

# A case report of neuroendocrine tumor (G3) at lower rectum with liver metastasis

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## Abstract

**Rationale:** Rectal neuroendocrine tumor is a rare disease that is difficult to diagnose by clinical and imageological examinations. The treatment of rectal neuroendocrine tumors is still controversial.

**Patient concerns:** A 50-year-old woman complained of abdominal pain beneath the xiphoid process for 1 day. Physical checkup revealed tenderness at the right upper abdomen. A fecal occult blood test was positive. MRI showed an occupation lesion in the right lobe of the liver. Colonoscopy examination showed a lesion at the lower rectum with an ulcerated surface that was tough in texture. No abnormality was found in the tumor markers.

**Diagnosis:** Rectal neuroendocrine tumor (G3) with liver metastasis.

**Interventions:** Neoadjuvant chemotherapy followed by laparoscopic surgery was given.

**Outcomes:** The patient followed up regularly in the outpatient department for 13 months after surgery, and no sign of recurrence was found.

**Lessons:** Neoadjuvant chemotherapy followed by laparoscopic surgery is a new idea for the treatment of rectal neuroendocrine carcinoma with distant metastasis, which offers favorable conditions for saving the anus during the surgery to enhance the patient's quality of life.

**Abbreviations:** CD56 = cluster of differentiation 56, CgA = chromogranin A, CT = computed tomography, D1 = Day 1, D1–3 = from Day 1 to Day 3, D1–5 = from Day 1 to Day 5, D8 = Day 8, DNA = deoxyribonucleic acid, EOB-MRI = Gd-EOB-DTPA-enhanced MRI, EP = etoposide + cisplatin, Gd-EOB-DTPA = gadolinium ethoxybenzyl diethylenetriaminepentaacetic acid, GEP-NETs = gastroenteropancreatic neuroendocrine tumors, HE = hematoxylin–eosin staining, HPF = high power field, IHC = immunohistochemistry, IP = irinotecan + cisplatin, K-C = knee–chest posture, Ki-67 = antigen ki67, MRI = magnetic resonance imaging, NCCN = National Comprehensive Cancer Network, NET = neuroendocrine tumor, Syn = synaptophysin, T1WI = T1-weighted image, T2WI = T2-weighted image.

**Keywords:** liver metastasis, neoadjuvant chemotherapy, neuroendocrine tumor at the lower rectum, surgery

## 1. Introduction

Neuroendocrine tumors (NETs) are a heterogeneous group of rare tumors with different and complex clinical behaviors, originating from peptidergic neurons and neuroendocrine cells throughout the body, and most are gastroenteropancreatic neuroendocrine tumors (GEP-NETs).<sup>[1]</sup> Generally, the incidence of GEP-NETs has increased continuously worldwide over the last decades due to the increased availability of diagnostic tools and awareness.<sup>[2]</sup> In addition, the rectum has become the most common tumor location, with 37.4% of GEP-NETs.<sup>[1]</sup> Only few

studies on rectal neuroendocrine tumors have been available until now. In addition, there has been no agreement about the treatment strategy and prognosis prediction.

We report a case about a 50-year-old woman diagnosed with a rectal neuroendocrine tumor (G3) with liver metastasis treated with neoadjuvant chemotherapy followed by laparoscopic surgery, in order to explore whether there are safer and more effective treatment options.

## 2. Case report

This study was approved by the Ethics Committee and Institutional Review Board of the First Affiliated Hospital of Chongqing Medical University. Written informed consent was obtained from the patient for publication of this report.

The patient was a 50-year-old woman. In June 2016, she was sent to the emergency department of local hospital for "pain beneath the xiphoid process for one day." Physical examinations revealed tenderness at the right upper abdomen. The result of a fecal occult blood test was positive. Relevant examinations were further made to clarify the diagnosis: Abdominal ultrasound and contrast-enhanced computed tomography (CT) examinations found an occupation lesion in the right lobe of the liver. Gd-EOB-DTPA-enhanced magnetic resonance imaging (EOB-MRI) suggested the neoplasm was likely to be a metastatic lesion with intratumoral hemorrhage (Fig. 1). To find the primary lesion, the patient received gastrointestinal examinations. Colonoscopy examination showed

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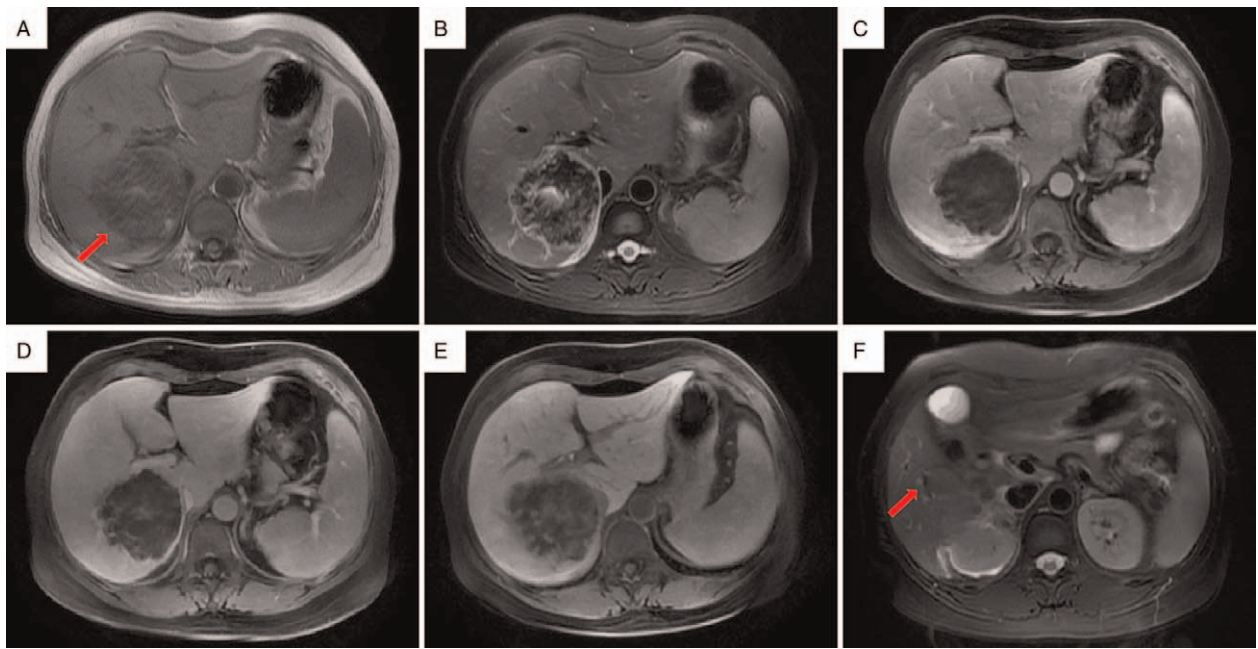
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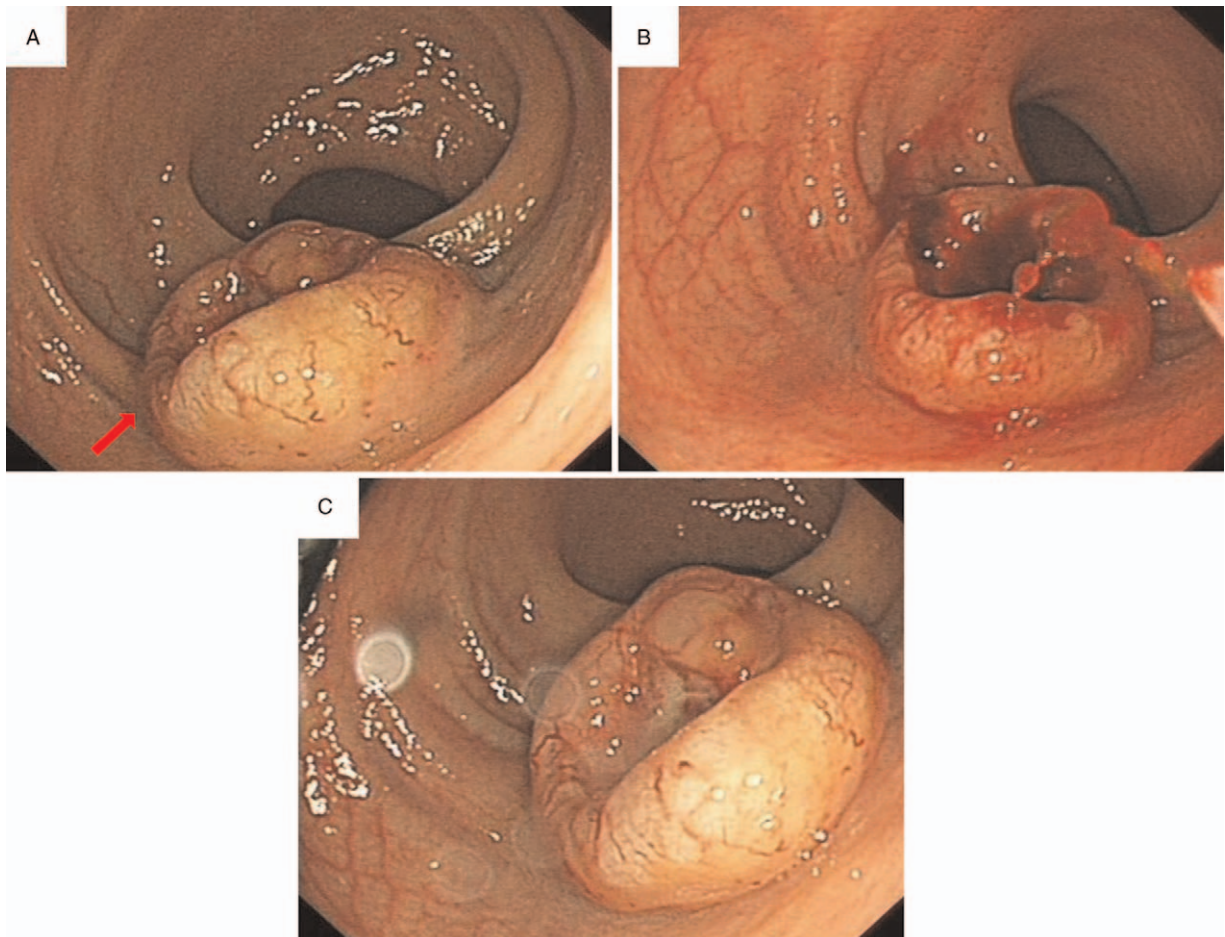
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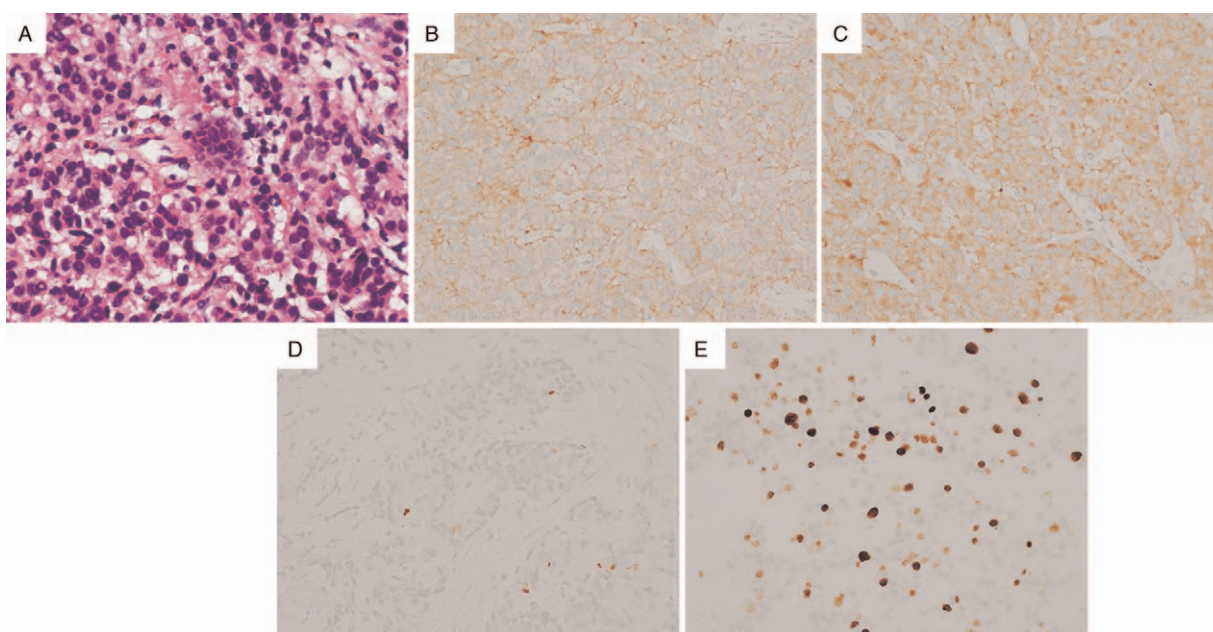
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**Figure 1.** In June 2016, a mass with a diameter of 7.3 cm was observed at the right lobe of the liver, which invaded segment 6, 7, 8 (S6, S7, and S8), displaying low signals on T1-weighted image (T1WI, A, red arrow head) and high signals on T2-weighted image (T2WI, B). There were slightly high signals on T1WI considered hemorrhages (A). The solid components showed heterogeneous and delayed enhancement (C and D) and persistent enhancement at hepatobiliary phase (E). We found that another nodule at S5 showed similar signals (F, red arrow head). (Images were gathered from the Second Clinical College of Army Medical University.)



**Figure 2.** The lesion (A, red arrow head) at the lower rectum under colonoscopy. (Images were gathered from the Second Clinical College of Army Medical University.)



**Figure 3.** Neuroendocrine tumor at the rectum (A,  $\times 400$ , HE), CD56 IHC (B,  $\times 400$ ), Syn IHC (C,  $\times 400$ ), CgA IHC (D,  $\times 400$ ), Ki-67 IHC (E,  $\times 400$ ).

a lesion with a diameter of 3.0 cm at the distance of 4.0 cm from the anus with ulcerated surface; it was tough in texture (Fig. 2). The biopsy result was neuroendocrine tumor (G3) with 8 mitotic figures within 10 HPF (Fig. 3A). Tumor cell immunohistochemistry examination results were as follows: CD56 (weakly+) (Fig. 3B), Syn (+) (Fig. 3C), CgA (a small number of scattered cells were positive) (Fig. 3D), Ki-67 20% to 25% (Fig. 3E). No abnormality was found in the tumor markers. The patient refused any treatment at that time.

After 2 months, the patient had bloody stool with a small amount of fresh blood coating the surface of the stool. She then came to our hospital for further treatment. Digital rectal examination (K-C) showed a palpable mass of 2.0 cm  $\times$  2.5 cm located 4.0 cm from the anus and in the direction between 5 and 6 o'clock. The mass had a tough texture and unsmooth surface, and its shape was dented. The finger cot was covered with blood. Follow-up abdominal and pelvic enhanced CT scan found a mass at the right side of lower rectum with mesorectal fascia lymphadenectasis; the lobulated mass at the right lobe of liver was considered a metastatic tumor.

Compared with the images gathered in June 2016, the liver mass decreased in size possibly because of the absorption of hemorrhage (Fig. 4). We decided to treat the patient with the EP regimen of neoadjuvant chemotherapy (etoposide 100 mg D1–5 + nedaplatin 40 mg D1–3) after a multidisciplinary discussion in our hospital. The patient had the symptom of facial flushing during the chemotherapy. After 2 cycles of chemotherapy, a follow-up (in September 2016) abdominal and pelvic enhanced CT examination implied the liver mass became larger but the mass at the rectum was shrinking (Fig. 5). After a multidisciplinary discussion and making evaluations, we concluded the patient's disease had progressed. Therefore, the next chemotherapy regimen was switched to the IP regimen (irinotecan 120 mg D1, D8 + nedaplatin 60 mg D1, D8).

In consideration of the neuroendocrine symptom, the patient was also given long-acting octreotide once per month and 30 mg every time. In the second cycle of chemotherapy with the IP

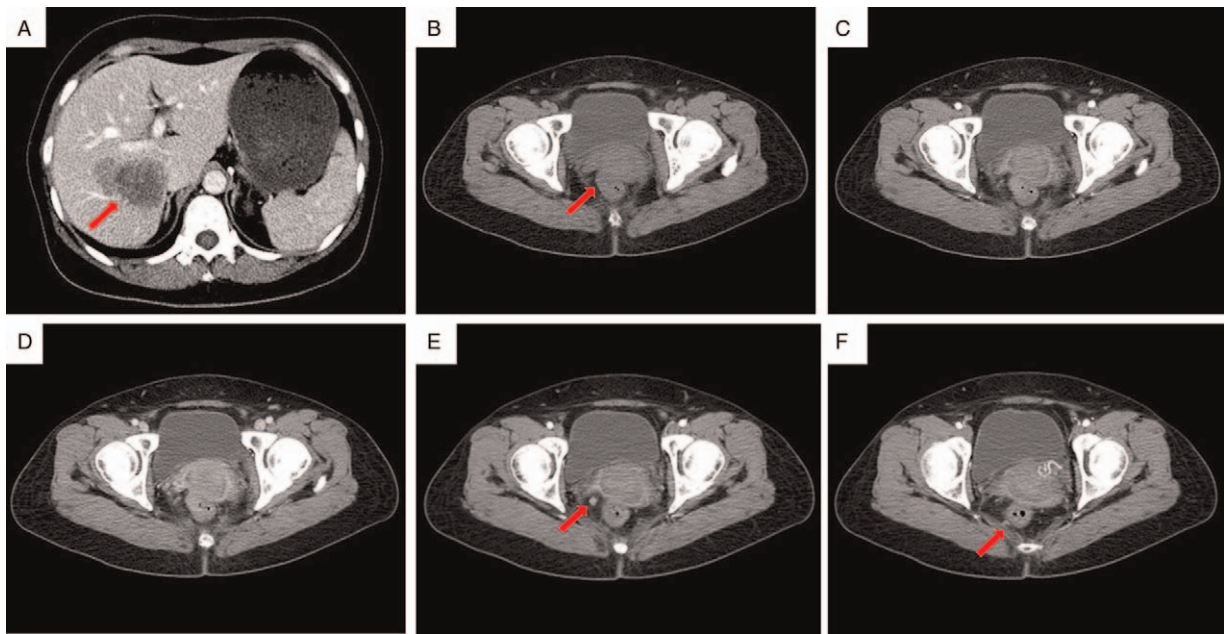
regimen, the patient came up with third-degree marrow suppression; the symptom of facial flushing persisted. Considering the poor effect of the chemotherapy, we decided to suspend the chemotherapy and implement surgery. The preoperative MRI examination of the whole abdomen and pelvis showed no significant changes of the lesions at the rectum and the liver compared with the CT images in September 2016.

In November 2016, the patient had an operation of the laparoscopic low anterior resection of rectum, prophylactic fistulation of ileum, right hemi-hepatectomy and cholecystectomy. Fourteen days after surgery, the symptom of facial flushing achieved remission. The postoperative pathological diagnosis was neuroendocrine tumor of the rectum (G2), invading the whole layer but excluding the proximal, distal and circumferential margins. The mitotic figures were 2 to 5/10 HPF (Fig. 6A). Tumor metastasis was observed at the peri-intestinal lymph nodes (7/8). For the lesion on the liver, the mitotic figures were 4 to 6/10 HPF (Fig. 6B). No tumor involvement at the gallbladder and distal anastomosis. Rectal tumor IHC results were CgA (partial +), Syn (diffusely +), Ki-67 10% (+) (Fig. 6C). Hepatic tumor IHC results were Ki-67 15% (+) (Fig. 6D).

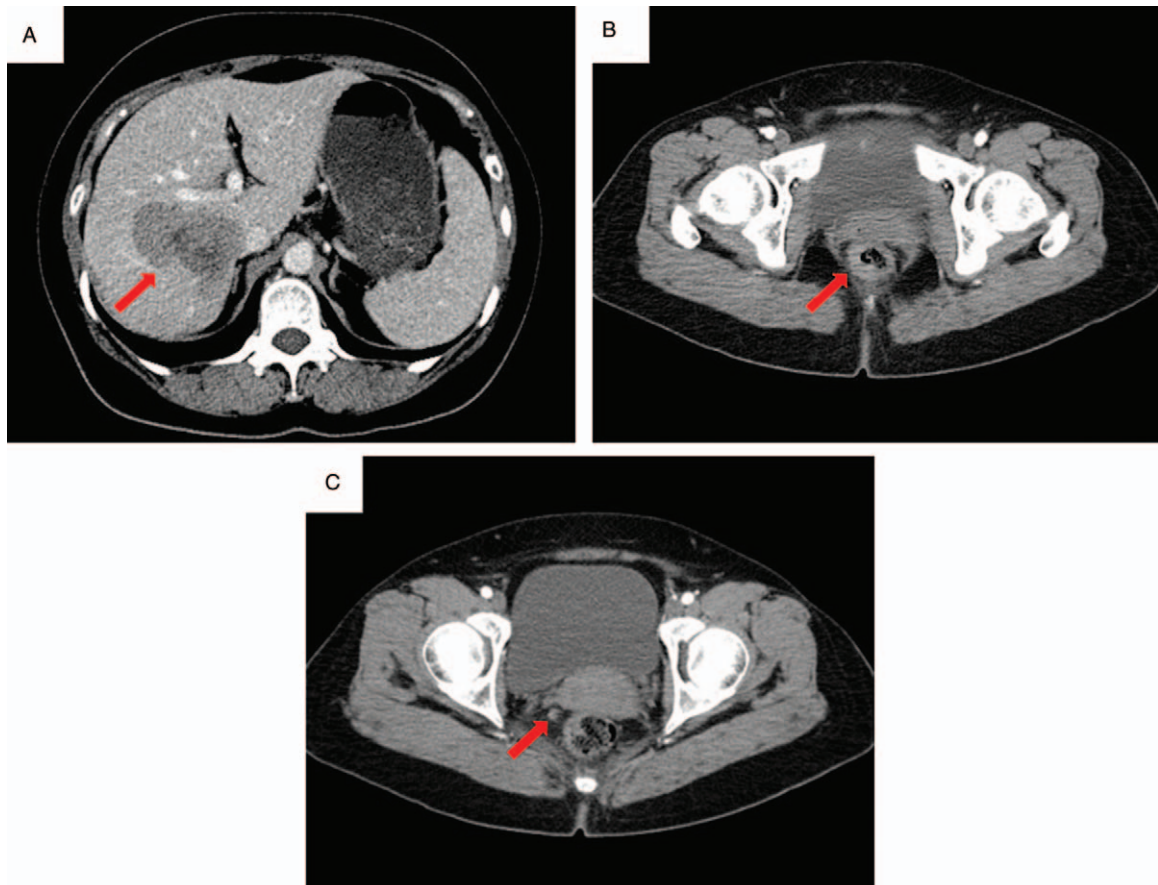
The patient returned for follow-up visits in February, May, September, and December 2017, and the patient underwent ileostomy reversal surgery in our hospital in May 2017. Until December 2017, no signs of recurrence were found, and the patient did not suffer from any discomfort, such as anorexia, abdominal pain, abdominal distension, or diarrhea. The performance status (PS) score was 0.

### 3. Discussion

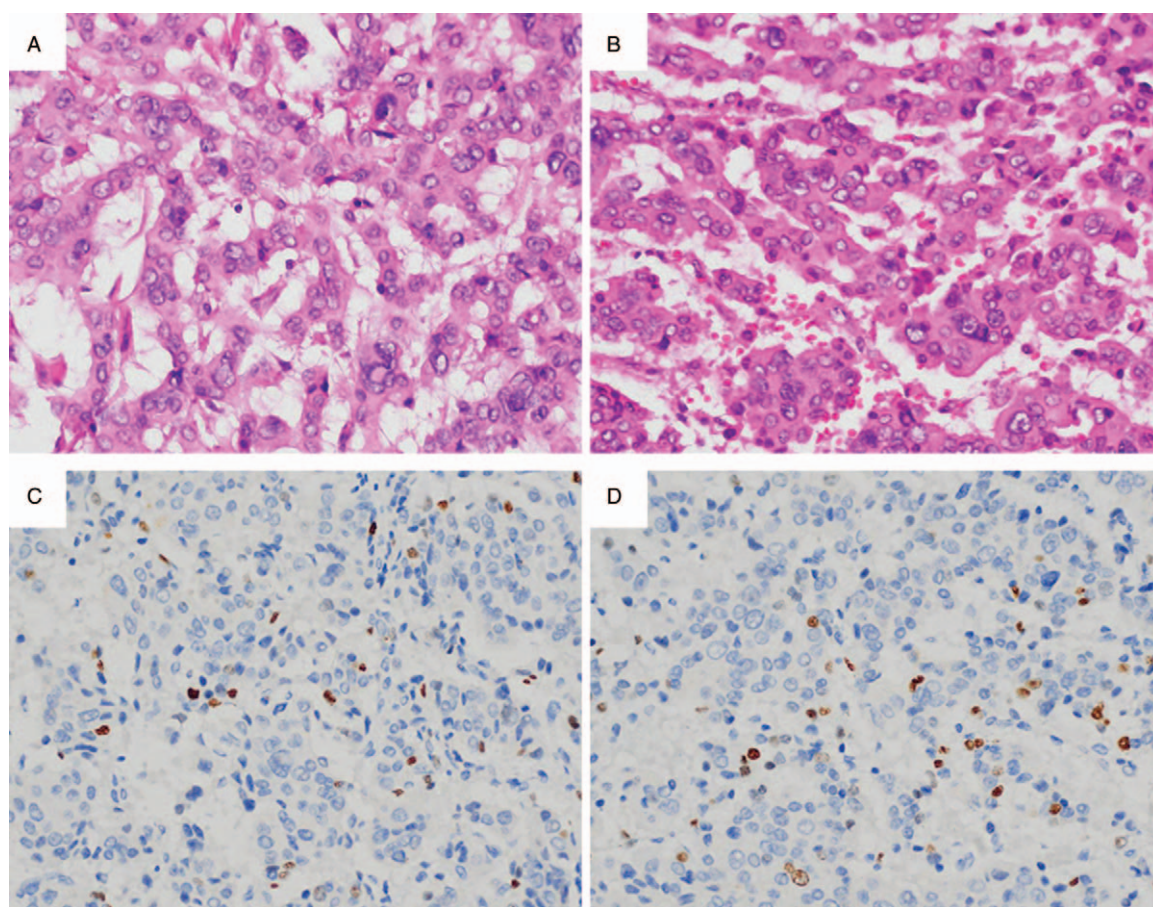
Studies have shown two-thirds of patients with colorectal high-grade NETs present with metastatic disease.<sup>[3]</sup> The liver is the main site of metastases for gastrointestinal tumors.<sup>[4]</sup> Published research articles and consensus report support that MRI is becoming the gold standard in liver metastasis detection. EOB-MRI of liver is as the most accurate imaging modality for



**Figure 4.** In August 2016, a lobulated well-defined mass showed at the right lobe of the liver, with the size of 5.8 cm × 4.1 cm. The degree of enhancement at venous phase was lower than the surrounding normal liver tissue (A, red arrow head). An ulcerative mass on the right side of the lower rectum, with the size of 1.7 cm × 2.4 cm which had regular figure and unclear margin (B, red arrow head) and it showed obvious continuous enhancement (C and D). Multiple lymph nodes were shown in the mesorectal area, among which the right anterior lymph node with a diameter of 0.8 cm was enlarged (E, red arrow head), and the right posterior lymph node was closely related to the mesorectal fascia (F, red arrow head).



**Figure 5.** In September 2016, the size of the mass (6.8 cm × 4.5 cm) at the right lobe of the liver (A, red arrow head) was larger than that in August 2016. The rectal mass was getting smaller; it was approximately 1.2 cm × 2.0 cm (B, red arrow head). There were no significant changes in the size of the lymph nodes (C, red arrow head).



**Figure 6.** Postoperative rectal neuroendocrine tumor (A,  $\times 400$ , HE). Neuroendocrine tumor at the liver (B,  $\times 400$ , HE). IHC results of Ki-67 of the rectal lesion (C,  $\times 400$ ). IHC results of Ki-67 of the hepatic lesion (D,  $\times 400$ ).

preoperative diagnosis of liver metastases from colorectal cancers.<sup>[4,5]</sup> Some literature reported it is of high sensitivity and specificity to identify metastatic lesions smaller than 1.0 cm, while CT could barely observe the metastatic nodules with the size of less than 2.0 cm.<sup>[6]</sup> We had discovered a small nodule at segment 5 (S5) of our patient's liver in EOB-MRI but hidden in CT images, which is accordance with the previous reports.<sup>[7]</sup> Therefore, in order to confirm the number, size, and nature of the lesions, we recommend EOB-MRI of liver should be used as the first-line method in patients who would undergo curative surgery or metastasectomy to avoid omitting the small metastatic lesions.

As to the treatment of metastatic rectal neuroendocrine tumor, Smith et al<sup>[3]</sup> reported that resection of tumor was not associated with survival in either localized or metastatic disease. The guidelines of the European Society of Neuroendocrine Oncology recommend adjuvant chemotherapy for patients without symptoms such as bowel obstruction or rectal bleeding.<sup>[8]</sup> However, the guidelines of the National Comprehensive Cancer Network (NCCN) of the United States advise that the primary and metastatic lesions both should be completely removed when condition permits.<sup>[9]</sup> If radical surgery is not feasible, cytoreduction surgery followed by adjuvant chemotherapy is the secondary option. For GEP-NETs with poor differentiation, the platinum-based regimen combined with etoposide or topotecan has the efficiency as high as 53% to 67% is regarded as the first-line chemotherapeutic regimen,<sup>[10]</sup> but the survival time is under 16 months.<sup>[11]</sup>

In our case, the patient's facial flushing symptom had not been effectively alleviated by giving long-acting octreotide, but was completely relieved after surgery. This is consistent with the description that surgery is the most effective treatment.<sup>[9]</sup> Different from the conventional treatment of using postoperative chemotherapy or chemotherapy alone without surgery, the patient in our case underwent preoperative neoadjuvant chemotherapy, and the result manifested the pathological staging of the tumor degraded from G3 to G2. The primary lesion declined in size and the Ki-67 index and the mitotic figures of the primary tumor cells decreased significantly after chemotherapy proved the EP regimen was effective for primary lesion. The reason could be that neoadjuvant chemotherapy can reduce the speed of deoxyribonucleic acid (DNA) synthesis of neuroendocrine tumor cells, inhibit the proliferation of tumor cells, and decrease the mitotic figures, to cause significant degenerative changes in tumor cells. Therefore, this therapy plan offers favorable conditions for saving the anus during the surgery and enhancing the patient's quality of life. It provides a new idea for the treatment of rectal neuroendocrine carcinoma, and it is also the innovation point of our case report. Comparison of the results of postoperative pathology between the metastatic and primary lesion, both the Ki-67 index and mitotic figures of the metastatic tumor cells were higher than those of the primary lesion, indicating that the metastatic tumor cells had greater likelihood of malignant behavior than the primary tumor cells. How to apply the neoadjuvant chemotherapy with appropriate dosage at

the suitable time to improve the prognosis and quality of life of the patients diagnosed as lower rectal neuroendocrine carcinoma with distant metastasis and how to control the progress of the metastatic lesions are still big challenges, on account of lacking enough clinical research.

### Author contributions

Huayan Yuan and Yuanyuan Yang contributed equally to this work and are cofirst authors. Huayan Yuan and Yuanyuan Yang designed this article. Wuyi Wang collected the clinical data and Yuanyuan Yang collected the radiology images. Huayan Yuan and Yuanyuan Yang wrote the manuscript. All authors read and edited the manuscript. Yong Cheng is a guarantor of integrity of the entire study.

**Data curation:** Wuyi Wang.

**Writing – original draft:** Huayan Yuan, Yuanyuan Yang.

**Writing – review & editing:** Yong Cheng.

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