

Case Report

Curative intent radical cholecystectomy followed by hyperthermic intraperitoneal chemotherapy in ruptured intraductal papillary neoplasm of gallbladder with invasive carcinoma

Gyeonggyu Choi¹, Seokwon Jang², Munseok Choi³, Seungyeon Yang⁴, Chunggeun Lee⁵, Chang Moo Kang^{1,2}

¹Yonsei University College of Medicine, Seoul, Korea,

²Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery, Yonsei University College of Medicine, Seoul, Korea,

³Department of Surgery, Yongin Severance Hospital, Yonsei University College of Medicine, Yongin, Korea,

⁴Division of Colorectal Surgery, Department of Surgery, Yonsei University College of Medicine, Seoul, Korea,

⁵Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Korea

Gallbladder cancer has a poor prognosis, especially in peritoneal carcinomatosis related to perforation of the gallbladder followed by bile spillage. Previously, curative-intent treatment was not considered in carcinomatosis from cancer of the biliary tract. A 72-year-old male was referred to the hospital with a perforated gallbladder cancer. Intraoperatively, the tumor was confined to the gallbladder and liver. We presented a case of intention-to-curative resection of perforated gallbladder cancer followed by intraoperative hyperthermic intraperitoneal chemotherapy.

Key Words: Gallbladder cancer; Peritoneal carcinomatosis; Hyperthermic intraperitoneal chemotherapy; Cholecystectomy

INTRODUCTION

With the active application of laparoscopic cholecystectomy for benign gallbladder diseases, gallbladder cancer incidence has increased. However, most cases are found in an advanced stage at the time of diagnosis. As a result, gallbladder cancer has a dismal prognosis with a 5-year overall survival rate of 5%–17% [1] especially, perforation or bile spillage can be related to peritoneal carcinomatosis and a poor prognosis [2].

Cytoreductive surgery with hyperthermic intraperitoneal

chemotherapy (HIPEC) has been proposed as a potential option to treat peritoneal surface disease [3,4]. However, only a few peritoneal carcinomatosis cases of biliary tract origin were reported to be treated by this surgical option [5-8]. Considering that perforated gallbladder cancer is associated with a poor prognosis, only palliative treatment may be provided for those patients.

Herein, we presented a case that was successfully treated by intention-to-curative resection of perforated gallbladder cancer followed by intraoperative HIPEC.

CASE

Case presentation

In April 2020, a 72-year-old male patient was admitted for a known perforated gallbladder cancer. It was found during the evaluation of abdominal pain in the primary health care clinic, where endoscopic retrograde biliary drainage insertion was done due to obstructive jaundice. He had a history of hypertension and dyslipidemia. He had no known family history of malignancy. He does not smoke nor excessively drink alcohol.

Received: May 21, 2021, **Revised:** July 26, 2021,
Accepted: August 9, 2021

Corresponding author: Chang Moo Kang

Division of Hepatobiliary and Pancreatic Surgery, Department of Surgery,
Yonsei University College of Medicine, Ludlow Faculty Research Building #201,
50 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea
Tel: +82-2-2228-2135, Fax: +82-2-313-8289, E-mail: cmkang@yuhs.ac
ORCID: <https://orcid.org/0000-0002-5382-4658>



Copyright © The Korean Association of Hepato-Biliary-Pancreatic Surgery
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.



Fig. 1. Preoperative findings. Computed tomography (CT) scan shows a distended gallbladder (GB) with multiple polypoid lesions and irregular GB wall thickening (white arrows, A). Note pericholecystic tumor extension due to perforation of the GB (white star, B). Positron emission tomography-computed tomography shows heterogeneous hypermetabolic lesion along GB wall (white arrows) and in the distal portion of the common bile duct (white thick arrow, C).

Physical examination showed abdominal discomfort and tenderness, and his abdominal pain was rated as 6/10 on the visual analogue scale.

Laboratory results revealed the following: aspartate transaminase, 24 U/L; alanine transaminase, 21 U/L; total bilirubin, 0.8 mg/dL; gamma glutamyl transferase, 99 U/L; alkaline phosphatase, 113 U/L; serum C-reactive protein, 286.6 mg/L; carcinoembryonic antigen, 1.55 ng/mL; and cancer antigen 19-9, 20.1 U/mL.

Abdomen-pelvic computerized tomography (Fig. 1A, 1B), and positron emission tomography-computed tomography (Fig. 1C) showed a gallbladder cancer extended to common bile duct with peritoneal involvements due to gallbladder perforation. Magnetic resonance imaging showed irregular papillary lesions of variable size along the inner wall of the distended gallbladder, and endoscopic retrograde cholangiopancreatography (ERCP) showed amorphous filling defects in the common bile duct and mucin-producing tumor. ERCP biopsy revealed

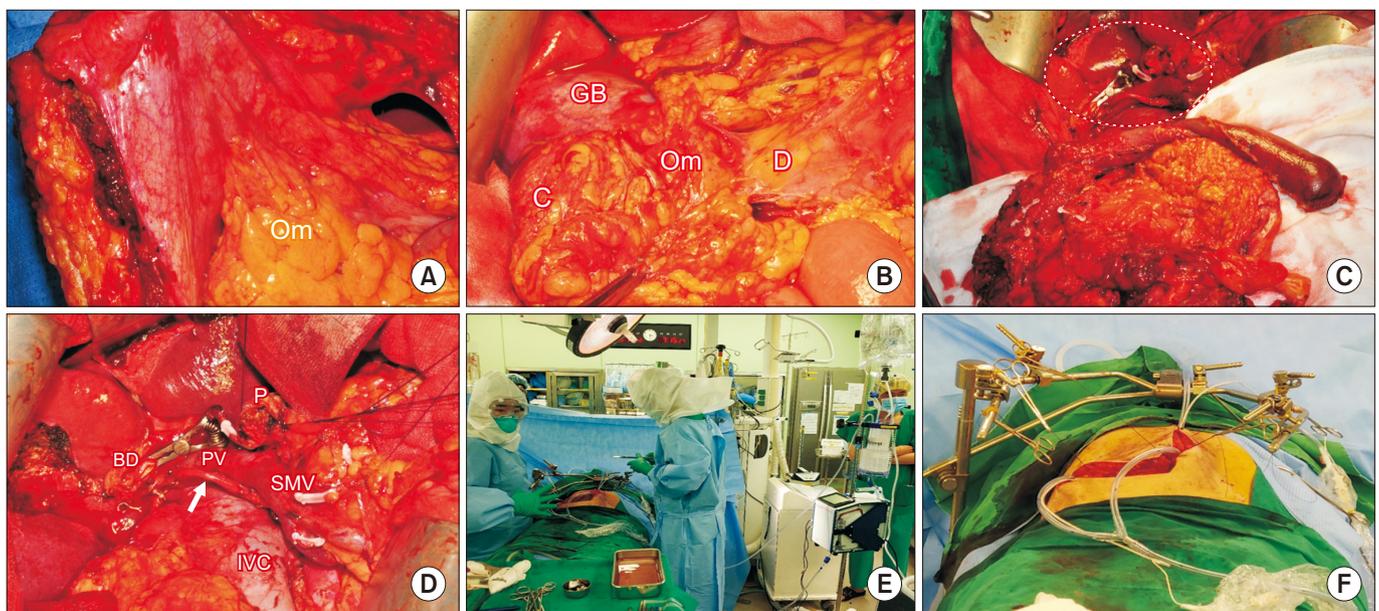


Fig. 2. Intra-operation findings. Localized peritoneal seeding was noted around GB and omentum (A). Omentum covering the perforated portion of the GB, adherent to colon and duodenum (B). Pylorus preserving pancreaticoduodenectomy (PPPD) was performed with right hemicolectomy to remove the minimal peritoneal seeding around GB. Dotted circle indicates surgical field after PPPD (C). Surgical field after curative intent PPPD (white arrow, aberrant right hepatic artery from superior mesenteric artery) (D). Operation room view for intraoperative HIPEC with mitomycin-C (E). Indwelling two-way catheter for continuous circulation of chemotherapeutic agent with temporary closure of the abdominal wound (F). Om, omentum; GB, gallbladder; C, colon; D, duodenum; PV, portal vein; SMV, superior mesenteric vein; IVC, inferior vena cava; BD, bile duct; P, pancreas; HIPEC, hyperthermic intraperitoneal chemotherapy.

intraductal papillary neoplasms of the bile duct (IPNB) with associated invasive carcinoma.

Operative finding

The patient underwent diagnostic laparoscopy on May 12th, 2020. No definitely disseminated intraperitoneal seeding was noted. Subsequent open conversion was performed for active exploratory laparotomy. After careful exploration, potential peritoneal seeding was thought to be limited around perforated gallbladder and liver due to omental adhesion (Fig. 2A, 2B). Therefore, curative intent pylorus preserving pancreaticoduodenectomy with additional right hemicolectomy (Fig. 2C, 2D) was done, followed by HIPEC with mitomycin-C was performed (Fig. 2E, 2F). HIPEC lasted for one hour and 40 minutes, and the appropriate amount was calculated using the body surface area (BSA) of the patient. The initial dose was BSA (m²) multiplied by 17.5, and the additional dose was multiplied by 8.8. After the initial dose was given, an additional dose was injected twice every 30 minutes.

Postoperative course

Overall, the recovery of the patient was smooth. The postoperative pancreatic fistula (POPF) was noted on postoperative day three, but it spontaneously disappeared without specific medical management (biochemical leak). The patient resumed an oral diet on postoperative day five. Postoperative neutropenia was noted on postoperative day 13. The absolute neutrophil count increased after a single subcutaneous injection of 50 µg grasin prefilled syringe injection (filgrastim) (Fig. 3). On postoperative day 18, the patient was discharged.

Pathological examination

Gross findings for the specimen included a diffuse papillary growth on the gallbladder and cystic duct mucosa, which measured 12.0 cm × 8.0 cm. Gallbladder cancer arising from intraductal papillary neoplasm of the bile duct was reported to invade the perimuscular connective tissue on the peritoneal side, without involvement of the serosa (pT2a), and also invaded the gallbladder and common bile duct. Given that the tumor did not involve serosa, it had spread along the mucosa and originated from papillary growth that extended to the cystic duct.

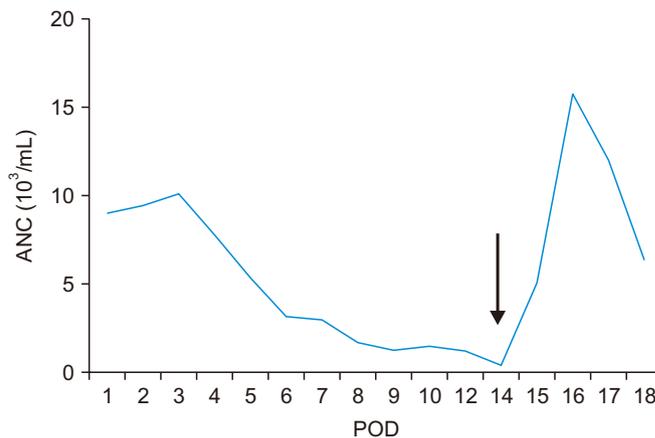


Fig. 3. Change of absolute neutrophil count after surgery. ANC was improved after injecting G-CSF on POD #14 (thick white arrow). ANC, absolute neutrophil count; G-CSF, granulocyte-colony stimulating factor; POD, postoperative day.

All resection margins were negative for carcinoma cells. Total retrieved lymph nodes were 28 without any positive nodes (Fig. 4).

Follow-up

The patient completed six cycles of gemcitabine, cisplatin and abraxane as postoperative adjuvant chemotherapy. He was still alive one year following surgery, without any evidence of tumor recurrence.

DISCUSSION

IPNB characterized by dilated bile ducts that are filled with pre-invasive papillary or villous biliary neoplasm, are regarded as premalignant lesions to progress to invasive carcinoma (IPNB associated with an invasive carcinoma). There are several studies showing histopathological similarity to pancreatic intraductal papillary mucinous neoplasm (IPMN) [9,10]. Moreover, long-term survival of IPMN associated with an invasive carcinoma was found to be higher than that of resected pancreatic ductal adenocarcinoma [11,12]. In fact, it is rare to investigate the long-term surgical outcome of IPNB. Recently,

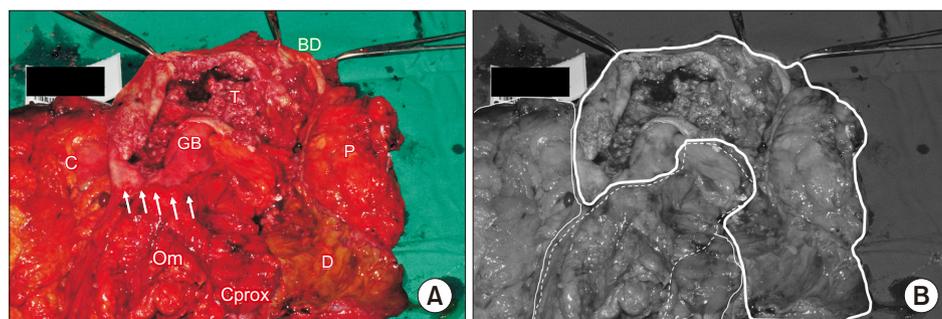


Fig. 4. Surgical specimen. En-block resection was performed for perforated GB cancer (white arrows, sealed up perforation site) (A). Individual surgical specimens were outlined. Thin white line, resected colon area; thick white line, surgical specimen of PPPD; white dotted line, omentum (B). BD, bile duct; T, tumor; GB, gallbladder; C, colon; Cprox, proximal colon; D, duodenum; P, pancreas; Om, omentum.

Bennett et al. [13] reported that the 5-year overall survival and disease-free survival for this series were 51% and 57%, respectively. This result was similar to previously reported long-term oncologic outcome [9], suggesting that IPNB may have better prognosis when compared with typical adenocarcinoma of biliary tract as shown in IPMN counterpart.

In general, the prognosis of advanced stage of gallbladder cancer is dismal, but some specific patients group seems to benefit from multidisciplinary aggressive surgical treatment [14,15]. In addition, long-term survival in radically resected patients with limited carcinomatosis of gallbladder cancer was reported [16]. Until now, cytoreductive surgery followed by HIPEC was used in only a few cases of carcinomatosis from biliary tract cancer [5,6]. Randle et al. [17] reported five cases of gallbladder adenocarcinoma who underwent cytoreductive surgery followed by HIPEC. Major morbidity was noted to be 17% and no mortality was found. The median survival time was 22.4 months and the 3-year overall survival rate was 30%, suggesting a potential survival benefit in dismal clinical situation.

In this case, there were several reasons for authors to perform curative intent radical cholecystectomy followed by HIPEC. First, under diagnostic laparoscopy, the extent of peritoneal seeding appeared to be minimal and well-localization by omental wrapping. According to histological findings, the peritoneal tissue was found free of carcinoma. However, potential seeding was highly suspected due to omental adhesion and gallbladder perforation noted on preoperative images and intraoperative findings.

Second, tumor biology of IPNB with associated invasive carcinoma was expected to be considerably superior than that of known gallbladder adenocarcinoma. Lastly, the general condition of the patient was good enough to endure the long-time aggressive surgical procedure, and his life expectancy was thought to be longer when considering his current age. Tumor within the mid bile duct was also noted on preoperative images, and local peritoneal seeding around perforated gallbladder was severely adherent to the right colon and mesentery, which was thought to be challenging to be separated. For margin-negative resection, pancreaticoduodenectomy and right hemicolectomy were added for en-block resection, with the perforated gallbladder sealed up by the omentum remaining untouched. The gallbladder was considered to be free of liver invasion, and cholecystectomy was performed by peeling off the gallbladder plate instead of combine liver wedge resection. The effect of combined liver resection in radical cholecystectomy is still controversial, but recent studies [18-20] have shown no difference in survival, and further studies are needed.

The patient experienced no other surgery-related complication but transient leukopenia, which was treated by granulocyte-colony stimulating factor injection. Because the cancer had progressed to the peritoneum by perforation, the patient was given adjuvant chemotherapy to decrease postoperative re-

currence and enhance prognosis. The patient had no evidence of disease for more than a year following surgery, indicating that aggressive surgical intervention with curative purpose followed by HIPEC was safe and viable in a well-selected perforated gallbladder cancer patient.

As far as the authors know, the present case was thought to be the first report in Korea about a curative intent surgical approach followed by HIPEC in a patient with perforated gallbladder cancer with a potential peritoneal seeding. Till now, there is no strong evidences regarding oncologic effect of HIPEC in gallbladder cancer with peritoneal seeding. It is unknown whether the current treatment is beneficial to the patient. In the near future, further experiences of HIPEC in gallbladder cancer with long-term follow up period should be mandatory to address the potential role of HIPEC in well-selected gallbladder cancer.

FUNDING

None.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

ORCID

Gyeonggyu Choi, <https://orcid.org/0000-0002-3581-7366>
 Seokwon Jang, <https://orcid.org/0000-0003-3201-9358>
 Munseok Choi, <https://orcid.org/0000-0002-9844-4747>
 Seungyoon Yang, <https://orcid.org/0000-0001-8129-7712>
 Chunggeun Lee, <https://orcid.org/0000-0001-5151-5096>
 Chang Moo Kang, <https://orcid.org/0000-0002-5382-4658>

AUTHOR CONTRIBUTIONS

Conceptualization: CMK. Data curation: GC, SJ, MC. Methodology: SY, CL. Visualization: GC, CMK. Writing - original draft: GC. Writing - review & editing: SY, CL, CMK.

REFERENCES

1. Kim YJ, Kim K. Conditional survival in patients with gallbladder cancer. *Chin J Cancer* 2017;36:85.
2. Nishio H, Nagino M, Ebata T, Yokoyama Y, Igami T, Nimura Y. Aggressive surgery for stage IV gallbladder carcinoma; what are the contraindications? *J Hepatobiliary Pancreat Surg* 2007;14:351-357.
3. van Driel WJ, Koole SN, Sikorska K, Schagen van Leeuwen JH, Schreuder HWR, Hermans RHM, et al. Hyperthermic intraperitoneal chemotherapy in ovarian cancer. *N Engl J Med* 2018;378:230-240.
4. Vanounou T, Garfinkle R. Evaluation of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal carcino-

- matosis of colorectal origin in the era of value-based medicine. *Ann Surg Oncol* 2016;23:2556-2561.
5. Goéré D, Passot G, Gelli M, Levine EA, Bartlett DL, Sugarbaker PH, et al. Complete cytoreductive surgery plus HIPEC for peritoneal metastases from unusual cancer sites of origin: results from a worldwide analysis issue of the Peritoneal Surface Oncology Group International (PSOGI). *Int J Hyperthermia* 2017;33:520-527.
 6. Glehen O, Gilly FN, Boutitie F, Bereder JM, Quenet F, Sideris L, et al. Toward curative treatment of peritoneal carcinomatosis from non-ovarian origin by cytoreductive surgery combined with perioperative intraperitoneal chemotherapy: a multi-institutional study of 1,290 patients. *Cancer* 2010;116:5608-5618.
 7. Levine EA, Stewart JH 4th, Russell GB, Geisinger KR, Loggie BL, Shen P. Cytoreductive surgery and intraperitoneal hyperthermic chemotherapy for peritoneal surface malignancy: experience with 501 procedures. *J Am Coll Surg* 2007;204:943-953; discussion 953-955.
 8. Glockzin G, Renner P, Popp FC, Dahlke MH, von Breitenbuch P, Schlitt HJ, et al. Hepatobiliary procedures in patients undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *Ann Surg Oncol* 2011;18:1052-1059.
 9. Rocha FG, Lee H, Katabi N, DeMatteo RP, Fong Y, D'Angelica MI, et al. Intraductal papillary neoplasm of the bile duct: a biliary equivalent to intraductal papillary mucinous neoplasm of the pancreas? *Hepatology* 2012;56:1352-1360.
 10. Nakanuma Y, Kakuda Y, Uesaka K. Characterization of intraductal papillary neoplasm of the bile duct with respect to the histopathologic similarities to pancreatic intraductal papillary mucinous neoplasm. *Gut Liver* 2019;13:617-627.
 11. Wasif N, Bentrem DJ, Farrell JJ, Ko CY, Hines OJ, Reber HA, et al. Invasive intraductal papillary mucinous neoplasm versus sporadic pancreatic adenocarcinoma: a stage-matched comparison of outcomes. *Cancer* 2010;116:3369-3377.
 12. Choi M, Chong JU, Hwang HK, Seo HI, Yang K, Ryu JH, et al. Role of postoperative adjuvant therapy in resected invasive intraductal papillary mucinous neoplasm of the pancreas: a multicenter external validation. *J Hepatobiliary Pancreat Sci* 2021. <https://doi.org/10.1002/jhbp.996> [in press]
 13. Bennett S, Marginean EC, Paquin-Gobeil M, Wasserman J, Weaver J, Mimeault R, et al. Clinical and pathological features of intraductal papillary neoplasm of the biliary tract and gallbladder. *HPB (Oxford)* 2015;17:811-818.
 14. Castelo Branco M, Estevinho F, Correia Pinto J, Honavar M, Raposo C, Silva AC, et al. Gallbladder cancer: complete resection after second line treatment in stage IV disease. *J Gastrointest Cancer* 2019;50:564-567.
 15. Kuga D, Ebata T, Yokoyama Y, Igami T, Sugawara G, Mizuno T, et al. Long-term survival after multidisciplinary therapy for residual gallbladder cancer with peritoneal dissemination: a case report. *Surg Case Rep* 2017;3:76.
 16. Kang MJ, Song Y, Jang JY, Han IW, Kim SW. Role of radical surgery in patients with stage IV gallbladder cancer. *HPB (Oxford)* 2012;14:805-811.
 17. Randle RW, Levine EA, Clark CJ, Stewart JH, Shen P, Votanopoulos KI. Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy for gallbladder cancer: a retrospective review. *Am Surg* 2014;80:710-713.
 18. Kwon W, Kim H, Han Y, Hwang YJ, Kim SG, Kwon HJ, et al. Role of tumour location and surgical extent on prognosis in T2 gallbladder cancer: an international multicentre study. *Br J Surg* 2020;107:1334-1343.
 19. Yuza K, Sakata J, Prasoon P, Hirose Y, Ohashi T, Toge K, et al. Long-term outcomes of surgical resection for T1b gallbladder cancer: an institutional evaluation. *BMC Cancer* 2020;20:20.
 20. Navarro JG, Kang I, Hwang HK, Yoon DS, Lee WJ, Kang CM. Oncologic safety of laparoscopic radical cholecystectomy in pT2 gallbladder cancer: a propensity score matching analysis compared to open approach. *Medicine (Baltimore)* 2020;99:e20039.