Int J Clin Exp Med 2015;8(1):869-875
www.ijcem.com /ISSN:1940-5901/IJCEM0003023

Original Article

Surgical approach does not influence the outcome of incidental gallbladder carcinoma

Wei-Jie Zhang[1,2*], Gui-Fang Xu[3*], Zhi-Qiang Tian[4], Guog-Zhong Wu[4], Hao Wang[1,2], Wen-Xian Guan[1,2]

[1]Department of Gastrointestinal Surgery, Drum Tower Hospital Clinical College of Nanjing Medical University, Nanjing, China; [2]Department of Gastrointestinal Surgery, Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China; [3]Department of Gastroenterology, Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing; [4]Department of General Surgery, 101th Hospital of People's Liberation Army, Wuxi. [*]Co-first authors.

Received October 8, 2014; Accepted December 29, 2014; Epub January 15, 2015; Published January 30, 2015

Abstract: Several reports claim that there is a risk that laparoscopic cholecystectomy (LC) might worsen the prognosis of unsuspected gallbladder cancer. The aim of this study was to evaluate whether the surgical approach influence the outcome in patients with incidental gallbladder carcinoma. Methods: A retrospective study was done of 28 patients who were diagnosed with unsuspected gallbladder carcinoma who had undergone cholecystectomy for benign gallbladder disease at our institution between 1999 and 2007. 20 patients (4 men and 16 women, aged from 37 to 81 years) undergoing LC (group A) and 8 patients (6 men and 2 women, aged from 43 to 88 years) undergoing open cholecystectomy (OC) (group B) with incidental diagnosed GC. We evaluated the outcome in the two groups correlating the cumulative survival rates with tumor stage and surgical technique (LC or OC), time of diagnosis (after or during cholecystectomy). Results: nine patients (69.2 %) in group A and four patients (30.8%) in group B had recurrence. Survival rate was statistically correlated to tumor stage ($P<0.0001$) Survival rate was statistically correlated with tumor stage but neither with the surgical approach used to perform cholecystectomy, nor with time of diagnosis (intra- or post-operatively). Conclusion: These results would seem to lend support to the opinion that LC does not worsen the prognosis for incidental GC, regardless of whether the tumor was detected during or after cholecystectomy.

Keywords: Gallbladder carcinoma, laparoscopic cholecystectomy, prognostic factors, tumor stage

Introduction

Gallbladder carcinoma (GC) is the fifth most common cancer of the gastrointestinal tract. There are no specific clinical symptoms or signs, and most patients have advanced disease at presentation. The 5-year prognosis for all stages of GCs is about 5% [1], while the median survival for patients with suspected cancers is 9.2 months, and for those with incidentally diagnosed cancers, 26.5 months [2].

In the era of laparoscopy many GBC are diagnosed after laparoscopic cholecystectomy and most of these tumors are in an early stage. The major concern about the use of laparoscopic surgery for patients with GC is recurrence at the level of scars or trocar holes and the spread of tumor cells resulting from creation of pneumoperitoneum [3, 4], although some studies suggested that the prognosis after LC was not significantly different from that reported in the literature after open cholecystectomy (OC) [5, 6].

The objective of this study was to evaluate which factors influence the outcome of GC diagnosed during or after cholecystectomy, and to evaluate whether the prognosis is worsen after LC than after OC.

Methods

A retrospective study was performed on the 28 patients who were diagnosed with unsuspected gallbladder carcinoma out of 11,574 who had undergone cholecystectomy for benign gallbladder disease at our institution from January

Table 1. TNM staging system for gallbladder carcinoma*

Primary Tumor	
TX	No description of the tumor's extent is possible because of incomplete information
T0	No evidence of primary tumor
Tis (carcinoma in situ)	Cancer cells are limited to the epithelium (the innermost layer of the gallbladder) and have not invaded deeper layers of the gallbladder
T1	The tumor invades into the lamina propria or the muscle layer (muscularis)
T1a	Tumor invades lamina propria
T1b	Tumor invades the muscle layer below the mucosa and lamina propria
T2	The tumor invades perimuscular fibrous tissue with no extension beyond the serosa or into the liver
T3	The tumor extends through the serosa and/or directly invades the liver and/or invades one other adjacent organ.
T4	The tumor invades the main blood vessels leading into the liver (portal vein or hepatic artery) or has reached more than one organ outside of the liver.
Regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
Distant Metastasis	
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
Stage	
0	Tis, N0, M0
IA	T1 (a or b), N0, M0
IB	T2, N0, M0
IIA	T3, N0, M0
IIB	T1-3, N1, M0
III	T4, any N, M0
IV	Any T, any N, M1

*According to AJCC (American Joint Committee on Cancer, AJCC) Cancer Staging Manual, Sixth Edition, 2002 [4].

Table 2. Therapy according to stage, diagnosis and survival period

Stage	Patient (Gender/age)	Diagnosis	Type of operation	Further operation	Survival, months (each patient)[a]
Tis	M/76	Post-	LC	No	35+
Tis	F/53	Post-	LC	No	125+
Tis	F/78	Post-	LC	No	44+
Tis	F/62	Post-	LC	No	89+
T1a	F/63	Intra--	LC	No	120+
T1a	F/75	Post-	LC	No	43+
T1b	F/66	Intra-	LC	No	6+
T1b	F/77	Intra-	LC	No	89
T2	F/63	Intra-	LC	Yes	29
T2	M/63	Intra-	LC	Yes	38
T2	F/59	Intra-	LC	Yes	47+
T2	F/76	Post-	LC	No	35
T2	F/62	Post-	LC		21
T2	F/65	Post-	LC		57+
T3	F/37	Intra-	LC	Yes	10+
T3	F/68	Intra-	LC	No (refused)	20
T3	F/77	Post-	LC	No (refused)	16
T3	M/57	Post-	LC	No (refused)	19
T4	F/81	Intra-	LC	biopsy	6
T4	M/56	Intra-	LC	biopsy	8
T1a	F/56	Intra-	OC		16+
T1b	F/61	Intra-	OC		70+
T1b	F/77	Intra-	OC		25+
T1b	F/74	Intra-	OC		6+
T1b	F/43	Intra-	OC		78
T2	M/66	Post-	OC		24
T2	F/88	Intra-	OC	No (refused)	31
T3	M/50	Post-	OC		12

Intra-, intraoperatively; Post-, Postoperatively. [a]A plus sign indicates patients who were alive at the end of the follow-up period.

1999 to December 2007. In all patients GC was detected incidentally by the pathologist during or after surgery. All the clinical records, histopathological reports data, operative records, and survival rates of patients with incidental carcinoma were analyzed. Tumor staging had been done according to pathological tumor staging (pT) as detailed in (**Table 1**) [7].

Cholecystectomy was performed by standard technique and a retrieval bag during laparoscopic operation was used in all cases when a perforation of gallbladder occurred so as to prevent stone spillage.

Also, if the gallbladder wall acutely inflamed, thick walled or filled with pus (empyema gallbladder), a retrieval bag was used to prevent gallbladder rupture during extraction and port-site infection. We placed an abdominal drain in the subhepatic region if there was bile spillage during operation or if the gallbladder is acutely inflamed with extensive adhesions and more than usual bleeding during surgery.

All patients were followed up between 3 and 6 months after surgery, and then every 6 months, by using carbohydrate antigen 19-9 (CA 19-9) and carcinoembryonic antigen (CEA) levels, ultrasonography, and enhanced CT when necessary. The recurrence of disease has been considered as any recurrence of tumor: distant metastasis, wide spread or local peritoneal seeding and port-site or scar recurrence.

The cumulative survival rate was calculated according to the Kaplan–Meier method and correlation between survival rate and type of cholecystectomy (LC or OC), time of diagnosis (after or during cholecystectomy) and pathological stage was examined using the log-rank test. A *P*-values of <0.05 were considered to denote statistically significant differences. Statistical analyses were carried out using SPSS (SPSS 12.0 for Windows; SPSS, Chicago, IL, USA) software.

Results

Of the 11,574 patients who underwent cholecystectomy, the histological samples revealed 20 cases (0.19%) of unsuspected GC out of 10,466 LCs (group A) and 8 cases (0.72%) out of 1108 OCs (group B).

In group A, the patients included four men and sixteen women, the median age was 65.7 years (range, 37-81 years) and in group B, the patients included six men and two women, the median age was 63.5 years (range, 43-88 years).

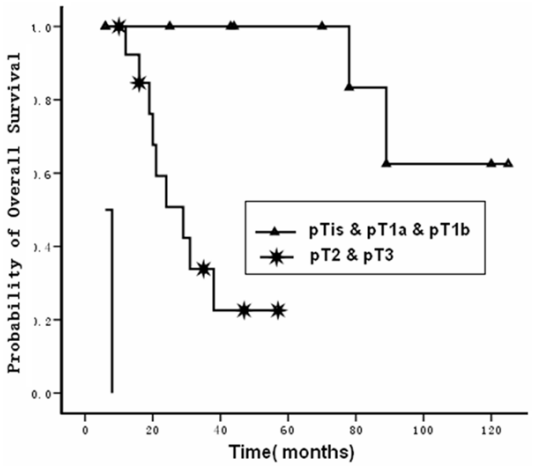

Figure 1. Survival for patients according to TNM stage (χ^2=43.816, *P*<0.0001, log-rank test), and no patient with pT4 tumor was censored.

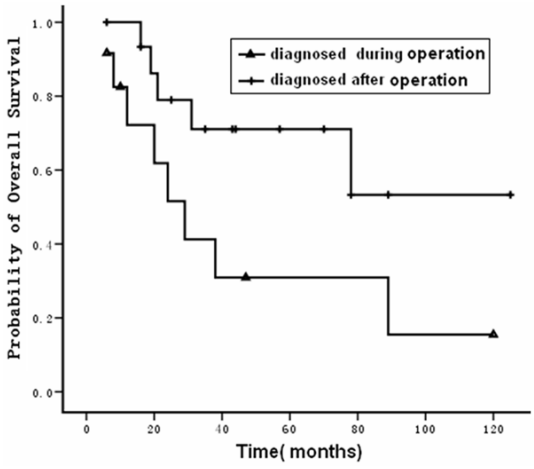

Figure 2. Survival for patients with GC discovered incidentally after and during operation (χ^2=3.712, *P*=0.054, log-rank test).

All patients with GC were not detected before surgery in any of these cases. The preoperative diagnosis of these 28 patients was: cholelithiasis (15), chronic cholecystitis (2), gallbladder polyp (polypoid lesion) (10), and adenomyomatosis diagnosed by MRT (magnetic resonance tomography) (1).

The tumor stage of all patients is reported in **Table 2**. According to the pathological tumor node metastases (TNM) staging system there were four patients with pTis adenocarcinoma (four after LC), three patients with pT1a adenocarcinoma (two after LC and one after OC), six patients with pT1b adenocarcinoma (two after LC and four after OC), eight patients with pT2 adenocarcinoma (six after LC and two after OC), five patients with pT3 adenocarcinoma (four after LC and one after OC) and two patients with pT4 adenocarcinoma (two after LC).

Patients with pT1a (3) or pT1b (6) tumors had no additional surgery and there was no recurrence occurred. In the remaining patients presented with pT2, pT3 or pT4 tumors, except three pT3 (group A) and one pT2 (group B) patients' relative refused to undergo a radical operation, additional radical surgery had performed within the primary operation for patients diagnosed intraoperatively, and the remaining 5 patients underwent additional radical surgery 12 (2), 16 (2) and 18 (1) days after first operation; the other with T4 were considered inoperable, only performed biopsy in order to allow for proper pathologic diagnosis and staging,

Median follow-up time of these patients was 60 months (range 6-129 months). During this period, Recurrence of disease occurred in 13 out of 28 patients (46.4%): in nine patients after LC (69.2%) and four after OC (30.8%), the occurrence rate between the two groups were no significant difference (P=1).

There were four patients, who had a retrieval bag used in group A. Recurrences occurred after a mean of 8.5 months (range 6-11) in group A and after a mean of 12.5 months (range 8-19) in group B. The difference between the two groups is not statistically significant (P=0.062). Patients with pT2 or above underwent further surgery. They underwent regional lymphadenectomy and excision of the liver bed. Further surgery was not performed on patients with early cancer (pTis and pT1) (**Table 2**).

In the group A, nine patients with pT2 (3), pT3 (4) and pT4 (2) developed recurrence (5 liver metastases, 1 lung metastasis, 1 stomach metastasis, 1 bile duct metastasis, 1 pancreas metastasis, but port site metastases were not present in any of our patients) and died after median 19 months (range 3-47 months). There were four patients with pT1b (1), pT2 (2) and pT3 (1) developed recurrence (2 liver metastases,) and died after median 27.5 months (range 11-78 months) in the group B. Survival rate was statistically correlated to the depth of cancer invasion (P<0.0001) (**Figure 1**), but there was no significant difference between those who were diagnosed with GC during or after opera-

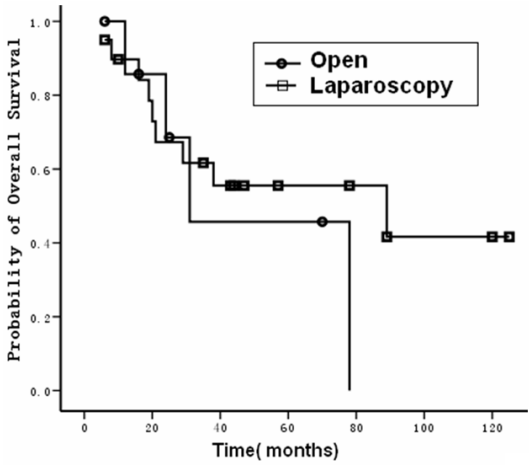

Figure 3. Survival for patients with GC discovered incidentally in group A and during group B (χ^2=0.475, *P*=0.491, log-rank test).

tion (P=0.054) and surgical approach (*P*=0.491) (**Figures 2**, **3**)

Discussion

GC is a relatively rare neoplasm and has been considered to be a highly lethal disease. A preoperative diagnosis of GC is difficult not only in the early stages but also in more advanced stages. Incidental GCs have been diagnosed during or after cholecystectomy [8, 9] and first described by Marcial-Rojas RA et al [10]. In the age of laparoscopic cholecystectomy, GC detected incidentally is encountered in 0.2-2.9% of cases [11-13].

In our study, patients with GC were all unsuspected findings during or after cholecystectomy, the disease was present in 0.24% (0.19% in group A and 7.2% in group B, respectively) of our patients.

In the absence of significant evidence on the better outcome following laparoscopic surgery, we hypothesis that it is not the laparoscopy or open technique that influences outcomes, but factors such as stage of the lesion and intraoperative events such as inadvertent perforation of the gall bladder with spillage of bile and improper specimen retrieval. Indeed, the use of a protective retrieval bag is considered ideal during extraction of the GC, but this precaution does not always exclude an intraperitoneal seeding event [14]. In our experience, a retrieval bag is advised in cases with perforation of gallbladder and markedly thicker wall, so as to prevent stone spillage, port-site recurrence and intraperitoneal dissemination.

Surgical resection is the only potentially curative therapy for GC. All gallbladders must be opened and examined carefully for any suspicious lesions before the abdomen is closed. The most appropriate way of diagnosis at present is to macroscopically examine gallbladder mucosa during surgery and to perform frozen section diagnosis of suspected lesions, and the entire lesion should be examined when necessary [9].

Disease management depends on the depth of tumor invasion through the gallbladder wall (T stage), and the involvement of the surgical margins, as these are the two major determinants of prognosis; the presence of lymph node metastasis and perineural invasion are also relevant, although information about nodal involvement (N stage) is usually not available.

There is a consensus that simple cholecystectomy is an adequate treatment for Tis and pT1a lesion, and tumors greater than stage pT2 should be treated by an additional radical operation. However, there is controversy in the management of T1 disease which includes T1a (mucosa) and T1b (muscle) substages. Some authors reported long-term survival after simple cholecystectomy and did not recommend radical resection for T1b disease [15-17], and Recently, Wakai et a [18] found 10-year survival for T1b tumors after simple cholecystectomy was 87% and recommended that it should be performed as standard procedure. However, some reported high locoregional recurrence and poor survival has been found in patients with incidental gallbladder cancer treated with simple cholecystectomy [5, 14, 19, 20]. As a consequence, they advocate aggressive surgery for pT1b disease.

In the current study, patients with Tis, pT1a and 1b tumors underwent simple cholecystectomy without any recurrences; a negative margin has been confirmed by intraoperative frozen biopsy, and there was no case with a positive margin in this series. Tis, T1a and T1b tumor have a good prognosis after OC as well as after LCT2 or beyond tumors have a poor prognosis in our study, and patients with pT4 with the shortest survival time. We believe a radical cholecystectomy and lymph node dissection is advisable.

LC seems not to worsen the outcome in patients with unsuspected GC. Cucinotta et al [5] concluded in their study that survival rate was statistically correlated with tumor stage (early or advanced cancer) but not with the surgical approach used to perform cholecystectomy (LC or OC). In a different study, Sarli et al [6] described 20 incidentals GC (nine after LC and 11 after OC). They correlated the survival rates with type of surgery (LC or OC) and with stage of disease, finding a statistically significant correlation with tumor stage but not with the surgical approach performed. The outcome in patients with GC incidentally diagnosed during or after cholecystectomy in our study was similar to that found in the above mentioned studies.

The surgical approach correlates with time, site and type of recurrence but not with the overall survival. Although recurrence of the disease was diagnosed earlier in the group of patients undergoing LC, no differences in survival rates were observed in group A and group B. Possibly, earlier diagnosis of recurrence after LC was a consequence of a more intensive follow-up.

Conclusions

In our study, there seems to be a tendency that the patients with postoperatively diagnosed carcinoma had a better survival than that of intraoperatively. This is likely because they have smaller tumors, and therefore were not noticed at the time of surgery.

However, there were four patients (40%) with pTis carcinoma in the postoperative group, and no one with T4 stage. The group with the intraoperative detected carcinomas consists of 8 patients (72.7%) with local advanced tumors, including two inoperable T4 patients.

Thus, although the limited number of cases observed does not allow for definite conclusions, the results of this study would seem to sustain the opinion that GC is a curable malignancy if diagnosed as an incidental finding at an early stage and that LC has no adverse effect on the outcome of patients with incidental GC, regardless of whether the tumor was detected during or after cholecystectomy. Given the limitations of retrospective data and small sample size, further study needed to define the definitely results.

Acknowledgements

Authors like to thank Dr Nishank Jain for statistical analysis.

Disclosure of conflict of interest

None.

Address correspondence to: Wen-Xian Guan, Department of Gastrointestinal Surgery, Drum Tower Hospital Clinical College of Nanjing Medical University, Nanjing, China; Department of Gastrointestinal Surgery, Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, China. E-mail: zhangweijie1616@163.com

References

[1] Misra S, Chaturvedi A, Misra NC, Sharma ID. Carcinoma of the gall bladder. Lancet Oncol 2003; 2: 167-76.

[2] Wullstein C, Woeste G, Barkhausen S, Gross E, Hopt UT. Do complications related to laparoscopic cholecystectomy influence the prognosis of gallbladder cancer? Surg Endosc 2002; 16: 828-32.

[3] Wibbenmeyer LA, Wade TP, Chen RC, Meyer RC, Turgeon RP, Andrus CH. Laparoscopic cholecystectomy can disseminate in situ carcinoma of the gallbladder. J Am Coll Surg 1995; 181: 504-510.

[4] Jacobi CA, Sabat R, Bohm B, Zieren H, Volk H, Müller J. Pneumoperitoneum with carbon dioxide stimulates growth of malignant colonic cells. Surgery 1997; 121: 72-8.

[5] 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: 795-8.

[6] Sarli L, Contini S, Sansebastiano G, Gobbi S, Costi R, Roncoroni L. Does laparoscopic cholecystectomy worsen the prognosis of unsuspected gallbladder cancer? Arch Surg 2000; 135: 1340-4.

[7] Greene FL, Page DL, Fleming ID, Fritz A, Balch CM. AJCC Cancer Staging Handbook 6th Edition. New York: Springer-Verlag; 2002. pp. 155-156.

[8] Toyonaga T, Chijiiwa K, Nakano K, Noshiro H, Yamaguchi K, Sada M, Terasaka R, Konomi K, Nishikata F, Tanaka M. Completion radical surgery after cholecystectomy for accidentally undiagnosed gallbladder carcinoma. World J Surg 2003; 27: 266-71.

[9] Zhang WJ, Xu GF, Zou XP, Wang WB, Yu JC, Wu GZ, Lu CL. Incidental gallbladder carcinoma diagnosed during or after laparoscopic cholecystectomy. World J Surg 2009; 33: 2651-2656.

[10] Marcial-Rojas RA, Medina R. Unsuspected carcinoma of the gallbladder in acute and chronic cholecystitis. Ann Surg 1961; 153: 289-298.
[11] Kwon AH, Imamura A, Kitade H, Kamiyama Y. Unsuspected gallbladder cancer diagnosed during or after laparoscopic cholecystectomy. J Surg Oncol 2008; 97: 241-245.
[12] Antonakis P, Alexakis N, Mylonaki D, Leandros E, Konstadoulakis MM, Zografos M, Androulakis G. Incidental finding of gallbladder carcinoma detected during or after laparoscopic cholecystectomy. Eur J Surg Oncol 2003; 29: 358-360.
[13] Romano F, Franciosi C, Caprotti R, De Fina S, Porta G, Visintini G, Uggeri F. Laparoscopic cholecystectomy and unsuspected gallbladder cancer. Eur J Surg Oncol 2001; 27: 225-228.
[14] Tantia O, Jain M, Khanna S, Sen B. Incidental carcinoma gallbladder during laparoscopic cholecystectomy for symptomatic gall stone disease. Surg Endosc 2009; 23: 2041-2046
[15] Puhalla H, Wild T, Bareck E, Pokorny H, Ploner M, Soliman T, Stremitzer S, Depisch D, Laengle F, Gruenberger T. Long-term follow-up of surgically treated gallbladder cancer patients. Eur J Surg Oncol 2002; 28: 857-63.
[16] Wakai T, Shirai Y, Hatakeyama K. Radical second resection provides survival benefit for patients with T2 gallbladder carcinoma first discovered after laparoscopic cholecystectomy. World J Surg 2002; 26: 867-71.
[17] Sun CD, Zhang BY, Wu LQ, Lee WJ. Laparoscopic cholecystectomy for treatment of unexpected early-stage gallbladder cancer. J Surg Oncol 2005; 91: 253-257.
[18] Wakai T, Shirai Y, Yokoyama N, Nagakura S, Watanabe H, Hatakeyama K. Early gallbladder carcinoma does not warrant radical resection. Br J Surg 2001; 88: 675-678.
[19] Rodriguez Otero JC, Proske A, Luján M, Poletto L, Pezzotto SM, Fein L, Otero JR, Celoria G. Gallbladder cancer: surgical results after cholecystectomy in 25 patients with lamina propria invasion and 26 patients with muscular layer invasion. J Hepatobiliary Pancreat Surg 2006; 13: 562-566.
[20] Ito H, Matros E, Brooks DC, Osteen RT, Zinner MJ, Swanson RS, Ashley SW, Whang EE. Treatment outcomes associated with surgery for gall bladder cancer: a 20-year experience. J Gastrointest Surg 2004; 8: 183-90.