Neuroendocrine Tumors of the Gallbladder
An Evaluation and Reassessment of Management Strategy

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Background: Gallbladder neuroendocrine tumors (GB-NETs) represent only 0.5% of all NETs, and little is known about their biological behavior. We sought to provide an overview of the current state of knowledge about GB-NETs and provide a recommendation for management.

Study: A PubMed search was undertaken using the following criteria: primary gallbladder and carcinoid or NET. We also interrogated the SEER 9, 13 and 17 registries (1973 to 2005) and the Niigata registry (2003) to assess the epidemiology and clinicopathological characteristics. Finally, we compared the clinical presentation, management and prognosis of GB-NETs to that of gallbladder adenocarcinoma.

Results: GB-NETs probably derive from either a multipotent stem cell or neuroendocrine cells in intestinal or gastric metaplasia of the gallbladder epithelium, which occurs consequent upon cholelithiasis/chronic inflammation. Clinically and at surgery, GB-NETs are indistinguishable from gallbladder cancer (GBC) and "carcinoid syndrome" is evident in only ~1%.The median survival was only 9.8 months among 278 cases of GB-NETs reported in SEER. The 5 year survival rate for tumors classified as carcinoids/neuroendocrine carcinoma or small cell cancer (SCC) was 36.9 and 0%, respectively. Soga divided GB-NETs into typical and variant carcinoids with 5 year survival rates of 60.4% and 21.3% respectively.

Conclusions: GB-NETs have an aggressive behavior, and once diagnosed, extensive surgical management and careful NET follow up with CT scan is mandatory to facilitate early detection of recurrence. Since more aggressive surgical management for GBC has shown increased survival rates for these tumors, a similar strategy seems reasonable for GB-NETs. However, in high grade metastatic tumors, the primary management is mainly medical.

Key Words: Gallbladder, neuroendocrine, tumor, cancer, carcinoid

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The Surveillance, Epidemiology and End Results (SEER) program of the United States National Cancer Institute was initiated in 1973 and currently covers 17 geographical areas in the US which comprise approximately 26% of the population.[1] The overall incidence of neuroendocrine tumors (NETs) in the SEER database has significantly increased in the United States over the past three decades.[2,3] Thus in 2004, NETs comprised 1.25% of all malignancies indicating an overall increase in incidence of approximately 6% per year since 1973.[4] This significant increase in incidence could be attributed to both better imaging techniques and better understanding of the disease. The majority (66%) occur in the gastrointestinal tract.[4] The second most common location is the bronchopulmonary system (31%), followed by less frequent locations including the ovaries, testes, hepatobiliary system, and pancreas.[4] The current WHO classification of NETs divides them into subgroups of well-differentiated neuroendocrine tumors (previously referred to as typical carcinoid) (WHO1), which exhibit benign behavior or uncertain malignant potential, well-differentiated neuroendocrine carcinoma (previously atypical carcinoid) (WHO2), characterized by low-grade malignancy, such as poorly differentiated small cell (SCC) (oat cell) and large cell neuroendocrine carcinomas (LCNEC) (poorly differentiated neuroendocrine carcinoma) of high-grade malignancy (WHO3) (Table 1).[5] The first case of primary NET tumor (a classic carcinoid) of the gallbladder was reported in 1929 by Joel.[6] Since then, small cell carcinomas, SCC, and LCNEC of the gallbladder have all been described to have neuroendocrine differentiation. Primary NETs of the gallbladder are particularly rare and in the SEER registry, only 278 cases have been reported between 1973 and 2005, and represent 0.5% of all NETs, and ~2% of gallbladder cancers (Tables 2, 3).[3] Given the rarity of the lesion, it is often overlooked. Alternatively when identified at routine pathological examination as a component of cholecystectomy for cholelithiasis, considerable controversy and confusion regarding ideal management follow. In this review, we investigate the cellular origin of gallbladder NETs, describe their epidemiology, clinical presentation, pathological diagnosis, treatment and prognostic outcome with a view to providing a rationale for an appropriate management strategy. We also compared differences in tumor grading and staging between different SEER stages using 2-tailed χ^2 tests (Graphpad: Prism 4.0).

INCIDENCE AND EPIDEMIOLOGY

Gall bladder cancer (GBC) first described in 1777 by deStoll,[7] is a rare (1.2/100,000 in the US) and highly lethal disease and the sixth most common gastrointestinal cancer.[1] Jemal (2005) reviewing the US SEER data

TABLE 1. Classification of Neuroendocrine Tumors of the Gastroenteropancreatic System (GEP-NET)

1a	Well-differentiated neuroendocrine tumor (WHO 1)
1b	Well-differentiated neuroendocrine carcinoma (WHO 2)
2	Poorly differentiated neuroendocrine carcinoma (WHO 3)

reported that of 7480 cases of biliary tract cancer, the majority arose from the gallbladder and that 3340 patients were expected to die from this disease.[8] In a recent study from the Memorial Sloan-Kettering Cancer Centre (MSKCC) 435 gall bladder cancer cases were identified between 1995 and 2005; 391 (88%) adenocarcinoma, 18 (4%) squamous, 13 (3%) neuroendocrine, and 7 (2%) sarcoma, indicating a slightly higher NET incidence than previously reported.[9] Among the 435 tumors, 65.5% were found in women and 47% were found incidentally at cholecystectomy.

In a retrospective analysis of 25 reported GB-NETs, the age at presentation ranged from 26 to 79 years (median 64) and 68% were women.[10] Among 36 cases of SCC, 76% were female, median age was 65 years (range 37 to 82 y), and 72% had cholelithiasis.[11] GB-LCNEC are exceedingly rare and only ~10 cases have been described.[12,13] According to the SEER 9, 13 and 17 registries (1973 to 2005), containing 278 GB-NETs, the incidence of GB-NETs (all subgroups) in the US is 0.2 to 0.3/100,000.[1] Sixty eight % were women and the age range 25 to 85+ years peaking in ages 75 to 79 years, and the incidence was similar in the Caucasian and African-American population.

Soga (1997) reported and analyzed 138 gallbladder "endocrinomas" in the Niigata Registry for Gut-pancreatic Endocrinomas.[14] This series comprised two groups: the carcinoid group (n = 101) including typical (WHO1) and atypical (WHO2) NETs and the variant group (n = 37) which included cases with SCC/oat cell neuroendocrine carcinoma (OCC), neuroendocrine carcinoma (NEC) or endocrine cell carcinoma (ECC)(WHO3).[15]

Simultaneous occurrence of GB-NET and renal carcinoma or rectal NET has been described, underlining the generally increased risk for synchronous or metachronous neoplasms as evident with NETs in general.[16,17]

CELL OF ORIGIN

Neuroendocrine (NE) cells occur throughout the entire gut, and overall constitute the largest group of hormone-producing cells in the body, the diffuse neuroendocrine system (DNES).[18] It is now accepted that NE cells derive from local multipotent gastrointestinal stem cells, rather than by migration from the neural crest as initially proposed.[19] However, the mechanisms that regulate phenotype expression and differentiation of cells of the diffuse endocrine-cell system are poorly understood. Similarly, the basis for the development of neoplasia in the DNES which mainly occurs in the gastrointestinal tract and bronchopulmonary system is poorly understood.[20] They range from indolent, unrecognized entities often found serendipitously to highly active, metastatic secretory tumors which is predominantly the case for ileal NETs.[21–23] Despite the fact that NETs at diverse anatomic sites may share some basic histological, clinical, and biological properties, the individual behavior of each tumor may vary substantially in terms of local aggression and metastasis. To some extent this depends on which neuroendocrine cell type and organ they originate from but the relevant molecular determinants specific to the prediction of local invasion, development of desmoplasia and metastasis are as yet poorly defined.[24] There are least 13 types of gut neuroendocrine cells (EC, ECL, D, G, PP, etc), all of which produce a variety of bioactive peptides or amines, of which some examples are serotonin, somatostatin, histamine, and gastrin.[25]

In 1905, the German pathologist Karl Albert Ludwig Aschoff (1866 to 1942) was the first to describe metaplasia in the gallbladder with gastric gland formation in the epithelium secondary to chronic inflammation due to cholelithiasis.[26] Two decades later, Nicholson observed that 17/24 (71%) of gallbladders with chronic inflammation contained gastric like glands.[27] In 1954, using the Masson-Hamperl and Gomorri silver staining techniques, Christie reported the presence of argentaffin cells in human inflamed gallbladder mucosa with secondary metaplasia.[28] Christie also noted aggregates of argentaffin cells within the metaplastic epithelium and suggested that these could represent precursor lesions to gallbladder carcinoids.[28]

More recent investigations have confirmed that NE cells are not present in normal gallbladder mucosa, while gallbladder mucosa undergoing intestinal or/and gastric metaplasia expresses a variety of different NE cells, including serotonin, histamine, gastrin, somatostatin, and glucagon containing cells.[29–31] In an investigation of 103 gallbladders with cholelithiasis, 12/103 (11.7%) had intestinal metaplasia.[32] Among those cases with metaplasia, chromogranin A and serotonin were expressed in 83.3% and 50% respectively. Others reports have suggested an even higher incidence, with predominantly gastric metaplasia in ~70%, of gallbladders removed with cholecystitis.[29] Virtually all published reports on GB-NETs describe coexisting gallstones and chronic cholecystitis.[10,33,34] Cholelithiasis is the most important risk factor for gallbladder cancer worldwide, most common in women, and both gallbladder adenocarcinomas and GB-NETs are overrepresented among women (68%).[35] Additionally, among 12 patients with GB-SCC, all had a positive history of gallstones, 6/6 investigated with immunohistochemistry were chromogranin A and neuron specific enolase positive, and 7/12 demonstrated foci of adenocarcinoma.[36] Interestingly, a majority of gallbladder adenocarcinomas also exhibit a gastric/intestinal type of differentiation and chromogranin A positive cells.[37,38] There are also several reports on coexistence of GB-NETs and gallbladder adenocarcinomas, and the possibility for a direct transition between the tumors remains an intriguing possibility as has been proposed for gastric adenocarcinomas and gastric neuroendocrine tumors.[10,30,39–41]

TABLE 2. Histology of 5051 Gallbladder Tumors in SEER 17 (2000-2005)

	N	%
Adenocarcinoma, NOS	3868	76.6
Carcinoma, NOS	550	10.9
Cholangiocarcinoma	184	3.6
Neuroendocrine tumors	105	2.1
Adenosquamous carcinoma	100	2.0
Others	244	4.7

Others: Signet ring carcinoma, Squamous cell carcinoma, NOS, Lymphoma, NOS, Sarcoma, Giant cell and spindle cell carcinoma, Large cell carcinoma, NOS, Malignant melanoma, NOS.

TABLE 3. Distribution of Gallbladder NET Histological Subtypes in the SEER Data Bases

	Pan SEER9 (1973-05)	SEER9 Early SEER (1973-91)	SEER13 Mid SEER (1992-99)	SEER17 Late SEER (2000-05)
Large cell neuroendocrine carcinoma	0	0	0	1 (1.0)
Small cell (Oat cell) carcinoma	33 (35.1)	19 (67.9)	10 (19.6)	32 (30.5)
Carcinoid tumor, malignant	35 (37.2)	7 (25)	21 (41.2)	34 (32.4)
Enterochromaffin cell carcinoid	1 (1.1)	0	1 (2.0)	0
Adenocarcinoid tumor	1 (1.1)	0	1 (2.0)	0
Neuroendocrine carcinoma	24 (25.5)	2 (7.1)	18 (35.3)	36 (34.3)
Adenocarcinoma with neuroendocrine differentiation	0	0	0	2 (1.9)
Total	94	28	51	105

SEER indicates surveillance, epidemiology and end results.

Heterotopic pancreatic tissue in the gallbladder is an exceedingly rare condition (< 50 reported cases) with potential relevance for gall bladder neoplasia.[42–44] The ectopic pancreatic tissue demonstrates typical islet peptide-immunoreactive cells scattered within an active exocrine parenchyma, and the condition may result in acute pancreatitis and secondary cholecystitis.[43,45,46] It has been hypothesized that the amylase/trypsin leakage that damages the gallbladder mucosa may lead to precancerous lesions and eventually neoplasia.[47] It is also possible that NETs may arise in ectopic pancreatic tissue in a similar fashion as in Meckel's diverticuli.[48] Pancreatic polypeptide positive gallbladder carcinoids have been described suggesting the possibility of a heterotopic pancreas origin.[49,50] In addition an insulin-secreting GB-NET causing hypoglycaemia in association with a GB-adenocarcinoma has also been reported.[51]

It has been proposed that the heterotopic pancreatic tissue should be surgically removed to avoid secondary complications.[42]

Except for a single case report of a clear cell gallbladder carcinoid in a patient with von Hippel-Lindau (VHL) disease,[52] no association to genetic traits has been established. In this particular case, the tumor was histologically similar to the clear cell endocrine pancreatic tumor characteristically associated with VHL.

Several neuropeptides [neuropeptide Y, pituitary adenyl cyclase activating peptide (PCAP), somatostatin, substance P and VIP] have been demonstrated in the nerve fibers in the human gallbladder wall.[53] In addition, Chromogranin A positive paraganglionic tissue has been observed in the subserosal connective tissues of gallbladders after resection for chronic cholecystitis with gallstones,[54] and a handful of gallbladder paragangliomas associated with multiple endocrine neoplasia have also been described.[55]

In summary, in the progression of chronic cholecystitis, gallbladder mucosal epithelial cells deviate from their normal differentiation pathway to develop a gastric or intestinal phenotype. It thus seems plausible that the cell origin for gallbladder NETs may have two sources. Either an undifferentiated stem cell or else a mucosal neuroendocrine cell in the setting of chronic inflammatory induced gallbladder epithelial metaplasia in which malignant transformation takes place. A third but less possible origin would be nerve fibers in the gallbladder wall based on the fact that neuropeptides have been demonstrated in gallbladder nerve fibers.[53]

PATHOLOGY

The Pan SEER 9 (1973 to 2005) has reported the grade of GB-NETs in 41 cases. From this number 2.4% were well-differentiated, 7.3% moderately-differentiated, 26.3% poorly differentiated, and 63.4% undifferentiated/anaplastic (Table 4). Between SEER 13 (1973 to 1991) and SEER 17 (2000 to 2005), a change towards a somewhat less aggressive grade at diagnosis was observed, nevertheless a majority, 51.1% and 34.0%, were poorly differentiated and anaplastic, respectively in SEER 17. A less extensive spread at diagnosis in late compared to early SEER was also observed (SEER 13, 8.0% localized, 36.0% regional and 56.0% distant, compared to 43.7%, 27.2% and 29.1%, respectively in SEER 17) (Table 5). These observations suggest that more sophisticated diagnostic tools have led to diagnosis at an earlier grade and stage. Macroscopically there is no particular site where gallbladder NETs arise and the lesion is evident in the gallbladder neck, fundus or body. Soga categorized the size of gallbladder NETs in 98 cases, including those in which the size was expressed by comparisons such as a pea, a small finger-tip, and so on.[15] The incidence of tumors measuring 50 mm or less in the greatest diameter was significantly higher in the carcinoid group as compared to the variant group (85.2% vs. 52.9%).[15] The overall rate of metastasis was 43.5% and 42.6% in the carcinoid group, and 45.9% in the variant group which was mainly to the liver and lymph nodes.[15] The average tumor size in cases with metastases was significantly larger than those without metastases in the carcinoid group (44.8 mm vs. 19.1 mm), while there was no difference in the variant group with the average tumor sizes of 58.8 mm and 58.5 mm respectively.[15]

The identification of neuroendocrine cells is necessary to define a gallbladder NET. Neuroendocrine cells of DNES are identifiable by (a) the presence of dense core granules ultra-structurally, and (b) the immunohistochemical (IHC) expression of marker proteins (ie, general neuroendocrine markers) such as chromogranin A (CgA), synaptophysin and neuron specific enolase (NSE), as well as other cell type-specific amine and peptide hormones serotonin, histamine, gastrin etc.[56] In the Niigata registry, immunohistochemical evaluation was undertaken in 77 cases (55.8%) and the two peptides most commonly identified were CgA (91.9%) and NSE (84.8%).[15] Of note was the statistically significant immunohistochemically assessed elevation of CgA (100% vs. 66.7%) between the carcinoid group and the variant group.[15]

TABLE 4. GB-NETs Grade at Diagnosis

	All Grades	Well Differentiated; Grade I	Moderately Differentiated; Grade II	Poorly Differentiated; Grade III	Undifferentiated; Anaplastic; Grade IV	Unknown
PanSEER9*(1973-05)	94	1 (2.4)	3 (7.3)	11 (26.3)	26 (63.4)	53
Non-SCC	61	1 (5.9)	3 (17.6)	8 (47.1)	5 (29.4)	44
SCC	33	0	0	2 (8.7)	21 (91.3)	10
SEER9 (1973-91)	28	0	0	2 (12.5)	14 (87.5)	12
Non-SCC	9	0	0	1 (50.0)	1 (50.0)	7
SCC	19	0	0	1 (7.1)	13 (92.9)	5
SEER13†(1992-99)	51	1 (3.8)	2 (7.7)	10 (38.5)	13 (50.0)	25
Non-SCC	41	1 (5.9)	2 (11.8)	9 (52.9)	5 (29.4)	24
SCC	10	0	0	1 (11.0)	8 (88.9)	1
SEER17‡(2000-05)	105	3 (6.4)	7 (14.9)	24 (51.1)	16 (34.0)	58
Non-SCC	73	2 (7.1)	7 (25.0)	13 (46.4)	4 (14.3)	45
SCC	32	1 (4.8)	0	8 (38.1)	12 (57.1)	11

Numbers in brackets represent percentage of tumors with known grade.
*χ^2: 33.5, $P < 0.0001$: Significant difference in distribution of grade at diagnosis between Non-SCC and SCC in PanSEER9 (more GradeIV in SCC, more unknowns in Non-SCC).
†χ^2: 19.7, $P = 0.0006$: Significant difference in distribution of grade at diagnosis between Non-SCC and SCC in SEER13 (more GradeIV in SCC, more unknowns in Non-SCC).
‡χ^2: 21.48, $P = 0.0003$: Significant difference in distribution of grade at diagnosis between Non-SCC and SCC in SEER13 (more GradeIV in SCC, more unknowns in Non-SCC).
SCC indicates small cell carcinoma; SEER, surveillance, epidemiology and end results.

Neuroendocrine Tumors and Carcinomas

The gross appearance is often a cauliflower-shaped solid yellow lesion that arises at the lamina propria, with subsequent infiltration through the muscle layer and extension into the serosa (Fig. 1A).[10] Well differentiated NETs (typical carcinoids), by definition, are tumors with NE differentiation and classical histological architecture of trabecular, insular, or ribbon-like cell clusters, with no or minimal cellular pleomorphism and sparse mitoses. Only 5 well differentiated NETs were registered in SEER, indicating that the entity of ''benign'' NETs are very rare in the gallbladder. Neuroendocrine carcinomas, refer to more aggressive forms of poorly-differentiated NETs with increased mitotic activity and the absence or limited extent of necrosis (Fig. 1B).[57–59] Variable amounts of fibrosis may also surround the tumor nests.[59] As the normal gallbladder epithelium does not contain neuroendocrine cells, the tumors arise in intestinal or gastric metaplasia secondary to cholelithiasis and chronic cholecystitis. Immunohistochemical staining is positive for neuroendocrine markers (CgA and NSE) but may also demonstrate specific positivity for amines or peptides (serotonin, histamine, glucagon, gastrin, somatostatin etc).

Poorly Differentiated Neuroendocrine Carcinomas (SCC and LCNEC)

These poorly differentiated tumors resemble their more common counterparts arising in the bronchopulmonary

TABLE 5. Stage of GB-NETs at Diagnosis

	All Stages	In Situ	Localized	Regional	Distant	Unknown
PanSEER9*	94	0	36 (39.6)	26 (28.6)	29 (31.9)	3
Non-SCC	61	0	25 (41.7)	14 (23.3)	11 (18.3)	11
SCC	33	0	1 (3.2)	12 (38.7)	18 (58.1)	2
SEER9 (1973-91)†	28	0	2 (8.0)	9 (36.0)	14 (56.0)	3
Non-SCC	9	0	2 (25.0)	4 (50.0)	2 (25.0)	1
SCC	19	0	0	5 (29.4)	12 (70.1)	2
SEER13 (1992-99)‡	51	0	23 (46.0)	13 (26)	14 (28.0)	1
Non-SCC	41	0	22 (55.0)	9 (22.5)	9 (22.5)	1
SCC	10	0	1 (10.0)	4 (40.0)	5 (50.0)	0
SEER17 (2000-05)§	105	0	45 (43.7)	28 (27.2)	30 (29.1)	2
Non-SCC	73	0	41 (56.9)	13 (18.1)	18 (25.0)	1
SCC	32	0	4 (12.9)	15 (48.4)	12 (38.7)	1

Numbers in brackets represent percentage of tumors with known stage.
*χ^2: 18.3, $P < 0.0001$: Significant difference in distribution of histology between Non-SCC and SCC in PanSEER (more distant disease in SCC).
†χ^2: 6.9, $P = 0.03$: Significant difference in distribution of histology between Non-SCC and SCC in SEER9 (more distant disease in SCC).
‡χ^2: 6.6, $P < 0.04$: Significant difference in distribution of histology between Non-SCC and SCC in SEER13 (more localized disease in Non-SCC).
§χ^2: 18.3, $P < 0.0001$: Significant difference in distribution of histology between Non-SCC and SCC in SEER17 (more localized disease in Non-SCC).
SCC indicates small cell carcinoma; SEER, surveillance, epidemiology and end results.

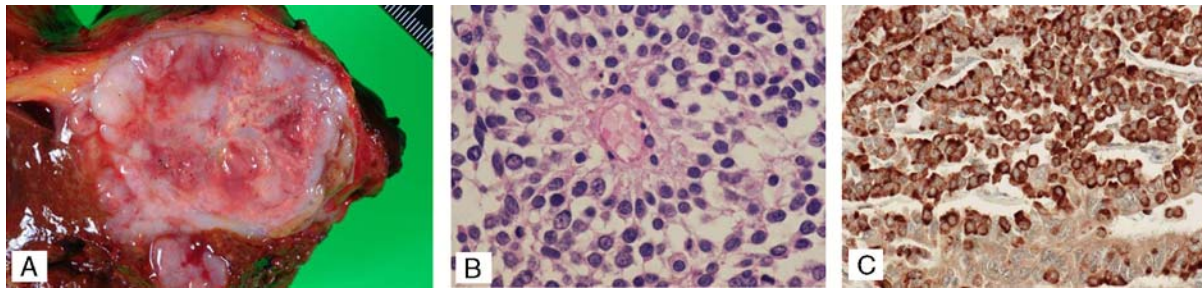

FIGURE 1. A, Cut section in a 4 cm gallbladder NET showing areas of hemorrhage and necrosis. B, Microscopic picture of a gallbladder NET showing characteristic polygonal cells and cell nests. C, Immunohistochemical CgA staining of a gallbladder NET. 233 × 57 mm (300 × 300 DPI).

system. They exhibit similar histological features and aggressive behavior with a high propensity for invasive growth, and early lymph node and distant metastases, and have an exceedingly poor prognosis.[60,61] Similar to other GB-NETs, they arise in areas of intestinal/gastric metaplasia in the gallbladder.[13,62]

Small Cell Carcinoma

Grossly, SCC may vary from covert lesions unapparent to largely necrotic, exophytic, or ulcerative masses.[36] More than 90% are poorly differentiated or anaplastic with regional or distant spread at diagnosis (Tables 4, 5). The most common metastatic sites are nodes (88%), liver (88%), lung (23%), and peritoneum (19%).[11] Histopathologically, the WHO classification defines SCCs as neuroendocrine tumors with >10 mitoses/2 mm^2 and small cell cytological features. The cellularity is typically very high with hyperchromatic nuclei, absent or very small nucleoli with scant cytoplasm, a high-nuclear to cytoplasmaic ratio, and a round or fusiform shape. The mitotic rate is very high.[61,63] Immunohistochemical staining shows strong positive staining for neuroendocrine markers (chromogranin A and synaptophysin).[61] In comparison to NETs which usually are diffusely positive for neuroendocrine markers, SCCs show more focal staining.[36] The tumor often grows in sheets without a specific pattern, but most tumors exhibit classic neuroendocrine growth patterns with rosettes, peripheral palisading, organoid nesting, strands and ribbons.[63] The general architecture of most parts of the tumor is however, usually poorly preserved, and large areas of necrosis separating small islands of viable tumor are common.[63] A combination of gallbladder SCC and adenocarcinoma is quite common and in the, 36 reported SCC, 8 (22%) were mixed with adenocarcinoma.[11]

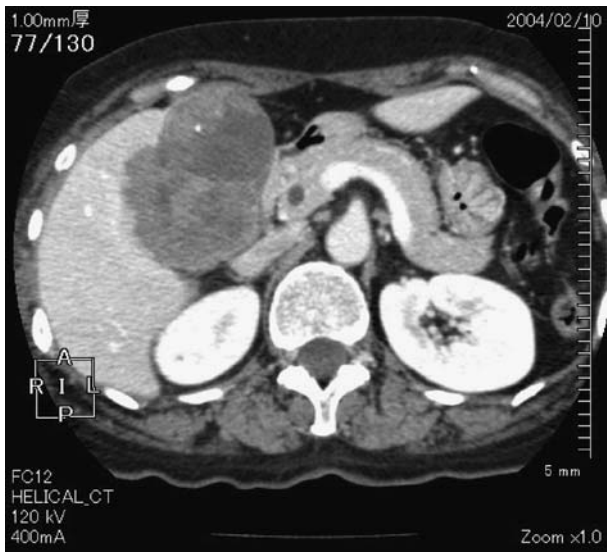

FIGURE 2. CT scan showing a gallbladder mass (NET). 125 × 117 mm (300 × 300 DPI).

Large Cell Neuroendocrine Carcinoma

In the WHO classification, LCNECs are considered NE tumors with >10 mitoses/2 mm^2 and cytologic features of a large cell carcinoma.[64] They consist of polygonal shaped cells that are about three times larger than SCLC, grow in an organoid pattern, exhibit cellular palisading or rosette-like areas and have abundant, often large patches of necrosis.[13] They have a low nuclear to cytoplasmatic ratio, and nuclear pleomorphism with a granular chromatin pattern is common.[61] Immunohistochemical staining show strong cytoplasmic staining for neuroendocrine markers (chromogranin A and synaptophysin).[61] The mitosis rate is high. LCNECs commonly metastasize and often present with an advanced disease at diagnosis.[65,66] As with other GB-NETs, LCNEC may also occur mixed with adenocarcinomas.[12,13]

DIAGNOSIS

The diagnosis of a gallbladder NET is rarely made preoperatively since the presentation generally consists of non-specific symptoms including upper abdominal pain, discomfort, jaundice, and weight loss. The presence of the carcinoid syndrome is very rare (< 1%) and the majority of lesions are identified incidentally at the time of cholecystectomy for cholelithiasis. Among 12 patients with SCC, all presented with features of symptomatic cholecystitis (right upper quadrant pain) and ultrasonographic demonstration of gallstones.[36] None, however, had obstructive jaundice, weight loss, paraneoplastic or endocrine symptoms.[36] In the Niigata series, abdominal pain, discomfort and associated cholelithiasis were the predominant clinical presentation in the carcinoid group (WHO1 + 2). The incidence of associated cholelithiasis in the variant group was 56% and the

overall number of patients which presented with carcinoid syndrome was 4/138.[15]

In our analysis of the SEER data results, significant statistical difference in distribution of tumor grade at diagnosis between Non-SCC and SCC was identified in Pan SEER 9, SEER 13 and SEER 17 ($P < 0.0001$, $P = 0.0006$, $P = 0.0003$ respectively) (Table 4). More grade IV tumors were identified in SCC and more unknown tumors in Non-SCC. In respect to tumor stage (Table 5), distant metastasis was statistically significant in SCC compared to Non-SCC in Pan SEER 9, SEER 9, 13 and 17 ($P < 0.0001$, $P = 0.003$, $P < 0.04$, $P < 0.0001$ respectively).

It is not possible to differentiate preoperatively between gallbladder adenocarcinoma and a gallbladder NET with imaging techniques. Ultrasound examination of the abdomen usually reveals a well-defined mass with a heterogeneous echogenicity in the gallbladder fossa, usually confirmed by contrast-enhanced computed tomography scan.[67] The sensitivity of ultrasonography in the identification of GBC is ~44%.[68] If, however, the lesion has infiltrated the liver or there is lymph node metastasis, the diagnostic accuracy is greater. The endoscopic ultrasonographic (EUS) appearance of GBC is of a hypoechoic mass with or without gallbladder wall calcification.[69] Both transabdominal ultrasound and EUS enable fine needle aspiration (FNA) of the primary tumor, lymph nodes, or liver for cytology and improve the diagnostic sensitivity from 74 to 90% as compared to transabdominal ultrasonography alone.[70] Magnetic resonance cholangiopancreatography (MRCP) or endoscopic retrograde cholangiopancreatography (ERCP) may provide some additional information in regard to the extent of the encroachment of the lesion on the extrahepatic biliary tree. In addition to imaging the tumor and the ducts by ultrasound or ERCP, computerized axial tomography (CT) (Fig. 2) is necessary to define the extent of loco-regional disease and determine the T stage.[71] Since most NETs exhibit overexpression of somatostatin receptors, somatostatin analogue scintigraphy (SRS) is effective in identifying such tumors.[72] Positron Emission Tomography (PET) detects accumulation of radiolabeled biological substances such as 18F-fluorodeoxyglucose (FDG) in tumor tissue. More NET specific PET tracers include the use of radiolabeled somatostatin analogs. Combinations of PET with CT or MRI imaging systems are especially effective as they generally have a particularly high sensitivity (>90%) for detection of NET.[73–75] From these modalities 6-[fluoride-18]fluoro-levodopa [(18)F-DOPA PET] improved tumor localization compared with conventional imaging and 18F-TOCA PET improved the diagnostic accuracy for the detection of metastases.[73–75] The role of these modalities in the detection of GB-NETs, however, remains to be evaluated. If a gallbladder tumor presents along with a very large hepatic mass and/or extensive lymphadenopathy at diagnosis, a NET should be considered. However, similar presentation is also common for other neoplasms including advanced GB-adenocarcinomas, cholangiocarcinoma, hepatocellular carcinoma, or hepatic metastasis involving the gallbladder.[61] Extensive lymph node enlargement is also seen with gallbladder lymphoma.[61]

MANAGEMENT

The only curative therapeutic modality for gallbladder cancer in general is complete en bloc surgical resection. In lesions identified incidentally (47%) at cholecystectomy, however, re-exploration reveals that 74% have residual disease, indicating poor prognosis.[9] Additionally, despite a more aggressive surgical approach, the majority of patients who have undergone a potentially curative resection for GBC will develop recurrent metastatic disease. Among 99 patients who underwent "curative" surgery for GBC, median survival was only 30.3 months.[9]

The surgical treatment of gallbladder NETs varies widely, ranging from cholecystectomy alone to extensive surgical resections, including regional lymph node clearances and hepatic lobectomy.[2] No rational surgical strategy currently exists 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. The role of radiotherapy and chemotherapy in the management of these patients is unclear since in general NETs are insensitive to traditional radiotherapy.[76]

Chemotherapy has been reported to be of unpredictable value in high-grade NETs arising in other sites but is usually proposed as the best form of palliation.[77] It is thus possible that high-grade GB-NETs, especially SCC with a high mitotic index may, like their counterpart in the lung,[60] benefit from aggressive surgical resection in combination with chemotherapy[11] if resectability is possible. In a small series of five SCC, this approach resulted in a median survival of 31 months compared to only 4 months (if treated with cholecystectomy alone) as reported in other studies.[11] The chemotherapeutic agents of choice are cisplatin, gemcitabine and etoposide plus 5-flurouracil.[78] If the tumor is non-resectable, the primary management in this setting is therefore medical and not surgical.

Biotherapy including SST analogs and interferons together with peptide receptor radionucleotide therapy have been reported as effective in achieving symptom control in SST receptor positive inoperable gastroenteropancreatic (GEP) NETs.[79] It is likely that these modalities may also be applicable for inoperable GB-NETs but there are no current studies that provide analysable information.

Given the lack of data on GB-NETs, the best management strategy may reflect elements that have been utilized for the management of gallbladder carcinoma in terms of staging which may provide the most effective basis for a management strategy.

In individuals where the gallbladder NET is a $T_{in\ situ}$ or T1 tumor, simple cholecystectomy is probably adequate therapy. For more advanced GB-NETs ($\geq$T2/N0–N2), the outcome is usually poor, but better outcomes are likely to be evident with aggressive radical operative therapy. This should include radical cholecystectomy and regional lymphadenectomy[71] combined with a hepatic resection to obtain an adequate clear margin.

Early recognition of the presence of a gallbladder NET should be followed by a detailed pathological analysis to firstly confirm the presence of a NET and thereafter determine whether the phenotype is pure neuroendocrine or has a goblet/mucin or adenocarcinoma components. Assessment of the Ki67, mitotic index, presence of mucin, penetration of the serosa, lymph node metastasis and hepatic infiltration are necessary to define the need for lymph node clearance and hepatic segmentectomy. With an increased level of histopahological assessment and aggressive operative resection, the survival outcome should improve for limited GB-NETs.[11,71] Since failure to identify the lesion early and local recurrence are the key issues, the need for pro-active surgical intervention is critical to

optimise a favorable outcome. A reasonable follow up schedule should comprise six CT scans for three years to provide early identification of disease recurrence. Thereafter, annual assessment may be adequate for up to 10 years as these tumors are known for late recurrence.

PROGNOSIS

The accurate assessment of prognosis is not possible given that some reported series have no stratification of the type of gallbladder NET and in others, the classification system is not clearly defined. Overall, it is apparent that there is an outcome distinction between well-differentiated and poorly-differentiated NET lesions. In addition, it seems that the presence of a mucinous or adenocarcinoma phenotype carries a far worse prognosis. Evidence of elevated Ki67 and high mitotic index are likely to be predictive of a poor outcome much as has been described in other NETs. Invasion of adjacent structures is an important negative predictor of outcome, whereas if the tumor is localized to the gallbladder wall the prognosis is better.[10,80] Among 18 carcinoid cases for which long term survival was documented, median survival was, however only 11 months.[10] The addition of chemotherapy or radiotherapy did not change survival.[10] The median survival of 13 GB-NETs diagnosed at MSKCC (1995 to 2005) was 9.8 months, and was slightly worse than the 10.3 month survival reported for all previously reported 435 GBCs. Ten of the 13 GB-NETs had high-grade and metastatic disease and seven were treated with platinum-based chemotherapy.[9] The reported SEER (9, 13, and 17) survivals for all GB-NETs are; 1-year (43 to 45%), 2-year (30 to 33%), 3-year (28 to 31%), 4-year (22 to 26%), and 5-year (22 to 25%). Pan-SEER 9 demonstrates a 62% one-year and a 37% five-year survival of carcinoids, while the corresponding values for SCC are only 21% and 0%, respectively (Fig. 3). Although the median survival for SCC is only ~4 months, there are indications, however, that aggressive multimodal treatment (surgery and chemotherapy) may prolong survival for SCC.[11] The prognosis for LCNEC is comparable to that of SCC, and long-term survival has been observed in only one published case with a small (< 1 cm) localized tumor.[13]

In Soga's study, curative resection (complete resection of the tumor ± lymphadenectomy and segmental resection) was carried out in 65.2% of the total series, 77.2% in the carcinoid group and 32.4% in the variant group.[15] He reported a statistically significant difference in the five-year-survival rates between the carcinoid group and the variant group (60.4% vs. 21.3%). No significant difference was evident between the typical carcinoids and atypical carcinoids (65.9% vs. 43.1%) and this form of classification appears to reflect the prevailing experience.[15]

It is worth noting that as more aggressive surgical approaches have been introduced for gallbladder adenocarcinoma that the survival rates have impoved. Thus in comparing outcomes from the later (1997 to 2002) to the earlier period (1990 to 1996), median survival has doubled from 9 months to 17 months and 5-year survival rates increased from 7 to 35%.[81,82] It would therefore seem reasonable to predict that adoption of a similar strategy for gallbladder NETs might likely result in a better outcome. Unfortunately the popular misconception that NETs are benign lesions and the failure to understand the biological nature of GB-Nets has often led to their under treatment and local recurrence.

CONCLUSIONS

Neuroendocrine cells usually do not exist in the normal gallbladder and occur only in intestinal or gastric metaplastic gallbladder mucosa which is seen secondary to cholelithiasis and chronic cholecystitis. The symptomatology of GB-NETs is nonspecific and their diagnosis is often made at cholecystectomy for cholecystolithisis or polyps. That's why the diagnosis of GB-NETs should be considered when a polyp/tumor is found on imaging studies in patients with cholelithiasis or chronic cholecystitis.

Analysis of the SEER registries demonstrates that GB-NETs are usually high-grade tumors which are diagnosed at a late stage, exemplified by their poor 5-year survival of

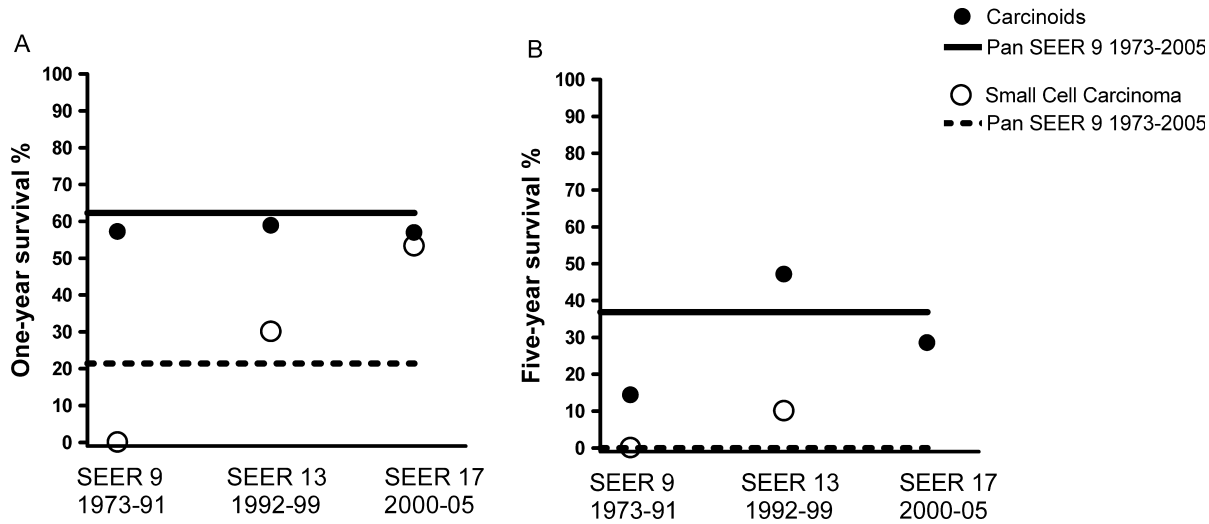

FIGURE 3. A, One-year survival for tumors classified as carcinoids (●) and small cell carcinoma (○). Pan SEER 1-year survival for carcinoids was 62.3%, while only 21.4% for small cell carcinoma. B, Five-year survival for tumors classified as carcinoids (●) and small cell carcinoma (○). Pan SEER five-year survival for carcinoids was 36.9%, while 0% for small cell carcinoma. 89 × 43 mm (1200 × 1200 DPI).

~20%. It is a misconception that these tumors behave less aggressively than GB adenocarcinomas which have a similar prognosis in the SEER data base.[1] Based on the difficulty in distinguishing between gallbladder NETs and GBC preoperatively and the increased survival rates for GBC based on aggressive surgical management, we propose that it would be practical to adopt the the same surgical management strategy for gallbladder NETs. The exception would be in those individuals with a well differentiated localized tumor where a simple cholecystectomy may be adequate. The vast majority of GB-NETs, however, require cholecystectomy and regional lymphadenectomy combined with a hepatic resection to obtain adequate clear margins. The effect of chemotherapeutic therapy remains uncertain, but given that these tumors are usually highly proliferative, it is likely that some palliative effect, especially for SCC, may be possible.

In conclusion, an increased awareness and understanding of the biological background of this tumor entity is required. In order to improve survival of GB-NETs aggressive surgical management appears to be the only effective proposal at this time and the tumors should be considered as, highly malignant and comparable to the more common gallbladder adenocarcinoma.

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