



Radical cholecystectomy without liver resection for peritoneal side early incidental gallbladder cancer

Gaetano Piccolo, Matteo Barabino, Guglielmo Niccolò Piozzi, Paolo Pietro Bianchi

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade B

Novelty: Grade B

Creativity or Innovation: Grade B

Scientific Significance: Grade B

P-Reviewer: Li Z

Received: March 26, 2024

Revised: August 1, 2024

Accepted: August 6, 2024

Published online: August 28, 2024

Processing time: 153 Days and 12.1 Hours



Gaetano Piccolo, Matteo Barabino, Paolo Pietro Bianchi, Department of Health Sciences (DISS), University of Milan, San Paolo Hospital, Milan 20142, Lombardy, Italy

Guglielmo Niccolò Piozzi, Department of Colorectal Surgery, Portsmouth Hospitals University NHS Trust, Portsmouth, United Kingdom

Corresponding author: Gaetano Piccolo, FACS, MD, PhD, Attending Doctor, Department of Health Sciences (DISS), University of Milan, San Paolo Hospital, Via Antonio di Rudini 8, Milan 20142, Lombardy, Italy. gpiccolo1983@gmail.com

Abstract

Gallbladder cancer (GBC) is a rare disease with a poor prognosis. Simple cholecystectomy may be an adequate treatment only for very early disease (Tis, T1a), whereas reoperation is recommended for more advanced disease (T1b and T2). Radical cholecystectomy should have two fundamental objectives: To radically resect the liver parenchyma and to achieve adequate clearance of the lymph nodes. However, recent studies have shown that compared with lymph node dissection alone, liver resection does not improve survival outcomes. The oncological roles of lymphadenectomy and liver resection is distinct. Therefore, for patients with incidental GBC without liver invasion, hepatic resection is not always mandatory.

Key Words: Incidental gallbladder cancer; Reoperation; Radical cholecystectomy; Early stage; Liver resection

©The Author(s) 2024. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Hepatic resection for incidental gallbladder cancer (IGC) should aim to: Remove the tumor that has directly invaded the liver through the gallbladder bed and prevent micrometastases that may recur around the gallbladder bed. No consensus is available regarding the extension of liver resection according to its tumor location (hepatic or peritoneal side) and whether hepatic resection can prevent liver recurrence. According to the recent studies, radical cholecystectomy without liver resection may be an adequate treatment for patients with peritoneal side T2 IGC.

Citation: Piccolo G, Barabino M, Piozzi GN, Bianchi PP. Radical cholecystectomy without liver resection for peritoneal side early incidental gallbladder cancer. *World J Gastroenterol* 2024; 30(32): 3739-3742

URL: <https://www.wjgnet.com/1007-9327/full/v30/i32/3739.htm>

DOI: <https://dx.doi.org/10.3748/wjg.v30.i32.3739>

INTRODUCTION

A comprehensive evaluation of tumor depth is essential for the treatment of incidental gallbladder cancer (IGC). Standard cholecystectomy may be an adequate treatment for very early cancers such as carcinoma in situ or a tumor invading the mucosa (Tis and T1a). On the other hand, when the muscularis layer (T1b) or the perimuscular connective tissue (T2) are involved, radical cholecystectomy is the only treatment strategy for long-term survival. For this reason, it is believed that reoperation should have two fundamental objectives: (1) To radically resect the liver parenchyma; and (2) to achieve adequate lymphatic clearance. However, the oncological role of lymphadenectomy and liver resection is distinct. The incidence rate of occult lymphatic metastasis varies according to tumor depth invasion, accounting for 15%–25% and 30%–50% of T1b and T2 IGC cases, respectively[1]. Therefore, for early-stage tumors (T1b, T2), the goal of surgery is adequate lymphadenectomy. On the other hand, the incidence of residual disease in the gallbladder bed and whether hepatic resection prevents liver recurrence are unclear. Recent studies have shown better survival rates for patients with pT1b tumors after cholecystectomy alone without liver resection[2,3]. With respect to incidental pT2 gallbladder cancer (GBC), the incidence of residual liver disease ranges between 0% and 10% at the time of reoperation[1]. Moreover, for patients with peritoneal-side pT2 GBC, recent studies have shown that liver resection does not improve survival compared with lymphadenectomy alone[4,5]. The incidence of intrahepatic and gallbladder bed recurrence is low (2.5%–5% and 0%–2%, respectively)[6,7]. Therefore, for patients with peritoneal-side pT2 GBC, liver resection is not always mandatory.

WHAT IS THE APPROPRIATE EXTENT OF HEPATIC RESECTION DURING REOPERATION FOR PATIENTS WITH PT2 IGC?

A study on IGC management during laparoscopic cholecystectomy was published by the authors of the *World Journal of Gastroenterology* in 2012 and has gained great attention throughout the years[1]. We propose wedge resection of the gallbladder bed instead of hepatectomy as appropriate liver resection for all patients with IGC at an early stage (pT1b and pT2)[1].

Achieving radical (R0) resection, rather than the type of hepatic resection, is the most relevant factor impacting oncological outcome[1]. Many studies from Japan have shown that oncological outcomes are similar between patients who undergo wedge resection and those who undergo bisegmentectomy (S4b + S5) for pT2 IGC[8,9]. The same results were obtained in the West. A multicenter study by Pawlik *et al*[10] revealed that patients who had undergone major hepatic resection, such as anatomical bisegmentectomy (S4b + S5) or right hemihepatectomy had similar mortality risk as patients undergoing hepatic wedge resection.

A more nihilistic view of liver resection during radical cholecystectomy was reported by Balakrishnan *et al*[11]. In the multicenter retrospective Operative Management of Gallbladder Cancer cohort study. This is the largest contemporary multicenter study on the surgical outcomes of GBC patients.

This study showed that liver resection (wedge resection, segment S4b/S5 resection, or major hepatectomy) was not associated with improved recurrence-free survival (RFS) or overall survival (OS) compared with cholecystectomy alone for all patients at any stage (T1b to T4)[11]. Wedge resection was associated with improved RFS compared with other types of liver resection (bisegmentectomy, right hemihepatectomy) or cholecystectomy alone only in patients with T2 cancer according to univariate analysis[11]. These results confirm that major hepatectomy or extended resection is associated with higher morbidity and mortality rates without any significant oncological benefit.

WHAT IS THE OPTIMAL EXTENT OF LIVER RESECTION FOR PT2 IGC ACCORDING TO ITS TUMOR LOCATION?

Recent studies have shown that tumor location (hepatic or peritoneal side) is an important prognostic factor for patients with pT2 GBC. Patients with hepatic-sided T2b GBC (T2b) had worse oncological outcomes than patients with peritoneal-sided cancer (T2a)[6]. Balakrishnan *et al*[11] reported that patients with T2b disease ($n = 276$) were associated with poorer survival than those with T2a disease ($n = 239$) in a subgroup analysis. The authors reported 3-year RFS rates of 54.5% $\pm$ 4.3% *vs* 67.7% $\pm$ 4.3% ($P = 0.003$) and 3-year OS rates of 68.0% $\pm$ 3.6% *vs* 77.7% $\pm$ 3.4% ($P = 0.044$) between T2a and T2b, respectively.

The survival curves of patients with pT2b GBC closely resembled those of patients with pT3 tumors[11]. The venous and lymphatic drainage routes of T2b tumors is towards the hepatic parenchyma, whilst the drainage routes of T2a are towards the hepatoduodenal ligament or the hepatic hilum[11]. However, the optimal extent of resection for T2 GBC,

according to its site, has not yet been confirmed. Lee *et al*[6] reviewed the records of 256 patients with T2 GBC (202 primary and 54 incidental cases) who underwent R0 resection at six Korean institutions between January 2000 and December 2015. After patient selection, the series of 192 patients were divided into two groups: 93 patients with hepatic-sided tumors (pT2b) and 99 patients with peritoneal-sided tumors (pT2a). The authors evaluated the oncological outcomes of patients who underwent radical cholecystectomy, including lymphadenectomy and liver resection or lymphadenectomy without liver resection. In the first group, multivariate analysis revealed that lymph node metastasis and dissection, without liver resection, were independent prognostic factors for shorter survival.

On the other hand, for peritoneal T2 GBC, venous invasion was the only independent prognostic factor for a shorter survival time. The authors concluded that radical cholecystectomy including lymph node dissection without liver resection is a valid oncological treatment for patients with peritoneal side T2 GBC[6]. The difference between the two T stage subgroups (T2a and T2b) disappears when patients with incidental diagnoses are excluded from the analysis.

Park *et al*[7], in a prospective study, compared patients with primary T2 GBC who underwent radical cholecystectomy with and without liver resection. They conducted 2:1 propensity score matching (100 *vs* 50 patients). In this study, all patients underwent a cholecystectomy, including resection of the cystic plate, to reduce the risk of perforation and to avoid underestimating for some patients at risk of perforating the serosa (pT3). A subgroup analysis was performed to evaluate the survival outcomes at each T2 sub-stage (T2a and T2b). The 5-year disease free survival rates were similar in patients with and without liver resection during radical cholecystectomy in both T-stage subgroups (T2a: 77.8% *vs* 81.8%, respectively, $P = 0.988$; T2b: 88.1% *vs* 71.5%, respectively, $P = 0.196$). The 5-year OS rates also did not differ significantly between the two groups in either T-stage subgroup (T2a: 81.9% *vs* 75.6%, respectively, $P = 0.760$; T2b: 74.1% *vs* 61.7%, respectively, $P = 0.417$). In both groups, extrahepatic recurrence was predominant, with only one case of recurrence in the gallbladder bed in patients in the lymphadenectomy without liver resection group. The majority of patients who underwent surgery for T2 GBC developed extrahepatic recurrence, whereas local recurrence in the gallbladder bed was rare[7].

CONCLUSION

Radical cholecystectomy without liver resection may be an adequate treatment for patients with peritoneal-side T2 IGC. For these patients, the reoperation strategy should be changed since the goal of surgical treatment is not liver resection but adequate lymphadenectomy. Larger studies proving long-term outcome benefits are needed.

FOOTNOTES

Author contributions: Piccolo G conducted conceptualization, formal analysis, supervision and investigation; Piccolo G and Piozzi GN conducted writing original draft preparation; Barabino M and Bianchi PP conducted writing, review and editing. The authors read and approved the final manuscript.

Conflict-of-interest statement: The corresponding author declares that the manuscript has been submitted on behalf of all authors. All authors declare that they have no competing interests.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

Country of origin: Italy

ORCID number: Gaetano Piccolo 0000-0002-4942-7705; Matteo Barabino 0000-0001-9525-9063; Guglielmo Niccolò Piozzi 0000-0001-6667-9202; Paolo Pietro Bianchi 0000-0002-2690-3502.

S-Editor: Liu H

L-Editor: A

P-Editor: Chen YX

REFERENCES

- 1 Cavallaro A, Piccolo G, Panebianco V, Lo Menzo E, Berretta M, Zanghi A, Di Vita M, Cappellani A. Incidental gallbladder cancer during laparoscopic cholecystectomy: managing an unexpected finding. *World J Gastroenterol* 2012; **18**: 4019-4027 [PMID: 22912553 DOI: 10.3748/wjg.v18.i30.4019]
- 2 Lee H, Kwon W, Han Y, Kim JR, Kim SW, Jang JY. Optimal extent of surgery for early gallbladder cancer with regard to long-term survival: a meta-analysis. *J Hepatobiliary Pancreat Sci* 2018; **25**: 131-141 [PMID: 29117469 DOI: 10.1002/jhbp.521]
- 3 Kim HS, Park JW, Kim H, Han Y, Kwon W, Kim SW, Hwang YJ, Kim SG, Kwon HJ, Vinuela E, Járufe N, Roa JC, Han IW, Heo JS, Choi SH, Choi DW, Ahn KS, Kang KJ, Lee W, Jeong CY, Hong SC, Troncso A, Losada H, Han SS, Park SJ, Yanagimoto H, Endo I, Kubota K,

- Wakai T, Ajiki T, Adsay NV, Jang JY. Optimal surgical treatment in patients with T1b gallbladder cancer: An international multicenter study. *J Hepatobiliary Pancreat Sci* 2018; **25**: 533-543 [PMID: [30562839](#) DOI: [10.1002/jhbp.593](#)]
- 4 Lee H, Choi DW, Park JY, Youn S, Kwon W, Heo JS, Choi SH, Jang KT. Surgical Strategy for T2 Gallbladder Cancer According to Tumor Location. *Ann Surg Oncol* 2015; **22**: 2779-2786 [PMID: [25519930](#) DOI: [10.1245/s10434-014-4300-7](#)]
- 5 Shindoh J, de Aretxabala X, Aloia TA, Roa JC, Roa I, Zimmitti G, Javle M, Conrad C, Maru DM, Aoki T, Vigano L, Ribero D, Kokudo N, Capussotti L, Vauthey JN. Tumor location is a strong predictor of tumor progression and survival in T2 gallbladder cancer: an international multicenter study. *Ann Surg* 2015; **261**: 733-739 [PMID: [24854451](#) DOI: [10.1097/SLA.0000000000000728](#)]
- 6 Lee W, Jeong CY, Jang JY, Kim YH, Roh YH, Kim KW, Kang SH, Yoon MH, Seo HI, Yun SP, Park JI, Jung BH, Shin DH, Choi YI, Moon HH, Chu CW, Ryu JH, Yang K, Park YM, Hong SC. Do hepatic-sided tumors require more extensive resection than peritoneal-sided tumors in patients with T2 gallbladder cancer? Results of a retrospective multicenter study. *Surgery* 2017; **162**: 515-524 [PMID: [28629653](#) DOI: [10.1016/j.surg.2017.05.004](#)]
- 7 Park Y, Lee JS, Lee B, Jo Y, Lee E, Kang M, Kwon W, Lim CS, Jang JY, Han HS, Yoon YS. Prognostic Effect of Liver Resection in Extended Cholecystectomy for T2 Gallbladder Cancer Revisited: A Retrospective Cohort Study With Propensity Score-matched Analysis. *Ann Surg* 2023; **278**: 985-993 [PMID: [37218510](#) DOI: [10.1097/SLA.0000000000005908](#)]
- 8 Choi KS, Choi SB, Park P, Kim WB, Choi SY. Clinical characteristics of incidental or unsuspected gallbladder cancers diagnosed during or after cholecystectomy: a systematic review and meta-analysis. *World J Gastroenterol* 2015; **21**: 1315-1323 [PMID: [25632207](#) DOI: [10.3748/wjg.v21.i4.1315](#)]
- 9 Lv TR, Yang C, Regmi P, Ma WJ, Hu HJ, Liu F, Yin CH, Jin YW, Li FY. The role of laparoscopic surgery in the surgical management of gallbladder carcinoma: A systematic review and meta-analysis. *Asian J Surg* 2021; **44**: 1493-1502 [PMID: [33895048](#) DOI: [10.1016/j.asjsur.2021.03.015](#)]
- 10 Pawlik TM, Gleisner AL, Vigano L, Kooby DA, Bauer TW, Frilling A, Adams RB, Staley CA, Trindade EN, Schulick RD, Choti MA, Capussotti L. Incidence of finding residual disease for incidental gallbladder carcinoma: implications for re-resection. *J Gastrointest Surg* 2007; **11**: 1478-86; discussion 1486 [PMID: [17846848](#) DOI: [10.1007/s11605-007-0309-6](#)]
- 11 Balakrishnan A, Barmounakis P, Demir N, Jah A, Spiers HVM, Talukder S, Martin JL, Gibbs P, Harper SJF, Huguet EL, Kosmoliaptsis V, Liao SS, Praseedom RK, Basu B, de Aretxabala X, Lendoire J, Maithel S, Branes A, Andersson B, Serrablo A, Adsay V; OMEGA Study Investigators. Surgical outcomes of gallbladder cancer: the OMEGA retrospective, multicentre, international cohort study. *EClinicalMedicine* 2023; **59**: 101951 [PMID: [37125405](#) DOI: [10.1016/j.eclinm.2023.101951](#)]



Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA

Telephone: +1-925-3991568

E-mail: office@baishideng.com

Help Desk: <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

