Primary Gallbladder Neuroendocrine Tumors: Insights into a Rare Histology Using a Large National Database

Reed I. Ayabe, MD[1], Michael Wach, MD[1], Samantha Ruff, MD[1], Sean Martin, MD[1], Laurence Diggs, MD[2], Timothy Wiemken, PhD, MPH[3], Leslie Hinyard, PhD, MSW[3], Jeremy L. Davis, MD[1], Carrie Luu, MD[2], Jonathan M. Hernandez, MD[1]

[1]Surgical Oncology Program, National Cancer Institute, National Institutes of Health, Bethesda, MD

[2]Division of General Surgery, Department of Surgery, Saint Louis University Hospital, St. Louis, MO

[3]Saint Louis University Center for Health Outcomes Research (SLUCOR), St. Louis, MO

Abstract

Background.—Primary gallbladder neuroendocrine tumors (NETs) are rare, poorly understood cancers infrequently encountered at even the largest of tertiary referral centers. We therefore sought to identify a large cohort of patients with gallbladder NETs using a national database, with the aim of defining treatment modalities employed and survival associated with these uncommon malignancies.

Methods.—Patients with primary gallbladder NETs were identified in the National Cancer Database, and clinicopathologic characteristics were recorded. A univariate log-rank survival analysis was completed for patients who underwent resection. Parameters found to be significant were entered into a multivariate accelerated failure time analysis. For context, survival comparisons were included for patients who underwent resections for NETs at any gastrointestinal site and for gallbladder adenocarcinoma.

Results.—Overall, 754 patients with gallbladder NETs were identified. Patients were predominantly female ($n = 518$, 69%), White ($n = 503$, 67%), presented with stage IV disease ($n = 295$, 39%) and had high-grade lesions ($n = 312$, 41%). The majority underwent resection ($n = 480$, 64%), primarily simple cholecystectomy ($n = 431$, 90%), whereas a minority received multimodal therapy ($n = 145$, 21%). Among patients who underwent resection, older age ($p = 0.001$), large cell histology ($p = 0.012$), and positive margins ($p = 0.030$) were independently associated with worse overall survival. Patients with gallbladder NETs had improved survival relative to those with gallbladder adenocarcinoma ($p = 0.001$), but significantly worse survival than patients with NETs from other gastrointestinal sites ($p<0.001$).

J. M. Hernandez, MD jonathan.hernandez@nih.gov.

Conclusions.—Primary gallbladder NETs are aggressive lesions that carry a worse prognosis than NETs of other gastrointestinal sites. Older age, positive margins, and large cell histology are associated with abbreviated survival after resection.

Gallbladder cancer is an aggressive malignancy with an annual incidence of 1.13 cases per 100,000 in the US and an overall 5-year survival rate of <20%.[1] The vast majority of gallbladder cancers are adenocarcinomas.[2,3] Primary gallbladder neuroendocrine tumors (NETs) are very rare, accounting for only 2–3% of primary gallbladder neoplasms.[3,4]

Due to their rarity, the literature on gallbladder NETs is limited to case reports and small case series, with no specific staging system for prognostication.[5–7] Currently, gallbladder neuroendocrine carcinomas are classified using the same American Joint Committee on Cancer (AJCC) staging system as gallbladder adenocarcinomas, although it is known that NETs from other gastrointestinal sites generally have a more indolent clinical course than adenocarcinomas.[8–10] Knowledge of the optimal management for gallbladder NETs is equally limited. The National Comprehensive Cancer Network (NCCN) and North American Neuroendocrine Tumor Society (NANETS) clinical guidelines do not address gallbladder NETs, and the treatment strategies employed for these tumors in case reports vary significantly.[11–13] The most consistently practiced treatment for gallbladder NETs is complete resection, which is extrapolated from gallbladder adenocarcinoma management.[4,5] However, little is known about patient outcomes after resection and the factors that have the greatest impact on survival.

The use of single-institution retrospective data to study gallbladder NETs is difficult due to prohibitively small sample sizes. Fortunately, large national datasets have made it possible to gain insight into these rare neoplasms by amassing data from thousands of hospitals nationwide. In this study, we use the National Cancer Database (NCDB) to evaluate gallbladder NETs, with three aims: (1) describe clinical characteristics and treatment patterns; (2) determine factors associated with survival in patients who undergo resection; and (3) compare the survival of patients undergoing resection of gallbladder NETs with that of patients undergoing resection for gallbladder adenocarcinoma and NETs from other gastrointestinal primary sites.

METHODS

Data Source

We performed a retrospective cohort study using the NCDB Participant User Files (PUFs) for gallbladder tumors. This study was exempt for review from our Institutional Review Board. The NCDB is a joint program of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society, and is a hospital-based registry with data from more than 1500 CoC-accredited hospitals. It includes information about patient demographics, comorbidities, disease stage, and the first course of treatment for 70% of newly diagnosed cancer cases in the US. The CoC and American Cancer Society have not verified and are not responsible for the analytic or statistical methodology used or for the conclusions drawn from these data.

Selection of the Study Population

The study population included patients 18 years and older who were diagnosed with gallbladder NETs from 2004 to 2015 in the NCDB gallbladder PUFs (International Classification of Diseases for Oncology, Third Edition [ICD-O-3] code C23.9). Patients with histologically confirmed neuroendocrine carcinoma not otherwise specified (NOS; 8246/3), small cell neuroendocrine carcinoma (8041/3), large cell neuroendocrine carcinoma (8013/3), and typical carcinoid (8240/3) were identified, and descriptive patient and tumor data were collected. Patients with a missing surgical status were excluded. The remaining patients were stratified into those managed operatively and those managed without an operation. Further survival analysis was then restricted to those patients who underwent an operation and had a reported histologic grade (Fig. 1).

Patient and Tumor Characteristics

Patient and tumor characteristics were examined, including age, sex, race, Charlson–Deyo score, tumor size, stage, grade, histologic subtype, and sites of metastasis. Race was classified as White, Black, or other, which included small numbers of Asian, Asian Indian, Middle Eastern, Pacific Islander, and Native American populations. Tumor size was stratified into <25 mm versus 25 mm for the purpose of multivariate analysis, with the threshold of 25 mm chosen because it was the median tumor size in this cohort. Stage was based on the AJCC guidelines for gallbladder adenocarcinoma. Nomenclature for histologic subtype has changed over the last 2 decades, and is also known to vary between institutions. The World Health Organization (WHO) and European Neuroendocrine Tumor Society (ENETS) systems of nomenclature state that high-grade NETs may be classified as neuroendocrine carcinomas, while the designation of typical carcinoid should be reserved for low-grade NETs. However, we noted that the majority of patients reported as having typical carcinoid in the NCDB had grade 3 tumors. To avoid confusion stemming from inconsistent nomenclature, the histologic subtypes of neuroendocrine carcinoma NOS and typical carcinoid were combined into one group called neuroendocrine carcinoma. A Kruskal–Wallis test was used to compare median tumor sizes of the three different histologies.

Treatment Characteristics

Surgical management was defined using surgery of the primary site codes, and was inclusive of cholecystectomy (considered simple or total surgical removal of the primary site [– 30, – 40]), radical cholecystectomy (– 60), debulking (– 50), and surgical resection NOS (– 90). Margins were classified as microscopically negative (R0) or microscopically positive (R1), both without gross residual tumor remaining after surgery. Debulking operations and grossly positive margins were classified as R2 resections. Receipt of neoadjuvant and adjuvant chemotherapy or radiation was also included in the analysis.

Survival Analysis

The primary outcome of the survival analysis was overall survival (OS), which was based on all-cause mortality and was calculated from the date of diagnosis to the date of death. Patients alive at the date of last contact were censored. Kaplan–Meier curves were created to

explore differences in survival between study variables. Univariate analysis of the association between study variables and OS was completed using the log-rank test.

To evaluate the adjusted survival time accounting for variables that were significant on univariate analysis, a multivariate accelerated failure time (AFT) model with a log-normal distribution was used. Patients with missing data for factors of interest were excluded from the multivariate model.

Comparison with Neuroendocrine Tumors from Other Sites and Gallbladder Adenocarcinoma

Due to the paucity of data regarding outcomes of gallbladder NETs, a separate survival analysis was completed comparing patients with resected gallbladder NETs with those with resected NETs arising from other gastrointestinal primary sites and resected gallbladder adenocarcinoma. Patients were selected from the NCDB PUF files for pancreas (code C25.0–C25.9), small bowel (code C17.0–C17.9), appendix (code C18.1), colon (code C18.0, C18.2–C18.9), rectum (code C19.9, C20.9), and stomach (code C16.0–16.9) using the same criteria used to select patients for the survival analysis above (Fig. 1). Patients with adenocarcinoma histology (codes 8140/3, 8144/3, 8310/3, 8480/3, 8490/3) were also selected from the NCDB gallbladder PUFs using these selection criteria. OS was compared using Kaplan–Meier curves and the log-rank test.

All statistical tests were performed using SPSS® version 25.0 (IBM Corporation, Armonk, NY, USA) or R version 3.5.0 (The R Foundation for Statistical Computing, Vienna, Austria). All tests were two-sided, and a p value <0.05 was considered statistically significant.

RESULTS

Patient and Tumor Characteristics

Overall, 754 patients with primary gallbladder NETs were identified, accounting for 2.3% of the 32,457 patients with gallbladder tumors in the database. The median patient age was 66 years. Patients were predominantly female ($n = 518$, 69%) and White ($n = 503$, 67%). The majority of patients had a Charlson–Deyo comorbidity score of 0 ($n = 538$, 71%). The median primary tumor size was 26 mm, and nearly half of the patients presented with stage IV disease ($n = 295$, 39%). Of these patients, the site of distant metastasis was documented in 148 cases (50%) and was most commonly the liver ($n = 126$). Of the cases reporting tumor grade, high-grade lesions (grade 3 and undifferentiated) were predominant ($n = 312$, 41%). The most common histologic subtype was neuroendocrine carcinoma ($n = 464$, 62%), followed by small cell neuroendocrine carcinoma ($n = 217$, 29%) and large cell neuroendocrine carcinoma ($n = 67$, 9%) (Table 1). The median size of large cell tumors (35 mm) and small cell tumors (45 mm) was greater than the median size of neuroendocrine carcinomas (12 mm) (p<0.001).

Treatment Patterns

More than half of the patients in this cohort underwent resection of their disease ($n = 480$, 64%). The vast majority of these operations were documented as a simple cholecystectomy

($n = 431$, 90%), while a few patients underwent a radical cholecystectomy ($n = 29$, 6%). An R0 resection was accomplished in most cases ($n = 323$, 67%). Of the patients who underwent an operation, most ($n = 335$, 70%) did not receive any additional therapy. Of the 272 patients who did not undergo a resection, 52% ($n = 141$) were treated with chemotherapy alone and 11% ($n = 30$) were treated with chemotherapy and radiotherapy. Ninety-nine patients (36%) did not receive any documented treatment (Table 2).

Factors Associated with Survival

Three hundred patients underwent tumor extirpation and had a documented histologic grade. The median OS for this cohort was 25 months. On univariate log-rank analysis, race, Charlson–Deyo score, large and small cell histologies, tumor size (electronic supplementary Figure 1), AJCC stage, tumor grade, margin status, and receipt of multimodal therapy were all associated with significant differences in survival. These factors were entered into a multivariate AFT analysis, which demonstrated that older age (time ratio (TR) 0.95, 95% confidence interval [CI] 0.93–0.98), large cell histology (TR 0.36, 95% CI 0.16–0.80), and positive surgical margins (TR 0.43, 95% CI 0.20–0.92) were independently associated with decreased survival (Table 3).

Survival Comparison with Other Neuroendocrine Tumors and Adenocarcinoma

Patients with NETs arising in other abdominal organs, as well as patients with gallbladder adenocarcinoma, were selected using the same criteria used to identify the survival cohort (Fig. 1). Patients with NETs arising in the pancreas ($n = 8611$), small bowel ($n = 19,275$), appendix ($n = 5221$), colon ($n = 4881$), rectum ($n = 6625$), and stomach ($n = 3297$) were included, as well as patients with gallbladder adenocarcinoma ($n = 16,228$). The median OS of patients with gallbladder NETs (25 months) was found to be significantly shorter than that of patients with NETs from any of the other abdominal primary sites ($p<0.001$) (Fig. 2a). Conversely, survival with gallbladder NETs was significantly longer than survival with gallbladder adenocarcinoma (25 vs. 17 months; $p = 0.001$) (Fig. 2b).

DISCUSSION

Primary gallbladder NETs are rare, accounting for 2.3% of gallbladder cancers in the NCDB. The existing literature on these tumors is limited to case reports and single-institution series, the largest of which includes 25 patients [5,6, 14–19]. In this study, we evaluated a cohort of 754 patients with primary gallbladder NETs and found that patients frequently present with metastatic disease and high-grade histology. Of the patients undergoing resection, which was almost always simple cholecystectomy, large cell histology and positive margins predict a particularly abbreviated OS. In order to frame the survival of patients undergoing a resection for gallbladder NETs into a familiar context for the practicing clinician, we documented and compared the survival of patients undergoing resection for gastrointestinal NETs and gallbladder adenocarcinoma using the same national database. In doing so, we demonstrated that gallbladder NETs have the worst survival of all gastrointestinal NETs, albeit superior to patients with gallbladder adenocarcinoma.

Due to their rarity, there is no specific staging system or clinical guideline to inform prognostication and management of gallbladder NETs. The AJCC 8th edition includes individual staging criteria for NETs of the stomach, ampulla, small bowel, appendix, large bowel, and pancreas, while gallbladder NETs are staged using the same schema as gallbladder adenocarcinoma.[10] Similarly, the NCCN and NANETS guidelines discuss the management of gastric, small bowel, pancreatic, and large bowel NETs as distinct entities, but do not address the management of gallbladder NETs.[11,12] Given the difficulty of accumulating enough patients for a meaningful single- or even multi-institutional retrospective review, large nationwide datasets such as the NCDB are ideally suited for the investigation of rare malignancies such as gallbladder NETs.[20,21] In the study of gallbladder adenocarcinoma, which itself is an uncommon disease, the NCDB has been used to describe trends in treatment and management,[22] validate changes to the AJCC staging system,[23] and, most recently, to elucidate the efficacy of multimodal therapy for locally advanced disease.[24,25] Similarly, NETs of the colon and rectum, small bowel, and appendix have been investigated using the NCDB and the Surveillance, Epidemiology, and End Results (SEER) database, providing information that has informed the recommendations of the NCCN.[11,26–28] While our data lack the necessary power to construct a new staging system or propose clinical guidelines for gallbladder NETs, they do provide a valuable reference to help clinicians estimate prognosis and evaluate management options when this rare disease is encountered.

Review of published case reports suggests that the management of gallbladder NETs is highly inconsistent, ranging from simple cholecystectomy to radical resection with varying combinations of systemic agents and radiation extrapolated from regimens for biliary tract adenocarcinomas and gastrointestinal NETs.[4–6,13,17, 18,29–31] These treatment options are nearly impossible to study in a prospective fashion due to the scarcity of these tumors. One of our aims was to simply describe how these tumors are currently being managed in the large cohort made available by the NCDB. We found that the majority of patients with gallbladder NETs were treated surgically, primarily with a simple cholecystectomy. A small minority underwent radical cholecystectomy, and most did not receive multimodal therapy. Of those who were treated non-operatively, most received systemic chemotherapy alone. Unfortunately, the NCDB does not contain data regarding the types of systemic agents used. Existing case reports suggest that these tumors are frequently treated with combinations of a platinum agent with gemcitabine or etoposide, with occasional partial responses to both regimens.[6, 13]

Our survival analysis revealed that large cell histology portends a particularly poor prognosis for patients with gallbladder NETs. Large cell NETs are characterized by a high mitotic rate (>10 mitoses/2 mm^2), polygonal cells that are approximately three times larger than those of small cell NETs, irregular nuclei, cellular palisading, and, frequently, large areas of necrosis.[4,5] In a 2010 literature review evaluating 29 case reports of poorly differentiated gallbladder NETs, Iype et al. found that large cell histology was associated with worse prognosis and reduced responsiveness to chemotherapy.[13] While a finding of large cell histology is likely to be made after resection, it may be informative to the treating oncologist if identified during metastatic work-up, especially considering the targetable ALK rearrangement identified in a fraction of pulmonary large cell NETs.[32]

While this study offers valuable insight into gallbladder NETs, it does have significant limitations. As is the case with nationwide database reviews, our study was limited by the quality and granularity of the data reported. Several potentially important parameters, such as depth of tumor penetration into the gallbladder wall, extent of lymph node evaluation, and lymph node status, could not be included in the survival analysis because the majority of patients did not have these variables reported. Furthermore, it was not possible to determine whether the diagnosis of gallbladder NET was made incidentally during cholecystectomy, a scenario that could impact the treatment rendered and, potentially, the clinical outcome. The lack of data on specific systemic therapies also made it impossible to identify chemotherapeutic regimens that may have been more effective than others. Finally, the NCDB also does not document genetic syndromes such as von Hippel–Lindau disease, neurofibromatosis, or multiple endocrine neoplasia, which are associated with a significant number of NETs and may affect prognosis.

CONCLUSIONS

Primary gallbladder NETs are rare, aggressive neoplasms that are often high-grade and present at an advanced stage. Complete tumor extirpation should be pursued when feasible. Older age, positive margins, and large cell histology are independently associated with poor survival among patients undergoing resection.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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NCDB Gallbladder Patients
(N = 32,457)

→ 31,703 patients with non-neuroendocrine histology excluded

Neuroendocrine Histology
(N = 754)
Used to collect descriptive data on patient and tumor characteristics

→ 2 Patients with unknown treatment excluded

Non-Operative Patients
(N = 272)
Used to collect descriptive data on treatment patterns (Table 2)

Operative Patients
(N = 480)
Used to collect descriptive data on treatment patterns (Table 2)

→ 180 patients with unknown grade excluded

Survival Cohort
(N = 300)
Used for survival analysis (Table 3) and comparison to NET from other primary sites (Figure 2)
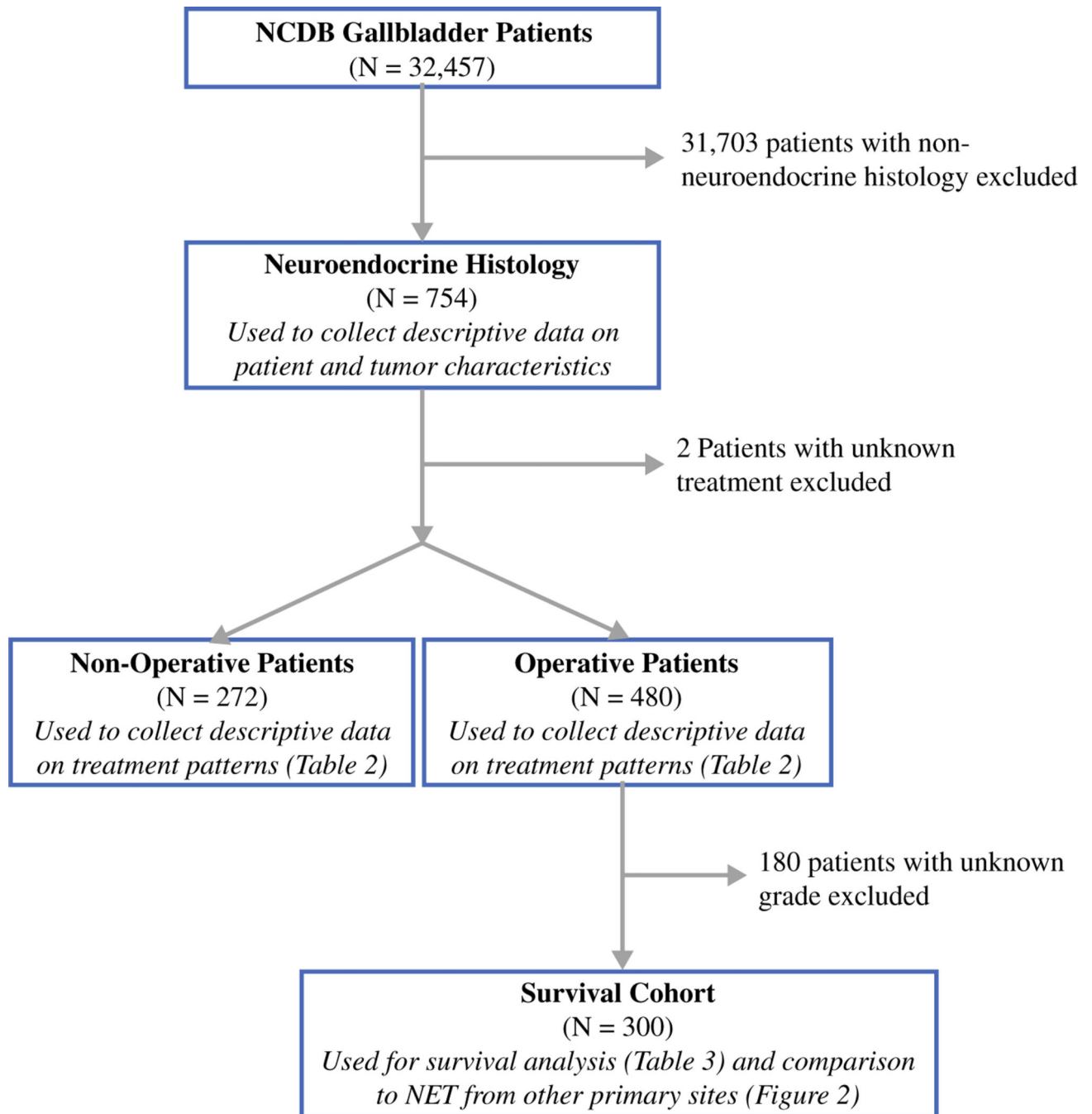
FIG. 1.
Selection of the study cohort. *NCDB* National Cancer Database, *NET* neuroendocrine tumor
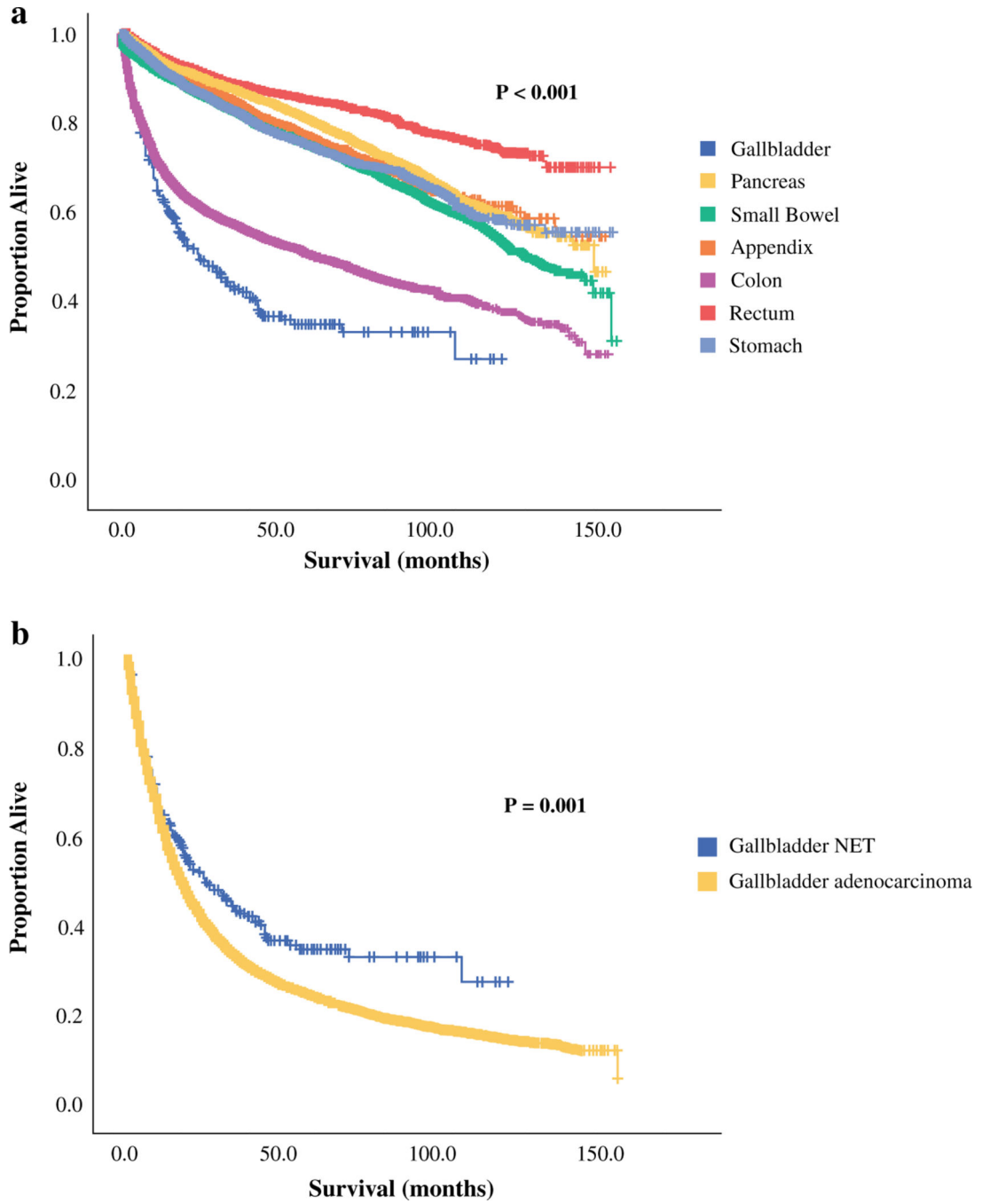
FIG. 2.

Kaplan–Meier survival curves comparing patients with resected gallbladder NETs with **a** patients with resected NETs from other gastrointestinal primary sites, and **b** patients with resected gallbladder adenocarcinoma. Median OS for patients with gallbladder NETs ($n = 300$) was 25 months, and median OS for patients with resected small bowel ($n = 19{,}275$) and colon ($n = 4881$) NETs was 130 months and 65 months, respectively. Median OS for NETs of the pancreas, appendix, rectum, and stomach was not reached, while median OS for

resected gallbladder adenocarcinoma (n = 16,228) was 17 months. *NETs* neuroendocrine tumors, *OS* overall survival

TABLE 1

Characteristics of patients with primary gallbladder NETs

Characteristic	All patients
[*N* = 754]	
Median age, years	66
Sex	
Female	518 (69)
Male	236 (31)
Race	
White	503 (67)
Black	130 (17)
Other	121 (16)
Charlson–Deyo score	
0	538 (71)
1	157 (21)
2	59 (8)
Tumor histology	
Neuroendocrine carcinoma	464 (62)
Small cell neuroendocrine carcinoma	217 (29)
Large cell neuroendocrine carcinoma	67 (9)
Median tumor size, mm	26
AJCC stage[a]	
I	205 (27)
II	77 (10)
III	121 (16)
IV	295 (39)
Positive regional nodes[a]	
Yes	111 (15)
No	72 (47)
Tumor grade[a]	
1	93 (12)
2	21 (3)
3 or undifferentiated	312 (41)
Site of metastasis	
Liver	126 (17)
Bone	10 (1)
Lung	7 (1)
Brain	5 (1)
Unspecified	147 (19)

Data are expressed as *n* (%)

NETs neuroendocrine tumors, *AJCC* American Joint Committee on Cancer

[a]Missing data were omitted

TABLE 2

Management of primary gallbladder NETs

Management	Operative [*N* = 480]	Non-operative [*N* = 272]
Chemotherapy	99 (21)	141 (52)
Radiation	8 (2)	2 (1)
Chemotherapy and radiation	38 (8)	30 (11)
No medical management	335 (70)	99 (36)
Extent of operation		
Cholecystectomy	431 (90)	
Radical cholecystectomy	29 (6)	
Debulking	3 (1)	
Surgical resection, NOS	17 (3)	
Margin status		
R0	323 (67)	
R1	59 (12)	
R2	12 (3)	
Positive, NOS	33 (7)	
Unknown	53 (11)	

Data are expressed as *n* (%)

NETs neuroendocrine tumors, *NOS* not otherwise specified

TABLE 3

Univariate comparisons and multivariate accelerated failure time survival analysis of patients [$n = 300$] who underwent resection of gallbladder NETs

Variable	Operative patients (%)	Median OS (months)	95% CI	Univariate p value	Time ratio	95% CI	Multivariate p value
Median age	64	–	–	–	0.95	0.93–0.98	0.001
Sex				0.648			
Female	197 (66)	27	16–37		–	–	–
Male	103 (34)	24	10–38				
Race				0.040			
White	212 (71)	24	15–32		Reference		
Black	44 (15)	16	9–24		0.91	0.36–2.31	0.835
Other	44 (15)	NR	–		3.87	1.27–11.81	0.017
Charlson–Deyo score				0.001			
0	200 (67)	34	19–48		Reference		
1	77 (26)	17	5–29		1.05	0.51–2.15	0.899
2	23 (8)	6	2–9		0.31	0.09–1.13	0.076
Tumor histology				<0.001			
Neuroendocrine carcinoma	196 (65)	51	26–75		Reference		
Small cell neuroendocrine carcinoma	56 (19)	11	7–15		0.54	0.24–1.19	0.124
Large cell neuroendocrine carcinoma	48 (16)	11	5–16		0.36	0.16–0.8	0.012
Tumor size, mm [a]				<0.001			
<25	114 (38)	NR	–		Reference		
25	113 (38)	13	9–18		0.94	0.42–2.09	0.878
AJCC stage [a]				<0.001			
I	94 (31)	NR	–		Reference		
II	51 (17)	41	9–73		3.40	0.63–18.40	0.156
III	56 (19)	24	16–32		3.77	0.65–21.94	0.139
IV	84 (28)	9	6–11		1.17	0.23–6.10	0.850
Tumor grade				<0.001			
1	91 (30)	NR	–		Reference		
2	19 (6)	51	0–113		0.23	0.05–1.09	0.064
3 or undifferentiated	190 (63)	14	9–18		0.32	0.07–1.60	0.167

Variable	Operative patients (%)	Median OS (months)	95% CI	Univariate *p* value	Time ratio	95% CI	Multivariate *p* value
Positive margins [a]				<0.001			
No	186 (62)	NR	–		Reference		
Yes	83 (28)	9	6–12		0.43	0.20–0.92	0.030
Multimodal therapy				0.003			
No	186 (62)	43	25–61		Reference		
Yes	114 (38)	17	13–21		0.68	0.33–1.41	0.300

NETs neuroendocrine tumors, *OS* overall survival, *CI* confidence interval, *AJCC* American Joint Committee on Cancer, *NR* not reached

[a]Missing data were omitted