Surgical outcome of carcinosarcoma of the gall bladder: A review

Takehiro Okabayashi, Zhao-Li Sun, Robert A Montgomery, Kazuhiro Hanazaki

Abstract

Carcinosarcoma, which comprises less than one percent of all gall bladder neoplasms, is characterized by the presence of variable proportions of carcinomatous and sarcomatous elements. Recently, several reports have described patients suffering from carcinosarcoma of the gall bladder. However, there are no large studies regarding the clinicopathologic features, therapeutic management, and surgical outcome of this disease because the number of patients who undergo resection at a single institution is limited. The purpose of the present study was to analyze these 36 cases to clarify the factors that might influence surgical outcome, including survival rates after surgery, and to determine the prognostic factors of carcinosarcoma of the gall bladder.

INTRODUCTION

Adenocarcinoma is the most common type of malignant tumor generated in the gall bladder, whereas carcinosarcoma is rare with an incidence of less than one percent of all malignant gall bladder neoplasms[1]. Carcinosarcomas are composed of variable proportions of both carcinomatous and sarcomatous elements. Recently, several reports have described patients suffering from carcinosarcoma of the gall bladder. However, there are no large studies that report the clinicopathologic features, therapeutic management, and surgical outcome for this disease because the number of patients who undergo resection at a single institution is limited.

In the literature, there are well-presented data from 36 reported patients who underwent surgical resection for carcinosarcoma of the gall bladder with intent to cure[2-28]. The purpose of the present study was to analyze these 36 cases to clarify the factors that might influence surgical outcome, including survival rates after surgery, and to determine the prognostic factors of carcinosarcoma of the gall bladder.

PATIENTS

We analyzed data from 36 patients reported in the literature from 1971 to 2009[2-28] who underwent surgical management for carcinosarcoma of the gall bladder (Table 1). These patients consisted of 10 male and 26 female with a mean age of 67.7 years (range 45 to 90 years). The mean body mass index (BMI) was 21.9 kg/m² (range 14.6 to 33.3 kg/m²).

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Key words: Gall bladder; Carcinosarcoma; Spindle cell carcinoma; Surgery; Outcome

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years). The outcome of each case was obtained from the published data. We evaluated the clinicopathological findings including clinical symptoms, tumor location, tumor size, the number and size of gall bladder stones, depth of the tumor invasion, tumor stage according to International Union Against Cancer (UICC) criteria, pathological features, and survival rates. All patients had undergone attempted curative resection for carcinosarcoma of the gall bladder. Survival rates were estimated by using the Kaplan-Meier method and were compared by using the log-rank test[20]. Values were expressed as mean ± SD. Differences in proportions were evaluated by the Pearson χ² test. *P < 0.05 was considered to be statistically significant.

### Table 1

| Author          | Year | Age (yr) | Sex | Palpation | Position | Stone | Size (cm) | Depth | SCC | Stage | Survival (mo) |
|-----------------|------|----------|-----|-----------|----------|-------|-----------|-------|-----|-------|--------------|
| Mehdra et al[9] | 1971 | 45       | F   | *         | Neck     | +     | 10        | si    | +   | III   | 4            |
| Higgs et al[10] | 1973 | 77       | M   | -         | Neck     | -     | ND        | bd    | +   | IVa   | 1            |
| Mansori et al[11] | 1980 | 81       | M   | +         | Body     | -     | 15        | liver | ND  | IVa   | 1,5          |
| Aldovini et al[12] | 1982 | 75       | F   | +         | Body     | +     | 9         | mp    | -   | III   | 3            |
| Von Kuster et al[13] | 1982 | 77       | F   | -         | Fundus   | -     | 3         | mp    | ND  | IVa   | 3            |
| Born et al[14]  | 1984 | 90       | F   | -         | Body     | 15    | du        | ND    | IVa | III   | 3            |
| Inoue et al[15] | 1986 | 53       | M   | +         | Neck     | -     | 11        | bd    | +   | IVa   | 17           |
| Suster et al[16] | 1987 | 54       | F   | +         | Body     | +     | 8         | si    | +   | III   | 12           |
| Lumsden et al[17] | 1988 | 81       | F   | +         | Neck     | -     | 5         | mp    | ND  | II    | 12           |
| Guo et al[18]   | 1990 | 69       | M   | ND        | ND      | ND    | ND        | ND    | -   | -     | 3            |
| Ishihara et al[19] | 1990 | 58       | F   | -         | Fundus   | -     | 8         | mp    | -   | II    | 7            |
| Nishihara et al[20] | 1993 | 63       | F   | ND        | ND      | -     | 9.5       | ND    | -   | ND    | 3            |
| Nishihara et al[21] | 1993 | 66       | F   | ND        | ND      | ND    | 5         | ND    | -   | ND    | 19           |
| Fujii et al[22] | 1994 | 70       | F   | ND        | ND      | ND    | 4.2       | ND    | -   | ND    | 7            |
| Tsuchiya et al[23] | 1994 | 75       | F   | ND        | ND      | ND    | 16        | ND    | +   | ND    | 6            |
| Lumsden et al[17] | 1995 | 80       | F   | ND        | ND      | ND    | 5         | ND    | -   | ND    | 1,5          |
| Fagot et al[24] | 1996 | 83       | F   | -         | Fundus   | +     | 4.5       | mp    | ND  | II    | 12           |
| Nakagawa et al[25] | 1996 | 66       | F   | -         | Fundus   | -     | 7         | liver | ND  | IVa   | ND           |
| Rys et al[26]   | 1998 | 67       | F   | +         | Fundus   | 15    | liver, chn| ND    | IVa | 2     |
| Enzor et al[27] | 1999 | 65       | F   | +         | ND      | +     | 10        | mp    | ND  | II    | 16           |
| Aoki et al[28]  | 2000 | 49       | F   | -         | Body     | -     | 6         | liver | ND  | IVa   | 7            |
| Hotta et al[18] | 2002 | 53       | M   | +         | Body     | +     | 11        | -     | -   | II    | 7            |
| Kim et al[29]   | 2003 | 61       | F   | +         | Neck     | -     | 4.5       | si    | -   | IVa   | 2            |
| Takahashi et al[30] | 2004 | 84       | F   | -         | Body     | -     | 8         | si    | +   | IVa   | 2            |
| Huguet et al[31] | 2005 | 64       | F   | -         | Body     | -     | 12        | panc  | +   | IVa   | 4            |
| Soderberg et al[32] | 2005 | 68       | F   | -         | Neck     | -     | 9         | bd    | -   | IVa   | 5            |
| Kubota et al[33] | 2006 | 72       | M   | +         | Body     | -     | 7         | liver, chn| IVa | 8            |
| Liu et al[34]   | 2009 | 51       | M   | ND        | ND      | ND    | si        | -     | -   | IVa   | 3            |
| Fagot et al[24] | 2009 | 65       | F   | ND        | ND      | ND    | si        | -     | -   | IVa   | 0.7          |
| Liu et al[34]   | 2009 | 56       | F   | ND        | ND      | ND    | si        | -     | -   | IVa   | 5            |
| Agarwal et al[35] | 2009 | 60       | F   | +         | Body     | -     | 7         | mp    | -   | II    | 3            |
| Uzun et al[36]  | 2009 | 70       | M   | +         | Fundus   | -     | 10        | mp    | -   | II    | 54           |
| Shimada et al[37] | 2009 | 69       | M   | -         | Body     | +     | 9         | si    | -   | II    | 6            |
| Present case    | 2009 | 72       | F   | -         | Body     | -     | 2.5       | mp    | -   | II    | 60           |

1Alive patients. SCC: Squamous cell carcinoma component; si: Serosal invasion; bd: Bile duct; mp: Muscularis propria; chn: Colon; panc: Pancreas; ND: Not described; Stage: Classification according to UICC (International Union Against Cancer).

### DIAGNOSIS OF CARCINOSARCOMA OF THE GALL BLADDER

Table 1 lists the 36 patients who underwent curative surgical resection for carcinosarcoma of the gall bladder and summarizes the clinical features and outcome. In these patients, carcinosarcoma was not associated with any specific clinical syndromes. All patients presented clinical symptoms, such as abdominal pain, fever, anorexia, nausea, vomiting, painless jaundice, anorexia, and/or body weight loss (data not shown). In 56% of cases in which carcinosarcoma of the gall bladder was diagnosed, it was recognized as a palpable mass. The size of gall bladder carcinosarcomas appears to be larger than that of gall bladder carcinomas. The mean size of carcinosarcomas of the gall bladder was 8.4 ± 3.7 cm (range, 2.5-16 cm) in 29 patients with available data (Table 1).

Accurate preoperative diagnosis of carcinosarcoma of the gall bladder is very difficult because imaging studies cannot differentiate it from carcinoma of the gall bladder. Abdominal angiography often shows neovascularity and staining of carcinosarcomas of the gall bladder, whereas computed tomography (CT) shows an enhanced solid mass lesion. Differential diagnosis includes gall bladder carcinoma when there is calcification, calcified gall stones, or porcelain gall bladder, and carcinosarcoma of the gall bladder is suspected when calcification is observed within the tumor on CT examination[19]. However, more detailed imaging
data is needed to improve diagnosis of carcinosarcoma of the gall bladder. Carcinosarcoma of the gall bladder is not associated with specific radiological findings or serum data, including tumor markers (carcinoembryonic antigen, carbohydrate antigen 19-9, or squamous cell carcinoma antigen). Carcinosarcoma of the gall bladder should be considered as a differential diagnosis of neoplasms of the gall bladder, especially when patients present with severe abdominal symptoms and/or a large tumor size.

Table 2 summarizes the trends of the incidence of carcinosarcoma of the gall bladder. These data reveal that despite advancements in diagnostic techniques and equipment in recent years, the frequency of resections in patients with gall bladder carcinosarcomas has not increased.

**PATHOLOGICAL FEATURES OF GALL BLADDER CARCINOSARCOMA**

Carcinosarcoma is characterized by malignancy of both the epithelial and mesenchymal components of the same tissue. Its diagnosis requires the presence and intermingling of both histological components. In most reported cases of gall bladder carcinosarcoma the epithelial component is adenocarcinoma, although a squamous cell carcinoma component is also often present. The mesenchymal component varies from homogeneous sarcoma to more heterotopic elements such as malignant bone, cartilage, and other mesenchymal tissues.[22-27] Sarcomatous change or squamous change from adenocarcinoma leads to aggressive spread and metastasis. Squamous cell carcinomas grow at twice the speed of adenocarcinomas[30-32]. Therefore, once an adenocarcinoma transforms to an adenocarcinoma with a squamous component, the carcinoma exhibits a high degree of malignancy. For our series of carcinosarcoma of the gall bladder patients, the presence of either cartilage, rhabdoid tumor or a squamous component was not a significant prognostic factor.

The homogeneous sarcoma was usually a spindle cell type in these cases. The pathogenesis of carcinosarcoma is poorly understood. Several theories have been proposed to explain the admixture of epithelial and mesenchymal tissues in these neoplasms: (1) mesenchymal reaction, (2) true sarcoma (including the collision neoplasm hypothesis), (3) malignant proliferation of epithelial origin (including the stromal induction/metaplasia model), (4) an embryonic cell rest origin, and (5) the totipotential stem cell hypothesis.[24,33] The third theory is supported by reports based on immunohistochemical findings.[19,24] Sarcomatous change of carcinoma can be induced by radiotherapy, alterations to the p53 gene, and the production of bone morphogenetic protein by cancer cells.[34-36] A recent report suggests that genetic and gene expression alterations may underlie the
sarcomatous change or epithelial mesenchymal transition in cholangiocarcinoma[37]. On the other hand, it has been speculated that these neoplasms arise from totipotential stem cells, rest cells of myoblasts that retain the capability of transformation, primitive undifferentiated mullerian stroma, or paramesonephric tissue[5,22,38].

MANAGEMENT OF RESECTABLE CARCINOSARCOMA OF THE GALL BLADDER

Since carcinosarcomas are uncommon tumors with a poor prognosis, the outcomes related to various therapeutic interventions are not well defined and no optimal postoperative adjuvant therapy has been established.

Table 1 shows tumor location and the clinicopathological features of the 36 reported cases of carcinosarcoma of the gall bladder. Six cases (25.0%) arose in the neck of the gall bladder, 12 in the body of the gall bladder (50.0%), and the other 6 cases arose in the fundus of the gall bladder (25.0%). Among these cases, the incidence of tumor invasion of the muscularis propria was 35.7%, and in the remaining 63.3% of cases the tumor had perforated the visceral peritoneum or had invaded other organs. Although carcinosarcoma of the gall bladder has different clinicopathological features from adenocarcinoma, the treatment strategies are similar. It is considered that surgical treatment remains the only curative management option for carcinosarcoma of the gall bladder. Simple cholecystectomy and extended cholecystectomy, including cholecystectomy with the adjacent liver bed, with the extrahepatic bile duct, with partial resection of the small intestine and/or colon, and with pancreaticoduodenectomy, were performed in 9 (36.0%) and 16 (64.0%) of cases, respectively. Extended cholecystectomy was performed for carcinosarcoma of the gall bladder because most of these cases presented with a large mass invading adjacent organs.

PROGNOSIS AFTER SURGICAL RESECTION

The overall 1-, 2-, and 3-year survival rates after surgery were 37.2%, 31.0%, and 31.0%, respectively (Figure 1). By comparing the survival rate among the subgroups identified by each predictive factor with the univariate analysis of the prognostic factors, two factors, namely (1) the presence of serosal invasion and/or involvement into other organs, and (2) advanced stage according to the classification of UICC in resected specimens, were found to be significantly associated with a poor outcome after surgery (Table 2).

The cases examined in the current study were patients recruited for surgical treatment of carcinosarcoma of the gall bladder with intent to cure; however, the current overall 5-year survival rate of 31.0%, which included an in-hospital mortality rate of 8.3%, was comparable to or worse than the reported rates for adenocarcinoma of the gall bladder. It is likely that the overall and median survival is poor because two-thirds of the patients with carcinosarcoma of the gall bladder in this study had serosal invasion and/or involvement of other organs. This finding suggests that carcinosarcoma has greater malignant potential than adenocarcinoma of the gall bladder. The 5-year survival rate after curative resection for carcinosarcoma of the gall bladder was 88.9% when tumor invasion was restricted to the muscularis propria.

Due to limited experience, the staging system could not be defined, nor has any consensus been established on the management of carcinosarcoma of the gall bladder. Here, we used statistical analysis to support a correlation between the staging system for carcinoma of the gall bladder according to UICC and the classification of carcinosarcoma of the gall bladder. In addition, the 5-year survival rate was 87.5% even when resection with intent to cure was performed for stage II tumors. The three cases surviving more than 3 years included a patient where tumor involvement was limited to the muscularis propria[11,27]. Although curative resection provides the best hope for long-term survival with early stage tumors, only 35.7% of gall bladder carcinosarcoma cases are discovered at the early stage (stage II). It is likely that the overall and median survivals are poor in this study because 64.3% of patients with carcinosarcoma of the gall bladder had tumors at stage III or IV. As shown in Table 2, curative resection and stage II tumors are significant factors for a favorable prognosis for patients with carcinosarcoma of the gall bladder, thus an early diagnosis is required for a better outcome after treatment.

Recurrence was evaluated for twelve patients in this study. The major sites of recurrence were the liver (10 patients), lymph nodes (5 patients), and peritoneal cavity (4 patients). The median time to recurrence was less than one year. From the time of surgery, recurrence occurred within half a year in 8 patients (80.0%). The median time to recurrence for patients who died was only 1.5 mo. The invasive nature and aggressive malignant biology of carcinosarcoma explains the limited number of resectable cases. The results of this study suggest that adjuvant strategies would be beneficial for pre- and post-operatively diagnosed carcinosarcoma. Previous studies reported the use of chemoradiotherapy after...
surgical resection of carcinosarcoma of the gall bladder, but this treatment did not significantly improve patient prognosis[10,18,19,22,29].

CONCLUSION

Prognosis is poor following curative resection for carcinosarcoma of the gall bladder because of recurrence as systemic metastasis of the liver and peritoneal dissemination. In addition, a large proportion of these patients have recurrence during the postoperative early period. Consensus of opinion as to surgical indication for this tumor has not yet been achieved. Surgical treatment strategies based on the appropriate surgical indication are essential for improvement of surgical outcome because curative resection is usually not possible for advanced disease. For these reasons, once a diagnosis of carcinosarcoma of the gall bladder is made it is important to inform patients and their family regarding the biological behavior of this uncommon disease and the proposed prognosis following curative surgical treatment.

Exploration of new radiation techniques and of chemotherapeutic regimens with new drugs is required for the treatment of carcinosarcoma of the gall bladder because conventional chemotherapy and radiotherapy do not increase patient survival. Novel ‘molecularly targeted’ agents may improve surgical outcome. The prognosis of carcinosarcoma of the gall bladder remains poor despite curative resection, thus efforts to improve surgical outcome should continue for this rare, worldwide disease. Furthermore, the collection of epidemiologic data and pathologic findings will be required to determine the appropriate surgical indication for this tumor.

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