Int J Clin Exp Med 2018;11(4):3866-3872
www.ijcem.com /ISSN:1940-5901/IJCEM0067973

Original Article

Comparison of characteristics and survival between incidental and suspected gallbladder carcinoma

Xinwei Yang[1*], Junyi Chen[2*], Zhijian Wen[3*], Yan Ling[4*], Jue Yang[1], Xinzhou Yan[1], Baohua Zhang[1], Feng Shen[1], Mengchao Wu[1]

[1]Eastern Hepatobiliary Surgery Hospital, The Second Military Medical University, Shanghai, China; [2]Department of General Surgery, Shanghai Fourth People's Hospital, Shanghai, China; [3]Department of Hepatobiliary Pancreatic Vascular Surgery, No.174 Hospital of PLA, Xiamen University, Xiamen, China; [4]International Cooperation Laboratory on Signal Transduction, Eastern Hepatobiliary Surgery Institute, The Second Military Medical University, Shanghai, China. [*]Equal contributors.

Received October 26, 2017; Accepted March 14, 2018; Epub April 15, 2018; Published April 30, 2018

Abstract: At present, the prognostic impact of incidentally discovered GBC (PI-GBC) and preoperative suspected GBC (PS-GBC) has not been widely studied. We enrolled 276 gallbladder carcinoma (GBC) patients upon whom surgical resection with curative intent was performed between January 2004 and December 2014. Of the 276 patients, 80 were identified with postoperative incidentally discovered gallbladder cancer (PI-GBC) and 196 were suspected with preoperative imaging (PS-GBC). Postoperative incidental gallbladder cancer (PI-GBC) was of lower T-stage ($p<0.001$), the lower presence of hepatic invasion ($p<0.001$) and lymph node metastasis ($p<0.001$), less intra-operative bleeding ($p<0.001$), less operative time ($p=0.001$), and less postoperative complication (5.0% vs. 17.9%, $p=0.004$). In the 276 GBC group, multivariate analysis revealed that only T stage, lymph node metastasis and tumour location were independent prognostic factors were independent prognostic factors. Postoperative incidental gallbladder cancer has a significantly lower degree malignant and better survival than preoperatively suspected GBC. However, incidental gallbladder cancer is not an independent factor that affects the prognosis. Incidental gallbladder cancer does not predict better prognosis, while it is worth the attention of clinicians.

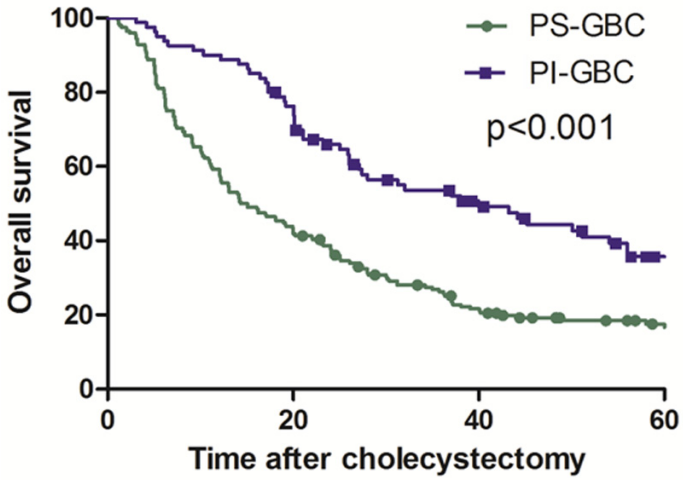
Keywords: Gallbladder cancer, incidental, suspected, tumor characteristics, prognosis

Introduction

Gallbladder cancer (GBC) is the most common malignancy of the biliary tract, accounting for 80%-95% of the biliary cancers worldwide [1]. The global rates for GBC exhibit striking variability, reaching epidemic levels for some regions and ethnicities. A satisfactory outcome of GBC patients is critically dependent on an early diagnosis and most of these patients are usually faced with a poor prognosis due to diagnosis at advanced stages [2]. In patients undergoing surgery, extensive hepatectomy, with or without portal vein lymphadenectomy and bile duct resection, is often required of disease eradication, but with high morbidity and incidental mortality [3].

Several retrospective studies have examined prognostic factors for patients with GBC. Tumor stage, according to the American Joint Committee on Cancer (AJCC) staging system, is the strongest overall predictor of patient survival [4, 5]. Other prognostic factors include the extent of surgical re-section, lymph node status, age, and sex [5, 6]. The presentation and management of incidental GBC have been described previously [7, 8]. There are scant data, however, on the importance of incidental discovery of GBC as a prognostic indicator of patient survival. Incidental GBC may represent early-stage cancer that would eventually progress to symptomatic disease, or it may represent a unique histological entity with a different prognosis. In addition, it has not been analyzed in detail and is still controversial.

The current study examines large sample data from hepatobiliary centerin in order to understand the clinical differences between inciden-



Group	Number	1 year	3 year	5 year	Median survival
PS-GBC	196	57.5%	25.7%	16.6%	14.3±2.08 (10.21,18.39)
PI-GBC	80	88.8%	52.2%	33.0%	39.9±7.56 (25.15,54.78)

Figure 1. Actuarial survival curve between 80 PI-GBC and 196 PS-GBC patients following surgical resection with curative intent.

tal and suspected GBC. We hope to explore the impact of time of diagnosis on survival in patients with GBC and the interaction between preoperative suspicion and other known prognostic factors.

Materials and methods

Subjects

A prospectively maintained hepatobiliary surgery database at the Eastern Hepatobiliary Hospital was reviewed for all patients with a diagnosis of GBC that underwent surgical resection with curative intent between January 2004 and December 2014. Permission from the Second Military Medical University's Institutional Review Board was obtained prior to data review. Written informed consent was obtained from all patients for surgical treatment and pathological examinations, according to institutional guidelines. All methods were carried out in accordance with relevant guidelines and regulations. All experimental protocols were approved by the Licensing Committee of the Second Military Medical University.

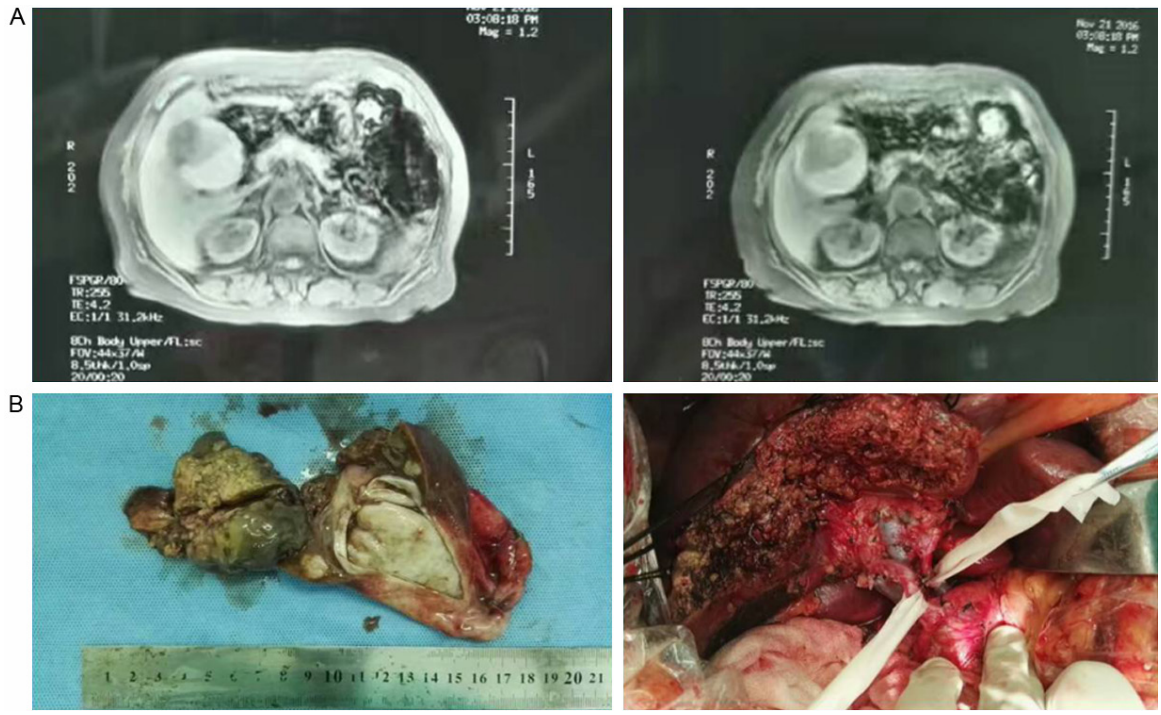
Resection completeness was classified by: R0 without residuals on hepatic margins, R1 microscopically positive margin, and R2 macroscopic residuals on hepatic margins. R0 or R1 resections were considered to be surgical resection with curative intent. All patients that had undergone either palliative or exploratory surgery were excluded from analysis. In our experience, extensive invasion to the hepatoduodenal ligament, excessive presence of liver or peritoneal metastases beyond areas near the gallbladder, or bulky lymph node metastases have been considered a contraindication to surgery. Accor-ding to the 7th UICC/AJCC TNM [9], involvement of periaortic, pericaval, superior mesenteric ar-tery, and/or celiac artery lymph nodes are classified as N2. Involvement of inter-aortocaval lymph nodes is considered to be M1. Routine sampling of inter-aortocaval lymph nodes was not performed for this study.

Surgical procedures

Surgical procedures used to treat patients are summarized as follows. All patients underwent en bloc dissection of regional lymph nodes (lymph nodes along the hepatoduodenal ligament and common hepatic artery and behind pancreatic head) (**Figure 2**). Hepatectomies were carried out in all 276 patients. Resection of laparoscopic port sites was routinely performed in all patients receiving laparoscopic cholecystectomy. Combined resection of adjacent organs was performed as long as R0 resection could be expected.

Statistical analysis

Data were analyzed with SPSS Version 17.0 for Windows (SPSS, Inc., Chicago, IL, USA) and significance level was set at $p<0.05$. Overall survival was measured from the day of operation to death, including death due to cancer or other causes, or to the last day of follow up. Comparison between the two groups was performed using Student's t-test for parametric data and Mann-Whitney U-test for non-parametric data. Chi-square test was used for categorical data. Survival curves were estimated with Kaplan-Meier method and compared by log-rank test. Cox regression analysis was carried out to determine which factor was the best prognostic determinant.



Figue 2. A. Enhanced computed tomography (CT) was performed in preoperatively suspected gallbladder carcinoma. B. Typical operative field after wedge resection with a 3-cm margin (including segments IVb/V) and skeletonization of the hepatoduodenal ligament.

Results

Demographic data

Of the 276 patients managed with curative intent for GBC during this 10-year inclusion period, 196 (71.0%) had preoperative suspicion of malignancy (preoperative suspicion GBC, PS-GBC) and 80 (29.0%) were discovered incidentally (postoperative incidentally discovered GBC, PI-GBC). All patients were followed up for a mean period of 76.7 months.

*Comparison of tumor characteristics between PS-GBC and PI-GBC (**Table 1**)*

The two cohorts were similar in age, gender, histological differentiation, extent of liver resection, and combined resections of adjacent organs but some tumor characteristics differed significantly. A higher proportion of associated gallstones was associated with PI-GBC (p= 0.013), suggesting that presence of incidentally discovered gallbladder cancer might be covered by the symptoms of gallstones. Rates of hepatic invasion (p<0.0001) and nodal metastases (p<0.0001) were also significantly higher in PS-GBC. A more advanced T category was associated with preoperative suspicion GBC, suggesting more seriously local tumor invasion in PS-GBC patients. More intra-operative bleeding and operative time were found in PS-GBC group (P<0.001 and P=0.001), suggesting a wider range of lesion resection performed in PS-GBC patients. However, R0 resection rate was similar between PS-GBC and PI-GBC (P=0.518). There was no significant difference in mortality between PS-GBC and PI-GBC (P=0.577). Morbidity was significantly lower in PI-GBC patients than in PS-GBC patients (5.0% vs. 17.9%, p=0.004). Average postoperative hospital stay in PS-GBC patients was 13.2 days (range: 4-85 days), longer than PI-GBC patients (P=0.001).

Survival data in all 276 GBC patients

Median survival for PI-GBC was 39.9 versus 14.3 months for PS-GBC (p<0.001). Cumulative 1-, 3-, and 5-year survival rates in PI-GBC group (88.8%, 52.2%, and 33.0%, respectively) were significantly better than those in the PS-GBC group (57.5%, 25.7%, and 16.6%, p<0.001; **Figure 1**).

Table 1. Demographic data of postoperative incidentally discovered gallbladder cancer (PI-GBC) and preoperatively suspected gallbladder carcinoma (PS-GBC)

	PS-GBC (n=196)	PI-GBC (n=80)	*p*-Value
Gender (Male:female)	81:115	27:53	0.242
Mean age (range)	59.7±11.0 (23-83)	57.6±9.7 (34-62)	0.137
Postoperative hospital stay	13.2±8.9 (4-85)	10.4±5.3 (5-51)	0.001
Associated gallbladder disease			0.013
Gallstones	95 (48.5%)	52 (65.0%)	
Nil	101 (51.5%)	28 (35.0%)	
Histologic type			0.217
Well differentiated	5 (2.6%)	5 (6.2%)	
Moderately differentiated	164 (83.6%)	61 (76.3%)	
Poorly differentiated	27 (13.8%)	14 (17.5%)	
Extent of liver resection			0.277
Major hepatectomy (>3 segments)	5 (2.6%)	1 (1.2%)	
Anatomical segments IV-V	55 (28.0%)	16 (20.0%)	
Gallbladder bed	136 (69.4%)	63 (78.8%)	
Combined resection of adjacent organs	18 (9.2%)	3 (3.8%)	0.195
Hepatic invasion	115 (58.7%)	16 (20.0%)	0.000
Lymph node metastasis	113 (57.7%)	18 (22.5%)	0.000
pT			0.000
pT1-2	13 (6.6%)	20 (25.0%)	
pT3-4	183 (93.4%)	60 (75.0%)	
Intra-operative bleeding (ml)	444.0±406.8 (50-3200)	279.2±157.3 (30-900)	0.000
Operative time (min)	233.1±89.3 (90-520)	226.4±71.6 (85-440)	0.001
R0:R1	183:13	77:3	0.518
Mortality (number of patients)	6 (3.06%)	2 (2.5%)	0.577

CRAO, Combined resection of adjacent organs. Note that adjacent organs include the pancreas, duodenum, stomach, and/or colon other than the liver and extrahepatic bile duct.

Risk factors in all 276 GBC patients

To identify factors influencing long-term survival in all 276 GBC patients, univariate and multivariate analyses were performed. In univariate analysis, depth of invasion of the cancer (T stage), age, lymph node metastasis, histologic differentiation, hepatic invasion, combined resection of adjacent organs, intraoperative blood loss, extrahepatic bile duct resection, tumour location, extent of liver resection and preoperative suspicion were identified as significant prognostic factors (**Table 2**). In multivariate analysis, only T stage, hepatic invasion and the time from cholecystectomy to referral for re-operation were independent prognostic factor (**Table 3**). However, incidental gallbladder cancer was not an independent prognostic factor in multivariate analysis.

Discussion

Cancer of the gallbladder, a rare entity with poor prognosis, is often discovered incidentally during or after cholecystectomy. Approximately 0.2% of patients undergoing cholecystectomy will have incidental discovery of GBC (IGC) [10, 11]. As the number of cholecystectomy operations increases, it is likely that the number of incidentally discovered GBC will also increase. An incidentally discovered GBC during the initial operation forces the surgeon to make a quick decision and presents an unexpected challenge especially in postoperatively IGC patients. In order to effectively manage the diagnosis of disease and counseling patients, it is necessary to understand the tumor characteristics and survival between incidental and suspected gallbladder carcinoma.

Table 2. Univariate analysis of clinicopathologic variables related to survival in GBC patients who underwent surgical resection with curative intent (n=276)

Variables	Cutoff levels	Number	Survival rates (%)			*P* value
			1 year	3 year	5 year	
Age (yr)						0.007
	<60	140	67.9	42.9	30.1	
	≥60	136	68.4	25.3	12.3	
Gender						0.119
	Male	108	64.8	28.8	21.0	
	Female	168	70.2	37.7	23.7	
Associated gallstone						0.716
	Present	147	67.3	34.1	20.6	
	Absent	129	69.0	34.3	23.7	
pT (TNM)						0.000
	pT1 and 2	33	90.9	78.2	63.2	
	pT3 and 4	243	65.0	28.2	16.2	
Lymph node metastasis						0.000
	Negative	145	82.1	48.7	34.3	
	Positive	31	52.7	18.3	9.4	
Histologic differentiation						0.047
	Well/Moderate	235	71.7	34.6	23.2	
	Poor	41	51.2	26.1	15.2	
Hepatic invasion						0.000
	Present	131	53.4	20.3	10.9	
	Absent	145	81.4	46.9	32.4	
Combined resection of adjacent organs						0.000
	Present	171	57.3	21.0	10.7	
	Absent	105	85.7	56.0	40.9	
Intraoperative blood loss						0.000
	<500	203	74.9	39.0	26.7	
	≥500	73	49.3	20.5	9.8	
Pathology						0.308
	Adenocarcinoma	242	68.2	32.4	21.0	
	Not Adenocarcinoma	34	67.6	46.7	29.1	
Tumor location						0.001
	Neck	68	61.8	19.8	8.3	
	Body+tail	208	70.2	38.9	26.9	
Extrahepatic bile duct resection						0.000
	Present	71	60.6	18.9	7.9	
	Absent	205	70.7	39.5	27.3	
Extent of liver resection						0.000
	Gallbladder bed	77	81.8	50.9	32.5	
	Anatomical segments IV-V	109	65.1	32.6	24.7	
	Major hepatectomy (>3 segments)	90	60.0	21.9	8.5	
Incidentally discovered GBC						0.000
	Present	80	90.0	53.6	35.7	
	Absent	196	59.2	26.3	16.6	

At present, the prognostic impact of incidentally discovered GBC and preoperative suspected GBC has not been widely studied. It is not clear whether incidental discovered gallbladder cancer has the same prognosis, or poorer prognosis, compared with the same stage of non-incidental gallbladder cancer. For incidental discovered gallbladder cancers, it is likely that

Table 3. Results of multivariate analysis

Variable	Regression coefficient	Standard error	*P* value	Relative risk	95% Confidence interval
Age	0.209	0.146	0.153	1.233	0.925-1.642
pT	0.888	0.287	0.002	2.429	1.383-4.267
Lymphatic metastasis	0.446	0.153	0.003	1.563	1.158-2.108
Histological differentiation	-0.294	0.200	0.142	0.745	0.504-1.103
Liver invasion	0.270	0.246	0.272	1.310	0.809-2.122
Combined resection of adjacent organs	0.269	0.297	0.366	1.308	0.731-2.341
Intraoperative blood loss	0.268	0.162	0.099	1.307	0.951-1.797
Tumor location	-0.514	0.195	0.008	0.598	0.409-0.876
Extrahepatic bile duct removal	-0.094	0.234	0.689	0.910	0.575-1.441
Extent of liver resection	0.102	0.102	0.317	1.108	0.907-1.354
Incidentally discovered GBC	-0.219	0.183	0.232	0.803	0.561-1.150

the combined presence of cholecystitis complicates the diagnosis of gallbladder cancer. Several studies have reported the negative impact of cholecystitis on survival [12-14], although the exact mechanism has not been studied. Considering the relatively high proportion of residual cancerous lesions after re-operation in this study, incomplete en bloc resection during cholecystectomy that causes spillage of cancer cells may affect the prognosis of gallbladder cancer. Many studies warrant radical resection to improve survival [15-17]. In contrast, a study reported that the tumor characteristics differed between suspected and incidental gallbladder cancer, and suggested that incidental gallbladder cancer has a significant better median survival [8]. In this study, we also found that the overall prognosis of incidentally discovered gallbladder cancer was better than preoperative suspected gallbladder cancer. This is why we strongly recommend reoperation in patients with postoperative incidentally discovered GBC. However, it is worth noting that incidentally discovered GBC was not the independent risk factors. This reminds us that there are special pathological features of the incidentally discovered GBC, but this does not mean that these patients have an earlier tumor stage and a better prognosis. Therefore, in clinical work, clinicians and patients should be valued. The independent influence of the prognosis of gallbladder cancer is still the T stage of the tumor, lymph node invasion, and tumour location. This is consistent with our previous literature reports [18, 19].

Early-stage diagnosis and treatment, as well as varying pre- and intraoperative techniques, certainly impact survival with GBC, but they do not adequately explain the significance of incidental diagnosis [8, 20, 21]. Controlling for age, extent of surgery, the presence of gallstone disease, country of origin, and stage of tumor are unable to explain the association. We hypothesize that these data may suggest a previously unrecognized histological difference between cancer that becomes symptomatic and that which is detected only incidentally. It is possible that the growth patterns in these two situations differ biologically and carry different prognoses for the patient. Further research is warranted to fully understand the implications of the current study.

In conclusion, postoperative incidental gallbladder cancer has a significantly lower degree malignant and better survival than preoperatively suspected GBC. However, incidental gallbladder cancer is not an independent factor that affects the prognosis. Incidental gallbladder cancer does not predict better prognosis, while it is worth the attention of clinicians.

Acknowledgements

This study was supported by grants from National Natural Science Foundation of China (Grant No: 81372674) and Shanghai Health Bureau (Grant No: 20124Y154 and 20164Y-0109). We are grateful to Jing Du for assisting in the preparation of this manuscript.

Declaration of conflict of interest

None.

Address correspondence to: Baohua Zhang and Feng Shen, Eastern Hepatobiliary Surgery Hospital, The Second Military Medical University, 225 Changhai Road, Shanghai 200438, China. Tel: +86-15900439699; 86-21-81875261; E-mail: weice-

lia@163.com (BHZ); shenfengdfgd@yahoo.com.cn (FS)

References

[1] Bazoua G, Hamza N, Lazim T. Do we need histology for a normal-looking gallbladder? J Hepatobiliary Pancreat Surg 2007; 14: 564-568.

[2] Hundal R, Shaffer EA. Gallbladder cancer: epidemiology and outcome. Clin Epidemiol 2014; 6: 99-109.

[3] Fong Y, Jarnagin W, Blumgart LH. Gallbladder cancer: comparison of patients presenting initially for definitive operation with thosepresenting after prior noncurative intervention. Ann Surg 2000; 232: 557-569.

[4] Löhe F, Meimarakis G, Schauer C, Angele M, Jauch KW, Schauer RJ. The time of diagnosis impacts surgical management but not the outcome of patients with gallbladder carcinoma. Eur J Med Res 2009; 14: 345-351.

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

[6] Kayahara M, Nagakawa T, Nakagawara H, Kitagawa H, Ohta T. Prognostic factors for gallbladder cancer in Japan. Ann Surg 2008; 248: 807-814.

[7] 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: 1478-1486.

[8] Mazer LM, Losada HF, Chaudhry RM, Velazquez-Ramirez GA, Donohue JH, Kooby DA, Nagorney DM, Adsay NV, Sarmiento JM. Tumor characteristics and survival analysis of incidental versus suspected gallbladdercarcinoma. J Gastrointest Surg 2012; 16: 1311-1317.

[9] Edge SB, Byrd DR, Compton CC, Krebs (Krankheit). AJCC cancer staging manual. 7th ed. Springer; New York, NY: 2010. Gallbladder Cancer; Springer Berlin 2011; pp. 211-7.

[10] Muratore A, Polastri R, Bouzari H, Vergara V, Capussotti L. Radical surgery for gallbladder cancer: a worthwhile operation? Eur J Surg Oncol 2000; 26: 160-163.

[11] Goetze TO, Paolucci V. Adequate extent in radical re-resection of incidental gallbladder carcinoma: analysis of the German Registry. Surg Endosc 2010; 24: 2156-2164.

[12] Choi SB, Han HJ, Kim CY, Kim WB, Song TJ, Suh SO, et al. Incidental gallbladder cancer diagnosed following laparoscopic cholecystectomy. World J Surg 2009; 33: 2657-2663.

[13] Clemente G, Nuzzo G, De Rose AM, Giovannini I, La Torre G, Ardito F, Giuliante F. Unexpected gallbladder cancer after laparoscopic cholecystectomy for acute cholecystitis: aworrisome picture. J Gastrointest Surg 2012; 16: 1462-1468.

[14] Han HS, Cho JY, Yoon YS, Ahn KS, Kim H. Preoperative inflammation is a prognostic factor for gallbladder carcinoma. Br J Surg 2011; 98: 111-116.

[15] Glauser PM, Strub D, Käser SA, Mattiello D, Rieben F, Maurer CA. Incidence, management,and outcome of incidental gallbladder carcinoma: analysis of the database of the Swiss association of laparoscopic and thoracoscopic surgery. Surg Endosc 2010; 24: 2281-2286.

[16] Yip VS, Gomez D, Brown S, Byrne C, White D, Fenwick SW, Poston GJ, Malik HZ. Management of incidental and suspicious gallbladder cancer: foucus on early referral to a tertiary centre. HPB (Oxford) 2014; 16: 641-647.

[17] Fuks D, Regimbeau JM, Le Treut YP, Bachellier P, Raventos A, Pruvot FR, Chiche L, Farges O. Incidental gallbladder cancer by the AFC-GBC-2009 Study Group. World J Surg 2011; 35: 1887-1897.

[18] Yang XW, Yuan JM, Chen JY, Yang J, Gao QG, Yan XZ, Zhang BH, Feng S, Wu MC. The prognostic importance of jaundice in surgical resection with curative intent for gallbladder cancer. BMC Cancer 2014; 14: 652.

[19] Yang XW, Yang J, Li L, Man XB, Zhang BH, Shen F, Wu MC. Analysis of the relationships between clinicopathologic factors and survival in gallbladder cancer following surgical resection with curative intent. PLoS One 2012; 7: e51513.

[20] Cucinotta E, Lorenzini C, Melita G, Iapichino G, Currò G. Incidental gall bladder carcinoma: does the surgical approach influence the outcome? ANZ J Surg 2005; 75: 795-798.

[21] Chan KM, Yeh TS, Jan YY, Chen MF. Laparoscopic cholecystectomy for early gallbladder carcinoma: long-term outcome in comparison with conventional open cholecystectomy. Surg Endosc 2006; 20: 1867-1871.