



# Rapidly Extensive Recurrence of Esophageal Neuroendocrine Carcinoma After Complete Pathologic Response to Definitive Chemoradiation

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## ABSTRACT

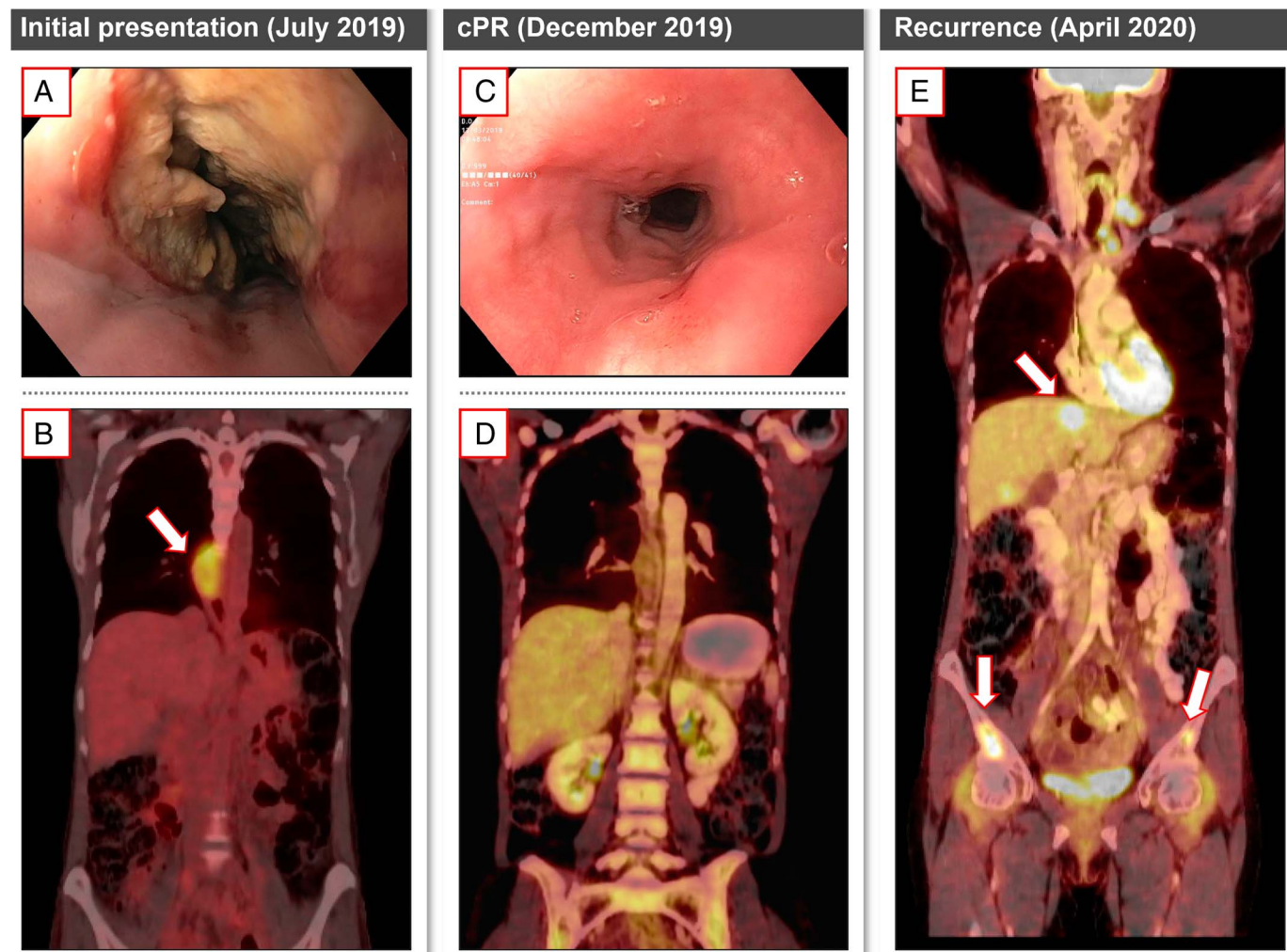
Primary esophageal neuroendocrine carcinoma is a rare, aggressive malignancy lacking evidence-based treatment guidelines. The timing and nature of relapse after successful treatment of locoregional disease are not well characterized. We report a patient lacking risk factors for esophageal cancer who rapidly developed extensive disease recurrence 4 months after achieving complete pathologic response to nonsurgical treatment. Although optimal survival for early stage nonmetastatic disease is achieved by esophagectomy with adjuvant therapy, definitive chemotherapy is also appropriate for late stage nonmetastatic patients. There are presently no protocols for maintenance therapy. We highlight complex treatment considerations for this rare malignancy.

## INTRODUCTION

Primary neuroendocrine esophageal carcinoma (eNEC) is a rare and aggressive subtype of esophageal malignancy with poor prognosis.<sup>1</sup> It accounts for ~2% of esophageal cancers in the United States/Europe.<sup>2</sup> Overall 5-year survival is <5%, with metastatic preference for the liver, lungs, and lymph nodes.<sup>3</sup> Deriving from stem cells in the esophageal epithelium, eNEC is histologically subclassified into small-cell (>80%) and large-cell carcinoma.<sup>4,5</sup> Like small-cell lung cancer (SCLC), it is a high-grade, poorly differentiated neuroendocrine tumor.<sup>6</sup> Hormonally inactive, it rarely produces a recognizable syndrome. Given its rarity, eNEC is difficult to study prospectively and lacks evidence-based treatment guidelines.<sup>7</sup> Providers have adopted treatment regimens from SCLC.<sup>8,9</sup> The benefits of definitive chemoradiation (dCRT) vs surgical regimens for varying disease stages are debated.<sup>7,8,10,11</sup> High-intensity, multimodal therapy is required, given eNEC's aggressive and unpredictable course. We present a unique case of rapidly extensive recurrence of eNEC after complete pathologic response to dCRT and evaluate the recent literature on this malignancy.

## CASE REPORT

A 51-year-old woman with no gastrointestinal, smoking, or alcohol misuse history presented with 3 weeks of epigastric pain, mild acid reflux, and dysphagia unresolved by pantoprazole. Endoscopy by gastroenterology revealed a 4-cm necrotic, midesophageal ulcer with NEC histology. Medical oncology determined T3N2M0 disease stage with endoscopic ultrasound, brain magnetic resonance imaging, and positron emission tomography-computed tomography (PET-CT) (Figure 1). After discussing treatment options, including an evaluation by general surgery, dCRT was selected, given the National Comprehensive Cancer Network's endorsement of dCRT as a possible alternative to surgery, the high morbidity of radical esophagectomy, and the overall lack of established treatment guidelines.<sup>9</sup> Comanaged by medical and radiation oncology, dCRT (cisplatin/etoposide) was completed in 6 months with symptom resolution. PET-CT revealed resolution of the initial fluorodeoxyglucose-avid ulcer and gastrohepatic lymph nodes (Figure 1). Endoscopy with esophageal biopsies was normal, confirming complete pathologic response (Figure 1).



**Figure 1.** Comparison of esophagogastroduodenoscopy and positron emission tomography–computed tomography findings at initial presentation (July 2019), complete pathologic response after definitive chemotherapy (December 2019), and recurrence (April 2020). Arrows indicate the fluorodeoxyglucose (FDG)-avid masses of interest (the primary esophageal tumor and metastatic lesions). (A) July 2019: 4-cm, necrotic, half-circumferential, cratered ulcer spanning between 28 and 34 cm from the incisors. (B) Increased F-fluoro-2-deoxy-d-glucose activity confined to the midesophageal mass and gastrohepatic lymph nodes. (C) December 2019: near-complete resolution of the original ulcerated lesion, with biopsies returning as normal squamous mucosa. (D) Near-complete resolution of abnormal esophageal F-fluoro-2-deoxy-d-glucose uptake, with decreased uptake at the gastrohepatic lymph nodes. (E) April 2020: no significant endoscopic change from December aside from mild reulceration of the lesion (measuring approximately 1 cm) and biopsies still normal. Interval development of F-fluoro-2-deoxy-d-glucose-avid masses within the liver, iliac bones, L2/L3 vertebral bodies, left scapula, right posterior sacrum, thoracic lymph nodes, and right chest wall subcutaneous tissue.

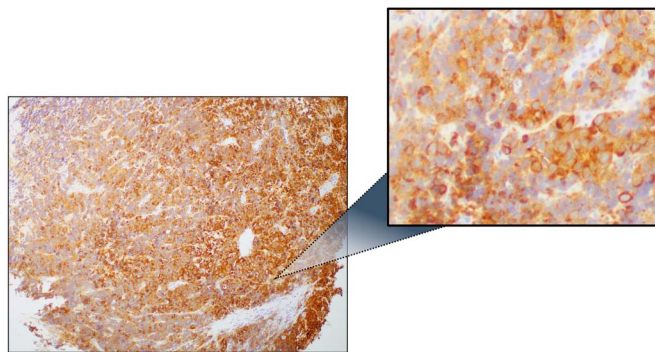
After 3 months of atezolizumab for subsequent maintenance, chest pain occurred concerning for relapse. PET-CT was, therefore, repeated, showing fluorodeoxyglucose-avid masses in the liver, bones, thoracic lymph nodes, and subcutaneous tissue (Figure 1). Biopsy of the hepatic lesions by interventional radiology confirmed metastatic NEC, despite a normal repeat endoscopy. Because all metastases demonstrated significant uptake on gallium dotatate PET-CT, she was started on combination salvage therapy with systemic (capecitabine, temozolomide, and lanreotide) and targeted radionuclide (lutetium Lu 177 dotatate) treatments, with the latter managed by nuclear medicine. She was also regularly seen by palliative care, social workers, and nutritionists. Repeat PET-CT 4 months later demonstrated progression, so treatments were discontinued.

She started hospice care and passed 18 months after diagnosis (Figure 2).

## DISCUSSION

Our patient was atypical in age, sex, and risk factor profile for esophageal malignancy. A systematic review of eNEC reported a mean age of 63.8 and a male-to-female ratio of 1.57:1.<sup>12</sup> Furthermore, 88.7% of patients had a history of significant tobacco smoking, alcohol consumption, and/or achalasia.<sup>12</sup>

Our patient's lesion at the midesophagus to distal esophagus measured 4 cm and staged as T3N2M0. Although univariate analyses declare patient age, tumor size, and T stage as significant



### Synaptophysin

**Figure 2.** Biopsy histopathology (July) confirming primary esophageal neuroendocrine carcinoma. Homogeneous, small, round, purple/blue cells on hematoxylin and eosin stain staining are characteristic of this high-grade, poorly differentiated neuroendocrine malignancy. Immunohistochemistry was positive for specific neuroendocrine markers: synaptophysin (shown), chromogranin, and CD56. The neoplasm was strongly Ki-67 positive (80%–90% of cells), reflecting its highly proliferative nature. Staining was negative for adenocarcinoma markers, including mucicarmine and CDX2. Negative staining for CD45, SOX10, and CD30 ruled out hematopoietic, neural crest, or lymphatic tissue origin, respectively.

prognostic factors for overall survival (OS) in nonmetastatic eNEC, multivariate analyses reveal N stage to be the only independently significant factor.<sup>2,7,12</sup> Thus, our patient's positive prognostic factors were her age and smaller than average tumor size, although her more advanced initial staging (T3 and N2) than average limited her OS outlook. Metastatic potential remains substantial regardless of initial disease parameters.<sup>13</sup> For treatment, the National Comprehensive Cancer Network recommends surgical resection and adjuvant chemotherapy for resectable, localized eNECs.<sup>9</sup> However, dCRT with a platinum agent and etoposide is a suggested alternative, especially with the morbidity of esophagectomy. Given the rarity of eNEC, many clinicians refer to SCLC protocols.<sup>6,8,9</sup>

In the United States, eNEC is more commonly treated with dCRT than in East Asia. An U.S. database study found that only 10.8% and 7.4% of localized (node-negative) and locoregional (node-positive) cases, respectively, were treated with esophagectomy, compared with 35.8% and 63.0% with dCRT.<sup>11</sup> Although esophagectomy led to significantly improved 3-year OS compared with dCRT for localized disease (50.5% vs 30.9%), the survival difference was insignificant for locoregional cases.

By contrast, surgical resection is more routinely performed in East Asia for operable eNEC.<sup>7,10,14,15</sup> In Korea, limited NECs larger than 1.0 cm are resected, regardless of regional lymph node involvement.<sup>14</sup> A single institution Chinese study found that 65.8% and 18.4% of nonmetastatic eNEC underwent radical esophagectomy with lymphadenectomy and dCRT, respectively.<sup>7</sup> For Stage III cases (like our patient), median survival was significantly longer for those who underwent esophagectomy preceded by neoadjuvant chemotherapy than for those who forwent surgery (43.0 vs 15.0 months). Another

Chinese study found that although Stage I–IIB patients derived the most survival benefit from surgery with adjuvant therapy, surgery may only benefit Stage III patients if preceded by neoadjuvant therapy.<sup>10</sup> Even so, the authors remained uncertain whether any surgery would be superior to dCRT for this patient subset.

Despite our maintenance trial with the PD-L1 inhibitor atezolizumab, recurrence manifested 3 months after initiation. Given the pathophysiologic similarities between eNEC and SCLC, we hypothesized that agents with demonstrated survival benefit in SCLC—such as atezolizumab—may also be efficacious for eNEC.<sup>16</sup> The efficacy of immune checkpoint inhibition in poorly differentiated neuroendocrine tumors other than SCLC is under investigation, with 2 notable ongoing Phase II trials in eNEC.<sup>17,18</sup>

Aside from being the first to characterize off-label use of immune checkpoint inhibition in eNEC, our report is also notable for recognizing the urgent need for maintenance therapy. Because SCLC and eNEC have extraordinary metastatic potential even after the primary tumor is addressed, optimizing maintenance therapy after dCRT should be a key priority.<sup>19</sup> The only eNEC case report substantively addressing this topic used S-1/apatinib after salvage esophagectomy, leading to a >40-month postoperative survival.<sup>20</sup>

For a younger patient without risk factors, diagnosis with a prognostically grim malignancy is devastating. Coordinating multidisciplinary care to manage a cancer lacking established treatment guidelines is a necessary challenge. Our case underscores the importance of candid communication, anticipatory guidance, and shared decision-making.

## DISCLOSURES

**Author contributions:** MM Wang reviewed the literature and wrote and approved the manuscript. SK Singh edited and approved the manuscript and is the article guarantor.

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Informed consent was obtained for this case report.

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