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Hepatobiliary

Biliary Stone Disease in Patients with Neuroendocrine Tumors Treated with Somatostatin Analogs: A Multicenter Study

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Neuroendocrine neoplasms • Gallstones • Adverse events • Prophylactic cholecystectomy • Ursodeoxycholic acid

Abstract

Background. Somatostatin analogs (SSAs) are the mainstay of neuroendocrine tumor (NET) treatment. Biliary stone disease is reported as a common side effect of SSAs, with a frequency ranging from 10% to 63%. Studies on SSA-treated patients for acromegaly report an increased incidence of biliary stone disease compared with the general population, whereas data on patients with NETs are few. Guidelines are based on weak evidence, thus resulting in conflicting recommendations. The aim of the study is to evaluate biliary stone disease incidence, complications, and risk factors in a large population of SSA-treated patients with NETs.

Materials and Methods. A retrospective analysis of a prospectively collected database was performed. Patients with a diagnosis of NET in seven dedicated centers from 1995 to 2017 were included at the time of SSA start.

Results. A total of 754 SSA-treated patients were evaluated. Patients with history of cholecystectomy or with known biliary stone disease were excluded; 478 patients were included. Among them, 118 patients (24.7%) received prophylactic ursodeoxycholic acid (UDCA). During the study period, 129 patients (27.0%) developed biliary stone disease; of them, 36 (27.9%) developed biliary complications. On multivariate analysis, primary gastrointestinal (GI)-NET (hazard ratio [HR] 1.76) and related surgery (HR 1.58) were independent risk factors for biliary stone disease.

Conclusion. We report a high incidence of biliary stone disease particularly in GI-NET or GI surgery. UDCA prophylaxis does not seem to have a protective role. Our data suggest that all patients with primary GI-NET or undergoing abdominal surgery should be considered for prophylactic cholecystectomy; no conclusion could be drawn on the indication of prophylactic cholecystectomy in patients with primary pancreatic or thoracic NET for whom abdominal surgery is not planned. ***The Oncologist*** 2020;25:259–265

Implications for Practice: The results of this study confirm an increased rate of gallstones development and related complications in patients with neuroendocrine tumors (NETs) treated with somatostatin analogs (SSAs). NETs of the gastrointestinal (GI) tract and related surgery are independent risk factors for biliary stone disease development. Therefore, all patients with primary GI-NET or undergoing abdominal surgery should be considered for prophylactic cholecystectomy. Data on other subgroups are not exhaustive, and management also evaluating additional clinical features (life expectancy, surgical and anesthesiological risks) should be considered. Prophylactic treatment with ursodeoxycholic acid does not seem to be a protective factor for SSA-related biliary stone disease.

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Introduction

Somatostatin analogs (SSAs) represent the backbone of neuroendocrine tumor (NET) treatment. SSAs (octreotide long-acting release [LAR] and lanreotide Autogel) act by binding to somatostatin receptors, variously expressed on neuroendocrine cells, resulting in both antisecretive and antiproliferative activity [1]. Thus, SSAs are used in patients with advanced gastro-entero-pancreatic or thoracic NETs to control not only hormones hypersecretion in functionally active NETs but also tumor growth.

SSAs are usually well tolerated and side effects are mostly mild [2, 3]. One of the most severe side effects of SSA is biliary stone disease; its occurrence is clinically relevant because it may lead to treatment discontinuation or to medical or surgical procedures to treat complications [2].

Several studies reported an increased gallstone incidence in patients receiving SSAs if compared with the general population, although with very variable data; however, most of these studies have been conducted among patients with acromegaly [2–6]. In fact, only few studies are specifically focused in patients with NETs, and all are retrospective in nature; the observed incidence of biliary stone disease in this specific population ranges from 36% to 63% [7–11].

The European Association for the Study of the Liver (EASL) guidelines identify SSA-treated patients as a high-risk group for developing gallstone disease; thus, the use of prophylactic ursodeoxycholic acid (UDCA) is weakly suggested, despite low-quality evidence [12]. On the other hand, both European Neuroendocrine Tumor Society (ENETS) and North American Neuroendocrine Tumor Society (NANETS) guidelines result in weak clinical recommendations only on prophylactic cholecystectomy, and UDCA prophylaxis is not taken into consideration [1, 13].

The aim of our study was to evaluate the incidence of biliary stone disease in a large population of patients with NETs treated with SSAs; we also assessed risk factors for stone incidence and for biliary complications, with a particular focus on debated issues such as the role of UDCA prophylaxis.

Materials and Methods

Study Design

A retrospective analysis of a multicenter prospectively collected database was performed. All consecutive patients with NETs starting SSA treatment at seven Italian dedicated centers from 1995 to 2017 were analyzed. All data were prospectively retrieved at the center where the patient had been enrolled and then collected in a single computerized data sheet.

Study inclusion criteria were as follows: histological diagnosis of neuroendocrine neoplasms (NENs) of any grade and site, and treatment start with SSAs for metastatic or nonresectable disease at conventional or unconventional dose between January 1995 and December 2017. Patients with a history of cholecystectomy or biliary stone disease at the time of SSA start were excluded. Included patients were followed up until development of biliary complications, death, or SSAs withdrawal; the database was closed in September 2018.

The histological specimens were examined by a NEN-dedicated pathologist at each center. When required, an additional centralized revision of the tumor specimen was performed. Tumors were classified according to the 2010 World Health Organization (WHO) classification (gastro-entero-pancreatic neuroendocrine tumors) [14] or 2004 WHO classification (thoracic neuroendocrine tumors) [15] and the ENETS grading system [1]. Ki-67 proliferation index was expressed as a percentage based on the count of Ki-67-positive cells in 2,000 tumor cells in the areas of the highest immunostaining.

SSA treatment and clinical follow-up have been conducted according to the most recent ENETS guidelines [1, 16, 17]. Due to the few and conflicting recommendations, UDCA prophylaxis was prescribed on a case-by-case evaluation according to physicians' discretion [1, 12].

The following data were collected: gender, age at the time of SSAs start, primary NEN site, WHO classification, grade, functionality, presence of multiple endocrine neoplasia type 1 (MEN 1) syndrome, surgery of primary tumor or hepatic metastases, type, dose and duration of treatment with SSAs, and prophylactic treatment with UDCA. Unconventional SSAs dose was defined as an increased frequency of drug administration (lanreotide Autogel 120 mg or octreotide LAR 30 mg every 21 days) [18].

Definitions

Incidence of biliary stone disease was defined as the identification, on ultrasound (US) or cross-sectional imaging, of suspected findings and subsequent confirmation of gallstones with a dedicated US evaluation. The occurrence of any condition related to biliary stone disease, such as biliary colic, acute cholecystitis, cholangitis, biliary pancreatitis, or obstructive jaundice, was classified as a biliary complication. Biliary stone disease-free survival (BsDFS) was defined as the interval between the start of SSAs and the time of biliary stone disease occurrence. Biliary complications disease-free survival (BcDFS) was defined as the interval between the start of SSAs and the time of biliary complications occurrence (only in patients with biliary stone disease).

All patients or their legal representatives provided written informed consent for anonymous review of their data for research purpose. The study protocol was approved by a local institutional review board (Comitato Etico Indipendente, S. Orsola-Malpighi University Hospital, Bologna, Italy) and was conducted in accordance with the principles of the Declaration of Helsinki (6th revision, 2008).

Statistical Analysis

The distribution of the continuous variables was reported as median (range); categorical variables were described as number (percentage). Risk factors for biliary stone disease and related complications were evaluated by univariate and multivariate analysis using the Cox proportional hazards method and expressed as hazard ratio (HR) and 95% confidence interval (CI). The multivariate model was designed using the

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forward stepwise method after including all variables. Analysis A included also the variable SSA type (lanreotide Autogel vs. octreotide LAR); thus, patients sequentially treated with both octreotide and lanreotide Autogel have been censored. Analysis B was conducted in order to include all patients in the multivariate model; therefore, the limiting variable (SSA type, lanreotide Autogel vs. octreotide LAR) has been excluded.

BsDFS and BcDFS were measured using the Kaplan-Meier method, and the results were compared using the log-rank test.

The *p* value was considered significant when inferior to .05. Statistical analysis was performed using a dedicated software (IBM – SPSS Statistics v. 22.0; IBM Corp., Armonk, NY).

Results

Study Population

Seven hundred fifty-four patients treated with SSAs for advanced disease were included. Among them, 225 patients with a history of cholecystectomy and 51 with known biliary stone disease were excluded from the analysis. Finally, 478 patients were evaluated; baseline characteristics are described in Table 1.

Two hundred sixty-three patients (55.0%) were male. Median age at SSA start was 61 years (range 18–87). Primary tumor site was gastrointestinal (GI) tract in 211 patients (44.1%), pancreas in 184 (38.5%), lung in 47 (9.8%), and unknown in 36 (7.5%). As for WHO classification, 280 patients (58.6%) had a NET G1 or typical lung carcinoid and 156 (32.6%) a NET G2 or atypical lung carcinoid; data were missing in 42 cases (8.8%).

MEN 1 syndrome was present in 38 patients (7.9%). Eighty-seven patients (18.2%) had a functioning tumor. Among them, 59 presented with carcinoid syndrome, 10 Zollinger-Ellison syndrome, 8 insulinoma syndrome, 5 parathyroid hormone-related peptide hypercalcemia, 2 glucagonoma syndrome, 2 Cushing syndrome, and 1 VIPoma syndrome.

Primary tumor surgery was performed in 218 (45.6%) patients: of them, 133 underwent resection of GI tract (gastric or ileal resection or partial or total colectomy), 48 pancreatic surgery, and 37 thoracic surgery. Fifty-one patients (10.7%) underwent hepatic surgery for liver metastases.

As for SSA treatment, 276 patients (57.7%) received octreotide LAR 30 mg every 28 days, 144 (30.1%) lanreotide Autogel 120 mg every 28 days, and 58 (12.1%) both, sequentially. Forty patients (8.4%) received SSAs at unconventional doses (lanreotide Autogel 120 mg or octreotide LAR 30 mg every 21 days). Median duration of SSAs was 31.5 months (range 1–263 months). One hundred eighteen patients (24.7%) received prophylactic UDCA (with variable dosing schedules based on local clinical practice).

Table 1. Baseline characteristics of the study population

Characteristic	Patients (*n* = 478)
Demographic	
Gender (male), *n* (%)	263 (55.0)
Median age (range) at SSA start, years	61 (18–87)
Primary tumor site	
Gastrointestinal tract, *n* (%)	211 (44.1)
Pancreas, *n* (%)	184 (38.5)
Lung, *n* (%)	47 (9.8)
Unknown, *n* (%)	36 (7.5)
WHO classification	
G1 or typical carcinoid, *n* (%)	280 (58.6)
G2 or atypical carcinoid, *n* (%)	156 (32.6)
Missing data, *n* (%)	42 (8.8)
MEN 1 syndrome, *n* (%)	38 (7.9)
Functioning tumors, *n* (%)	87 (18.2)
Carcinoid syndrome, *n*	59
Zollinger-Ellison syndrome, *n*	10
Insulinoma syndrome, *n*	8
PTH-rP hypercalcemia, *n*	5
Cushing syndrome, *n*	2
Glucagonoma syndrome, *n*	2
VIPoma syndrome, *n*	1
Surgery	
Primary tumor surgery, *n* (%)	218 (45.6)
Pancreatic surgery, *n*	48
Gastrointestinal surgery, *n*	133
Thoracic surgery, *n*	37
Liver metastases surgery, *n* (%)	51 (10.7)
Medical treatment	
SSAs treatment characteristics	
Octreotide LAR, *n* (%)	276 (57.7)
Lanreotide Autogel, *n* (%)	144 (30.1)
Both, *n* (%)	58 (12.1)
Conventional doses, *n* (%)	438 (91.6)
Unconventional doses, *n* (%)	40 (8.4)
UDCA prophylaxis	118 (24.7)

Abbreviations: LAR, long-acting release; MEN 1, multiple endocrine neoplasia type 1; PTH-rP, parathyroid hormone-related peptide; SSA, somatostatin analogs; UDCA, ursodeoxycholic acid; WHO, World Health Organization.

Biliary Stone Disease Frequency and Risk Factors

Patients were followed up for a median of 31.5 (1–263) months. During the study period, 129 patients (27.0%) developed gallstones.

Risk factors for biliary stone disease are reported in Table 2. At univariate analysis, significant risk factors were GI primary tumor (HR 2.36, $p < .001$) and related surgery (HR 2.33, $p < .001$). Gender, age, MEN 1 syndrome, functionality of primary tumor, hepatic metastases surgery, SSA type, and dose were not related to biliary stone disease development.

Multivariate Analysis A (performed after exclusion of 58 patients sequentially treated with both lanreotide Autogel and octreotide LAR, 420 patients) identified only GI primary tumor (HR 1.89, $p = .012$) as an independent risk factor for biliary stone disease development. Multivariate Analysis B

Table 2. Risk factors for biliary stone disease

	Univariate analysis			Multivariate analysis A[a]			Multivariate analysis B[b]		
Characteristic	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**
Male (gender)	1.00	0.70–1.42	.998	—	—	—	—	—	—
Age	1.01	0.99–1.02	.182	—	—	—	—	—	—
MEN 1 syndrome	0.82	0.43–1.57	.549	—	—	—	—	—	—
Gastrointestinal primary tumor	**2.36**	**1.64–3.39**	**<.001**	**1.89**	**1.15–3.09**	**.012**	**1.76**	**1.10–2.82**	**.018**
Functioning tumor	1.14	0.75–1.72	.547	—	—	—	—	—	—
Gastrointestinal surgery	**2.33**	**1.64–3.30**	**<.001**	1.59	0.98–2.58	.058	**1.58**	**1.003–2.49**	**.049**
Liver metastases surgery	1.26	0.77–2.05	.357	—	—	—	—	—	—
UDCA prophylaxis	0.99	0.67–1.47	.952	—	—	—	—	—	—
Lanreotide vs. octreotide LAR	1.44	0.95–2.17	.082	1.49	0.99–2.25	.059	—[c]	—[c]	—[c]
Unconventional dose SSA	1.32	0.79–2–21	.281	—	—	—	—	—	—

[a]Analysis A: Analysis performed on 420 patients (excluding 58 patients sequentially treated with both lanreotide Autogel and octreotide LAR).
[b]Analysis B: Analysis performed on the entire population of 478 patients.
[c]Parameter not included in analysis.
Significant risk factors at multivariate analysis are marked in bold.
Abbreviations: CI, confidence interval; HR, hazard ratio; LAR, long-acting release; MEN 1, multiple endocrine neoplasia type 1; SSA, somatostatin analogs; UDCA, ursodeoxycholic acid.

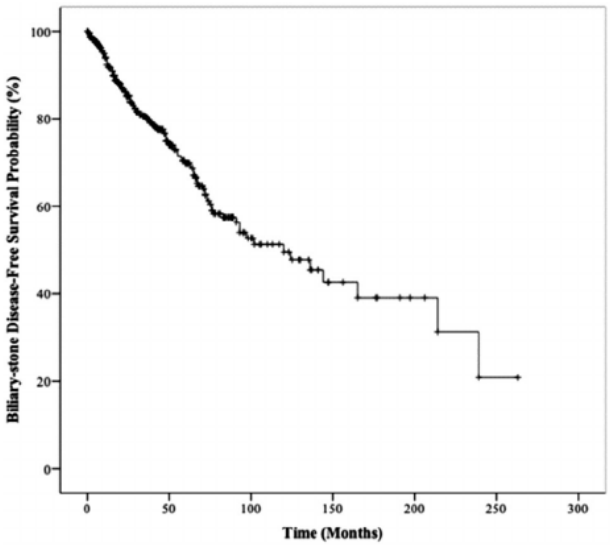

Figure 1. Kaplan-Meier estimates of biliary stone disease-free survival in patients with neuroendocrine tumors treated with somatostatin analogs.

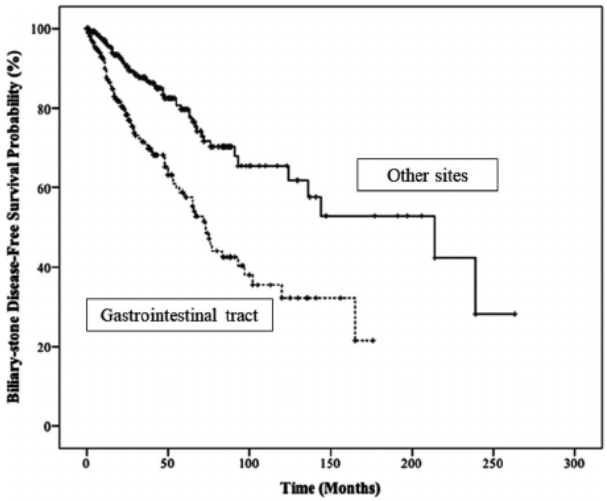

Figure 2. Kaplan-Meier estimates of biliary stone disease-free survival according to the site of primary tumor: gastrointestinal tract (dotted line) versus other sites (continuous line); $p < .001$.

(performed on the entire population of 478 patients) identified both GI primary (HR 1.76, $p = .018$) and related GI surgery (HR 1.58, $p = .049$) as independent risk factors for biliary stone disease development.

Biliary Stone Disease-Free Survival

Figure 1 shows Kaplan-Meier curve for BsDFS; median BsDFS was 120 months (95% CI: 87.7–152.3 months). Significant differences in BsDFS were observed according to primary tumor site; in particular, Figure 2 shows Kaplan-Meier curves for BsDFS according to primary GI tumor versus other primary tumor sites (median 73 months, 95% CI: 62.7–83.3 months vs. 214 months, 95% CI: 101.3–326.6 months; $p < .001$).

Figure 3 shows Kaplan-Meier curves for BsDFS comparing patients who underwent GI primary tumor surgery versus all other patients (median 65 months, 95% CI: 51.3–78.7 months vs. 165 months, 95% CI: 106.6–223.4 months; $p < .001$).

No difference was observed when correlating BsDFS to gender (median in male: 120 months, female: 102 months; $p = .998$), MEN 1 syndrome (median with MEN 1 syndrome: 93 months, without MEN 1 syndrome: 120 months; $p = .547$), hormone secretion syndrome (median in patients with syndrome: 120 months, without syndrome: 136 months; $p = .545$), hepatic metastases surgery (median yes: 124 months, no: 120 months; $p = .355$), UDCA prophylaxis (median with prophylaxis: 120 months, without prophylaxis: 124 months; $p = .952$), SSA type (median octreotide LAR: 136

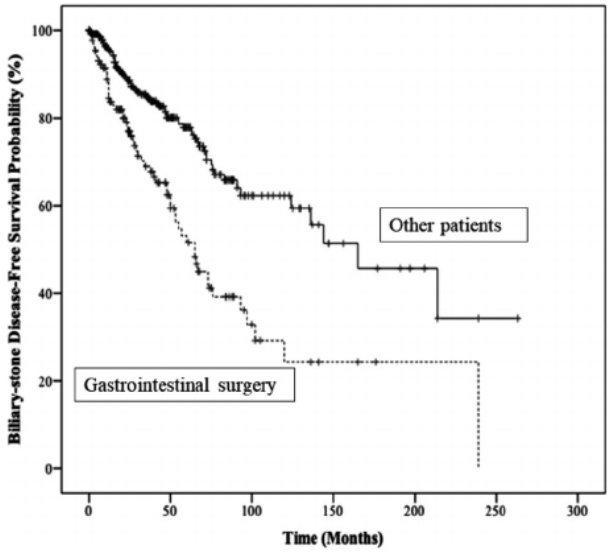

Figure 3. Kaplan-Meier estimates of biliary stone disease-free survival according to surgery of gastrointestinal primary tumor (dotted line) versus other patients (continuous line); $p < .001$.

Table 3. Risk factors for biliary complications

	Univariate analysis		
Characteristic	**HR**	**95% CI**	***p* value**
Male (gender)	0.78	0.39–1.53	.467
MEN 1 syndrome	0.70	0.21–2.35	.563
Gastrointestinal primary tumor	2.06	0.97–4.36	.060
Functioning tumor	0.61	0.27–1.38	.239
Gastrointestinal surgery	1.11	0.57–2.16	.764
Liver metastases surgery	0.31	0.07–1.29	.108
UDCA prophylaxis	0.58	0.25–1.34	.206
Lanreotide vs. octreotide LAR	0.78	0.33–1.83	.570
Unconventional dose SSAs	0.47	0.14–1.55	.217

Abbreviations: CI, confidence interval; HR, hazard ratio; LAR, long-acting release; MEN 1, multiple endocrine neoplasia type 1; SSAs, somatostatin analogs; UDCA, ursodeoxycholic acid.

months, median lanreotide Autogel: 76 months; $p = .079$), and SSA dose (median conventional dose: 136 months, unconventional dose: 71 months; $p = .278$).

Biliary Stone Disease Complications and Risk Factors

During the study period, 36 patients (7.5% of the entire population) developed biliary complications such as biliary colic, acute cholecystitis, cholangitis, biliary pancreatitis, or obstructive jaundice. Twenty-five patients required surgery, whereas 11 received pharmacological treatment. Among 129 patients who developed biliary stone disease during treatment, 27.9% presented a biliary complication. Median BcDFS was 102 months (95% CI: 61.9–142.0 months).

At univariate analysis, none of the tested factors (gender, MEN 1 syndrome, site and functionality of primary tumor, surgery of primary tumor or liver metastases, SSAs type and dose, UDCA prophylaxis) were related to the development of biliary complications (Table 3). Kaplan-Meier curves analysis did not identify any correlation with BcDFS.

Discussion

To the best of our knowledge, we conducted the largest study specifically dealing with biliary stone disease in patients with NENs treated with SSAs and observed a high frequency (27%) of biliary stone disease occurrence.

As stated by EASL guidelines, we agree that SSA-treated patients with NENs should be considered a high-risk population for biliary stone disease [12]. Based on our results, this population has a higher frequency of biliary stone disease compared with the general population, where the prevalence is 10%–20%. As for complications, in the general population, 0.7%–2.5% of patients with asymptomatic gallstones develop gallstone-related symptoms yearly; the annual incidence of complications is 0.1%–0.3% [12, 19–21]. Thus, our study population can be considered at high risk not only for gallstone developments but also for related complications.

Data from CLARINET and PROMID trials showed a sensibly lower frequency (10%–14%), probably due to a shorter period of exposure to SSAs (with a median of 14 months in PROMID and 24 months in the CLARINET study vs. 31.5 in our analysis) and a shorter follow-up [10, 11].

A previous single-center analysis from our institute reported a comparably high frequency of biliary stone disease (36.6%) [7]. Other retrospective studies based on patients with NENs reported a prevalence of 52%–63%, but studies on this specific population are few [8, 9]. On the contrary, many studies on patients receiving SSAs to treat acromegaly are available, reporting a very variable biliary stone frequency (3%–56% in the first 2 years of treatment) [2, 4, 6]. However, patients with acromegaly are not comparable to those with NETs, because acromegaly has already been identified as a risk factor for gallstones occurrence per se [3].

The role of SSAs in the pathogenesis of gallstone disease is related to several factors. First, SSAs tend to inhibit meal-stimulated cholecystokinin release, resulting in reduced gallbladder motility [4, 6]. In addition, SSAs slow intestinal transit, allowing intestinal bacteria to increase the amounts of deoxycholate, which favors the aggregation of cholesterol crystals into stones. Finally, SSAs inhibit postprandial Oddi's sphincter relaxation, further increasing bile stasis [22, 23].

We identified GI-NET and surgery for primary GI-NET as independent risk factors for biliary stone disease development. Despite the fact that studies on cholesterol and bile acids metabolism in patients with GI-NET are lacking, it has been previously reported that patients who underwent ileal resection have an increased risk of stone disease because of reduced ileal bile acid absorption [23, 24].

Several ileal diseases, such as Crohn's disease or radiation enteritis, may lead to a "broken" enterohepatic circulation, playing a pivotal role in the pathogenesis of gallstone formation. These conditions may lead to bile acid malabsorption and pool depletion, resulting in cholesterol-supersaturated bile [24–26]. Another possible explanation involves an altered microbiota, often coexisting in intestinal diseases, that could enhance the deconjugation of bilirubin and bile acids with an upregulation of enterohepatic cycle of bile pigment and

formation of pigment stones [27]. Finally, no study dealt with the hypothetical role in this setting of the release of active substances at a local level (e.g., serotonin, FGF19) that could alter GI motility.

UDCA prophylaxis is indicated in high-risk patients (i.e., rapid weight loss in obese patients) to reduce the incidence of biliary stone disease [12]. ENETS guidelines do not express any recommendation about the use of UDCA in patients with NENs receiving SSAs [1]. On the contrary, EASL guidelines recommend consideration of its use during SSA-treatment [12]. Interestingly, we did not observe any effect of UDCA on the development of gallstones when used as prophylactic treatment or when used to reduce the risk of biliary complications in patients with gallstones.

Moreover, no patient had to permanently discontinue SSA-treatment because of biliary stone disease or any of its complications. After medical or surgical treatment, at resolution of symptoms if present, all patients could resume SSA-therapy.

The main limit of the study is the retrospective design that could lead to an inhomogeneous diagnostic and therapeutic management. In particular, no standardization on planned exams or treatment schedule has been conceived; however, only NEN-dedicated centers have been included, in order to have a better adherence to available guidelines and reduce discrepancies. The study population underwent scheduled US or computed tomography scan as suggested by most recent guidelines for the oncological follow-up [16, 17]. Because of the retrospective nature of this study, a specific workup for the diagnosis or follow-up of biliary stone disease was not preplanned. Similarly, owing to conflicting recommendations, the management of UDCA prophylaxis and the treatment of biliary stone disease was not planned, but it was conducted at physician's choice following local clinical practice. Therefore, our observation of the ineffective role of UDCA cannot be considered conclusive and should be addressed in a dedicated trial.

Our study has for the first time clearly identified which subgroups of SSA-treated patients with NETs have a higher risk of biliary stone disease. We also observed that these patients presented a high rate of biliary-related complications (up to 30%) and that a significant amount of them (up to 70%) required cholecystectomy, despite underlying advanced oncological disease.

Current ENETS guidelines weakly suggest considering prophylactic cholecystectomy in patients who are candidates for abdominal surgery; indications are even weaker when surgery is not planned [1].

NANETS guidelines recommend prophylactic cholecystectomy only if performed at the time of primary tumor resection in patients with small-bowel NETs who are candidates for long-term SSAs; cholecystectomy is not suggested in asymptomatic patients [13]. Moreover, no recommendation is available in North American guidelines on the role of prophylactic cholecystectomy in primary tumor other than intestinal.

Conclusion

Our data suggest that prophylactic cholecystectomy is recommended in all patients undergoing surgery for primary GI-NETs. In all other patients undergoing abdominal surgery for any indication other than GI-NET resection, prophylactic cholecystectomy is suggested. On the other hand, patients with GI-NETs with long-life expectancy and who are candidates for long-term SSA-treatment where resection of primary is not indicated should be considered for prophylactic cholecystectomy on a case-by-case evaluation because of the cumulative high risk of biliary stone disease and related complications. With the available data, no conclusion could be drawn on the indication of prophylactic cholecystectomy in patients with primary pancreatic or thoracic NETs for whom abdominal surgery is not planned. Further prospective studies should be conducted to investigate these matters.

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Disclosures

The authors indicated no financial relationships.

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