Gastroenteropancreatic—origin neuroendocrine carcinomas

Three case reports with favorable responses following localized radiotherapy and a review of literature

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1. Introduction

Neuroendocrine tumors (NETs) are neoplasms that originate from endocrine (hormonal) cells throughout the body.\textsuperscript{[1]} Among the NETs, gastrointestinal-origin NETs are relatively rare; however their incidence has been rising in recent decades.\textsuperscript{[2]} Currently, gastrointestinal-origin NETs are distinguished as gastroenteropancreatic (GEP) NETs by several investigators.\textsuperscript{[3–6]} Up to 2000, the World Health Organization (WHO) classification of morphologically aggressive neuroendocrine neoplasms were named as “poorly differentiated endocrine carcinoma.”\textsuperscript{[7]} In 2010, the WHO classification of NETs was divided as Grade 1, Grade 2, and Grade 3. Grade 3 was termed as neuroendocrine carcinomas (NECs), which include all poorly differentiated neoplasms or any NETs with a Ki-67 index higher than 20%. Because of its rarity, the treatment of NECs has many options. The 2013 North American Neuroendocrine Tumor Society (NANETS) guidelines are well known for outlining NET treatment including NECs.\textsuperscript{[8]} In the NANETS guidelines, radiotherapy (RT) is recommended in limited cases of postoperative aim along with chemotherapy after surgery or unresectable locoregional disease. In unresectable locoregional disease, RT is recommended with concurrent or sequential chemotherapy. Table 1 presents the NANETS guidelines of RT. RT has a limited role for treatment in there guidelines; therefore, only a few reports have focused on treatment responses and outcomes following RT in NECs patients. Here, we report a case series of unresectable or progressed NECs from GEP origins treated with...
local RT. We summarize the treatment outcomes after RT and present a literature review focusing on the treatment of NECs from GEP using RT.

2. Materials and methods

We obtained approval from the institutional review board of Catholic ethics committee (board director: Jeong Soo Kim, MD) for this case series and also acquired a consent to publish from the patients.

2.1. Case no. 1

An 82-year-old male patient was diagnosed with lower esophageal mass and enlarged lymph nodes in the gastrohepatic area (Fig. 1A). The patient had history of gastric adenoma and gastroesophageal reflux disease for 3 years. An endoscopic biopsy was conducted and the result was NEC, small cell type. Table 2 presents pathological characteristics.

Based on multidisciplinary discussion, we determined treatment with concurrent chemoradiotherapy (CCRT) rather than surgical resection due to poor general condition of the patient. Patient performance status was Eastern Corporative Oncology Group (ECOG) grade 2 and he refused chemotherapy; therefore, RT alone was employed. The target volume of RT included both the esophageal lesion and enlarged lymph nodes in the gastrohepatic area (Fig. 1D). The RT dose was 50 Gy in 25 fractions with field reduction at 40 Gy. He experienced poor oral intake due to radiation-induced esophagitis and general weakness after 40 Gy of RT sessions.

| Tumor location | Case 1 | Case 2 | Case 3 |
|----------------|--------|--------|--------|
| Differentiation| Poorly differentiated | Poorly differentiated | Poorly differentiated |
| Ki-67 | 90% | 70% | 80% |
| CD56 | Positive | Positive | Negative |
| Synaptophysin | Positive | Positive | Weakly positive |
| Chromogranin-A | Positive | Very weakly positive | Weakly positive |
| Cell type | Small cell type | Small cell type | Mixed type |

Table 2: Pathology and immunohistochemical features.

Table 1: NANETS guidelines for the treatment of poorly differentiated NECs (RT).

| Disease stage | Intervention | Recommendation |
|---------------|--------------|----------------|
| Locoregional disease, resectable clinical stage T1–2, N0 | Surgical resection, including removal of tumor with negative margins. Risk of recurrence is high, however. | Recommend |
| Clinical stage in excess of T1–2, N0 | Postoperative therapy with 4 to 6 cycles of cisplatin or carboplatin and etoposide. Radiation should only be considered in cases where risk of local recurrence is considered high and morbidity is low. | Recommend |
| | Chemotherapy with or without concurrent radiotherapy. | |
| Locoregional disease, unresectable | Surgery where morbidity is low, particularly where risk of obstruction is high. Risk of recurrence is high, however. Consider postoperative therapy with 4 to 6 cycles of cisplatin or carboplatin and etoposide. Radiation should only be considered in cases where risk of local recurrence is considered high and morbidity is low. | Consider |
| | Platinum-based chemotherapy regimen [cisplatin or carboplatin and etoposide] for 4 to 6 cycles with concurrent or sequential radiation | Recommend |

Note: Retrieved from “Consensus Guidelines for the Management and Treatment of Neuroendocrine Tumors” by P. Kunz et al. 2013. Pancreas, 42, p. 576.

Figure 1. Computed tomography (CT) images of lower esophagus and gastrohepatic lesions at initial diagnosis (A), positron emission tomography CT images (B), CT images 4 mo after radiotherapy (RT) (C), and RT plans (D) of Case 1.
Four months after RT, computed tomography (CT) scan indicated remarkable regression of the original NEC lesions (Fig. 1C). However, other lymph nodes suggesting new metastases appeared in the upper paratracheal and paraaortic lesions 2 months later. He was not able to undergo chemotherapy after RT due to poor general condition and the patient expired a month later due to disease progression.

2.2. Case no. 2

A 52-year-old female patient visited our hospital with dyspepsia and abdominal discomfort. Esophagogastroduodenal endoscopy showed no specific findings. In abdominal pelvis CT scans, a 9.8-cm-sized heterogeneous enhanced mass was found in the lesser sac abutting the stomach, pancreas, and liver (Fig. 2A). She underwent ultrasound-guided biopsy on the mass and the mass was revealed to be NEC. The pathologic report of the biopsy specimen is presented in Table 2.

She underwent 2 cycles of etoposide-cisplatin chemotherapy as the initial treatment; however, the response evaluation indicated stable disease with aggravated symptoms. Thus, we decided to administer CCRT with the etoposide-cisplatin regimen. The RT dose was 54 Gy in 30 fractions using intensity modulated RT. Three months after RT, the mass showed partial regression with a longest diameter of 7.5 cm. Six months after RT, the lesion further shrunk to 5 cm at the longest diameter (Fig. 2C). During follow-up, a new soft tissue density lesion appeared on CT scans. The perirectal mass regressed on follow-up CT scans (Fig. 2C) in 4 months after RT. However, a new metastatic lymph node was found at the inferior mesenteric artery root. RT was employed again on that lymph node along with a paraaortic lymph node chain up to 50 Gy in 20 fractions. The lesion completely regressed 3 months after RT. Six months after the second RT, there was no evidence of recurrence in the RT field and he received 2 cycles of irinotecan-cisplatin chemotherapy. However, liver metastasis and several metastatic lymph nodes in paraaortic, porta hepatis, and hepatoduodenal areas were identified on abdominal CT scans 4 months after chemotherapy. The biopsy specimens from 3 patients (case no. 1–3) are shown in Figure 4.

2.3. Case no. 3

A 54-year-old male patient visited our hospital with anal pain and bleeding. He had been treated with tenofovir and raltegravir for human immunodeficiency virus infection. On abdominal CT scans, there was an enhancing mass with central necrosis at the left wall of the distal rectum (Fig. 3A). Initially, we diagnosed the lesion as clinical T3 stage rectal cancer. Several enlarged perirectal lymph nodes were identified in positron emission tomography CT scans (Fig. 3B), and there was no evidence of distant metastases at that time. However, a small hypodense lesion was identified at S5 lobe in a magnetic resonance imaging of the liver. A trans-anal excision was conducted and the mass was proven to be NEC. The detailed pathologic report is listed in Table 1. Based on the multidisciplinary discussion, RT was administered on a pelvic operative bed due to suspected residual disease that appeared on postoperative CT scans. The RT dose was 59.4 Gy in 33 fractions for targeting the pelvic mass area, including whole pelvic irradiation up to 45 Gy in 25 fractions. The perirectal mass regressed on follow-up CT scans (Fig. 3C) in 4 months after RT. However, a new metastatic lymph node was found at the inferior mesenteric artery root. RT was employed again on that lymph node along with a paraaortic lymph node chain up to 50 Gy in 20 fractions. The lesion completely regressed 3 months after RT. Six months after the second RT, there was no evidence of recurrence in the RT field and he received 2 cycles of etoposide-cisplatin chemotherapy. However, liver metastasis and several metastatic lymph nodes in paraaortic, porta hepatis, and hepatoduodenal areas were identified on abdominal CT scans 4 months after chemotherapy. The biopsy specimens from 3 patients (case no. 1–3) are shown in Figure 4.

3. Discussion

NETs are rare, accounting for <1% of all malignant disease in the United States. However, the incidence of NETs has significantly increased in recent years in the US and the incidence of GEP-origin NETs has also increased. NEC is the most malignant NET types. The new WHO classification
Figure 3. Computed tomography (CT) images of rectal mass at initial RT simulation CT (A), positron emission tomography CT images (B), 4 mo after radiotherapy (C), and RT plans (D) of Case 3.

Figure 4. Biopsy specimens from 3 cases are shown (Hematoxylin-Eosin, ×400 in 1-A, 2-A, and 3-A, CD 56, ×400 in 1-B and 2-B, chromogranin-A, ×400 in 3-B, Ki-67, ×400 in 1-C, 2-C, and 3-C). The detailed pathological and immunohistochemical characteristics are described in Table 2.
system for gastrointestinal NETs categorizes NETs regardless of the primary tumor origin. This classification categorizes tumors according to grade by tumor proliferation: well-differentiated NETs and poorly differentiated NECs. Well-differentiated NETs were further separated into 2 subgroups: grade 1, representing tumors with proliferative index of <2% (or mitotic counts of ≤2 per 10 high-power fields) equivalent to carcinoid tumors, and grade 2, with proliferative indices ranging from 2% to 20% (or mitotic counts of 3–20 per 10 high-power fields). NECs are categorized as grade 3, with proliferative indices of >20% (or mitotic counts >20 per 10 high-power fields). NECs are subclassified as large or small cell types.

Prognosis of NECs varies based on disease stage at diagnosis. According to a review by Sorbye et al,[4] the median survival is 38 months for localized disease, 16 months for regional disease, and 5 months for distant disease based on SEER data. Large cell types have a favorable prognosis relative to small cell GEP-NECs with a 5-year survival rate of 32% (versus 6%).[11]

The NANETS guidelines outline NET treatments, including treatment for NECs.[8] Although RT plays a critical role in a number of gastrointestinal tumors,[12,13] the role of RT is very limited in the treatment of NECs according to the guidelines (Table 1); however, no prospective or designed study has included RT in the treatment of GEP-NECs. Also, the role of RT is mentioned in the NCCN guidelines for NETs[14] where RT is recommended in resectable or locoregionally unresectable poorly differentiated NECs (Fig. 5), which is similar to the NANETS guidelines.

There is no comprehensive review of RT treatment response in GEP-origin NECs; however, there have been a few studies of individual organs (Table 3). The pancreas is the most frequent site of NETs within GEP-origin NETs, and treatment results are relatively well known in pancreatic NETs. Contessa et al[15] reported the treatment result of RT on pancreatic NETs. Within 36 observed patients, 39% showed the response with RT and 13% of patients showed complete responses. All patients who showed radiographic progression received RT at ≤32 Gy. In terms of symptom palliation, 90% of patients had symptom relief. Arvold et al[19] reported that the adjuvant RT for the patients with poor pathologic features or positive resection margins improved the local control rates that were comparable to those in the surgery alone group.

In anorectal-origin NECs, Brieau et al[16] compared treatment results between RT and surgery in nonmetastatic NECs. In 24 cohorts, 15 patients did not receive surgical resection, 12 patients received CCRT, and 3 patients received chemotherapy. Six patients had local recurrence that was not worse than surgical group’s results of 5 patients. Median time to progression and overall survival had no differences. The investigators concluded that RT with adequate chemotherapy is not inferior to surgical treatment, suggesting high probability of metastatic dissemination even in patients with localized tumors.[8,20]

In the upper gastrointestinal tract, Ku et al[17] reported that the addition of CCRT after chemotherapy in localized disease patient helps to achieve improving local control rate and treatment response. Azakami et al[18] reported a case of similar rapid regression with RT in a gastric NEC patient. Similar to our cases,

| Investigator       | Location | Patients | Treatment | RT dose      | Role of RT                          |
|-------------------|----------|----------|-----------|--------------|-------------------------------------|
| Contessa et al (2009)[15] | Pancreas | 36       | RT alone  | Median 49.6 Gy  | CR 13%                               |
|                   |          |          |           | PR 26%       |                                     |
|                   |          |          |           | SD 56%       |                                     |
| Brieau et al (2015)[16] | Anorectal | 12      | CCRT      | 40–50 Gy     | CR 40%                              |
|                   |          |          |           | PR 40%       |                                     |
| Ku et al (2008)[17] | Esophagus | 14      | Chemotherapy followed by CCRT | 45–50.4 Gy | All long-term survivor received CCRT |
| Azakami et al (2016)[18] | Stomach  | 1        | CCRT with 5FU | 40 Gy/16 Fx | Near CR                             |

CCRT = concurrent chemoradiation, CR = complete response, Fx = fractions, PR = partial response, SD = stable disease.
she had poor general condition and old age with a 7-cm-sized gastric mass and the mass almost regressed after RT of 40 Gy in 16 fraction schedules. However, distant metastasis developed 2 months after RT. The authors suggested that RT is a useful palliative treatment option for providing symptom relief in gastric NECs.

In our cases, RT showed favorable responses with NEC masses (2 complete responses, 1 partial response) and the patients had improved general condition after RT. Indeed, the first-line chemotherapy for NECs normally includes platinum-based treatment with etoposide, which is not suitable for patients with poor general condition. Thus, RT can be used for patients with inoperable conditions or unfavorable tumor locations and can be a potentially curative aim following chemotherapy with improved condition. Also, patients with old age or who are unfit to receive chemotherapy could benefit from RT.

However, mainstream of GEP-NECs treatment remains focused on how to prevent distant failure because most recurrences are distant and not local. Thus NANETS guidelines recommend adjuvant chemotherapy after surgical resection and additional imaging is recommended between surgery and the start of chemotherapy, because rapid recurrence can occur right after surgery. In our cases, 2 patients (Case no. 1 and 3) showed distant failure despite a complete response of the irradiated fields. Neither of these patients received chemotherapy before RT.

4. Conclusions

GEP-origin NECs are rare tumors and show aggressive metastasis even in clinically localized disease. Although outcome is dismal, RT can be a useful treatment option for patients with inoperable conditions and suffering from large NECs masses. Combined systemic chemotherapy should be considered to decrease the distant failure rate.

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