<table>
<thead>
<tr>
<th>Article Type</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPINION REVIEW</td>
<td>Whipple’s operation with a modified centralization concept: A model in low-volume Caribbean centers</td>
<td>Cawich SO, Pearce NW, Narayansingh V, Shukla P, Deshpande RR</td>
</tr>
<tr>
<td>REVIEW</td>
<td>Role of micronutrients in Alzheimer’s disease: Review of available evidence</td>
<td>Fei HX, Qian CF, Wu XM, Wei YH, Huang JY, Wei LH</td>
</tr>
<tr>
<td>MINIREVIEWS</td>
<td>Application of imaging techniques in pancreaticobiliary maljunction</td>
<td>Wang JY, Mu PY, Xu YK, Bai YY, Shen DH</td>
</tr>
<tr>
<td></td>
<td>Update on gut microbiota in gastrointestinal diseases</td>
<td>Nishida A, Nishino K, Ohno M, Sakai K, Owaki Y, Noda Y, Imaeda H</td>
</tr>
<tr>
<td></td>
<td>Vascular complications of pancreatitis</td>
<td>Kalas MA, Leon M, Chavez LO, Canalizo E, Sarani S</td>
</tr>
<tr>
<td>ORIGINAL ARTICLE</td>
<td>Network pharmacology and molecular docking reveal zedoary turmeric-trisomes in Inflammatory bowel disease with intestinal fibrosis</td>
<td>Zheng L, Ji YY, Dai YC, Wen XL, Wu SC</td>
</tr>
<tr>
<td>Case Control Study</td>
<td>Comprehensive proteomic signature and identification of CDKN2A as a promising prognostic biomarker and therapeutic target of colorectal cancer</td>
<td>Wang QQ, Zhou YC, Zhou Ge YJ, Qin G, Yin TF, Zhao DY, Tan C, Yao SK</td>
</tr>
<tr>
<td>Retrospective Cohort Study</td>
<td>Is anoplasty superior to scar revision surgery for post-hemorrhoidectomy anal stenosis? Six years of experience</td>
<td>Weng YT, Chu KJ, Lin KH, Chang CK, Kang JC, Chen CY, Hu JM, Pu TW</td>
</tr>
<tr>
<td>Retrospective Study</td>
<td>Short- (30-90 days) and mid-term (1-3 years) outcomes and prognostic factors of patients with esophageal cancer undergoing surgical treatments</td>
<td>Shi MK, Mei YQ, Shi JL</td>
</tr>
</tbody>
</table>
### Contents

**Effectiveness of pulsed radiofrequency on the medial cervical branches for cervical facet joint pain**

Chang MC, Yang S  

**Clinical performance evaluation of O-Ring Halcyon Linac: A real-world study**


**Correlation between the warning symptoms and prognosis of cardiac arrest**

Zheng K, Bai Y, Zhai QR, Du LF, Ge HX, Wang GX, Ma QB  

**Serum ferritin levels in children with attention deficit hyperactivity disorder and tic disorder**

Tang CY, Wen F  

**Application of metagenomic next-generation sequencing in the diagnosis of infectious diseases of the central nervous system after empirical treatment**

Chen YY, Guo Y, Xue XH, Pang F  

**Prognostic role of multiple abnormal genes in non-small-cell lung cancer**


**Prospective single-center feasible study of innovative autorelease bile duct supporter to delay adverse events after endoscopic papillectomy**


**Performance of Dexcom G5 and FreeStyle Libre sensors tested simultaneously in people with type 1 or 2 diabetes and advanced chronic kidney disease**

Ólafsdóttir AF, Andelin M, Saeed A, Sofizadeh S, Hamoodi H, Jansson PA, Lind M  

**Complications of chronic pancreatitis prior to and following surgical treatment: A proposal for classification**

Murruste M, Kirsimägi Ü, Kase K, Veršinina T, Talving P, Lepner U  

**Effects of comprehensive nursing on postoperative complications, mental status and quality of life in patients with glioma**

Dong H, Zhang XL, Deng CX, Luo B  

**Predictors of long-term anxiety and depression in discharged COVID-19 patients: A follow-up study**

Boyraz RK, Şahan E, Boylu ME, Korunlar I  

**Same-day single-dose vs large-volume split-dose regimens of polyethylene glycol for bowel preparation: A systematic review and meta-analysis**

## Contents

**World Journal of Clinical Cases**
Thrice Monthly Volume 10 Number 22 August 6, 2022

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>7859</td>
<td>Rectal nonsteroidal anti-inflammatory drugs, glyceryl trinitrate, or combinations for prophylaxis of post-endoscopic retrograde cholangiopancreatography pancreatitis: A network meta-analysis</td>
<td>Shi QQ, Huang GX, Li W, Yang JR, Ning XY</td>
</tr>
<tr>
<td>7872</td>
<td>Effect of celecoxib on improving depression: A systematic review and meta-analysis</td>
<td>Wang Z, Wu Q, Wang Q</td>
</tr>
</tbody>
</table>

### CASE REPORT

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>7883</td>
<td>Rectal mature teratoma: A case report</td>
<td>Liu JL, Sun PL</td>
</tr>
<tr>
<td>7890</td>
<td>Antibiotic and glucocorticoid-induced recapitulated hematological remission in acute myeloid leukemia: A case report and review of literature</td>
<td>Sun XY, Yang XD, Yang XQ, Ju B, Xu NN, Xu J, Zhao XC</td>
</tr>
<tr>
<td>7899</td>
<td>Non-secretory multiple myeloma expressed as multiple extramedullary plasmacytoma with an endobronchial lesion mimicking metastatic cancer: A case report</td>
<td>Lee SB, Park CY, Lee HJ, Hong R, Kim WS, Park SG</td>
</tr>
<tr>
<td>7906</td>
<td>Latamoxef-induced severe thrombocytopenia during the treatment of pulmonary infection: A case report</td>
<td>Zhang RY, Zhang JJ, Li JM, Xu YY, Xu YH, Cai XJ</td>
</tr>
<tr>
<td>7913</td>
<td>Multicentric reticulohistiocytosis with prominent skin lesions and arthritis: A case report</td>
<td>Xu XL, Liang XH, Liu J, Deng X, Zhang L, Wang ZG</td>
</tr>
<tr>
<td>7931</td>
<td>Primary hypertension in a postoperative paraganglioma patient: A case report</td>
<td>Wei JH, Yan HL</td>
</tr>
<tr>
<td>7936</td>
<td>Long-term survival of gastric mixed neuroendocrine-non-neuroendocrine neoplasm: Two case reports</td>
<td>Woo LT, Ding YF, Mao CY, Qian J, Zhang XM, Xu N</td>
</tr>
<tr>
<td>7944</td>
<td>Percutaneous transforaminal endoscopic decompression combined with percutaneous vertebroplasty in treatment of lumbar vertebral body metastases: A case report</td>
<td>Ran Q, Li T, Kuang ZP, Guo XH</td>
</tr>
<tr>
<td>7950</td>
<td>Atypical imaging features of the primary spinal cord glioblastoma: A case report</td>
<td>Liang XY, Chen YP, Li Q, Zhou ZW</td>
</tr>
<tr>
<td>7960</td>
<td>Resection with limb salvage in an Asian male adolescent with Ewing’s sarcoma: A case report</td>
<td>Lai CY, Chen KJ, Ho TY, Li LY, Kuo CC, Chen HT, Fong YC</td>
</tr>
<tr>
<td>7968</td>
<td>Early detection of circulating tumor DNA and successful treatment with osimertinib in the790met-positive leptomeningeal metastatic lung cancer: A case report</td>
<td>Xu LQ, Wang YJ, Shen SL, Wu Y, Duan HZ</td>
</tr>
</tbody>
</table>
Delayed arterial symptomatic epidural hematoma on the 14th day after posterior lumbar interbody fusion: A case report
Hao SS, Gao ZF, Li HK, Liu S, Dong SL, Chen HL, Zhang ZF

Clinical and genetic analysis of nonketotic hyperglycinemia: A case report
Ning JJ, Li F, Li SQ

Ectopic Cushing's syndrome in a patient with metastatic Merkel cell carcinoma: A case report
Ishay A, Touma E, Vornicova O, Dodik-Gad R, Goldman T, Bisharat N

Occurrence of MYD88L265P and CD79B mutations in diffuse large b cell lymphoma with bone marrow infiltration: A case report
Huang WY, Weng ZY

Rare case of compartment syndrome provoked by inhalation of polyurethane agent: A case report
Choi JH, Oh HM, Hwang JH, Kim KS, Lee SY

Acute ischemic Stroke combined with Stanford type A aortic dissection: A case report and literature review
He ZY, Yao LP, Wang XK, Chen NY, Zhao JJ, Zhou Q, Yang XF

Compound-honeysuckle-induced drug eruption with special manifestations: A case report
Zhou LF, Lu R

Spontaneous internal carotid artery pseudoaneurysm complicated with ischemic stroke in a young man: A case report and review of literature
Zhong YL, Feng JP, Luo H, Gong XH, Wei ZH

Microcystic adnexal carcinoma misdiagnosed as a "recurrent epidermal cyst": A case report
Yang SX, Mou Y, Wang S, Hu X, Li FQ

Accidental discovery of appendiceal carcinoma during gynecological surgery: A case report
Wang L, Dong Y, Chen YH, Wang YN, Sun L

Intra-ampullary papillary-tubular neoplasm combined with ampullary neuroendocrine carcinoma: A case report
Zavrtanik H, Lucar B, Tomažič A

LETTER TO THE EDITOR

Commentary on "Primary orbital monophasic synovial sarcoma with calcification: A case report"
Tokar O, Aydin S, Karavas E
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https://www.wjgnet.com/bpg/gerinfo/208

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https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/gerinfo/239

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Long-term survival of gastric mixed neuroendocrine-non-neuroendocrine neoplasm: Two case reports

Lun-Tao Woo, Yong-Feng Ding, Chen-Yu Mao, Jiong Qian, Xiu-Ming Zhang, Nong Xu

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Abstract

BACKGROUND
Gastric mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN), which consists of neuroendocrine and non-neuroendocrine components, is quite rare. Until now, most data on gastric MiNEN come from clinical cases, without large-scale retrospective studies or controlled clinical trials. Consequently, no consensus regarding the origin, molecular characteristics, or appropriate treatment of MiNEN has been reached so far. We conducted chemotherapy of irinotecan plus cisplatin (IP regimen) and surgery in two patients with gastric MiNEN, which had never been used in treating this kind of tumor, leading to their long-term survival for more than 3 and 7 years, respectively.

CASE SUMMARY
We present two patients (one male and one female) with gastric MiNEN, with the primary manifestation of recurrent upper abdominal pain. After they were referred to our hospital, a diagnosis of gastric MiNEN was defined with the help of CT scan, and histopathological and immunohistochemical examinations on the samples of gastrointestinal endoscopy or radical surgery. The male patient (case 1) were found to have metastases in the reginal lymph nodes and the left liver. He received four cycles of IP regimens first, then the gastrectomy and partial left liver resection, followed by additional two cycles of IP chemotherapy. The female patient (case 2) underwent a laparoscopic gastrectomy, and received six cycles of IP regimen. She was found to have metastatic lesions in the right lung 2 years after that, and underwent video-assisted thoracoscopic surgery (VATS) of the lower lobe of the right lung. The two patients have now survived for more than 3 years and 7 years, respectively, without any evidence of recurrence or metastases.

CONCLUSION
IP regimen, combined with curative-intent surgery if feasible, could be considered as the priority in the choice of front-line chemotherapy for gastric MiNEN.
Key Words: Gastric; Irinotecan plus cisplatin; Long-term survival; Mixed neuroendocrine-non-neuroendocrine neoplasm; Case report

Core Tip: Mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN) is a rare, highly aggressive tumor with a poor prognosis (median overall survival less than 12 mo), and no consensus regarding the appropriate treatment has been reached so far. We conducted chemotherapy of irinotecan plus cisplatin regimen and surgery in two patients with gastric MiNEN, which had not been used to treat this kind of tumor before, leading to their long-term survival for more than 3 and 7 years, respectively. Our reports may provide a reference for other clinicians.

INTRODUCTION

Gastric mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN), which consists of neuroendocrine and non-neuroendocrine components, is quite rare, accounting for about 7% of all gastric neuroendocrine neoplasms and 25% of all gastric poor differentiated neuroendocrine carcinomas, but their prevalence has not been explored specifically so far[1]. Gastrointestinal tumor with an exocrine and a neuroendocrine component was first described by Cordier in 1924[2]. Many different names had been used since then, causing confusion among clinicians, surgeons, and pathologists, such as composite carcinoïd, mucin-producing carcinoïd argentaffin cell adenocarcinoma, mixed exocrine-endocrine tumors, mixed adenoneuroendocrine carcinomas, and so on[3]. In the 2019 WHO Classification of Tumors of the Digestive System, the term MiNEN has been used when referring to this kind of tumor[4]. Until now, most data on gastric MiNEN come from clinical cases[5-8], without large-scale retrospective studies or controlled clinical trials. Consequently, no consensus regarding the origin, molecular characteristics, or appropriate treatment of MiNEN has been reached so far.

Due to the lack of knowledge of gastric MiNEN, this tumor has a quite poor prognosis, presenting with a short median survival of less than 12 mo[5,9]. The preferred treatment for high-grade MiNENs is currently suggested to be combining etoposide and a platinum salt (EP regimen) or the combinations of 5-fluorouracil and irinotecan or temozolomide or amrubicin[1]. However, we conducted chemotherapy of irinotecan plus cisplatin (IP regimen) and surgery in two patients with gastric MiNEN, leading to their long-term survival for more than 3 and 7 years, respectively. Here, we present the process of diagnosis and treatment and a brief review of the literature to improve our understanding of the tumor.

CASE PRESENTATION

Chief complaints

Case 1: A 63-year-old man was admitted to the hospital because of frequent upper abdominal pain for over 1 mo.

Case 2: A 54-year-old female patient was admitted to the hospital with recurrent epigastric pain for more than 7 years.

History of present illness

Case 1: The patient felt frequent upper abdominal pain for over 1 mo, so he underwent upper gastrointestinal endoscopy and magnetic resonance imaging at a local hospital. Then he was diagnosed as having gastric MiNEN with metastases in the regional lymph nodes and the left liver. He came to our hospital soon after, and was admitted because of “gastric cancer”.

Case 2: The patient had recurrent epigastric pain for 7 years, and the pain got worse on an empty stomach. She took omeprazole herself without obvious relief. Then she underwent upper gastrointestinal endoscopy at a local hospital and was diagnosed as having gastric cancer. So the patient came to our hospital for surgery and was admitted because of “gastric cancer”.

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History of past illness
Case 1: This patient had a history of hypertension for more than 10 years and herniorrhaphy surgery 5 years ago.
Case 2: The patient was diagnosed with chronic nasosinusitis, thyroiditis, cholecystolithiasis, hepatic cyst, and hepatic haemangioma.

Personal and family history
Case 1: The patient's father was dead, and his mother was healthy.
Case 2: The patient's father was dead; her mother and little brother were alive.

Physical examination
Case 1: The physical examination revealed the following: Temperature: 36.5 °C; pulse: 86/min; respiration rate: 14/min; blood pressure: 122/82mmHg. In the upper gastrointestinal endoscopy, no enlarged superficial lymph nodes, no abdominal wall varicosis, and no gastrointestinal peristalsis (Figure 1A).
Case 2: The physical examination revealed the following: Temperature: 37.1 °C; pulse: 80/min; respiration rate: 16/min; blood pressure: 118/76mmHg. Upper gastrointestinal endoscopy confirmed the gastric cancer (Figure 1B).

Laboratory examinations
Case 1: Laboratory examinations revealed the following: Red blood cell count (RBC) 4.2 × 10^{12}/L; hemoglobin (Hb) 110 g/L; white blood cell count (WBC) 6.8 × 10^{9}/L; platelet count (PLT) 126 × 10^{9}/L. The pathological examination and immunohistochemistry (IHC) confirmed the gastric MiNEN and the tumor was composed of two different components. The adenocarcinoma component was positive for cytokeratin 18 (CK18), and the neuroendocrine carcinoma component was positive for chromogranin A (CgA) and synaptophysin (Syn) (Ki67 index 80%) (Figure 2A1-A5). A high mitotic activity was seen (> 20 mitoses/10 high power fields [HPFs]).
Case 2: Laboratory examinations revealed the following: RBC 3.8 × 10^{12}/L; Hb 102g/L; WBC 8.4 × 10^{9}/L; PLT 208 × 10^{9}/L. The histopathological examination revealed tumor infiltration into the subserosal layer, with 11 regional lymph node metastases (pT4aN3aM0 stage). The tumor was composed of two different components, of which the adenocarcinoma component (positive for CKpan and CK18) accounted for 20% and neuroendocrine carcinoma component (positive for CKpan, CK18, CgA, and Syn; Ki67 index 60%) accounted for 80% (Figure 2C1-3). The mitotic activity was high (about 40 mitoses/10 HPFs).

Imaging examinations
Case 1: CT revealed the tumor infiltration into the omentum majus, with metastases to regional lymph nodes and the left liver (stage IV). Subsequently, the patient received four cycles of IP regimen as first-line chemotherapy. CT after the second and third cycles of chemotherapy revealed that the lesion in the left liver and regional nodes decreased markedly (Figure 3). Then, gastrectomy and partial left liver resection were performed and the histopathological examination confirmed that the neuroendocrine component of those lesions basically disappeared, only with adenocarcinoma component remaining in one regional lymph node (Figure 2B1 and 2B2). Metastases in the left liver totally disappeared (pT1aN1M0 stage). Two cycles of IP chemotherapy ensued after the operation.
Case 2: CT showed that the tumor infiltrated into the stomach wall and metastasized to regional lymph nodes.

FINAL DIAGNOSIS
Case 1: Gastric MiNEN (metastases to the left liver).
Case 2: Gastric MiNEN.

TREATMENT
Case 1: The patient received four cycles of IP regimen as first-line chemotherapy, then gastrectomy and partial left liver resection were performed.
OUTCOME AND FOLLOW-UP

Case 1: The patient has survived for more than 3 years without any evidence of recurrence or metastases.

Case 2: Two years after treatment, CT re-examination revealed metastatic lesions in the lower lobe of the right lung and video-assisted thoracoscopic surgery (VATS) was performed. Histopathological examination confirmed the neuroendocrine carcinoma (positive for CK7, CgA, and Syn; Ki67 index 30%) infiltration, with no metastases in regional lymph nodes. After the surgery, the patient did not undergo any further chemotherapy or radiotherapy and has survived for more than 7 years without any evidence of recurrence or metastases.

DISCUSSION

MiNEN is rare, especially in the stomach. To date, there is no consensus on the definition of MiNEN, especially the minimum proportion of each component. According to the WHO classification of digestive system tumors, MiNEN should contain both adenocarcinoma and neuroendocrine carcinoma components and each component is not less than 30%. However, this cutoff value has not been universally accepted, as it is defined arbitrarily rather than on proven clinical evidence and a minor (i.e., < 30%) poorly differentiated neuroendocrine carcinoma (PDNEC) component can impair prognosis [1, 9, 10]. Pham et al. [5] once reported a case in which the adenocarcinoma component accounted for 10%-20% of the tumor, just as the case in our two patients. Park et al. [11] found that a minor proportion (10%-30%) of PDNEC component would negatively influence the prognosis of patients with gastric MiNENs in a study including 88 patients. Consequently, the current 30% threshold, without sufficient prognostic value, may be not mandatory for defining MiNEN.

Most gastrointestinal MiNENs are highly aggressive, with a poor prognosis and median survival of less than 12 mo [5, 9]. At present, the diagnosis mainly relies on pathological examination and IHC of surgical specimen [5, 10]. CK, carcinoembryonic antigen, and caudal type homeobox 2 are used as markers for adenocarcinoma components, and Syn, CgA, and CD56 for neuroendocrine components [12]. In our two cases, the adenocarcinoma components were positive for CK18 or CKpan, and neuroendocrine component positive for CgA and Syn.

Until now, most studies suggest that surgical resection should be the main treatment for gastrointestinal MiNENs. Pham et al. [5] argued that palliative surgery remains essential even if the patients have developed distant metastases. Our two patients underwent resection of the primary lesion and metastatic lesion, respectively, and both of them achieved long-term survival, being in good condition, without any evidence of recurrence to date. Therefore, we believe that curative-intent surgery if feasible, is crucial for the treatment of MiNEN, as recommended by other authors [12-14].
There is still no consensus regarding the standard front-line chemotherapy against MiNENs[5]. Platinum combined with etoposide (EP) regimen is found to be the most recommended first-line therapy for gastroenteropancreatic neuroendocrine carcinomas (GEPNECs)[5,15,16]. The preferred treatment for high-grade MiNENs is also suggested to be EP regimen or the combinations of 5-fluorouracil and irinotecan or temozolomide or amrubicin[1]. Yamaguchi et al[17] compared IP regimen and EP regimen in treating GEPNECs, discovering that the IP group had a higher response rate (50% vs 28%, respectively; \( P = 0.001 \)). When it comes to irinotecan and etoposide, there were some studies demonstrating a lower incidence of grade 4 adverse events and treatment-related deaths in the irinotecan group than in the etoposide group when treating digestive neuroendocrine carcinoma[15,17]. IP regimen is also better than irinotecan monotherapy when comparing progression-free survival and disease control rate[18]. Therefore, we thought that IP regimen could be used for our two patients. Surprisingly, both of them achieved long-time survival for more than 3 years and 7 years, respectively.
which are much longer than those in other studies[3]. It may suggest that IP regimen could be considered as the priority in the choice of front-line chemotherapy for gastric MiNEN. To the best of our knowledge, we were the first to use IP regimen along with surgical resection for patients with gastric MiNENs.

To date, the effect of Ki67 proliferation index variation on prognosis remains unclear. Shi et al[19] discovered that the Ki67 index would rise in 40% (n = 30) patients and decline in 13.3% patients with gastroenteropancreatic NEC during the treatment. In addition, Panzuto, Botling, and their colleagues [20,21] found that the Ki67 index of patients tends to rise at time of disease progression, and median OS was significantly shorter in patients with rising Ki67 index (50.2 vs 115.1 m, hazard ratio = 3.89, 95% confidence interval [CI]: 1.91-7.94, P < 0.001). The Ki67 index of the patient in case 2 declined from 60% to 30% after IP regimen treatment, which was associated with a long-term survival. This, to some extent, may indicate that the decrease of Ki67 index is related to a better prognosis, which still needs further study.

At present, the most common genetic changes found in MiNENs include TP53, KRAS, BRAF, APC, PIK3CA, MYC, etc[22-25]. We wonder if our two patients share some common genetic changes, which could be part of the reason for their long-term survival. Next-generation sequencing tests were performed on the surgical specimens of them, revealing that they were all proved to be microsatellite stable (MSS), and the tumor mutation burden (TMB) was 4.06 mut/Mb and 2.03 mut/Mb, respectively. TP53 mutation was found in patient 1, and BRCA2 mutation, along with copy number increase in nine genes (MET, FGFR1, FGFR4, CDK4, CDK6, CDKN2A, ERBB3, RIT1, and VEGFA) in patient 2. We may assume that MSS and TMB fewer than 10 mut/Mb could be associated with improved response to IP regimen from the tests result. It still needs further studies to explore which genetic changes may indicate a better prognosis in patients with MiNEN receiving IP regimen treatment.
CONCLUSION

Gastric MiNEN is a rare malignant tumor without specific clinical symptoms. Histopathological and immunohistochemical examinations are requisite for pathologists and physicians to make diagnosis. Palliative surgery remains essential even when patients have undergone distant metastases. In the choice of front-line chemotherapy, we believe that IP regimen could be considered as the priority. More prospective studies are urgently needed to explore better treatment options for patients with gastric MiNEN.

FOOTNOTES

Author contributions: Woo LT performed the bibliographic retrieval and wrote the paper; Ding YF contributed to the paper revision; Mao CY and Qian J provided the data and detailed information of the patients; Zhang XM performed the pathological examination and immunohistochemistry of the specimens; Xu N conceived the whole idea and contributed to the manuscript revision.

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