2 cm) was performed for two patients without liver parenchymal invasion or vascular inflow involvement. For another patient with liver parenchymal invasion, the segment \square b/V resection was performed. The surgically removed specimen of all patients were diagnosed as poorly differentiated gallbladder malignancy based on intraoperative histological examination. Thus, they all underwent laparoscopic radical cholecystectomy, and D2 lymph nodes dissection, including the LNs around gallbladder, extrahepatic bile duct, hepatoduodenal ligament plus peri-pancreatic head area, inter-aortocaval area and celiac axis area, was performed for all three patients (Fig. 2). The margin of cystic duct was sent to frozen section as well and all cases showed negative margin of cystic duct. According to postoperative pathological report, all patients were diagnosed as poorly differentiated GB-NEC with clear resection margins, and TNM stage were \square A (T3N0M0), \square B (T3N1M0) and \square B (T3N2M0), respectively. Chromogranin A (CgA) and synaptophysin (Syn) were positive in all cases. Ki-67 index ranged from 50–80%, and mitotic count ranged from 4 to 40.

Table 1
Clinical features of three gallbladder neuroendocrine carcinoma cases.

No.	1	2	3
Sex	Female	Female	Male
Age (years)	37	44	84
BMI	26.57	19.53	17.70
Clinical manifestation			
Right upper quadrant pain	Yes	Yes	No
Weight loss	No	No	No
Jaundice	No	No	No
Diarrhea	No	No	No
Flushing	No	No	No
Gallbladder stone	Yes	Yes	No
Pathological results			
Tumor size (cm)	4.3 × 3.5 × 2.1	5.5 × 3.0 × 2.0	5.0 × 4.0 × 4.0
TNM grade	▯B (T3N2M0)	▯A (T3N0M0)	▯B (T3N1M0)
Ki-67 (%)	80	50	65
Mitotic rate (mitoses/2 mm ²)	40	40	4
Cystic duct margin	Negative	Negative	Negative
Immunohistochemistry			
CgA	Positive	Positive	Positive
Syn	Positive	Positive	Positive
No. number, BMI body mass index, CgA chromogranin A, Syn synaptophysin.			

No patient encountered postoperative bleeding, bile leakage, abdominal abscess, gastrointestinal fistulas or pulmonary complication (Table 2). No patients underwent re-operation during postoperative stay. The average days of oral diet recovery, drainage tubes removal and postoperative hospital stay were 2.0 days, 9.3 days and 11.7 days, respectively. One patient underwent chemotherapies with two cycles of etoposide plus cisplatin, and presented with liver and bile duct recurrence at 2.3 months after surgery, with the overall survival of 4.6 months. One patient underwent chemotherapies with seven cycles of etoposide plus cisplatin, and presented with liver, LNs, and bile duct recurrence at 3.3 months after surgery with the overall survival of 16.8 months. Another patient did not receive postoperative chemotherapy due to his poor general condition and presented with liver metastasis at 3.0 months after surgery. As of the last follow-up, he is still alive with the overall survival of 8.5 months.

Table 2
Postoperative outcomes of three gallbladder neuroendocrine carcinoma cases.

No.	Postoperative complications	Oral diet recovery (days)	Drainage tubes removal (days)	Postoperative hospital stays (days)	Chemotherapy	Recurrent sites	Tumor-free survival time (months)	Overall survival time (months)
1	No	3	15	16	Yes	Liver, Bile duct	3.3	4.6
2	No	2	7	8	Yes	Liver, Bile duct, LNs	2.3	16.8
3	No	1	6	11	No	Liver	3.0	8.5

No. number, LNs lymph nodes.

Discussion

Due to the malignant potential of GB-NEC, surgical resection remains as the most important treatment [5]. However, because of some reasons, including the rarity, little knowledge on the pathogenesis, biological features and clinicopathological characteristics of this disease, there is no consensus of surgical strategies and guidelines of the GB-NEC. In clinical practice, the treatment of GB-NEC refers to gallbladder adenocarcinoma. With the improvement of surgical techniques, laparoscopic surgery for gallbladder carcinomas is increasing. Compared with conventional laparotomy, our department found that laparoscopic surgery for gallbladder carcinomas may provide comparable perioperative outcomes and it is helpful for less intraoperative bleeding, shorter postoperative days of oral diet recovery and hospital stays [6]. In the study performed by Liu et al., all three patients with GB-NEC at T1bN0M0 stage underwent laparoscopic cholecystectomy with gallbladder bed cauterization, and no recurrences were found during the at least 26.0 months' follow-up without any postoperative chemotherapy or radiotherapy (Table 3) [7]. However, there are few reports discussing laparoscopic surgery for GB-NECs at advanced stages. Kim et al. reported a 77-year-old female at TNM II B stage (T3N1M0) underwent laparoscopic radical cholecystectomy and combined chemoradiation therapy, and no evidence of recurrence was found over the follow-up period of 14.0 months [8]. In current study, all three patients were diagnosed at advanced stage and underwent laparoscopic radical cholecystectomy with the median overall survival time of 8.5 months. Compared with laparotomy, laparoscopic surgery provided a comparable overall survival. Liu et al. reported one patient with GB-NEC at TNM II B stage underwent open radical cholecystectomy with the overall survival of 5.0 months [9]. In the study performed by Chen et al.,⁴ the overall survival time of one patient at TNM II B stage undergoing open radical cholecystectomy was 5.7 months. In terms of the short-term outcome, in our study, no patient presented severe postoperative complication including bile leakage, abdominal abscess, gastrointestinal fistulas and pulmonary complication. No patient underwent re-operation during postoperative hospitalization.

Table 3
Comparison between laparotomy and laparoscopy for gallbladder neuroendocrine carcinoma.

Surgical method					
	Laparotomy			Laparoscopy	
Study [Refs.]	Liu et al [9]	Chen et al [4]	Liu et al [7]	Kim et al [8]	Present study
No. of cases	1	1	3	1	3
TNM stage	1 ♂B (T3N1M0)	1 ♂B (T3N2M0)	3 ♂ (T1bN0M0)	1 ♂B (T3N1M0)	1 ♂A (T3N0M0) 1 ♂B (T3N1M0) 1 ♂B (T3N2M0)
Surgery	Open radical cholecystectomy	Open radical cholecystectomy	Laparoscopic cholecystectomy	Laparoscopic radical cholecystectomy	Laparoscopic radical cholecystectomy
Metastasis sites	LN's	LN's	No	LN's, Liver	Liver 1, LN's 2
Recurrent sites	NA	NA	No	No	LN's 1 Liver 3 Bile duct 2
Median tumor-free survival time (month)	NA	NA	29.0 (26.0–42.0)	14.0	3.0 (2.3–3.3)
Median overall survival time (month)	5.0	5.7	29.0 (26.0–42.0)	14.0	8.5 (4.6–16.8)
No. number, LN's lymph nodes, NA not available.					

Port sites recurrence or peritoneal dissemination caused by inadequate manipulation to handle gallbladder, intraoperative gallbladder perforation, and CO2 pneumoperitoneum are the reasons for restricting the use of laparoscopic approach for gallbladder carcinoma [10–12]. However, gallbladder rupture can be avoided through the surgeon's clinical experience and careful operation. For gallbladder carcinomas in situ and T1N0M0 phase, pure cholecystectomy could be enough. For those in advanced stage, en-bloc resection of the gallbladder and liver parenchyma should be performed during the operation. Moreover, compared with laparotomy, laparoscopic surgery could provide a comparable number of lymph nodes resected [13]. Kitagawa et al. reported that the tumor-free survival rates of laparoscopic radical cholecystectomy tended to be superior to those of open radical cholecystectomy for gallbladder carcinomas [14]. Previous study by Agarwal et al. showed that the tumor-free survival time in laparoscopic group was comparable to those in the laparotomy group [15]. In our study, en-bloc resection of the gallbladder and liver parenchyma was strictly performed during the operation with negative microscopic margins and a protective plastic bag was routinely employed for specimen removal to prevent port sites recurrence or peritoneal dissemination. No gallbladder rupture occurred during the operation. In addition, D2 lymph nodes dissection was performed for all three patients. However, all three patients presented with liver and/or bile duct recurrence after surgery with the median tumor-free survival time of 3.0 months. One reason may be that GB-NEC at advanced stages is more malignant than gallbladder adenocarcinoma, so the scope of liver resection and lymph nodes dissection may be insufficient in contrast to gallbladder adenocarcinoma. In our study, all three patients were not clearly

diagnosed as GB-NEC by preoperative examination and intraoperative frozen pathological examination, but were diagnosed as GB-NEC by postoperative pathology and immunohistochemistry. Therefore, we did not adopt a more aggressive surgical approach during the operation. We can only conjecture that for patients diagnosed as GB-NEC, it may be possible to reduce the postoperative tumor recurrence by expanding the resection scope, but this needs more research to confirm. Because there are no studies on the tumor-free survival time of patients with advanced GB-NEC undergoing open radical cholecystectomy at present, we can't compare the tumor-free survival time of laparotomy and laparoscopic surgery. The potential tumor-free survival benefit of laparoscopic surgery for patients with advanced GB-NEC remains controversial.

Conclusion

Laparoscopic surgery may be considered a potential treatment for advanced GB-NEC in selected patients. However, further studies are needed to investigate the tumor-free survival benefit of laparoscopic surgery, and whether expanding the resection scope could reduce postoperative recurrence. The sample size of our report is limited and more research with a larger sample size is needed, our experience will be very helpful for surgeons when they need to decide the surgical options for patients with advanced GB-NEC.

Declarations

Authors' contributions

Hongwu Chu and Jungang Zhang designed the study; Hongwu Chu drafted the manuscript; Ying Shi collected the clinical data; Changwei Dou, Fangqiang Wei and Chengwu Zhang performed the operation; Jungang Zhang and Dongsheng Huang reviewed the manuscript.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

The data sets during and/or analyzed during the current study available from the corresponding author on reasonable request.

Consent for publication

Written informed consents for publication of patients' clinical details and clinical images were obtained from patients.

Ethics approval and consent to participate

The case report was approved and supervised by the Clinical Research Ethics Committee of the Zhejiang Provincial People's Hospital of Hangzhou, China.

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