

Original Article

Clinical epidemiological survey of gallbladder carcinoma in northwestern China, 2009–2013: 2379 cases in 17 centers

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Abstract

Objective: To analyze the clinical epidemiological characteristics of patients with gallbladder carcinoma recruited from 17 hospitals in five northwestern provinces of China (Shaanxi Province, Gansu Province, Qinghai Province, Ningxia Hui Autonomous Region, and Xinjiang Uygur Autonomous Region) from 2009 to 2013, and to summarize the clinical diagnosis and treatment data of gallbladder carcinoma.

Methods: Clinical information of 2379 patients with gallbladder carcinoma from 17 hospitals in five northwestern provinces of China was retrospectively collected and analyzed using the “Questionnaire for Gallbladder Carcinoma Patients in Northwestern Area of China.” All information was verified with EpiData software and analyzed with SPSS 13.0 software.

Results: (1) Gallbladder carcinoma accounted for 2.7% (2379/86,609) of all biliary tract diseases during the study period, which was significantly higher than that from 1986 to 1998 ($P < 0.001$). (2) Gallbladder carcinoma was more prone to occur in elderly women. The male:female incidence ratio was 1.0:2.1, the average age of onset of disease was 63.7 ± 11.3 years, and the incidence

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was higher in farmers than in other occupational groups. (3) A total of 57.2% (1360/2379) of patients with gallbladder carcinoma also had gallstones. (4) Abdominal pain (1796/2379, 75.5%) and jaundice (727/2379, 30.6%) were the most common clinical manifestations, 81.2% (1527/1881) were positive in those receiving B ultrasound examinations and 90.7% (1567/1727) were positive in those undergoing computed tomography, and 64.5% (1124/1742) of patients with gallbladder carcinoma were positive for carbohydrate antigen (CA) 19-9. (5) The pathological type of gallbladder carcinoma was mainly moderately and poorly differentiated adenocarcinoma with a high degree of malignancy. At admission, 55.1% (1091/1981) of patients had stage IV cancer among patients with TNM staging information; 55.9% (1331/2379) had lymphatic metastasis, 29.7% (706/2379) had bile duct metastasis, and 53.1% (1263/2379) had liver metastasis. (6) A total of 283 patients (283/2379, 11.9%) had incidentally detected gallbladder carcinoma. (7) The rate of radical surgical resection was 30.4% (723/2379).

Conclusion: The proportion of gallbladder carcinoma in biliary tract diseases in the northwestern area of China was significantly higher from 2009 to 2013 than from 1986 to 1998. Gallbladder carcinoma was common in older women and mainly diagnosed at an advanced stage. Compared with other surveys in different regions, the rate of metastasis in this survey was high, leading to a low resection rate. Populations at high risk should undergo B-ultrasound examinations at regular follow-up intervals to increase the rate of early diagnosis of gallbladder carcinoma.

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Keywords: Gallbladder carcinoma; Epidemiology; Incidence; Risk factor; Northwestern China

Introduction

Gallbladder carcinoma is the most common malignant tumor in the biliary tract and the sixth most common gastrointestinal cancer.¹ Gallbladder carcinoma has a low early diagnosis rate, a low radical surgical resection rate, and an extremely poor prognosis. In one study, the average survival period of patients with advanced gallbladder carcinoma was 6 months, and the 5-year survival rate was only 5%.² The worldwide incidence rate of gallbladder carcinoma is low (<2/100,000), but shows obvious regional and ethnic differences.³ The prevalence is higher in Chile, Poland, northern India, and South Korea, and is the highest in Chile (female incidence rate of 27.3/100,000).² In 2009, the morbidity rate of gallbladder cancer and cholangiocarcinoma in Chinese cancer registration areas was 4.31/100,000, and the population-standardized incidence rate was 1.93/100,000,⁴ which was equal to the worldwide level. However, an epidemiological survey of gallbladder carcinoma in China from 1986 to 1998 showed that gallbladder carcinoma was more prevalent in the northwestern area of China.⁵ In the present survey, we analyzed the clinical epidemiological characteristics of patients with gallbladder carcinoma from five northwestern provinces of China and summarized the diagnosis and treatment of gallbladder carcinoma.

Methods

Data sources

We retrospectively collected clinical information of 2379 patients with gallbladder carcinoma recruited from

17 tertiary hospitals in 5 northwestern provinces of China from January 2009 to December 2013. This study was approved by the medical ethics committee of each hospital. The 17 involved hospitals are the largest local hospitals, allowing for accurate reflection of the clinical features and epidemiological characteristics of gallbladder carcinoma in the northwestern area of China. Meanwhile, the total number of patients with biliary tract diseases was collected from the information department of each hospital according to the biliary tract disease codes (K80, K81, K82, and K83) of the International Classification of Diseases, 10th Revision (ICD-10). The total number of patients with abdominal surgical diseases was collected from the Patient Discharge Form.

Diagnostic criteria

Gallbladder carcinoma was diagnosed according to the definition formulated by the World Health Organization in 2010.⁶ The diagnosis included type I diagnosis (histopathological findings) and type II diagnosis (clinical and imaging examination). Two senior pathologists from the Department of Pathology of the First Affiliated Hospital of Xi'an Jiaotong University examined all pathological sections and made the type I diagnosis. The TNM stage was determined based on the 7th edition of the 2010 diagnostic criteria of the American Joint Committee on Cancer.⁷

Survey

All involved patients were surveyed with the "Questionnaire for Gallbladder Carcinoma Patients in Northwestern Area of China," which was filled out by

local clinicians. The questionnaire has four parts: (1) general information and living behavior of patients, including their gender, age, occupation, hobbies, and menstrual and reproductive history; (2) medical and family history, including gallstones, cholecystitis, malignant tumors, and other gastrointestinal diseases; (3) clinical features and diagnostic methods, including disease duration, main symptoms and signs, and imaging and biochemical tests performed; and (4) pathological characteristics and treatment data, including tumor location, size, metastasis, histological type, and surgical methods.

Statistical analysis

All information was input and verified using Epi-Data software, and data processing and analysis were performed using SPSS 13.0 software (SPSS, Inc., Chicago, IL, USA). Measurement data were expressed as the mean \pm standard deviation. Count data were expressed as percentages and differences between the groups were compared using the χ^2 test. A *P* value of <0.05 was defined as statistically significant.

Results

In total, 2478 patients with gallbladder carcinoma were involved in this study, and 99 of them were excluded owing to incomplete data. Finally, 2379 patients were analyzed. Among the analyzed patients, 1274 (53.6%) received a type I diagnosis (histopathological findings) and 1105 (46.4%) received a type II diagnosis (clinical and imaging examination). Onset and diagnosis occurred in the year 2009 in 414 patients (17.4%), 2010 in 387 patients (16.3%), 2011 in 481 patients (20.2%), 2012 in 503 patients (21.1%), and 2013 in 594 patients (25.0%).

The proportion of gallbladder carcinoma in all biliary tract diseases and abdominal surgical diseases in northwestern area of China

In this survey, we detected the proportion of gallbladder carcinoma in all biliary tract diseases and abdominal surgical diseases during the same period to indirectly estimate the incidence of gallbladder carcinoma in the northwestern area of China. The results showed that the proportion of patients with gallbladder carcinoma in patients with biliary tract disease was 1.6%–6.8% (average, 2.7%; 2379/86,609) in the five provinces from 2009 to 2013, while this proportion was 1.0%–3.8% (average, 2.0%; 577/28,447) from 1986 to 1998 (*P* < 0.001). The proportion was higher in Xinjiang Uygur Autonomous Region, Qinghai Province, and Gansu Province, but lower in Shaanxi Province and Ningxia Hui Autonomous Region. The proportion of patients with gallbladder carcinoma in patients who underwent abdominal surgery during the same period was 0.4%–0.9% (average, 0.7%; 2379/334,565) (Table 1).

General characteristics of patients with gallbladder carcinoma in northwestern area of China

The 2379 patients analyzed in this study included 770 men and 1609 women; the male:female ratio was 1.0:2.1. The patients' age ranged from 20 to 99 years, with a mean of 63.7 ± 11.3 years. Those aged ≤ 55 years accounted for 18.7% (144/770) of all male patients, those aged 56–65 years accounted for 26.1% (201/770), and those aged 66–75 years accounted for 35.7% (275/770). Those aged ≤ 55 years accounted for 25.9% (417/1609) of all female patients, those aged 56–65 years accounted for 30.0% (483/1609), and those aged 66–75 years accounted for 31.0% (499/

Table 1
Changes in the proportion of gallbladder carcinoma in biliary tract diseases and abdominal surgical diseases in northwest China.

Region	Proportion of gallbladder carcinoma in biliary tract diseases during the same period			Proportion of gallbladder carcinoma in abdominal surgical diseases during the same period		
	Zou et al. ⁵ % (n)	In our group, % (n)	<i>P</i>	Zou et al. ⁵ % (n)	In our group, % (n)	<i>P</i>
Shaanxi Province	3.8 (249/6553)	2.5 (1627/64,139)	<0.001	1.1 (249/22,636)	0.9 (1627/187,856)	<0.001
Gansu Province	1.3 (84/6462)	3.4 (205/6007)	<0.001	0.3 (84/28,000)	0.4 (205/50,510)	0.019
Ningxia Hui Autonomous Region	2.7 (126/4599)	1.9 (172/9066)	0.001	0.8 (126/16,478)	0.5 (172/36,873)	<0.001
Qinghai Province	1.0 (60/6000)	1.6 (40/2484)	0.018	0.2 (60/30,000)	0.4 (40/9414)	<0.001
Xinjiang Uygur Autonomous Region	1.2 (58/4833)	6.8 (335/4913)	<0.001	—	0.7 (335/49,912)	—
Total	2.0 (577/28,447)	2.7 (2379/86,609)	<0.001	—	0.7 (2379/334,565)	—

—: No data.

1609). In terms of the patients' menstrual and reproductive history, the average age at menarche was 14.6 ± 1.4 years, the cumulative menstruation time was 34.1 ± 3.9 years, and the average number of pregnancies was 3.1 ± 1.5 . In terms of occupation, 1336 patients were farmers (56.2%), 272 were workers (11.4%), 123 were officials (5.2%), and 648 had other occupations (27.2%).

Gallbladder carcinoma accompanied by biliary tract disease

Among all 2379 patients analyzed, 1360 (57.2%) had gallstones, 34 (1.4%) had biliary tract stones, and 106 (4.5%) had both gallstones and biliary tract stones. A total of 803 patients (33.8%) had a history of cholecystitis, including 55 (2.3%) with acalculous cholecystitis and 748 (31.4%) with cholelithiasis. A total of 67 patients (2.8%) had gallbladder polyps.

Clinical features, imaging techniques, and laboratory tests in patients with gallbladder carcinoma

Clinical manifestations included abdominal pain in 1796 patients (75.5%), jaundice in 727 (30.6%), anorexia in 474 (19.9%), abdominal distension in 461 (19.4%), emaciation in 238 (10.0%), fever in 113 (4.7%), an abdominal mass in 88 (3.7%), and no symptoms in 172 (7.2%). Imaging examinations (number of positive cases/total number of cases) included B-ultrasound (1527/1881, 81.2%), computed tomography (CT; 1567/1727, 90.7%), and magnetic resonance imaging (550/677, 81.2%). Tumor markers (number of abnormal cases/total number of cases) included carbohydrate antigen (CA) 19-9 (1124/1742, 64.5%), CA125 (742/1486, 49.9%), and carcinoembryonic antigen (CEA) (761/1705, 44.6%).

Clinicopathological information of patients with gallbladder carcinoma

Among the 2379 analyzed patients, 1274 (53.6%) were pathologically diagnosed. A total of 1090 patients had adenocarcinoma (1090/1274, 85.6%), including 155 with highly differentiated adenocarcinoma (155/1090, 14.2%), 452 with moderately differentiated adenocarcinoma (452/1090, 41.5%), 405 with poorly differentiated adenocarcinoma (405/1090, 37.2%) and 78 without information of differentiation (78/1090, 7.2%); 61 with adenosquamous carcinoma (61/1274, 4.8%), 38 with mucinous adenocarcinoma (38/1274, 3.0%), 21 with malignant adenoma (21/1274, 1.6%), 21 with squamous

cell carcinoma (21/1274, 1.6%), 20 with papillary adenocarcinoma (20/1274, 1.6%), and 23 with other types of cancer (23/1274, 1.8%). Lymph node metastasis was classified as N0 in 1048 patients (44.1%), N1 in 633 (26.6%) and N2 in 698 (29.3%). Bile duct and liver metastasis were identified in 29.7% (706/2379) and 53.1% (1263/2379) of patients, respectively. Among the 1981 patients with TNM staging information, 72 had stage I cancer (3.6%), 144 had stage II (7.3%), 341 had stage IIIA (17.2%), 333 had stage IIIB (16.8%), 253 had stage IVA (12.8%), and 838 had stage IVB (42.3%).

Among all 2379 patients with gallbladder carcinoma, 283 had incidentally detected gallbladder carcinoma (11.9%), including 101 whose cancer was detected during surgery (101/283, 35.7%) and 182 whose cancer was detected after surgery (182/283, 64.3%).

Treatment of gallbladder carcinoma

Among all 2379 patients with gallbladder carcinoma, 1486 (62.5%) received surgical treatment. The surgical treatment included radical resection in 641 patients (641/1486, 43.1%), extended radical resection in 82 (82/1486, 5.5%), palliative surgery in 499 (499/1486, 33.6%), percutaneous transhepatic cholangiodrainage in 195 (195/1486, 13.1%), and endoscopic retrograde cholangiopancreatography stenting in 69 (69/1486, 4.6%). The rate of radical surgical resection was 30.4% (723/2379). A total of 74 patients underwent postoperative chemotherapy (74/1486, 5.0%), mainly the oxaliplatin, fluorouracil and leucovorin (FOL/FOX) regimen; 1 patient underwent preoperative neoadjuvant chemotherapy, and 4 underwent postoperative radiotherapy.

Comparison of the present survey with other surveys in different regions

The ratio of gender, average age, and pathological type in this survey were consistent with those in other studies in different regions. However, the rate of metastasis in this survey was high, leading to a low resection rate (Table 2).

Discussion

Changes in the proportion of gallbladder carcinoma in biliary tract diseases and abdominal surgical diseases in northwestern area of China

According to the national epidemiological survey from 1986 to 1998, the proportion of gallbladder

Table 2
Clinical epidemiological survey on gallbladder carcinoma in different regions.

Author	Country	Year	n	Ratio of GBC to BTD (%)	Ratio of gender (male:female)	Average age (year)	Accompanied with gallstones (%)	Pathological type	Lymphatic metastasis (%)	Bile duct metastasis (%)	Liver metastasis (%)	Surgical resection rate (%)
Zou et al ⁵	China	1986–1989	3922	0.9–3.8	1.0:2.0	57.5	49.7	Mainly adenocarcinoma	37.3	25.3	36.8	–
Hamdami et al ⁸	India	2004–2011	198	–	1.0:3.0	55	86.0	Mainly adenocarcinoma	26.3	–	53.0	33.8
Duffy et al ⁹	USA	1995–2005	435	–	1.0:1.9	67 (M)	–	Mainly adenocarcinoma	–	–	–	43.0
Alexander et al ¹⁰	Netherlands	1975–2008	659	–	1.0:2.8	72 (M)	–	Mainly adenocarcinoma	–	–	–	64.5
Roa et al ¹¹	Chile	1987–2005	1366	–	1.0:4.9	61.5	–	Mainly adenocarcinoma	60.4	–	–	–
In our group	China	2009–2013	2379	1.6–6.8	1.0:2.1	63.7	57.2	Mainly adenocarcinoma	55.9	29.7	53.1	30.4

GBC: gallbladder carcinoma; BTD: biliary tract diseases; M: median. –: No data.

carcinoma in all biliary tract diseases in the northwestern area of China was 1.0%–3.8%, with a mean of 2.0% (577/28,447).⁵ The present survey demonstrated that the proportion of gallbladder carcinoma in all biliary tract diseases in the northwestern area of China was 1.6%–6.8%, with a mean of 2.7% (2379/86,609). The proportion of gallbladder carcinoma in all biliary tract diseases was significantly higher in the present study than in the previous survey ($P < 0.001$). This might reflect the incidence of gallbladder carcinoma in the northwestern area of China is increasing over time, indicating that this region of China is a high-risk area for gallbladder carcinoma and more detailed study is warranted.

The proportion of gallbladder carcinoma in all biliary tract diseases was higher in the Xinjiang Uygur Autonomous Region, Qinghai Province and Gansu Province in the present study than in the previous survey, but was lower in Shaanxi Province and Ningxia Hui Autonomous Region; these differences were statistically significant between the two periods. Only one hospital each from Qinghai Province, Ningxia Hui Autonomous Region, and Xinjiang Uygur Autonomous Region were involved in the present survey, which is consistent with the previous survey.⁵ Although the number of hospitals from Gansu Province decreased from 3 in the previous survey to 2 in the present survey, the number of hospitals from Shaanxi Province increased from 4 to 12. Therefore, the present survey may better reflect the epidemiological characteristics of gallbladder carcinoma in northwest China. However, owing to the limitations of time and manpower and the small size of primary hospitals, the hospitals involved in this survey were large local hospitals; no primary hospitals were involved in this study. Therefore, the proportion of gallbladder carcinoma in biliary tract diseases in this survey is higher than in the actual clinical setting, necessitating future population-based epidemiological surveys.

Epidemiological characteristics of patients with gallbladder carcinoma in northwest China

The average age of patients with gallbladder carcinoma in the present survey was 63.7 ± 11.3 years, which is higher than that in the previous finding.⁵ Patients aged 56–75 years accounted for 61.3% (1458/2379) of all patients, which can be explained by the increase in the average life expectancy and aging of the population. The male:female ratio was 1.0:2.1, indicating that women are more susceptible to gallbladder

carcinoma; this is also consistent with the results of studies in different regions.^{5,8–11} The higher incidence of gallbladder carcinoma in women seems to be mediated by estrogen levels.¹² Pandey et al¹³ found that multiple pregnancies significantly increased the risk of gallbladder cancer, which is associated with the higher levels of progesterone and endogenous estrogen during pregnancy. This survey showed that the average number of pregnancies was 3.1 ± 1.5 . Additionally, farmers accounted for the largest percentage of gallbladder carcinoma patients, indicating differences between urban and rural populations.

Among the 2379 patients with gallbladder carcinoma, 57.2% had gallstones. Gallstones are widely recognized to induce chronic mechanical damage, and carcinogens in bile may trigger epithelial proliferation in the mucous membrane of the gallbladder, resulting in malignancy.² Therefore, patients with a long-term history of gallbladder stones should be recommended to undergo surgery or regular follow-up.

Clinical manifestations of gallbladder carcinoma

No specific clinical manifestations of early gallbladder carcinoma were observed in the present survey. Among all 2379 patients with gallbladder carcinoma, 283 had incidentally detected gallbladder carcinoma, accounting for 11.9% of all patients. Therefore, misdiagnosis of gallbladder cancer is still common, and the cause of misdiagnosis is a lack of vigilance and attention. Pathological examination showed that the majority of the patients (85.6%) had adenocarcinoma, which was consistent with other studies;^{5,8–11} 55.9% had lymph node metastasis, 29.7% had biliary tract invasion, 53.1% had liver metastasis, and all of these rates were higher than those in the previous findings.⁵ According to the TNM staging classification, 1091 of 1981 (55.1%) patients were classified as having stage IV cancer. We found that most patients with a higher degree of malignancy and more advanced invasion ability were at an advanced stage when they presented to the hospital. This is currently the main problem in the diagnosis and treatment of gallbladder carcinoma, and it is an important factor for a poor prognosis. Therefore, it is very important to improve the rate of early diagnosis.

Among all patients with gallbladder carcinoma receiving B-ultrasound and CT examination, 81.2% and 90.7% were positive, respectively. B ultrasound is the preferred examination technique for biliary tract disease because of its simplicity, feasibility, and non-invasiveness. CT is superior to type B ultrasound in

terms of qualitative diagnosis, but it is not sensitive enough for early diagnosis. CT is more sensitive than B ultrasound for patients at advanced stages with respect to determining the nature of the tumor and detecting metastasis, which helps in preoperative staging and formulating surgical protocols. The combination of B ultrasound and CT can improve the detection rate of gallbladder carcinoma.³ Patients at high risk of gallbladder carcinoma include (1) women aged >55 years with cholelithiasis, (2) those with a >10-year history of cholelithiasis and cholecystitis, (3) those with a lesion having >1 cm diameter in the gallbladder neck and body as detected by B ultrasound and accompanied by stones, and (4) those with a gallstone diameter >3 cm. Careful attention to the findings of various radiographic examination techniques is required to improve the early diagnosis rate.

In this survey, 64.5% of patients with gallbladder carcinoma were positive for CA19-9, 49.9% were positive for CA125, and 44.6% were positive for CEA. CA19-9, CA125, and CEA play a crucial role in the clinical staging and preoperative evaluation of gallbladder carcinoma, and combined detection can improve the diagnostic rate. Recent studies demonstrated that CA242 is another specific marker of gallbladder carcinoma. With a diagnostic sensitivity of up to 84%, it is expected to become a more sensitive marker than CEA, CA19-9, and CA125.¹⁴

Treatment of gallbladder carcinoma

Surgery remains the dominant treatment of gallbladder carcinoma and the only way to achieve long-term survival. The choice of surgical approach depends on the clinicopathological stage.¹⁵ Of all 2379 patients with gallbladder carcinoma in the present study, 1486 (62.5%) underwent surgery. Among them, 723 received radical surgical resection, accounting for 30.4% of all patients. With the development of liver transplantation and liver surgical techniques as well as improvements in perioperative support care, an increasing number of patients with advanced gallbladder carcinoma are benefiting from extended radical resection.^{16,17} For those who undergo failed radical resection, we recommended palliative surgery to improve the quality of life and relieve symptoms with the expectation of attenuating gastrointestinal and biliary obstruction. Additionally, adjuvant therapy such as radiotherapy and chemotherapy may be applied to improve the prognosis.

However, this is a cross-sectional retrospective hospital-based clinical epidemiological survey, which

is different from a population-based epidemiological survey. We could not determine the incidence or mortality of gallbladder carcinoma in this region. Our study showed the epidemiological characteristics and clinical manifestations of patients with gallbladder carcinoma in northwest China. However, the selection and information bias may affect the final results owing to the limitations of this retrospective study, necessitating population-based epidemiological surveys and a prospective study in the future.

Conflicts of interest

All authors declare no potential conflicts of interest, including specific financial interests, relationships, and affiliations relevant to the subject of this manuscript.

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