


CASE REPORT

Open Access



Locally advanced gallbladder cancer treated with effective chemotherapy and subsequent curative resection: a case report

Masashi Inoue^{1*} , Keishi Hakoda¹, Hiroyuki Sawada¹, Ryuichi Hotta¹, Ichiro Ohmori¹, Kazuaki Miyamoto¹, Kazuhiro Toyota¹, Seiji Sadamoto¹ and Tadateru Takahashi^{1,2}

Abstract

Background: Surgical resection of gallbladder cancer with negative margins is the only potentially curative therapy. Most patients with gallbladder cancer are diagnosed in an advanced stage and, despite the availability of several chemotherapies, the prognosis remains dismal. We report a case of locally advanced gallbladder cancer that was successfully treated with effective cisplatin plus gemcitabine, followed by curative resection.

Case presentation: A 55-year-old Japanese female was hospitalized with right hypochondrial pain. Enhanced computed tomography revealed a 49 × 47 mm mass at the neck of the gallbladder, with suspected invasion of the liver and right hepatic artery. Endoscopic retrograde cholangiopancreatography demonstrated displacement of the upper bile duct. Intraductal ultrasonography showed irregular wall thickening and disappearance of the wall structure in bile ducts from the B4 branch to distal B2 and B3. Percutaneous transhepatic biliary biopsy revealed a poorly differentiated carcinoma. The patient was diagnosed with unresectable gallbladder cancer (T4N0M0 stage IVA). Cisplatin plus gemcitabine chemotherapy was initiated. After six courses of chemotherapy, enhanced computed tomography showed that the mass in the neck of the gallbladder had shrunk to 30 mm. Endoscopic retrograde cholangiopancreatography showed improvement of the hilar duct stenosis. A biopsy of the bile duct mucosa showed no malignant cells in the branch of the left and right hepatic ducts, the left hepatic duct, or the intrapancreatic ducts. The patient underwent conversion surgery with right and segment 4a liver resection, extrahepatic duct resection, and cholangiojejunostomy. The histopathologic diagnosis showed that the tumor cells had shrunk to 2 × 1 mm, and that R0 resection of the T2aN0M0 stage IIA tumor was successful.

Conclusion: Although conversion surgery for gallbladder cancer is rarely possible, curative resection may offer a better prognosis, and it is important to regularly pursue possibilities for surgical resection even during chemotherapy.

Keywords: Gallbladder cancer, Chemotherapy, Resection, Conversion surgery, Case report

Introduction

Gallbladder cancer (GBC) is a rare disease accounting for 4% of all gastrointestinal malignancies, but there is a higher incidence in countries such as India, Japan, Chile, and Mexico [1, 2]. Due to the lack of early symptoms, most of the patients with GBC are diagnosed at advanced stage, in which the 5-year survival is less than 10% [2, 3]. Surgical resection of GBC with negative margins is the only potentially curative therapy [2]. Despite

*Correspondence: inoue.masashi.uv@mail.hosp.go.jp

¹ Department of Surgery, National Hospital Organization Higashihiroshima Medical Center, 513 Jike, Saijo-cho, Higashihiroshima, Hiroshima 739-0041, Japan

Full list of author information is available at the end of the article



© The Author(s) 2022. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

the application of aggressive surgical approach and radical resections, the prognosis of GBC remains dismal [4].

Chemotherapy is the standard treatment for unresectable gallbladder cancer. Combination chemotherapies with gemcitabine and cisplatin (GC) or gemcitabine and S-1 (GS) are recommended as first-line chemotherapy regimens for nonresectable biliary tract cancer. Combination chemotherapy with gemcitabine, cisplatin, and S-1 (GCS) is also a candidate regimen [5]. On the other hand, there are few reports on conversion surgery after chemotherapy.

Herein, we report a case of locally advanced GBC that was successfully treated with effective cisplatin plus gemcitabine followed by curative resection.

Case presentation

A 55-year-old Japanese female was hospitalized with right hypochondrial pain. Laboratory tests showed elevated hepatobiliary enzymes and C-reactive protein. Serum levels of carcinoembryonic antigen and carbohydrate antigen 19-9 were 0.8 ng/ml and 3.2 U/ml, respectively. Enhanced computed tomography (eCT) imaging revealed a 49 × 47 mm mass at the neck of the gallbladder, with suspected invasion of the liver and right hepatic artery (Fig. 1). Endoscopic retrograde cholangiopancreatography (ERCP) demonstrated displacement of the upper bile duct. Intraductal ultrasonography (IDUS) showed irregular wall thickening

and disappearance of the wall structure in bile ducts from the B4 branch to distal B2 and B3. Percutaneous transhepatic biliary biopsy revealed a poorly differentiated carcinoma (Fig. 2). The patient was diagnosed with unresectable gallbladder cancer [GBC (T4N0M0 stage IVA)]. Cisplatin plus gemcitabine chemotherapy was initiated. After six courses of chemotherapy without severe adverse events, a CT examination showed that the mass in the neck of the gallbladder had shrunk to 30 mm, ERCP showed improvement of the hilar duct stenosis (Fig. 3), and IDUS revealed localized wall thickening in the extra pancreatic ducts, starting at the branch of the left and right hepatic ducts. A biopsy of the bile duct mucosa showed no malignant cells in the branch of the left and right hepatic ducts, the left hepatic duct, or the intrapancreatic ducts (Fig. 4). The patient was scheduled for conversion surgery. The right hepatic artery was in close proximity to the tumor and involvement was suspected; the left hepatic artery was distant from the tumor. In addition, segment 4a was included in the resection range for gallbladder bed resection. Right and segment 4a liver resection and extrahepatic bile duct resection was scheduled. The residual liver capacity was 40% according to the planned surgical procedure. The indocyanine green (ICG) 15-minute value was 4.6% and the plasma clearance rate of ICG (ICGK) was 0.162. The future liver remnant ICGK (ICGK-F) was 0.065, which met the

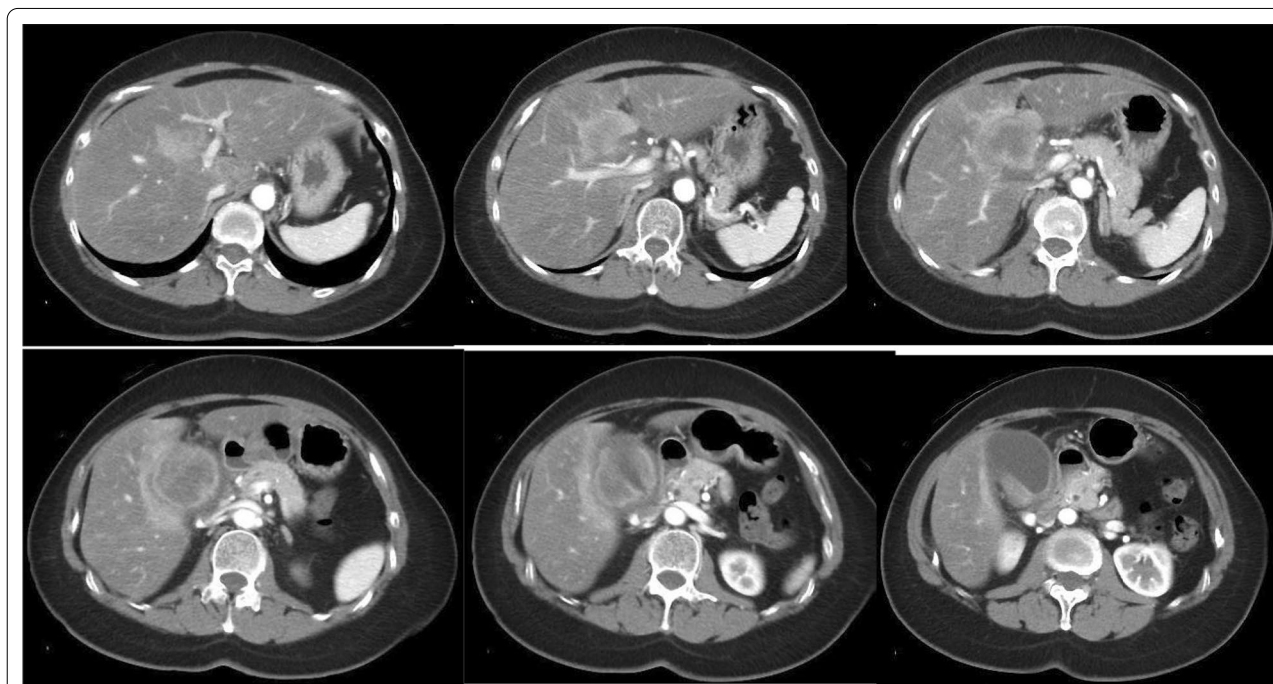
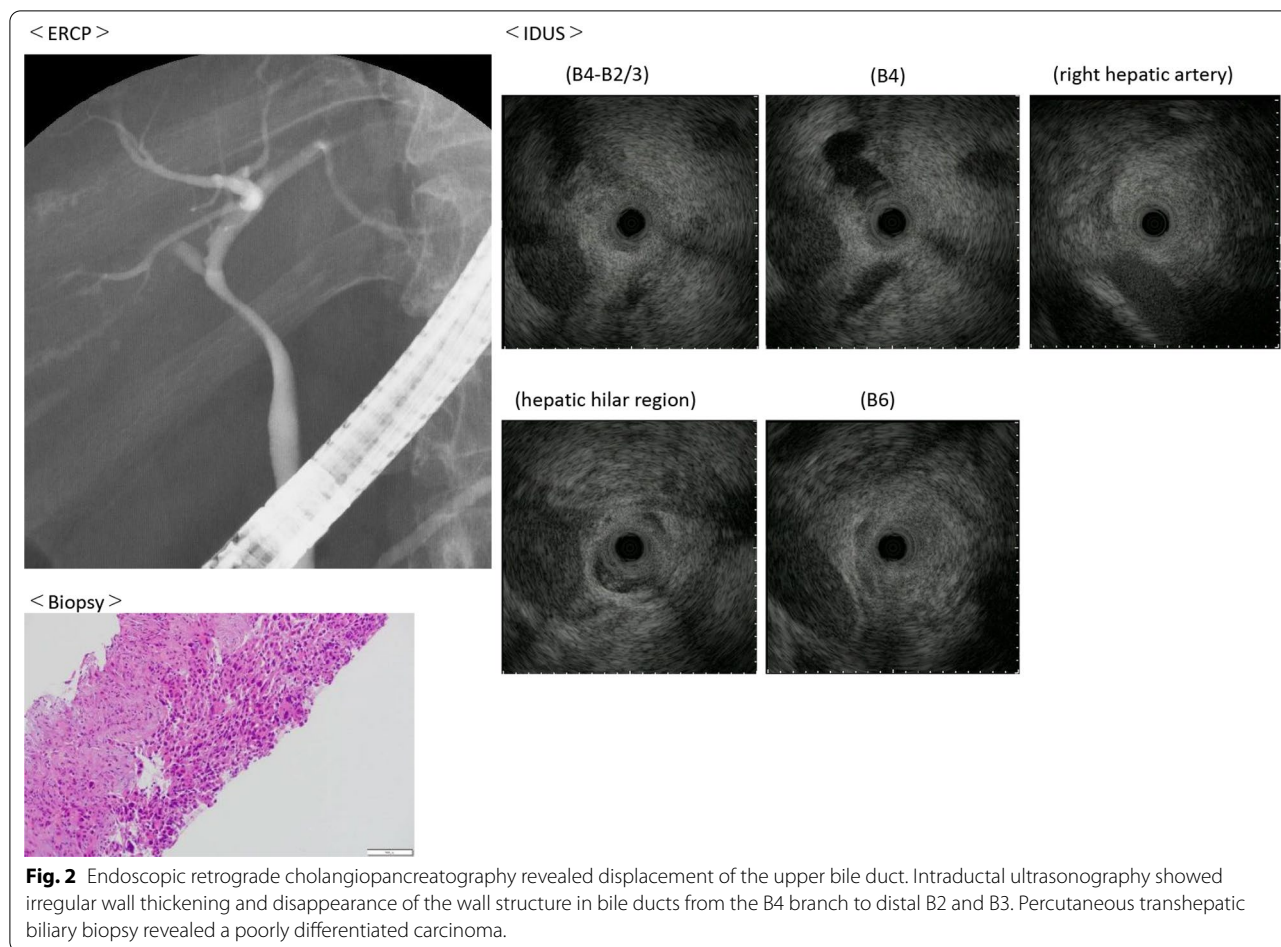


Fig. 1 CT revealed a 49 × 47 mm mass at the neck of the gallbladder, with suspected infiltration of the liver and right hepatic artery.



standard hepatectomy range at our hospital, and the ICGK-F was > 0.05; thus, surgery was performed. We performed a right liver/S4a resection, extrahepatic duct resection, and cholangiojejunostomy. The surgical findings showed no retention of ascites, peritoneal dissemination, or liver metastases. After Kocher maneuver, #16 lymph node was not swelling and did not dissect. The # 13a lymph node was dissected from the posterior surface of the pancreatic head. The anterior surface of the hepatoduodenal ligament was dissected, and the # 8 lymph node was dissected. The common bile duct was dissected at the upper edge of the duodenum and the pancreatic stump was sutured. The stump of the common bile duct was examined by immediate frozen-section analysis, and no malignant cells were found. The right hepatic artery, which ran on the dorsal side of the bile duct, was fixed by the bile duct and could not be dissected. The right hepatic artery was ligated and dissected at the bifurcation. The #12b and 12p lymph nodes were dissected, and the right branch of the portal vein was ligated and dissected at the bifurcation of the left and right portal veins. After right and S4a liver

dissection was performed, the left bile duct and jejunum were anastomosed. The histopathologic diagnosis showed that the tumor cells had shrunk to 2 × 1 mm, and that R0 resection of the T2aN0M0 stage II tumor was successful. Residual tumor cells were found in a small part of the gallbladder neck and gallbladder wall at the hilum of the liver. The perimeter of the tumor cells was highly fibrotic, obscuring the layered structure of the gallbladder wall, gallbladder bed, and extrahepatic bile duct. We reasoned that the change was due to the disappearance of tumor cells associated with chemotherapy. Most of the gallbladder wall was highly fibrotic, with no residual tumor cells. No tumor cells were found in the mucosal epithelium of the cystic duct and intrahepatic extrahepatic bile duct. A high degree of fibrosis was observed near the right hepatic artery in the hilar region, but no infiltration of tumor cells was observed. No exposure of tumor cells was observed at the left intrahepatic bile duct stump (Fig. 5).

The patient was discharged from the hospital and there was no evidence of recurrence 12 months after surgery.

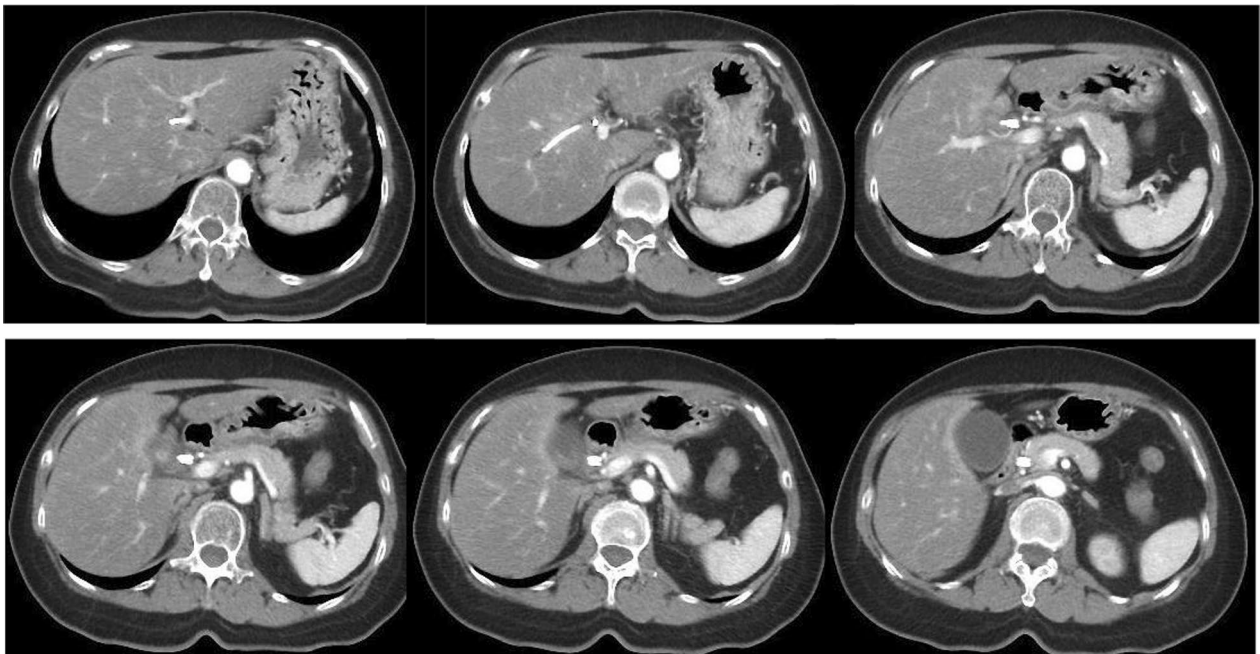


Fig. 3 After six courses of chemotherapy, computed tomography examination showed that the mass in the neck of the gallbladder had shrunk to 3 cm, and endoscopic retrograde cholangiopancreatography showed improvement of hilar duct stenosis.

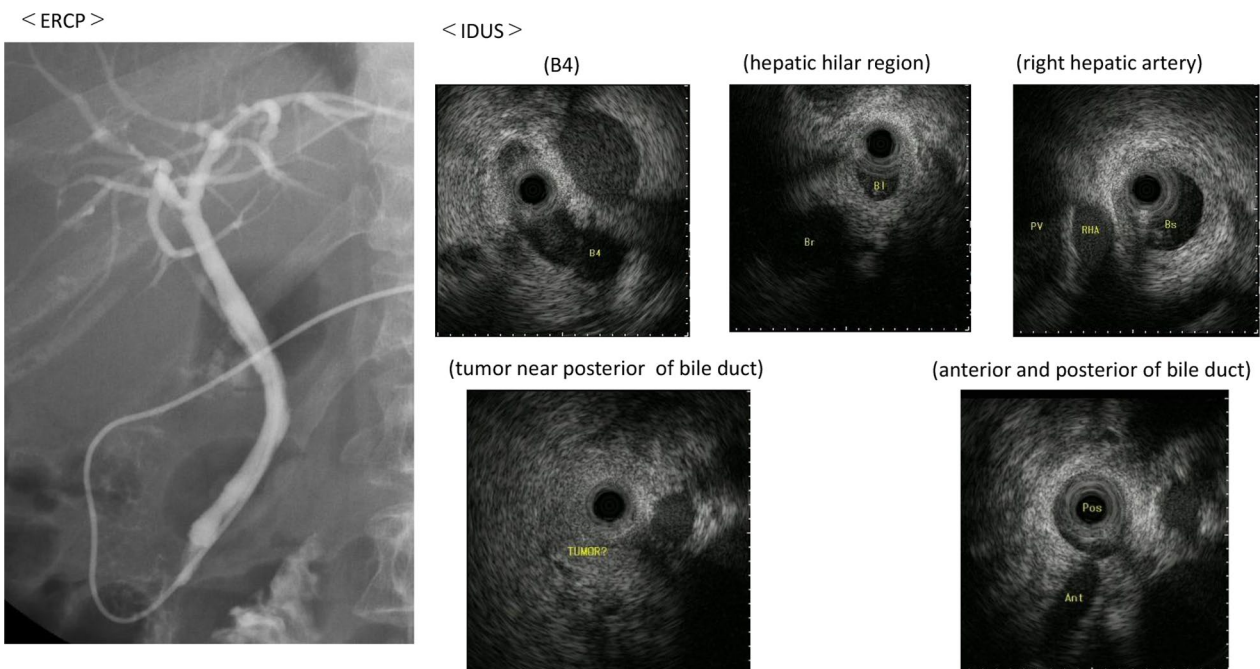
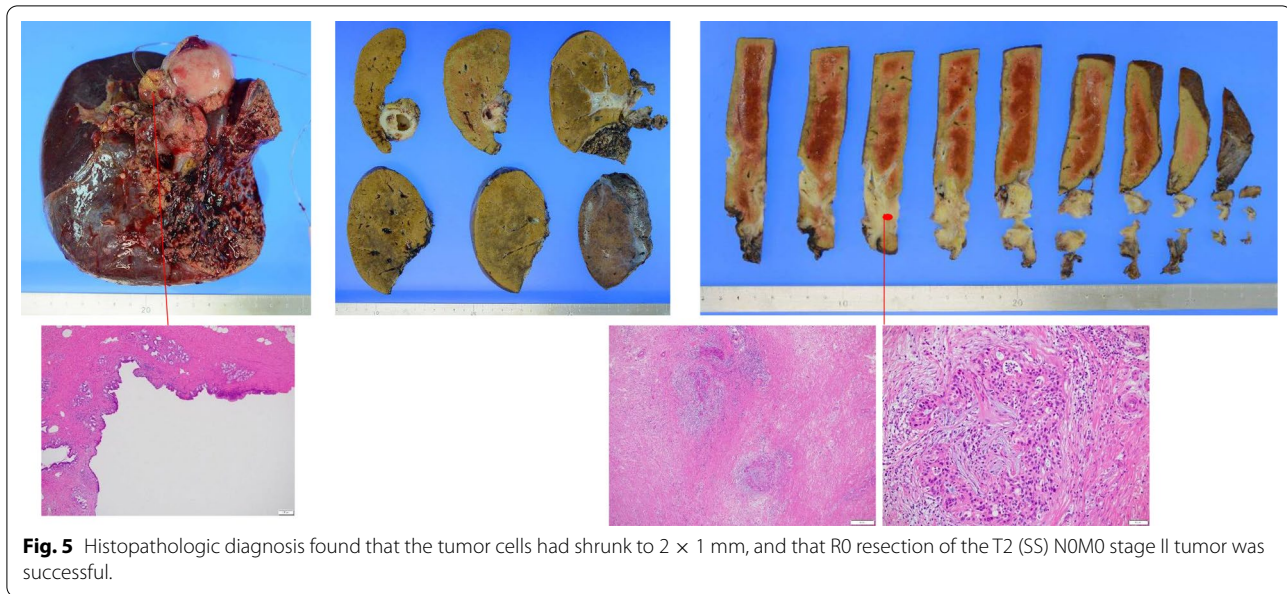


Fig. 4 Intraductal ultrasonography revealed localized wall thickening in the extra-pancreatic ducts starting at the branch of the left and right hepatic ducts. Biopsy of bile duct mucosa found no malignant cells in the branch of the left and right hepatic ducts, the left hepatic duct, or the intrapancreatic ducts.



Discussion

The curative treatment for biliary tract cancer is surgical resection, but biliary tract cancer can be unresectable due to a number of factors. As with other diseases, patient factors include a general health status that is a contraindication for surgical resection, and decreased hepatic reserve when hepatectomy is required. The standard value of future liver remnant function differs depending on the facility, and many facilities set the resectable limit by their own method [6, 7]. Among the tumor factors, cases with distant metastases are treated as unresectable [5]. Multiple intrahepatic metastases are often thought to be unresectable because the prognosis after resection is generally poor [8, 9]. The Bismuth–Corlette classification represents the affected site of the bile duct in hilar cholangiocarcinoma, but is often used to determine resectability [10, 11]. Bismuth IV, which extends to the secondary bifurcation (regional branch) of the left and right bile ducts, is considered unresectable [12, 13]. With respect to vascular invasion, bilateral portal vein invasion, hepatic artery invasion on the planned remnant liver side, and common hepatic artery invasion are also considered unresectable. [5] Some surgeons, however, believe that a three-segment resection of the liver and combined resection of the portal vein and hepatic artery can be performed [14–18]. Thus, there is not sufficient consensus on the limit of resection due to local extension [19–21].

In our case, eCT and IDUS suggested hepatic invasion, right hepatic artery invasion, and extension to the secondary bifurcation of the left bile duct, thus nonresectable GBC was diagnosed. Combination chemotherapies

with gemcitabine and cisplatin (GC) or gemcitabine and S-1 (GS) are recommended as first-line chemotherapy regimens for nonresectable biliary tract cancer. Combination chemotherapy with gemcitabine, cisplatin, and S-1 (GCS) is also a candidate regimen [5]. In this case, GC therapy was selected. In the ABC-02 study, conducted in the United Kingdom, the median survival time of the gemcitabine monotherapy group and the gemcitabine and cisplatin combination therapy group was 8.1 and 11.7 months, respectively [22].

Since gemcitabine or S-1 have been administered to GBC, there have been case reports of conversion surgery. Based on a review of the PubMed database using the key words “gallbladder cancer,” “chemotherapy,” and “resection,” we found six cases of conversion therapy for initially unresectable locally advanced gallbladder cancer, including our case (Table 1) [23, 24]. Survival after surgery of three cases of R0 resection were from 6 to 42 months, and all cases were alive. On the other hand, duration of survival of three cases of R1 resection were from 8 to 19 months, and all cases were dead. Even in conversion surgery, achievement of curative resection was important for good prognosis.

Recently, neoadjuvant chemotherapy has been proposed, knowing the potential for an increase in the resectability rate and overall survival. Hakeem *et al.* [25] reported a systematic review involving 398 patients who were treated with neoadjuvant chemotherapy and 76 patients who received chemoradiotherapy. Of these patients, 50.4% were considered suitable for surgical resection and 191 (40.3%) underwent curative resection. The R0 rate for the entire cohort was 35.4%. The

Table 1 Reported cases of conversion therapy for initially unresectable locally advanced gallbladder cancer

Case	Year	Author	Age	Sex	Reasons for unresectability	Chemotherapy	Operation	Stage	Curability	Survival after surgery (months)	Status
1	2013	Kato	57	F	Arterial invasion	GEM	Right hepatectomy, caudate lobectomy, bile duct resection	IVa	R0	42	Alive
2	2013	Kato	57	F	Arterial invasion	GEM	Right hepatectomy, caudate lobectomy, bile duct resection	IVa	R1	18	Dead
3	2013	Kato	57	F	Arterial invasion, portal vein invasion	GEM	S4a + 5, bile duct resection	IVa	R1	19	Dead
4	2013	Kato	61	M	Arterial invasion	GEM	S4a + 5, bile duct resection	IVa	R1	8	Dead
5	2014	Einama	60	F	Arterial invasion	S-1	Right hepatectomy, bile duct resection	IVa	R0	30	Alive

overall survival ranged from 18.5 to 50.1 months for patients who underwent curative resection versus 5.0–10.8 months for the nonresected group. However, this analysis is not enough to support the routine use of neoadjuvant therapy for GBC because the only patients with advanced GBC that may benefit from neoadjuvant therapy are those who will subsequently achieve an curative resection, accounting for only a third of the whole cohort.

In our case, eCT showed a marked reduction of the mass after six courses of GC therapy. An intraductal biopsy was performed by ERCP to rule out bile duct extension. The presence or absence of invasion to the right hepatic artery and hepatic invasion could not be evaluated. The liver remnant function was good and curative resection was considered possible by right and segment 4a liver resection and extrahepatic bile duct resection; thus, conversion surgery was performed. In the resected specimen, the tumor showed a marked shrinkage of approximately 2 mm. Residual tumor cells were found in a small part of the gallbladder neck and gallbladder wall at the hilum of the liver. No hepatic invasion, extrahepatic bile duct extension, or right hepatic artery invasion was observed. Limited surgery, such as liver segment 4a + 5 resection and extended cholecystectomy might have been possible while performing immediate frozen-section analysis, but the fibrosis that reflected the disappearance of tumor cells made it difficult to ablate the right hepatic artery. In GBC cases with suspected vascular invasion before chemotherapy, though chemotherapy is effective, surgery after chemotherapy may require major surgery.

This is a case of advanced GBC with a pathologically proven remarkable response to GC therapy.

This case is of a locally advanced GBC with marked tumor shrinkage with GC therapy. There are no reports that achieve a complete response from chemotherapy alone. Therefore, curative resection following GC therapy was important for the patient. There are few reports on conversion surgery for unresectable GB; therefore, the optimal chemotherapy regimen, preoperative period, and indications for curative surgery optimal surgical techniques are not clear. The short-term results, such as R0 resection rate and safety, and long-term results are also unclear. Further accumulation of cases is necessary.

Conclusion

Although conversion surgery for GBC is rarely possible, curative resection may offer a better prognosis, and it is important to regularly pursue possibilities for surgical resection even during chemotherapy.

Abbreviations

GBC: Gallbladder cancer; eCT: Enhanced computed tomography; ERCP: Endoscopic retrograde cholangiopancreatography; IDUS: Intraductal ultrasonography; ICG: Indocyanine green; ICGK: Plasma clearance rate of ICG; ICGK-F: Future liver remnant ICGK; GC: Gemcitabine and cisplatin; GS: Gemcitabine and S-1; GCS: Gemcitabine, cisplatin, and S-1.

Acknowledgements

Not applicable.

Authors' contributions

MI wrote the manuscript and designed the study. MY, SS, TM, WS, TI, TS, and TO proofread the manuscript. All authors read and approved the final manuscript.

Funding

Not applicable.

Availability of data and materials

Not applicable.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

All authors declare that they have no conflict of interest.

Author details

¹Department of Surgery, National Hospital Organization Higashihiroshima Medical Center, 513 Jike, Saijo-cho, Higashihiroshima, Hiroshima 739-0041, Japan. ²Department of Gastrointestinal and Transplant Surgery, Applied Life Sciences, Institute of Biomedical and Health Sciences, Hiroshima University, Higashihiroshima, Hiroshima, Japan.

Received: 29 July 2021 Accepted: 21 November 2021

Published online: 17 January 2022

References

- Lai CH, Lau WY. Gallbladder cancer—a comprehensive review. *Surgeon*. 2008;6(2):101–10.
- Misra S, Chaturvedi A, Misra NC, Sharma ID. Carcinoma of the gallbladder. *Lancet Oncol*. 2003;4(3):167–76.
- Jin LX, Pitt SC, Hall BL, Pitt HA. Aggressive surgical management of gallbladder cancer: at what cost? *Surgery (St Louis)*. 2013;154(2):266–73.
- Verslype C, Prenen H, Van Cutsem E. The role of chemotherapy in biliary tract carcinoma. *HPB (Oxford)*. 2008;10(3):164–7.
- Clinical practice guidelines for the management of biliary tract cancers 2019: The 3rd English edition.
- Yokoyama Y, Nishio H, Ebata T, et al. Value of indocyanine green clearance of the future liver remnant in predicting outcome after resection for biliary cancer. *Br J Surg*. 2010;97:1260–8.
- Vauthey JN, Chaoui A, Do KA, et al. Standardized measurement of the future liver remnant prior to extended liver resection: methodology and clinical associations. *Surgery*. 2000;127:512–9.
- Endo I, Gonen M, Yopp AC, et al. Intrahepatic cholangiocarcinoma: rising frequency, improved survival, and determinants of outcome after resection. *Ann Surg*. 2008;248:84–96.
- Konstantinidis IT, Groot Koerkamp B, Do RK, et al. Unresectable intrahepatic cholangiocarcinoma: systemic plus hepatic arterial infusion chemotherapy is associated with longer survival in comparison with systemic chemotherapy alone. *Cancer*. 2016;122:758–65.

10. Croome KP, Rosen CB, Heimbach JK, *et al.* Is liver transplantation appropriate for patients with potentially resectable de novo hilar cholangiocarcinoma? *J Am Coll Surg.* 2015;221:130–9.
11. Tan JW, Hu BS, Chu YJ, *et al.* One-stage resection for Bismuth type IV hilar cholangiocarcinoma with high hilar resection and parenchyma-preserving strategies: a cohort study. *World J Surg.* 2013;37:614–21.
12. Jarnagin WR, Fong Y, DeMatteo RP, *et al.* Staging, resectability, and outcome in 225 patients with hilar cholangiocarcinoma. *Ann Surg.* 2001;234:507–17.
13. Matsuo K, Rocha FG, Ito K, *et al.* The Blumgart preoperative staging system for hilar cholangiocarcinoma: analysis of resectability and outcomes in 380 patients. *J Am Coll Surg.* 2012;215:343–55.
14. Neuhaus P, Jonas S, Bechstein WO, *et al.* Extended resection for hilar cholangiocarcinoma. *Ann Surg.* 1999;230:808–18.
15. Shimizu H, Kimura F, Yoshidome H, *et al.* Aggressive surgical resection for hilar cholangiocarcinoma of the left-side predominance: radicality and safety of left-sided hepatectomy. *Ann Surg.* 2010;251:281–6.
16. Nagino M, Niura Y, Nishio H, *et al.* Hepatectomy with simultaneous resection of the portal vein and hepatic artery for advanced perihilar cholangiocarcinoma: an audit of 50 consecutive cases. *Ann Surg.* 2010;252:115–23.
17. Miyazaki M, Kato A, Ito H, *et al.* Combined vascular resection in operative resection for hilar cholangiocarcinoma: does it work or not? *Surgery.* 2007;141:581–8.
18. Kwon W, Jang JY, Chang YR, *et al.* Suggestions for improving perihilar cholangiocarcinoma staging based on an evaluation of the seventh edition AJCC system. *J Gastrointest Surg.* 2015;19:666–74.
19. Monsour JC, Aloia TA, Crane CH, *et al.* Hilar cholangiocarcinoma: expert consensus statement. *HPB (Oxford).* 2015;17:691–9.
20. Abbas S, Sandroussi C. Systematic review and meta-analysis of the role of vascular resection in the treatment of hilar cholangiocarcinoma. *HPB (Oxford).* 2013;15:492–503.
21. Banales JM, Cardinale V, Carpino G, *et al.* Expert consensus document: cholangiocarcinoma: current knowledge and future perspective consensus statement from the European Network for the Study of Cholangiocarcinoma (ENCS-CCA). *Nat Rev Gastroenterol Hepatol.* 2016;13:261–80.
22. Vlle J, Wasan H, Palmer DH, *et al.* Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *N Engl J Med.* 2010;362:1273–81.
23. Kato A, Shimizu H, Ohtsuka M, Yoshidome H, Yoshitomi H, Furukawa K, *et al.* Surgical resection after downsizing chemotherapy for initially unresectable locally advanced biliary tract cancer: a retrospective single-center study. *Ann Surg Oncol.* 2013;20(1):318–24.
24. Einama T, Uchida K, Taniguchi M, Ota Y, Watanabe K, Imai K, *et al.* Successful curative resection of gallbladder cancer following S-1 chemotherapy: a case report and review of the literature. *Oncol Lett.* 2014;8(6):2443–7.
25. Hakeem AR, Papoulas M, Menon KV. The role of neoadjuvant chemotherapy or chemoradiotherapy for advanced gallbladder cancer—a systematic review. *Eur J Surg Oncol.* 2019;45(2):83–91.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

