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# Report on The Outcomes of Two Cases After Surgical Resections of Rectal Neuroendocrine Carcinomas

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## Abstract

High-grade neuroendocrine carcinoma (NEC) accounts for < 1% of all tumors of the large intestine [1]. This malignant tumor is characterized by the expression of synaptophysin or chromogranin A and a high proliferation by the number of mitoses or the Ki-67-positive fraction of >20% [2]. Poor survival of colorectal NECs has been well known [3]. Hereby, we report on the outcomes of two cases of high grade rectal NECs after surgical procedures.

**Case 1:** A 61 years old man with anal bleeding continued over one month was admitted. The entire periphery of the tumor was found by colonoscopy after admission. A quasi-emergency operation was performed because of his symptoms of rectal tumor. We performed a sphincter saving operation, with open surgery with positive pathological resection margin. Local recurrent tumor was found six months later. He died 9 months after operation.

**Case 2:** A 63 years old man suffering from continuous anal bleeding over two months was admitted. The entire periphery of the tumor was palpable by digital examination in 2-3 cm from anal verge. We evaluated this carcinoma as unresectable according to the information from the CT examination. We tried neo adjuvant chemo-radio therapy. Finally, Abdominoperineal Resection (APR) was performed by open surgery. Adjuvant chemotherapy was given. However, he died 8 months after the operation with local recurrence and distant metastases. We conclude that surgery is not a recommended treatment for local advanced rectal neuroendocrine carcinoma. Prospective or retrospective multicenter study is necessary to overrule the standard treatment method for this disease.

## Introduction

High-grade Neuroendocrine Carcinoma (NEC) accounts for < 1% of all tumors of the large intestine [1]. This malignant tumor is characterized by the expression of synaptophysin or chromogranin A and a high proliferation by the number of mitoses or the Ki-67-positive fraction of [2]. Treatment of colorectal NECs is not standardized yet [4]. And poor survival of colorectal NECs was a problem clinically [3]. Hereby, we report the outcomes of two cases of high grade rectal NECs after surgical procedures.

## Case 1

A 61 years old man with anal bleeding continued over one month was admitted to the outpatient clinic in our hospital. Biochemical examination of blood was shown in (Table 1).

| | |
|---|---|
| WBC 6,500 /μl | BUN 7mg/dl |
| Hb 13.8g/dl | Cre 0.65mg/dl |
| Plt 290000/μl | AST 23U/L |
| | ALT 33U/L |
| | CRP 3.49mg/dl |
| PT-INR 1.11 | CEA 2.2ng/ml |
| APTT 37sec | CA19-9 2.7mg/dl |
| Fbg 378mg/dl | |

**Table 1:** Case 1- Biochemical examination of blood.

There was no anemia and tumor marker's level were in normal. The entire periphery of the tumor was found by colonoscopy after admission. It was located rectosigmoid. We did not find any distant metastases by Computed Tomography (CT). Quasi-emergency operation was performed because of his continuing anal bleeding and stenosis symptoms of rectal tumor such as abdominal distension, defecation disorders, in spite of his long history of schizophrenia. We performed sphincter saving operation, Low Anterior Resection (LAR) by open surgery with positive pathological resection margin. Chromogranin A and Synaptophysin were positive, a proliferation reflected by the numbers of mitoses was >20 and the Ki-67-positive fraction was 35.43%, immunologically (Figures 1,2). According to the findings, this tumor was diagnosed as high-grade rectal NEC. The patient was discharged from the hospital day 18 without any adjuvant chemotherapy because of his schizophrenia. Local recurrent tumor was found by CT examination six months later. He died 9 months after operation.

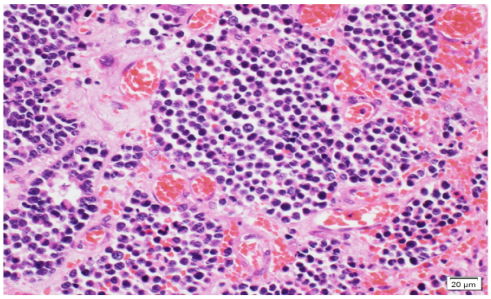

**Figure 1:** Histopathological findings of case 1 stained by Hematoxylin Eosin.

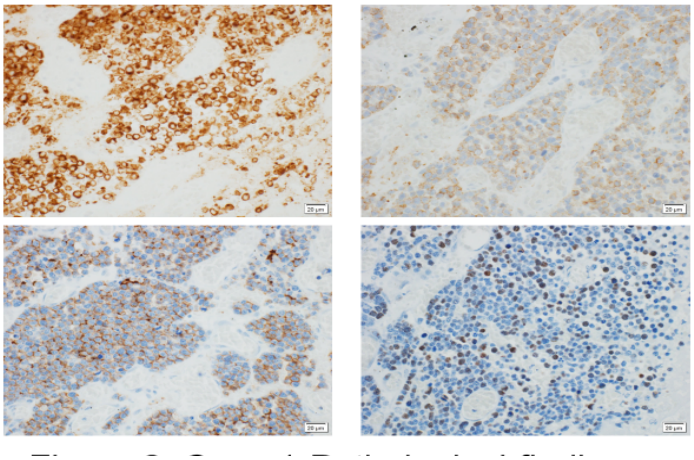

**Figure 2:** Immunopathological findings of case 1 stained by Synaptophysin (upper left), Chromogranin A (upper right), CD56 (lower left), and Ki-67 (lower right).

## Case 2

A 63 years old man suffering from continuous anal bleeding over two months was admitted outpatient clinic in our hospital. The entire periphery of the tumor was palpable by digital examination in 2-3 cm from anal verge. There was no anemia or increasing tumor marker (Table 2). This tumor was diagnosed rectal NEC by the biopsy using colonoscopy. Because Sypaptophysin was positive and Ki-67-positive fraction was 30.10% by the immunological pathological findings (Figures 3,4). We evaluated this carcinoma as unrespectable according to the information of CT examination. We tried neo adjuvant chemo-radio therapy shown in (Table 3). CT examination after this therapy showed that the rectal carcinoma and perirectal lymph node metastasis were also smaller than before (Figure 5). Finally, Abdominoperineal Resection (APR) was performed by open surgery. Lymph node metastases were found, and surgical margin was positive pathologically. Adjuvant chemotherapy was done shown in (Table 4). He died 8 months after operation with local recurrence and distant metastases. Discussion: Neuroendocrine Carcinomas (NECs) are a rare and highly malignant. It can arise in the digestive tract and Pancreas. The grading system is based on the Ki-67 proliferation index or mitotic count according to the World Health Organization (WHO) 2010 classification (Table 5). The incidence rate of Colorectal NECs (CRNECs) was less than 1-2% of colorectal cancers [1,5]. The surgical treatment of CRNECs should be treated according to the guidelines for adenocarcinoma [4]. Smith et.al described no statistical significant difference in survival after the resection of the primary tumor retrospectively [6].

| | |
|---|---|
| WBC 6,500 /μl | BUN 16mg/dl |
| Hb 13.2g/dl | Cre 0.82mg/dl |
| Plt 320000/μl | AST 21U/L |
| | ALT 19U/L |
| | CRP 0.38mg/dl |
| PT-INR 1.12 | CEA 2.5ng/ml |
| APTT 32sec | CA19-9 3.6mg/dl |
| Fbg 399mg/dl | |

**Table 2:** Case 2- Biochemical examination of blood.

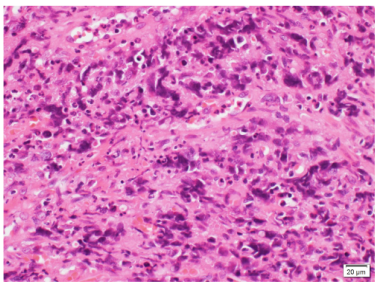

**Figure 3:** Histopathological findings of case 2 stained by Hematoxylin Eosin.

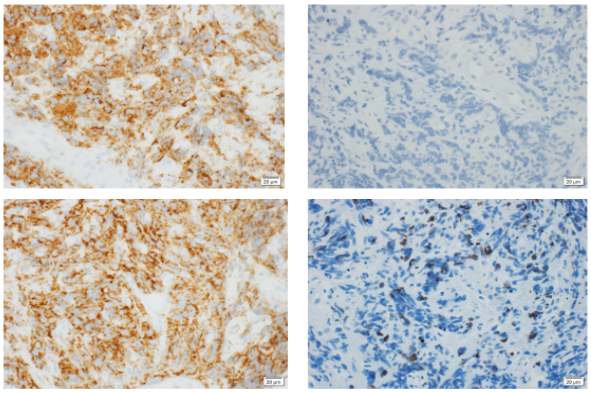

**Figure 4:** Immunopathological findings of case 1 stained by Synaptophysin (upper left), Chromogranin A (upper right), CD56 (lower left), and Ki-67 (lower right).

| | | |
|---|---|---|
| Levofolinate calcium | 260mg | × 8 |
| Oxaliplatin | 110mg | |
| Fluorouracil | 3670mg | |
| Radiation | total 50.4 Gy | |

**Table 3:** Case 2-The regime of neo adjuvant chemo- radiotherapy.

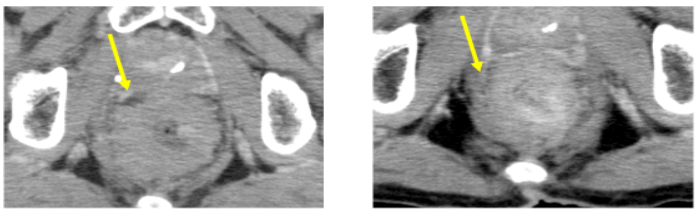

**Figure 5:** The image of CT before preoperative chemo-radiotherapy (left). The carcinoma invasion to the prostate and packed in pelvis was shown. The image of CT after preoperative chemo-radiotherapy (right). The invasion of carcinoma to prostate was unclear and the size of carcinoma was smaller than before.

| | | |
|---|---|---|
| Tegafur/Gimeracil/Oteracil | 100mg | × 7 |
| Bevacizumab | 420mg | |
| Irinotecan Hydrochloride Hydrate | 120mg | |

**Table 4:** Case 2-The regime of adjuvant chemo- radiotherapy after operation.

| Neuroendocrine Neoplasma Type | Grade | Ki-67 Index | Mitotic Count(per 10 HPF) |
|---|---|---|---|
| Neuroendocrine Tumor (Carcinoid) | G1 | ≤2% | <2 |
| Neuroendocrine Tumor | G2 | 3%-20% | 2-20 |
| Neuroendocrine Carcinoma | G3 | >20% | >20 |
| Mixed adenoneuroendocrine carcinoma (MANEC) | G1-G3(mostly G3 component) | All ranges | All ranges |

**Table 5:** World Health Organization (WHO) 2010 Classification.

Our two cases were diagnosed high-grade NEC by the expression of synaptophysin or chromogranin A and high rate of the Ki-67 positive fraction. Operations were performed on both of two cases.

- Case 1 was quasi-emergency operation because of his continuing anal bleeding and stenosis symptoms.
- For cases 2, preoperative adjuvant chemo-radio therapy was performed according to the regime as same as the adenocarcinoma. This therapy was effective to be able to resect the primary tumor. However, we could not resect primary tumors completely.

After operation, rapid growing of the local recurrence was found in two cases and distant metastases were found for number 2 case. The postoperative lives of two cases were both very short. It supports the study by Smith, et.al [6]. The surgery should be performed in case of limited decease [4]. Combination chemotherapy of 5-fluorouracil and cisplatin should not be considered as first-line chemotherapy and radiotherapy is not recommended as a solitary treatment [4]. We tried chemo-radiotherapy combined with FOLFOX and radiation for case number 2. We performed surgery. As the adjuvant therapy, oral 5-fluorouracil combined the injection of irinotecan was administered. But the recurrence of tumor was very aggressive in case number 2. Recent articles describe the prognosis of this disease as very poor [7,8]. H. Sorbye reported the median survival in patients with advanced gastrointestinal neuroendocrine carcinoma (WHO G3) receiving chemotherapy was 11 months. Tomohiro Yamaguchi, et al. describes median overall survival of 31 advanced colorectal neuroendocrine carcinoma with systemic chemotherapy was 7.6 months. Our two cases had no distant metastases when we performed operation. However, recurrent tumors were growing rapidly with or without chemotherapy. Finally, survival of two cases was very poor.

## Conclusion

We conclude that surgery is not a recommended treatment for the local advanced rectal neuroendocrine carcinoma. Prospective or retrospective multicenter study is necessary to indicate the standard treatment method for this disease.

## Declarations of interest

None

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