Clinical Case Report

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Gastroenteropancreatic—origin neuroendocrine carcinomas

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

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Abstract

Rationale: The radiotherapy (RT) responses of gastroenteropancreatic (GEP)-origin neuroendocrine tumors remain unclear. We report cases of favorable response after localized RT of GEP-origin neuroendocrine carcinomas (GEP-NECs).

Patient concerns: 1. An 82-year-old male presented with a lower esophageal mass. Positron emission tomography computed tomography (PET-CT) scan showed a lower esophageal mass and gastrohepatic lymph nodes. 2. A 52-year-old female presented with abdominal discomfort. CT scan showed a 9.8 cm-sized enhancing mass in the lesser sac abutting the stomach, pancreas and liver. 3. A 54-year-old male patient presented with anal pain and bleeding. CT scan showed a remnant mass in the perirectal area after trans-anal excision.

Diagnoses: The diagnoses of GEP-NECs were pathologically confirmed by biopsy or excision, and immunohistochemical stainings of Ki-67, CD56, synaptophysin and chromogranin-A.

Interventions: 1. The patient was treated with definitive RT. 2. The patient was treated with RT after two cycles of etoposide-cisplatin chemotherapy. 3. The patient was treated with adjuvant RT.

Outcomes: 1. Complete remission was achieved based on CT scan four months after RT. 2. CT scan showed partial regression of the mass with a 5 cm-diameter at six months after RT. Adjuvant chemotherapy was administered after RT. 3. The residual mass was almost completely regressed at CT scan four months after RT.

Lessons: In cases of GEP-NECs, RT can be a useful treatment modality with favorable tumor response for patients with inoperable conditions or those suffering from bulky tumor masses.

Abbreviations: 5FU = fluorouracil, CD56 = neural cell adhesion molecule, ECOG = Eastern Corporative Oncology Group, GEP = gastroenteropancreatic, NANETs = North American Neuroendocrine Tumor Society, NECs = neuroendocrine carcinomas, NETs = neuroendocrine tumors.

Keywords: gastrointestinal neoplasms, neuroendocrine carcinoma, pancreatic neoplasms, radiotherapy

1. Introduction

Neuroendocrine tumors (NETs) are neoplasms that originate from endocrine (hormonal) cells throughout the body.[1] Among the NETs, gastrointestinal-origin NETs are relatively rare; however their incidence has been rising in recent decades.[2] Currently, gastrointestinal-origin NETs are distinguished as gastroenteropancreatic (GEP) NETs by several investigators.[3–6] Up to 2000, the World Health Organization (WHO) classification of morphologically aggressive neuroendocrine neoplasms were named as "poorly differentiated endocrine carcinoma."[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.[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

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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.

Table 2

Pathology and immunohistochemical features.

	Case 1	Case 2	Case 3
Tumor location	Lower esophagus	Pancreas	Rectum
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 1

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

Treatment of poorly differentiated NECs		
Generally for NETs, lines of therapy have not been established. When multiple options are listed, list order does not imply order of therapy		
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
	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
Clinical stage in excess of T1–2, N0	Chemotherapy with or without concurrent radiotherapy.	Recommend
	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
Locoregional disease, unresectable	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.

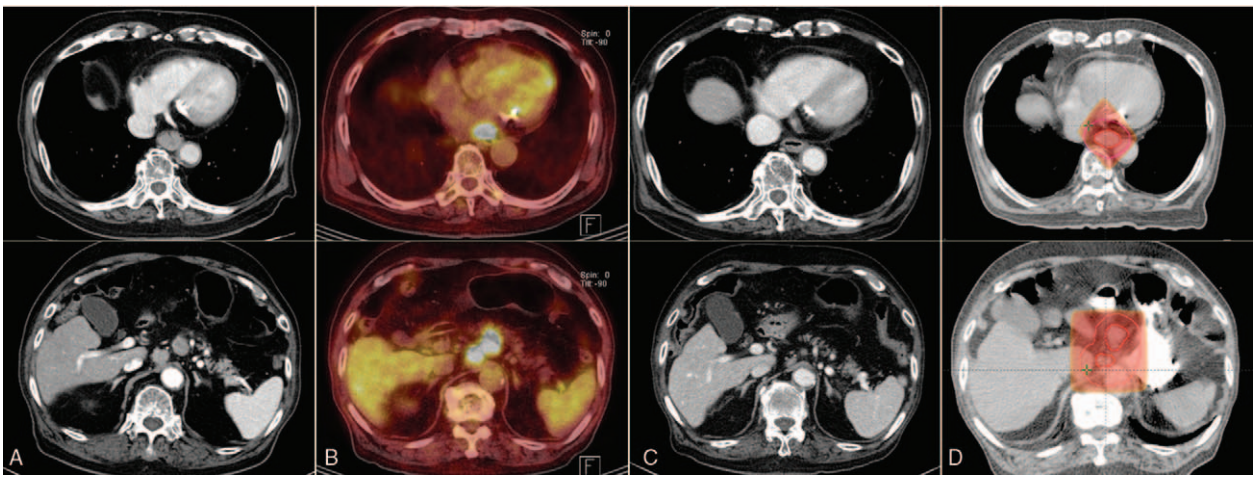

Figure 1. Computed tomography (CT) images of lower esophagus and gastrohepatic lesions at initial diagnosis (A), positron emission tomography CT images (B), CT images 4 mo after radiotherapy (RT) (C), and RT plans (D) of Case 1.

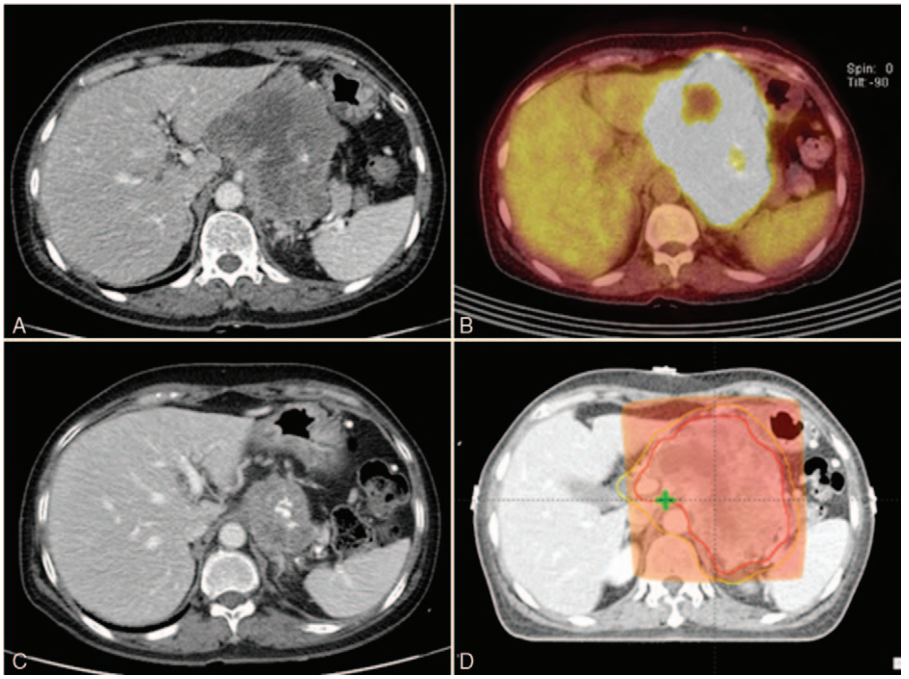

Figure 2. Computed tomography (CT) images of pancreas NEC at initial diagnosis (A), positron emission tomography CT images (B), 6 mo after radiotherapy (RT) (C), and RT plans (D) of Case 2.

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 shrank to 5 cm at the longest diameter (Fig. 2C). During follow-up, a new soft tissue density lesion appeared at the same site 11 months after RT. There was no evidence of NECs in the biopsy. She received 3 cycles of irinotecan-cisplatin chemotherapy and the soft tissue density lesion showed a partial response in diameter reduction from 6.5 to 5.5 cm. No new lesions were identified on CT scans.

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.[4] However, the incidence of NETs has significantly increased in recent years in the US[1] and the incidence of GEP-origin NETs has also increased.[2,9,10] NEC is the most malignant NET types. The new WHO classification

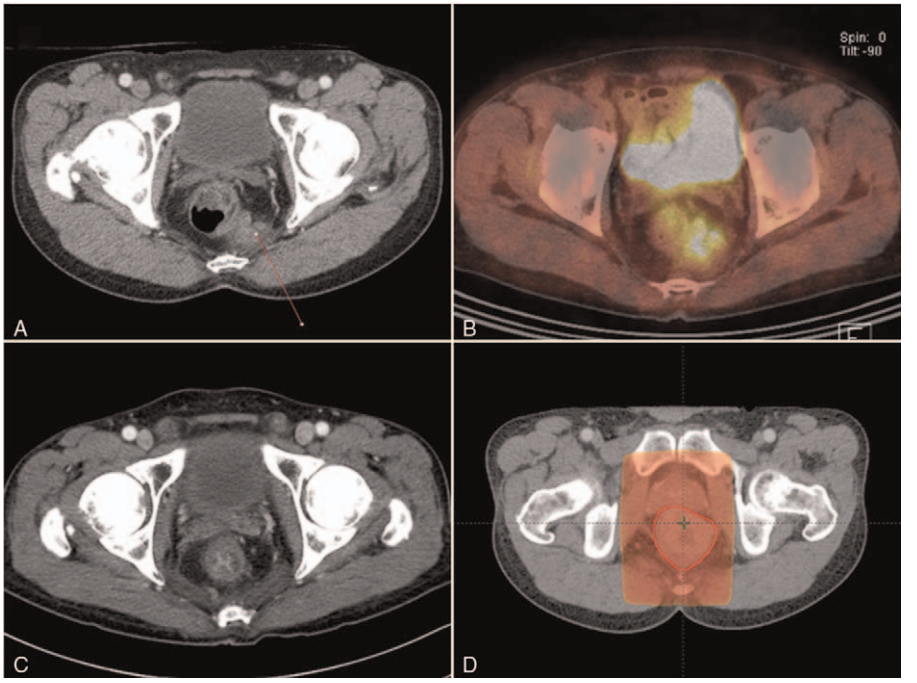

Figure 3. Computed tomography (CT) images of rectal mass at initial RT simulation CT (A), positron emission tomography CT images (B), 4 mo after radiotherapy (C), and RT plans (D) of Case 3.

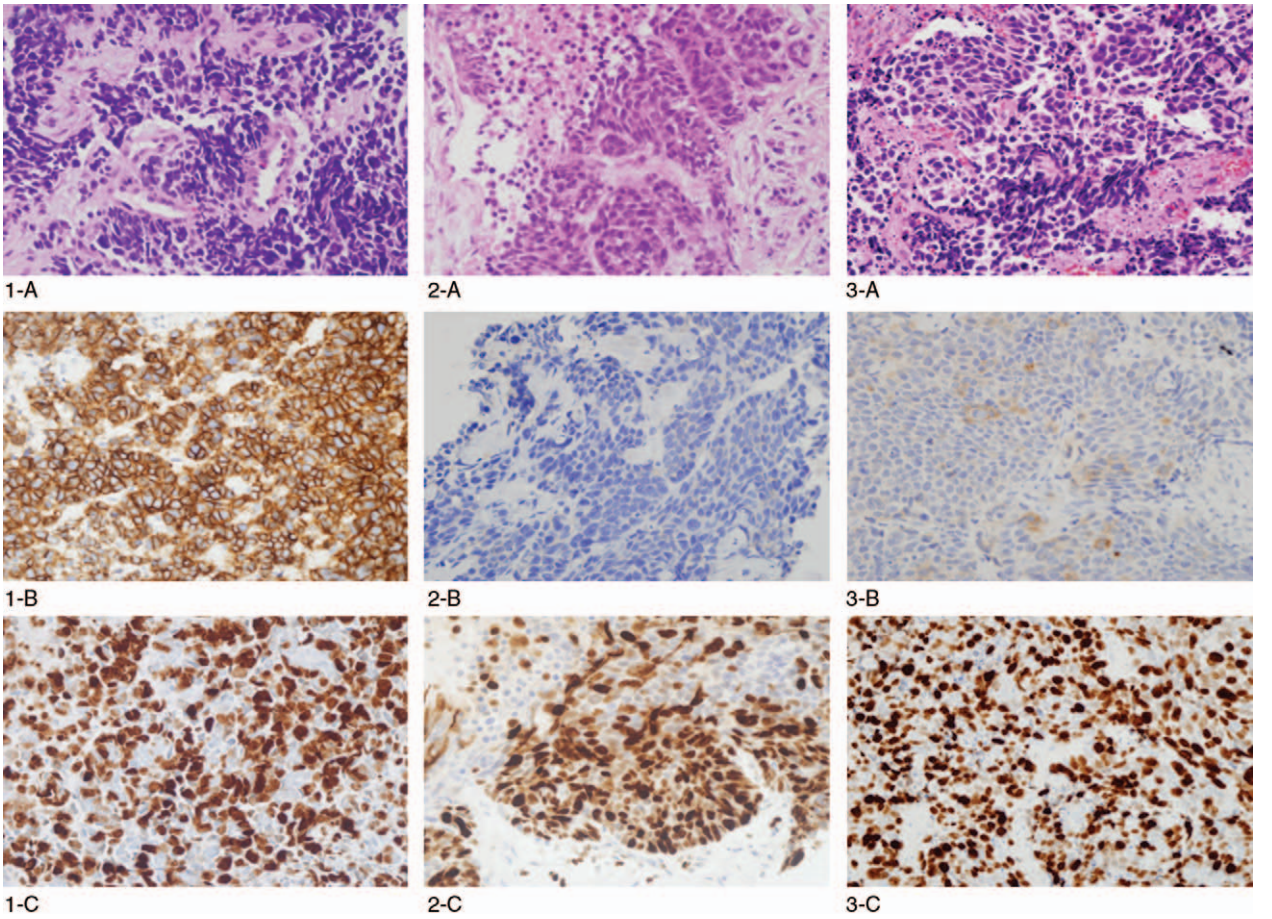

Figure 4. Biopsy specimens from 3 cases are shown (Hematoxylin-Eosin, × 400 in 1-A, 2-A, and 3-A, CD 56, ×400 in 1-B and 2-B, chromogranin-A, ×400 in 3-B, Ki-67, ×400 in 1-C, 2-C, and 3-C). The detailed pathological and immunohistochemical characteristics are described in Table 2.

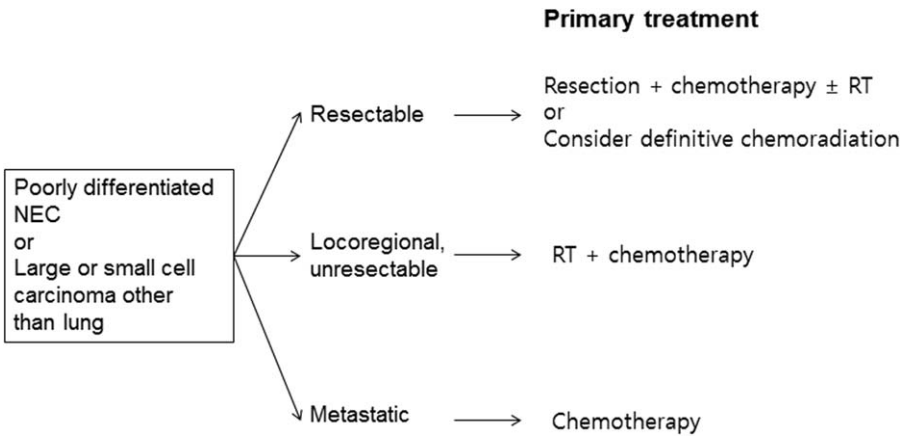

Figure 5. NCCN guidelines for treatment of poorly differentiated NECs, Version 2. 2016 (Retrieved https://www.nccn.org/professionals/physician_gls/f_guidelines.asp#neuroendocrine).

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,

Table 3

Reports of RT responses in GEP-NECs.

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,[21,22] 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.[4] Thus NANETS guidelines recommend adjuvant chemotherapy after surgical resection[8] 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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