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**Case Report**

# Long-term Survival of a Case of Rectal Neuroendocrine Carcinoma with Liver Metastasis

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**Abstract**: Colorectal neuroendocrine carcinoma (NEC) is extremely rare and has a dismal prognosis. However, no standardized treatment strategy has been established for this lesion. For patients with NEC and distant metastasis, disease stabilization is difficult even after treatment with multidisciplinary strategies including chemotherapy. Here we describe a case of rectal NEC that presented as multiple liver metastases; a favorable prognosis was obtained after treatment with a multidisciplinary strategy that included surgery, irradiation, and chemotherapy. A 66-year-old male presented with diarrhea and constipation. Colonoscopy and a computed tomography (CT) scan revealed a rectal mass involving all of the luminal circumference, after which a diagnosis of NEC was confirmed by pathological examination. A CT scan also revealed several liver metastases in S5, S6, and S8. Abdominoperineal resection with total mesenteric excision and lymphadenectomy, including the lateral area, was performed. After resection, we administered radiation for local disease control in the lateral area. We also administered chemotherapy consisting of cisplatin and irinotecan for the liver metastases because only the endocrine cell component constituted this tumor. After chemotherapy, a CT scan was performed to confirm that the liver metastasis in S5 and S6 had disappeared, and it was shown that the other lesion in S8 had shrunk substantially (it eventually disappeared). Then, 48 months after resection, all metastatic liver tumors were under good control, and no other recurrent lesion was recognized. In conclusion, a multidisciplinary strategy including optimal chemotherapy seems to be important to achieve a favorable prognosis of NEC of the colorectum with distant metastasis..

**Key words**: rectal neuroendocrine carcinoma, liver metastasis, chemotherapy

## Introduction

According to the WHO 2019 classification[1)], gastrointestinal neuroendocrine neoplasms are classified as G1, G2, or G3 NET (neuroendocrine tumors) or NEC (neuroendocrine carcinomas), based on mitotic count, Ki67 labeling index, and pathological differentiation. This classification considers cell differentiation and proliferation, but does not consider the mechanism of tumor

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development and tumor origin, and thus, some confusion remains with regard to the histological classification. NET and NEC are grouped as different categories because the mechanism of development of both tumors is different. The origin of NEC seems to be adenocarcinoma, while NET arises from endocrine cell; in addition, NEC contains both neuroendocrine and adenocarcinoma components[2]. Regarding NEC of the colon and rectum, these two components have a distinct propensity to influence the efficacy of chemotherapy, and thus, the chemotherapy regimen selected for this lesion should be considered in association with the amount of these two components[3]. Therefore, chemotherapy depends on which component is dominant in its contribution to the tumor, which seems to be necessary for good outcomes of colorectal NEC. Here, we present a case of rectal NEC with multiple liver metastases that achieved a favorable prognosis after management with a multidisciplinary strategy, including chemotherapy, after consideration of the ratio of both the adenocarcinoma and neuroendocrine components.

## Case report

A-66-year-old male presented with diarrhea and constipation. Colonoscopic examination revealed a rectal mass located 2 cm from the anal verge that involved the entire luminal circumference; the biopsy confirmed a diagnosis of NEC (Fig. 1A). A computed tomography (CT) scan was completed and revealed a large irregular mass surrounding the lower rectum, substantial lymph node swelling (Fig. 1B), and several liver lesions in S8 (Fig. 2A), S5 (Fig. 2D), and S6 (Fig. 2G), which were considered metastases. However, no other metastases were observed. Abdominoperineal resection with total mesenteric excision and lymphadenectomy around the inferior mesenteric artery and lateral area was performed. Gross findings of the lesion included the identification of two submucosal tumor-like masses with ulcers and several prominences. On microscopic examination, small- to medium-sized cells with relatively scant cytoplasm that had

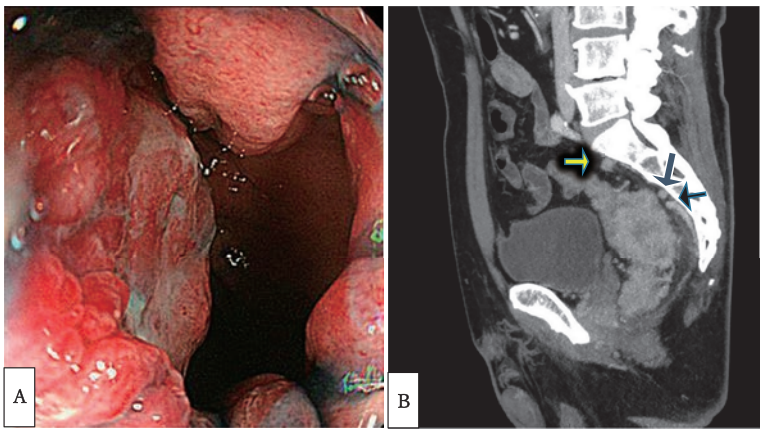



Fig. 1. Colonoscopy
A : Endoscopic view revealed a rectal mass located 2 cm from the anal verge that involved the entire luminal circumference.
B : Contrast-enhanced computed tomography scan revealed a large irregular mass surrounding the lower rectum with substantial lymph node swelling (arrows).

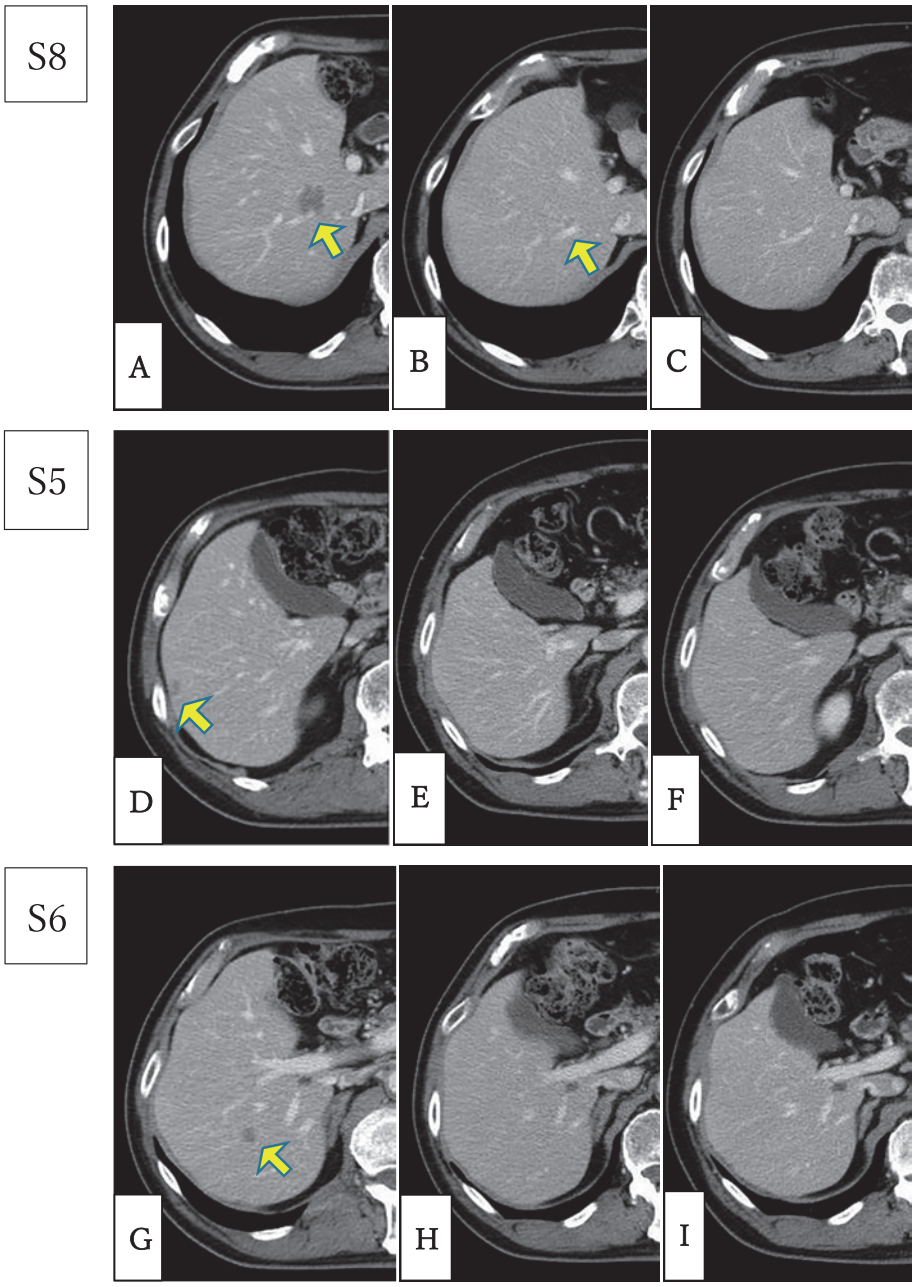



Fig. 2. Image of an abdominal contrast-enhanced computed tomography scan. Computed tomography scan revealed liver metastases before surgery (A, D, G), after chemotherapy (B, E, H), and at 48 months after surgery (C, F, I) in S8 (A, B, C), S5 (D, E, F), and S6 (G, H, I) (arrows). All tumors had diminished (B) or disappeared after treatment (E, H), and the patient did not experience recurrence (C, F, I).

proliferated in nests or cords were seen. The cells contained oval nuclei with granular chromatin and inconspicuous nucleoli. Mitotic figures were frequent. No adenocarcinoma component was observed (Fig. 3A). Immunohistochemically, MIB-1 revealed positive nuclear staining in more than 60% of all nuclei (Fig. 3B), and most cells were positive for NCAM (CD56) (Fig. 3C);

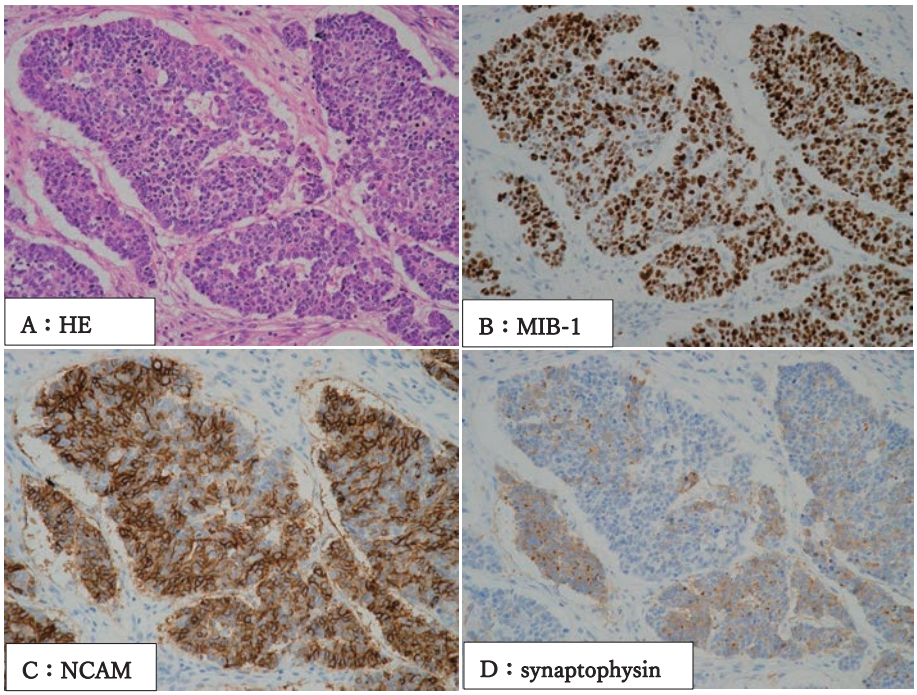
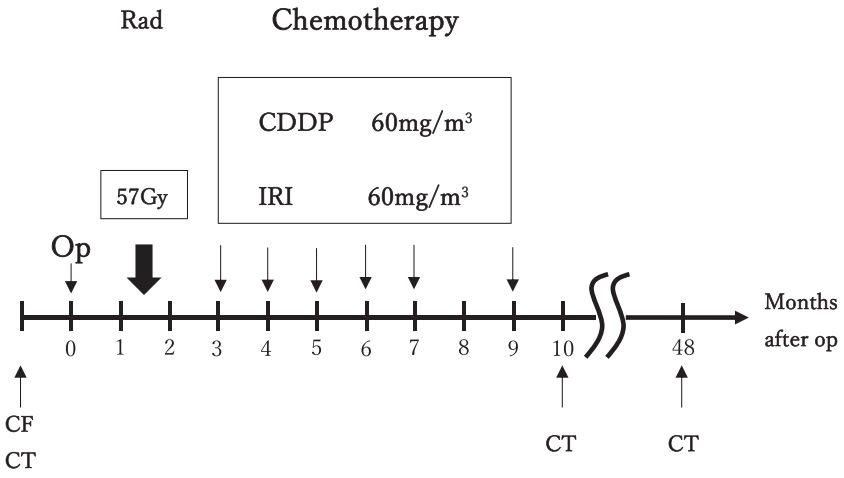



Fig. 3. Histological and immunohistochemical examination of the tumor (Magnification 200×)
A : (**H&E**) By hematoxylin-eosin staining, small- to medium-sized cells with relatively scant cytoplasm that had proliferated in nests or cords were observed. The cells possessed oval nuclei with granular chromatin and inconspicuous nucleoli, and no adenocarcinoma component was recognized.
B : (**MIB-1**) MIB-1 immunohistochemistry revealed positive nuclear staining in up to 60% of all nuclei.
C : (**NCAM**) Most cells were positive for NCAM (CD56).
D : (**synaptophysin**) Approximately one-third of all cells were weakly positive for synaptophysin.

moreover, approximately one-third of the cells were weakly positive for synaptophysin (Fig. 3D), but chromogranin A was not expressed. This tumor was confirmed as a small-cell-type NEC (SCNEC). The tumor involved the full thickness of the rectal wall and 16 regional lymph nodes (of 29 examined nodes); No 251, 253, and 283rt were metastatic nodes.

The clinical and histopathological findings confirmed the diagnosis of neuroendocrine cell carcinoma of the rectum with lymph node and liver metastases. After surgery, radiation therapy (57 Gy) was administered for local control of the lateral lymph node area. And chemotherapy with cisplatin (60 mg/m$^3$/cycle) and irinotecan (60 mg/m$^3$ × 3 times/cycle) were initiated for liver metastases because this tumor was composed of only endocrine cell and did not contain adenocarcinoma cell. After 6 chemotherapy cycles, a CT scan was performed to evaluate whether the liver metastases in S5 (Fig. 2E) and S6 (Fig. 2H) had disappeared and whether the other lesion in S8 had shrunk substantially (Fig. 2B). Then, 48 months after resection, the liver metastases had completely disappeared, and the tumor continued to regress (Fig. 2C, F, I); no other recurrent lesion was observed (Fig. 4).




CF: colonoscopy
CT: computed tomography
Op: operation
Rad: radiation therapy
CDDP: cisplatin
IRI: irinotecan

Fig. 4. Schema of the treatment schedule

## Discussion

Colorectal NEC is rare (accounts for less than 1% of all colorectal adenocarcinomas) and is associated with an extremely poor prognosis because most patients have metastatic disease at the time of diagnosis[3]. Treatment strategies of colorectal NEC are based on modalities extrapolated from retrospective reports and are not based on prospective studies. Actually, even today, patients with colorectal NEC in Japan are usually treated with several strategies, such as surgical resection and radiation, according to Japanese colorectal guideline[4]. However, in metastatic patients, the efficacy of surgical resection and radiation for this lesion is uncertain. Although surgical resection for colorectal NEC with oncological excision of metastatic lymph nodes is the primary treatment for local disease control, it is not associated with superior outcomes except in patients with localized lesions and early disease[5, 6]. Radiation also does not lead to a conclusive benefit[7, 8]. On the contrary, chemotherapy has been suggested to offer some benefits and good control when systemic treatment is initiated earlier. Published reports have confirmed two types of chemotherapy regimens: those that are platinum-based (cisplatin or carboplatin + etoposide or irinotecan ± paclitaxel)[3, 9, 10] and those that are 5-FU-based (oxaliplatin or irinotecan + folinic acid + 5FU)[3]. The efficacy of platinum-based chemotherapy for NEC is based on lung carcinoma guidelines because the endocrine cell component of this neoplasm is similar to that of small-cell lung carcinoma[10]. Therefore, the regimen of cisplatin + irinotecan regimen planed 4-6 cycles, is recommended in Japan[11, 12].

Furthermore, NEC contains both endocrine and adenocarcinoma cell components; these influence the growth and biological behaviors of NEC, which depend on the ratio of these two components[2]. According to the Japanese classification[13], gastrointestinal NEC was classified as

4 different types based on the amount of the neuroendocrine and adenocarcinoma cell components. This classification differs from the WHO 2019 classification, which does not mention the ratio of these two components. Smith *et al*[3] reported that 5-FU-based regimens were effective against the adenocarcinoma component, while platinum-based regimens were effective against the endocrine cell component. According to these reports, chemotherapy for NEC is influenced by the response of these two components (endocrine cell and adenocarcinoma), and the chemotherapy regimen, which depends on the NEC components, seems to constitute a key role of the treatment strategy. Therefore, to obtain a better response, we believe that chemotherapy should be selected after consideration of the biological behavior of the endocrine and adenocarcinoma components.

In our case, only the endocrine cell component constituted the primary tumor, and no adenocarcinoma component was observed. Therefore, a chemotherapy regimen consisting of cisplatin and irinotecan was selected. After 6 courses of chemotherapy, two metastatic liver tumors in 3 locations disappeared, and the other tumor was largely reduced. As a result, this case achieved a long-term survival of 46 months after surgery on the image diagnosis. Such cases of colorectal NEC with liver metastases that achieve long-term survival are rare in published reports, which have presented patients who have survived for 18, 1, and 4 months[3, 14, 15]. Despite the liver metastasis in our case, after local control by surgery and radiation therapy, platinum-based chemotherapy was very effective, and long-term survival was achieved in our case. The reason that chemotherapy may have been so effective was that it was selected based on the components of the tumor.

In conclusion, colorectal NEC is a rare and difficult tumor to treat. However, multidisciplinary treatment, especially optimal chemotherapy in association with the component of this tumor, appears to be important to obtain adequate control.

**Authors' Contribution**

Takeshi Marumori designed the study and wrote the initial draft of the manuscript. Kazuhiro Hiyama, Taichi Mafune, and Kohei Ohno carried out analysis and assisted in the preparation of the manuscript. Hisashi Horiguchi contributed to pathological analysis. All authors had critically reviewed the manuscript. All authors also approved the final view of the manuscript and agreed to be accountable for the aspect of this study related to accuracy or integrity.

**Conflict of Interest disclosure**

The authors declare that they have no conflict of interest.

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