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**Comparison of clinical outcome of small cell neuroendocrine carcinoma and adenocarcinoma of the gallbladder**

Yun SP *et al.* Small cell neuroendocrine carcinoma of the gallbladder

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**Abstract**

**AIM:** To analyze and 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 T2/T3 GB cancer were enrolled for this study. Forty-two patients were included in this study. Thirty-eight patients were diagnosed with GB-adenocarcinoma and 4 patients were diagnosed with GB-NEC-SCC. In the GB-adenocarcinoma group, a radical operation was performed in 28 patients, and 10 patients underwent simple cholecystectomy. In the GB-NEC-SCC group, a radical operation was performed in 3 patients, and 1 patient underwent simple cholecystectomy. Comparative analysis of the two group was performed, including clinicopathological features and survival rates.

**RESULTS:** The median age of the patients was 68 years old (35-83) and females comprised 26 of the patients. The age of GB-adenocarcinoma patients was older than that of GB-NEC-SCC patients, significantly (67.89 ± 11.15 *vs* 55.75 ± 10.31, *P =* 0.029). The median tumor size of GB-adenocarcinoma was 2.56 ± 1.75 cm and GB-NEC-SCC was 3.98 cm ± 3.74 cm. The size of GB-NEC-SCC was larger than GB-adenocarcinoma; however, there was no significant difference between the two groups. In the comparison of tumors over 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 5 years was 77.0%. In the GB-adenocarcinoma group, the overall 5-year survival rate was 74.8% and in the GB-NEC-SCC group, the overall 5-year survival rate was 100%, respectively. There was no significant difference between the two groups (*P =* 0.896).

**CONCLUSION:** When considering its aggressive oncological feature of GB-NEC-SCC, it seems appropriate to adopt a strategy as similar with performing surgery for GB-adenocarcinoma including radical cholecystectomy and liver resection for treating patients with GB-NEC-SCC.

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

**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 were limited to case reports with a literature review. This study compared the demographics and survival rates of gallbladder adenocarcinoma and small cell neuroendocrine carcinoma of the gallbladder (GB-NEC-SCC) retrospectively, and reported the clinicopathological features of GB-NEC-SCC, based on individual experiences.

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**INTRODUCTION**

Gallbladder (GB) cancer (GBC) is an aggressive disease with characteristics of late presentation, rapid progression, and dismal results. The vast majority of GBCs (85%–90%) are adenocarcinomas. Other histologic types of GBCs 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 malignant potential. NETs include well-differentiated NETs (classical carcinoid tumors), well-differentiated neuroendocrine carcinoma (atypical carcinoids or malignant carcinoids), poorly differentiated neuroendocrine carcinoma (high grade carcinoma – small-cell/large-cell types), and mixed exocrine-endocrine carcinoma. Primary NETs of the gallbladder are particularly rare, and in the SEER registry, only 278 cases have been reported between 1973 and 2005, representing 0.5% of all NETs[[1](#_ENREF_1),[2](#_ENREF_2)], and 54 cases of small cell neuroendocrine carcinoma of the gallbladder (GB-NEC-SCC) were reported in another SEER-based study[[3](#_ENREF_3)]. Neuroendocrine carcinomas of the gallbladder (GB-NECs) are uncommon neoplasms, and therefore, little is known about their demographics and clinical courses. There have been several hypotheses about the origination of neuroendocrine tumors of gallbladder (GB-NETs). First, neuroendocrine cells usually are not seen in the normal gallbladder and occur only in the intestinal or gastric metaplastic gallbladder mucosa, occurring secondary to cholelithiasis and chronic cholecystitis[[2](#_ENREF_2)]. Because of the expression of various NE cells in this way, it is possible for NETs to occur. Secondly, heterotopic pancreatic tissue in the gallbladder is an especially rare condition[[4](#_ENREF_4),[5](#_ENREF_5)]. It is also possible that NETs may arise in ectopic pancreatic tissue.

Although classical well-differentiated NET and GB-NEC-SCC are the most common neuroendocrine tumors of the gallbladder, most of our knowledge about these tumors is limited and based on isolated case reports or a very small series[[3](#_ENREF_3)]. 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 clinicopathological features of GB-NEC-SCC, based on individual experiences.

**MATERIALS AND METHODS**

***Patients***

From March 2007 to September 2012 in Pusan National University Hospital, patients who underwent resection of T2/T3 GB cancer were enrolled for this study. Based on the medical records, a retrospective review was performed. We excluded patients with squamous carcinoma, papillary carcinoma and mucinous carcinoma in this study; finally, 42 patients were included. Thirty-eight patients were diagnosed with GB-adenocarcinoma and 4 patients with GB-NEC-SCC. We analyzed and compared the demographics and survival rates between GB-adenocarcinoma and GB-NEC-SCC, and described the clinicopathological features of GB-NEC-SCC. The study was approved by the institutional review board.

***Operation methods***

We examined the specimen of GB after laparoscopic or open cholecystectomy to identify suspicious lesions; if suspicious lesions detected, they were sent to a pathologist for frozen section biopsy. In the case of T2 and over GBC that was reported by the pathologist, we performed radical cholecystectomy including S4b, S5 segmentectomy of the liver. If GBC of T2 and over was suspected by macroscopic appearance during exploration, we performed radical cholecystectomy and liver resection attaching GB. Patient 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***

In this study, GB-NET was diagnosed according to the World Health Organization (WHO) classification published in 2010[[6](#_ENREF_6)]. The grade of NET was classified according to the WHO classification and European Neuroendocrine Tumor Society (ENETS) grading system (Table 1)[[6-9](#_ENREF_6)]. GB-NET-SCC was diagnosed if the following diagnostic criteria were fulfilled: (1) Positive expression of more than one type with immunohistochemical staining, such as expression of chromogranin A and synaptophysin, or a cluster of differentiation 56 (CD56), indicating the presence of neural cell adhesion molecules[[2](#_ENREF_2),[10](#_ENREF_10)]; and (2) Histopathologically, the presence of high grade and small cell cytological features and very high cellularity with hyperchromatic nuclei, absent or very small nucleoli with scant cytoplasm, a high-nuclear to cytoplasmic ratio, and a round or fusiform shape (according to the definition of SCCs by the WHO classification, which classifies SCCs as neuroendocrine tumors)[[2](#_ENREF_2),[10](#_ENREF_10),[11](#_ENREF_11)].

***Statistical analysis***

Categorical variables between the GB-adenocarcinoma group and GB-NEC-SCC were compared by the chi-square test or Fisher’s exact test. Age, tumor size and lymph node ratio were compared by *t*-test and the Mann–Whitney *u*-test. 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, USA).

**RESULTS**

The median age of the patients was 68 years old (35–83) and females comprised 26 of the patients (female/male ratio, 1.6:1). The age of GB-adenocarcinoma patients was older than that of GB-NEC-SCC patients, significantly. The percentage of patients over the age of 65 was 69% (29/42). There were no significant differences between the two groups. The characteristics of the patients and the comparison of the two groups are presented in Table 2. The median tumor size of GB-adenocarcinoma was 2.56 ± 1.75 cm and GB-NEC-SCC was 3.98 ± 3.74 cm. The size of GB-NEC-SCC was larger than GB-adenocarcinoma; however, there was no significant difference between the two groups. When comparing tumors over 2cm, T stage (T2 *vs* T3), lymphovascular invasion, perineural invasion, lymph node metastasis, and lymph node ratio were not significantly different between the two groups.

The overall survival rate of the 42 patients at 5 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 5-year survival rate was 100%, respectively. There was no significant difference between the two groups (*P =* 0.896) (Figure 2).

Table 3 shows the pathological features of patients in the GB-NEC-SCC group. Three of the four patients were women, and the mean age was 55.8 years. A radical operation was performed in 3 patients, and one patient underwent simple cholecystectomy. One patient (out of the 3 patients) who had direct invasion to the duodenum and ascending colon underwent hepatopancreaticoduodenectomy and right hemicolectomy. Two patients (out of 4) were observed to have lymph node metastases. In the immunohistochemical staining, synaptophysin and chromogranin A was positive in 2 patients, and the Ki-67 index was more than 25% in all cases (Figure 3).

**DISCUSSION**

Biliary NET comprises less than 1% of all NETs[[12-15](#_ENREF_12)]. Especially, GB-NEC-SCC was extremely rare in a review of nearly 13,981 cases of carcinoids from the SEER database, with only 54 cases found[[3](#_ENREF_3)]. 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.

Albores-Saavedra *et al*[[3](#_ENREF_3)] reported that GB-NEC-SCCs, like GB-adenocarcinomas, were more common in females. Likewise, GB-adenocarcinoma and GB-NEC-SCC were common in females (GB-adenocarcinoma, 23/38; GB-NEC-SCC, 3/4) in this study. And the age of GB-NEC-SCC patients was younger than that of 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, and 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[[2](#_ENREF_2),[16](#_ENREF_16)]. Despite the development of imaging studies, the differential diagnosis between GB-adenocarcinoma and GB-NEC preoperatively by performing imaging studies such as ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI) is still difficult. However, according to a recent study, the combination of positron emission tomography (PET) with CT or MRI was effective for the detection of NETs, and these modalities generally could obtain a high level of sensitivity[[17](#_ENREF_17), [18](#_ENREF_18)]. In the present study, all cases of GB-NEC-SCC were diagnosed with GB-adenocarcinoma in preoperative imaging studies. Measuring chromogranin A is known to be helpful to diagnose NET preoperatively. 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 the preoperative diagnosis of NETs[[19](#_ENREF_19)]. However, the measurement of chromogranin A to diagnose GB-NET before surgery is not cost-effective.

The poorly differentiated neuroendocrine carcinoma include GB-NEC-SCCs and large cell neuroendocrine carcinomas of the gallbladder (GB-NEC-LCCs). GB-NEC-LCCs show large cell size, low nuclear to cytoplasmic ratio, and frequent nucleoli, which these are key cytologic features that help distinguish GB-NEC-LCCs from GB-NEC-SCCs[[20](#_ENREF_20)]. According to Iype *et al*[[16](#_ENREF_16)], GB-NEC-LCCs appear to have a worse prognosis than GB-NEC-SCCs in the gallbladder. In the present study, there were no patients with GB-NEC-LCCs. Grossly, GB-NEC-SCC may vary from unapparent covert lesions to largely necrotic, exophytic, or ulcerative masses[[21](#_ENREF_21)]. In this study, 2 cases showed a fungating mass, 1 case showed a well-defined solid polypoid mass and 1 case showed a well-circumscribed solid multilobulated mass measuring 9.5 cm. Eltawil *et al*[[2](#_ENREF_2)] reported that histologically, more than 90% of GB-NEC-SCC are poorly differentiated or anaplastic, with regional or distant spread at diagnosis. In this study, 1 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 in the 36 reported cases of SCC, 28 pure small cell carcinomas and 8 combined small cell carcinomas with adenocarcinoma were reported in the literature[[22](#_ENREF_22)]. Our cases showed 2 cases of combined small cell carcinoma with adenocarcinoma.

In general, the only curative therapeutic modality for gallbladder cancer which is a higher grade than T1 is radical cholecystectomy, including cholecystectomy, hepatoduodenal lymph node dissection and hepatic resection[[23-25](#_ENREF_23)]. However, despite a more aggressive surgical approach, the majority of patients who have undergone potentially curative resection for GBC will develop recurrent metastatic disease. The surgical treatment of 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[[2](#_ENREF_2),[23-25](#_ENREF_23)]. For more advanced GB-NEC, the prognosis is usually poor, but better outcomes can be obtained by aggressive radical operative therapy[[26](#_ENREF_26)]. But there has been no rational surgical strategy currently 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[[2](#_ENREF_2)]. In a previous study, cholecystectomy was performed in 12 patients, with a median survival of 4.5 mo, and radical resection was performed in 2 GB-NEC-SCC patients, with survivals of 4 and 20 mo[[22](#_ENREF_22)]. In our study, among 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 5-year survival was not significantly different from the survival of patients undergoing a radical operation (78.4% *vs* 72.7 %, *P* = 0.471). According to previous research, a significant advantage of 5-year survival rate was observed in a patient with T2 stage undergoing radical operation compared to those who received only simple cholecystectomy (simple cholecystectomy, 17%-65% *vs* radical operation, 38%-100%)[[23](#_ENREF_23)]. We think the reason for this opposite result is that, first, the number of patients with simple cholecystectomy was small, and secondly, favorable histopathological features such as a tumor size less than 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[[22](#_ENREF_22)] 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 1 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 3 patients and these patients are still alive.

The role of radiotherapy and chemotherapy in the management of GB-NEC-SCC is unclear. In general, NETs are insensitive to traditional radiotherapy[[27](#_ENREF_27)]. According to several case reports, the chemotherapeutic agents including cisplatin, gemcitabine and etoposide plus 5-flurouracil (5-FU) can lead to a partial response, resulting in palliation and the addition of a marginal advantage[[16](#_ENREF_16),[28](#_ENREF_28)]. In the present study, after radical cholecystectomy, 2 patients underwent concurrent chemoradiation therapy (etoposide plus 5-FU, and cisplatin plus 5-FU) and they have been followed, without recurrence, for 37 months and 50 months, 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[[29](#_ENREF_29),[30](#_ENREF_30)]. According to SEER data, the 1-year survival of GB-NEC-SCC was 21% and 5-year survival was 0%, but GB-NETs have a similar prognosis to GB-adenocarcinoma according to the SEER data base[[2](#_ENREF_2)]. Although the prognosis of GB-NEC-SCC is poor, past studies reported that aggressive multimodal treatment may prolong survival for GB-NEC-SCC[[2](#_ENREF_2),[16](#_ENREF_16),[22](#_ENREF_22)]. Therefore, it seems acceptable to adopt a similar strategy including radical cholecystectomy for gallbladder NEC, and doing so is likely to result in a better outcome. This study showed a similar result to previous studies in that the 5-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 significant and 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 cancer (GBC) is an aggressive disease and the vast majority of GBCs (85%–90%) are adenocarcinomas. Small cell neuroendocrine carcinomas of the gallbladder (GB-NEC-SCC) was 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 neuroendocrine tumors of the gallbladder, 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 GBC, including 4 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 clinicopathological features of GB-NEC-SCC. It is quite significant and 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 neuroendocrine carcinoma (atypical carcinoids or malignant carcinoids), poorly differentiated neuroendocrine carcinoma (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, especially, there is a comparison for the demographics and survival rates with GB-adenocarcinomas. This scientific paper is well written and provides some new and useful information regarding the GB-NEC-SCCs

**References**

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| 1 **Yao JC**, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, Abdalla EK, Fleming JB, Vauthey JN, Rashid A, Evans DB. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol* 2008; **26**: 3063-3072 [PMID: 18565894 DOI: 10.1200/jco.2007.15.4377]2 **Eltawil KM**, Gustafsson BI, Kidd M, Modlin IM. Neuroendocrine tumors of the gallbladder: an evaluation and reassessment of management strategy. *J Clin Gastroenterol* ; **44**: 687-695 [PMID: 20375728 DOI: 10.1097/MCG.0b013e3181d7a6d4]3 **Albores-Saavedra J**, Batich K, Hossain S, Henson DE, Schwartz AM. Carcinoid tumors and small-cell carcinomas of the gallbladder and extrahepatic bile ducts: a comparative study based on 221 cases from the Surveillance, Epidemiology, and End Results Program. *Ann Diagn Pathol* 2009; **13**: 378-383 [PMID: 19917473 DOI: 10.1016/j.anndiagpath.2009.08.002]4 **Neupert G**, Appel P, Braun S, Tonus C. [Heterotopic pancreas in the gallbladder. Diagnosis, therapy, and course of a rare developmental anomaly of the pancreas]. *Chirurg* 2007; **78**: 261-264 [PMID: 16775679 DOI: 10.1007/s00104-006-1203-6]5 **Murakami M**, Tsutsumi Y. Aberrant pancreatic tissue accompanied by heterotopic gastric mucosa in the gall-bladder. *Pathol Int* 1999; **49**: 580-582 [PMID: 10469405]6 Bosman FT, Carneiro F, Hruban RH, Theise ND. WHO classification of tumours of the digestive system. 4th ed. Lyon: The International Agency for Research on Cancer; 2010.7 **Rindi G**, Klöppel G, Alhman H, Caplin M, Couvelard A, de Herder WW, Erikssson B, Falchetti A, Falconi M, Komminoth P, Körner M, Lopes JM, McNicol AM, Nilsson O, Perren A, Scarpa A, Scoazec JY, Wiedenmann B. TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. *Virchows Arch* 2006; **449**: 395-401 [PMID: 16967267 DOI: 10.1007/s00428-006-0250-1]8 **Rindi G**, Klöppel G, Couvelard A, Komminoth P, Körner M, Lopes JM, McNicol AM, Nilsson O, Perren A, Scarpa A, Scoazec JY, Wiedenmann B. TNM staging of midgut and hindgut (neuro) endocrine tumors: a consensus proposal including a grading system. *Virchows Arch* 2007; **451**: 757-762 [PMID: 17674042 DOI: 10.1007/s00428-007-0452-1]9 **Klimstra DS**, Modlin IR, Coppola D, Lloyd RV, Suster S. The pathologic classification of neuroendocrine tumors: a review of nomenclature, grading, and staging systems. *Pancreas* 2010; **39**: 707-712 [PMID: 20664470 DOI: 10.1097/MPA.0b013e3181ec124e]10 **Jun SR**, Lee JM, Han JK, Choi BI. High-grade neuroendocrine carcinomas of the gallbladder and bile duct: Report of four cases with pathological correlation. *J Comput Assist Tomogr* ; **30**: 604-609 [PMID: 16845291]11 **Lane JE**, Walker AN, Ayers GW, Foster JL, Williams JT. Small-cell undifferentiated carcinoma of neuroendocrine type originating in the gallbladder. *Curr Surg* ; **59**: 495-497 [PMID: 15727797]12 **Modlin IM**, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. *Cancer* 2003; **97**: 934-959 [PMID: 12569593 DOI: 10.1002/cncr.11105]13 **Chamberlain RS**, Blumgart LH. Carcinoid tumors of the extrahepatic bile duct. A rare cause of malignant biliary obstruction. *Cancer* 1999; **86**: 1959-1965 [PMID: 10570419]14 Albores-Saavedra J, Henson DE, Klimstra D. Endocrine and benign mesenchymal tumors of the extrahepatic bile duct. In: Rosai J, Sobin LH, editors. Tumor of the Gallbladder, Extrahepatic Bile Ducts, and Ampulla of Vater. 3rd ed. Washington, DC: Armed Forces Institute of Pathology, 2000; 217–22115 **Kim J**, Lee WJ, Lee SH, Lee KB, Ryu JK, Kim YT, Kim SW, Yoon YB, Hwang JH, Han HS, Woo SM, Park SJ. Clinical features of 20 patients with curatively resected biliary neuroendocrine tumours. *Dig Liver Dis* 2011; **43**: 965-970 [PMID: 21856258 DOI: 10.1016/j.dld.2011.07.010]16 **Iype S**, Mirza TA, Propper DJ, Bhattacharya S, Feakins RM, Kocher HM. Neuroendocrine tumours of the gallbladder: three cases and a review of the literature. *Postgrad Med J* 2009; **85**: 213-218 [PMID: 19417172 DOI: 10.1136/pgmj.2008.070649]17 **Koopmans KP**, de Vries EG, Kema IP, Elsinga PH, Neels OC, Sluiter WJ, van der Horst-Schrivers AN, Jager PL. Staging of carcinoid tumours with 18F-DOPA PET: a prospective, diagnostic accuracy study. *Lancet Oncol* 2006; **7**: 728-734 [PMID: 16945767 DOI: 10.1016/s1470-2045(06)70801-4]18 **Seemann MD**. Detection of metastases from gastrointestinal neuroendocrine tumors: prospective comparison of 18F-TOCA PET, triple-phase CT, and PET/CT. *Technol Cancer Res Treat* 2007; **6**: 213-220 [PMID: 17535030]19 Modlin IM, Gustafsson BI, Moss SF, Pavel M, Tsolakis AV. Chromogranin A—biological function and clinical utility in neuro endocrine tumor disease. Annals of surgical oncology 2010; 17: 2427-2443 [DOI: 10.1245/s10434-010-1006-3]20 **Sasatomi E**, Nalesnik MA, Marsh JW. Neuroendocrine carcinoma of the extrahepatic bile duct: case report and literature review. *World J Gastroenterol* 2013; **19**: 4616-4623 [PMID: 23901240 DOI: 10.3748/wjg.v19.i28.4616]21 **Maitra A**, Tascilar M, Hruban RH, Offerhaus GJ, Albores-Saavedra J. Small cell carcinoma of the gallbladder: a clinicopathologic, immunohistochemical, and molecular pathology study of 12 cases. *Am J Surg Pathol* 2001; **25**: 595-601 [PMID: 11342770]22 **Moskal TL**, Zhang PJ, Nava HR. Small cell carcinoma of the gallbladder. *J Surg Oncol* 1999; **70**: 54-59 [PMID: 9989422]23 **Sikora SS**, Singh RK. Surgical strategies in patients with gallbladder cancer: nihilism to optimism. *J Surg Oncol* 2006; **93**: 670-681 [PMID: 16724356 DOI: 10.1002/jso.20535]24 **Wise PE**, Shi YY, Washington MK, Chapman WC, Wright JK, Sharp KW, Pinson CW. Radical resection improves survival for patients with pT2 gallbladder carcinoma. *Am Surg* 2001; **67**: 1041-1047 [PMID: 11730220]25 **Ogura Y**, Tabata M, Kawarada Y, Mizumoto R. Effect of hepatic invasion on the choice of hepatic resection for advanced carcinoma of the gallbladder: histologic analysis of 32 surgical cases. *World J Surg* 1998; **22**: 262-26; discussion 262-26; [PMID: 9494418]26 **Reid KM**, Ramos-De la Medina A, Donohue JH. Diagnosis and surgical management of gallbladder cancer: a review. *J Gastrointest Surg* 2007; **11**: 671-681 [PMID: 17468929 DOI: 10.1007/s11605-006-0075-x]27 **Modlin IM**, Kidd M, Drozdov I, Siddique ZL, Gustafsson BI. Pharmacotherapy of neuroendocrine cancers. *Expert Opin Pharmacother* 2008; **9**: 2617-2626 [PMID: 18803449 DOI: 10.1517/14656566.9.15.2617]28 **Bhutani V**, Dutta U, Nagi B, Nijhawan R, Singh K. Endocrine cell carcinoma of gall bladder. *Indian J Gastroenterol* ; **20**: 109-110 [PMID: 11400802]29 **Deehan DJ**, Heys SD, Kernohan N, Eremin O. Carcinoid tumour of the gall bladder: two case reports and a review of published works. *Gut* 1993; **34**: 1274-1276 [PMID: 8406168]30 **Porter JM**, Kalloo AN, Abernathy EC, Yeo CJ. Carcinoid tumor of the gallbladder: laparoscopic resection and review of the literature. *Surgery* 1992; **112**: 100-105 [PMID: 1535733] |

**P-Reviewer:** Cao GW, Shu J, Shimizu Y, **S-Editor:** Yu J **L-Editor** **E-Editor**

**Figure 1 The overall survival rate of the 42 patients at 5 years.** The overall survival rate of the 42 patients at 5 years was 77.0%.

**Figure 2 The overall 5-year survival rate of adenocarcinoma of the gallbladder and small cell neuroendocrine carcinoma of the gallbladder.** There was no statistically significant difference in overall survival between adenocarcinoma of the gallbladder (GB-adenocarcinoma) and small cell neuroendocrine carcinoma of the gallbladder (GB-NEC-SCC) (*P =* 0.896).

A

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**B**



C



**Figure 3 Immunohistochemical staining of small cell neuroendocrine carcinoma of the gallbladder.** A, B: On Tumor cells are positive for synaptophysin (A × 400) and chromogranin A (B × 400); C: Immunohistochemical staining of Ki-67. In this case, the Ki-67 labeling index is about 30% (× 400).

**Table 1 Grading systems for gastroenteropancreatic neuroendocrine tumor by World Health Organization and European Neuroendocrine Tumor Society**

|  |  |
| --- | --- |
| **Grade** | **GET-NETs** |
| Low grade (ENETS G1) | < 2 mitoses / 10 HPF AND < 3% Ki67 index |
| Intermediate grade (ENETS G2) | 2-20 mitoses / 10 HPF OR 3%-20% Ki67 index |
| High grade (ENETS G3) | >20 mitoses / 10 HPF OR >20% Ki67 index |

GEP-NET: Gastroenteropancreatic neuroendocrine tumor; WHO: World Health Organization; ENETS: European Neuroendocrine Tumor Society; HPF: High power fields.

**Table 2 Comparison of clinicopathological features between gallbladder adenocarcinoma and small cell neuroendocrine carcinoma of the gallbladder**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **GB-adenocarcinoma****(*n* = 38)** | **GB-NEC-SCC****(*n* = 4)** | ***P* value** |
| Sex Male female | 1523 | 13 | 1.000 |
| Age  | 67.89 ± 11.15 | 55.75 ± 10.31 | 0.029 |
| Age above 65< 65≥ 65 | 1028 | 31 | 0.080 |
| OperationSimple cholecystectomyExtended cholecystectomy | 1028 | 13 | 1.000 |
| Tumor size | 2.56 ± 1.75 | 3.98 ± 3.74 | 0.788 |
| Tumor size above 2cm < 2cm ≥ 2cm | 1121 | 22 | 0.609 |
| T stageT2T3 | 344 | 31 | 0.410 |
| Lymphovascular invasion-+ | 298 | 22 | 0.245 |
| Perineural invasion-+ | 2611 | 13 | 0.107 |
| Lymph node metastasis-+ | 189 | 12 | 0.537 |
| Lymph node ratio | 0.15 ± 0.29 | 0.18 ± 0.28 | 0.485 |
| Recurrence-+ | 2810 | 31 | 1.000 |

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

**Table 3 Clinicopathological features of 4 patients with small cell neuroendocrine carcinoma of the gallbladder**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Patient 1** | **Patient 2** | **Patient 3** | **Patient 4** |
| Sex | Female | Male | Female | Female |
| Age | 49 | 66 | 63 | 45 |
| Size | 1.9 | 1.5 | 3.0 | 9.5 |
| Operation | RC | RC | C | RC1 |
| Combined adenocarcinoma | - | + | - | + |
| Gross finding | polypoid | fungating | fungating | mutilobulated |
| Lymphovascular invasion | + | - | - | + |
| Perineural invasion  | + | + | + | - |
| T stage | T2 | T2 | T2 | T3 |
| Lymph node metastasis | 0/15 | 1/2 | 0/0 | 1/39 |
| Mitosis (/10HPF) | 2 | 8 | 20 | 22 |
| Synaptophysin | + | + | - | - |
| Chromogranin A | + | + | - | - |
| CD56 | + | + | + | + |
| P53 | + | + | NA | NA |
| Ki67 | 30% | 25% | 40% | 50% |

1 This patient underwent hepatopancreaticoduodenectomy and right hemicolectomy.

RC: Radical cholecystectomy; C: Cholecystectomy; HPF: High power fields; NA: Information not available.

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

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Age** | **Sex** | **Size** | **Metastasis or local invasion** | **Mixed tumor** | **Survival (mo)** | **T stage** | **Chromogranin A** | **Recurrence (site)** | **Operation type** |
| Moskal *et al*[[22](#_ENREF_22)], 1999 | 69 | F | NA | Regional LN meta, pancreas inv | + | 44 | T3 | NA | + (abdomen) | Radical operation |
| Moskal *et al*[[22](#_ENREF_22)], 1999 | 57 | F | NA | Regional LN meta, liver inv | - | 31 | T3 | NA | + (abdomen, bone) | Radical operation |
| Moskal *et al*[[22](#_ENREF_22)], 1999 | 69 | M | NA | Regional LN meta | - | 21 | T2 | NA | + (retroperitoneum) | Cholecystectomy |
| Moskal *et al*[[22](#_ENREF_22)], 1999 | 71 | F | NA | Regional LN meta peritoneum meta | + | 13 | T2 | NA | + (retroperitoneum) | Cholecystectomy |
| Moskal *et al*[[22](#_ENREF_22)], 1999 | 40 | M | NA | Regional LN meta | + | 189, alive | T2 | NA | + (lung, abdomen) | Cholecystectomy |
| Maitra *et al*[[21](#_ENREF_21)], 2001 | 85 | F | 4.0 | Liver meta | + | 13 | T2 or more | + | NA | Surg |
| Maitra *et al*[[21](#_ENREF_21)], 2001 | 77 | F | 2.8 | Pancreas inv, LN meta | + | 25 | T2 or more | NA | NA | Surg |
| Maitra *et al*[[21](#_ENREF_21)], 2001 | 43 | F | 2.0 | Liver meta | + | 9 | T2 or more | + | NA | Surg |
| Maitra *et al*[[21](#_ENREF_21)], 2001 | 73 | F | 2.5 | LN meta | + | 7 | T2 or more | + | NA | Surg |
| Maitra *et al*[[21](#_ENREF_21)], 2001 | 82 | M | 1.0 | Liver meta | + | 8 | T2 or more | NA | NA | Surg |
| Maitra *et a*l[[21](#_ENREF_21)], 2001 | 77 | F | 3.0 | - | + | 10 | T2 or more | + | NA | Surg |
| Maitra *et al*[[21](#_ENREF_21)], 2001 | 73 | M | 6.3 | Liver meta | - | 6 | T2 or more | NA | NA | Surg |
| Maitra *et al*[[21](#_ENREF_21)], 2001 | 71 | M | NA | - | - | 3 | T1 | NA | NA | Surg |
| Maitra *et al*[[21](#_ENREF_21)], 2001 | 37 | F | 8.0 | LN meta | - | 7 | T2 or more | NA | NA | Surg |
| Maitra *et al*[[21](#_ENREF_21)], 2001 | 68 | M | 2.0 | LN meta | - | 14 | T2 or more | + | NA | Surg |
| Maitra *et al*[[21](#_ENREF_21)], 2001 | 67 | F | 2.8 | - | - | NA | T2 or more | + | NA | Surg |
| Maitra *et al*[[21](#_ENREF_21)], 2001 | 78 | M | 1.8 | LN meta | - | 16 | T2 or more | NA | NA | Surg |
| Lane *et al*[[11](#_ENREF_11)], 2002 | 67 | M | NA | - | - | 11 | T1b | + | + (liver, LN) | Cholecystectomy |
| Iype *et al*[[16](#_ENREF_16)], 2008 | 32 | F | 2.0 | Regional LN meta, liver meta | - | 14, alive | T2 | + | + (liver, LN) | Radical operation |
| Current study, 2014 | 49 | F | 1.9 | - | - | 37, alive | T2 | + | - | Radical operation |
| Current study, 2014 | 66 | M | 1.5 | Regional LN meta | + | 13, alive | T2 | + | - | Radical operation |
| Current study, 2014 | 63 | F | 3.0 | - | - | 67, died | T2 | - | + (liver) | cholecystectomy |
| Current study, 2014 | 45 | F | 9.5 | LN inv, colon inv, liver inv | + | 50, alive | T3 | - | - | Radical operation |

F: Female; M: Male; LN: Lymph node; meta: metastasis; inv: invasion; Surg: Extent of surgery not reported; NA: Information not available.