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Original Article

Prognostic Significance of Race and Tumor Size in Carcinosarcoma of Gallbladder: a Meta-Analysis of 68 Cases

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Abstract: Carcinosarcoma of gallbladder, also named sarcomatoid carcinoma and spindle cell carcinoma, is a rare neoplasm. Its clinical features and prognostic determinants are still poorly understood due to its rarity. We identified 67 qualified cases in published literatures and 1 in our institution. 52 of them were females and 16 males (F:M=3.25:1). 27 were Japanese patients and the rest were mainly from the United States and Europe. The mean age was 68.8 years (median 68 years, range 45-91 years). The average tumor size was 6.9 cm (median 5 cm, range 1.0-24.0 cm, n=49). Adenocarcinoma was the most common epithelial component (79.2%) and squamous cell carcinoma was the least common (9.4%). Spindle cell type was the most common mesenchymal component (44.6%) and osteoid was the least common (5.4%). The mean survival was 17.5 months (median 5 months, range 0 to 85 months, n=56). The 1-year and 5-year survival rates were 19±5% and 16±5% (mean±SD), respectively. Kaplan Meier survival analysis was conducted to examine the prognostic value of various clinical parameters. We found Japanese patients had longer survival time than non-Japanese ones (mean=19.9 months vs 11.5 months, median=6 vs 4 months, n=27 vs 24, p=0.022). Patients with smaller tumor (<5.0 cm) had longer survival time (in months) than those with larger tumor (mean 26.6 vs 17.7, median 11 vs 5, n=14 vs 27, p=0.028). The presence of gallstone, epithelial and mesenchymal component types, age and sex of the patients were not significant prognostic factors. In summary, race (Japanese vs non-Janpanese) and tumor size are important prognostic factors in carcinosarcoma of gallbladder and they may be used for prognostification.
Key Words: Gallbladder, carcinoma, carcinosarcoma, survival outcomes, meta-analysis, Japan

Introduction

Carcinosarcoma of gallbladder (CSGB) is a rare neoplasm characterized by the presence of both carcinomatous and sarcomatous components. Currently, 67 cases have been reported in the world literature, and 31 cases in English literature [1]. Several names are or have been used for this entity, including sarcomatoid carcinoma of gallbladder (GB) and spindle cell carcinoma of GB. Some pathologists also include this entity in the category of undifferentiated carcinoma of GB without further subclassification. CSGB is considered a malignant epithelial neoplasm [2]. A dismal survival has been reported in patients with CSGB, ranging from 2.9 to 6 months [3, 4]. However, little has been learned about its clinical features and prognostic factors. Here, we identified 68 qualified CSGB cases in world literature and our institution, and sought to characterize this disease by meta-analysis.

Materials and Methods

Case Identification and Selection

We conducted a computerized search in Pubmed of US National Library of Medicine (NLM) and ISI Web of Science (WOS) database through internet in May 2007. Because of the rarity of this neoplasm, neither language nor time limit, was set in the literature search. Terms of "carcinosarcoma AND gallbladder", ""sarcomatoid carcinoma" AND gallbladder",

and ""spindle cell carcinoma" AND gallbladder" were used independently. A combination of these search results was performed by inputting citations into the "clipboard" function of PubMed, or the "Marked List" function of WOS. Original articles were retrieved and reviewed. Additional cases were then identified through the review process. We also identified one case in our institution by searching our patient database.

A case was selected and included in this study if it: (1) presented a reliable histopathological diagnosis of CSGB; (2) presented both gender and age information of the patient; and (3) published in a peer-reviewed journal as original paper (including case report) or found in our patient database. All of the case entries were assessed by two of the authors (LZ and ZC) independently.

Data Extraction

The following data were extracted from original articles or pathological report, if available: (1) gender and age of the patient at the time of CSGB diagnosis (including incidental findings of CSGB during autopsy); (2) the last name of first author and the year of publication; (3) whether the patient was Japanese; (4) tumor size in greatest dimension; (5) survival time after the diagnosis of CSGB; (6) differentiation components of the tumor; and (7) presence of stone in gallbladder.

Statistical Analysis

Kaplan-Meier survival, life table, and frequency analyses of age, gender, race, tumor size, differentiation components, and presence of stone in gallbladder were performed by using SPSS version 14.0 (Chicago, IL). The patients, who were lost during follow-up, were censored in the Kaplan-Meier analysis, and were presented with the latest follow-up date. A P value less than 0.05 was considered statistically significant.

Results

Case Collection

We identified a total of 50 articles in Pubmed, including 44 articles by searching " carcinosarcoma AND gallbladder", 4 by """sarcomatoid carcinoma" AND gallbladder" and 7 by ""spindle cell carcinoma" AND gallbladder", respectively. In WOS database, 32 articles were found by searching "carcinosarcoma AND gallbladder", 9 by ""sarcomatoid carcinoma" AND gallbladder" and 22 by ""spindle cell carcinoma" AND gallbladder", with a total of 48 articles. Among all these articles identified by computerized search in both Pubmed and WOS as of May 2007, 34 articles met criteria mentioned above, and were included in this study. They provided information of 48 patients. Additional 19 qualified reports, each presented one patient, were collected by manually reviewing those articles. Thus, a total of 53 articles and 67 patients identified in world literature were qualified. With one additional patient in our institution, overall 68 patients were included in this series (see **Supplemental Table 1**).

Clinical Features

Among the 68 patients, 52 were females and 16 were males (F:M=3.25:1). The distribution of patient's age was a normal distribution, ranged from 45 to 91 years, with a mean of 68.8 years and a median of 68 years (**Figure 1A**). The mean age was 69.0 years for women (range 45 to 91 years, median 68 years), and 68.2 for men (range 50 to 91 years, median 69 years). The youngest patient was 45 years old reported by MeHrotra *et al* in 1971 [5], and the oldest 2 patients were 91 years old reported by Appelman *et al* in 1970 [6] and Von Kruster *et al* in 1982 [7]. Among the 49 cases with available information on tumor size, the distribution of tumor size was a skewed normal distribution (**Figure 1B**). The tumor size ranged from 1 to 24 cm, with a median of 5 cm and a mean of 6.9 cm. The largest tumor was identified in our institution and was present with direct liver invasion. The patient was alive in his last follow-up 3 months after surgery. The smallest tumor was 1 cm in greatest dimension, reported by Nishihara *et al* in 1990 [3]. Despite a small tumor size, he died of disease 11 months after surgery. Among those 51 cases with stone information, 33 of them (66.7%) had stones in the gallbladder and 17 (33.3%) did not.

Among the 53 cases with available information regarding epithelial components, 42 (79.2%) were classified as adenocarcinoma, 5 (9.4%) as squamous cell carcinoma, and 6 (11.3%) as admixture of both. Among the 56 cases with available information regarding mesenchymal component, 25 (44.6%) were classified as

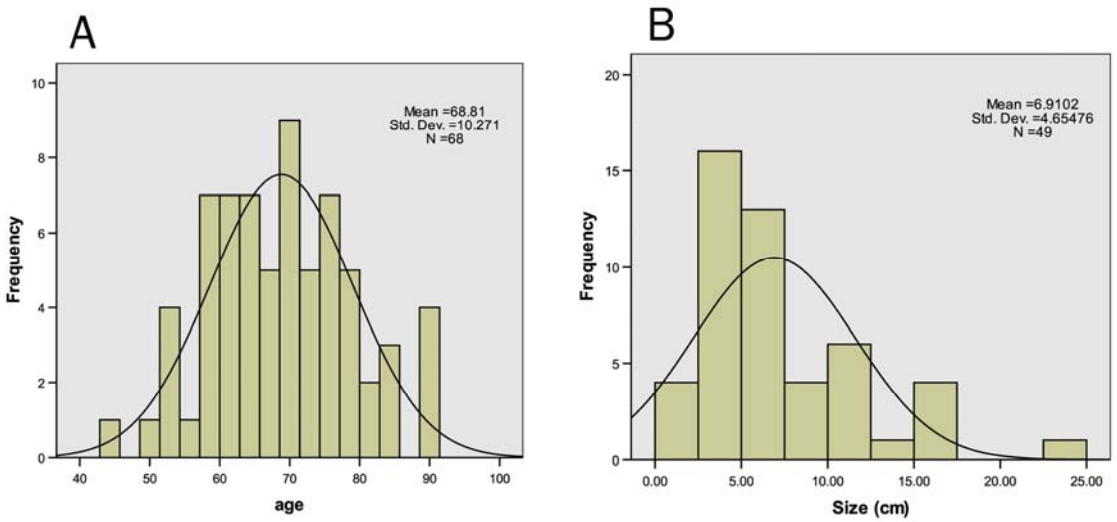

Figure 1 Distribution of CSGB patients' age (**A**) and tumor size (**B**)

spindle cell, 6 (10.7%) as chondroid, 5 (8.9%) as rhabdomyoid, 3 (5.4%) as osteoid, and 17 (30.4%) as other histopathological types including admixture of all mesenchymal components as listed above.

Among the 56 cases with available survival information, the mean survival was 17.5 months, ranging from 0 to 85 months (**Figure 2A**). The median survival was 5 months. The 1-year and 5-year survival rates were 19±5% and 16±5% (Mean±SD), respectively. The longest survivor was reported by Nishihara *et al* in 1993 [8] that the patient who had a 7.2 cm tumor died of disease 7 years and 1 month after surgery.

Prognostic Factor Identification

In order to identify a prognostic factor for survival in CSGB, we conducted Kaplan-Meier survival analysis in the patients with survival data. We examined the prognostic value of age, gender, tumor size, race (Japanese vs Non-Japanese), epithelial components, mesenchymal components, and presence of stone in gallbladder.

We found race and tumor size were of significant prognostic value in CSGB patients. This study included 27 Japanese and 24 non-Japanese (including 1 Korean). The non-Japanese patients were mainly from US and Europe. Japanese patients had longer survival (in month) than non-Japanese ones (mean=19.9 vs 11.5, median=6 vs 4, P=0.022, **Figure 2B**). In 40 patients with both survival and tumor size data, we found that patients with smaller tumor (<5.0 cm) survived longer than those with larger tumor (≥5.0 cm). A mean survival time of 26.6 and 17.7 months and a median of 11 and 5 months had been identified for these two groups, respectively (P=0.028, **Figure 2C**).

No significant difference was found in survivals among different groups of age, gender, presence of stone in gallbladder, epithelial components, or mesenchymal components by using Kaplan-Meier survival analysis (P>0.05).

Discussion

Karl Landsteiner reported the first case of CSGB in 1907 [9]. To our knowledge, 67 cases have been reported in literature worldwide since then [1], and 31 are in English literature [10]. A poor prognosis was demonstrated in 1984 [4]. However, the prognostic factors of CSGB have not been explored yet due to its rarity. Its clinical features also remain largely unknown. We therefore investigated these features of CSGB by meta-analysis on 67 qualified cases reported in world literature, as well as 1 case identified in our institution. Among them, 14 reports in peer-reviewed Japanese journals were rarely included in literature reviews in English, and might provide valuable ethnical information.

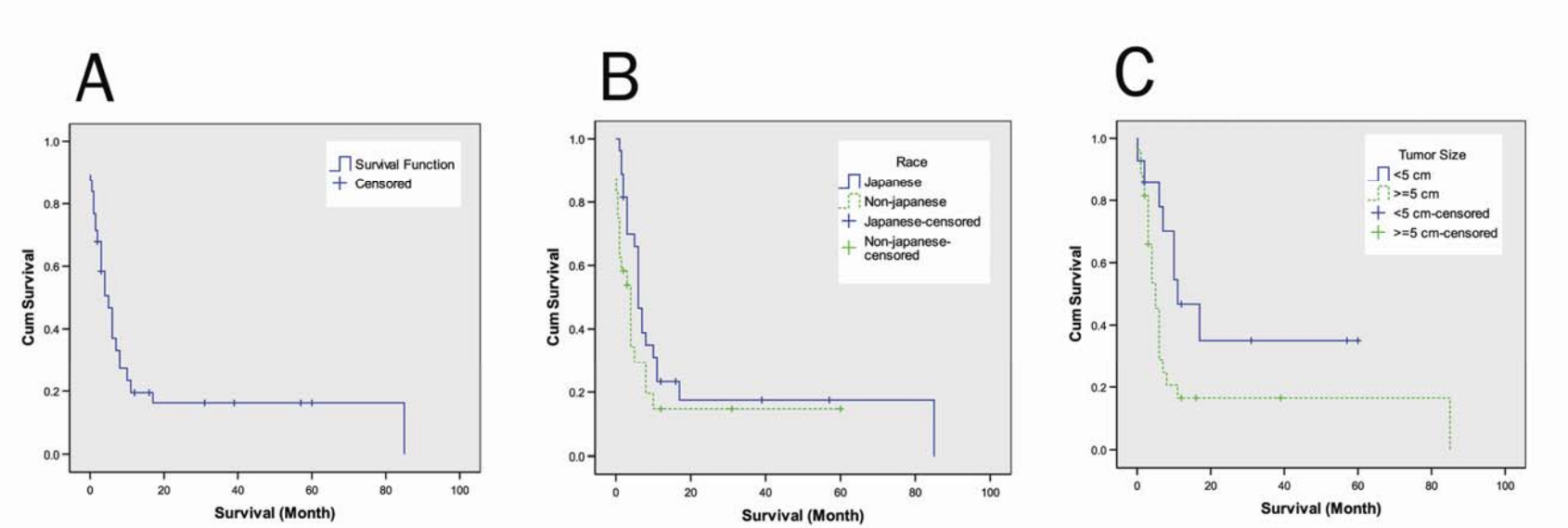

Figure 2 A. Overall cumulative survival of all 68 patients with CSGB. **B**. Cumulative survivals of Japanese (blue) and non-Japanese (green) patients with CSGB. **C**. Cumulative survivals of CSGB patients with tumor size either ≥ 5 cm (green) or < 5 cm (blue).

CSGB is a malignant tumor of gallbladder with both epithelial (carcinomatous) and mesenchymal (sarcomatous) components. It shares many clinical features with carcinoma of GB (CGB), a counterpart of CSGB with only epithelial component [2, 7] and a possible worse prognosis. The mean age at diagnosis of CSGB was reported 66.5 to 72 years [1, 4, 8, 11]. More precisely, our meta-analysis showed that the mean age was 68.8 years with a normal distribution and a median of 68 years. The female-to-male ratio was 3.25 to 1 in this series, which is consistent with previously reported ratio of 3.2 to 1 [4]. Similar demographics have been observed in CGB patients, such as female predominance, more than 90% of patients over the age of 60, and the peak incidence in the seventh decade of life [12, 13].

The mean survival of CSGB was 17.5 months, and the median was 5 months in our study with a 1-year survival rate of 19±5% and 5-year of 16±5% (Mean±SD). The longest survivor was reported in 2002 [14], who had survived 5 years and 7 months post-operatively. Therefore, in comparison with the reported 0-10% 5-year survivals of CGB [12], CSGB in general has a similar but slightly better prognosis (16±5% 5-year survival).

Although the histogenesis of CGB and CSGB is not yet clear, we speculate that the development of sarcomatous component may be attributed to de-differentiation of CGB or stem/progenitor cells in GB, and may cause a higher malignant potential than the epthelial/carcinomatous component only. In this study, 56 cases had information about the epithelial and mesenchymal components. The most common epithelial component was adenocarcinoma, representing 79.2% of the cases (**Figure 3A**), followed by a mixture of adecnoarcinoma and squamous cell carcinoma in 11.3%, and then squamous cell carcinoma only in 9.4%. The most frequent mesenchymal component was spindle cell composing 44.6% of the cases, and the least common was osteoid (5.4%). As found in our index case, a combination of spindle cell (**Figure 3B**) and chondroid (**Figure 3C**) features may also be present as the mesenchymal component of CSGB.

Ajiki and colleagues first categorized the mesenchymal components by analyzing 36 reported CSGB cases with survival information [15]. They found that the median survival of patients with spindle cell component is slightly longer than those with chondroid or rhabdoid (6 vs 4 months). However, no statistical significance was found among the survivals of those groups. As suggested by the authors, the small sample size might have contributed to the failure of reaching statistical significance [15]. Our study included slightly more cases

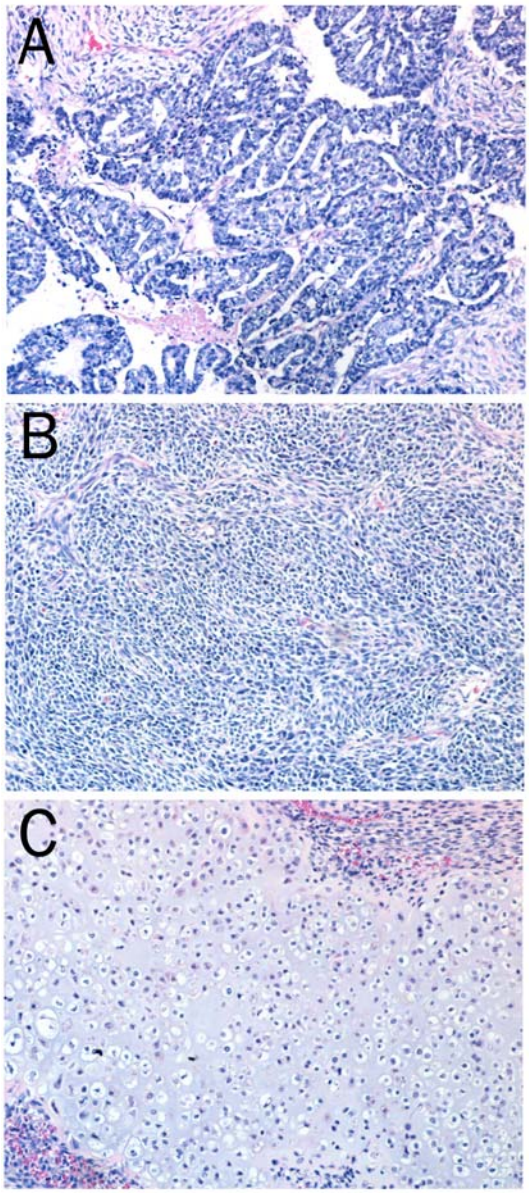

Figure 3 Representative images of adeno-carcinomatous (**A**), spindle cell (**B**) and chondroid components (**C**) of CSGB (H&E stains, original magnifications: 200x)

(45 vs 36), and may be of greater statistical power. We divided all cases with histo-pathologcal information into 5 groups by their mesenchymal component types, namely, spindle cell, chondroid, rhabdoid, osteoid and admixure. Our Kaplan Meier analysis showed that no significant difference between those groups, and suggested little prognostic value of mesenchymal component types in CSGB patients.

We further examined the prognostic value of the counterpart of mesenchymal component, epithelial components. This is the first study, to our knowledge, exploring the prognostic value of epithelial components in CSGB. Among adnocarcinomatous, squamous and mixed types of CSGB, no survival difference was found by Kaplan Meier analysis, either.

Our data hence showed that the histological sub-type of CSGB, either mesenchymal or epithelial, was of little help in predicting prognosis. Our finding is supported by Ajiki's study on 36 reported cases [15]. Of note, our study and Ajiki's are both based on reported cases, and should have led to a similar, if not the same, conclusion. A larger scale case series study might be needed to characterize the prognostic value of epithelial and mesenchymal component types.

We continued to search for valuable prognostic factors for CSGB, and hoped to expand our understanding of this disease. Many studies have focused on the prognosis of CGB, and may shed light on our search of CSGB prognostic factors. The clinical and/or pathological staging remains the most critical prognostic factor for CGB [12, 16], including Nevin and TNM systems. Other prognostic factors include race, high grade, and low tumor mucopolysaccharidosis [12]. In modified Nevin staging system, stage I is defined as tumor limited to the mucosa, stage II as tumor invasion into the muscularis layer, stage III as transmural tumor with direct invasion to liver, stage IV as presence of lymph node metastasis, and stage V as presence of distant metastasis [12, 17].

The depth of tumor invasion is a critical factor for T classification in both staging systems [12, 17]. The tumor size is closely related to local invasion for the relative thin layer of gallbladder wall. However, its prognostic value has not yet been examined in CGB or CSGB. We therefore studied the 49 cases with tumor size information. The median tumor size of these cases was 5 cm (mean 6.9 cm, range 1-24 cm). The largest tumor was 24 cm. The patient had tumor extending to liver at the time of diagnosis, and was alive for 3 months after his surgery. The second largest tumor was 16 cm, and the patient died of disease 7 months later [8]. About 30% CSGB patents had either metastasis or local spread at the time of diagnosis [11].

In 41 patients with both tumor size and survival information, Kaplan Meier survival analysis showed that patients with tumor ≥5 cm had a significantly shorter survival than those with tumor size smaller than 5 cm (mean 26.6 vs 17.7 months, median 11 vs 5 months, P=0.028, **Figure 2C**). However, there was no survival difference among the two groups of patients divided by tumor size of 3, 4 or 6 cm. It is possible that more frequent local invasions or higher grade of tumor may be present in tumors larger than 5cm than in tumors smaller than 5 cm. This may also be attributed to more aggressive tumor behaviors or worse tumor staging, though confirmation study on such a hypothesis is still needed to further characterize the "worse" tumors and help individualize treatment for the patients. Interestingly, our Kaplan-Meier analysis data showed that tumor size 6 cm was of little use for the prognosis prediction.

Gallstones were found in 66.7% of CSGB cases with gallstone information in our study, and have been reported in 75-83 % of CSGB cases [1, 4, 11]. The rates of gallstones in CSGB patients were similar to those in CGB patients (78-85%) [13]. Many studies have suggested that the presence of gallstones is one of the most important risk factors for CGB. For instance, CGB risk was directly proportional to the size of gallstones. Moreover, epithelial dysplasia, atypical hyperplasia, and carcinoma in situ were incidentally seen in 83%, 13.5%, and 3.5% of cholecystectomy specimens with cholecystitis, respectively. Those lines of evidence indicate that gallstone may be associated with the development of CGB [12], and may provide useful prognostic information. However, only 1-5% of patients with gallstone developed CGB, and the majority (75-90%) of CGB patients did not have gallstones. Therefore, gallstone may have a very limited role in CGB progression or prediction of CGB prognosis. In

order to examine the prognostic value of gallstone presence in CSGB, we carried out a Kaplan-Meier analysis, and found that there was no significant survival difference between patients with and without gallstones. Our data suggest that a limit emphasis should be given to the presence of gallstone when one evaluates the prognosis of CSGB patients. We also speculate some factors other than gallstone may play an important role in the progression of CSGB.

Race is another known risk factor for CGB, with high incidence in Japan, Chile, South America, and India [12]. It is also of great prognostic value. For instance, the survival of Japanese is much better than in Indian and in American [12]. The Japanese 5-year survival rates were 42% for resectable and 2% for nonresectable gallbladder cancers, both better than the Westerners [18]. The median survival of CGB in Japan is 12 months with the longest survival of 5 years and 7 months [14]. Our data indicate Japanese CSGB patients also had longer survival than non-Japanese. It is speculated that multiple factors might contribute to such a better prognosis in Japanese, including genetic variation, early detection, and more sophisticated surgery.

Loss of heterozygosity (LOH) on 17p was found as the most frequent genetic change in both intramural and invasive carcinomas of Japanese [19]. A study on 32 gallbladder carcinoma cases and 11 dysplasia cases of Korean also showed LOH on 17p increased in both dysplasia and subsequent stages, while LOH on 5p only increased in early stage [20]. Not surprisingly, Chilean patients of gallbladder carcinoma had frequent (78%) LOH on 17p13, which harbors tumor suppressor gene TP53 [21]. Direct comparison study showed that the TP53 mutation does exist and its frequencies in CGB are similar between Japanese (13 out of 22) and Chilean (12 out of 20), indicating an important role of TP53 in CGB development among those high risk populations [22]. However, studies in Greek patients of CGB did not reveal significant or frequent alteration of TP53 [23]. There might be a genetic predisposition of TP53 alterations or losses in Japanese and Chilean, which led to such a higher incidence of CGB in them than in Greek. Interestingly, those TP53 mutation patterns of Japanese and Chilean are also different [22], further indicating an important role of ethnicity or race related genetic predisposition in CGB development. We speculate that such a genetic predisposition may also involve in CSGB development, given the significant prognostic value of race in CSGB. To examine this speculation, population genetic and tumor biology studies are needed.

Since many preoperative diagnosed CGBs are advanced diseases, early detection may promote survivals. The Japanese group was one of the first who utilized computerized tomography to diagnose CGB in early 1980 [4]. Their extensive experience and advanced technology may have led to an early detection of CSGB and CGB, and therefore resulted in a better survival in Japanese. This assumption is supported by the evidence that the rates of Japanese stage I CGB is 36.0% and stage IV 38.6% [18], while the world wide general stage I is only 26% and stage IV 39.8% [16]. We had very limited precise tumor staging information in the CSGB cases of this study, and could not examine whether Japanese patients also had an earlier stage in reported CSGB cases. It is recommended to examine the survival of Japanese CSGB and CGB patients by stage matched studies.

In addition, as early as in 1981, Japanese Society of Biliary Surgery developed guidelines for CGB, which recommended extensive surgery [18]. Ten years after the publication, Shirai and colleagues reported that the use of radical cholecystectomy led to a much higher 5-year survival rate than simple cholecystectomy (90% vs 40%) in patients with T2 or T3 tumors. In 1997, European group reported a similarly better prognosis in patients treated with radical cholcystectomy compared to simple cholecystectomy [12]. The current 5-year survival rates of stage I and stage IV CGB patients in Japan are 77% and 9%, respectively, which are much higher than that before the wide use of extensive surgery [18]. In the US, the 5-year survival rates of stage I and stage IV patients were only 39% and 1%, respectively [17], and the 2-year survival rates for stage I and stage IV were 19% and 2% [12]. Japanese surgeons suggested that a detailed specimen examination and extensive resection might have contributed to the improved survival rates in Japanese CGB patients [18]. These measures may also apply to CSGB.

In conclusion, Japanese patients and patients

with tumor smaller than 5 cm have longer survival and therefore, race and tumor size should be considered as major components in future staging system for CSGB, although genetic variation, earlier detection of CSGB, and more extensive surgery may also contribute to the better prognosis in Japanese. Our data also indicate that the presence of gallstone, epithelial and mesenchymal component types, age and sex are of little prognostic value. Although meta-analysis has been used as a powerful tool for rare entities and controversial issues in clinical studies, the accuracy of the diagnoses and the reliability of the clinical information may vary, and bring errors to the study. Such a limitation has been noted and compensated with a higher standard of selection and review work done by 2 of the authors for every single article or case. In the future, a larger scale case series may provide additional information in terms of accuracy and reliability.

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