Original article

The Benefit of Extended Radical Surgery for Incidental Gallbladder Carcinoma

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Abbreviations: IGC: incidental gallbladder carcinoma

Key words: incidental gallbladder carcinoma, extended radical surgery

Abstract

Purpose: The appropriate treatment for incidental gallbladder carcinoma (IGC) remains controversial. We aimed to clarify the benefit of extended radical surgery for treating IGC. **Methods**: The treatment and prognosis of 28 patients with IGC in our hospital were analyzed retrospectively. **Results**: Out of 28 cases, 10 patients were diagnosed as T1a (m), 5 as T1b (mp) and 13 as T2 (ss) after initial cholecystectomy. The T1a cases (T1a group) were followed-up with good prognosis. In the 18 cases of T1b or T2, additional S4a+5 segmentectomy of the liver and bile duct resection (extended radical surgery) was performed in 9 cases (re-resected group), while 9 cases were observed without any additional treatment due to the general condition of the patients (no-treatment group). The re-resected group showed favorable prognosis, with an 88.9% rate of 5-year disease specific survival (DSS), which was significantly better than that of the non-treatment group (30.5%, p=0.015) and comparable to that of the T1a group (90.0%, p=0.97). Upon examination of the re-resected specimens, 44% (4/9) were found to have residual disease. **Conclusion**: Additional extended radical surgery improved the prognosis of patients with IGC, suggesting that there is curative potential in most cases.

Introduction

Gallbladder carcinoma (GBC) is the sixth most common gastrointestinal cancer worldwide [1] and results in lethal neoplasm with a poor prognosis [2-4]. Recently, several reports have indicated that GBC with radical surgical treatment can significantly improve the prognosis for those patients who are able to undergo complete resection [5, 6]. Despite this, the current literature suggests that only 4-16% of GBC cases are treated using radical surgery [7, 8], suggesting that the poor prognosis of GBC might be partly the result of improper treatment. The appropriate treatment for GBC is still controversial with respect to the validity of extensive hepatectomy, lymph node dissection and bile duct resection. The most favorable approach depends on the stage of the disease; however, accurate preoperative staging of GBC is extremely difficult, and, in some cases, even diagnosing malignancy seems to be a challenge.

In spite of recently improved imaging modalities, some GBC cases are still diagnosed as cholecystitis and/or polyps, after which malignant tumors are pathologically detected after simple cholecystectomy. The recent popularization of cholecystectomy has made the incidental discovery of gallbladder carcinoma more common; it is becoming increasingly important, therefore, to determine the appropriate approach for treating the disease. These incidentally found GBCs (incidental gallbladder carcinoma; IGC) are

not necessarily in their early stages, as T2 and T3 tumors are frequently found upon initial diagnosis. In cases of T1a disease, simple cholecystectomy is sufficient and no additional treatment is necessary [9]; however, tumors graded higher than T1b are reported to have lymph node metastasis, while T2 tumors are reported to have liver involvement in 26% of cases [10]. Both lymph node metastasis and liver involvement potentially result in locoregional failure after simple cholecystectomy. Therefore, it seems likely that the appropriate treatment for IGC patients with tumors graded higher than T1b should be additional resection.

In our hospital, extended radical surgery (cholecystectomy with S4a5 segmentectomy of the liver, lymph node dissection around the hepatoduodenal ligament and extrahepatic bile duct resection) is the standard treatment for T2 GBC and has been applied to IGC cases as well. Here, we report the results and prognosis of patients who underwent extended radical surgery with discussion of the procedure as a curative treatment for IGC.

Patients and Methods

Patients

Between January 1996 and September 2012, 28 patients at Ogaki Municipal Hospital were diagnosed with cholecystitis and/or gallbladder polyps and underwent simple cholecystectomy, after which postoperative pathological examination of the resected specimen revealed gallbladder carcinoma. The mean age of the patients was 74.6 years (range 52-92); there were 16 males and 12 females. The tumors were classified as follows: T1a (mucosa; n=10), T1b (muscularis propria; n=5) or T2 (subserosa; n=13). While 10 cases of T1a tumor were followed-up without any further treatment (T1a group), the patients with T1b and T2 tumors underwent additional resection (S4a5 segmentectomy of the liver and bile duct resection with lymph node dissection) provided they seemed able to tolerate the procedure. In total, there 9 cases received additional resection (re-resected group) and 9 cases did not (no-treatment group). The reasons for avoiding a second surgery were lower performance status (n=7) and concurrent disease (n=2; acute myocardial infarction and chronic liver damage). In the re-resected group, perioperative complications occurred in 5 cases; the complications included wound dehiscence (n=3), cholangitis (n=1) and cerebral bleeding (n=1). The mean interval between the initial and second surgery was 34.9 days (range 24-56 days). A comparison

of these 3 groups (T1a, re-resected and no-treatment group) is shown in Table 1 (UICC TMN classification was employed to stage the tumors), revealing that there are no statistically significant differences in patients' background between re-resected and no-treatment group. The median length of follow-up was 4.2 years (range: 0.6-16.7 years).

Surgical procedure

Before the second radical surgery, patients underwent MDCT (multi-detector computed tomography) to confirm residual tumor and regional lymph node enlargement. Bile duct anatomy was verified using ERCP (endoscopic retrograde cholangiopancreatography) or MRCP (magnetic resonance cholangiopancreatography). Our principal surgical procedure for IGC consists of an en bloc resection of the extrahepatic bile duct, regional lymph nodes and the liver (segments 4a (inferior position of the medial segment) and 5 (inferior segment of anterior section)).

After making a midline and right subcostal incision, we first performed the Kocher maneuver to verify the absence of macroscopic para-aortic lymph node metastasis. We then dissected the lymph nodes behind the pancreatic head and cut off bile flow downstream of the extrahepatic bile duct at the superior border of the pancreatic head.

The hepatic artery and portal vein were exposed to complete lymph node dissection in the hepatoduodenal ligament. The lymph nodes around the common hepatic artery were also dissected. After skeletonization of the hepatoduodenal ligament, hepatic transection was performed using an ultrasonic surgical aspirator under intermittent total hepatic inflow vascular occlusion (15-min clamp and 3-min declamp). The common hepatic duct was then divided, and, finally, reconstruction of bile duct (choledochojejunostomy) and alimentary tract was performed.

Statistics

Patient survival was defined as the time between the initial surgery and time of death or most recent follow-up. Postoperative survival was calculated using the Kaplan-Meier method. Differences in the survival curves were compared using the log-rank test. The characteristics of the cases were compared using the Chi-square test or Fisher's exact test, as appropriate. All statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) ver. 18.0 (SPSS, Inc., Chicago, IL). A P value < 0.05 was considered statistically significant.

Results

Case presentation

A 77-year-old female visited our hospital with the chief complaint of right hypochondrial pain. Abdominal US and CT revealed inflammation and a thickened wall of the gallbladder with stones (Fig 1A and B). Simple cholecystectomy was performed with a diagnosis of cholecystolithiasis and chronic cholecystitis. Postoperative pathological examination revealed papillary adenocarcinoma of the gallbladder with a T2 tumor classification (Figs 1C and D). Six weeks after the initial surgery, the patient underwent S4a5 segmentectomy of the liver and bile duct resection with dissection of the lymph nodes in the hepatoduodenal ligament, around the common hepatic artery and behind the pancreas (Fig 1E). Residual tumor tissue was found around the bile duct close to the surgical margin of the cystic duct (Fig 1F). No positive lymph node involvement was found. The patient has been followed-up for 2.5 years without any sign of recurrent disease.

Pathological findings

The pathological type of all tumors was adenocarcinoma, consisting of papillary adenocarcinoma (n=7), well differentiated adenocarcinoma (n=15), moderately

differentiated adenocarcinoma (n=4) and poorly differentiated adenocarcinoma (n=1) (table 1). Microscopic vascular, lymphatic and/or perineural invasion was found in 7 cases (2 in the non-treatment group and 5 in the re-resected group). The mean number of dissected lymph nodes was 6.7 per case (range 3-12). Of the 9 cases with additional resection, residual disease was found in the re-resected specimens in 4 cases (44.4%); 2 in the margin of the cystic duct and 2 as lymph node metastasis in the hepatoduodenal ligament. No microscopic liver involvement was found. All of the re-resected cases were diagnosed as complete resection (R0) with negative surgical margins and no other clinical evidence of residual tumor.

The postoperative course of the re-resected group

Figure 2 shows a flow chart summary of the cases. No additional treatment was provided in T1a cases; all T1a patients were followed-up with good prognoses, except in 1 case wherein there was preoperative perforation of the gallbladder (the patient died 1 year after surgery due to peritoneal dissemination). The 18 cases of T1b and T2 tumors include the non-treatment group (n=9) and the re-resected group (n=9). Although not statistically significant, the re-resected group had a lower rate of recurrence (28.6%; 2/9) than the non-treatment group (55.6%; 5/9). Table 2 shows detailed information related

to the recurrent cases. One patient with T1a tumor developed local recurrence and peritoneal dissemination, most likely due to gallbladder perforation. Two cases of recurrence occurred in the re-resected group; both were distant metastasis without any local recurrence. The cause of death in non-treatment group was recurrence of gallbladder cancer in all cases (n=5).

Survival

Postoperative survival curves were analyzed based on disease-specific survival (Figure 3). The 5-year survival rate of all candidates was as good as 72.9%. The T1a group (n=10) showed good prognosis without additional resection (5-year survival = 90.0%); however, one patient relapsed. The survival rates were significantly different between the re-resected group and the no-treatment group (5-year survival = 88.9% and 30.5%, respectively, p=0.015). Within the re-resected group, T-classification, N-status, vascular/lymphatic infiltration, neural invasion, pathological type and existence of residual tumor had no significant impacts on survival, presumably because of the small number of patients included in this study.

Discussion

Although the rate of IGC in cholecystectomy patients is only 1% or lower [11-13], the number of incidentally found gallbladder carcinomas is increasing. This is most likely due to the increasing frequency of laparoscopic cholecystectomy [14, 15]. Although IGC is believed to be benign preoperatively, once diagnosed, the disease may be in its later stages. Tumors staged higher than T1b might have residual disease including lymph node involvement, liver bed infiltration and bile duct involvement. To identify the appropriate surgical procedure and potential prognostic factors, there have been several reports characterizing IGC patients by the TNM stage, surgical procedure, existence of residual disease and prognosis [15-22]. With respect to surgical treatment, the three important factors for determining the most appropriate procedure are liver resection, lymph node dissection and bile duct resection.

Residual cancer in the liver bed has reportedly been found in 7% of T2 and 36.4% of T3 [16] tumors, suggesting that at least liver bed resection is warranted in these cases; however, the question of whether liver bed resection or systematic hepatectomy including S4a5 hepatic resection should be recommended for ICG is still controversial. Goetze et al have suggested that wedge-resection results in better survival for patients with T1 tumors, but segmentectomy of the liver is more effective in T2 tumors [19].

Anatomically, the gallbladder drains into sections S4a and S5 of the liver, and, as a result, we routinely perform S4a5 segmentectomy for all gallbladder carcinoma cases with a preoperative diagnosis of T2 tumor as well as for all IGC cases.

You et al reported finding lymph node metastasis in 3.8% of T1b tumors, while no lymph node metastasis was found in T1a tumors [23]. In T2 tumors, the rate of lymph node metastasis was reported to be as high as 46% [24], while another study reported that 9% of T2 ICG cases were found to have lymph node metastasis [18]. These results suggest that in ICG cases with tumors that are more advanced than stage T1b, patients should undergo lymphadenectomy to achieve R0 resection.

The validity of bile duct resection has also been the subject of debate. While there are surgeons who routinely perform resection of the common bile duct, several reports have suggested that the procedure does not increase survival and have instead recommended preservation of the common bile duct [25, 26]. We support the resection of the extrahepatic bile duct because lymph node dissection of the hepatoduodenal ligament can be incomplete without biliary resection, and lymph node resection may result in ischemia of the bile duct. In IGC cases, some patients present with positive cystic duct margins, and 40% of those were reported to have common bile duct involvement [16] . In the present study, 2 cases were found to have residual tumor in the cystic duct margin,

suggesting that some, but not all, of the cases benefit from biliary resection.

One of the most common types of recurrence in IGC cases is local reappearance, which may be due to residual disease remaining after incomplete resection. The decision to perform additional resection tends to be determined based on the pathological findings from the initial surgical specimen, in which the surgical margin status or lymphatic and/or vessel infiltration suggests the most probable type of residual disease. Although the pathology results of the initial surgery help us to determine which (if any) second procedure is appropriate, these results tend to lack sufficient information [27]. In our study, two resected specimens were found to have residual cancer in the margin of the cystic duct. In both cases, pathological examination failed to detect a positive surgical margin in the initial cholecystectomy specimens. This suggests that additional resection should not be determined solely based on the pathological evaluation of the surgical margin. Moreover, both recurrent diseases in our re-resected group were distant metastases without any sign of local recurrence, which suggests that our procedure might be able to control the disease locally and significantly improve prognosis. On the other hand, we did not find any residual cancer of the liver bed, indicating that S4a5 segmentectomy of the liver might have been excessive surgery in our cases. This is also supported by the reports in which Horiguchi et al found no beneficial effect of S4a5

resection, compared to gallbladder bed resection, on the prognosis of T2 gallbladder carcinoma [28].

There should be debates whether T1b patients need additional resection or not. Not surprisingly, the recurrence rate of no-treatment group is higher in T2 than T1b cases in our study; 4 out of 5 T2 cases (80%) recurred, while 1 out of 4 T1b patients (25%) recurred. While the number of the cases are distinctly too small to discuss the necessity of additional resection for T1b disease, given that the type of recurrence of this T1b case was local, additional resection might have been curative for this patient.

Another probable type of IGC recurrence is peritoneal dissemination including the port site. In the current era of laparoscopic surgery, the number of IGC cases located during laparoscopic cholecystectomy is estimated to increase. Port site recurrence and peritoneal dissemination due to intra-operative perforation of the gallbladder are inevitable matters in IGC cases. However, Goetze et al reported that the primary access technique had no effect on prognosis [29], and Fuks et al reported that port site resection was not associated with improved survival for patients with IGC [30]. Because this study included only 6 patients with laparoscopic cholecystectomy, we cannot conclude whether port site resection should be performed routinely as part of ICG treatment. We have to gather more information to determine the appropriate treatment

for ICG after laparoscopic cholecystectomy with respect to port site resection.

Historically, IGC has been a difficult disease to treat, and there is no established treatment for the disease. In recent years, the prognosis of IGC patients has reportedly been better than those with non-incidental gallbladder carcinoma [15, 16]; this may in part be because IGC tends to be diagnosed at an earlier stage than non-incidental GBC. Notably, Shih et al have reported, after analyzing only patients with stage II cancer, better prognoses in the IGC group than in the non-incidental GBC group [15]. These reports suggest that ICG cases can be cured. However, previous studies have reported 5-year survival rates of IGC patients of as low as 30 to 60%, which suggests that some of the patients in these studies had not been treated properly. We have been performing the same operation consecutively in every case of IGC (S4a5 segmentectomy of the liver, lymphadenectomy and extrahepatic bile duct resection) and have achieved a 5 year DSS as good as 88.9%, which, in our study, was significantly better than the non-resected group and equivalent to the T1a group. This favorable outcome is partly because all of the cases included were less than T2 and stage II. However, the outcome might also suggest that our procedure is sufficient and appropriate to treat IGC, even though the amount of tissue resected might be excessive in some cases. As long as the surgery can be performed safely and with minimal complications, we should not hesitate to use

extended radical resection to treat IGC.

Conclusion

Although the number of the patients is too small to verify the benefit of our policy statistically, our results reveal that IGC can be cured, provided patients are given the appropriate treatment.

Author Contribution

Study design, acquisition of data, manuscript drafted by; JY

Analysis and interpretation; JY, YK

Revision; YK, AM, YT, SO, MI

There is no conflict of interest.

References

1. Hariharan D, Saied A, Kocher HM. Analysis of mortality rates for gallbladder cancer across the world. HPB (Oxford). 2008;10(5):327-31.

2. Nimura Y. Extended surgery in bilio-pancreatic cancer: the Japanese experience. Semin Oncol. 2002;29(6 Suppl 20):17-22.

3. Boutros C, Gary M, Baldwin K, Somasundar P. Gallbladder cancer: past, present and an uncertain future. Surg Oncol. 2012;21(4):e183-91.

4. Henson DE, Albores-Saavedra J, Corle D. Carcinoma of the gallbladder. Histologic types, stage of disease, grade, and survival rates. Cancer. 1992;70(6):1493-7.

5. Pilgrim CH, Groeschl RT, Turaga KK, Gamblin TC. Key factors influencing prognosis in relation to gallbladder cancer. Dig Dis Sci. 2013;58(9):2455-62.

6. Butte JM, Matsuo K, Gonen M, D'Angelica MI, Waugh E, Allen PJ, et al. Gallbladder cancer: differences in presentation, surgical treatment, and survival in patients treated at centers in three countries. J Am Coll Surg. 2011;212(1):50-61.

7. Jensen EH, Abraham A, Habermann EB, Al-Refaie WB, Vickers SM, Virnig BA, et al. A critical analysis of the surgical management of early-stage gallbladder cancer in the United States. J Gastrointest Surg. 2009;13(4):722-7.

8. Wright BE, Lee CC, Iddings DM, Kavanagh M, Bilchik AJ. Management of T2 gallbladder cancer: are practice patterns consistent with national recommendations? Am J Surg. 2007;194(6):820-5; discussion 5-6.

9. Shirai Y, Yoshida K, Tsukada K, Muto T, Watanabe H. Radical surgery for gallbladder carcinoma. Long-term results. Ann Surg. 1992;216(5):565-8.

10. Ito H, Ito K, D'Angelica M, Gonen M, Klimstra D, Allen P, et al. Accurate staging for gallbladder cancer: implications for surgical therapy and pathological assessment. Ann Surg. 2011;254(2):320-5.

11. Frauenschuh D, Greim R, Kraas E. How to proceed in patients with carcinoma detected after laparoscopic cholecystectomy. Langenbecks Arch Surg. 2000;385(8):495-500.

12. Romano F, Franciosi C, Caprotti R, De Fina S, Porta G, Visintini G, et al. Laparoscopic cholecystectomy and unsuspected gallbladder cancer. Eur J Surg Oncol. 2001;27(3):225-8.

13. Wysocki A, Bobrzynski A, Krzywon J, Budzynski A. Laparoscopic cholecystectomy and gallbladder cancer. Surg Endosc. 1999;13(9):899-901.

14. Steinert R, Nestler G, Sagynaliev E, Muller J, Lippert H, Reymond MA.

Laparoscopic cholecystectomy and gallbladder cancer. J Surg Oncol. 2006;93(8):682-9.

15. Shih SP, Schulick RD, Cameron JL, Lillemoe KD, Pitt HA, Choti MA, et al. Gallbladder cancer: the role of laparoscopy and radical resection. Ann Surg. 2007;245(6):893-901.

16. Pawlik TM, Gleisner AL, Vigano L, Kooby DA, Bauer TW, Frilling A, et al. Incidence of finding residual disease for incidental gallbladder carcinoma: implications for re-resection. J Gastrointest Surg. 2007;11(11):1478-86; discussion 86-7.

17. Lendoire JC, Gil L, Duek F, Quarin C, Garay V, Raffin G, et al. Relevance of residual disease after liver resection for incidental gallbladder cancer. HPB (Oxford). 2012;14(8):548-53.

18. Goetze TO, Paolucci V. The prognostic impact of positive lymph nodes in stages T1 to T3 incidental gallbladder carcinoma: results of the German Registry. Surg Endosc. 2012;26(5):1382-9.

19. Goetze TO, Paolucci V. Adequate extent in radical re-resection of incidental gallbladder carcinoma: analysis of the German Registry. Surg Endosc. 2010;24(9):2156-64.

20. Shibata K, Uchida H, Iwaki K, Kai S, Ohta M, Kitano S. Lymphatic invasion: an important prognostic factor for stages T1b-T3 gallbladder cancer and an indication for additional radical resection of incidental gallbladder cancer. World J Surg. 2009;33(5):1035-41.

21. Varshney S, Butturini G, Gupta R. Incidental carcinoma of the gallbladder. Eur J Surg Oncol. 2002;28(1):4-10.

22. Yildirim E, Celen O, Gulben K, Berberoglu U. The surgical management of incidental gallbladder carcinoma. Eur J Surg Oncol. 2005;31(1):45-52.

23. You DD, Lee HG, Paik KY, Heo JS, Choi SH, Choi DW. What is an adequate extent of resection for T1 gallbladder cancers? Ann Surg. 2008;247(5):835-8.

24. Bartlett DL, Fong Y, Fortner JG, Brennan MF, Blumgart LH. Long-term results after resection for gallbladder cancer. Implications for staging and management. Ann Surg. 1996;224(5):639-46.

25. Pawlik TM, Choti MA. Biology dictates prognosis following resection of gallbladder carcinoma: sometimes less is more. Ann Surg Oncol. 2009;16(4):787-8.

26. Araida T, Higuchi R, Hamano M, Kodera Y, Takeshita N, Ota T, et al. Should the extrahepatic bile duct be resected or preserved in R0 radical surgery for advanced gallbladder carcinoma? Results of a Japanese Society of Biliary Surgery Survey: a multicenter study. Surg Today. 2009;39(9):770-9.

27. Chatelain D, Fuks D, Farges O, Attencourt C, Pruvot FR, Regimbeau JM. Pathology report assessment of incidental gallbladder carcinoma diagnosed from

cholecystectomy specimens: results of a French multicentre survey. Dig Liver Dis. 2013;45(12):1056-60.

28. Horiguchi A, Miyakawa S, Ishihara S, Miyazaki M, Ohtsuka M, Shimizu H, et al. Gallbladder bed resection or hepatectomy of segments 4a and 5 for pT2 gallbladder carcinoma: analysis of Japanese registration cases by the study group for biliary surgery of the Japanese Society of Hepato-Biliary-Pancreatic Surgery. J Hepatobiliary Pancreat Sci. 2013;20(5):518-24.

29. Goetze TO, Paolucci V. Prognosis of incidental gallbladder carcinoma is not influenced by the primary access technique: analysis of 837 incidental gallbladder carcinomas in the German Registry. Surg Endosc. 2013;27(8):2821-8.

30. Fuks D, Regimbeau JM, Pessaux P, Bachellier P, Raventos A, Mantion G, et al. Is port-site resection necessary in the surgical management of gallbladder cancer? J Visc Surg. 2012;150(4):277-84.

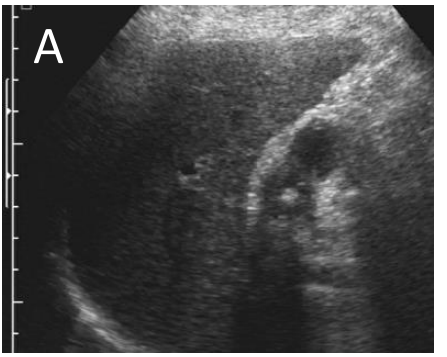
Figure Legends

Fig 1. Case example images

A: Ultrasonography revealed stones in the gallbladder and gallbladder wall thickness. B: CT revealed stones and wall thickness as well. C: Macroscopically, the wall appeared severely thickened with the rough appearance of mucosa. D: Pathological evaluation revealed papillary adenocarcinoma stage T2. E: Additional treatment was performed (S4a5 segmentectomy of the liver, lymphadenectomy and extrahepatic bile duct resection). F: Residual disease was found in the area close to the cystic duct margin.

Fig 2. Flow-chart of all cases showing tumor recurrence.

Fig 3. Disease-specific survival (DSS) of all patients (A) and individually for each of the 3 groups (B). The re-resected group showed significantly better survival than the no-treatment group ($p=0.015$).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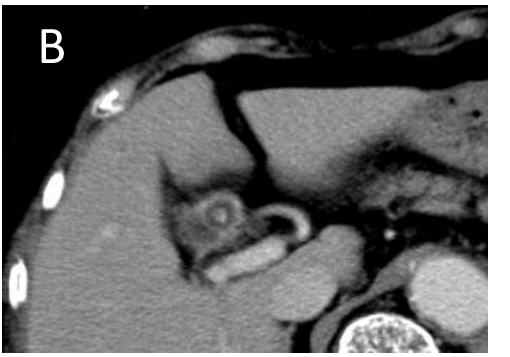
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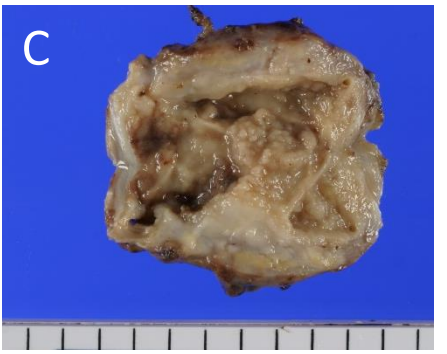
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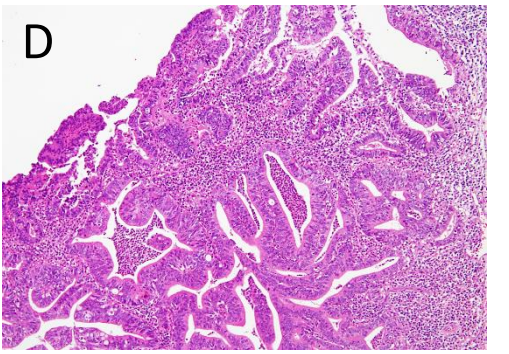
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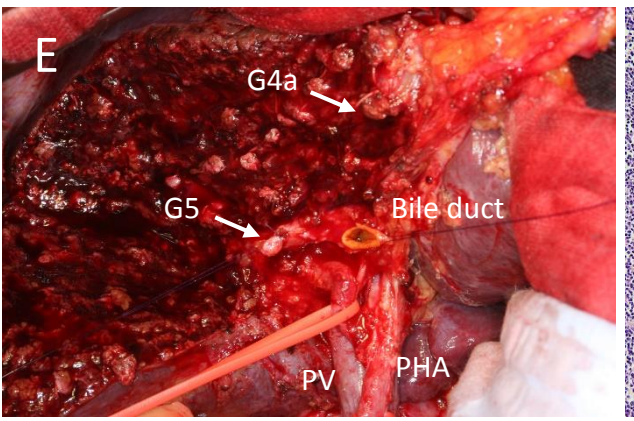
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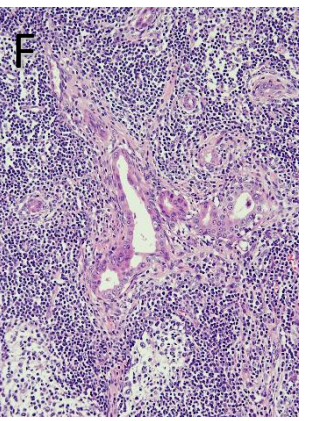
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Figure 2

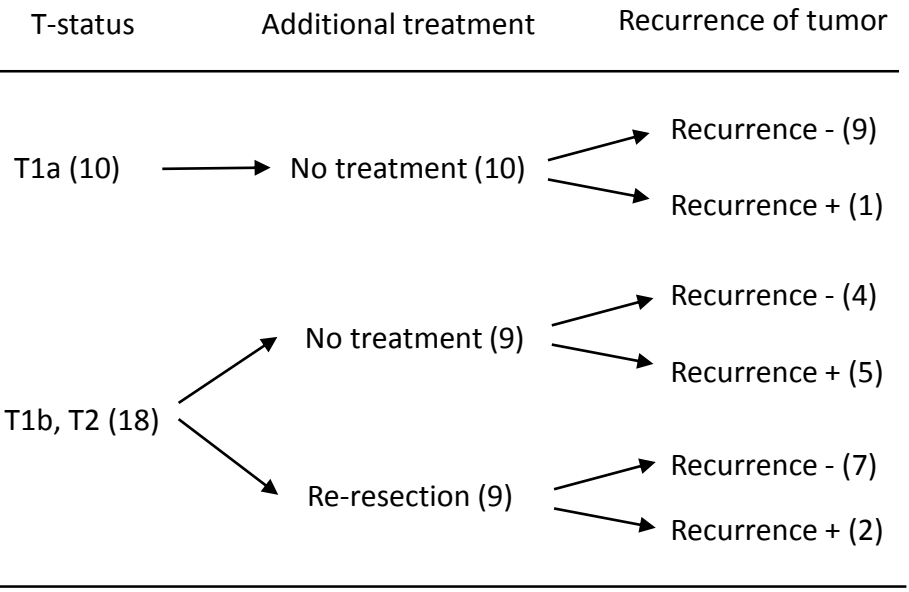

Figure 3

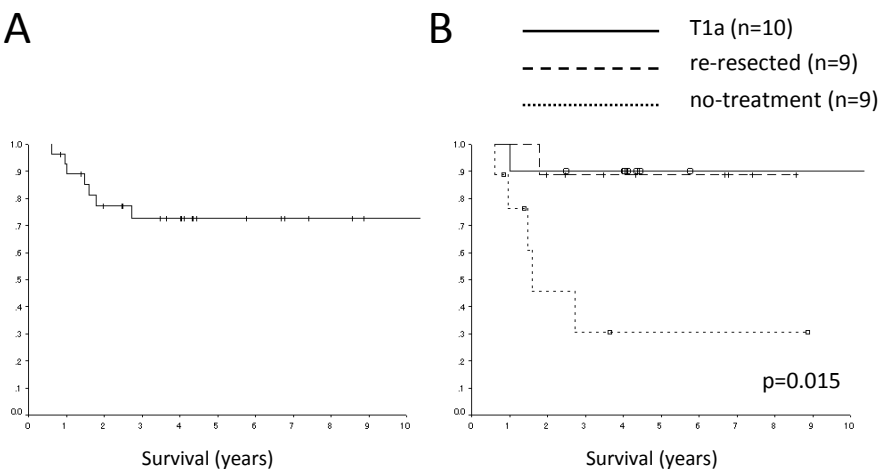

Table 1. Comparison of 3 groups, classified based on tumor stage

	T1a (n=10)	T1b+T2 (re-resected; n=9)	T1b+T2 (no-treatment; n=9)	*p value
age (years)	73.2 (56-92)	73.8 (52-82)	76.9 (62-88)	0.91
gender (male/ female)	7/3	5/4	4/5	>0.99
initial operation (laparoscopic/open)	4/6	1/8	1/8	>0.99
pathological type(papillary/well/mod/poor)	4/4/2/0	2/5/1/1	1/6/2/0	>0.99
T (1a/1b/2)	10/0/0	0/1/8	0/4/5	0.29
stage (IA/IB/IIB)	10/0/0	1/6/2	4/5/0	0.16

*p value was calculated between the re-resected and no-treatment groups

Table 2: Details related to disease recurrence

#	age (years)	gender	initial method of cholecystectomy	*pathological type	T	N	stage	2nd operation	type of recurrence	survival (years)	status
1	78	male	open	well	T1a	0	IA	not applied	local, para-aortic LN	1	dead
2	68	male	open	mod	T1b	0	IA	not applied	local	1.5	dead
3	62	female	laparoscopic	well	T2	0	IB	not applied	port site, peritoneal	1.6	dead
4	83	female	open	pap	T2	0	IB	not applied	not defined	0.6	dead
5	72	male	open	well	T2	0	IB	not applied	liver and peritoneal	2.7	dead
6	81	female	open	mod	T2	0	IB	not applied	not defined	0.9	dead
7	76	female	open	well	T2	0	IB	extended surgery	lung and liver	6.8	alive
8	52	female	laparoscopic	mod	T2	1	IIB	extended surgery	para-aortic LN	1.8	dead

*well; well differentiated adenocarcinoma, mod; moderately differentiated adenocarcinoma, poor; poorly differentiated adenocarcinoma
pap; papillary adenocarcinoma