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The clinical profiles, management, and prognostic factors of biliary mixed neuroendocrine nonneuroendocrine neoplasms

A systematic review of the literature

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Abstract

Background: Mixed neuroendocrine nonneuroendocrine neoplasms (MiNENs) originating from the biliary system (gallbladder, biliary tract, or ampulla of Vater) are extremely rare and have not been discussed in detail or systematically. We aimed to present the demographics, clinicopathological characteristics, management, and prognostic factors of biliary MiNENs.

Methods: A systematic search of electronic biomedical databases (Web of Science, PUBMED, and Embase) was performed to identify eligible studies. Survival was analyzed with the Kaplan–Meier method. Log-rank tests were used to evaluate the differences between groups, and the effects of various clinical and histopathological features on prognosis were analyzed by univariate and multivariate Cox regression.

Results: Fifty-three publications (patients, n = 67) were included. The median overall survival time was 21.0 months. Fifty-one patients (76.1%) underwent radical surgery and median survival for 41 months ($P < .001$). Twenty-two patients who received adjuvant radiochemotherapy treatment after radical surgery had a median survival for 43 months ($P = .076$). Radical resection ($P < .001$), Ki-67 index ($P = .011$), tumor stage ($P < .001$), neuroendocrine (NEC) grade ($P = .011$), and non-NEC grade ($P = .017$) were independent statistically significant prognostic factors according to univariate analysis; radical resection ($P = .010$) and small morphological subtype ($P = .036$) were independent statistically significant prognostic factors associated with higher overall survival according to multivariate analysis, and radical resection ($P = .005$) and age < 65 years ($P = .026$) were associated with higher recurrence free survival time.

Conclusion: Radical resection is essential for long-term survival. Aggressive multimodality therapy with adjuvant radiochemotherapy and biotherapy may improve survival of biliary MiNENs. Further randomized controlled trials are needed to determine the standard treatment.

Abbreviations: AV = ampulla of Vater, BD = bile duct, GB = gallbladder, MANEC = mixed adenoneuroendocrine carcinoma, MiNEN = mixed neuroendocrine nonneuroendocrine neoplasm.

Keywords: biliary tract, MANEC, MiNEN, mixed adenoneuroendocrine carcinoma, mixed neuroendocrine nonneuroendocrine neoplasm, survival outcomes

1. Introduction

Mixed tumors exhibiting combinations of neuroendocrine and nonneuroendocrine histology can occur in almost all organs, including the esophagus, stomach, small bowel, cecum, colon, rectum, and anus. In 1987, Lewin[1] proposed the classification of tumors as collision tumors, combined tumors, and amphicrine tumors. The gray zone between pure neuroendocrine and mixed neuroendocrine tumors has always been controversial, and to date, there is no accurate definition. Tumors with neuroendocrine and nonneuroendocrine components can exhibit variable

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morphological features, differing degrees of differentiation, and 1 of 3 different patterns,[2] namely, composite, collision, or amphicrine.

According to the 2010 WHO classification system,[3] neuroendocrine neoplasms are categorized as NET G1 to G3 and mixed adenoneuroendocrine carcinoma (MANEC). The corresponding G1 to G3 mitotic count ranges are less than 2 per 10 HPF, 2 to 20 per 10 HPF, and more than 20 per 10 HPF, and the corresponding Ki-67 index ranges are ≤2%, 3% to 20%, and >20%, respectively. In 2017, the WHO renamed MANECs "mixed neuroendocrine nonneuroendocrine neoplasms" (MiNENs).[4] In this update, the threshold of each component continued to be 30%, but the definition went beyond an exocrine component; moreover, the more general term "nonneuroendocrine" was replaced, leading to the inclusion of squamous and sarcoma, and the term "carcinoma" was replaced by the term "neoplasm," indicating that it was unnecessary for one or both components to be malignant. Thus, this update extended the applicability of the disease name.

Biliary (gallbladder, biliary tract, and ampulla of Vater) MiNENs are extremely rare diagnoses. This systematic literature review examines the epidemiology, clinical profiles, management, and prognostic factors of biliary MiNENs.

2. Materials and methods

This study does not require ethical review because the extracted data involved in the article are all published.

2.1. Search strategy

A systematic literature review was conducted in the PubMed, Web of Science, and Embase databases. The following search heading terms were used: "mixed neuroendocrine nonneuroendocrine neoplasm," "MiNEN," "mixed adenoneuroendocrine carcinoma," or "MANEC."

2.2. Screening process

The eligibility criteria were as follows: randomized clinical trials, observational studies, retrospective studies, and case reports; a publication time prior to January 2020; the gallbladder, bile duct or ampulla of Vater as the tumor location; and available data on survival dates. The exclusion criteria were as follows: MiNEN or MANEC were used with a different meaning; either component accounted for less than 30%; full articles were not available; MiNENs from outside the biliary system, which could not be selectively extracted and discarded; or the article (or at least the abstract) was not written in English.

2.3. Data extraction

Each of the 2 independent reviewers used established strategies to search the databases and to select the articles, and a third investigator reviewed each study to determine whether it would be included. The following information was extracted from each study: name of the first author; year of publication online; patient country, age, and sex; clinical features; tumor marker; imaging findings; tumor location; tumor size; preoperative endoscopic diagnosis with biopsy or cytology, nonneuroendocrine component, and differentiation; neuroendocrine component and grade; immunohistochemistry; Ki-67 index and mitotic count; genetics and molecular characteristics; treatment (including palliative or curative surgical methods, adjuvant chemotherapy, radiotherapy, biological therapy, or supportive care); tumor stage, tumor locoregional involvement (perineural or lymphovascular), and distant metastasis; and outcome (including disease-free survival, recurrence, or death).

2.4. Data analysis

The overall survival was defined as the time from the initial pathological diagnosis to death or the last follow-up. Kaplan–Meier analysis was used to evaluate the survival time. The differences between groups were evaluated with the log-rank test and the χ^2 test or Fisher's exact test, and univariate and multivariate Cox proportional hazard regression analyses were used to evaluate the effects of various clinical and histopathological features on prognosis. All tests were bilateral, and a P value $< .05$ was considered statistically significant. All statistical analyses were performed using SSPS (version 18). The primary observational indicators were survival data associated with clinical and pathological characteristics and management.

3. Results

3.1. Search results and characteristics

A total of 587 publications were screened. Ultimately, 53 studies (5–57) (n = 67 patients) were included, which were all case reports or case series (Fig. 1). Among the 67 patients, the median age was 63 years (range from 34 to 89), 27 (40.3%) patients were male, and 47 (59.7%) patients were female; the tumor locations were as follows: gallbladder, 58.2% (n = 39); bile duct, 9.0% (n = 6); and ampulla of Vater, 32.8% (n = 22). The median maximum diameter of the tumor (n = 53) was 25.0 mm (range from 5 to 152). The chief complaints (n = 50) were abdominal pain in 62.0%, fever in 16.0%, jaundice in 40.0%, weight loss in 14.0%, anorexia in 8.0%, and nausea or vomiting in 20.0% of cases; 8.0% were asymptomatic. The accuracy of preoperative endoscopic diagnoses with biopsy or cytology was 24.1% (n = 7). Positive tumor markers included carbohydrate antigen 19-9 (CA19-9) in 32.4% (n = 34) and carcinoembryonic antigen (CEA) in 8.7% (n = 23) of cases. The characteristics of the patients are summarized in Table 1 and Table S1 (see TableS1, Supplemental Content, http://links.lww.com/MD/F418, which illustrates characteristics of patients according to tumor stage), and the immunohistochemistry data are summarized in Table S2 (see TableS2, Supplemental Content, http://links.lww.com/MD/F419, which illustrates immunohistochemical staining results according to tumor location).

3.2. Management and clinical outcomes

All patients received surgical treatment. Fifty-one patients received radical surgery and 22 (43.1%) of them received adjuvant radiochemotherapy; 16 patients received palliative surgery and 5 (31.3%) of them received adjuvant radiochemotherapy. Radical cholecystectomy was the most common surgical procedure, and the combination of etoposide with carboplatin was the most common adjuvant chemotherapy. In total, 2 patients received radiotherapy and 3 patients received biotherapy. The treatment modalities of the patients are shown in Figure 2.

The median OS was 21.0 months (95% CI: 21.2–24.8) and the median RFS was 15.1 months (95% CI: 9.2–24.4). The results of

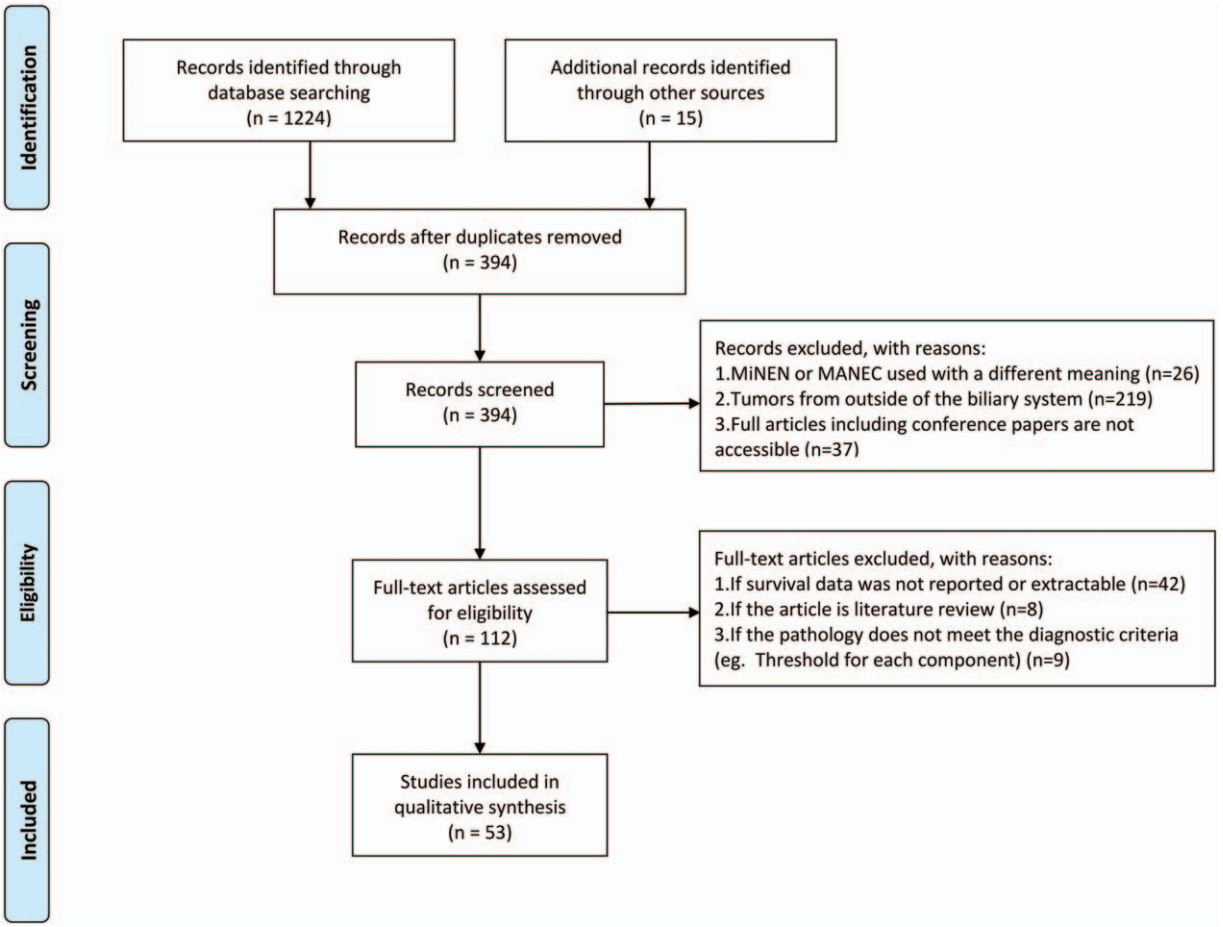

Figure 1. PRISMA algorithm for selection of studies of biliary MiNENs. MiNEN = mixed neuroendocrine nonneuroendocrine neoplasm, n = number of studies, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

the univariate analysis of OS are summarized in Figure 3 and Table S3 (see TableS3, Supplemental Content, http://links.lww.com/MD/F420, which illustrates univariate analyses of prognostic factors for overall survival). R0 resection ($P < .001$) (vs R1), MD tumor stage ($P < .001$) (vs ED and LAD), Ki-67 ≥ 50% ($P = .011$) (vs < 50), G3 neuroendocrine (NEC) grade ($P = .011$) (vs G1–2), and poorly non-NEC grade (vs moderate and well) ($P = .017$) were positive prognostic factors for worse OS. Adjuvant radiochemotherapy group (CR) with R0 resection ($P = .076$) (vs NCR) may have clinical significance for better OS.

The multivariate analysis, in Figure 4 and Table S4 (see TableS4, Supplemental Content, http://links.lww.com/MD/F421, which illustrates multivariate Cox regression analysis of OS and RFS), indicated that R1 resection (HR 3.220; 95% CI 1.983–142.191, $P = .010$) and large morphological subtype (HR 5.727; 95% CI 1.123–29.210, $P = .036$) were independent statistically significant prognostic factors associated with lower OS and that R1 resection (HR 20.737; 95% CI 2.510–171.344, $P = .005$) and age >65 years (HR 4.144; 95% CI 1.181–14.544, $P = .026$) were associated with lower RFS.

4. Discussion

This current systematic review included all studies with a diagnosis of biliary MiNENs that were confirmed by pathology. The included studies were all case reports or series.

The preoperative diagnosis of these tumors is a dilemma.[58] Laboratory examinations such as analyses of tumor markers do not seem to be good diagnostic tools, and imaging examination[59] can identify the location of the tumor but, in most cases, cannot differentiate tumor components because these tumors have no specific clinical features. Preoperative endoscopic diagnosis by biopsy or cytology has a positive rate of only 23.9%. First, biopsy or cytology[60] may not be able to distinguish each of the pure components in MiNENs. In most cases, the adenocarcinoma component is on the surface, and the neuroendocrine component is in the deep layer. Due to limitations involving the location and depth of biopsy, most of the biopsy results of the obtained tumor samples are adenocarcinoma, and in patients with advanced tumors, biopsies are often used to examine the components of the metastatic tumors, which always have only 1 component. Second, there is also controversy about the validity of the 30% threshold as a criterion for distinguishing MiNENs from their single-component counterparts.[2] At present, there are no relevant clinical trials proving that this threshold is meaningful, and most of the time, only a small part of another component can be obtained.

Immunohistochemistry is very important for identifying the components of MiNENs and has been described in most of the literature. Common markers include chromogranin A (CgA), neuroendocrine synaptophysin (Syn), differentiation cluster (CD) 56, biliary cytokeratins 7 and 20 (CK7, CK20), and CDX2.

Table 1

Review of the literature: basic clinicopathological characteristics of patients with biliary MiNENs.

First author	Year	Age (yr)	Gender	Location	Tumor size (mm)	Tumor stage	Surgery	Adjuvant therapy	Ki-67 index (%)	NEC grade	Non-NEC grade	Outcome (mouth)
Mayol et al[5]	1988	34	M	AV	30	MD	PD	NCR	NA	G3	Poorly	DOD, 16
Jones et al[6]	1989	64	F	AV	15	LAD	PD	NCR	NA	G2	Well	DF, 35
Burke et al[7]	1990	45	M	AV	NA	LAD	PD	NCR	NA	G3	NA	DF, 24
Misonou et al[8]	1990	47	F	AV	30	MD	BDR + cho	NCR	NA	G3	NA	RD, 9
Cavazzana et al[9]	1991	71	F	GB	52	MD	RC	NCR	NA	G3	Poorly	DOD, 4
Duan et al[10]	1991	70	M	GB	10	MD	RC	NCR	70	G3	Poorly	DOD, 1
Iida et al[11]	1992	62	F	GB	65	MD	RC	CR	60	G3	Poorly	DOD, 5
Nishihara et al[12]	1994	71	F	GB	NA	LAD	RC	NCR	NA	NA	NA	DF, 20
Alex et al[13]	1998	63	F	AV	15	LAD	PD	NCR	NA	G2	NA	DF, 24
Moskal et al[14]	1999	69	F	GB	NA	LAD	RC	CR	NA	G3	Poorly	DOD, 44
Moskal et al[15]	1999	71	F	GB	NA	MD	RC	CR	NA	G3	Poorly	DOD, 13
Moskal et al[16]	1999	40	M	GB	15	ED	RC + cho	CR	30	G3	Well	DF, 189
Eriguchi et al[17]	2000	81	F	GB	26	LAD	RC	NCR	NA	G3	NA	DF, 8
Papotti et al[18]	2000	50	F	GB	10	LAD	RC	NCR	50	G3	Well	DF, 12
Sakaki et al[19]	2000	79	F	GB	33	LAD	RC	NCR	40	G2	NA	DF, 8
Yannakou et al[20]	2001	72	F	GB	NA	MD	RC	NCR	NA	G3	Poorly	DOD, 2
Moncur et al[21]	2002	78	M	AV	23	MD	BDR + cho	NCR	NA	G3	NA	DF, 2
Koea et al[22]	2004	68	F	GB	NA	MD	RC	CR	NA	G3	Poorly	DOD, 6
Nassar et al[23]	2006	89	F	AV	NA	MD	BDR + cho	NCR	NA	G3	NA	DF, 6
Manzanares et al[24]	2005	75	M	AV	15	MD	PD	NCR	NA	G3	Poorly	DOD, 14
Shimizu et al[25]	2006	58	M	GB	150	MD	RC	NCR	80	G3	Poorly	DOD, 4
Tsuchiya et al[26]	2006	36	F	GB	10	LAD	RC	NCR	NA	G3	NA	DF, 12
Ferrando et al[27]	2007	64	M	AV	40	MD	BDR + cho	NCR	NA	G3	Poorly	DOD, 14
Oshiro et al[28]	2008	55	F	GB	49	LAD	RC	NCR	40	G3	NA	DF, 20
Iype et al[29]	2009	85	M	GB	15	LAD	RC	CR	NA	G3	NA	DOD, 21
Deschamps et al[30]	2010	49	F	AV	12	LAD	PD	CR	2	G1	NA	DF, 36
Sato et al[31]	2010	68	F	GB	NA	MD	RC	NCR	NA	G3	Well	DF, 12
Paniz et al[32]	2011	48	F	GB	NA	LAD	PD	CR	NA	NA	NA	DOD, 7
Song et al[33]	2012	55	F	GB	70	LAD	RC + LR	CR	20	G3	Moderately	DF, 7
Shintaku et al[34]	2013	80	M	GB	82	ED	RC	NCR	19	G2	Well	DF, 8
Meguro et al[35]	2014	54	F	GB	90	ED	RC + cho	NCR	70	NA	Poorly	DF, 24
Wysocki et al[36]	2014	65	M	BD	36	LAD	BDR + cho	NCR	80	G3	Poorly	DOD, 5
Lee et al[37]	2014	75	M	BD	20	ED	BDR + cho	NCR	NA	NA	NA	DF, 11
Zhang et al[38]	2014	69	M	AV	15	ED	PD	NCR	NA	NA	NA	DF, 33
Chen et al[39]	2014	34	M	GB	27	LAD	RC	CR	53	G3	NA	RD, 4
Liu et al[40]	2015	63	F	GB	20	ED	RC	NCR	80	G3	Moderately	DF, 12
Huang et al[41]	2015	43	F	AV	20	LAD	PD	CR	25	G3	Poorly	DOD, 20
		60	F	AV	17	LAD	PD	CR	40	G3	Poorly	DOD, 15
Takemoto et al[42]	2017	80	F	GB	13	LAD	RC + cho	CR	80	NA	Well	RD, 8
Komo et al[43]	2017	82	M	BD	18	LAD	SSPD	NCR	37	NA	NA	DF, 7
Izumo et al[44]	2017	66	M	BD	10	LAD	SSPD	NCR	30	NA	NA	DF, 30
Mahansaria et al[45]	2017	37	M	AV	40	LAD	PD	CR	50	G3	Moderately	DOD, 12
		39	M	AV	40	LAD	PD	NCR	50	G3	Poorly	DF, 13
		64	F	AV	15	LAD	PD	CR	40	G3	Poorly	RD, 16
Lin et al[46]	2018	43	F	GB	74	LAD	RC + LR	CR	NA	G3	Poorly	DF, 21
Fornelli et al[47]	2018	49	M	AV	15	ED	PD	CR	NA	NA	Poorly	DF, 84
Yoshioka et al[48]	2018	82	M	AV	25	ED	PD	NCR	NA	NA	NA	DF, 24
Ginori et al[49]	2018	69	M	AV	20	LAD	PD	NCR	20	NA	NA	DOD, 12
Duzkoylu et al[50]	2018	73	M	AV	10	LAD	PD	CR	70	G3	Poorly	DOD, 3
Naruse et al[51]	2018	71	M	BD	5	ED	PD	NCR	2	G1	Well	DF, 26
	2019	56	F	GB	152	LAD	LC + LR	CR	NA	NA	Moderately	RD, 2
Kamei et al[52]	2019	53	F	GB	35	MD	LR	CR	70	NA	Poorly	DOD, 41
Kanetkar et al[53]	2019	77	F	GB	NA	LAD	RC	CR	NA	NA	NA	DF, 6
		63	F	GB	NA	ED	RC	CR	NA	NA	NA	DF, 3
		50	M	GB	NA	ED	RC	CR	NA	NA	NA	DF, 3
		47	F	GB	NA	LAD	RC	CR	NA	NA	NA	DF, 22
		64	F	GB	NA	LAD	RC	CR	NA	NA	NA	DOD, 7
Zheng et al[54]	2019	62	M	GB	29	ED	RC	NCR	NA	NA	NA	DOD, 23
		62	M	GB	29	ED	RC	NCR	NA	NA	NA	DOD, 23
		62	F	GB	29	ED	RC	NCR	NA	NA	NA	DOD, 23
		62	F	GB	29	ED	RC	NCR	NA	NA	NA	DOD, 23

(*continued*)

Table 1

(continued).

First author	Year	Age (yr)	Gender	Location	Tumor size (mm)	Tumor stage	Surgery	Adjuvant therapy	Ki-67 index (%)	NEC grade	Non-NEC grade	Outcome (mouth)
		62	F	GB	29	ED	RC	NCR	NA	NA	NA	DOD, 23
		62	F	AV	29	ED	PD	NCR	NA	NA	NA	DOD, 23
Zhang et al[55]	2019	64	M	BD	20	LAD	BDR + cho	CR	95	G3	NA	RD, 7
Yoshimachi et al[56]	2019	75	F	AV	25	LAD	SSPD	CR	63	G3	Moderately	DOD, 10
Sciarra et al[57]	2019	66	F	GB	95	ED	RC	NCR	50	NA	Moderately	DF, 5

5-fluo = 5-fluorouracil, AV = ampulla of Vater, BD = bile duct, BDR = bile duct resection, carbo = carboplatin, Cho = choledochojejunostomy, cisp = cisplatin, CT = adjuvant chemotherapy, DF = disease free, DOD = dead of disease, etopo = etoposide, GB = gallbladder, gemci = gemcitabine, LR = partial liver resection, NA = not available, oxali = oxaliplatin, PD = pancreaticoduodenectomy, PPPD = pylorus-preserving pancreaticoduodenectomy, RC = radical cholecystectomy, RD = recurrent disease, RT = radiotherapy, SSPD = subtotal stomach-preserving pancreaticoduodenectomy.

As Table S3, http://links.lww.com/MD/F420 shows, the Ki-67 index drives prognostic factors, which is in accordance with previous research.[61] CgA seems to have no significance with survival.

The standard regimen of systemic treatments was not clear. All patients underwent surgery, and some patients with distant metastasis underwent surgery for symptom relief or to reduce the tumor volume. A total of 27 (40.3%) patients had adjuvant

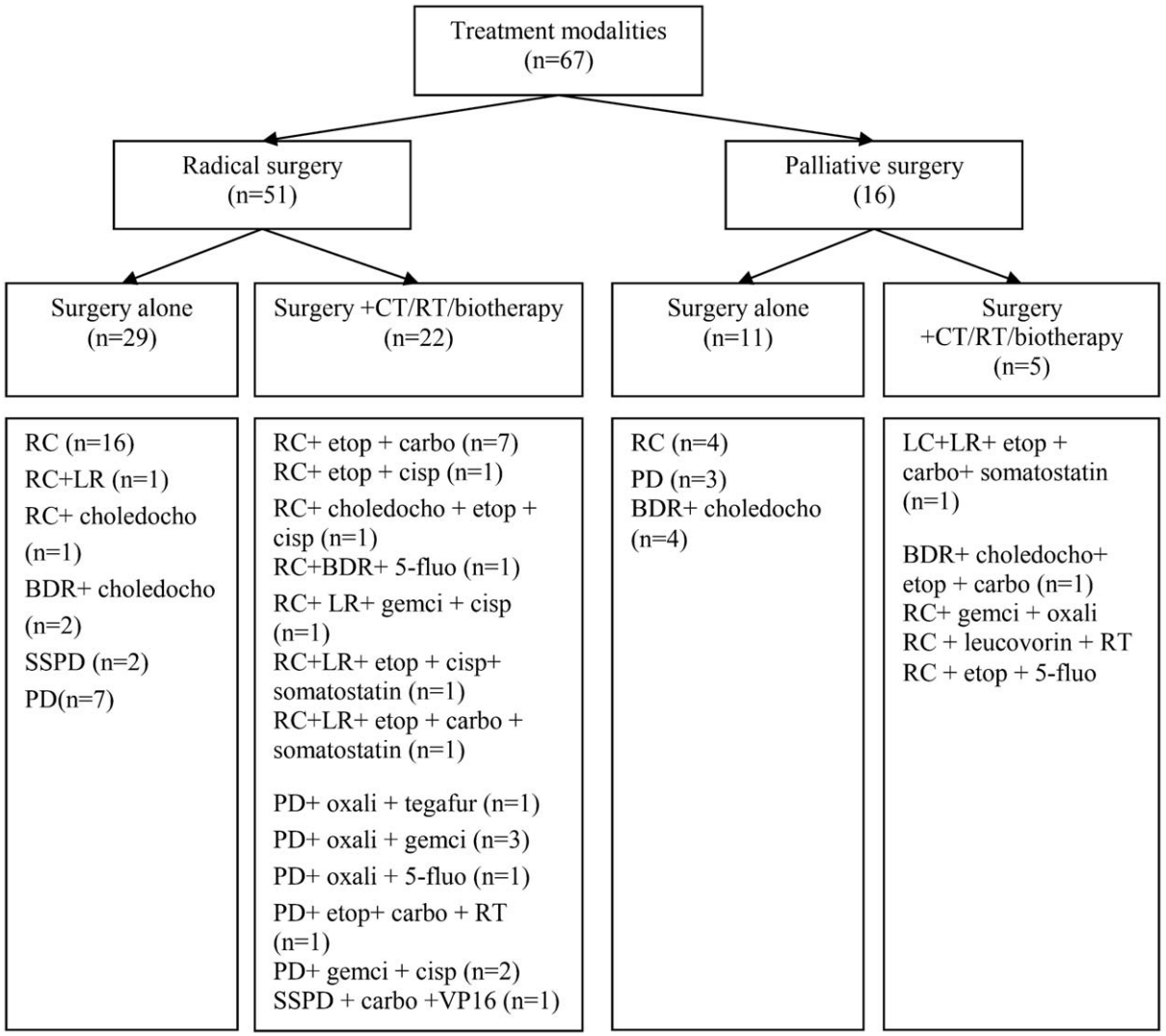

Figure 2. Treatment modalities of patients with a diagnosis of biliary mixed neuroendocrine nonneuroendocrine neoplasms. 5-fluo = 5-fluorouracil, BDR = bile duct resection, carbo = carboplatin, choledocho = choledochojejunostomy, cisp = cisplatin, CT = adjuvant chemotherapy, etopo = etoposide, gemci = gemcitabine, LR = partial liver resection, oxali = oxaliplatin, PD = pancreaticoduodenectomy, PPPD = pylorus-preserving pancreaticoduodenectomy, RC = radical cholecystectomy, RT = radiotherapy, SSPD = subtotal stomach-preserving pancreaticoduodenectomy.

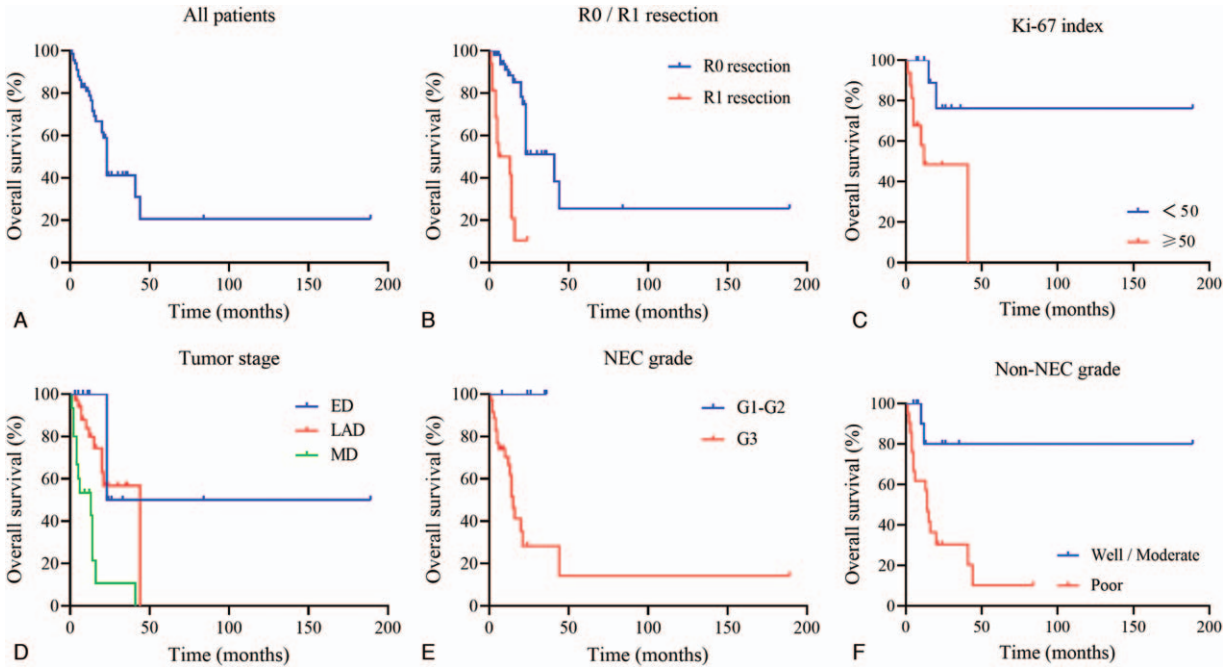

Figure 3. Univariate analysis of the survival times of patients with a diagnosis of biliary MiNEN. (A) Kaplan–Meier curves for overall survival of all patients, (B) overall survival by R0/R1 resection, (C) overall survival by Ki-67 index, (D) overall survival by tumor stage, (E) overall survival by NEC grade, (F) overall survival by non-NEC grade. MiNEN = mixed neuroendocrine nonneuroendocrine neoplasm, NEC = neuroendocrine.

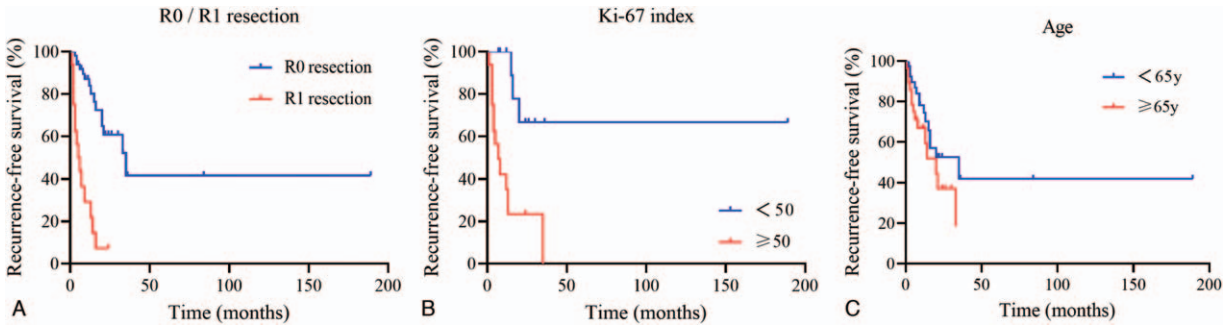

Figure 4. Multivariate Cox regression analysis of OS and RFS among patients with a diagnosis of biliary MiNEN. (A) Recurrence-free survival by R0/R1 resection, (B) recurrence-free survival by Ki-67 index, (C) recurrence-free survival by age. MiNEN = mixed neuroendocrine nonneuroendocrine neoplasm

chemoradiotherapy and biological therapy. Adjuvant treatment seems to improve survival time. At present, adjuvant therapy mostly comes from clinical practice guidelines, which propose a treatment algorithm based on a pure neuroendocrine or nonneuroendocrine component. Thus, adjuvant chemoradiotherapy, the standard of care, is controversial.

The median OS of patients with biliary MiNENs was 21.0 months, which was worse than that of patients with tumors of the gastroenteropancreatic tract according to a systematic review. The OS and RFS times for biliary MiNENs and neuroendocrine neoplasms were not different.[2]

In conclusion, radical resection is essential for long-term survival; aggressive multimodality therapy with adjuvant radiochemotherapy and biotherapy may improve the survival of biliary MiNENs. Further randomized controlled trials are needed to determine the standard treatment. The biliary MiNEN survival time is equivalent to that for pure neuroendocrine carcinomas at the same location and worse than that for gastroenteropancreatic MiNENs.

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Conceptualization: Qiong Yu, Kai Liu.
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