

Clinical outcome and long term results after surgical treatment of biliary cystadenoma and cystadenocarcinoma

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Backgrounds/Aims: Biliary cystadenoma (BCA) and cystadenocarcinoma (BCCA) are rare cystic hepatic neoplasms. Prior reports concerning the proper surgical treatment and long-term survival are scarce. We report our experience and survival outcome of 30 patients over the last 25 years. **Methods:** We retrospectively reviewed the clinicopathologic data of the pathologically confirmed 18 BCA and 12 BCCA patients, who underwent operations from 1983 to 2006, at the Seoul National University Hospital. **Results:** The patients consisted of 8 men and 22 women with a mean age of 51 years. With abdominal computed tomography scans, 73.3% (n=22) were preoperatively diagnosed as BCA or BCCA, and differentiating BCCA from BCA was accurate in 58.3% patients. R0 resection was achieved in 90% (n=27). The differentiating factors included the presence of mural nodule (4/18 vs. 8/12; $p=0.009$) and mucinous content (2/9 vs. 8/1; $p=0.005$), and tumor size tending to be larger in BCCA (11.7 cm vs. 7.9 cm; $p=0.067$). Overall 5-year and 10-year survival rates of BCCA were 72.9% and 60.9%, respectively. Of patients with BCCA, 4 experienced recurrence. In case of recurrence, patients tended to be younger than 50 years ($p=0.061$) and the lesions tended to be larger than those without recurrence ($p=0.088$). **Conclusions:** Preoperative differentiations of BCA from simple cyst, and BCCA from BCA are still difficult. Complete removal of the tumor, via major hepatectomy, should be considered, especially in the younger age group with large tumor. (*Korean J Hepatobiliary Pancreat Surg* 2012;16:24-28)

Key Words: Biliary tract; Cystadenoma; Cystadenocarcinoma; Survival rate; Malignancy

INTRODUCTION

Biliary cystadenoma (BCA) and cystadenocarcinoma (BCCA) are rare cystic neoplasms of the liver, consisting of 4.6% of cystic neoplasms of the liver.¹ Improvements in imaging technologies have made it possible to detect the cystic neoplasms of the liver in a much better manner with greater efficiency than the earlier approaches. Since, the BCA is considered a premalignant lesion,² it should be differentiated from benign cystic lesions of the liver, such as simple hepatic cyst or abscess. Furthermore, preoperative accurate differentiation of BCCA from BCA is not established yet. It is difficult to determine a proper surgical treatment when preoperative diagnosis is obscure, so enucleation, fulguration or fenestration for BCA has been performed frequently.³⁻⁶ In this study, we evaluated

the clinical and pathological characteristics of BCA and BCCA and tried to reveal the factors associated with malignancy and recurrence, as comparing those characteristics between BCA and BCCA.

METHODS

The clinicopathologic data of 30 patients with the diagnosis of BCA (n=18) or BCCA (n=12), who underwent operation between September 1983 and May 2006 at Seoul National University Hospital were retrospectively reviewed. The patient demographic information, clinical presentations, radiological details, surgical data, pathology, postoperative courses, and long-term survivals were evaluated. For the purpose of mortality survey, the database of the National Statistical Office of Korea was used.

Received: October 13, 2011; **Revised:** November 26, 2011; **Accepted:** December 20, 2011

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Table 1. Clinical characteristics of the patients with biliary cystadenoma or cystadenocarcinoma

	Total (n=30)
Age (yrs, mean±SD)	50.7±14.2
Sex (M : F)	1 : 2.75
Symptom at presentation	22 (73.3%)
Pain	10 (33.3%)
Mass	7 (23.3%)
Fever	2 (6.7%)
Others	3 (10.0%)
Concurrent neoplasm	4 (13.3%)
Operation	
Cyst excision	8 (26.7%)
Sectionectomy (extended)	7 (23.3%)
Hemihepatectomy	13 (65.0%)
Open biopsy	2 (6.7%)
Follow up (months, median)	28 (range, 0-162)

Data were analyzed with SPSS Statistics version 19.0 (IBM Corp., Somers, NY, USA). Categorical data were compared using the Fisher's exact test and linear-by-linear association. Continuous variables were compared by using the Student's t-test. Cumulative survival data were calculated by the Kaplan-Meier method and compared by using the log-rank test. Results were presented as means±standard deviation (SD) and a *p*-value of <0.05 was considered statistically significant.

RESULTS

Demographics

The patients consisted of 8 men and 22 women, with a mean age of 51 years at the time of the operation (range: 18-77). Patient demographics are listed in Table 1. Twenty-two patients (73.3%) were symptomatic at presentation. Nine patients (30%) had received earlier interventions, including 6 percutaneous aspirations, 3 percutaneous drainages, and one partial cystectomy. Six patients who were initially diagnosed as having a simple cyst were finally diagnosed as BCA, after median of 4 years (range: 0-25), because of cyst size increase (median 5 cm, range: 3-14 cm) or development of various symptoms.

Preoperative diagnosis

The laboratory data, including liver function test, alpha-fetoprotein (AFP), chorioembryonic antigen (CEA), CA 19-9, were not helpful for the diagnosis. This is so,

Table 2. Modalities used for diagnosis of biliary cystadenoma (BCA) or cystadenocarcinoma (BCCA)

	Total (n=30)
Diagnostic modality	
Ultrasonography	15 (50.0%)
Computed tomography	28 (93.3%)
Magnetic resonance imaging	3 (10.0%)
Magnetic resonance cholangiopancreatography	2 (6.7%)
Endoscopic retrograde cholangiopancreatography	4 (13.3%)
Needle biopsy	8 (26.7%)
BCA	2 (6.7%)
BCCA	1 (3.3%)
Negative results	5 (16.7%)
Preoperative diagnostic accuracy	18 (60%)

since it was all within normal limits except in two patients with BCCA who had elevated CA 19-9 (690 U/ml) or AFP (229 ng/ml). Needle biopsy was performed in 8 patients (26.7%), which revealed 2 BCA and 1 BCCA and the other 5 specimens showed negative result (Table 2).

Of the 30 total patients, 28 underwent abdominal CT scans (Fig. 1). Magnetic resonance cholangiopancreatography or endoscopic retrograde cholangiopancreatography was additionally performed. Based on radiologic imaging study, preoperative diagnosis was accurate in 61% (n=11) of BCA patients. Others were diagnosed as a simple cyst, hemangioma, choledochal cyst, hepatocellular carcinoma or cholangiocarcinoma. In cases with BCCA, preoperative diagnosis was accurate in 58.3% (n=7). Other 4 patients were diagnosed as BCA, and the other as a simple cyst.

Operation and perioperative morbidity

Types of surgery are listed in Table 1. Almost all of the patients with BCA, 17 of 18 (94.4%) had complete removal of the cystadenoma. The remaining 1 patient found the liver cyst, incidentally, and underwent partial excision with an impression of a simple cyst, which was diagnosed as BCA postoperatively. Complete removal of the cystadenocarcinoma occurred in 10 of 12 patients with BCCA (83.3%). Of the remaining 2 patients with BCCA, 1 patient with preoperative diagnosis of a simple cyst underwent partial cyst excision and the other 1 patient with duodenum and inferior vena cava invasion underwent open biopsy and percutaneous drainage.

There were 3 cases of postoperative complication. Of

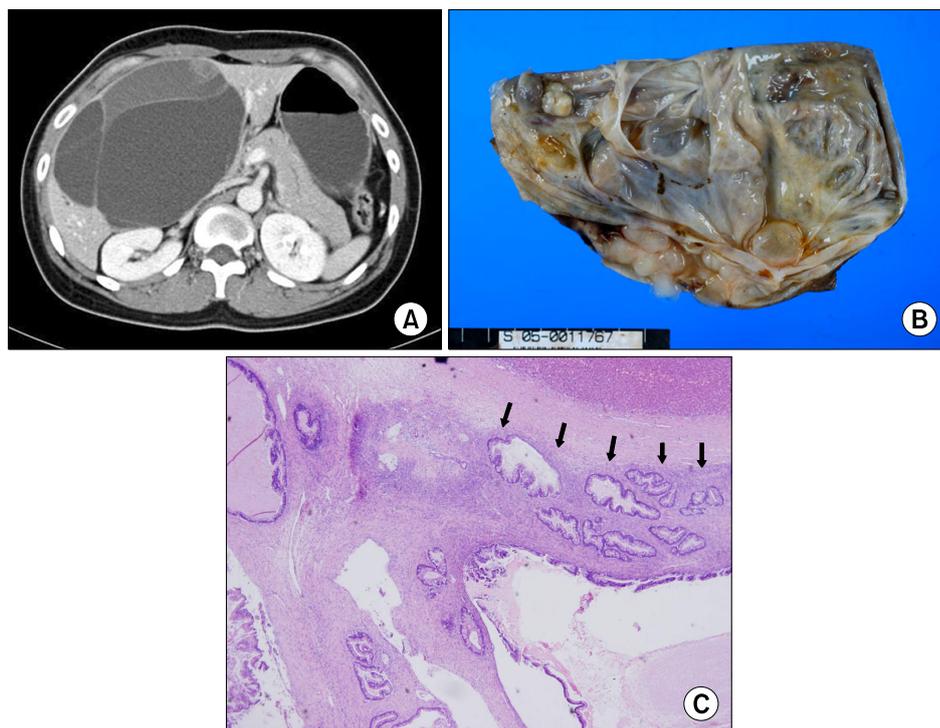


Fig. 1. A 37-years-old female patient was diagnosed preoperatively as biliary cystadenocarcinoma. (A) CT scan revealed multiseptated cystic mass with mural nodule. (B) Gross specimen of the patient revealed a mural nodule arising from the cyst wall. (C) Papillary growing mucosa of the cyst wall with invading glands into the stroma (arrow) is identified with microscopic exam (H&E, $\times 40$).

Table 3. Comparison of clinicopathologic findings between biliary cystadenoma (BCA) and cystadenocarcinoma (BCCA)

Factor	BCA (n=18)	BCCA (n=12)	p-value
Age (yrs, mean \pm SD)	51.6 \pm 15.3	49.3 \pm 12.8	0.271
Sex (M : F)	1 : 3.5	1 : 2	0.678
Preoperative diagnostic accuracy	11 (61.1%)	7 (58.3%)	0.648
Septation	10 (58.8%)	9 (75%)	0.405
Mural nodule	4 (23.5%)	8 (66.7%)	0.009
Size (cm)	7.9 \pm 1.2	11.7 \pm 1.7	0.067
Location			0.131
Right	5 (27.8%)	6 (50%)	
Left	11 (61.1%)	6 (50%)	
Bilateral	1 (5.6%)	0	
Extrahepatic	1 (5.6%)	0	
Multiplicity			0.660
Single	15 (83.3%)	9 (75%)	
Multiple	3 (16.7%)	3 (25%)	
Content			0.005
Mucin	2 (11.8%)	8 (66.7%)	
Serous	7 (41.2%)	1 (8.3%)	
Mural nodule	1 (5.9%)	5 (41.7%)	0.056

which, 2 patients developed postoperative bile leakage: these were resolved after percutaneous drainage. The remaining 1 patient developed postoperative bleeding, which was successfully controlled with an operation at postoperative day 1.

Differentiation between BCA and BCCA

Postoperative pathology revealed 18 cases of BCA and 12 cases of BCCA. Mural nodules were more often observed in patients with BCCA (66.7% vs. 23.5%, $p=0.009$). Most of BCA (83.3%) and BCCA (75%) were of single lesion. Lymph node metastasis was not identified in both BCA and BCCA. The size of the tumor tended to be larger in BCCA (11.7 cm vs. 7.9 cm, $p=0.067$). Mucinous content was more frequent in BCCA (66.7% vs. 11.8%, $p=0.005$). Mural nodules were more often observed in BCCA with marginal significance (41.7% vs. 5.9%, $p=0.056$). Resection margin was clear in all cases of BCA, while in one case of BCCA. Pathology revealed positive deep hepatic resection margin after left lateral sectionectomy with curative intent (Table 3).

Prognosis

There was no recurrence or postoperative death in BCA. However, in BCCA, three patients died of disease and overall 5-year and 10-year survival rates of BCCA were 72.9% and 60.9%, respectively (Fig. 2).

Recurrence was observed in four patients with BCCA (Table 4). One patient who underwent partial cyst excision with preoperative diagnosis of a simple cyst had a recurrence after 1 year and received curative right

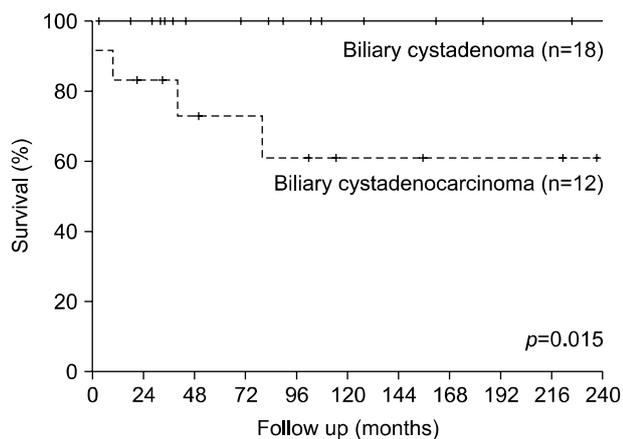


Fig. 2. Overall survival according to the pathology.

hemihepatectomy. The other three patients had recurrence after curative resection. The first was a 43-year-old female who died at 3 months after left lateral sectionectomy, with disseminated liver metastasis. Second, a 49-year-old male died at 10 months after extended left hemihepatectomy, with peritoneal seeding. As for the last, an 18-year-old female died at 80 months after left lateral sectionectomy, with brain, bone and kidney metastasis. Recurred patients tended to be younger than 50 years ($p=0.061$) and the size of the lesion tended to be larger (15.5 cm vs. 9.8 cm, $p=0.088$). However, statistical significance was not found due to small sample size.

DISCUSSION

Biliary cystadenoma and cystadenocarcinomas are rare cystic neoplasms of the liver, that may occur in the liver or in the extrahepatic biliary system, which was first reported in 1892 by Keen.⁷ The incidence of intrahepatic biliary cystadenomas is estimated between one in 20,000 to 100,000 people, while the incidence of cystadenocarcinomas is approximately one per 10 million patients.⁸ This case series is the largest single institution report to our knowledge to date, with 18 BCA and 12 BCCA patients.

More than 80% of cystadenomas are reported in women.³ In this study, 73.3% ($n=22$) of patients were females. Lauffer et al reported that, in contrast to the female predominance in BCA, BCCA occurred more often in male.⁹ But in this case series, male consisted 22.2% in BCA and 33.3% in BCCA. This revealed no statistical

Table 4. Factors associated with recurrence in patients with biliary cystadenocarcinoma

Factor	Recurrence (n=4)	No recurrence (n=8)	p-value
Age (yrs, mean±SD)	40±15	54±9	0.061
≤ 50	4 (100%)	2 (25%)	
> 50	0	6 (75%)	
Sex (M : F)	1 : 3	3 : 5	NS
Symptomatic at presentation	4 (100%)	7 (87.5%)	NS
Septation	2 (50%)	7 (87.5%)	NS
Mural nodule	2 (50%)	6 (75%)	NS
Size (cm, mean±SD)	15.5±7	9.8±4.7	0.088
Multiple lesion	0	3 (37.5%)	NS
Mucinous content	3 (75%)	5 (62.5%)	NS
Mural nodule	1 (25%)	4 (50%)	NS
Positive resection margin	1 (25%)	0	NS

difference between the two groups.

Until late 1990s, needle biopsy or aspiration cytology was generally performed for diagnosis of cystic hepatic neoplasms at our institution. Wee et al. reported that fine needle aspiration cytology of the cyst contents could be a good diagnostic tool.¹⁰ However, the positive results of percutaneous needle biopsy and aspiration cytology in this case series were less than desired. Based on these results, the imaging technique has now employed to replace needle biopsy or aspiration cytology at our institution.

The most helpful radiologic studies were abdominal CT and ultrasonography, as reported by prior case series.^{5,6,11} A well-encapsulated multilobular cyst with internal septations and a thickened irregular wall were diagnostic for BCA.¹¹ Overall diagnosis as BCA or BCCA was achieved in 73.3% of the patients. However, the differentiation criteria between BCA and BCCA have not been established.^{2,11,12} Devaney et al. reported that the septation without nodularity suggested the diagnosis of BCA, whereas the septation with mural nodules or presence of discrete mural nodule was suggestive of BCCA.¹³ As shown in our case series, the presence of mural nodule within the cyst represented a possibility of BCCA ($p=0.009$). In case of BCCA, 11 of 12 patients were preoperatively diagnosed as BCA or BCCA. Differentiation of BCCA from BCA with preoperative imaging was accurate in 58.3%. However, limitation of preoperative differentiation between BCA and BCCA did not affect the treatment strategy. Each was treated equally to achieve complete removal of the tumor

with safety margin.

Complete surgical excision is the only curative treatment for BCA and BCCA.^{3,4,13} BCA and BCCA cannot be reliably differentiated on the basis of radiologic and macroscopic criteria.^{3,4,12,14} Without complete excision, local recurrence and risk of malignancy transformation is increased.^{6,9,15} Davies et al. reported high recurrence rate of up to 50%, after local excision in extrahepatic BCA.¹⁶ However, when tumors are large, loss of large liver volume may be inevitable, and thus remnant liver function must be considered carefully. We performed major hepatic resection in majority of patients without definite post-operative complications. Hemihepatectomies, including extended hemihepatectomies, undergone by 13 out of the 30 patients (43.3%). Although, liver resection was more extensive than any other prior reports, there was no severe complication or operative mortality. In addition, recurrence was related to younger age and larger size of tumor. Therefore, when considering operation in patients with these characteristics, more extensive surgery should be performed to achieve sufficient safety margins.

The rate of malignant transformation is reported to be as high as 30%.¹³ Natural course of malignant transformation was not observed because there was no delay for operation, once BCA was suspected. However, we experienced a case of 62-year-old female having two synchronous lesions, a BCA as well as a BCCA.

Differentiation of BCA from simple cyst according to radiologic findings was still difficult. During the follow-up for cystic neoplasms of the liver, increasing size and development of a symptom may be suggestive for BCA. Although, presence of a mural nodule and mucinous content were suggestive for BCCA, differentiation of BCCA from BCA was quite challenging. Planning an operation of BCA, possibility of BCCA must be considered and complete excision of the tumor should be performed. In younger patients with large sized tumor, major hepatectomy might be performed to reduce a risk of

recurrence.

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