

## Retrospective Study

## Clinical outcomes of small cell neuroendocrine carcinoma and adenocarcinoma of the gallbladder

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### Abstract

**AIM:** To compare the demographics and survival rates between gallbladder adenocarcinoma (GB-adenocarcinoma) and small cell neuroendocrine carcinoma of the gallbladder (GB-NEC-SCC).

**METHODS:** From March 2007 to September 2012, patients who underwent resection of tumor stage T2/T3 GB cancer were enrolled for this study. Forty-two patients were included in this study, including 38 diagnosed with GB-adenocarcinoma and four diagnosed with GB-NEC-SCC. In the GB-adenocarcinoma group, a radical operation was performed in 28 patients, and ten patients underwent simple cholecystectomy. In the GB-NEC-SCC group, a radical operation was performed in three patients, and one patient underwent simple cholecystectomy. Comparative analysis of the two groups was performed, including clinicopathologic features and survival rates.

**RESULTS:** The median age of the patients was 68 y (range: 35-83 years) and females comprised 26/42 of the patients. GB-adenocarcinoma patients were significantly older than GB-NEC-SCC patients ( $67.89 \pm 11.15$  vs  $55.75 \pm 10.31$  years;  $P = 0.029$ ). The median tumor size in GB-adenocarcinoma patients was  $2.56 \pm 1.75$  cm and  $3.98 \pm 3.74$  cm in GB-NEC-SCC patients; however, there was no significant difference between the two groups. For tumors  $> 2$  cm, T stage (T2 vs T3), lymphovascular invasion, perineural invasion, lymph node metastasis and lymph node ratio showed no significant differences between the two groups. The overall survival rate of the 42 patients at five years was 77.0%. In the GB-adenocarcinoma group, the overall five-year survival rate was 74.8%, and survival in the GB-NEC-SCC group was 100%, which was not significantly different between the two groups.

**CONCLUSION:** The strategy for treating patients with GB-NEC-SCC should be similar to that used for treating GB-adenocarcinoma, including radical cholecystectomy and liver resection.

**Key words:** Gallbladder adenocarcinoma; Gallbladder cancer; Radical resection; Small cell neuroendocrine

carcinoma; Survival

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**Core tip:** Small cell neuroendocrine carcinomas of the gallbladder are uncommon neoplasms, and therefore, little is known about their demographics and clinical course. Furthermore, the studies of the gallbladder neuroendocrine tumor and neuroendocrine carcinoma are limited to case reports with literature review. This study retrospectively compared the demographics and survival rates of gallbladder adenocarcinoma and small cell neuroendocrine carcinoma of the gallbladder, and reports the clinicopathologic features of small cell neuroendocrine carcinoma of the gallbladder, based on individual experiences.

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## INTRODUCTION

Gallbladder (GB) cancer is an aggressive disease with characteristics of late presentation, rapid progression, and dismal results, the vast majority of which (85%-90%) are adenocarcinomas. Other histologic types of GB cancers include squamous, adenosquamous, and neuroendocrine carcinoma (NEC). Primary NECs of the gallbladder are very rare and are unknown in detail.

All neuroendocrine tumors (NET) have a malignant potential. NETs include well-differentiated NETs (classical carcinoid tumors), well-differentiated NECs (atypical carcinoids or malignant carcinoids), poorly differentiated NECs (high grade carcinoma: small-cell/large-cell types), and mixed exocrine-endocrine carcinomas. Primary NETs of the GB are particularly rare, and in the Surveillance, Epidemiology, and End Results (SEER) registry, only 278 cases have been reported between 1973 and 2005, representing 0.5% of all NETs<sup>[1,2]</sup>, and 54 cases of small cell NEC of the GB (GB-NEC-SCC) were reported in another SEER-based study<sup>[3]</sup>. There have been several hypotheses about the origination of NETs of the GB. First, neuroendocrine cells usually are not seen in the normal GB and occur only in the intestinal or gastric metaplastic GB mucosa, occurring secondary to cholelithiasis and chronic cholecystitis<sup>[2]</sup>. Because of the expression of various neuroendocrine cells in this way, it is possible for NETs to occur. Secondly, heterotopic pancreatic tissue in the GB is an especially rare condition<sup>[4,5]</sup>. It is also possible that NETs may arise in ectopic pancreatic tissue.

Although classical well-differentiated NETs and GB-NEC-SCC are the most common neuroendocrine tumors

**Table 1** Grading of gastroenteropancreatic neuroendocrine tumors

Grade	GET-NETs
Low (ENETS G1)	< 2 mitoses/10 HPF and < 3% Ki-67 index
Intermediate (ENETS G2)	2-20 mitoses/10 HPF or 3%-20% Ki-67 index
High (ENETS G3)	> 20 mitoses/10 HPF or > 20% Ki-67 index

ENETS: European Neuroendocrine Tumor Society; HPF: High-power fields.

of the GB, most of our knowledge about these tumors is limited and based on isolated case reports or a very small series<sup>[3]</sup>. The purpose of this study was to analyze and compare the demographics and survival rates of GB-adenocarcinoma and GB-NEC-SCC, and to report the clinicopathologic features of GB-NEC-SCC, based on individual experiences.

## MATERIALS AND METHODS

### Patients

Patients at Pusan National University Hospital who underwent resection of tumor stage T2/T3 GB cancer between March 2007 and September 2012 were enrolled in this study. Based on the medical records, a retrospective review was performed. We excluded patients with squamous carcinoma, papillary carcinoma and mucinous carcinoma; finally, 42 patients were included. Thirty-eight patients were diagnosed with GB-adenocarcinoma and four patients were diagnosed with GB-NEC-SCC. The study was approved by the institutional review board.

### Operation methods

We examined GB specimens taken from laparoscopic or open cholecystectomy to identify suspicious lesions. Lesions were sent to a pathologist for frozen-section biopsy. For cases reported by the pathologist as  $\geq$  T2 GB cancer, we performed radical cholecystectomy including S4b, S5 segmentectomy of the liver. If GB cancer  $\geq$  T2 was suspected by macroscopic appearance during exploration, we performed radical cholecystectomy and liver resection attaching GB. Patients who refused the second radical operation for T2 stage and those who were not able to receive radical operation due to severe morbidities underwent simple cholecystectomy.

### Histopathology

GB-NET was diagnosed according to the World Health Organization (WHO) classification published in 2010<sup>[6]</sup>. The grade of NET was classified according to the WHO classification and European Neuroendocrine Tumor Society grading system (Table 1)<sup>[6-9]</sup>. GB-NEC-SCC was diagnosed if the following diagnostic criteria were fulfilled: (1) positive immunohistochemical staining of more than one protein, including chromogranin A and synaptophysin, or a cluster of differentiation 56, indicating the presence of neural cell adhesion molecules<sup>[2,10]</sup>; and (2) histopathologic presence of

Table 2 Clinicopathologic features

Characteristic	GB-adenocarcinoma (n = 38)	GB-NEC-SCC (n = 4)	P value
Sex			1.000
Male	15	1	
female	23	3	
Age, yr	67.89 ± 11.15	55.75 ± 10.31	0.029
Age groups, n			0.080
< 65 yr	10	3	
≥ 65 yr	28	1	
Operation type, n			1.000
Simple cholecystectomy	10	1	
Extended cholecystectomy	28	3	
Tumor size, cm	2.56 ± 1.75	3.98 ± 3.74	0.788
Tumor size groups, n			0.609
< 2 cm	11	2	
≥ 2 cm	21	2	
Tumor stage, n			0.410
T2	34	3	
T3	4	1	
Lymphovascular invasion, n			0.245
-	29	2	
+	8	2	
Perineural invasion, n			0.107
-	26	1	
+	11	3	
Lymph node metastasis, n			0.537
-	18	1	
+	9	2	
Lymph node ratio	0.15 ± 0.29	0.18 ± 0.28	0.485
Recurrence, n			1.000
-	28	3	
+	10	1	

GB: Gallbladder; GB-NEC-SCC: Small cell neuroendocrine carcinoma of the gallbladder.

high-grade and small cell cytologic features, very high cellularity with hyperchromatic nuclei, absence of very small nucleoli with scant cytoplasm, high nuclear-to-cytoplasmic ratio, and a round or fusiform shape (according to the classification of SCCs as NETs by the WHO)<sup>[2,10,11]</sup>.

### Statistical analysis

Categorical variables between the GB-adenocarcinoma and GB-NEC-SCC groups were compared by the  $\chi^2$  or Fisher's exact tests. Age, tumor size and lymph node ratio were compared by Student's *t* and Mann-Whitney *U* tests. The comparison of overall survival was analyzed by the log rank test. *P* values less than 0.05 were considered statistically significant. All statistical analyses were performed using the SPSS version 13.0 for Windows (SPSS Inc., Chicago, IL, United States).

## RESULTS

The median age of the patients was 68 year (range: 35-83 year) and females comprised 26/42 of the patients (female/male ratio, 1.6:1). The age of GB-adenocarcinoma patients was significantly older than that of GB-NEC-SCC patients (*P* < 0.05) (Table 2).

Table 3 Clinicopathologic features of patients with small cell neuroendocrine carcinoma of the gallbladder

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4
Sex	Female	Male	Female	Female
Age, yr	49	66	63	45
Tumor size, cm	1.9	1.5	3	9.5
Operation	RC	RC	C	RC <sup>1</sup>
Combined adenocarcinoma	-	+	-	+
Gross finding	Polypoid	Fungating	Fungating	Mutilobulated
Lymphovascular invasion	+	-	-	+
Perineural invasion	+	+	+	-
Tumor stage	T2	T2	T2	T3
Lymph node metastasis	0/15	1/2	0/0	1/39
Mitosis (/10 HPF)	2	8	20	22
Synaptophysin	+	+	-	-
Chromogranin A	+	+	-	-
CD56	+	+	+	+
P53	+	+	NA	NA
Ki-67	30%	25%	40%	50%

<sup>1</sup>This patient underwent hepatopancreaticoduodenectomy and right hemicolectomy. C: Cholecystectomy; HPF: High-power fields; NA: Not available; RC: Radical cholecystectomy.

The percentage of patients over the age of 65 year was 69% (29/42), which did not differ between the groups. The median tumor size of GB-adenocarcinoma was not significantly different than GB-NEC-SCC (2.56 ± 1.75 *vs* 3.98 ± 3.74). When comparing tumors > 2 cm, T stage (T2 *vs* T3), lymphovascular invasion, perineural invasion, lymph node metastasis, and lymph node ratio were not significantly different between the two groups. Table 3 shows the pathologic features of the four patients in the GB-NEC-SCC group.

The overall survival rate of the 42 patients at five years was 77.0% (Figure 1). In the GB-adenocarcinoma group, the overall 5-year survival rate was 74.8% (radical operation, 78.4% *vs* simple cholecystectomy, 72.7%, *P* = 0.471) and in the GB-NEC-SCC group, the overall five-year survival rate was 100% (Figure 2). There was no significant difference between the two groups (*P* = 0.896). Immunohistochemical staining for synaptophysin, chromogranin A and Ki-67 is presented in Figure 3.

## DISCUSSION

Biliary NET comprises less than 1% of all NETs<sup>[12-15]</sup>. In particular, GB-NEC-SCC is extremely rare, with only 54 cases found in a review of nearly 13981 cases of carcinoids from the SEER database<sup>[3]</sup>. Furthermore, the studies of the GB-NEC-SCC were limited to case reports with a literature review (Table 4). In this regard, a study of the comparison between GB-adenocarcinoma and GB-NEC-SCC is thought to be meaningful.

In this study, we found that GB-adenocarcinoma and GB-NEC-SCC were common in females (23/38 and 3/4, respectively), consistent with findings by Albores-Saavedra *et al.*<sup>[3]</sup>. Furthermore, GB-NEC-SCC patients

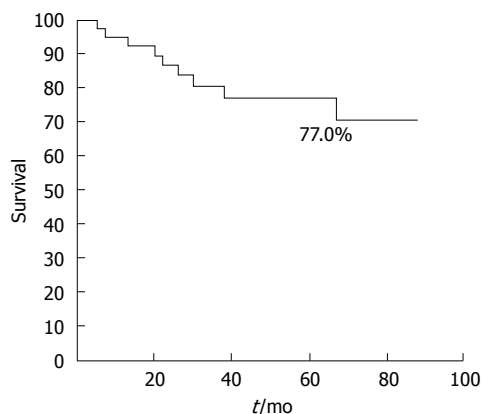


Figure 1 Overall five-year survival rate.

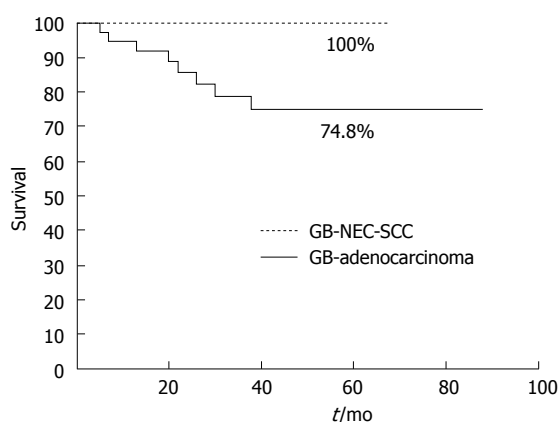


Figure 2 Five-year group survival rates. gallbladder (GB)-adenocarcinoma, adenocarcinoma of the gallbladder; small cell neuroendocrine carcinoma of the gallbladder (GB-NEC-SCC), small cell neuroendocrine carcinoma of the gallbladder.

were younger than GB-adenocarcinoma patients. Previous studies reported that a preoperative diagnosis of GB-NEC is very difficult because the presentation generally consists of non-specific symptoms, including right hypochondrial pain or discomfort and weight loss. Additionally, the presence of carcinoid syndrome is rare, and the majority of lesions are identified incidentally at the time of cholecystectomy performed for gallbladder stones<sup>[2,16]</sup>. Despite the development of imaging studies, preoperative differentiation between GB-adenocarcinoma and GB-NEC by ultrasound, computed tomography, or magnetic resonance imaging is still difficult. However, according to a recent study, the combination of positron emission tomography with computed tomography or magnetic resonance imaging was effective for the detection of NETs, and these modalities generally could obtain a high level of sensitivity<sup>[17,18]</sup>. In the present study, all cases of GB-NEC-SCC were diagnosed as GB-adenocarcinoma in preoperative imaging studies. Measurement of chromogranin A is known to be helpful for preoperatively diagnosing NET. Chromogranin A is elevated in 90% of gut NETs, and it correlates with the tumor burden and recurrence, and therefore, chromogranin A may be an effective biology marker in

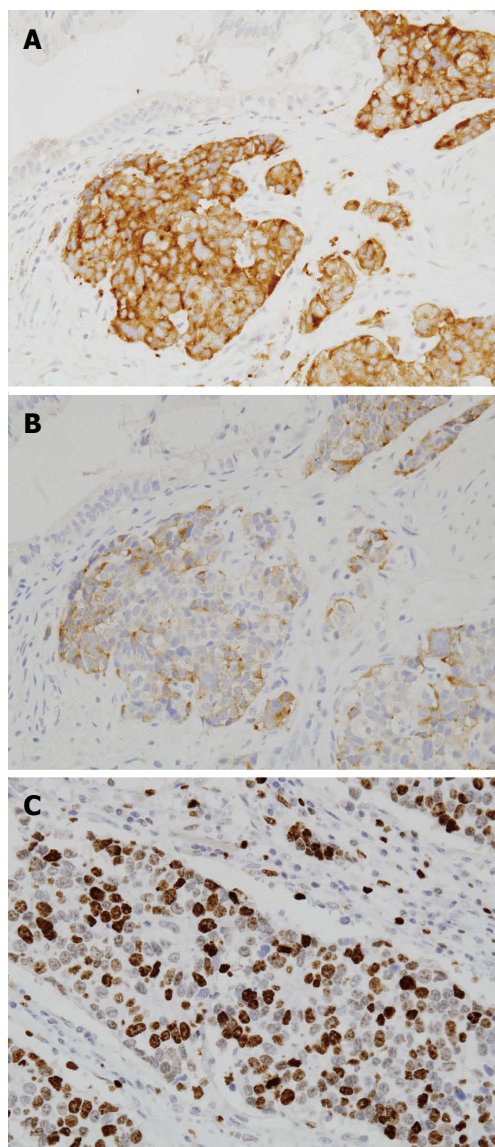


Figure 3 Immunohistochemical staining of small cell neuroendocrine carcinoma of the gallbladder. Immunostaining for A: Synaptophysin; B: Chromogranin A; C: Ki-67; × 400 magnification.

the preoperative diagnosis of NETs<sup>[19]</sup>. However, the measurement of chromogranin A to diagnose GB-NET before surgery is not cost-effective.

Though not observed in any of the patients in this study, poorly differentiated large cell GB-NECs show large cell size, low nuclear to cytoplasmic ratio, and frequent nucleoli, which are key cytologic features distinguishing them from GB-NEC-SCCs<sup>[20]</sup>. According to Iype *et al*<sup>[6]</sup>, these NECs have a worse prognosis than GB-NEC-SCCs in the gallbladder. Grossly, GB-NEC-SCC may vary from unapparent covert lesions to largely necrotic, exophytic, or ulcerative masses<sup>[21]</sup>. In this study, two cases showed a fungating mass, one case showed a well-defined solid polypoid mass, and one case showed a well-circumscribed solid, multilobulated mass measuring 9.5 cm. Eltawil *et al*<sup>[2]</sup> reported that histologically, more than 90% of GB-NEC-SCC are poorly differentiated or

Table 4 Small cell neuroendocrine carcinoma of the gallbladder of the literature

Ref.	Age (yr)	Sex	Size (cm)	Meta or local inv	Mixed tumor	Survival (mo)	Tumor stage	Chromogranin A	Recurrence (site)	Operation type
Moskal <i>et al</i> <sup>[22]</sup> , 1999	69	F	NA	Regional LN meta, pancreas inv	+	44	T3	NA	+ (abdomen)	Radical
	57	F	NA	Regional LN meta, liver inv	-	31	T3	NA	+ (abdomen, bone)	Radical
	69	M	NA	Regional LN meta	-	21	T2	NA	+ (retroperitoneum)	C
	71	F	NA	Regional LN meta peritoneum meta	+	13	T2	NA	+ (retroperitoneum)	C
Maitra <i>et al</i> <sup>[21]</sup> , 2001	40	M	NA	Regional LN meta	+	189, alive	T2	NA	+ (lung, abdomen)	C
	85	F	4.0	Liver meta	+	13	≥ T2	+	NA	Surg
	77	F	2.8	Pancreas inv, LN meta	+	25	≥ T2	NA	NA	Surg
	43	F	2.0	Liver meta	+	9	≥ T2	+	NA	Surg
	73	F	2.5	LN meta	+	7	≥ T2	+	NA	Surg
	82	M	1.0	Liver meta	+	8	≥ T2	NA	NA	Surg
	77	F	3.0	-	+	10	≥ T2	+	NA	Surg
	73	M	6.3	Liver meta	-	6	≥ T2	NA	NA	Surg
	71	M	NA	-	-	3	T1	NA	NA	Surg
	37	F	8.0	LN meta	-	7	≥ T2	NA	NA	Surg
	68	M	2.0	LN meta	-	14	≥ T2	+	NA	Surg
	67	F	2.8	-	-	NA	≥ T2	+	NA	Surg
	78	M	1.8	LN meta	-	16	≥ T2	NA	NA	Surg
	67	M	NA	-	-	11	T1b	+	+ (liver, LN)	C
Lane <i>et al</i> <sup>[11]</sup> , 2002										
Iype <i>et al</i> <sup>[16]</sup> , 2008	32	F	2.0	Regional LN meta, liver meta	-	14, alive	T2	+	+ (liver, LN)	Radical
Current study, 2014	49	F	1.9	-	-	37, alive	T2	+	-	Radical
	66	M	1.5	Regional LN meta	+	13, alive	T2	+	-	Radical
	63	F	3.0	-	-	67, died	T2	-	+ (liver)	C
	45	F	9.5	LN inv, colon inv, liver inv	+	50, alive	T3	-	-	Radical

C: Cholecystectomy; F: Female; inv: Invasion; LN: Lymph node; M: Male; meta: Metastasis; NA: Not available; Surg: Extent of surgery not reported.

anaplastic, with regional or distant spread at diagnosis. In this study, one patient with GB-NEC who had direct invasion of the duodenum and ascending colon (pT3) underwent hepatopancreaticoduodenectomy and right hemicolectomy. After surgery, the patient was observed without recurrence for 50 mo. A combination of GB-NEC-SCC and adenocarcinoma is quite common, and of the 36 cases of SCC reported in the literature, 28 were pure SCCs and 8 were combined with adenocarcinoma<sup>[22]</sup>. In our study, two of the cases were SCC combined with adenocarcinoma.

In general, the only curative therapeutic modality for GB cancer, which is a higher grade than T1, is radical cholecystectomy, including cholecystectomy, hepatoduodenal lymph node dissection and hepatic resection<sup>[23-25]</sup>. However, despite a more aggressive surgical approach, the majority of patients who have undergone potentially curative resection for GB cancer will develop recurrent metastatic disease. The surgical treatment for GB-NEC varies widely. For patients in whom the GB-NEC is a T *in situ* or T1 tumor, simple cholecystectomy is probably adequate treatment<sup>[2,23-25]</sup>. For more advanced GB-NEC, the prognosis is usually poor, but better outcomes can be obtained by aggressive radical operative therapy<sup>[26]</sup>. However, there has been no rational surgical strategy for a number of reasons, including the rarity of the disease, the lack of predictive prognostic factors, the inability to identify progression, and the limited understanding of the biology of the lesion<sup>[2]</sup>. In a previous study, cholecystectomy was performed

in 12 patients, with a median survival of 4.5 mo, and radical resection was performed in two GB-NEC-SCC patients, with survivals of 4 and 20 mo<sup>[22]</sup>. In our study, among the 42 patients who underwent surgery for GB-adenocarcinoma or GB-NEC-SCC, the median survival was 38 mo. Eleven patients refused a second radical operation for T2 stage after it had been incidentally discovered after cholecystectomy. These patients' overall five-year survivals were not significantly different from the survival of patients undergoing a radical operation. According to previous research, a significant advantage in the five-year survival rate was observed in patients with T2 stage undergoing radical operation compared to those who received only simple cholecystectomy (38%-100% *vs* 17%-65%)<sup>[23]</sup>. We think the reason for this opposite result is that, first, the number of patients with simple cholecystectomy was small, and secondly, favorable histopathologic features such as a tumor size < 2 cm, T2 stage, lack of lymphovascular invasion (simple cholecystectomy, 1/10 *vs* radical operation, 9/21) were seen in these patients.

Moskal *et al*<sup>[22]</sup> reported that the most common metastatic sites of GB-NEC-SCC were the nodes (88%), liver (88%), lung (23%), and peritoneum (19%). In the present study, T2 GB-NEC-SCC was confirmed in one patient after laparoscopic cholecystectomy; however, the patient refused a second radical operation. Fifty-nine months after surgery, the patient had liver metastases and died 67 mo after surgery. A radical operation was performed in three patients and these patients are still alive.

The roles of radiotherapy and chemotherapy in the management of GB-NEC-SCC are unclear. In general, NETs are insensitive to traditional radiotherapy<sup>[27]</sup>. According to several case reports, chemotherapeutic agents, including cisplatin, gemcitabine and etoposide plus 5-fluorouracil, can lead to a partial response, resulting in palliation and the addition of a marginal advantage<sup>[16,28]</sup>. In the present study, after radical cholecystectomy, two patients underwent concurrent chemoradiation therapy (5-fluorouracil plus etoposide or cisplatin) and they have been followed, without recurrence, for 37 mo and 50 mo, respectively.

There have only been a few reports in the literature about the prognosis of GB-NEC-SCC, and therefore, the prognosis and related factors are not generally known. Previous studies reported that an elevated Ki-67, high mitotic index and invasion of adjacent structures are likely to be predictive of a poor outcome<sup>[29,30]</sup>. According to SEER data, the one-year survival of GB-NEC-SCC was 21% and five-year survival was 0%, but GB-NETs have a similar prognosis to GB-adenocarcinoma<sup>[2]</sup>. Although the prognosis of GB-NEC-SCC is poor, past studies reported that aggressive multimodal treatment may prolong survival<sup>[2,16,22]</sup>. Therefore, it seems acceptable to adopt a similar strategy including radical cholecystectomy for GB-NEC, and doing so is likely to result in a better outcome. This study showed a similar result to previous studies in that the five-year survival rate between GB-adenocarcinoma and GB-NEC-SCC was not significantly different; however, we achieved a high survival rate for GB-NEC-SCC. We think this result was due to the performance of radical operations on these patients and the lower T stage in GB-NEC-SCC patients.

This study had some limitations. First, this was a retrospective study. Second, due to insufficient numbers of patients, we could not conduct a statistical comparison by multivariate analysis. However, it is quite important to compare GB-adenocarcinoma and GB-NEC-SCC based on curative resection using strict diagnostic criteria. Thus, the study was valuable in assessing the clinical course of patients with GB-NEC-SCCs after curative surgery.

## COMMENTS

### Background

Gallbladder (GB) cancer is an aggressive disease, and the vast majority (85%-90%) are adenocarcinomas. Small cell neuroendocrine carcinomas of the GB (GB-NEC-SCC) are extremely rare, and therefore, little is known about their demographics and clinical course.

### Research frontiers

Classical well-differentiated neuroendocrine tumor (NET) and GB-NEC-SCC are the most common NETs of the GB, most of our knowledge about these tumors is limited and based on isolated case reports or a very small series.

### Innovations and breakthroughs

The authors retrospectively reviewed 42 patients with GB cancer, including four patients with GB-NEC-SCC. The authors analyzed and compared the demographics and survival rates between GB-adenocarcinoma and GB-NEC-SCC, and described the clinicopathologic features of GB-NEC-SCC. It is quite important to compare GB-adenocarcinoma and GB-NEC-SCC based on curative resection using strict diagnostic criteria. Thus, the study was valuable in assessing the clinical course of patients with GB-NEC-SCCs after curative surgery.

## Applications

The study results suggest that on the basis of difficulty in distinguishing between GB-NEC and GB-adenocarcinoma preoperatively, and similar prognoses between the two groups, aggressive surgical management based on GB-adenocarcinoma may be effective for patients with GB-NECs.

## Terminology

NETs include well-differentiated NETs (classical carcinoid tumors), well-differentiated NEC (atypical carcinoids or malignant carcinoids), poorly differentiated NEC (high grade carcinoma: small-cell/large-cell types), and mixed exocrine-endocrine carcinoma.

## Peer review

This article investigates the clinical characteristics for GB-NEC-SCCs. Particularly, the demographics and survival rates are compared with GB-adenocarcinomas. This scientific paper is well written and provides some new and useful information regarding the GB-NEC-SCCs

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