

RESEARCH COMMUNICATION

Gallbladder Carcinoma: Analysis of Prognostic Factors in 132 Cases

Rui-Tao Wang, Xin-Sen Xu, Jun Liu, Chang Liu*

Abstract

Objective: To evaluate the prognostic factors of gallbladder carcinoma. **Methods:** Presentation, operative data, complications, and survival outcome were examined for 132 gallbladder carcinoma patients who underwent gallbladder surgery in our unit during 2002-2007, and follow-up results were obtained from every patient for univariate and multivariate survival analysis. **Results:** The univariate analysis showed that gallbladder lesion history, tumor cell differentiation, Nevin staging, preoperative lymph node metastasis and the surgical approach significantly correlated with the prognosis of the patients ($p < 0.05$). The results of the multivariate analysis (Cox regression) showed that gallbladder lesion history, Nevin staging and the surgical approach were independent predictors with relative risks of 6.9, 4.4, 2.8, respectively ($p = 0.002, 0.003, 0.008$). **Conclusion:** Gallbladder lesion history, Nevin staging and the surgical approach are independent prognostic factors for gallbladder carcinoma, a rapidly fatal disease. Therefore, early diagnosis, anti-infective therapy and radical surgery are greatly needed to improve the prognosis of gallbladder carcinoma.

Keywords: Gallbladder carcinoma - multivariate analysis - prognosis

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Introduction

The gallbladder carcinoma is a relatively rare disease, despite being the most leading morbidity in tumors of the biliary tract and the fifth most frequent of the gastrointestinal tract, with non-specific clinical presentation and poor prognosis (Fong et al., 2000). Because of the diagnostic difficulties and high degree of malignancy, the majority of patients have advanced disease at presentation (Ishak et al., 2011). When the tumor is confined to the gallbladder wall, the 5-year survival rate ranges from 10% to 30% (Yee et al., 2002). However, when the tumor invades the gallbladder serosa, local lymph nodes, or adjacent liver, the 5-year survival rate decreases to 5% (Yee et al., 2002; Czito et al., 2005). Thus how to make the early diagnosis for radical surgery, thereby to improve the overall survival and life quality of the gallbladder cancer patients is in urgent need. By making the retrospective analysis of the 132 cases of gallbladder cancer patients, the aim of this article is to explore the possible risk factors of the prognosis, so as to improve the survival rate of gallbladder carcinoma.

Materials and Methods

Baseline characteristics of the patients

Between 2002 and 2007, 132 consecutive patients with histological proven gallbladder cancer were treated at the First Affiliated Hospital, School of Medicine, Xi'an

Jiaotong University, China. There were 87 females and 45 males with the mean age of 59 (range 37-86) years. Varying degrees of weight loss were found in 72 patients 2 months before hospitalized, accounting for 55% of the total patients. History of gallbladder lesion such as chronic cholecystitis, gallstones and other biliary tract diseases was positive in 69 patients (52%). Presenting symptoms such as upper abdominal pain and jaundice occurred in 111 of the patients. With regards to the location of the tumor, 27 were developed from the bottom of the gallbladder, 54 were from the body, 37 were from both the bottom and the body, 14 were from the neck and 7 were from other parts. As classified by differentiation, 70 were poorly differentiated, 30 were moderately differentiated and 32 were well differentiated; As classified by the histological type, 119 were adenocarcinoma, 9 were adenosquamous and 4 were squamous; As classified by the pathological form, 90 were infiltrating type, 40 were mass type and 2 were of the both; As classified by levels of tumor infiltration, 6 were confined to mucosa, 11 were confined to muscle, 59 infiltrated the whole gallbladder wall, and 56 reached perimuscular connective tissue or organ. As classified by the Nevin stage, 6 were of stage I, 32 were of stage II, 43 were of stage III, 21 were of stage IV and 30 were of stage V. In all of the patients, 60 were detected of lymph node metastasis during surgery, while no clues were found in the other 72. The surgical procedures include simple cholecystectomy (34 cases), radical cholecystectomy (49 cases), palliative resection

Department of hepatobiliary surgery, the First Affiliated Hospital, School of Medicine, Xi'an Jiaotong University, Xi'an, Shaanxi Province, China *For correspondence: eyrechang@126.com

Table 1. Univariate Analysis of the Prognosis

Factors	No.	Mean survival time (month)	P	Factors	No.	Mean survival time (month)	P
Gender			0.63	Age			0.74
male	45	14.4		<65yrs	68	17.1	
female	87	16.9		>65yrs	64	14.9	
Weight changes			0.71	Gallbladder histories			0.016
loss	72	15.7		yes	69	11.9	
none	60	16.5		no	63	20.6	
Blood groups			0.22	Presenting symptoms			0.81
A	33	18.9		Abdominal pain	89	17.6	
B	52	13.7		jaundice	22	10.2	
O	32	15.5		others	21	15.7	
AB	15	19.1					
Tumor location of gallbladder			0.54	Nevin staging			0
bottom	27	23.9		Stage I	6	43.7	
body	54	15.5		Stage II	32	27	
body and bottom	30	12.6		Stage III	43	15.1	
neci	14	14.9		Stage IV	21	7.9	
others	7	7.1		Stage V	30	5.8	
Histological type			0.76	Pathological form mass type			~
adenocarcinoma squamous	119	16.4		infiltrating type,	40	23.5	
adenosquamous	4	8.3		mixed type	90	13	
	9	14.7			2	3	
Cell differentiation			0.016	Tumor infiltration mucosa			0.18
well	32	34.2		muscle	6	43.2	
moderately	30	16.9		whole wall	11	28.9	
poorly	70	7.4		perimuscular	59	16.5	
					56	10.1	
Lymph node metastasis			0.003	Surgical resection			0
yes	60	7.8		Simple	34	11.6	
no	72	22.9		Radical	49	28.6	
				palliative	20	7.2	
				others*	29	6.2	

Table 2. Multivariate Analysis of the Prognosis

factors	Regression coefficient	SE	wald	p	Relative risk
Gallbladder lesion histories	0.19	0.053	12.5	0.002	6.9
Nevin staging	0.003	0.001	11.8	0.003	4.4
Tumor cell differentiation	-0.68	1	0.42	0.51	0.51
Lymph node metastasis	2.3	0.99	5.4	0.06	1
Surgical procedure	0.25	0.83	0.087	0.008	2.8

(20 cases) and others (29 cases, such as exploratory laparotomy, U-tube drainage through the liver, T-tube drainage and tumor biopsy).

Methods

Thirteen statistical indices were selected from the baseline characteristics and surgery-related information of the gallbladder cancer patients. Analysis were made according to the indices as follows: gender, age, weight change, blood groups, presenting symptoms, gallbladder lesion histories, location of tumors, Nevin staging, histological type, pathological form, differentiation of the tumor cells, lymph node metastasis, surgical procedures and so on.

Statistics

Surgical procedures were reviewed and their impact on survival noted. Data were expressed as median and range and were analyzed by using correlation coefficient, Student's t-test and Chi-square test when appropriate with

the help of SPSS software (Version 13.0) by Statistical Department of Medical College of Xi'an Jiaotong University. The survival of the patients discharged from the hospital was determined using Kaplan Meier analysis. $p < 0.05$ was considered significant.

Results

Follow-up outcome

The follow-up of the 132 gallbladder carcinoma cases was implemented until April 2011, when 123 cases died (93%) while 9 cases (7%) survived. 14 cases died within a follow-up of 1-3 month after surgery, 26 died within 4-6 months, 43 died within 7-12 months, 35 died within 13-36 months, 10 died within 37-60 months, and 4 died beyond a follow-up period of 60 months. The 1-, 3-, 5-year survival rate of the gallbladder cancer is 37.1%, 10.6%, 3.0%, respectively. There were 37 cases suffered a recurrence of the gallbladder cancer. Metastasis occurred in 52 cases, in which 24 metastasized to liver, 4 to lungs, 6 to ovaries and 18 to multiple abdominal organs, with the other 43 cases without metastatic details. Recurrence developed in 47 patients after a period of 1-3 months, in 17 patients after 7-24 months, and there was no details about the other 43 patients.

Univariate analysis of the prognosis

Kaplan-Meier analysis and Log-rank test were made according to the indices mentioned above and the result

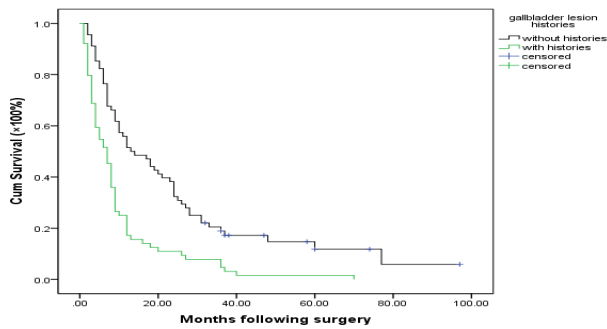


Figure 1. Survival Curves for Patients with Gallbladder Lesion Histories and Those with Negative Histories

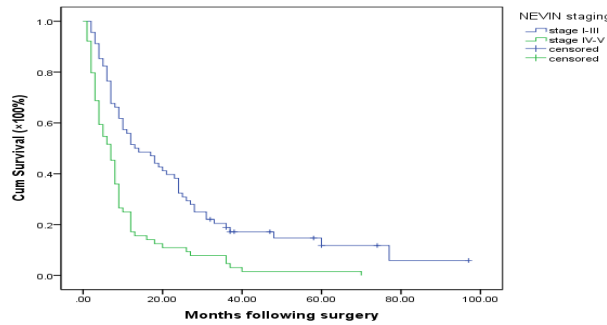


Figure 2. Survival Curves for Patients in Different Nevin Stages

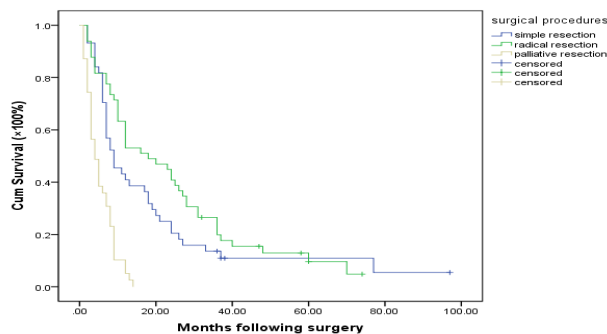


Figure 3. Survival Curves for Patients Underwent Different Surgical Procedures

showed that indices such as gender, age, weight change, blood groups, presenting symptoms, location of tumors, histological type, pathological form had no significant effect on the survival, while factors most influential on survival by univariate analysis included gallbladder lesion histories, Nevin staging, differentiation of the tumor cells, lymph node metastasis and surgical procedures ($p < 0.05$). Log-rank test was made for patients from Nevin stage I to stage IV, and showed that the 1-, 3-, 5-year survival rate of the radical surgery group significantly outweighed the simple excision group, palliative surgery group, and the other group ($p < 0.05$) (Table 1).

Multivariate analysis of the prognosis

When multivariate analysis of Cox proportional hazards is performed using gallbladder lesion histories, Nevin staging, differentiation of the tumor cells, lymph node metastasis and surgical procedures, results showed that gallbladder lesion histories, Nevin staging, and surgical procedures were independent predictors of outcome, and relative risk were 6.9, 4.4, 2.8, respectively ($p = 0.002, 0.003, 0.008$) (Table 2; Figure 1, 2, 3).

Discussion

DeStoll (1778) first described carcinoma of the gallbladder on the bases of two autopsies in 1777. Despite advances in hepatobiliary imaging techniques (Frezza et al., 1997; Ouchi et al., 1999), the preoperative diagnosis of gallbladder carcinoma remains a daunting task and the long-term survival remains dismal. This in part is related to the disease's non-specific presentation and its similarity to benign biliary tract disorders. Demographically, gallbladder carcinoma is more common in women and its frequency increases with age (Donohue et al., 1998). The etiology is unknown, but risk factors include cholelithiasis (found in 70–90% of cases), various carcinogens, ethnic background, benign tumors. Much controversy exists about the optimum surgical procedure for gallbladder cancer. Recommendations have ranged from simple cholecystectomy to ultraaggressive resections consisting of combined major liver resection and pancreaticoduodenectomy (Nimura et al., 1991). The major problem is that operations required for complete resection of cancer are associated with high morbidity and mortality (Ouchi et al., 1987; Ogura et al., 1991).

As a result of the geographical differences exist in morbidity, few reports from western countries pointed out the prognostic factors of gallbladder carcinoma. By analysis of limited cases of gallbladder carcinoma, previous studies reported that pathological characteristics and surgical procedures were significantly correlated with the prognosis of gallbladder cancer. In our study, the clinical data of 132 cases of gallbladder cancer patients who were confirmed by surgery and pathology in our hospital from 2002 to 2007 were collected. Cases of incomplete details and patients with the history of radiotherapy and chemotherapy that might lead to biased estimates were excluded from our study. Follow-up of each selected case continued for at least three years to analyze their post-discharge survival. Results of detailed analysis showed that gallbladder lesion histories, Nevin staging and surgical procedure were important prognostic indicators of gallbladder carcinoma, which further confirmed the significance of early diagnosis and treatment.

In previously reported series of patients with gallbladder cancer, the resection rates range from 17% to 47%, and the 5-year survival rates after complete resection vary from 18% to 58% (Puhalla et al., 2002; Ito et al., 2004). More and more people advocated extended radical cholecystectomy in patients of medium and advanced stage in order to improve the long-term survival. Todoroki et al (1999) reported that on the basis of simple cholecystectomy, complicated with surgical procedures including hepatic lobe resection, semi-hepatectomy, pancreaticoduodenectomies, partial gastrectomy or colectomy, the 5-year postoperative overall survival rate was around 25%-33%. Similarly, Sasaki et al (2006) reported that the 5-year overall survival rate of gallbladder cancer patients of Nevin IV stage who underwent expanded radical surgery was around 42.9%. Therefore, Schauer et al summarized that radical resection is a good prognostic factor for gallbladder cancer and even patients

of medium or advanced stage would get a relatively good survival after radical resection (Schauer et al., 2001). Meanwhile, Ríos Zambudio et al (2001) held the opinion that the Nevin staging is the most important predictor and radical resection would play a relative significant role only in gallbladder cancer patients of Nevin stage II and III. Recently, Jiang et al (2001) reported that the Nevin staging and surgical procedures significantly correlated with the prognosis of gallbladder cancer. He suggested that simple cholecystectomy should be performed for patients of the Nevin stage I while radical cholecystectomy would achieve better results for later stages. Although expanded radical cholecystectomy would not be able to prolong the survival of Nevin V, it might to some extent benefit the patients of stage IV. According to the results of our study, when the gallbladder cancer patients of the Nevin stage II and III underwent radical cholecystectomy or the expanded radical cholecystectomy, their overall survival time were significantly longer than the patients who underwent other therapies from the same stage ($p < 0.05$). The Cox analysis also suggested that different surgical approach is one of the important factors that affect the prognosis of survival time. Therefore, for patients of Nevin stage II and III, radical cholecystectomy or the expanded radical cholecystectomy is recommended if there is no surgical contraindication.

Currently, many scholars believe that infection is one of the pathogenesis that results in cancer. In our study, we explored the possibility that preoperative gallbladder lesion histories such as the cholecystitis or gallstones might have some impact on the prognosis of the gallbladder cancer patients. The following mechanisms were supposed as the way that bacterial infection caused tumor (Pandey et al., 2010): 1. The inhibition of host immune responses lead to the rapid development of tumor; 2. The bacteria promote the host to produce carcinogen; 3. Some bacteria become the host of tumorigenic virus, inside which the virus proliferate and promote tumor formation together with the bacteria; 4. Some bacteria can produce estrogen-like substances, thereby contributing to tumorigenesis. With regards to gallbladder cancer, the chronic infection and inflammation might also be an important contributing factor in tumorigenesis. It was also demonstrated by our study that gallbladder lesion histories was an independent predictor of postoperative survival. Thus, a targeted anti-infective treatment for gallbladder carcinoma patients will help to improve the prognosis.

The main limitation is that only a small number of patients were included in our study because this study was undertaken at a single institution. In addition, the strict restrictions of comprehensive information and follow-up period limited the number of clinical cases. Thus a larger scale prospective study is necessary. At present, it has reached a consensus about gallbladder cancer that early diagnosis and timely radical surgery are directly correlated with the prognosis of the patients. However, effective diagnostic indices for early diagnosis and radical surgery of gallbladder cancer are still under exploration to improve the survival rate and postoperative life quality.

In conclusion, results of our study showed that gallbladder lesion histories, Nevin staging, and surgical procedures were independent predictors of survival.

Therefore, early diagnosis by varieties of medical instrument, anti-infective therapy and radical surgery are in great need to completely remove the tumor tissue in time to improve the prognosis of gallbladder carcinoma.

References

- Czito BG, Hurwitz HI, Clough RW, et al (2005). Adjuvant external-beam radiotherapy with concurrent chemotherapy after resection of primary gallbladder carcinoma: a 23-year experience. *Int J Radiat Oncol Biol Phys*, **62**, 1030-4.
- DeStoll M. (1778) *Rationis Mendendi*, in *Nosocomio Practico vendobonensi*. Part 1 Lugduni Batavarum, Haak et Socios et A et J Honkoop.
- Donohue JH, Andrew KS, Herman RM (1998). The national cancer database report on carcinoma of the gallbladder, 1989-1995. *Cancer*, **83**, 2618-28.
- Fong YM, Jarnagin W, Blumgart LH (2000). Gallbladder cancer: comparison of patients presenting initially for definitive operation with those presenting after prior noncurative intervention. *Ann Surg*, **232**, 557-69.
- Frezza EE, Mezgebe H (1997). Gallbladder carcinoma: a 28 year experience. *Int Surg*, **82**, 295-300.
- Ishak G, Ribeiro FS, Costa DS, et al (2011). Gallbladder cancer: 10 years of experience at an Amazon reference hospital. *Rev Col Bras Cir*, **38**, 100-4.
- Ito H, Matros E, Brooks DC, et al (2004). Treatment outcomes associated with surgery for gallbladder cancer: A 20-year experience. *J Gastrointest Surg*, **8**, 183-90.
- Jiang JW, Dong SX, Zhou ZX, et al (2008). Surgical management for carcinoma of the gallbladder: a single-institution experience in 25 years. *Chin Med J*, **121**, 1900-5.
- Nimura Y, Hayakawa N, Kamiya J, et al (1991). Hepatopancreatoduodenectomy for advanced carcinoma of the biliary tract. *Hepatogastroenterology*, **38**, 170-5.
- Ogura Y, Mizumoto R, Isaji S, et al (1991). Radical operations for carcinoma of the gallbladder: present status in Japan. *World J Surg*, **15**, 337-43.
- Ouchi K, Owada Y, Matsuno S, Sato T (1987). Prognostic factors in the surgical treatment of gallbladder carcinoma. *Surgery*, **101**, 731-7.
- Ouchi K, Sugawara T, Ono H, et al (1999). Diagnostic capability and rational resectional surgery for early gallbladder cancer. *Hepatogastroenterology*, **46**, 1557-60.
- Pandey M, Mishra RR, Dixit R, et al (2010). *Helicobacter bilis* in human gallbladder cancer: results of a case-control study and a meta-analysis. *Asian Pac J Cancer Prev*, **11**, 343-7.
- Puhalla H, Wild T, Bareck E, et al (2002). Long-term follow-up of surgically treated gallbladder cancer patients. *Eur J Surg Oncol*, **28**, 857-63.
- Ríos Zambudio A, Sánchez Bueno F, García Marcilla JA, et al (2001). Prognostic factors in gallbladder cancer. *Gastroenterol Hepatol*, **24**, 281-6.
- Sasaki R, Itabashi H, Fujita T, et al (2006). Significance of extensive surgery including resection of the pancreas head for the treatment of gallbladder cancer from the perspective of mode of lymph node involvement and surgical outcome. *World Surg*, **30**, 36-42.
- Schauer RJ, Meyer G, Baretton G, et al (2001). Prognostic factors and long-term results after surgery for gallbladder carcinoma: a retrospective study of 127 patients. *Langenbecks Arch Surg*, **86**, 110-7.
- Todoroki T, Kawamoto T, Takahashi H, et al (1999). Treatment of gallbladder cancer by radical resection. *Br J Surg*, **86**, 622-7.
- Yee K, Sheppard BC, Domreis J, et al (2002). Cancers of the gallbladder and biliary ducts. *Oncology*, **16**, 939-49.