

Surgical outcome of carcinosarcoma of the gall bladder: A review

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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 of gall bladder carcinosarcoma at a single institution is limited. A Medline search was performed using the keywords 'gall bladder' and 'carcinosarcoma'. Additional articles were obtained from references within the papers identified by the Medline search. Optimal adjuvant chemotherapy and/or radiotherapy protocols for carcinosarcoma of the gall bladder have not been established. Curative surgical resection offers the only chance for long-term survival from this disease. The outcome of 36 patients who underwent surgical resection for carcinosarcoma of the gall bladder was poor; the 3-year overall survival rate was only 31.0% and the median survival time was 7.0 mo. Since the postoperative prognosis of carcinosarcoma of the gall bladder is worse than that of adenocarcinoma, new adjuvant chemotherapies and/or radiation techniques are essential for improvement of surgical outcome.

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

Table 1 Thirty six reported cases of surgical resection for carcinosarcoma of the gall bladder

Author	Year	Age (yr)	Sex	Palpation	Position	Stone	Size (cm)	Depth	SCC	Stage	Survival (mo)
Mehrotra <i>et al</i> ^[22]	1971	45	F	+	Neck	+	10	si	+	III	4
Higgs <i>et al</i> ^[3]	1973	77	M	-	Neck	-	ND	bd	+	IVa	1
Mansori <i>et al</i> ^[4]	1980	81	M	+	Body	-	15	liver	ND	IVa	1.5
Aldovini <i>et al</i> ^[5]	1982	75	F	+	Body	+	9	mp	-	III	8 ¹
Von Kuster <i>et al</i> ^[6]	1982	77	F	-	Fundus	-	3	mp	ND	II	31 ¹
Born <i>et al</i> ^[7]	1984	90	F	+	Body	+	15	du	ND	IVa	3
Inoshita <i>et al</i> ^[8]	1986	53	M	+	Neck	-	11	bd	+	IVa	17
Suster <i>et al</i> ^[9]	1987	54	F	+	Body	+	8	si	+	III	ND
Lumsden <i>et al</i> ^[10]	1988	81	F	+	Neck	-	5	mp	ND	II	12 ¹
Guo <i>et al</i> ^[11]	1988	69	M	ND	ND	ND	ND	ND	-	ND	3
		61	M	ND	ND	ND	ND	ND	-	ND	3
		66	M	ND	ND	ND	ND	ND	+	ND	19 ¹
Ishihara <i>et al</i> ^[12]	1990	58	F	-	Fundus	-	8	mp	-	II	7 ¹
Nishihara <i>et al</i> ^[13]	1993	63	F	ND	ND	-	9.5	ND	-	ND	39 ¹
		66	F	ND	ND	+	5	ND	-	ND	1
		70	F	ND	ND	-	4.2	ND	-	ND	7
		75	F	ND	ND	-	16	ND	+	ND	6
		80	F	ND	ND	-	5	ND	-	ND	1.5
Fagot <i>et al</i> ^[14]	1994	83	F	-	Fundus	+	4.5	mp	ND	II	12 ¹
Nakagawa <i>et al</i> ^[15]	1996	66	F	-	Fundus	-	7	liver	ND	IVa	ND
Rys <i>et al</i> ^[16]	1998	67	F	+	Fundus	-	15	liver, cln	ND	IVa	2
Eriguchi <i>et al</i> ^[17]	1999	65	F	+	ND	+	10	mp	ND	II	16 ¹
Ajiki <i>et al</i> ^[18]	2002	69	F	-	Body	+	6	liver	-	IVa	7
Hotta <i>et al</i> ^[19]	2002	53	M	+	Body	+	11	mp	-	II	7
Kim <i>et al</i> ^[20]	2003	61	F	+	Neck	-	4.5	si	-	IVa	2 ¹
Takahashi <i>et al</i> ^[21]	2004	84	F	-	Body	-	8	si	+	IVa	2
Huguet <i>et al</i> ^[22]	2005	64	F	-	Body	-	12	panc	+	IVa	4
Sodergren <i>et al</i> ^[23]	2005	68	F	-	Neck	-	9	bd	-	IVa	5
Kubota <i>et al</i> ^[24]	2006	72	M	+	Body	-	7	liver, col	-	IVa	8
Liu <i>et al</i> ^[25]	2009	51	M	ND	ND	ND	ND	si	-	IVa	3
		65	F	ND	ND	ND	ND	si	-	IVa	0.7
		56	F	ND	ND	ND	ND	si	-	IVa	5
Agarwal <i>et al</i> ^[26]	2009	60	F	+	Body	-	7	mp	-	II	3 ¹
Uzun <i>et al</i> ^[27]	2009	70	M	+	Fundus	-	10	mp	-	II	54 ¹
Shimada <i>et al</i> ^[28]	2009	69	M	-	Body	+	9	si	-	II	6 ¹
Present case	2009	72	F	-	Body	-	2.5	mp	-	II	60 ¹

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

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^[29]. Values were expressed as mean \pm SD. Differences in proportions were evaluated by the Pearson χ^2 test. $P < 0.05$ was considered to be statistically significant.

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^[15]. However, more detailed imaging

Table 2 Clinical characteristics after surgical resection for carcinosarcoma of the gall bladder

Characteristics	n	Survival rate (%)			Median survival in months (range)	P value
		1 yr	2 yr	3 yr		
Overall	36	37.2	31.0	31.0	7.0 (4.4-9.6)	
Age (yr)						
< 65	14	37.7	18.9	18.9	5.0 (0.3-9.7)	0.887
> 65	22	36.7	36.7	36.7	7.0 (4.2-9.8)	
Gender						
Male	10	36.0	24.0	24.0	6.0 (0.3-13.7)	0.877
Female	26	37.5	37.5	37.5	6.0 (3.3-8.7)	
Palpable mass						
Present	14	48.0	48.0	48.0	7.0	0.853
Absent	11	47.6	23.8	23.8	8.0 (0.0-16.9)	
Stone						
Present	10	40.0	-	-	7.0 (3.2-10.8)	0.937
Absent	20	42.1	33.7	33.7	7.0 (3.4-10.6)	
Size of the tumor (cm)						
< 5	8	60.0	60.0	60.0	-	0.361
> 5	21	36.6	24.4	24.4	7.0 (5.1-8.9)	
Si or organ invasion						
Present	18	9.2	0.0	0.0	4.0 (2.2-5.8)	0.001
Absent	10	88.9	88.9	88.9	-	
Scc component						
Present	8	28.6	14.3	-	4.0 (1.4-6.6)	0.291
Absent	16	31.2	31.2	31.2	7.0 (4.8-9.2)	
Stage						
II	10	87.5	87.5	87.5	-	0.001
III or IVa	18	13.8	0.0	0.0	4.0 (2.2-5.8)	
Changing trends						
1970-1989	12	45.5	30.3	-	4.0 (0.0-12.9)	0.920
1990-1999	10	44.4	44.4	-	7.0 (4.1-9.9)	
2000-2009	14	20.8	20.8	20.8	7.0 (4.8-9.2)	

Scc: Squamous cell carcinoma; Si: Serosal invasion; Stage: Classification according to International Union Against Cancer (UICC).

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 totipotent 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

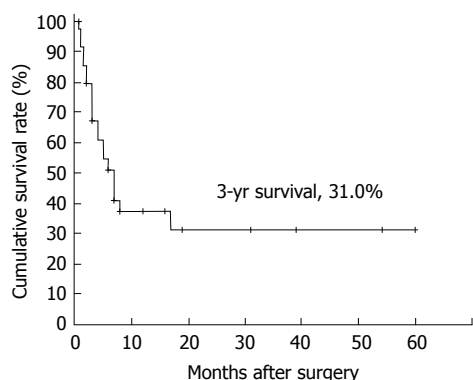


Figure 1 Survival after surgical resection for carcinosarcoma of the gall bladder ($n = 36$).

sarcomatous change or epithelial mesenchymal transition in cholangiocarcinoma^[37]. On the other hand, it has been speculated that these neoplasms arise from totipotent stem cells, rest cells of myoblasts that retain the capability of transformation, primitive undifferentiated müllerian 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^[13,27]. 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^[10,18,19,22,25].

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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REFERENCES

- 1 **Albores-Saavedra J**, Henson DE, Klimstra DS. Tumors of the Gallbladder, Extrahepatic Bile Ducts, and Ampulla of Vater. Series 3 Fascicle 8. Washington, DC: Armed Forces Institute of Pathology, 2000: 130-133
- 2 **Mehrotra TN**, Gupta SC, Naithani YP. Carcino-sarcoma of the gall bladder. *J Pathol* 1971; **104**: 145-148
- 3 **Higgs WR**, Mocega EE, Jordan PH Jr. Malignant mixed tumor of the gallbladder. *Cancer* 1973; **32**: 471-475
- 4 **Mansori KS**, Cho SY. Malignant mixed tumor of the gallbladder. *Am J Clin Pathol* 1980; **73**: 709-711
- 5 **Aldovini D**, Pisciole F, Togni R. Primary malignant mixed mesodermal tumor of the gallbladder. Report of a case and critical review of diagnostic criteria. *Virchows Arch A Pathol Anat Histol* 1982; **396**: 225-230
- 6 **Von Kuster LC**, Cohen C. Malignant mixed tumor of the gallbladder: report of two cases and a review of the literature. *Cancer* 1982; **50**: 1166-1170
- 7 **Born MW**, Ramey WG, Ryan SF, Gordon PE. Carcinosarcoma and carcinoma of the gallbladder. *Cancer* 1984; **53**: 2171-2177
- 8 **Inoshita S**. Phyllodes tumor (cystosarcoma phyllodes) of the breast. A clinicopathologic study of 45 cases. *Acta Pathol Jpn* 1988; **38**: 21-33
- 9 **Suster S**, Huszar M, Herczeg E, Bubis JJ. Adenosquamous carcinoma of the gallbladder with spindle cell features. A light microscopic and immunocytochemical study of a case. *Histopathology* 1987; **11**: 209-214
- 10 **Lumsden AB**, Mitchell WE, Vohman MD. Carcinosarcoma of the gallbladder: a case report and review of the literature. *Am Surg* 1988; **54**: 492-494
- 11 **Guo KJ**, Yamaguchi K, Enjoji M. Undifferentiated carcinoma of the gallbladder. A clinicopathologic, histochemical, and immunohistochemical study of 21 patients with a poor prognosis. *Cancer* 1988; **61**: 1872-1879
- 12 **Ishihara T**, Kawano H, Takahashi M, Yokota T, Uchino F, Matsumoto N, Fukuyama N. Carcinosarcoma of the gallbladder. A case report with immunohistochemical and ultrastructural studies. *Cancer* 1990; **66**: 992-997
- 13 **Nishihara K**, Tsuneyoshi M. Undifferentiated spindle cell carcinoma of the gallbladder: a clinicopathologic, immunohistochemical, and flow cytometric study of 11 cases. *Hum Pathol* 1993; **24**: 1298-1305
- 14 **Fagot H**, Fabre JM, Ramos J, Laffay V, Guillon F, Domergue J, Baumel H. Carcinosarcoma of the gallbladder. A case report and review of the literature. *J Clin Gastroenterol* 1994; **18**: 314-316
- 15 **Nakagawa T**, Yamakado K, Takeda K, Nakagawa T. An ossifying carcinosarcoma of the gallbladder: radiologic findings. *AJR Am J Roentgenol* 1996; **166**: 1233-1234
- 16 **Ryś J**, Kruczek A, Iliszko M, Babińska M, Wasilewska A, Limon J, Niezabitowski A. Sarcomatoid carcinoma (carcinosarcoma) of the gallbladder. *Gen Diagn Pathol* 1998; **143**: 321-325
- 17 **Eriguchi N**, Aoyagi S, Hara M, Hashino K, Imamura M, Sato S, Imamura I, Kutami R, Jimi A. A so-called carcinosarcoma of the gallbladder in a patient with multiple anomalies--a case report. *Kurume Med J* 1999; **46**: 175-179
- 18 **Ajiki T**, Nakamura T, Fujino Y, Suzuki Y, Takeyama Y, Ku Y, Kuroda Y, Ohbayashi C. Carcinosarcoma of the gallbladder with chondroid differentiation. *J Gastroenterol* 2002; **37**: 966-971
- 19 **Hotta T**, Tanimura H, Yokoyama S, Ura K, Yamaue H. So-called carcinosarcoma of the gallbladder; spindle cell carcinoma of the gallbladder: report of a case. *Surg Today* 2002; **32**: 462-467
- 20 **Kim MJ**, Yu E, Ro JY. Sarcomatoid carcinoma of the gallbladder with a rhabdoid tumor component. *Arch Pathol Lab Med* 2003; **127**: e406-e408
- 21 **Takahashi Y**, Fukushima J, Fukusato T, Shiga J. Sarcomatoid carcinoma with components of small cell carcinoma and undifferentiated carcinoma of the gallbladder. *Pathol Int* 2004; **54**: 866-871
- 22 **Huguet KL**, Hughes CB, Hewitt WR. Gallbladder carcinosarcoma: a case report and literature review. *J Gastrointest Surg* 2005; **9**: 818-821
- 23 **Sodergren MH**, Silva MA, Read-Jones SL, Hubscher SG, Mirza DF. Carcinosarcoma of the biliary tract: two case reports and a review of the literature. *Eur J Gastroenterol Hepatol* 2005; **17**: 683-685
- 24 **Kubota K**, Kakuta Y, Kawamura S, Abe Y, Inamori M, Kawamura H, Kirikoshi H, Kobayashi N, Saito S, Nakajima A. Undifferentiated spindle-cell carcinoma of the gallbladder: an immunohistochemical study. *J Hepatobiliary Pancreat Surg* 2006; **13**: 468-471
- 25 **Liu KH**, Yeh TS, Hwang TL, Jan YY, Chen MF. Surgical management of gallbladder sarcomatoid carcinoma. *World J Gastroenterol* 2009; **15**: 1876-1879
- 26 **Agarwal T**, Jain M, Goel A, Visayaragavan P, Gupta RK. Carcinosarcoma of the gallbladder. *Indian J Pathol Microbiol*

- 2009; **52**: 244-245
- 27 **Uzun MA**, Koksal N, Gunerhan Y, Celik A, Gunes P. Carcinosarcoma of the gallbladder: report of a case. *Surg Today* 2009; **39**: 168-171
- 28 **Shimada K**, Iwase K, Aono T, Nakai S, Takeda S, Fujii M, Koma M, Nishikawa K, Matsuda C, Hirota M, Fushimi H, Tanaka Y. Carcinosarcoma of the gallbladder producing alpha-fetoprotein and manifesting as leukocytosis with elevated serum granulocyte colony-stimulating factor: report of a case. *Surg Today* 2009; **39**: 241-246
- 29 **Kaplan EL**, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958; **53**: 457
- 30 **Okabayashi T**, Hanazaki K. Surgical outcome of adenosquamous carcinoma of the pancreas. *World J Gastroenterol* 2008; **14**: 6765-6770
- 31 **Okabayashi T**, Kobayashi M, Nishimori I, Namikawa T, Okamoto K, Onishi S, Araki K. Adenosquamous carcinoma of the extrahepatic biliary tract: clinicopathological analysis of Japanese cases of this uncommon disease. *J Gastroenterol* 2005; **40**: 192-199
- 32 **Kobayashi M**, Okabayashi T, Okamoto K, Namikawa T, Araki K. A clinicopathologic study of primary adenosquamous carcinoma of the liver. *J Clin Gastroenterol* 2005; **39**: 544-548
- 33 **Diebold-Berger S**, Vaiton JC, Pache JC, d'Amore ES. Undifferentiated carcinoma of the gallbladder. Report of a case with immunohistochemical findings. *Arch Pathol Lab Med* 1995; **119**: 279-282
- 34 **Goldman RL**, Weidner N. Pure squamous cell carcinoma of the larynx with cervical nodal metastasis showing rhabdomyosarcomatous differentiation. Clinical, pathologic, and immunohistochemical study of a unique example of divergent differentiation. *Am J Surg Pathol* 1993; **17**: 415-421
- 35 **Kawano R**, Takeshima Y, Inai K. Alteration of the p53 gene of lung carcinomas with sarcomatous transformation (spindle cell carcinoma): analysis of four cases. *Pathol Int* 1996; **46**: 38-45
- 36 **Hatakeyama S**, Satoh M, Yoshimura N, Otsu T. Immunocytochemical localization of bone morphogenetic proteins (BMPs) in salivary gland pleomorphic adenoma. *J Oral Pathol Med* 1994; **23**: 232-236
- 37 **Yoo HJ**, Yun BR, Kwon JH, Ahn HS, Seol MA, Lee MJ, Yu GR, Yu HC, Hong B, Choi K, Kim DG. Genetic and expression alterations in association with the sarcomatous change of cholangiocarcinoma cells. *Exp Mol Med* 2009; **41**: 102-115
- 38 **Albores-Saavedra J**, Cruz-Ortiz H, Alcantara-Vazques A, Henson DE. Unusual types of gallbladder carcinoma. A report of 16 cases. *Arch Pathol Lab Med* 1981; **105**: 287-293

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