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ORIGINAL ARTICLE

Unexpected Gallbladder Cancer after Laparoscopic Cholecystectomy for Acute Cholecystitis: A Worrisome Picture

Gennaro Clemente · Gennaro Nuzzo · Agostino Maria De Rose · Ivo Giovannini · Giuseppe La Torre · Francesco Ardito · Felice Giuliante

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Abstract
Objective The objective of this study is to assess the prognosis of unexpected gallbladder cancer diagnosed after laparoscopic cholecystectomy for acute cholecystitis.
Methods Data of all patients treated for unexpected gallbladder cancer after laparoscopic cholecystectomy at a tertiary care surgical center between January 1998 and December 2009 were reviewed. Demographics and clinical and pathological data of patients submitted to adjunctive revisional surgery were analyzed. Survival was calculated by the Kaplan–Meier method, and log-rank test was used to compare the survival curves. The Cox proportional hazard model was used to determine the effect on survival of urgent surgery for acute cholecystitis and of the other common factors such as age, gender, tumor grading, pT stage, nodal involvement, residual disease at re-exploration, and American Joint Committee on Cancer stage.
Results In the considered period, 34 patients with pT1b, pT2, or pT3 unexpected gallbladder cancer underwent a second standard revisional procedure including resection of liver segments 4b and 5, lymphadenectomy, and port-sites excision. Thirteen patients had previously undergone urgent surgery for acute cholecystitis; 21 had undergone a routine operation. The 5-year overall survival was 63.3 %. At multivariate analysis, G3 tumor grading (hazard ratio, 12.261; $p=0.002$), residual disease at re-exploration [hazard ratios (HR)=7.760, $p=0.004$], and urgent surgery for acute cholecystitis (HR=5.436, $p=0.012$) were independent predictors of poor prognosis.
Conclusions The prognosis of unexpected gallbladder cancer is worsened when laparoscopic cholecystectomy is performed for acute cholecystitits. The unfavorable impact of emergency surgery on prognosis might be related to intraoperative gallbladder emptying with bile spillage and cancer dissemination.

Keywords Cholecystitis · Gallbladder cancer · Laparoscopic cholecystectomy

G. Clemente (✉) · G. Nuzzo · A. M. De Rose · I. Giovannini · F. Ardito · F. Giuliante
Department of Surgical Sciences, Hepatobiliary Unit, Policlinico Gemelli, "A. Gemelli" Medical School, Catholic University of the Sacred Heart, Largo Gemelli 8, 00168 Rome, Italy
e-mail: gclemente@rm.unicatt.it

G. La Torre
Department of Public Health and Infectious Diseases, "La Sapienza" University, Rome, Italy

Introduction

Gallbladder cancer (GBC) is the most common tumor of the biliary tract.[1] It is a relatively rare disease in Western countries with an incidence, in the USA, of 1.2/100,000.[2] On the contrary, it is a more common cause of cancer mortality in Chile and north India, with the highest incidence rate of 10.6/100,000 in Delhi.[3] GBC is generally associated with a poor prognosis, mainly due to late diagnosis, with a reported 5-year survival rate of 5 %.[4,5] Nevertheless, GBC, incidentally discovered after cholecystectomy for stones or other indications, is a potentially curable disease with an intermediate or good prognosis in most cases. It is usually found as a surprise, with the histological examination of the resected gallbladder specimen, and an

adjunctive radical resection may be required depending on the depth of parietal invasion. Many factors such as pT-stage, metastatic nodal disease (pN), surgical margin status, residual disease at re-exploration, histological differentiation, lymphatic and perineural invasion, and overall stage have been shown to affect the outcome of GBC.[6–9]

In recent years, the widespread diffusion of laparoscopic surgery has caused an increase in the number of laparoscopic cholecystectomies and therefore an increase in early diagnoses of GBC. Shih et al.[1] reported that at the Johns Hopkins University, between 1995 and 2004, among 107 cases of cancer of the gallbladder, 53 were diagnosed incidentally. In a similar way, GBC was incidentally diagnosed in 47 % of cases during a 10-year period at the Memorial Sloan–Kettering Cancer Centre, as reported by Duffy et al.[2]

Laparoscopic cholecystectomy (LC) is at present the treatment of choice for symptomatic gallstones. Although in the early laparoscopic era, acute cholecystitis was considered as a contraindication to LC,[10] with the increasing of surgical experience, in subsequent studies, LC proved to be an optimal treatment also in acute cholecystitis.[11,12] The true incidence of cancer incidentally found after urgent cholecystectomy for acute cholecystitis is still unknown, and similarly unknown are the effects of acute colecystitits on the prognosis of the unexpected GBC (uGBC). In this study, we provide an assessment of the prognosis of uGBC diagnosed after laparoscopic cholecystectomy for acute cholecystitis.

Material and Methods

Data of all patients treated at our unit between January 1, 1998 and December 31, 2009 for uGBC detected after LC were reviewed. Among these, the clinical records of the patients who underwent revisional surgery were selected. Most of the patients were referred after receiving LC at another hospital. For each patient, demographics, clinical presentation, laboratory data, and preoperative ultrasound findings were taken into account. The criteria that led to the diagnosis of acute cholecystitits and consequent urgent surgery were analyzed in detail. Circumstances and operative details of the first procedure were accurately revised: emergency or elective surgery, handling, emptying of the gallbladder, occurrence of bile spillage, and method of gallbladder extraction (with or without bag) were noted. In addition, pathology findings after the first procedure were taken into account, and the original specimen after LC was re-reviewed to more accurately define the presence of inflammation, the depth of parietal invasion, and the presence of involved lymph nodes. The final staging was based on the criteria of the seventh edition of the American Joint Committee on Cancer (AJCC)/International Union Against Cancer (UICC) tumor–node–metastasis (TNM) manual.[13] Survival was the primary end point and was calculated as the distance in months from LC to the last clinical visit, or death.

Statistical Analysis

Survival rates were determined by the Kaplan–Meier method, and prognostic significance was assessed by univariate analysis (log-rank test) for the following variables: age <60 years, gender, surgery for acute cholecystitis, tumor grading, pT, pN, presence of residual disease at re-exploration, and AJCC/UICC final stage. Hazard ratios (HRs) with 95 % confidence intervals (95 % CI) estimated the relative risk of dying associated with each variable by a Cox proportional hazard model. Finally, a stepwise approach (backward elimination) was used to assess the variables independently associated with death at multivariate analysis. The significance level was set at $p<0.05$ (two-sided). Statistical analysis was performed with SPSS® software for Windows, release 13.0 (SPSS, Chicago, IL, USA).

Results

From January 1, 1998 to December 31, 2009, 44 patients with the diagnosis of uGBC detected after LC were seen at our unit. Among these, the patients with pTis or pT1a cancer, for whom cholecystectomy was considered as the definitive treatment, and the patients with distant metastases at restaging images or at abdominal re-exploration were excluded from the analysis.

Thirthy-four patients underwent a second standard revisional procedure with curative intent at a median distance of 29 days from LC (range, 10–134 days). These were 15 men and 19 women with a mean age of 59.9 years (range, 40–77 years) and form the basis of this report. Thirteen of them had been urgently submitted to LC with a preoperative diagnosis of acute cholecystitis.

All of them had the classic triad of right upper quadrant pain, leukocytosis, and fever. The diagnosis was always confirmed by abdominal ultrasound and, in some cases, also by CT scan. There was no suspicion of cancer at the time of surgery or in reviewing the available preoperative imaging.

Review of surgical records revealed that in the 13 patients who underwent emergency LC, the gallbladder was emptied by a controlled aspiration, whereas in the other 21 cases, the gallbladder was removed without emptying it. An endo-bag was always used for extraction.

Review of pathology material demonstrated muscular layer involvement in 5 patients (pT1b), perimuscular tissue involvement in 19 patients (pT2), and serosal involvement in 10 patients (pT3). Cystic lymph nodes were identified in five patients (14.7 %) and had metastases in four cases (80 %). Hystological type was adenocarcinoma in 28 cases,

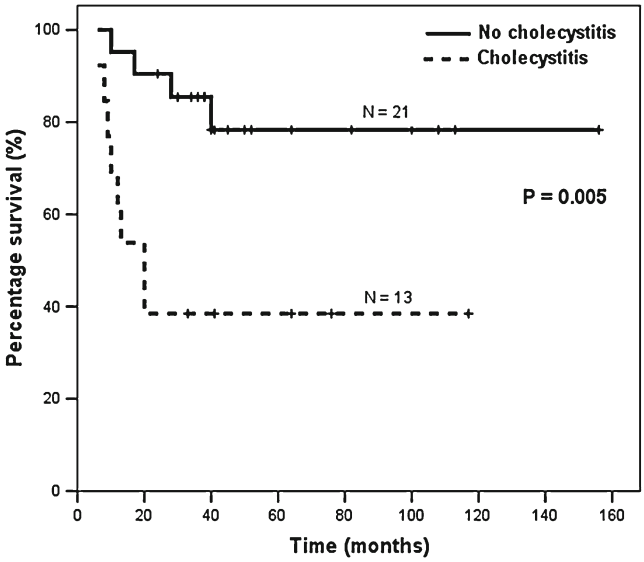

Fig. 1 Survival in patients with and without acute cholecystitis at the time of the first procedure

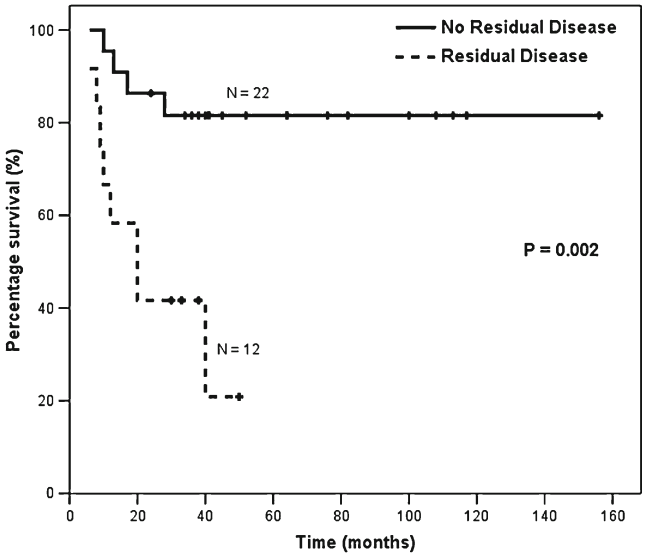

Fig. 3 Survival according to the presence of residual disease at the revision procedure

papillary adenocarcinoma in 3 cases, mucinous adenocarcinoma in 2 cases, and adenosquamous carcinoma in 1 case. Tumor grading was G1 in 8 patients, G2 in 21 patients, and G3 in 5 patients.

Histological examination of the gallbladder in the 13 patients with acute cholecystitis confirmed the presence of signs of inflammation.

Restaging images by CT evaluation showed absence of residual disease or distant metastases in all the 34 patients.

The standard revisional procedure included liver resection of S4b and S5 and lymphadenectomy of the hepatic pedicle, of superior retropancreatic nodes, and nodes along the common hepatic artery; port-site excision was performed using a previously described procedure.[14]

Examination of re-resection specimens showed residual disease in 12 patients (35.2 %). Three patients had residual disease at the gallbladder bed with metastatic regional lymph nodes; one patient had residual disease at the gallbladder bed and at one of the removed port-sites (the umbilical port-site); four patients had residual disease at the gallbladder bed only; three had metastatic regional lymph nodes only; and one patient had residual disease on a long cystic duct stump. In the latter case, an adjunctive resection of the cystic duct, without resection of the common bile

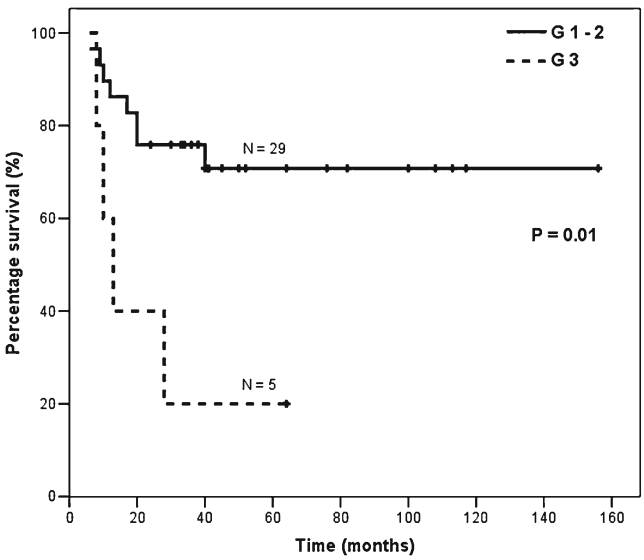

Fig. 2 Survival according to the grading of the tumor

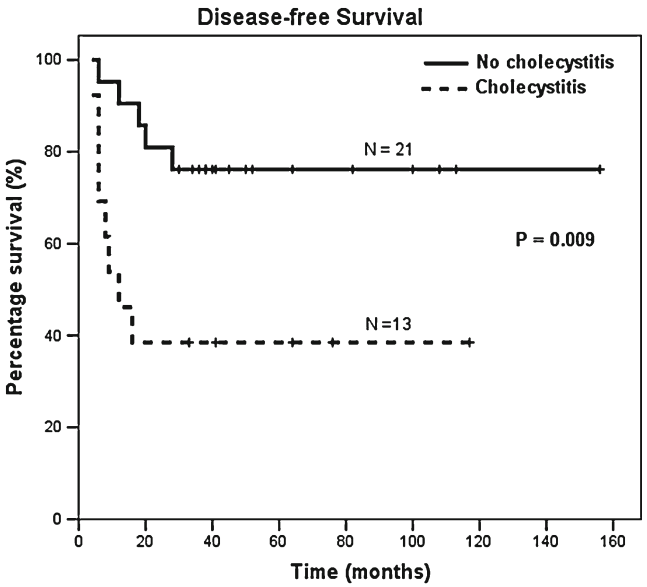

Fig. 4 Disease-free survival in patients with and without acute cholecystitis

duct, was performed to obtain a clean margin at frozen-section examination. A total of 182 lymph nodes were removed (median, 5 per patient), and 17 (9.3 %) of these were metastatic. Paradoxically, no metastatic lymph nodes were found in the four patients in whom metastatic cystic lymph nodes were detected at the first procedure. The final stage, according to the seventh edition of the AJCC/UICC TNM manual[13] was as follows: stage I, 5 patients; stage II, 12 patients; stage IIIA, 6 patients; and stage IIIB, 11 patients.

Overall 5-year survival was 63.3 %. In patients older than 60 years, it was lower than in younger patients (43.6 vs. 82.4 %; p=0.035) without relevant differences associated with sex (male vs. female, 59.3 % vs. 66.3; p=0.672) and was significantly lower after LC for acute cholecystitis than after elective LC (38.5 vs. 78.3 %; p=0.005; Fig. 1). Furthermore, 5-year survival was lower in patients with tumor grading G3 vs. G1–2 (20 vs. 70.8 %; p=0.010; Fig. 2) and decreased from 79.2 to 20 % in patients with tumor stage pT1–2 compared to pT3 (p=0.005). Finally, 5-year survival in patients with or without residual disease at re-exploration was 20.8 and 81.6 %, respectively (p=0.002; Fig. 3) and decreased from 82.4 to 42.4 % in patients with AJCC/UICC stages I–II compared to stages IIIA–IIIB (p=0.032). The disease-free survival was also significantly lower after LC for acute cholecystitis than after elective LC (p=0.009;

Table 1 Demographic and pathological data of the patients in this study

N	Patient	Age	Sex	Urgent/elective	pT	pN	Grading	Residual disease	Final stage	Follow-up (months)	Dead/alive
1	PR	40	M	E	T2	0	2	No	II	156	A
2	BE	67	F	E	T3	0	2	Yes	IIIA	40	D
3	BMA	77	F	U	T2	0	3	No	II	13	D
4	PG	53	M	U	T1b	0	1	No	I	117	A
5	DFFP	43	M	U	T3	0	2	Yes	IIIA	12	D
6	LMAG	54	M	E	T2	1	2	No	IIIB	108	A
7	MO	74	M	E	T1b	0	1	No	I	113	A
8	MA	42	F	E	T2	0	1	No	II	100	A
9	FS	61	M	U	T2	0	2	No	II	10	D
10	PG	70	F	U	T3	1	3	Yes	IIIB	8	D
11	CL	56	M	E	T2	0	2	No	II	82	A
12	DSG	73	F	E	T3	1	3	Yes	IIIB	10	D
13	CA	71	F	U	T1b	0	1	No	I	76	A
14	DAM	48	M	U	T2	1	2	Yes	IIIB	20	D
15	GA	66	F	E	T2	0	3	No	II	64	A
16	LLM	57	F	U	T2	0	1	No	II	64	A
17	FA	62	M	E	T3	0	3	No	IIIA	28	D
18	PL	65	M	U	T3	1	2	Yes	IIIB	20	D
19	MA	56	F	E	T3	0	1	No	IIIA	52	A
20	SS	62	M	E	T2	1	2	Yes	IIIB	50	A
21	PLP	50	F	E	T2	1	1	No	IIIB	45	A
22	DMM	48	F	U	T1b	0	2	No	I	41	A
23	PMR	59	F	E	T2	0	2	No	II	41	A
24	IW	52	M	U	T3	1	2	Yes	IIIB	9	D
25	DCM	61	F	E	T2	0	2	No	II	40	A
26	BC	65	F	E	T2	1	2	No	IIIB	38	A
27	SC	57	F	E	T2	0	2	Yes	II	38	A
28	VV	69	F	U	T2	0	2	Yes	IIIB	6	D
29	TA	58	F	E	T2	1	2	No	IIIB	36	A
30	CV	70	M	E	T1b	0	2	No	I	34	A
31	GP	56	F	U	T3	0	2	Yes	IIIA	33	A
32	DVA	63	F	E	T2	0	2	No	II	17	D
33	CFF	59	M	E	T3	0	2	Yes	IIIA	30	A
34	SM	75	M	E	T2	0	1	No	II	24	A

Fig. 4). Demographic and pathological data of the patients are reported in Table 1.

At multivariate analysis, residual disease at re-exploration (HR, 7.760; $p=0.004$), tumor grading (HR, 12.261; $p=0.002$), and urgent surgery for acute cholecystitis (HR, 5.436; $p=0.012$) were independent predictors of death (Table 2).

Discussion

Unexpected GBC is defined as an unsuspected cancer occasionally found in a patient submitted to cholecystectomy for stones or other indications. It is a relatively rare event that occurs in <1 % of cholecystectomies.[8] The definition should be properly restricted to cases where the diagnosis is truly unexpected: therefore, the patients whose preoperative investigations posed a suspicion of cancer should not be included in this group.

At any rate, uGBC still represents a challenge for the surgeon who is involved in informing the patient of his unexpected finding many days after cholecystectomy and in evaluating the indication for revisional surgery. There is consensus regarding the treatment of patients with a diagnosis of early stage uGBC (pTis and pT1a), for whom cholecystectomy alone represents adequate therapy, and the treatment of patients with major depth invasion (pT2 and pT3) who require a reoperation with resection of liver segments IVB and V, lymphadenectomy, trocar-site excision, and, in some cases, resection of the common bile duct. This radical surgery can significantly increase survival,[1] while there is also consensus in avoiding reoperation when the restaging images show too advanced disease. Diverging opinions still exist regarding stage pT1b cancer, for which some authors consider unnecessary any further treatment,[15] while revisional surgery is considered more adequate by the majority.[8,16,17]

In this study, we provide an assessment of the impact of acute cholecystitis on the prognosis of uGBC detected after LC. We evaluated 34 patients, 13 of whom underwent urgent cholecystectomy for acute cholecystitis. All these patients underwent a second standard revisional surgery. The assessment of prognostic factors by univariate analysis showed that acute cholecystitis, tumor grading, depth of parietal invasion, residual tumor at re-exploration, and overall tumor stage were all significantly related to prognosis, with a nearly significant impact of age ($p=0.035$). At multivariate analysis, only the

Table 2 Clinical and pathological factors influencing prognosis after re-resection for uGBC

Variable	No	Univariate analysis			Multivariate analysis		
		HR	95 % CI	*p* value[a]	HR	95 % CI	*p* value
Age							
≤60 years	17	1					
>60 years	17	3.705	1.00–13.726	0.035	–	–	–
Sex							
Female	19	1					
Male	15	1.274	0.41–3.958	0.672	–	–	–
Acute cholecystitis							
No	21	1					
Yes	13	4.763	1.42–15.929	0.005	5.436	1.442–20.496	0.012
Tumor grading							
G1–2	29	1					
G3	5	4.320	1.28–14.53	0.010	12.261	2.592–58.001	0.002
pT stage							
pT1–2	24	1					
pT3	10	4.547	1.43–14.483	0.005	–	–	–
Lymph-node metastases (pN1)							
No	24	1					
Yes	10	2.070	0.65–6.545	0.203	–	–	–
Residual disease							
No	22	1					
Yes	12	5.611	1.66–18.936	0.002	7.760	1.892–31.830	0.004
AJCC tumor stage							
I–II	17	1					
IIIA–IIIB	17	3.773	1.02–14.009	0.032	–	–	–

[a]Log-rank test

presence of residual tumor at the re-exploration, tumor grading, and acute cholecystitis were independent factors associated with poor prognosis.

Tumor grading and residual disease at re-exploration are well-known factors worsening the prognosis of uGBC. A well-differentiate tumor is a significant predictor of better survival.[18,19] Conversely, the presence of a residual tumor at the re-exploration is a highly negative prognostic factor.[16] In the multicenter experience reported by Pawlik et al.,[8] residual tumor was found at histology in 46.4 % of 115 patients, and the probability of this finding increased with the depth of the parietal invasion of the original uGBC.

Although it is known that uGBC can be diagnosed after cholecystectomy for acute cholecystitis, the implications relating acute cholecystitis to uGBC are far from being defined. In 1997, Liu and coworkers[20] stressed that it would be desirable to identify the patients who are at high risk for GBC before surgery for acute cholecystitis. They reported a percentage of uGBC of 8.75 % (7 out of 80 patients) in patients operated for acute cholecystitis. According to these authors,[20] additional preoperative work-up and open cholecystectomy should be advisable in elderly patients with acute cholecystitis, especially when liver function tests (bilirubin, alkaline phosphatase, and aspartate aminotransferase) are abnormal. Lam and coworkers[21] performed a retrospective analysis of patients with GBC who presented with acute cholecystititis, reporting an incidence of cancer of 2.3 % (63 out of 2,700 patients); in their experience, overall median survival was 5 months, and 5-year survival rate was 20.8 %. Kim and coworkers[22] reported 26 patients with uGBC, 19 of whom were operated on for acute cholecystitis, with an incidence of uGBC in acute cholecystitis of 1.6 %. Median survival for these patients was 32 months without significant differences according to age, presence of acute cholecystitis, or occurrence of intraoperative bile spillage. The authors concluded that the presence of acute cholecystitis does not affect the prognosis of uGBC after LC. However, it should be noted that among the 26 reported patients, only two received a second revisional surgery. Choi and coworkers[18] reported 33 patients with uGBC out of 3,145 LC (1.05 %): The presence of inflammation was a prognostic factor predictor of poor survival.

Our study shows that the presence of acute cholecystitis worsens the prognosis of uGBC after LC. Our results confirm, as reported by Choi et al.,[18] that finding of inflammation in addition to malignancy is a poor predictor of survival. There is no proven explanation for this finding; however, it is likely that emptying of the gallbladder during the operation, with some spillage of bile, may facilitate the peritoneal and systemic dissemination of the tumor. The possibility that laparoscopy in itself might facilitate cancer dissemination remains controversial. Some authors report that laparoscopy increases the risk of tumor spread, determines port-site recurrence, and eventually worsens the prognosis of unexpected GBC,[23] while other reports suggest that a carefully performed LC can be considered as an adequate treatment for early stage GBC.[24] At any rate, in elderly patients with acute cholecystitis, greater attention to clinical and instrumental details inducing the suspicion of GBC is justified. Cholecystectomy should be performed with great care avoiding any bile spillage, and the conversion from laparoscopic to open technique, when necessary, should not be considered as technical failure but as a safer means to handle the situation and to prevent worsening of the patient's prognosis.

References

1. Shih SP, Schulick RD, Cameron JL, Lillemoe KD, Pitt HA, Choti MA, Campbell KA, Yeo CJ, Talamini MA: Gallbladder cancer: the role of laparoscopy and radical resection. Ann Surg 2007; 245: 893–901
2. Duffy A, Capanu M, Abou-Alfa GK, Huitzil D, Jarnagin W, Fong Y, D'Angelica M, DeMatteo RP, Blumgart LH, O'Reilly EM: Gallbladder cancer (GBC): 10-Year experience at Memorial Sloan-Kettering Cancer Centre (MSKCC). J Surg Oncol 2008; 98; 485–489
3. Misra MC, Guleria S: Management of cancer gallbladder found as a surprise on a resected gallbladder specimen. J Surg Oncol 2006; 93: 690–698
4. Piehler JM, Crichlow RW: Primary carcinoma of the gallbladder. Surg Gynecol Obstet 1978; 147: 929–942
5. Cubertafond P, Gainant A, Cucchiaro G: Surgical treatment of 724 carcinomas of the gallbladder:results of the French Surgical Association Survey. Ann Surg 1994; 219: 275–280
6. 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: 639–646.
7. D'Angelica M, Dalal KM, DeMatteo RP, Fong Y, Blumgart LH, Jarnagin WR: Analysis of the extent of resection for adenocarcinoma of the gallbladder. Ann Surg Oncol 2009; 16:806–16.
8. 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.
9. Fong Y, Jarnagin W, Blumgart LH: Gallbladder cancer: comparison of patients presenting initially for definitive operation with those presenting after prior noncurative intervention. Ann Surg 2000; 232: 557–569
10. Cuschieri A, Dubois F, Moujel J, Mouret P, Becker H, Buess G, Trede M, Troidl H: The European experience with laparoscopic cholecystectomy. Am J Surg 1991; 161: 385–387
11. Johansson M, Thune A, Blomqvist A, Nelvin L, Lundell L: Management of the acute cholecystitits in the laparoscopic era: Results of a prospective, randomised, clinical trial. J Gastrointest Surg 2003; 7: 642–645
12. Casillas RA, Yegiyants S, Collins JC: Early laparoscopic cholecystectomy is the preferred management of acute cholecystitis. Arch Surg 2008; 143: 533–537
13. AJCC cancer staging manual; seventh edition. Springer 2010
14. Giuliante F, Ardito F, Vellone M, Clemente G, Nuzzo G: Port-sites excision for gallbladder cancer incidentally found after laparoscopic cholecystectomy. Am J Surg 2006; 191: 114–116

15. De Aretxabala X, Roa I, Hepp J, Maluenda F, Mordojovich G, Leon J, Roa GC: Early gallbladder cancer: is further treatment necessary? J Surg Oncol 2009; 100: 589–593
16. Butte JM, Waugh E, Meneses M, Parada H, De la Fuente HA: Incidental gallbladder cancer: analysis of surgical findings and survival. J Surg Oncol 2010; 102: 620–625
17. Shukla PJ, Barreto G, Kakade A, Shrikhande V: Revision surgery for incidental gallbladder cancer: factors influencing operability and further evidence for pT1b tumours. HPB 2008; 10: 43–47
18. Choi SB, Han HJ, Kim CY, Kim WB, Song TJ, Suh SO, Kim YC, Choi SY: Incidental gallbladder cancer diagnosed after laparoscopic cholecystectomy. World J Surg 2009; 33: 2657–2663
19. D'Angelica M, Dalal KM, DeMatteo RP, Fong Y, Blumgart LH, Jarnagin WR: Analysis of the extent of resection for adenocarcinoma of the gallbladder. Ann Surg Oncol 2009; 16: 806–816
20. Liu KJM, Richter HM, Cho MJ, Jarad J, Nadimpalli V, Donahue PE: Carcinoma involving the gallbladder in elderly patients presenting with acute cholecystitis. Surgery 1997; 122: 748–756
21. Lam CM, Yuen AW, Wai AC, Leung RM, Lee AY, Ng KK, Fan ST: Gallbladder cancer presenting with acute cholecystitis: a population-based study. Surg Endosc 2005; 19: 697–701
22. Kim JH, Kim WH, Kim JH, Yoo BM, Kim MW: Unsuspected gallbladder cancer diagnosed after laparoscopic cholecystectomy: focus on acute cholecystitis. World J Surg 2010; 34: 114–120
23. Shirai Y, Ohtani T, Hatakeyama K: Tumor dissemination during laparoscopic cholecystectomy for gallbladder carcinoma. Surg Endosc 1997; 11: 1224–1225
24. Cho JY, Han HS, Yoon YS, Ahn KS, Kim YH, Lee KH: Laparoscopic approach for suspected early-stage gallbladder carcinoma. Arch Surg 2010; 145: 128–133