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Undifferentiated carcinoma of the esophagus: a clinicopathological study of 16 cases[☆]

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Summary

Undifferentiated carcinoma of the esophagus is a rare histologic variant of esophageal carcinoma. Using criteria based on studies of undifferentiated carcinomas arising at other sites, we have collected 16 cases of resected esophageal undifferentiated carcinomas. Patients ranged in age from 39 to 84 years (mean, 65.5 years) and were predominantly male (94%). The tumors were characterized by an expansile growth pattern of neoplastic cells organized in solid sheets and without significant glandular, squamous, or neuroendocrine differentiation. The neoplastic cells had a syncytial-like appearance, little intervening stroma, and patchy tumor necrosis. In a subset of cases, the tumor cells adopted a sarcomatoid (n = 2), rhabdoid (n = 1), or minor component (<5%) of glandular morphology (n = 3). In 1 case, reactive osteoclast-like giant cells were found interspersed among the neoplastic cells. Lymphovascular invasion, perineural invasion, and lymph node metastases were identified in 88%, 56%, and 81% of cases, respectively. In 12 (75%) specimens, the background esophageal mucosa was notable for Barrett esophagus. Consistent with the epithelial nature of these neoplasms, cytokeratin positivity was identified in all cases. In addition, SALL4 expression was present in 8 (67%) of 12 cases. Follow-up information was available for 15 (94%) of 16 patients, all of whom were deceased. Survival after surgery ranged from 1 to 50 months (mean, 11.9 months). Before death, 67% patients had documented locoregional recurrence and/or distant organ metastases. In summary, esophageal undifferentiated carcinomas are aggressive neoplasms and associated with a high incidence of recurrence and/or metastases and a dismal prognosis.

Keywords

Esophagus; Esophagogastric; Gastroesophageal; Carcinoma; Undifferentiated; SALL4

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Supplementary data

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1. Introduction

Esophageal cancer is the eighth most common cancer type and the sixth most common cause of cancer-related deaths worldwide. It affects more than 450000 patients per year, and the incidence is increasing rapidly [1–3]. The 5-year overall survival ranges from 15% to 30%, and outcomes are significantly dependent on tumor stage [4,5]. Early diagnosis of esophageal cancer is associated with a good prognosis, whereas poor outcomes are related to advanced stages of disease and the propensity for metastasis. Squamous cell carcinoma and adenocarcinoma account for greater than 90% of all esophageal cancer cases [6,7]. In addition, the World Health Organization recognizes other histologic variants of esophageal cancer including undifferentiated carcinomas [8].

Undifferentiated carcinomas of the esophagus are rare neoplasms and associated with a poor prognosis. Reports of these neoplasms have been limited to large epidemiological and randomized clinical trials for esophageal cancer [6,7,9–14]. However, the prevalence of undifferentiated carcinoma within these studies varies widely and ranges from 0.15% to 4.5%. This disparity in prevalence may reflect the lack of diagnostic criteria for esophageal undifferentiated carcinomas. Other than the absence of identifiable histologic differentiation beyond an epithelial phenotype, a defining set of pathologic features for undifferentiated carcinomas has not been established. Considering that undifferentiated carcinomas are aggressive neoplasms, an accurate diagnosis and appropriate classification of these neoplasms are clinically relevant. Using criteria from prior studies of undifferentiated carcinomas arising at other sites, we have collected 16 cases of esophageal undifferentiated carcinoma and described their clinical, gross, microscopic, immunophenotypic, and follow-up findings.

2. Materials and methods

2.1. Case selection

Study approval was obtained from the University of Pittsburgh Institutional Review Board. A total of 269 esophagectomy specimens from patients treated for esophageal carcinoma at the University of Pittsburgh Medical Center were reviewed. Based on prior studies of undifferentiated carcinomas arising at other sites, each case was screened for a solid, sheet-like growth of neoplastic cells with less than 5% glandular, squamous, or neuroendocrine differentiation [15–22]. In addition, specific histologic patterns including signet ring cell formation and medullary growth were excluded. Among these 269 cases, 22 esophageal carcinomas fulfilled the initial selection criteria (as reviewed by A.D.S. and R.R.S.).

A representative tumor block from each case was selected for ancillary studies. Immunohistochemical stains for cytokeratin AE1/AE3 and CAM 5.2 were done to confirm the epithelial origin of all tumors. Glandular (mucicarmine and periodic acid–Schiff diastase), squamous (p40 and CK5/6), and neuroendocrine (synaptophysin and chromogranin A) markers were also performed. Cases with more than 5% staining of the neoplastic cells with any of the aforementioned markers were excluded from this study. Overall, 16 esophageal carcinomas were categorized as an undifferentiated carcinoma. A

review of the pathology reports from these 16 tumors revealed 1 diagnosed as undifferentiated carcinoma, whereas the remaining were diagnosed as poorly differentiated carcinoma (n = 8) and poorly differentiated adenocarcinoma (n = 7).

For all 16 cases, patient demographic data, history of tobacco and alcohol abuse, clinical presentation at the time of initial diagnostic workup, personal and family medical history, and whether the patient received neoadjuvant therapy were gathered from the patient's medical records. Clinical follow-up information was also obtained from patient's medical records including survival data. Gross pathology reports were reviewed to assess tumor location, size, and appearance.

All routine hematoxylin and eosin-stained slides for each undifferentiated carcinoma were analyzed for growth pattern, necrosis, perineural invasion, vascular invasion, margin assessment, and regional lymph node metastases. The background esophageal and gastric mucosa was also evaluated. Pathologic staging was determined in accordance with the guidelines of the seventh edition of the American Joint Committee on Cancer (AJCC) prognostic staging system [23].

2.2. Special stains, immunohistochemistry and in situ hybridization

Special stains and immunohistochemical labeling were performed on 4- μ m unstained whole sections. Slides were deparaffinized with serial xylene treatments. Special stains (mucicarmine and periodic acid-Schiff) were performed on the BenchMark XT system (Ventana Medical Systems; Tucson, AZ) per the manufacturer's protocol. For immunohistochemical stains, antigen retrieval was done using heated citrate solution (pH 6.0). Supplementary Table 1 summarizes the antibodies, clones, and dilutions used within this study. In situ hybridizations for Epstein-Barr virus were also performed using probes targeting Epstein-Barr early RNA (EBER; Ventana Medical Systems) on the Ventana Benchmark XT system. All cases tested for EBER were also tested for integrity of total RNA using an RNA-positive control probe.

3. Results

3.1. Clinical characteristics

The main clinical findings for each patient are summarized in Table 1. Patients at diagnosis ranged in age from 39 to 84 years (mean, 65.5 years; median, 67 years) and were predominantly male (15/16, 94%). At clinical presentation, patients experienced progressive dysphagia (n = 8, 50%), gastroesophageal reflux (n = 6, 38%), weight loss (n = 4), anemia (n = 2), chest pressure (n = 1), chest pain (n = 1), abdominal pain (n = 1), hematemesis (n = 1), anemia (n = 1), and dyspnea (n = 1). Other than gastroesophageal reflux, the duration of clinical symptoms ranged from 1 week to 6 months (mean, 9 weeks; median, 5.5 weeks). In 4 cases, the tumor was identified during endoscopic surveillance for Barrett esophagus. Past medical history was significant for tobacco usage in 7 (44%) patients and alcohol intake in 2 (13%) patients. In addition, 5 (31%) patients reported a prior history of cancer including 3 with prostatic adenocarcinoma, 1 with colorectal adenocarcinoma, and 1 with oral squamous cell carcinoma. None of the patients had a family medical history of esophageal cancer.

However, 2 (13%) patients disclosed first-degree relatives with gastrointestinal malignancies including pancreatic adenocarcinoma and colorectal adenocarcinoma. Before esophagogastrectomy, 2 (13%) patients received neoadjuvant chemoradiation.

3.2. Gross pathology

Grossly, 9 (56%) of 16 tumors were centered within the distal esophagus, whereas the remaining 7 (44%) were located at esophagogastric junction (Table 2). The tumors ranged in size from 1.0 to 8.0 cm (mean, 4.2 cm; median, 4.1 cm). All cases were exophytic with raised edges, but 13 (81%) tumors also showed a central area of depression and ulceration (Fig. 1A and C). On cross section, the peripheral borders of the tumors exhibited rounded edges and a smooth demarcation from the surrounding uninvolved esophagus and stomach (Fig. 1B and D).

3.3. Histopathologic and immunophenotypic findings

At low magnification, undifferentiated carcinomas were characterized by an expansile growth pattern of neoplastic cells organized in solid sheets with little intervening stroma (Fig. 2A). All of the tumors extended into the submucosa with most invading through the muscularis propria and into the adventitia (n = 11, 69%). In most cases (13/16, 81%), there was a sharp interface between the tumor and uninvolved parenchyma (Fig. 2B) with a patchy peritumoral lymphocytic infiltrate. The tumor surface was often necrotic (81%) and associated with a tumor size greater than 2.0 cm. In addition, scattered foci of tumor necrosis were present in all cases (Fig. 2C).

The neoplastic cells were medium to large with poorly defined amphophilic to slightly eosinophilic cytoplasm imparting a syncytial-like appearance. Cytologically, the nuclei were oval and vesicular with each containing at least 1, basophilic to deep-red nucleolus. Multiple mitotic figures including atypical forms were identified (Fig. 2D). In 2 cases, the tumor cells adopted a spindle cell morphology with large pleomorphic nuclei and reminiscent of a high-grade pleomorphic sarcoma (Fig. 3A). Osteoclast-like, multinucleated giant cells with bland cytologic features and without significant pleomorphism were found interspersed among neoplastic cells in 1 case (Fig. 3B). In another case, approximately 40% of the tumor cells had large, paranuclear hyaline inclusions within the cytoplasm resulting in an eccentrically placed nucleus and imparting a rhabdoid appearance (Fig. 3C). The presence of focal infiltrating adenocarcinoma (<5%) was found at the periphery of the tumor cell mass in 3 cases (Fig. 3D). No morphological evidence of squamous differentiation was identified in any of the undifferentiated carcinomas.

Lymphovascular (88%) and perineural invasion (56%) were common findings (Fig. 2E). Furthermore, regional lymph node metastasis was present in 13 (81%) cases. In 12 (75%) of 16 specimens, the background esophageal mucosa was notable for Barrett esophagus (Fig. 2F). Dysplasia within Barrett esophagus was identified in 5 (42%) of the 12 cases with 1 classified as low grade and 4 as high grade. Squamous dysplasia was absent in all specimens. In addition, surgical resection margins were negative for both dysplasia and tumor. Based on the seventh edition of the AJCC [23], undifferentiated carcinomas were staged as follows: 1 (6%) stage I, 3 (19%) stage II, and 12 (75%) stage III.

Immunohistochemical assessment revealed cytokeratin positivity in all cases. The neoplastic cells were diffusely positive for CAM 5.2 and patchy positive for AE1/AE3 (Fig. 4B and C). None of the cases was positive for squamous (p40 and CK5/6) or neuroendocrine (synaptophysin and chromogranin A) markers. Except for the 3 cases demonstrating focal glandular differentiation at the tumor periphery, special stains for mucicarmine and periodic acid–Schiff diastase were negative for mucin production. In addition, CK7 and CK20 were at least focally immunoreactive in 16 (100%) and 11 (69%) cases, respectively. CDX2 was focally positive in 1 (1%) case. The neoplastic cells were negative for HER2/neu (n = 16), Oct-3/4 (n = 12), CD30 (n = 10), S-100 protein (n = 10), TTF-1 (n = 6), desmin (n = 4), CD45 (n = 3), CD43 (n = 3), CD20 (n = 2), CD3 (n = 2), MLH1 (n = 2), PMS2 (n = 2), MSH2 (n = 2), and MSH6 (n = 2). In 4 cases, SMARCB1/INI1 was performed and exhibited retained nuclear expression. In situ hybridization for Epstein-Barr virus–encoded small RNA (EBER) was negative in all 16 tumors tested. Interestingly, SALL4 showed positive nuclear immunoreactivity in 8 (67%) of 12 cases with a variable expression pattern ranging from 20% to 70% (mean, 40%) of tumor nuclei (Fig. 4D).

3.4. Clinical outcome

Follow-up information was available for 15 (94%) of 16 patients, all of whom were deceased. Survival after surgery ranged from 1 to 50 months (mean, 11.9 months; median, 10 months). Before death, 10 (67%) of 15 patients had documented locoregional recurrence (n = 5) and/or distant organ metastases (n = 7) (Fig. 5). Among these 10 patients, the time to locoregional recurrence or metastasis ranged from 2 to 12 months (mean, 7.3 months; median, 7 months). Sites of metastases included liver, bone, lung, mesentery, omentum, and skin.

4. Discussion

An undifferentiated carcinoma is a rare and typically aggressive variant of carcinoma with a high incidence of metastases and dismal prognosis. These tumors have been reported to arise in virtually every anatomical site including sinonasal tract, thyroid, lung, pancreas, uterus, ovary, bladder, and others; however, our current understanding of esophageal undifferentiated carcinoma is limited [15–22]. In fact, although the current World Health Organization *Classification of Tumours of the Digestive System* recognizes esophageal undifferentiated carcinomas as a distinct entity, the clinical and pathologic features are not described [8]. Within the literature, studies characterizing these neoplasms have been isolated to large epidemiological studies with little gross and histologic information or individual case reports that lack correlative clinical data [6,7,9–12,24]. To the best of our knowledge, our study represents the largest clinicopathological description of esophageal undifferentiated carcinomas.

Analogous to undifferentiated carcinomas of other organ sites, inclusion criteria used herein for the esophagus was a solid, sheet-like growth of cytokeratin-positive neoplastic cells without significant (<5%) glandular, squamous, or neuroendocrine differentiation. Based on these defining features, undifferentiated carcinomas were centered within the distal esophagus or esophagogastric junction. Grossly, these tumors were exophytic and, on cross

section, had a pushing border. Additional histologic findings included an expansile growth pattern with a sharp demarcation from the uninvolved parenchyma, neoplastic cells with a syncytial-like appearance, little intervening stroma between neoplastic cells, and patchy tumor necrosis. Within a subset of cases, the tumor cells adopted a sarcomatoid, rhabdoid, or minor component of glandular morphology. In 1 case, reactive osteoclast-like giant cells were found interspersed among the neoplastic cells. Lymphovascular invasion, perineural invasion, and lymph node metastases were identified in most cases.

Although the prevalence of undifferentiated carcinomas of the esophagus cannot be ascertained from our study, previous reports by Le Roux et al [11] and van Meerten et al [14] estimate undifferentiated carcinomas represent between 3.8% and 4.0% of esophageal cancers. In contrast, a study of a large multi-institutional international database by the Worldwide Esophageal Cancer Collaboration reported undifferentiated carcinomas constituted 0.18% of esophageal cancers [7]. The discordance in prevalence is likely attributable to the lack of diagnostic criteria for this neoplastic entity. In our retrospective review of esophageal cancers, only 1 of 16 cases was diagnosed as an undifferentiated carcinoma. In the remaining cases, the diagnosis rendered was either a poorly differentiated carcinoma or poorly differentiated adenocarcinoma. Despite the absence of glandular differentiation, in most cases, a diagnosis of adenocarcinoma is not unreasonable.

Internationally, esophageal squamous cell carcinoma is the most prevalent histologic subtype, but in Western countries, esophageal cancer is a disease in epidemiological transition. Although the incidence of squamous cell carcinomas has declined because of decreased smoking and alcohol consumption, the incidence of esophageal adenocarcinoma has risen rapidly [25,26]. In the United States, the incidence of esophageal adenocarcinoma has increased by 600% in white males over the last 30 years [3,27,28]. Among the undifferentiated carcinomas within this study, focal adenocarcinoma was identified at the periphery of 3 cases. Furthermore, 75% of undifferentiated carcinomas occurred in the background of Barrett esophagus, a known precursor to esophageal adenocarcinoma. An argument could be made that undifferentiated carcinomas evolve from adenocarcinoma and should be classified as a histologic subtype of esophageal adenocarcinoma rather than a separate diagnostic category.

However, considering the aggressive nature of undifferentiated carcinomas, a clinical distinction from conventional esophageal adenocarcinoma may be justified. Sixty-seven percent of patients with esophageal undifferentiated carcinoma developed locoregional recurrence and/or distant metastases within 12 months of esophagectomy. Although our study cohort was small, overall survival rates at 1 and 5 years were 20% and 0%, respectively, with most tumors categorized as stage III by AJCC criteria. Similarly, the Worldwide Esophageal Cancer Collaboration reported a 1-year overall survival rate of less than 30% for undifferentiated carcinomas after esophagectomy [7]. In comparison, 1- and 5-year overall survival rates for AJCC stage III adenocarcinomas after esophagectomy were greater than 60% and greater than 20%, respectively [7].

Regardless of the histopathogenesis of esophageal undifferentiated carcinomas, an accurate pathologic diagnosis can be challenging. The differential diagnosis is wide and varies

depending upon the specific morphological features of a given undifferentiated carcinoma. For instance, the solid growth pattern of neoplastic cells can resemble a poorly differentiated, nonkeratinizing squamous cell carcinoma or a high-grade neuroendocrine carcinoma of the esophagus [29]. Two undifferentiated carcinomas within our series adopted a sarcomatoid appearance that could mimic an esophageal spindle cell squamous carcinoma [30]. Moreover, rhabdoid foci present within undifferentiated carcinomas may raise the consideration for melanoma, lymphoma, or a rhabdoid carcinoma of the gastrointestinal tract [31]. In difficult cases, immunohistochemical stains can be of assistance as undifferentiated carcinomas are negative for squamous (p40 and CK5/6) and neuroendocrine (synaptophysin and chromogranin A) differentiation. Immunohistochemical and in situ markers for melanoma (S-100 protein) and lymphoma (CD45, CD43, CD20, CD3, and EBER) are also negative. Furthermore, undifferentiated carcinomas retain nuclear expression for SMARCB1/INI1.

The tumor morphology, particularly the syncytial-like appearance of neoplastic cells, can be reminiscent of germ cell tumors. In fact, 67% of undifferentiated carcinomas expressed the embryonic cell pluripotency transcription factor, SALL4. Although SALL4 is a sensitive immunohistochemical marker for nonteratomatous germ cell tumors, a recent study by Miettinen et al [32] has shown that SALL4 is nonspecific and also expressed in nongerminoma cell tumors. These findings are supported by the absence of staining of additional germ cell markers (Oct-3/4 and CD30) in esophageal undifferentiated carcinomas. Nevertheless, the presence of SALL4 expression in undifferentiated carcinomas is intriguing. One third of the SALL4-positive colorectal adenocarcinomas identified by Miettinen et al had liver metastases. In addition, the authors found the highest frequency of SALL4 positivity among metastatic carcinomas of unknown origin. In a study by Ushiku et al [33], SALL4 was positive in 15% of gastric carcinomas and correlated with synchronous liver metastases. In hepatocellular carcinomas, SALL4 expression is associated with an unfavorable prognosis and overexpression of proliferative- and metastasis-related genes [34,35]. Furthermore, blocking SALL4 function in murine xenograft models inhibits tumor formation [34]. The high proportion of SALL4 positivity and metastases among esophageal undifferentiated carcinomas suggests that SALL4 may play a pivotal role in the pathogenesis of these neoplasms and, thus, a potential therapeutic target.

In summary, esophageal undifferentiated carcinomas are rare neoplasms and often associated with locoregional recurrence and/or distant metastasis. Considering the presence of focal adenocarcinoma, background Barrett esophagus, and the changing epidemiology of esophageal cancer, undifferentiated carcinomas of the esophagus may represent an aggressive histologic variant of esophageal adenocarcinoma. Future investigations aimed at understanding the pathogenesis of esophageal undifferentiated carcinomas will be critical in delineating their origin and designing optimal treatment strategies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1. Grossly, tumors were exophytic with raised edges and centered either in the esophagus or esophagogastric junction. A and C, In most cases, there was a central area of depression and ulceration. B and D, On cross section, the tumors had pushing borders with a smooth demarcation from the surrounding uninvolved esophagus and stomach.

Fig. 2.

At low magnification, undifferentiated carcinomas were characterized by an expansile growth pattern of neoplastic cells organized in solid sheets with little intervening stroma (A, original magnification $\times 40$) and a sharp interface between the tumor and uninvolved parenchyma (B, $\times 100$). C, Patchy tumor necrosis was identified interspersed throughout the neoplasm ($\times 200$). D, The tumor cells were poorly defined with amphophilic cytoplasm imparting a syncytial-like appearance ($\times 400$). E, Lymphovascular and perineural invasion

were frequent findings ($\times 100$). F, In most cases, the background esophageal mucosa was notable for Barrett esophagus ($\times 100$).

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Fig. 3.

A, In 2 cases, the tumor cells adopted a spindle cell morphology with large pleomorphic nuclei ($\times 400$). B, Osteoclast-like, multinucleated giant cells with bland cytologic features were found interspersed among neoplastic cells in 1 case ($\times 400$). C, In another case, the tumor cells had large, paranuclear hyaline inclusions within the cytoplasm imparting a rhabdoid appearance ($\times 400$). D, The presence of focal infiltrating adenocarcinoma ($<5\%$) was found at the periphery of the tumor cell mass in 3 cases ($\times 400$).

Fig. 4. Immunohistochemical analysis of esophageal undifferentiated carcinomas (A, hematoxylin and eosin, $\times 400$) showed diffuse positivity for CAM 5.2 (B, $\times 400$) and patchy positivity for AE1/AE3 (C, $\times 400$), confirming the epithelial nature of these neoplasms. D, In addition, SALL4 expression was identified in 67% of cases ($\times 400$).

Fig. 5. Follow-up radiographic imaging of esophageal undifferentiated carcinomas revealed frequent locoregional recurrences and/or distant metastases. For case 16, no distant metastases were identified on computed tomography imaging at the time of esophagectomy (A); however, within 7 months, a large liver metastasis was identified on follow-up magnetic resonance imaging (B, arrowhead). An initial positron emission tomography scan for case 15 showed no evidence of metastatic disease (C), but 8 months after esophagectomy, multiple organ metastases were identified, as seen here within the upper lumbar spine (D, arrowhead).

Table 1

Clinical characteristics of 16 patients with esophageal undifferentiated carcinoma

Case	Age (y)	Sex	Clinical presentation	Tobacco smoking (>10 pack-years)	Alcohol (>2 per day)	Past medical history of cancer	Family medical history of cancer	Follow-up (mo)
1	64	Male	Surveillance for Barrett esophagus and long-standing history of reflux	Yes	No	Colon cancer	No	Locoregional recurrence and bone metastasis (10); deceased (50)
2	67	Male	2-wk history of chest pain and anemia	Yes	Yes	No	No	Locoregional recurrence (12); deceased (12)
3	81	Male	Surveillance for Barrett esophagus and long-standing history of reflux	No	No	Prostate cancer	No	Liver and bone metastases (3); deceased (4)
4	48	Male	Surveillance for Barrett esophagus and long-standing history of reflux	No	No	No	No	Liver metastasis (7); deceased (9)
5	67	Male	1-mo history of abdominal pain and long-standing reflux	No	Yes	No	No	Locoregional recurrence (7); deceased (12)
6	80	Male	1-wk history of progressive dyspnea and anemia	No	No	Prostate cancer	No	Mesenteric and omental metastases (6); deceased (6)
7	64	Male	2-mo history of dysphagia and weight loss	No	No	No	Father with pancreatic cancer	Deceased (3)
8	77	Male	2-mo history of dysphagia and weight loss	Yes	No	Prostate cancer	No	Deceased (21)
9	69	Male	3-mo history of dysphagia	No	No	No	No	Deceased (1)
10	60	Male	Several weeks history of chest pressure and weight loss	Yes	No	No	No	Not available
11	70	Male	6-mo history of dysphagia	Yes	No	Oral cancer	No	Deceased (5)
12	49	Male	3-mo history of dysphagia	No	No	No	No	Deceased (12)
13	84	Male	Surveillance for Barrett esophagus and long-standing history of reflux	No	No	No	No	Locoregional recurrence (12); deceased (16)
14	55	Male	1-mo history of dysphagia	Yes	No	No	No	Skin metastasis (6); deceased (10)
15	74	Female	1-mo history of dysphagia and weight loss	Yes	No	No	Father with prostate	Lung, liver and bone metastases

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Case	Age (y)	Sex	Clinical presentation	Tobacco smoking (>10 pack-years)	Alcohol (>2 per day)	Past medical history of cancer	Family medical history of cancer	Follow-up (mo)
16	39	Male	1-mo history of dysphagia and long-standing reflux	No	No	No	cancer and mother with colon cancer	(8); deceased (12)
							No	Locoregional recurrence and liver metastasis (2); deceased (5)

Table 2

Pathologic findings for 16 cases of esophageal undifferentiated carcinoma

Case	Size (cm)	Tumor epicenter	Additional histologic findings	Perineural invasion	Angiolymphatic invasion	Lymph node metastases	Background Barrett esophagus	Pathologic stage
1	1.0	Esophagus	Focal glandular morphology	No	Yes	No	Yes	pT1bN0 (stage IB)
2	4.5	Esophagogastric junction	Focal glandular morphology	Yes	Yes	Yes	Yes	pT1bN2 (stage IIIA)
3	4.1	Esophagogastric junction	Spindle cell/sarcomatoid morphology	No	No	No	Yes	pT2N0 (stage IIA)
4	5.5	Esophagogastric junction	None	No	Yes	Yes	Yes	ypT2N1 (stage IIB)
5	3.8	Esophagogastric junction	None	No	Yes	Yes	Yes	pT2N2 (stage IIIA)
6	7.0	Esophagogastric junction	None	No	No	No	No	pT3N0 (stage IIA)
7	8.0	Esophagus	Rhabdoid morphology	Yes	Yes	Yes	No	pT3N1 (stage IIIA)
8	5.5	Esophagogastric junction	None	Yes	Yes	Yes	No	pT3N1 (stage IIIA)
9	3.0	Esophagus	None	Yes	Yes	Yes	No	pT3N1 (stage IIIA)
10	6.0	Esophagus	Focal glandular morphology	Yes	Yes	Yes	Yes	pT3N1 (stage IIIA)
11	3.0	Esophagus	None	No	Yes	Yes	Yes	pT3N1 (stage IIIA)
12	3.6	Esophagus	None	Yes	Yes	Yes	Yes	pT3N1 (stage IIIA)
13	2.0	Esophagus	None	Yes	Yes	Yes	Yes	pT3N1 (stage IIIA)
14	4.0	Esophagogastric junction	None	Yes	Yes	Yes	Yes	pT3N2 (stage IIIB)
15	5.3	Esophagus	Osteoclast-like giant cells	Yes	Yes	Yes	Yes	pT3N3 (stage IIIC)
16	1.1	Esophagus	Spindle cell/sarcomatoid morphology	No	Yes	Yes	Yes	ypT3N3 (stage IIIC)