Retrospective Study of Clinicopathologic Features and Prognosis of High-grade Neuroendocrine Carcinoma of the Esophagus

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Abstract: Clinicopathologic features of esophageal neuroendocrine carcinoma (NEC), apart from those of small-cell carcinoma, have not been characterized. We evaluated the clinicopathologic features and prognosis including overall survival of NEC of the esophagus. We identified 40 patients with esophageal NEC from our institutional database. All cancers had been clinically staged using endoscopic ultrasonography, computed tomography, and positron emission tomography. Neuroendocrine differentiation was confirmed by immunohistochemical staining. The NEC component was classified into small-cell and large-cell subtypes, and non-neuroendocrine components were evaluated. Patients with locoregional disease were treated with chemoradiation with or without surgery or with surgery only. Patients with distant metastasis were treated with systemic therapy. The extent of residual tumors was evaluated in esophagectomy specimens after preoperative chemoradiation. Twenty-seven patients had large-cell NEC, and 13 had small-cell neuroendocrine carcinoma. An adenocarcinoma component was present in 15 patients and squamous carcinoma component in 1 patient. Synaptophysin was positive in all cases, and chromogranin was positive in 31 cases. Seventeen patients had distant metastasis, and 21 had locoregional disease. Seventeen patients with locoregional disease received preoperative chemoradiation. Disease progressed in 7 patients, and 10 had residual tumor in resection specimens. Overall survival was better with locoregional disease than with distant metastasis ($P = 0.006$). Overall survival was better in patients with non-neuroendocrine component than in patients with pure NEC ($P = 0.031$). There was no difference in prognosis between patients with large-cell NEC and those with small-cell neuroendocrine carcinoma. Esophageal NEC is an aggressive tumor, and patients with mix NEC have better outcome.

Key Words: esophagus, carcinoma, neuroendocrine, small cell, mixed

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Esophageal small-cell carcinoma is a rare but aggressive neoplasm known to have a poor survival outcome and to display resistance to therapy.[5] The esophagus is the most common site of small-cell carcinoma in the gastrointestinal tract[4]; however, to our knowledge, studies encompassing the larger scope of esophageal carcinoma with different histologic patterns of neuroendocrine carcinoma (NEC) are not available in the literature. In addition, differences in survival outcome between esophageal NEC with and without a non-NEC component have not been reported. In the present retrospective study, we evaluated the clinicopathologic features and survival outcome of esophageal NEC and found that patients with locoregional disease and those with a non-neuroendocrine component had a better prognosis.

MATERIALS AND METHODS

Patients' Clinical and Histopathologic Assessments

We searched the institutional database of the Department of Pathology of The University of Texas M. D. Anderson Cancer Center to identify patients who were diagnosed with NEC, small-cell carcinoma, or mixed carcinoma (an NEC component and a non-neuroendocrine adenocarcinoma or squamous carcinoma component) of the esophagus or gastroesophageal junction. We identified 42 patients who underwent treatment between 1997 and 2007. Histopathologic slides were available for samples from 40 patients. A detailed retrospective chart review was performed to document staging, endoscopic findings, therapy, follow-up, and survival outcome. The study was approved by the institutional review board.

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Disease in all patients was clinically staged using endoscopic ultrasonography with fine-needle aspiration of suspicious regional lymph nodes, computed tomography, and positron emission tomography. Endoscopic findings included the presence and extent of Barrett esophagus (BE) and dysplasia, the location and stage of tumor, and subtyping of gastroesophageal junction tumors according to Siewert and Stein classification.[19] The later classification is based on location of epicenter of the tumor in relation to gastroesophageal junction. The gastroesophageal junction is identified as the most proximal end where the gastric folds end. Type 1 carcinoma is identified when epicenter of the tumor is more than 1 cm and less than 5-cm proximal to the gastroesophageal junction. Type 2 carcinoma is identified when epicenter of the tumor is less than 1-cm proximal and less than 2-cm distal to the gastroesophageal junction. Type 3 carcinoma is identified when epicenter of the tumor is more than 2 cm but less than 5-cm distal to the gastroesophageal junction.

Pretreatment biopsy samples were independently reviewed by 2 pathologists (D.M.M. and H.K.) for histologic subtyping of the carcinoma, the presence of intestinal metaplasia (BE), and the presence and grade of dysplasia. The NEC was classified as small-cell neuroendocrine carcinoma (SCNC) or large-cell NEC using the criteria recommended for NEC of the lung.[21] Table 1 shows the histologic features evaluated for SCNC and large-cell NEC. Neuroendocrine differentiation was confirmed by immunohistochemical staining for synaptophysin and chromogranin in all cases. In addition, any associated adenocarcinoma or squamous carcinoma component was noted. All patients with adenocarcinoma had either a distinct glandular component on hematoxylin-eosin stain or mucin as demonstrated by Mucicarmine or Periodic acid-Schiff stains. Cases of suspected squamous differentiation were confirmed by cytokeratin 5/6 and p63 immunohistochemical staining.

Disease in all patients was retrospectively staged according to the system described in the sixth edition of the *American Joint Committee on Cancer Atlas*.[2] Locoregional disease was defined as stages I, II, III, and IVA, and extensive disease was defined as stage IVB with distant metastasis. Staging in locoregional versus extensive disease group is similar to that recommended for pulmonary small-cell carcinoma by the Veterans Administration Lung Study Group.[26] The single patient with stage I disease was treated with surgery only. Patients with stages II, III, and IVA disease were treated with chemoradiation with or without subsequent esophageal resection or with esophageal resection only. All patients with stage IVB disease were treated with systemic therapy. The chemotherapy regimen consisted of platinum-based therapy as the first line of treatment. Patients who received radiation to the esophageal tumor underwent computed tomography scan treatment simulation followed by a radiation dose of 45 Gy in 25 fractions or of 50.4 Gy in 28 fractions, prescribed to cover 95% or more of a clinical target volume encompassing the primary tumor and involved lymphatic regions.

The resected specimens were reviewed for presence of BE and dysplasia, histologic type of the tumor, pathologic stage, and lymph node involvement. Specimens from patients treated with neoadjuvant therapy were evaluated for residual tumors by submission of the majority of grossly identifiable tumor or the entire tumor bed for histopathologic examination.[6]

Survival outcome data were derived by clinical chart review, tumor registry, and social security death index. Overall survival was calculated from the day of esophagogastroduodenoscopy and biopsy to the date of death or last follow-up.

Statistical Analysis

Statistical analysis was performed using SPSS software (SPSS Corp, Chicago, IL). Chi-square test was used to compare the categorical data with P value less than 0.05 considered to indicate significance. A Kaplan-Meier analysis was used to analyze survival, with comparison of median overall survival determined by log-rank (Mantle-Cox) test. A 2-sided $P < 0.05$ was considered to indicate significance.

RESULTS

Of the 40 patients for whom histopathologic material was available, 35 were men and 5 were women. The average age of patients was 63 years (range: 34 to 82 y). Eighteen patients presented with dysphagia without a prior history of gastroesophageal reflux. Ten patients had a history of gastroesophageal reflux disease, 2 of whom had been regularly screened by upper gastrointestinal endoscopy and 8 of whom had been evaluated for progressive symptoms of gastroesophageal reflux disease. Four patients presented with blood in stool or hematemesis.

TABLE 1. Histologic Criteria for SCNC and Large-cell NEC

SCNC	Large-cell NEC
Scant cytoplasm	Cytologic features of non-small-cell carcinoma, including large cell size and low nucleus: cytoplasm ratio
Fine granular nuclear chromatin with absent or inconspicuous nucleoli	Conspicuous to prominent nucleoli
High mitotic rate (more than 10/high-power field)	Coarse vesicular chromatin
Frequent necrosis	High mitotic rate (more than 10/high-power field) and necrosis
Positive immunostains for neuroendocrine markers	Positive immunostains for neuroendocrine markers

NEC indicates neuroendocrine carcinoma; SCNC, small-cell neuroendocrine carcinoma.

TABLE 2. Total Number of Cases and Histologic Subtypes

	SCNC	LCNC	Total
Mixed NEC with adenocarcinoma	3	12	15
Mixed NEC with squamous carcinoma	1	0	1
Pure NEC	9	15	24
Total	13	27	40

LCNC indicates large-cell neuroendocrine carcinoma; NEC, neuroendocrine carcinoma; SCNC, small-cell neuroendocrine carcinoma.

Six patients presented with symptoms related to metastatic sites. Presenting symptoms were unknown in 2 patients. Tumors were located in the proximal esophagus in 1 patient, the midesophagus in 5 patients, and the distal esophagus/gastroesophageal junction in 33 patients; tumor location was unknown in 1 patient. Sixteen gastroesophageal junction tumors were classified as Siewert type 2, 8 were type 3, and 1 was type 1. In all cases of Siewert types 3 and 2 tumors, the gastric cardia 4-cm distal to the gastroesophageal junction was free of tumor on endoscopic examination.

Table 2 shows number of cases with different histologic subtypes of esophageal NEC.

Synaptophysin was positive in all cases, and chromogranin was positive in 31 (78%) cases.

SCNC and Large Cell NEC

SCNC (Fig. 1) was present in 13 patients, and 27 patients had large-cell NEC (Fig. 2). Table 3 shows the comparison of clinicopathologic features of SCNC and large-cell NEC. No significant difference was noted in age, sex, or clinical presentation between 2 groups. However, more patients with large-cell NEC had BE as compared with SCNC.

Extensive disease (stage IVB) was identified at presentation in 13 patients with large-cell NEC and 4 with SCNC. Distant sites of metastases in large-cell NEC group included the liver (n = 5), abdominal lymph nodes (n = 4), bone (n = 1), lung (n = 3), and brain (n = 1). Distant sites of metastasis in SCNC included liver (n = 3) and bone (n = 1). Tissue samples (for cytologic analysis or biopsy) were available from metastatic sites of 11 patients, all of which showed pure neuroendocrine cytologic or histologic features. Three patients with large-cell NEC with extensive disease had BE on biopsy specimen including BE with high-grade dysplasia in 1 patient. None of the patients with SCNC and extensive disease had BE on the biopsy specimens. All patients with stage IVB disease were initially treated with platinum-based chemotherapy. Additionally, bone and brain metastases were treated with radiation.

Locoregional disease was identified in 13 patients with large-cell NEC and in 8 patients with SCNC. Ten patients with large-cell NEC were treated with preoperative chemoradiation; 8 of them had residual disease in esophageal resection specimens. In resection specimens, 7 patients had more than 50% residual tumor, and 1 patient had 20% residual tumor. Resection specimens from 6 patients showed pure NEC histologic features and mixed histologic features were seen in 2 patients.

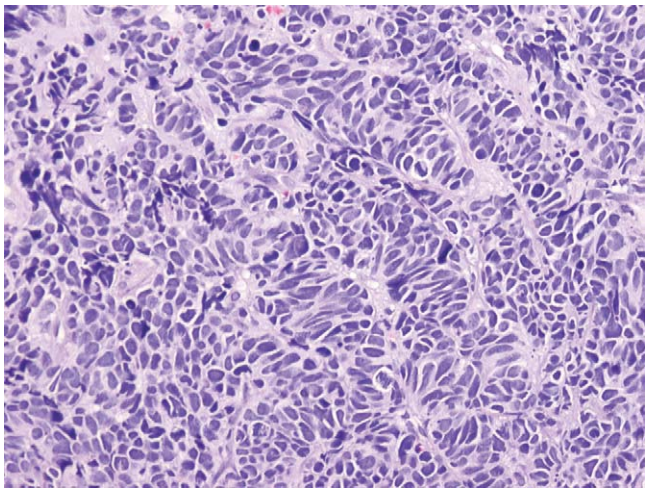

FIGURE 1. Small-cell neuroendocrine carcinoma (hematoxylin-eosin stain, 200 ×).

Postsurgical pathologic stage in these patients was stage IIA in 3, stage III in 2, and stage IVA in 1 patient. Disease progressed during preoperative treatment in 2 patients, precluding surgery. Three patients with large-cell NEC underwent surgery without preoperative chemoradiation. BE was identified in resection specimens of 5 patients. Four patients had long segment BE with high-grade dysplasia and 1 had short segment BE with high-grade dysplasia on resection specimens. Two patients had BE in 1 of the biopsy specimens. Five patients did not have BE either on preoperative biopsies or resection specimens. Out of 8 patients with SCNC and locoregional disease, 7 patients were treated with preoperative chemoradiation. Disease progressed during preoperative treatment in 5 patients, precluding surgery. Two patients underwent surgery, and resection specimens showed more than 50% residual tumor with mixed

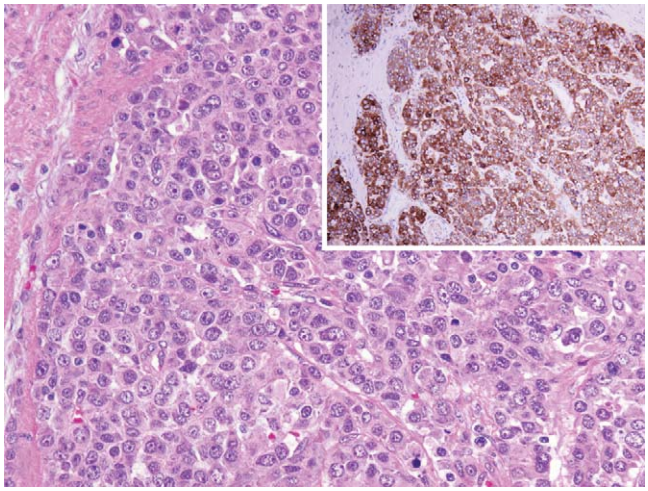

FIGURE 2. Large-cell NEC (hematoxylin-eosin stain and inset with synaptophysin stain, 200 ×). NEC indicates neuroendocrine carcinoma.

TABLE 3. Comparison of Clinical and Histopathologic Features of SCNC and Large-cell NEC

	SCNC (n = 13)	Large-cell NEC (n = 27)	*P*
Age (mean y)	67	61	NS
Sex, male/female	11/2	24/3	NS
Symptoms at presentation			NS
Dysphagia	6	12	NS
GERD with screening	0	2	NS
Progressive GERD	2	6	NS
Blood in stool/hematemesis	2	2	NS
Metastatic site	2	4	NS
NA	1	1	
BE	1	10	0.051
Stage			0.33*
I	0	1	NS
II	2	2	NS
III	4	6	NS
IVA	2	4	NS
IVB	4	13	NS
NA	1	1	
Treatment			
Surgery	1	3	NS
Chemoradiation + surgery	2	8	NS
Preoperative chemoradiation with progression on treatment	5	2	NS
Chemotherapy	4	13	NS
NA	1	1	
Median survival (mo)	16	22	0.43
Vital statistics			0.036
Alive	2	13	
Dead	11	12	
NA	0	2	

*Stages I to IVA vs. stage IVB.
BE indicates Barrett esophagus; GERD, gastroesophageal reflux disease; NA, not applicable; NS, not significant.

TABLE 4. Comparison of Clinical and Histopathologic Features of Mixed and Pure NEC

	Mixed (n = 16)	Pure NEC (n = 24)	*P*
Age (mean y)	65	60	NS
Sex, male/female	15/1	20/4	NS
Symptoms at presentation			NS
Dysphagia	7	11	NS
GERD with screening	1	1	NS
Progressive GERD	4	4	NS
Blood in stool/hematemesis	1	3	NS
Metastatic site	3	3	NS
NA	0	2	
BE	6	5	NS
Stage			0.037*
I	1	0	NS
II	3	1	NS
III	7	3	0.037
IVA	1	5	NS
IVB	4	13	0.036
NA	0	2	
Treatment			
Surgery	2	2	NS
Chemoradiation + surgery	8	2	0.037
Preoperative chemoradiation with progression on treatment	2	5	NS
Chemotherapy	4	13	0.036
NA	0	2	
Median survival (mo)	28	15	0.031
Vital statistics			0.33
Alive	8	7	
Dead	8	15	
NA	0	2	

*Stages I to IVA vs. stage IVB.
BE indicates Barrett esophagus; GERD, gastroesophageal reflux disease; NA, not applicable; NS, not significant.

histologic features. Postoperative pathologic stage was stage III in these 2 patients. One patient with SCC underwent surgery only. BE with high-grade dysplasia was identified in 1 case with SCNC. Squamous carcinoma in situ was identified in biopsy specimen from a patient with mixed SCNC and squamous carcinoma.

No significant difference was observed in stage distribution between SCNC and large-cell NEC (Table 3).

Mixed NEC and Pure NEC

Sixteen patients had mixed NEC and 24 patients had pure NEC (Table 4). Twelve patients had mixed large-cell NEC and adenocarcinoma (Figs. 3, 4), 3 patients had mixed SCNC and adenocarcinoma. One patient had mixed SCNC and squamous carcinoma (Fig. 5). Fifteen patients had pure large-cell NEC and 9 patients had pure SCNC.

Four patients with mixed adenocarcinoma and large-cell NEC had extensive disease at presentation. Metastatic sites included liver (n = 2), abdominal lymph nodes (n = 1), and brain (n = 1). No mixed SCNC patients had extensive disease. Thirteen patients with pure NEC had extensive disease. These included 9 patients with pure large-cell NEC and 4 patients with pure SCNC. The distant sites of metastasis included liver (n = 3), abdominal lymph nodes (n = 3), lung (n = 1), brain (n = 1), and bone (n = 1) in pure large-cell NEC group. The distant sites of metastasis were liver (n = 3) and bone (n = 1) in SCNC group. BE was identified in biopsy specimens of 3 pure large-cell NEC and 1 mixed large-cell NEC. BE was not identified in any of the pure SCNC patients. All patients with stage IVB disease were initially treated with platinum-based chemotherapy. Additionally, bone and brain metastases were treated with radiation.

Locoregional disease was identified in 12 mixed NEC and 9 pure NEC.

Twelve patients with mixed histology included 8 patients with mixed large-cell NEC and 3 mixed SCNC/adenocarcinoma and 1 patient with SCNC and squamous carcinoma. Six patients with mixed NEC/adenocarcinoma with locoregional disease underwent preoperative chemoradiation followed by esophageal resection and demonstrated more than 20% residual tumor on the specimen (more than 50% residual tumor in 5 and 20% residual tumor in 1). Postoperative pathology stage in 6 patients with mixed large-cell NEC included stage IIA (N = 3), stage III (N = 2), and stage IVa (N = 1). One patient with mixed large-cell NEC progressed on treatment precluding surgery. One patient with

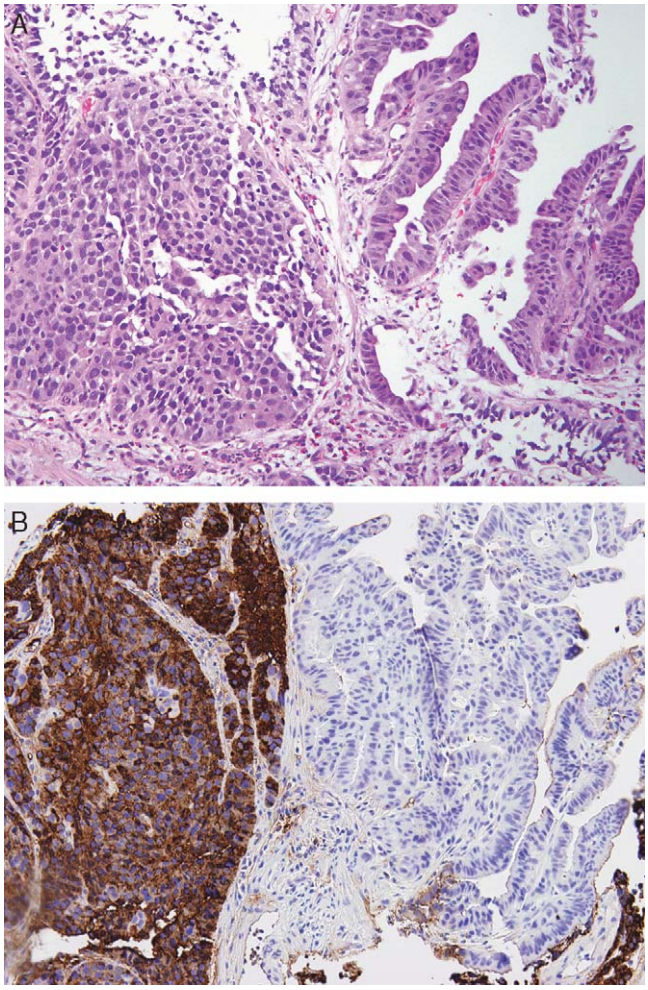

FIGURE 3. Mixed adenocarcinoma and large-cell NEC (100 ×). Hematoxylin-eosin (A) and chromogranin (B) stains show 2 distinct components of adenocarcinoma and NEC. NEC indicates neuroendocrine carcinoma.

mixed large-cell NEC/adenocarcinoma underwent surgery without preoperative chemoradiation. Four mixed large-cell NEC had BE with high-grade dysplasia on resection specimens. The patient with mixed SCNC and squamous carcinoma progressed on preoperative chemoradiation therapy precluding surgery. Squamous carcinoma in situ was identified in this patient with mixed SCNC and squamous carcinoma. Two patients with mixed SCNC/adenocarcinoma were treated with preoperative chemoradiation followed by surgery and demonstrated more than 50% residual tumor with mixed SCNC histology on resection specimens. One patient underwent surgery without preoperative chemoradiation. One patient with mixed SCNC and adenocarcinoma had BE with high-grade dysplasia on resection specimen.

Nine patients with locoregional disease and pure NEC histology included 5 patients with pure large-cell NEC and 4 pure SCNC. One patient with pure large-cell NEC was treated with preoperative chemoradiation followed by surgery and demonstrated more

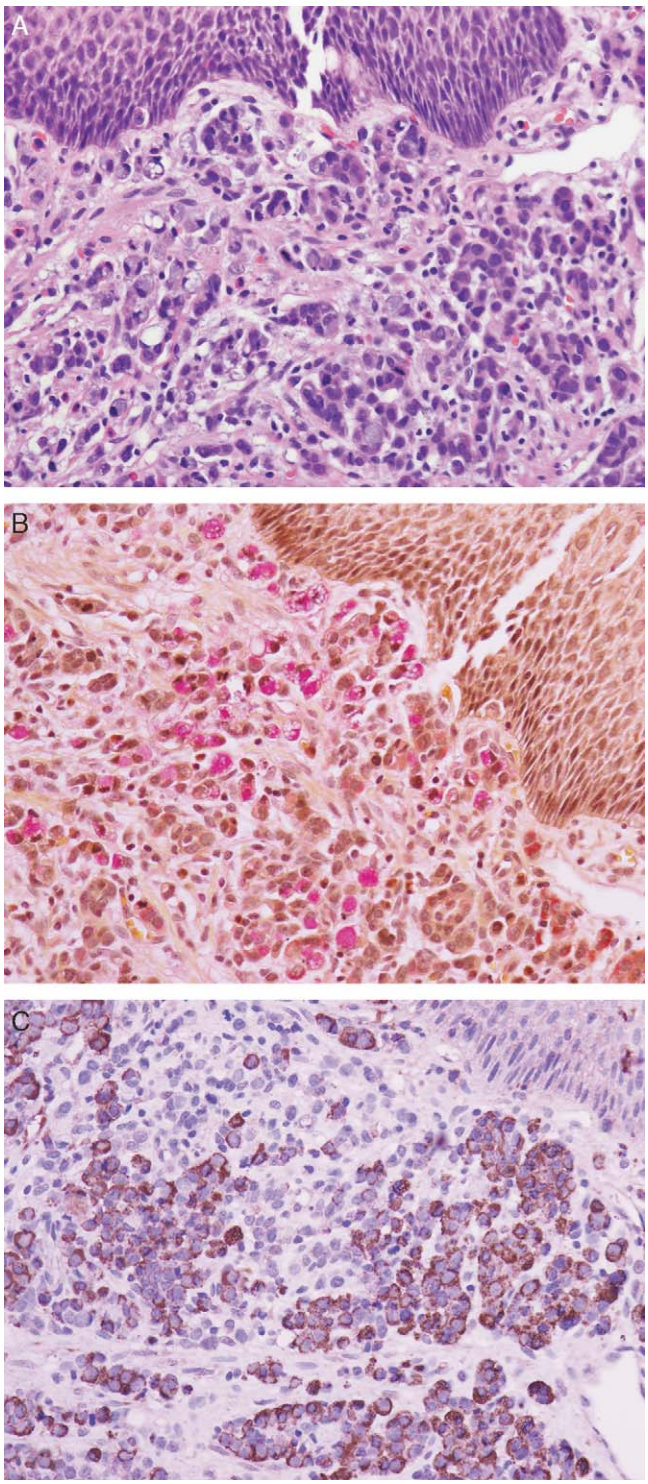

FIGURE 4. Mixed adenocarcinoma and NEC (100 ×). Hematoxylin-eosin (A), mucin (B), and synaptophysin (C) stains show intermixed adenocarcinoma and NEC. NEC indicates neuroendocrine carcinoma.

than 50% residual tumor and pure neuroendocrine histology. Postoperative pathology stage was stage III in this patient. Disease progressed on preoperative

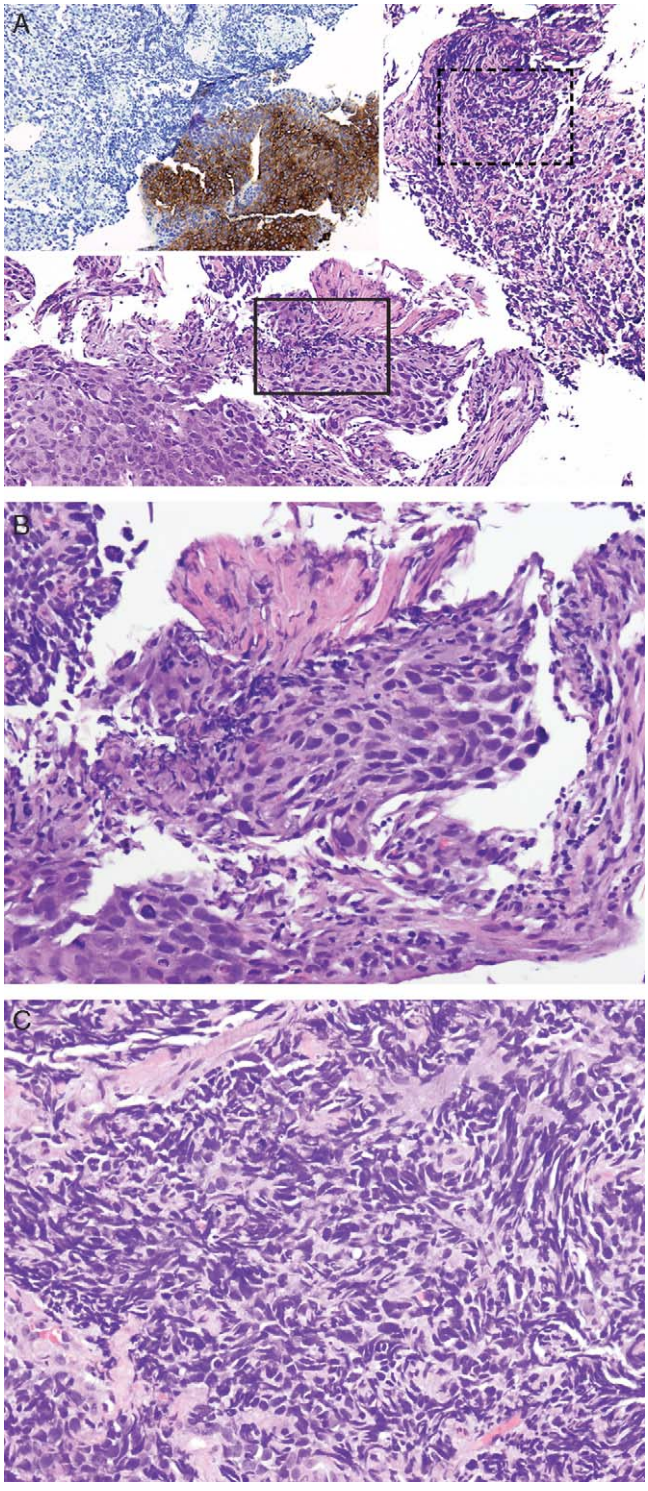

FIGURE 5. Mixed SCNC and squamous carcinoma. Hematoxylin-eosin stains (A, 10×; B and C, 100×) show distinct populations of squamous carcinoma and SCNC. The inset in panel A shows CK 5/6 immunopositivity in the squamous carcinoma component and immunonegativity in SCNC. SCNC indicates small-cell neuroendocrine carcinoma.

chemoradiation in 2 patients with pure large-cell NEC precluding surgery. Two patients underwent surgery without prior chemoradiation. One patient had BE with high-grade dysplasia on resection specimen and 1 patient had BE on preoperative biopsy. Three patients with pure SCNC progressed on preoperative chemoradiation precluding surgery and 1 patient showed more than 50% residual tumor with postoperative pathology stage III. No BE was identified in the pathology specimens for pure SCNC group.

More patients with mixed histology presented with locoregional disease as compared with pure NEC ($P = 0.037$).

Fourteen patients (66%) had surgery out of a total of 21 patients who were initially treated with the intent to resect. All patients (n = 10) who received preoperative neoadjuvant therapy had residual tumor in the resection specimens.

The median overall survival was 14 months (range: 2 to 49, SD 12.37) in these patients. On subgroup analysis, the median overall survival was 22 months (range: 2 to 43, SD 12.23) in patients with large-cell NEC, compared with 16 months (range: 7 to 49, SD 12.69) in patients with SCC ($P = 0.43$). Median overall survival was 28 months (range: 8 to 49, SD 13.95) in patients with localized disease, compared with 11 months (range: 3 to 33, SD 9.46) in patients with distant metastasis ($P = 0.006$, Fig. 6A). In addition, median survival was 28 months (range: 3 to 49, SD 13.24) in patients with mixed NEC and adenocarcinoma or squamous cell carcinoma components, compared with 15 months (range: 2 to 43, SD 10.64) in patients with pure NEC ($P = 0.031$, Fig. 6B). The difference in overall survival between patients with pure NEC and those with mixed NEC in patients with locoregional disease was not statistically significant ($P = 0.22$, Fig. 6C).

DISCUSSION

In the present study, we examined the significance of NEC and neuroendocrine differentiation in patients with cancer of the esophagus and found that localized disease and mix histology were predictors of a better outcome. Findings of male predominance, patients presenting with symptoms owing to effects of the mass, and a distal esophageal tumor location were similar to features of conventional adenocarcinoma of the esophagus. Higher number of patients with gastroesophageal junction tumors had Siewert type 3 carcinoma, raising a possibility of gastric primary. However, in all patients with Siewert type 2 and 3 carcinoma, the gastric cardia 4-cm distal to the gastroesophageal junction was free of tumor on endoscopic examination, excluding a gastric primary extending into the esophagus.

The prevalence of BE was lower (27%) than that seen for adenocarcinoma. BE with high-grade dysplasia was seen in 4 patients with mixed large-cell NEC, 1 patient with pure large-cell NEC, and 1 patient with mixed SCNC/adenocarcinoma. Prior studies of BE with

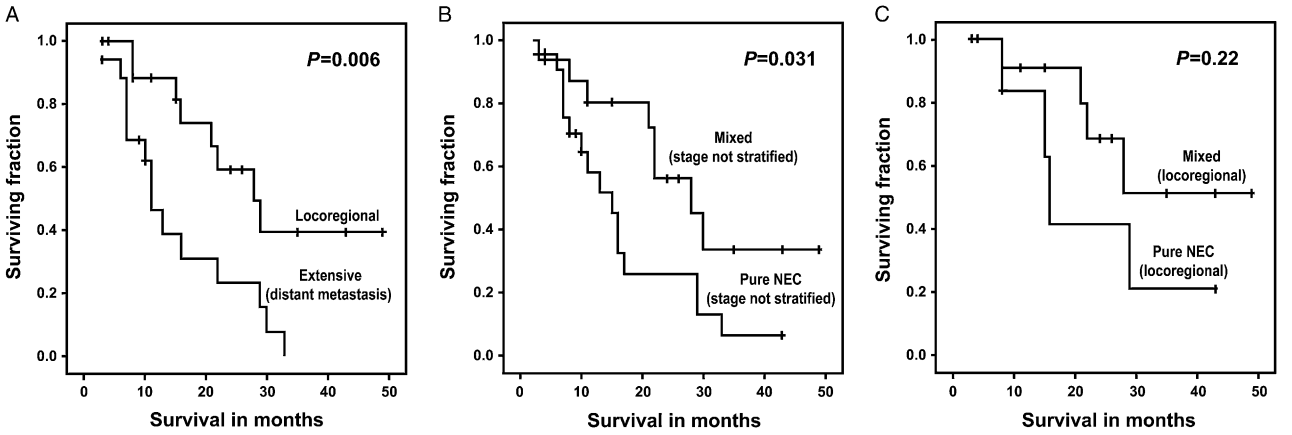

FIGURE 6. A, Kaplan-Meier survival analysis for localized versus extensive disease. B, Kaplan-Meier survival analysis for mixed versus pure NEC without stage stratification. C, Kaplan-Meier survival analysis for mixed versus pure NEC in patients with locoregional disease. NEC indicates neuroendocrine carcinoma.

esophageal NEC are limited as case reports.[18] Takubo et al,[20] Wu et al,[23] and Yamamoto et al[24] showed association of squamous carcinoma in situ in a small number of cases of small-cell carcinoma with or without squamous carcinoma component. The present study had only 1 case in which squamous carcinoma in situ was seen in association with mixed SCNC and squamous carcinoma. Overall, all the studies including present study have small number of patients with BE or squamous carcinoma in situ precluding evaluation of a definite association between BE or squamous carcinoma in situ and esophageal NEC.

Synaptophysin staining was more sensitive than chromogranin staining in identifying neuroendocrine differentiation, as was previously noted for gastrointestinal neuroendocrine tumors.[1]

Our results demonstrate the aggressive nature of esophageal NEC. The evidence supporting these results includes the presence of systemic disease at presentation in almost half (45%) of the patients, the poor response to preoperative chemoradiation therapy in patients with locoregional disease, and lower overall survival. These findings are similar to those of several previous studies of small-cell carcinoma.[10,12,16] Ku et al[13] in a study of 25 patients with esophageal small-cell carcinoma demonstrated male predominance and a lower percentage of patients presenting with extensive disease as compared with the present study. However, overall survival in that study was not very different from that in the present study in patients with either locoregional or extensive disease. Yun et al[25] in a study of 21 patients of small-cell carcinoma of esophagus showed male predominance with synaptophysin being positive in more tumors than chromogranin, similar findings with the present study. Hudson et al[11] showed slight female predominance. They showed higher percentage of cases presenting with extensive disease as compared with the present study. The survival in locoregional and extensive disease was comparable to the present study. In addition, they also found better overall survival in locoregional disease as compared with the extensive disease. However, in their study immunohistochemical stains were performed in 50% of patients and no tumors were stained with either synaptophysin or chromogranin. Noguchi et al[17] in a study of 6 patients showed all male patients, most of them presenting with extensive disease and had poor survival outcome. Casas et al,[5] in their literature review of esophageal small-cell carcinoma, demonstrated a better outcome for patients with locoregional disease who were treated with multimodality therapy rather than local therapy. In the present study, the majority of patients with locoregional disease were treated with multimodality therapy and had either progression of disease during treatment or substantial tumor remaining in the resection specimen. Although heterogeneity in preoperative chemotherapy regimens makes it difficult to provide conclusive evidence, our findings do suggest that preoperative chemoradiation in esophageal NEC may not be very effective and that surgical management should be considered as part of multimodality treatment for locoregional disease.

An attempt to subtype the esophageal NECs, as is done for lung tumors, was made because small-cell carcinoma of the esophagus has histologic similarities to the small-cell carcinoma of the lung and is treated more like small-cell carcinoma of the lung than like conventional esophageal carcinoma (adenocarcinoma or squamous carcinoma).[3,9,22] In addition, small-cell carcinoma of the lung and esophagus share some molecular abnormalities.[7,14,20] Mixed high-grade NECs (small-cell carcinoma or large-cell NEC) in the lung are primarily treated like a high-grade NEC. The difference between mixed and pure NEC in the esophagus is unknown. Our results suggest that pure NEC has higher stage at presentation compared with the mixed NEC. In addition, our results also indicate that patients with mixed NEC have more favorable prognosis than pure NEC. In

patients with locoregional disease, a trend toward better outcome was observed in those with mixed NEC. However, because of limited patient numbers, our findings cannot clarify whether histologic features are a predictor of behavior independent of clinical stage. Although more patients with large-cell NEC were alive than patients with SCNC at the time of last follow-up, we did not find any significant difference in overall survival between patients with large-cell NEC and those with SCNC. It has been hypothesized that carcinoma arises from a progenitor cell with the potential for multilineage differentiation.[8,15] It is likely that tumors that retain pure neuroendocrine differentiation result in a worse outcome than tumors that undergo dual differentiation. Alternatively, tumors with mixed differentiation may have been adenocarcinomas originally and then dedifferentiated with neuroendocrine features. These tumors potentially maintain some of the favorable prognostic features of the original adenocarcinoma.

Esophageal NEC is an infrequent neoplasm. Because of this, neuroendocrine differentiation can be overlooked, particularly in cases of mixed carcinoma. It is advisable to perform immunostains to identify neuroendocrine differentiation in cases where the tumor or part of the tumor is poorly differentiated and the poorly differentiated component cannot be classified as either adenocarcinoma or squamous carcinoma.

In summary, our study highlights the importance of identifying neuroendocrine differentiation in pure and mixed forms in esophageal carcinoma and provides evidence of better prognosis of mixed NEC.

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