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A rare rarity: Neuroendocrine tumor of the esophagus

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ABSTRACT

Esophageal Neuroendocrine tumors (NETs) are rare, aggressive and lacking specific symptoms.

This causes a diagnostic delay, worsening the prognosis. Numerous cases are reported in literature, without a consensus on the management. Our aim was to clarify epidemiology, clinical presentation, diagnostic, therapeutic management of esophageal NETs.

Extensive literature search identified a total of 226 articles. One hundred twenty-five articles (n = 1676) met the inclusion criteria, showing that: the incidence of esophageal NET varies geographically; men (60–70 years) are more affected; smoking and alcohol abuse are the major risk factors; dysphagia, weight loss, appetite loss are the most common clinical features. The histotypes include high-grade small and large cell esophageal carcinomas and low-grade carcinoid tumors. Mixed neuroendocrine/non-neuroendocrine neoplasms are the most common. Often the diagnosis occurs randomly on endoscopic examination. Circulating markers, functional combined with conventional imaging contributes to the diagnosis and management. Treatment depends on type, grade and stage of the tumor.

1. Introduction

Gastroenteropancreatic (GEP) neuroendocrine tumors (NETs) are relatively rare, with an incidence in the United States of 3.56 per 100 000 (Dasari et al., 2017; Schizas et al., 2017). Similar trends have also been observed in European countries (Schizas et al., 2017; Hauso et al., 2008)

Esophageal NETs are even rarer and are characterized by aggressive behavior, early dissemination, and poor prognosis if untreated (Pantvaidya et al., 2002; Wu et al., 2004; Estrozi and Bacchi, 2011; Babu Kanakasetty et al., 2016). Given their uncommon occurrence, for many years no systemic description of their clinical features or proposed treatment strategies was available (Chatni et al., 2008). Knowledge of this tumor is in fact based primarily on a number of case reports (Hoang et al., 2002; Chuah et al., 2005). However, more information is now emerging on their epidemiology, clinical features, management, and prognosis (Yun et al., 2007; Huang et al., 2013).

Most studies to date have included only a small number of patients, treated heterogeneously (Wu et al., 2004; Casas et al., 1997; Sun et al., 2007; Li et al., 2010). Three large studies recently described the epidemiology of primary esophageal NETs and proposed treatment strategies (Schizas et al., 2017; Ilett et al., 2015; Guo et al., 2016). Overall, the data suggest that the use of more sophisticated clinical and pathological diagnostic techniques has resulted in more cases diagnosed and hence a gradual rise in the tumor's incidence. A study based on the Netherlands Cancer Registry found a trend of increased incidence of poorly differentiated esophageal neuroendocrine carcinomas (NECs), especially large cell NECs, between the two periods of 19,902,000 and 20,012,010 (Korse et al., 2013).

The probability of encountering this malignancy in a clinical setting is also increasing, probably due to the more widespread diffusion of the World Health Organization (WHO) definition: the site of origin is related to the tumor's clinicopathologic behavior, and NETs should always be considered potentially malignant (Domenico et al., 2017).

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[1] 'NIKE' project (Neuroendocrine tumors Innovation Knowledge and Education) led by Prof Annamaria Colao and Dr Antongiulio Faggiano, aims at increasing the knowledge on NETs

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Despite this, the standard management of esophageal NETs has not yet been established, due to the paucity of available data. Given all the above, there is a need for a more structured body of scientific evidence in this field.

1.1. Aim

The aim of this study was to review the literature on the fundamental aspects of this "rare rarity" in the NET family.

2. Methods

We performed this systemic review according to the Cochrane Collaboration and PRISMA statement.

2.1. Data sources and searches

From May to December 2017 we searched for English-language articles in MEDLINE, EMBASE, Cochrane Library and SCOPUS. Search terms were: neuroendocrine tumor/ NET/ carcinoid/ NEN/ NEC/ MEEC/ MANEC AND esophagus/ esophageal tract/ cardias/ gastrointestinal/ gastroenteropancreatic/ esophageal small cell/ esophageal large cell. We updated the search in January 2018, but no further studies were included.

2.2. Study selection

Eligibility criteria for study selection included: 1) case report; and 2) case series. We selected studies reporting any outcomes: clinical features, diagnostic set-up, histological features, treatment protocols.

We excluded reviews, editorials, commentaries, letters, and meta-analyses.

Four independent reviewers evaluated all selected titles and abstracts, and for articles considered potentially eligible, full text reports were considered. Interobserver agreement was high (98%: 222/226 reports chosen for full text analysis). Where disagreement occurred, a unanimous decision was taken after open discussion. Fig. 1 shows the literature eligibility assessment.

We identified 226 studies as potentially relevant. Of these, 32 were excluded based on title and abstract content and 69/194 were excluded after full text analysis due to: non-English language, non-human studies, not case report articles or case series studies, no outcome of interest. A total of 125 studies were eligible and included in the review (see Table 1).

2.3. Data extraction and quality assessment

Selected trials gave details of 1676 subjects. Four reviewers independently extracted data on sample population (age, gender, clinical status, comorbidities), diagnostic assessment, histological features and treatment approaches. Table 1 summarizes the diagnostic and hystopathological features of selected studies. Two investigators performed quality control checks on extracted data.

2.4. Outcomes

Selected outcomes were: epidemiological data, clinicopathologic features, immunohistochemical findings, diagnostic workup, and treatment of esophageal NETs, as described below.

3. Results

A total of 133 studies (n = 1676) were eligible and included in the review

3.1. Epidemiology

The British pathologist McKeon first described two high-grade oat cell NETs of the esophagus in 1952 (McKeown, 1952). Almost 4000 cases have been reported in the literature since thenceforth (Pantvaidya et al., 2002; Wu et al., 2004; Huang et al., 2013; Ilett et al., 2015; Korse et al., 2013; Bennouna et al., 2000; Beyer et al., 1991; Briggs and Ibrahim, 1983; Chen et al., 2011; Craig et al., 1995; Ding et al., 2013; Doherty et al., 1984; Hou et al., 2013; Huncharek and Muscat, 1995; Kim et al., 2006; Kuo et al., 2011; Lam et al., 2000; Lee et al., 2007; Lu et al., 2013; Medgyesy et al., 2000; Nishimaki et al., 1997; Sorbye et al., 2013; Takubo et al., 1999; Tanaka et al., 2010; Terada, 2013; Wang et al., 2013; Yamaguchi et al., 2014; Yamashita et al., 2009; Yan et al.,

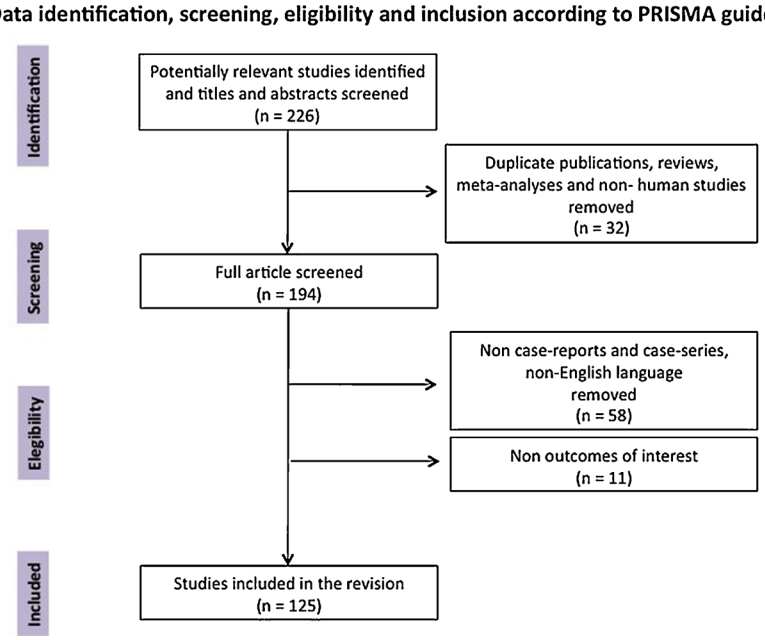

Fig. 1. Study flow diagram.
Records identified through PubMed, EMBASE, Cochrane, Scopus.

Table 1
NET of the esophagus: cases from literature.

Author, year	N° cases M-F	Mean age SD (range)	Imaging	Limited / Extensive	Hystology
(Adachi et al., 2014)	1 (M)	62	Endoscopy	LD	SqCC + SCEC
(Akagi et al., 2014)	1 (M)	76	Ba examination, endoscopy, CT	ED	SCEC
(Ando et al., 2011)	1 (M)	54	Ba examination, endoscopy, CT	ED	SCEC
(Atsumi et al., 2010)	11 (4 F;7 M)	69 (44-77)	Biopsy	LD (9),ED (2)	SCEC
(Babich et al., 2010)	1 (F)	58	Endoscopy + endoscopic US	LD	Esophagel carcinoid
(Basu and Nair, 2005)	2 (F)	63 & 65	CT + EUS + PET-CT	ED	SCEC
(Bennouna et al., 2000)	10 (3 F;7 M)	62 (48-73)	Esophagoscopy, endoscopy, biopsy	LD (4),ED (6)	SCEC
(Beyer et al., 1991)	11 (3 F;8 M)	(50-88)	Esophagography, CT	ED	SCEC
(Bibeau et al., 2008)	1 (M)	54	Endoscopic US + CT	ED	MANEC
(Briggs and Ibrahim, 1983)	23 (15 F;8 M)	58 (45-77)	NA	LD (7), ED (13), NA (3)	Oat cell carcinoma
(Brown et al., 1994)	1 (F)	30	Ba examination, endoscopy, CT	LD	Carcinoid tumor
(Chuah et al., 2005)	13	NA	Endoscopy	ED	SCEC
(Caldwell et al., 1991)	11	NA	NA	ED	Oat cell carcinoma
(Cary et al., 1993)	1 (M)	57	Ba examination, endoscopy, CT	LD	MANEC
(Chatni et al., 2008)	1 (M)	72	Endoscopy, CT	ED	SCEC
(Chen et al., 2007)	1 (M)	73	Endoscopy, CT, bronchoscopy	ED	Atypical carcinoid
(Chen et al., 2011)	40 (14 F;26 M)	57 (39-77)	Ba examination, abdominal US,biopsy	LD	SCEC
(Chen et al., 2014a)	44 (11 F;33 M)	NA	NA	LD (34),ED (10)	SCEC
(Chen et al., 2014b)	211(47 F; 166 M)	NA	NA	LD (148),ED (63)	SCEC
(Chin et al., 2008)	12 (1 F;11 M)	53-77	CT	LD	SCEC
(Chino et al., 2015)	1 (F)	57	Ba examination, endoscopy, CT	ED	SCEC
(Chong et al., 1979)	1 (M)	55	X-Ray, endoscopy	LD	MANEC
(Chow et al., 2001)	5(1 F;4 M)	40-70	NA	LD	SCEC
(Clark et al., 1996)	1 (F)	66	Endoscopy,CT	ED	SCEC
(Craig et al., 1995)	16 (6 F;11 M)	60 (39-72)	CT	ED	SCEC
(Cox et al., 1989)	1 (F)	60	Endoscopy, cranial CT and MRI	ED	SCEC
(Deepak et al., 2011)	1 (M)	61	Endoscopy, CT	ED	SCEC
(Ding et al., 2013)	106 (42 F;64 M)	NA	CT, endoscopic US	LD	SCEC
(Doherty et al., 1984)	6 (4 F;2 M)	(69-83)	Ba examination, endoscopy, biopsy, chest X-ray, bronchoscopy	LD (3),ED (3)	Oat cell carcinoma
(Eccles et al., 1989)	3 (2 F;1 M)	(38-70)	Endoscopy, bronhoscopy, liver US	LD (1),ED (2)	SCEC
(Egashira et al., 2017)	14	NA	NA	ED	NEC
(Fattahi Masoum et al., 2015)	1(F)	54	NA	NA	SCEC
(Feng et al., 2014)	6 (1 F; 5 M)	61-74	CT (1), MRI (5)	ED	SCEC
(Fenlon et al., 1995)	4 (3 F; 1 M)	49-75	Chest X-ray, bronchoscopy, Ba examination, endoscopy, CT	ED	SCEC
(Fukuchi M et al., 2015)	1 (M)	65	Incidental CEA high level, endoscopy, CT	ED	LCEC EG-junction
(Funakoshi et al., 2013)	1(M)	66	Ba examination, endoscopy, CT, PET-CT	ED	SCEC
(Gao et al., 2014)	8 (2 F;6 M)	59.5 (44-74)	Endoscopy	LD (4),ED (4)	SCEC
(Gonzalez et al., 2003)	1 (M)	75	Endoscopy	ED	Collision tumor (adenocarcinoma + oat cell carcinoma)
(Goscinski et al., 2015)	25 (13 F;12 M)	(<50 - >60)	Unknown	LD (3),ED (22)	SCEC
(Goto et al., 2007)	1 (M)	63	Abdominal and chest CT,endoscopy	ED	SCEC
(Gumprich et al., 2004)	1 (M)	62	NA	NA	Well-low differentiated NEC
(Hoang et al., 2002)	4	63 (48-82)	NA	LD	Carcinoid (2), carcinoid + adenocarcinoma (2)
(Horai et al., 1978)	7	NA	NA	NA	SCEC
(Hosokawa et al., 2005)	14 (M)	63 (37-71)	Esophagography, endoscopy, biopsy, abdominal CT, chest X-ray	LD (3),ED (11)	SCEC
(Hosseini et al., 2015)	22 (15 F;7 M)	61	NA	LD (14),ED (8)	SCEC
(Hou et al., 2013)	141	NA	Endoscopy	NA	SCEC
(Hsu et al., 2008)	1(M)	66	Upper GIendoscopy, biopsy, CT	NA	SCNECEG-junction
(Huang et al., 2013)	42	NA	Endoscopy, CT	ED	SCEC
(Huang et al., 2015)	1(F)	48	Endoscopy, PET-CT	ED	SCEC
(Hudson et al., 2007)	16	NA	Endoscopy, CT, US, CT bone scan	ED	SCEC
(Huncharek and Muscat, 1995)	13 (2 F;11 M)	(51-78)	Ba examination, endoscopy, biopsy, bronchoscopy, CT	LD (8),ED (5)	SCEC
(Imai et al., 1978)	1 (M)	62	Rx	ED	Oat cell carcinoma
(Isoyama et al., 2010)	3	NA	NA	LD	SCEC
(Johnson et al., 1984)	1(F)	66	Esophagography, CT, endoscopy biopsy	ED	SCEC
(Kadhim et al., 2016)	1 (M)	68	Endoscopy	ED	MANEC

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Table 1 (*continued*)

Author, year	N° cases M-F	Mean age SD (range)	Imaging	Limited / Extensive	Hystology
(Babu Kanakasetty et al., 2016)	43	NA	Endoscopy, CT	LD	NEN
(Kanno et al., 2007)	1 (F)	60	Endoscopy	ED	SCEC
(Kim et al., 2006)	1	NA	Endoscopy, CT, PET-CT	LD	NEC
(Kitajima et al., 2013)	1(M)	64	Endoscopy	LD	MANEC
(Kuriry and Swied, 2015)	1	NA	Endoscopy, CT, PET-CT	ED	High-grade large cell NET
(Kuo et al., 2011)	16 (2 F;14 M)	(34-83)	Esophagography, endoscopy biopsy, chest and abdomen CT	LD (8),ED (8)	SCEC
(Lam et al., 2000)	20 (6 F;14 M)	(40-84)	NA	LD (2),ED (18)	SCEC
(Law et al., 1994)	1 (F)	66	Endoscopy, biopsy	ED	SCEC
(Lee et al., 2007)	16	NA	Endoscpic US	LD	SCEC
(Lee et al., 2014)	20	NA	Endoscopic biopsy (17)	ED	NET (3), MANEC (2), poorly differentiated NEC (10)
(Lu et al., 2013)	11(2 F;9 M)	61 ± 12.9	Endoscopy	ED	SqCC + SCEC
(Lichtenstein et al., 2011)	1 (F)	59	Endoscopy	ED	SCEC
(Lim et al., 2013)	26 (5 F;21 M)	60.12 ± 9.3 (45-76)	Endoscopy	LD	Carcinoid tumor
(Linan Padilla et al., 2007)	1(M)	66	Endoscopy, TC, US	LD	SCEC
(Madroszyk et al., 2001)	3	NA	NA	ED	SCEC
(Makino et al., 2002)	1 (M)	63	Endoscopy, CT	ED	SCEC
(Matsuda et al., 2014)	1	NA	Endoscopy, CT, RMN	ED	NET
(Matsunaga et al., 2012)	1 (M)	73	NA	LD	SCEC
(Matsuoka et al., 2005)	1	NA	Endoscopy, CT	ED	SCEC
(McCullen et al., 1994)	1 (F)	44	Endoscopy, CT	ED	SCEC
(Medgyesy et al., 2000)	8 (2 F;6 M)	64 (29-88)	Endoscopy, biopsy + chest CT (4)bronchoscopy (4)	LD (6) ED (2)	SCEC
(Mimori et al., 1995)	2 (1 F; 1 M)	63 ± 5.65	Endoscopy, CT	ED	SCEC
(Muguruma et al., 2013)	1 (F)	61	Endoscopy, CT	ED	SCEC
(Mulder et al., 1991)	1	NA	Endoscopy, CT	ED	SCEC
(Nayal et al., 2015)	11(2 F;9 M)	60.5 ± 9.9	Endoscopy	ED	SCC/adjacent squamous dysplasia-carcinoma
(Nevarez et al., 2011)	1 (M)	76	Endoscopy, CT, PET-CT, US	LD	SCEC
(Nichols and Kelsen, 1989)	11	NA	Ba examination, endoscopy, TC, chest X-ray	ED	SCEC
(Nishimaki et al., 1997)	13	63.5 (50-78)	Endoscopy, US, CT	ED	SCEC
(Ohmura et al., 1997)	1	NA	NA	ED	SCEC
(Partensky et al., 1993)	1 (M)	64	CT, US	ED	Carcinoid
(Purdy and Gaffney, 1986)	1	NA	TC, chest X-ray	NA	MANEC
(Rosenthal and Lemkin, 1983)	1 (F)	74	NA	ED	SCEC
(Sabanathan et al., 1986)	3 (F)	69 ± 12.23	Ba examination, X-ray, endoscopy	ED	SCEC
(Sadanaga et al., 2009)	12 (3 F;9 M)	65 (53-82)	NA	ED	SCEC
(Saif and Vethody, 2016)	1 (M)	38	CT, PET-CT, endoscopy	ED	SCEC
(Schuerle et al., 2013)	1(M)	79	Endoscopy, biopsy, whole body CT	ED	SCEC
(Shimoda et al., 2006)	1(F)	63	Esophagography, endoscopy, biopsy, CT, increased pro-GRP	ED	SCEC
(Shinohara et al., 2014)	1(F)	84	Esophagography, endoscopy, biopsy	LD	SCEC
(Shirafuji et al., 2012)	1(F)	63	Abdominal CT, increased pro-GRP & NSE, biopsy of abdominallymph node	ED	SCEC
(Siegal et al., 1991)	1	76	NA	ED	Carcinoid tumor
(Sorbye et al., 2013)	12	NA	NA	NA	SCEC (9)
(Takubo et al., 1999)	21 (15 F;6 M)	48-89	NA	LD (5),ED (16)	12 MANEC,9 SCEC
(Tanabe et al., 1987)	1 (M)	68	Esophagography, endoscopy, biopsy, CT	LD	SCEC
(Tanaka et al., 2010)	7 (2 F-5 M)	61-73	Chest X-ray, Ba examination,endoscopy, bronchoscopy, CT, PET-CT	4 LD,3 ED	SCEC
(Terada, 2013)	6 (M)	73 (62-81)	NA	NA	SCEC (5),MANEC (1)
(Tetreault et al., 1999)	1(M)	48	Whole body, CT, endoscopy, biopsy	LD	SCEC
(Thapa et al., 2017)	1	NA	SSTR, PET-FDG	ED	Intermediate NET
(Tustumi et al., 2017)	14 (11 F; 3 M)	67.3 (47-80)	NA	LD (1),ED (12),Unknown(1)	Mixed (5),Pure SCEC (6),Pure LCEC (2),Carcinoid (1)
(Usami et al., 2010)	2 (M)	52-54	Endoscopy + CT	ED	SCEC
(Veits et al., 2013)	1(M)	68	Endoscopy	LD	MANECEG-junction
(Vos et al., 2011)	24 (15 F;9 M)	65 (59-69)	NA	LD (4),ED (20)	Pure SCEC (13),MANEC (11)
(Walker et al., 1989)	2(F;1 M)	61-66	Esophagography, endoscopy, biopsy, abdominal US, CT	LD (1),ED (1)	SCEC

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Table 1 (*continued*)

Author, year	N° cases M-F	Mean age SD (range)	Imaging	Limited / Extensive	Hystology
(Wang et al., 2013)	76 (16 F;60 M)	61 (41-84)	NA	LD	SCEC (61),MANEC (15)
(Watson et al., 1985)	1(F)	50	Scarica art	idem	MANEC
Wilson et al., 2000(Wilson et al., 2000)	1 (M)	51	CT, endoscopy, biopsy	LD	SCEC
(Wu et al., 2004)	9 (3 F; 6 M)	56 (45-66)	Ba examination,endoscopy, chest X-ray, liver US	LD	SCEC
(Xie et al., 2015)	73 (23 F-50 M)	65 (42-79)	Esophagography,endoscopy,biopsy, US, CT	LD	SCEC
(Yachida et al., 2001)	1(M)	77	Endoscopy, thoracoabdominal CT	ED	SCEC
(Yagi et al., 2015)	1(F)	43	Endoscopy for screening, endoscopic US, CT	LD	Esophageal NET
(Yamaguchi et al., 2014)	85	NA	NA	NA	SCEC, MANEC, NEC
(Yamamoto et al., 2007)	1(F)	77	Endoscopy	ED	Pleomorphic giant cell carcinoma + SCEC
(Yamashita et al., 2009)	9(3 F; 6 M)	63 (54-68)	Endoscopy,CT,PET-CT	LD (2),ED (7)	SCEC
Yan et al., 2014(Yan et al., 2014)	82 (29 F;53 M)	(38-82)	Ba examination, endoscopy, CT	LD (36),ED (46)	SCEC
(Yang et al., 2014)	1(F)	65	Endoscopy, chest CT	ED	Collision tumor: SCEC + SqCC
(Yazici et al., 2015)	1(F)	65	Esophagogastroscopy	Unknown	Collision tumor
(Yau et al., 2007)	10 (4 F;6 M)	69 (55-86)	Chest X-ray, esophagoscopy, bronchoscopy, thoracicand abdominal CT,pulmonary FT	LD (4),ED (6)	SCEC
(Yekeler et al., 2012)	1(F)	46	Chest CT, endoscopy	ED	SCEC
(Yun et al., 2007)	21 (5 F;16 M)	54 (38-76)	Ba examination, endoscopy,biopsy, abdomen US, chest X-ray or CT	LD (5),ED (13),Unknown (3)	SCEC (19),MANEC (2)
(Zhang et al., 2014)	38 (7 F;31 M)	61.3 (42-76)	NA	LD (3),ED (35)	SCEC
(Zhu et al., 2014)	64 (18 F;46 M)	58 (43-76)	Chest X-ray, Ba examination, endoscopic US, CT,brain MRI, bone CT, PET-CT	LD (11),ED (53)	SCEC (56),MANEC (8)

We reported case report and case series studies excluding the revisions of literature and meta-analayses.
Number of patients is in brackets. Ba: Barium; CEA: carcinoembryonic antigen; CT: computed tomography; EG: esophagogastric; F: female; FT: function test; GI: gastrointestinal; LCEC: large cell neuroendocrine carcinoma; M: male; MANEC: mixed adeno(neuro)endocrine carcinomas; NA: not applicable; NET: neuroendocrine tumor; NEC: neuroendocrine carcinoma NSE: neuron specific enolase; PET-CT: positron emission tomography- computed tomography; pro-GRP: pro-gastrin-releasing peptide; SCEC: small cell esophageal carcinoma; SCNEC: small cell neuroendocrine carcinoma; SqCC: squamous cell carcinoma;US: ultrasound; yrs: years.

2014; Yau et al., 2007; Reyes et al., 1980; Tennvall et al., 1990; Galanis et al., 1997; Poynton et al., 1997; Mitani et al., 2000; Cheuk et al., 2001; Nemoto et al., 2002; Osugi et al., 2002; Noguchi et al., 2003; Rosa et al., 2004; Lepage et al., 2007; Koide et al., 2007; Ku et al., 2008; Lv et al., 2008; Maru et al., 2008; Brennan et al., 2010; Nakajima et al., 2012; Kukar et al., 2013; Meng et al., 2013; Mori et al., 1989).

Its incidence among all esophageal malignancies is generally reported as between 0.4% and 2% (Babu Kanakasetty et al., 2016; Egashira et al., 2017), even if some small studies have reported incidences as low as 0.05% and as high as 7.6% (Pantvaidya et al., 2002; Wu et al., 2004; Yun et al., 2007; Bennouna et al., 2000; Maru et al., 2008; P. Gastrointestinal Pathology Study Group of Korean Society of et al., 2012; Lee et al., 2014; Nayal et al., 2015; Al Mansoor et al., 2013). The reported incidence varies geographically: 0.5–5.9% of all esophageal cancers in China, 1–2.8% in Westerners, and 0.8–2.8% in Japan (Huang et al., 2013). A 2005 nationwide Japanese survey estimated that the frequency of NETs ranges from 0.05% to 7.6% of all esophageal cancers (Briggs and Ibrahim, 1983; Doherty et al., 1984; Huncharek and Muscat, 1995; Law et al., 1994). Overall, its prevalence among gastrointestinal NETs is estimated at approximately 0.04–4.6% (Babu Kanakasetty et al., 2016; Yun et al., 2007).

Small cell esophageal carcinomas (SCECs), the most frequent histological finding in esophageal NETs, account for fewer than 1% of all malignant neoplasms (Chen et al., 2014a), 0.6–2.8% of all esophageal tumors (Chuah et al., 2005; Chen et al., 2014b; Lu et al., 2013) and 0.04–4.6% of all gastrointestinal NETs (Yang et al., 2014; Iwasa et al., 2010). Its incidence is highest in southeast Asian countries (Japan, Korea, and China) (Casas et al., 1997; Briggs and Ibrahim, 1983).

3.2. Clinical features

The initial symptoms of esophageal NET are similar to those of the more common histological forms, but are usually more aggressive. Table 2 summarized sympthomatological features described in case reports and case series of esophageal NET analyzed.

Dysphagia is the most common clinical feature, followed by weight and/or appetite loss. Retrosternal and epigastric pains, odynophagia, dysphonia, dyspnea, and digestive bleeding (hematemesis and melena) have also been described, though they are less frequent (Pantvaidya et al., 2002; Babu Kanakasetty et al., 2016; Yun et al., 2007; Huang et al., 2013; Bennouna et al., 2000; Beyer et al., 1991; Briggs and Ibrahim, 1983; Ku et al., 2008; Maru et al., 2008; Brennan et al., 2010; Mori et al., 1989). Some patients also experienced recurrent left laryngeal nerve injury and vocal cord paralysis. A small fraction has no symptoms and the diagnosis is incidental, usually upon endoscopic examination.

The symptoms generally arise 1–12 months before diagnosis. In the Al Mansoor meta-analysis the time to diagnosis was 4 weeks in 27 patients, 8–32 weeks in 65 patients and more than 32 weeks in 11 patients (Al Mansoor et al., 2013). Early diagnosis is difficult due to the late onset, absence or non-specificity of the symptoms. However, given the aggressiveness of the disease, the time to diagnosis is lower than that for other histological types (Bennouna et al., 2000).

Initial symptoms are sometimes related to metastatic sites (Maru et al., 2008). Given its low degree of differentiation, carcinoid syndrome is rarely described in esophageal NET. Lee et al. reported only one patient (3.8%) presenting hot flushes (Lee et al., 2014).

Table 2
Symptomathological features in NET of the esophagus. Data from cases in literature.

Symptoms	N° cases	References
Dysphagia	562	(Wu et al., 2004; Babu Kanakasetty et al., 2016; Chatni et al., 2008; Yun et al., 2007; Huang et al., 2013; Ilett et al., 2015; Schizas et al., 2017; Ando et al., 2011; Basu and Nair, 2005; Bennouna et al., 2000; Briggs and Ibrahim, 1983; Caldwell et al., 1991; Chen et al., 2007, 2011; Chong et al., 1979; Craig et al., 1995; Deepak et al., 2011; Pantvaidya et al., 2002; Eccles et al., 1989; Fattahi Masoum et al., 2015; Fenlon et al., 1995; Gonzalez et al., 2003; Hosokawa et al., 2005; Hsu et al., 2008; Huang et al., 2015; Huncharek and Muscat, 1995; Imai et al., 1978; Johnson et al., 1984; Kanno et al., 2007; Kim et al., 2006; Kuriry and Swied, 2015; Lam et al., 2000; Law et al., 1994; Lee et al., 2007, 2014; Lichtenstein et al., 2011; Linan Padilla et al., 2007; Makino et al., 2002; Matsuda et al., 2014; Matsuoka et al., 2005; McCullen et al., 1994; Medgyesy et al., 2000; Muguruma et al., 2013; Hauso et al., 2008; Purdy and Gaffney, 1986; Sadanaga et al., 2009; Schuerle et al., 2013; Terada, 2013; Tustumi et al., 2017; Usami et al., 2010; Veits et al., 2013; Vos et al., 2011; Wilson et al., 2000; Yachida et al., 2001; Yagi et al., 2015; Yamamoto et al., 2007; Yamashita et al., 2009; Yang et al., 2014; Yazici et al., 2015; Yau et al., 2007; Zhu et al., 2014)
Weight loss	234	(Wu et al., 2004; Babu Kanakasetty et al., 2016; Ando et al., 2011; Bennouna et al., 2000; Briggs and Ibrahim, 1983; Chen et al., 2007, 2014a; Clark et al., 1996; Doherty et al., 1984; Fattahi Masoum et al., 2015; Fenlon et al., 1995; Gonzalez et al., 2003; Johnson et al., 1984; Kuo et al., 2011; Lee et al., 2014; McCullen et al., 1994; Medgyesy et al., 2000; Tustumi et al., 2017; Vos et al., 2011; Walker et al., 1989; Wang et al., 2013)
Pain:	190	(Babu Kanakasetty et al., 2016; Yun et al., 2007; Chen et al., 2014a; Fenlon et al., 1995; Lam et al., 2000;
Retrosternal	115	Law et al., 1994; McCullen et al., 1994; Sabanathan et al., 1986; Vos et al., 2011; Wilson et al., 2000;
Epigastric	66	Yekeler et al., 2012)
Abdominal (distension and/or pain)	28	(Briggs and Ibrahim, 1983; Brown et al., 1994; Hosokawa et al., 2005; Huncharek and Muscat, 1995; Kuo
Chest	27	et al., 2011; Lee et al., 2007; Lichtenstein et al., 2011; Matsuda et al., 2014)
Odynophagia	13	(Chatni et al., 2008; Tetreault et al., 1999; Zhu et al., 2014)
Jaundice abdominal	1	(Wu et al., 2004; Goto et al., 2007; Huncharek and Muscat, 1995; Johnson et al., 1984; Lee et al., 2007;
Postprandial		Medgyesy et al., 2000)
		(Beyer et al., 1991; Kuo et al., 2011)
		(Ilett et al., 2015)
		(Kadhim et al., 2016)
Hoarseness	67	(Fenlon et al., 1995; Wang et al., 2013; Yamamoto et al., 2007; Zhu et al., 2014)
Reflux	59	(Bibeau et al., 2008; Briggs and Ibrahim, 1983; Cary et al., 1993; Doherty et al., 1984; Gonzalez et al., 2003; Wang et al., 2013; Huang et al., 2013)
GI bleeding	58	(Ilett et al., 2015; Wang et al., 2013)
Loss of appetite	46	(Babu Kanakasetty et al., 2016; Goto et al., 2007; Tanabe et al., 1987)
Carcinoid syndrome	44	(Babu Kanakasetty et al., 2016; Lee et al., 2014)
Hiccup	26	(Kuo et al., 2011)
Others: Weakness, Back fullness, Neck and axillary mass, Hematemesis, Shortness of breath, Anorexia, Dysphonia, Comatose state, Hemiplegia, Loss of consciousness, Dry cough/ Coughin spasm, Foreign body sensation, Headache, Vomiting, Heartburn, Epatic discomfort, Malaise, Melena, Barrett's esophagus, Diplopia, Esophagitis, Hypercalcemia (-> acute pancreatitis), Nausea, Pain in the neck, Paraneoplastic syndrome (sensorimotor neuropathy & anti-Hu-associated encephalomyelitis), SIADH, Sweating, Sweilling of multiple joints, Tarry stools, Vertigo, WDHA	≤ 20	(Ando et al., 2011; Babich et al., 2010; Bennouna et al., 2000; Beyer et al., 1991; Bibeau et al., 2008; Cary et al., 1993; Clark et al., 1996; Cox et al., 1989; Doherty et al., 1984; Fattahi Masoum et al., 2015; Feng et al., 2014; Fenlon et al., 1995; Fukuchi M et al., 2015; Gonzalez et al., 2003; Hsu et al., 2008; Huang et al., 2015; Kadhim et al., 2016; Kanno et al., 2007; Kuo et al., 2011; Lam et al., 2000; Law et al., 1994; Lee et al., 2014; Lim et al., 2013; Linan Padilla et al., 2007; McCullen et al., 1994; Mimori et al., 1995; Muguruma et al., 2013; Kadhim et al., 2016; Purdy and Gaffney, 1986; Saif and Vethody, 2016; Schuerle et al., 2013; Shimoda et al., 2006; Shinohara et al., 2014; Shirafuji et al., 2012; Tanabe et al., 1987; Terada, 2013; Usami et al., 2010; Watson et al., 1985; Yekeler et al., 2012)

GI: gastrointestinal; SIADH: Inappropriate secretion of anti diuretic hormone (ADH) syndrome; WDHA: watery diarrhea-hypokalemia-achlorhydria.

Paraneoplastic syndromes are reported more frequently. One case of ectopic secretion of vasoactive intestinal peptide causing watery diarrhea-hypokalemia-achlorhydria (WDHA) syndrome was described in a 50-year-old woman with esophageal mixed cell carcinoma (Watson et al., 1985). Inappropriate anti-diuretic hormone secretion and WDHA syndrome have also been reported (Saif and Vethody, 2016).

In many studies, all esophageal NETs were high grade (Pantvaidya et al., 2002; Yun et al., 2007; Ku et al., 2008; Maru et al., 2008), for this reason, at presentation metastases are found in 31–90% of cases (Bennouna et al., 2000). Lymph node metastases are common (Briggs and Ibrahim, 1983; Egashira et al., 2017; Kukar et al., 2013). Distant metastases are most often located in the liver, lungs and bone (Pantvaidya et al., 2002; Kuo et al., 2011; Vos et al., 2011; Wang et al., 2013; Koide et al., 2007). Brain metastases are relatively rare, compared to SCLC, 1.6% of all metastases (Ilett et al., 2015; Vos et al., 2011; Yau et al., 2007; Maru et al., 2008). Data pertaining to prognostic factors are unclear. While some studies found mixed esophageal NECs tended toward a better outcome than pure esophageal NECs without non-neuroendocrine components (Maru et al. 2008), this was not observed in other studies (Babu Kanakasetty et al., 2016; Takubo et al., 1999). Prognostic factors affecting survival are generally age (Nemoto et al., 2002), the extent of the disease (Ku et al., 2008; Maru et al., 2008), tumor-node-metastasis (TNM) classification (Wang et al., 2013) and local treatment versus local plus systemic treatment (Yun et al., 2007; Chen et al., 2014a; Ding et al., 2013) or chemotherapy (Chen et al., 2014b; Poynton et al., 1997; Lv et al., 2008).

Circulating NSE may also be predictive of survival (Yan et al. 2013): patients with NSE ≤ 17 ng/mL had a median survival of 18 months, while those with NSE > 17 ng/mL had a median survival of just 6 months. Leucine-rich repeating-containing G-protein coupled receptor 5 (LGR5) over expression was correlated to lymph node metastasis, tumor stage and response to chemotherapy, also showing a trend of poorer survival in comparison to patients with low LGR5 expression (Chen et al., 2014a).

3.3. Histopathological characteristics

The histological grading system of the 2010 WHO classification for digestive system NETs divides esophageal NETs into low-grade (G1, Ki67 < 3%), intermediate-grade (G2, Ki67 3–20%) NET, and high-

grade (G3, Ki67 > 20%) NECs, large- or small-cell type (Schizas et al., 2017; Funakoshi et al., 2013), mixed exocrine-endocrine carcinomas (MEECs), and mixed adeno(neuro)endocrine carcinomas (MANECs) (Schizas et al., 2017). These last two types are also called mixed neuroendocrine/non-neuroendocrine neoplasms (MiNETs). Mitotic rate is classified as G1 (<2/10 HPF), G2 (2–20/10 HPF), and G3 (>20/10 HPF); esophageal and cardial NETs are usually grade G3 (Bai et al., 2017).

MEECs and MANECs are distinguished from carcinomas with focal neuroendocrine differentiation by at least two major diagnostic criteria: (1) the extension of each component to at least 30%; (2) the detection of structural features of neuroendocrine components such as well-differentiated organoid, solid, or diffuse growth elements (Kitajima et al., 2013). A morphological classification has been proposed for these carcinomas that includes: (a) truly composite (or mixed) exocrine-endocrine tumors with both elements in more or less equal proportions, (b) amphicrine tumors with dual differentiation within the same cell, (c) collision tumors, in which two components are closely juxtaposed but not admixed (Lewin et al., 1987).

Primary esophageal NETs include SCEC, LCEC, atypical carcinoid tumor, typical carcinoid tumor, and combined endocrine tumor and adenocarcinoma (Hoang et al., 2002; Chuah et al., 2005). Fig. 2 showed the histopathological features of a case of poorly differentiated neuroendocrine carcinoma of the esophagus, large cell type.

Asterisk: Esophageal mucosa

SCECs are mainly located in the lower (48–56% of cases) or middle (40–45.5%) third of the esophagus. They are rarely found in the upper esophagus (5% of cases) (Medgyesy et al., 2000). This finding reflects the esophageal distribution of neuroendocrine cells (Pantvaidya et al., 2002; Babu Kanakasetty et al., 2016; Yun et al., 2007; Ilett et al., 2015; Bennouna et al., 2000; Beyer et al., 1991; Briggs and Ibrahim, 1983; Egashira et al., 2017; Hou et al., 2013; Lam et al., 2000; Lu et al., 2013; Vos et al., 2011; Zhu et al., 2014; Koide et al., 2007; Nakajima et al., 2012; Meng et al., 2013; Mori et al., 1989).

SCEC may consist of malignant cells in broad sheets, solid nests, or ribbon-like strands, and tend to involve the submucosa and deeper layers. Their cells may be small, spindle-like, round or ovoid, with features including scanty cytoplasm with few ribosomes, rough endoplasmic reticulum, occasional mitochondria, indistinct cell borders, hyperchromatic oval and polygonal nuclei with dense peripheral chromatin and a small inconspicuous or absent nucleolus (Chen et al., 2014a; Mori et al., 1989; Kim et al., 2016). The cell membranes are closely packed with a few narrow junctions. There may be necrosis in the central area. Lymphatic and blood vessel invasion by the tumor cells is common.

Esophageal NEC is a poorly differentiated, high-grade malignant neoplasm comprising small or intermediate-to-large cells with marked nuclear atypia, multifocal necrosis and a high number of mitoses (>20 per 10 high-power fields). Mixed esophageal NECs are more frequent than pure NECs (Babu Kanakasetty et al., 2016; Maru et al., 2008).

Immunohistochemistry staining for chromogranin A (CgA), synaptophysin and neuron-specific enolase (NSE) is usually positive with NETs, with synaptophysin proving the most sensitive marker. SCECs are often CgA-, synaptophysin- and NSE-positive (Osugi et al., 2002). The Ki-67 index is >20% (Morita et al., 2016). Immunohistochemical staining for neuronal cell adhesion molecules (CD56), thyroid transcription factor-1 (TTF-1), cytokeration 34bE12 (CK34bE12), cytokeratin (AE1/AE3), and cytokeratin 10/13 should also be performed (Lu et al., 2010). Bombesin and CD57 have been proposed as NE markers in these tumors (Noguchi et al., 2003).

On gross examination, esophageal NEC may present in different ways with relatively prominent features, including as a submucosal polypoid infiltrative growth usually covered by normal epithelium, or as an ulcerating hard tumor mass on the mucosal surface of the esophagus. Microscopically, the neuroendocrine cells present nested and trabecular growth with peripheral palisading and rosette formation in the tumors. A high frequency of venous, lymphatic and perineural invasion is also seen (Huang et al., 2013; Sadanaga et al., 2009).

Based on histopathological features, SCEC were divided into three subgroups: (1) oat cell carcinoma; (2) small cell carcinoma of intermediate type, composed of small malignant cells with nuclear characteristics similar to oat cell carcinoma, but with more abundant cytoplasm, and (3) small cell carcinoma combined with squamous and/or glandular components (Tennvall et al., 1990). On a molecular level, phosphatase and tensin homolog (PTEN) mutations have been reported in both SCEC and esophageal squamous cell carcinoma. Moreover, SCEC and esophageal squamous cell carcinoma show an overexpression of p53 (Li et al., 2010; Lam et al., 2000; Takubo et al., 1999; Terada, 2013), p16 (Li et al., 2010) and c-kit (Kim et al., 2006).

The areas of squamous differentiation may be immunohistochemically positive for keratins: CK5/6, CK8, and CK20 (Mori et al., 1989; Kim et al., 2016). The tumor cells may show a positive staining for ACTH and calcitonin, at least in some areas. All these data confirm that positive staining for neuroendocrine markers is mandatory for diagnosis of large and small cell esophageal NEC (Ilett et al., 2015; Funakoshi et al., 2013).

According to the Veterans' Administration Lung Study Group (VALSG), NECs can be categorized in two groups, limited disease (LD) and extensive disease (ED). For simplification, esophageal NECs may be diagnosed according to the TNM staging system of the 7th UICC-AJCC classification for esophageal carcinomas (see "Diagnosis" and "Treatment" below).

3.4. Diagnosis

Esophageal NETs are typically a random finding on endoscopic examination, developing in the lower third of the esophagus. They generally occur as a single lesion, but sometimes as an ulcerated or fungating mass, and deeply infiltrate the esophageal wall (Maru et al., 2008). Early diagnosis is therefore difficult and, as noted, they are usually found by chance (Hudson et al., 2007). A few patients may have systemic syndromes with abnormal hormone production, such as excessive secretion of antidiuretic hormone or ACTH, as reported above (see "Clinical Features" and "Histopathological Characteristics"). In the case of bigger tumors and more extensive disease, the most common initial symptoms are progressive dysphagia, anorexia, retrosternal and painful swallowing, hematemesis, hoarse voice and weight loss (Lu et al., 2013) (see Table 2).

Histological diagnosis is established by esophagogastroduodenoscopy (EGD) and biopsy with immunohistochemical and histochemical staining for common neuroendocrine markers, including neuron-specific enolase (NSE), synaptophysin, chromogranin A (CgA), CK (cytokeratin), and CD56 (lymphocyte antigen 56) (Hudson et al., 2007; Lu et al., 2013; Kukar et al., 2013). The evaluation of NE tumor markers should include CEA, NSE, SCC, CgA, and pro-gastrin releasing peptide (pro-GRP) (Egashira et al., 2017).

Imaging plays a pivotal role in the management of esophageal NETs by delineating the anatomic extent of the tumor. On barium esophagography, NETs present as bulky polypoid tumors that expand the esophageal lumen, sometimes associated with ulcerative, varicoid, or infiltrative growth pattern. Subsequently, EGD depicts the primary tumor mainly as a single elevated polypoid or nodular lesion.

Workup for evaluation and staging of potential regional or distant lymph node metastasis or adjacent organ invasion is mainly performed using contrast-enhanced multiphase CT. ^{18}F-fluoro-deoxy-glucose (FDG)PET/CT has been proposed for the staging and detection of any recurrence, as esophageal NET often behaves as an aggressive tumor with a propensity to metastasize extensively, mainly to the liver, lymph nodes, and bone marrow. Finally, endoscopic ultrasound remains the most useful technique for determining the extent of esophageal wall invasion and lymph node malignancy. Functional imaging such as 111In-pentetreotide (OctreoScan) or 123I-metaiodobenzylguanidine

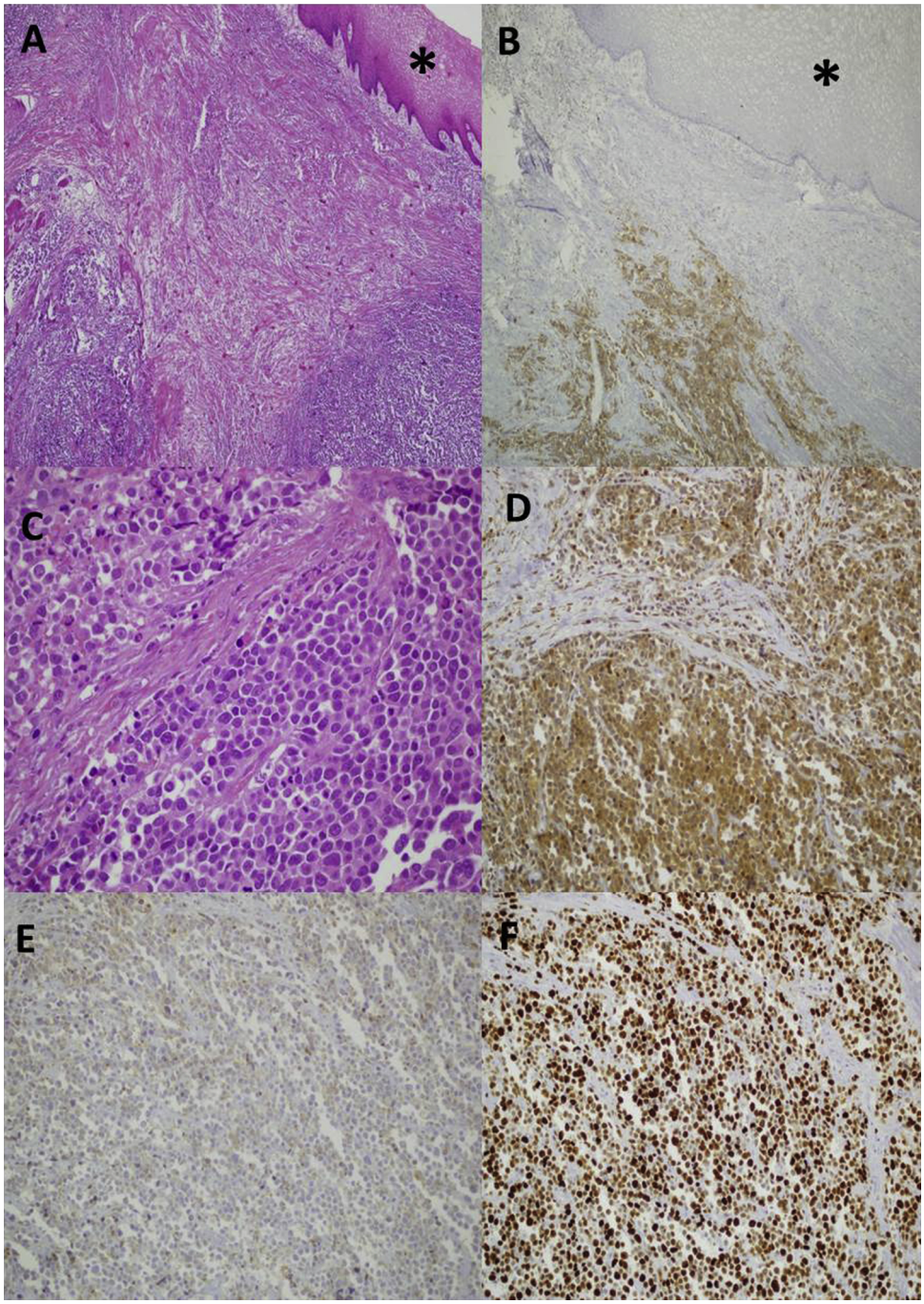

Fig. 2. Photomicrograph of poorly differentiated neuroendocrine carcinoma of the esophagus, large cell type, infiltrating the esophageal wall and undermining the esophageal mucosa. A) Haematoxylin and Eosin, x4 magnification; B) Synaptophysin, x10 magnification; C) Haematoxylin and Eosin, x40 magnification; D) Synaptophysin, x20 magnification; E) Chromogranin, x20 magnification; F) Ki67, x20 magnification.

(MIBG) may also contribute to the diagnosis and management of esophageal NETs, particularly in combination with CT or MRI findings (Schizas et al., 2017).

In all patients with more aggressive disease, calcium, phosphate, and alkaline phosphatase levels should be evaluated with whole-body PET to exclude bone metastases. Unless clinically indicated, brain magnetic resonance imaging (MRI) and radioactive isotope bone scans are not routinely performed (Craig et al., 1995; Kuo et al., 2011; Medgyesy et al., 2000).

According to the VALSG, patients with esophageal NETs are staged as LD when the lesions are confined to the esophagus and adjacent organs with or without lymph node involvement and as ED when they have spread beyond locoregional boundaries.

3.5. Treatment

The treatment of esophageal NETs is strictly dependent on their type (SCEC or LCEC), grade (G1, G2 or G3) and stage (LD, ED, or TNM classification). Due to their extreme rarity, the most effective therapeutic algorithm has not been established, even though the histological and clinical similarity of esophageal and lung NETs has led many researchers to recommend the use of similar therapeutic protocols, including chemotherapy, radiotherapy and surgery (Casas et al., 1997; Ilett et al., 2015; McFadden et al., 1989). In any case, monotherapy is not always sufficient: a multidisciplinary approach is more adequate.

Well-differentiated esophageal NETs (G1 and G2) should be treated surgically or, for inoperable or metastatic tumors, with somatostatin

analogs (Schizas et al., 2017; Babu Kanakasetty et al., 2016; Delle Fave et al., 2012). Different treatments have been evaluated for poorly differentiated esophageal NETs in an attempt to improve survival rates (Ding et al., 2013; Lu et al., 2013; Koide et al., 2007).

3.5.1. Surgery

Surgery generally consists of minimally invasive transhiatal esophagectomy; unlike classic transhiatal esofagectomy, this does not involve radical lymph node dissection, to reduce the risk of pulmonary complications. The minimally invasive procedure is recommended for early cancers in the middle (below the level of carina) and lower (type I and II esophagogastric junction tumors) third of the esophagus. However, it may also be feasible in upper esophageal carcinomas in some cases. It is also performed for advanced esophageal cancers in patients who are not fit to undergo a thoracotomy (Pisarska et al., 2017).

Transthoracic esophagectomy is also widely used. It has the advantage of a more extensive resection and may be associated with a longer disease-free survival than the transhiatal approach (Omloo et al., 2007). However, it has a profound effect on short- and long-term health-related quality of life, with the postoperative recovery period potentially taking more than half or even all the patient's remaining life expectancy. In patients who had undergone esophagectomy, quality of life was worse at 6 weeks than it had been preoperatively, and most quality of life indicators improved to their preoperative level only after 9 months (Scarpa et al., 2011; Darling, 2013).

3.5.2. Chemotherapy

Chemotherapy is the mainstay treatment for SCEC due to the frequent dissemination of these tumors at diagnosis and recurrence at distant sites. According to some reports, it is superior to surgery alone (Nichols and Kelsen, 1989; Isolauri et al., 1991). Table 3 shows chemotherapy schedule used in the selected studies.

Given its histological indistinguishability from SCLC, a platinum-based chemotherapy regimen has also been suggested for SCEC (Kelsen et al., 1980; Noda et al., 2002). The combinations of cisplatin plus irinotecan or etoposide are both active against SCEC, with an acceptable toxicity profile. However, irinotecan/cisplatin was associated with a higher median survival time than etoposide/cisplatin (12.8 months vs. 9.4 months, respectively) in patients with SCLC (Chin et al., 2008; Noda et al., 2002; Endo et al., 2005).

Other chemotherapy regimens including the combination of cyclophosphamide, vincristine, mitomycin and etoposide, of cyclophosphamide, doxorubicin and cisplatin, of carboplatin and etoposide, and of cisplatin and 5-fluorouracil are reported as successful adjuvant therapies (Chen et al., 2011; Meng et al., 2013; Tao et al., 2015). First-line treatment with a docetaxel-based regimen was also demonstrated to achieve a complete response in patients with ED (Chen et al., 2014b), while amrubicin was reported to be effective as second-line chemotherapy (Nagasaki et al., 2013).

3.5.3. Radiotherapy

Radiotherapy alone has been considered as a treatment for SCEC (Hudson et al., 2007), but with disappointing results in terms of survival (Doherty et al., 1984; Huncharek and Muscat, 1995; Medgyesy et al., 2000), notably when compared to chemotherapy alone (5 vs. 24 months, respectively) (Nemoto et al., 2002). The optimal radiation dose for SCEC-LD has not been established. In the treatment of SCLC, loco-regional recurrence is observed in approximately half of the patients receiving <50 Gy (Hazuka and Turrisi, 1993). For squamous cell esophageal cancer, a dose of 66 Gy in 2 Gy fractions is well tolerated, albeit associated with 64% of loco-regional recurrence in 64% and distant metastases in 46% of cases at 2 years (Wu et al., 2004). A dose of >60 Gy in SCEC was associated with a low rate of loco-regional recurrence, ranging from 14%–22% (Atsumi et al., 2010; Bennouna et al., 2000; Yamashita et al., 2009). However, loco-regional recurrence was also reported when radiotherapy was not used, although the rate was not specified (Chen et al., 2014b).

In any case, the optimal radiotherapy technique has not been established. Image-guided therapy for esophageal cancer improves target positioning and reduces errors (Hawkins et al., 2011), especially when used daily (Han et al., 2012), while radiotherapy plan optimization improves dose distributions to the tumor and normal tissue (Wills et al., 2009). In addition, arc radiation therapy (Martin et al., 2011) and tomotherapy (Nguyen et al., 2011) may reduce cardiopulmonary toxicities, while brachytherapy improves outcomes and quality of life in squamous esophageal cancers (Rosenblatt et al., 2010; Muijs et al., 2012). Peptide receptor radionuclide therapy with 177Lu-DOTATATE provided a 100% response and improvement in symptoms in a patient with esophageal NET (Thapa et al., 2017), even if, further studies are required to better evaluate its efficacy.

3.5.4. Combined therapies

The combination of local and systemic treatments (surgery plus chemotherapy and/or radiotherapy or chemoradiotherapy without surgery) has been widely reported in patients with SCEC (-LD and –ED), for the association with an improved median survival time in comparison with local treatments alone (surgery and/or radiotherapy) (Ding et al., 2013; Hou et al., 2013; Zhu et al., 2014).

A possible treatment algorithm for esophageal NECs, depending on the stage was postulated. For stage I/IIA, surgery was postulated for its effective in comparison to radiotherapy (29 months vs. 17 months). The median survival time of patients who received surgery alone was similar to those who received surgery and adjuvant chemotherapy. In stage IIB/III, chemotherapy improved median survival time compared to those who not received it (13 vs. 6.1 months). In stage IV, patients who received chemotherapy and radiotherapy had an improved median survival time over those treated with chemotherapy alone (13.2 vs. 8.9 months) (Chen et al., 2014b).

3.5.5. Survival time

Few cases of LCEC have been reported (Huang et al., 2013). No significant differences have been reported in survival rates between SCEC and LCEC treated in the same way (Maru et al., 2008).

The median survival time for SCEC-LD can reach 20 months (Ding et al., 2013; Doherty et al., 1984; Hou et al., 2013; Huncharek and Muscat, 1995), but for ED, the median survival time is just 6–12 months (Babu Kanakasetty et al., 2016). However, survival time cannot always be established clearly, as whether it is from diagnosis or from the start of treatment is often not specified (Bennouna et al., 2000; Beyer et al., 1991).

Survival time is affected by prognostic factors such as age (Nemoto et al., 2002), limited or extensive disease (Ku et al., 2008; Lv et al., 2008; Maru et al., 2008), stage (Wang et al., 2013), type of treatment (Chen et al., 2014b; Poynton et al., 1997; Al Mansoor et al., 2013) and biochemical parameters (s-NSE and Lgr5) (Chen et al., 2014b; Yan et al., 2014).

4. Discussion

Our systemic review of literature clarified the main aspects of esophageal NET, from epidemiology, to clinical presentation, to histopathology, to diagnostic and therapeutic management.

Esophageal NETs are a rare form in the already rare group of NETs. Information on the epidemiology of this rare disease is contradictory and partly unclear. In a recent case series study and literature review, Tutsumi et al. reported that of 2957 patients, 98% had SCEC (77% in Eastern countries; 23% in Western countries), 1.18% had large cell neuroendocrine carcinoma (LCEC) (6% in Eastern countries; 94% in Western countries) and 0.82% had carcinoid tumors (54% in Eastern countries; 43% in Western countries) (Tustumi et al., 2017). From the literature data as a whole, it can be seen that pure esophageal NETs are

Table 3
Chemotherapuetic schedules in esophageal NET. Data from cases in literature.

CHT principal schedules	Related schedules	References
Cisplatin, etoposide * † ° • +	Cisplatin, etoposide ± doxorubicin (or epirubicin), cyclophosphamide; Cisplatin, etoposide, 5 FU *; Cisplatin, etoposide -> cyclophosphamide, doxorubicin, vincristine °; Cisplatin, etoposide-> cyclopsphamide-> cytoxan, cisplatinum, carmustine •; Irinotecan/Cisplatin -> Etoposide/Cisplatin, -> Docetaxel -> Titanium silicate 1,-2; Etoposide +5 FU, cisplatin •	(Akagi et al., 2014; Atsumi et al., 2010; Chen et al., 2011; Clark et al., 1996; Ding et al., 2013; Fattahi Masoum et al., 2015; Feng et al., 2014; Hsu et al., 2008; Huncharek and Muscat, 1995; Kuo et al., 2011; Lee et al., 2014; Lu et al., 2013; Madroszyk et al., 2001; Nichols and Kelsen, 1989; Ohmura et al., 1997; Saif and Vethody, 2016; Shimoda et al., 2006; Tanaka et al., 2010; Tustumi et al., 2017; Vos et al., 2011; Xie et al., 2015; Yamaguchi et al., 2014; Yamashita et al., 2009; Yan et al., 2014; Yazici et al., 2015; Yau et al., 2007; Zhu et al., 2014) (Bennouna et al., 2000; Hosokawa et al., 2005; Medgyesy et al., 2000; Tetreault et al., 1999)
Carboplatin, etoposide * ° • †	Carboplatin, etopostide, irinotecan *; Topotecan -> carboplatin and etoposide •	(Atsumi et al., 2010; Linan Padilla et al., 2007; Makino et al., 2002; Vos et al., 2011; Yamaguchi et al., 2014; Zhu et al., 2014; Hosokawa et al., 2005; Schuerle et al., 2013)
Cisplatin, irinotecan * ° † •	Cisplatin, irinotecan first-line & amrubicin second-line *	(Ando et al., 2011; Atsumi et al., 2010; Feng et al., 2014; Hosokawa et al., 2005; Tustumi et al., 2017; Usami et al., 2010; Yamaguchi et al., 2014; Funakoshi et al., 2013)
Cisplatin, 5 FU * ° † •	Cisplatin, 5 FU -> irinotecan-> gemcitabine -> paclitaxel°;Cisplain, 5 FU, leucovorin °• †; 5-FU + cisplatin + bleomycin†; Cisplatin, 5 FU-> irinotecan,cisplatin°; 5 FU and nedaplatin + etoposide and cisplatin *	(Atsumi et al., 2010; Bibeau et al., 2008; Ding et al., 2013; Gao et al., 2014; Huncharek and Muscat, 1995; Usami et al., 2010; Yamamoto et al., 2007; Yekeler et al., 2012) (Wu et al., 2004; Estrozi and Bacchi, 2011; Matsuoka et al., 2005)
Cisplatin * °		(Huncharek and Muscat, 1995; Song et al., 2009)
Cyclophosphamide, etoposide* ° †	Cyclophosphamide, etoposide -> carboplatin + etoposide°; Cyclophosphamide, etoposide, vincirstine, doxorubicin†; Cyclophosphamide, etoposide, vincristine, 5 FU, lomustine*; Cyclophosphamide, cysplatin, vincristine, 5 FU°; Cyclophosphamide, etoposide, doxorubicin*°; Cyclophosphamide, adriamycin/epirubicin, vincas/etoposide; Cyclopsphamide, adriamycin, etoposide °; Cyclophosphamide, cisplatin, etoposide*; Cyclophosphamide, vincristine,doxorubicin, methotrexate, etoposide•; Cyclophosphamide, vincristine,doxorubicin, etoposide† Cyclophosphamide, etoposide, vincristine, mitomycin* ° Cisplatin, cyclophosphamide, doxorubicin * ° Cyclophosphamide, adriamycin, vincrisinte † Cyclophosphamide,vincristine ° + etoposide or doxorubicin* ° † or doxorubicin, cysplatin • Cyclophosphamide, vincirstine, doxorubicin, cysplatin * -> etoposide, carboplatin, melphalan •	(Clark et al., 1996; Eccles et al., 1989; Huncharek and Muscat, 1995; Matsunaga et al., 2012; McCullen et al., 1994; Medgyesy et al., 2000; Vos et al., 2011; Walker et al., 1989; Yau et al., 2007) (Bennouna et al., 2000; Caldwell et al., 1991; Chen et al., 2007, 2011; Huncharek and Muscat, 1995; Johnson et al., 1984; Matsunaga et al., 2012; McCullen et al., 1994; Medgyesy et al., 2000; Nichols and Kelsen, 1989; Rosenthal and Lemkin, 1983; Vos et al., 2011; Walker et al., 1989; Xie et al., 2015; Yau et al., 2007)
Etoposide * •		(Gao et al., 2014; Hosokawa et al., 2005)
Cisplatin, paclitaxel ° • †		(Chen et al., 2011)
Bleomycin ° •		(Imai et al., 1978; Sadanaga et al., 2009)
Docetaxel, oxaliplatin •		(Lu et al., 2013)

* alone; ° in association with radiotherapy; † in association with radiotherapy and surgery; • in association with surgery; + in association with Lanreotide. CHT. Chemotherapy; 5 FU: 5fluoruracile; UFT: tegafur/uracil.

even rarer, accounting for just 0.03% of esophageal cancers in one case study (Babu Kanakasetty et al., 2016).

Gender analysis of esophageal NETs revealed their predominance in men in their 60 s and 70s (Ilett et al., 2015; Guo et al., 2016). Two literature reviews established a male-to-female ratio of 1.6:1 (Casas et al., 1997; Bennouna et al., 2000), whereas recent investigations showed a male-to-female ratio of 2.6:1 (Wang et al., 2011; Song et al., 2009).

In a recent meta-analysis of the international literature, which investigated all eligible cases in relation to several clinical features including sex and age, 192 of 291 patients (61.3%) were male and 99 (31.6%) were female, with a male-to-female ratio of 1.94:1 (Al Mansoor et al., 2013). In a review of studies with more than 15 cases the male-to-female ratio ranged from 1.5:1 to 7:1 (Babu Kanakasetty et al., 2016). Few studies reported a predominance in women (Briggs and Ibrahim, 1983; Craig et al., 1995; Brennan et al., 2010)). It has been suggested that the predominance in men is due to the greater prevalence of risk factors (Al Mansoor et al., 2013). In both sexes, the median age was 60 years, with a reported age range of 31–89 years (Al Mansoor et al., 2013).

The risk factors for esophageal NEC seem to be those also typical of small cell lung carcinoma (SCLC), namely smoking and alcohol (Lam et al., 2000; Ku et al., 2008; Brennan et al., 2010; Ilett et al., 2015; Wang et al., 2013; Zhu et al., 2014; Al Mansoor et al., 2013). However, due to its rarity, it is difficult to establish a causal link between the suspected risk factors and esophageal NEC. In the Al Mansoor et al. study, of 99 patients with known risk factors, 82 had a history of smoking and/or alcohol abuse (30 smoking, 2 alcohol, 50 smoking and alcohol) and 3 of achalasia. Only 14 patients had no risk factors (Al Mansoor et al., 2013). Some patients had a history of Barrett's esophagus (Bennouna et al., 2000) and gastroesophageal reflux disease (Maru et al., 2008). Dietary factors including spicy food, overeating and fast food have been included among the risk factors, in common with esophageal squamous cell carcinoma (Zhu et al., 2014; Lu et al., 2010).

Esophageal NET can arise as part of MEN1 and MEN2 familial cancer syndrome, von Hippel-Lindau disease, type 1 neurofibromatosis (Recklinghausen disease) and tuberous sclerosis. Hypertrophic osteoarthropathy, consisting of proliferative periostitis of the tibia and fibula, was the initial symptom in a 38-year-old man with esophageal NEC (Saif and Vethody, 2016). Interestingly, treatments for esophageal NET resolved symptoms (Saif and Vethody, 2016; Watson et al., 1985).

For than that concerns histopathology, in a large review of GEP-NETs, Ilett and coauthors showed that many cases of esophageal NET were mixed NETs comprising neuroendocrine and non-neuroendocrine (adenocarcinoma or squamous cell carcinoma) components (Ilett et al., 2015).

Most esophageal NECs are SCECs (Pantvaidya et al., 2002; Wu et al., 2004; Babu Kanakasetty et al., 2016; Huang et al., 2013; Atsumi et al., 2010; Bennouna et al., 2000; Beyer et al., 1991; Briggs and Ibrahim, 1983; Chen et al., 2011; Chin et al., 2008; Craig et al., 1995; Ding et al., 2013; Doherty et al., 1984; Hosokawa et al., 2005; Hou et al., 2013; Huncharek and Muscat, 1995; Kim et al., 2006; Lam et al., 2000; Lu et al., 2013; Medgyesy et al., 2000; Nishimaki et al., 1997; Sadanaga et al., 2009; Takubo et al., 1999; Tanaka et al., 2010; Terada, 2013; Vos et al., 2011; Wang et al., 2013; Yamashita et al., 2009; Yau et al., 2007; Zhang et al., 2014; Tennvall et al., 1990; Galanis et al., 1997; Poynton et al., 1997; Mitani et al., 2000; Cheuk et al., 2001; Nemoto et al., 2002; Osugi et al., 2002; Noguchi et al., 2003; Lepage et al., 2007; Koide et al., 2007; Ku et al., 2008; Lv et al., 2008; Brennan et al., 2010; Nakajima et al., 2012; Meng et al., 2013; Grossman et al., 2011). In a Chinese study, the only statistically significant difference seen between SCEC and LCEC was age, with LCEC being found in older patients (Huang et al., 2013). This finding was supported by other authors, who also found no significant difference in survival between the two (Maru et al., 2008).

Of 2957 patients with esophageal NET evaluated in a recent review, only 23 patients had carcinoid tumors, 35 had LCEC and the vast majority (2899) had SCEC (Tustumi et al., 2017). In an American surgical study, patients with esophageal NET had the greatest proportion of high-grade tumors (92% vs. 8%) of the various primary sites studied. Compared to ileal NET, primary esophageal NETs were much more likely to be high grade (OR = 317) (Fitzgerald et al., 2017).

Conversion from esophageal squamous cell carcinoma to NEC has been reported in recurrent lesions after chemo- and radiotherapy (Morita et al., 2016). NE differentiation has also been observed in basaloid squamous carcinomas and adenocarcinomas (Cho et al., 2000; Wang et al., 2006).

The cellular origins of this tumor are debated. Two hypotheses are postulated: derivation from Merkel cells (Kim et al., 2006) and from Kulchitsky cells, or amine precursor uptake and decarboxylation (APUD) cells of neuroectodermal derivation in esophageal mucosa (Wu et al., 2004; Vos et al., 2011; Al Mansoor et al., 2013). Small and large cell NECs originate from endodermal pluripotential basal epithelial stem cells, the common precursor which usually differentiates into squamous cell carcinoma and sometimes into adenocarcinoma or small cell carcinoma (Pantvaidya et al., 2002; Wu et al., 2004; Li et al., 2010; Beyer et al., 1991; Briggs and Ibrahim, 1983; Chin et al., 2008; Craig et al., 1995; Hou et al., 2013; Lu et al., 2013; Takubo et al., 1999; Terada, 2013; Vos et al., 2011; Wang et al., 2013; Reyes et al., 1980; Tennvall et al., 1990; Mitani et al., 2000; Cheuk et al., 2001; Ku et al., 2008; Mori et al., 1989). The small cells retain their potential for further differentiation into mucin-producing or keratin-forming cells. This observation could explain the coexistence of SCECs and large cell NECs with adenocarcinoma and/or squamous cell carcinoma in the same lesion with “mixed” histology (Zhu et al., 2014).

Tateishi et al. (1976) discussed the histogenesis of SCEC from argyrophil (APUD) cells normally found among the basal cells of the covering epithelium. This hypothesis is supported by other authors, who postulated the derivation of this tumor from APUD cells (Imai et al., 1978; Rosen et al., 1975).

The treatment also offers many insights. The surgical treatment of SCEC has produced discordant results. Some studies report on long-term survival after surgery alone. In a series by Law et al., one patient with SCEC survived more than 5 years after surgery alone (Law et al., 1994), while Nishimaki et al. reported 2 patients with 106 and 64 months of survival after esophagectomy alone (Nishimaki et al., 1997). Tanaka et al. reported a survival time of 16 and 45 months for 2 patients treated with transthoracic esophagectomy (Tanaka et al., 2010). Interesting data on surgical treatment are also provided by Sun et al., who reported a 5-year survival rate of 18.2% in patients with stage I/II SCEC (Sun et al., 2007). Similarly, Chen et al. reported an improved survival in patients with stage I/II SCEC treated by surgery, compared with patients treated by other means (29 months vs. 17.4 months) (Chen et al., 2014a). Mitani et al. reported on 2 patients who survived 7 and 9 years after subtotal esophagectomy of mixed esophageal NECs, although adjuvant chemotherapy was added in the second case (Mitani et al., 2000).

A large retrospective analysis from the SEER database evaluated 387 patients with SCEC and 138 with LD. Patients treated by surgery had a better median survival time than those treated with radiotherapy (17 vs. 7 months) (Kukar et al., 2013). A retrospective analysis by Hou et al. showed a similar survival time for surgery alone (18 months) compared to surgery plus chemotherapy (15 months) and chemotherapy plus radiotherapy (17.1 months). Whereas, multidisciplinary modalities (surgery combined with chemotherapy and radiotherapy) achieved encouraging long-term survival (25 months; 5-year survival rates: 38.9%) in patients with resectable LD of SCEC (Hou et al., 2013).

Other studies did not find surgery beneficial for SCEC, with Lv et al. finding that surgical treatment was associated with a worse median survival time than chemotherapy alone (Lv et al., 2008).

Yamashita et al. reported a median survival time of 10.8 months and a 3-year overall survival rate of 55.6% in 9 patients with SCEC-LD treated with concurrent cisplatin/etoposide chemotherapy and radiotherapy (Yamashita et al., 2009). In a series reported by Ku et al., 11 of 14 patients with LD and 5 of 8 with ED were treated with a platinum and etoposide combination, with a median survival time of 22.3 and 8.5 months respectively. However, 2 of 8 patients with ED treated with cisplatin and irinotecan experienced progression and cisplatin/etoposide was prescribed as second-line treatment, with consequent remission (Ku et al., 2008). The combination of cisplatin and irinotecan was demonstrated to be effective for both LD and ED (Chin et al., 2008).

In a quite recent report by Nakajima et al., 7 of 8 patients with ED were treated with cisplatin/ irinotecan, with a median survival of 13.9 months (Nakajima et al., 2012). Similarly, Okuma et al. reported a median overall survival of 12.6 months for first line treatment with irinotecan/cisplatin in patients with SCEC-ED (Okuma et al., 2014).

Chemotherapy alone is active in both pure and mixed SCEC. In a meta-analysis by Raja et al., chemotherapy alone was associated with a better survival rate than surgery or radiotherapy alone. Survival was further improved by combining chemotherapy with surgery or radiotherapy (Raja et al., 2013). Similar results were reported by another meta-analysis by Al Mansoor et al., who showed that combined local plus systemic treatment led to an improvement in median survival time compared to local treatment (surgery or radiotherapy) (14.2 vs. 7.4 months, respectively) (Al Mansoor et al., 2013).

Yau et al. reported a survival of 4–62 months in patients with LD and 2–10 months in patients with ED treated with chemotherapy plus radiotherapy (Yau et al., 2007). In another series of 16 patients, of whom 5 with LD, treated by chemotherapy and subsequent radiotherapy a median survival time of 24.4 months was reported (Hudson et al., 2007). Similarly, Atsumi et al. reported 1-year and 3-year overall survival rates of 63% and 24% respectively after chemoradiotherapy in patients with LD (Atsumi et al., 2010). Interestingly, the concurrent administration of chemotherapy plus radiotherapy seems more effective than sequential treatment in terms of median survival time (Vos et al., 2011; Yamashita et al., 2009; Nakajima et al., 2012; Takada et al., 2002).

In patients with LD, surgery plus postoperative chemotherapy and surgery plus radiotherapy have also been evaluated in comparison with surgery alone, with surgery plus postoperative chemotherapy giving a better median survival time (Chen et al., 2011; Craig et al., 1995). Another study found that chemoradiotherapy was associated with a higher overall survival than surgery plus chemotherapy or surgery plus radiotherapy (Meng et al., 2013). Babu Kanakasetty et al. reported on 43 patients with pure esophageal NETs, 7 with NET-G2 and 36 with NEC-G3. Patients at stage II and III were treated by surgery alone when lymph nodes were negative, or with chemoradiotherapy when lymph

nodes were positive or in the presence of extratumoral extension, with a median overall survival of 18.5 months. Patients with locally advanced inoperable disease or distant metastases were treated by chemotherapy (G3) or octreotide long-acting release (LAR) (G2) (Babu Kanakasetty et al., 2016).

These review showed that knowledge of this disease is growing, and there is an increasing need for a systemic approach. Structured reporting of these rare tumors in a separate registry will enable an understanding of the tumor biology and the optimization of a targeted treatment strategy. In this view, future perspectives can enclose diagnostic and treatment aspects: (i) to better understand esophageal NET behavior, microsatellite instability has been investigated with specific tissue analysis and immunohistochemistry for mismatch repair proteins (MLH1, MSH2, MSH6 and PMS2) demonstrating a distinct molecular profile with a better prognosis (Sahnane et al., 2015). Further biomolecular analyses are needed to identify genomic predictor of prognosis and of clinical response to DNA-damaging treatment, as proposed by Zhou and colleagues (Zhou et al., 2015). (ii) High telomerase proliferative activity has been demonstrated in patients with SCEC (Chow et al., 2001). The inhibition of this activity has been shown to induce cell death and for this reason, a telomerase-based therapy may be considered as a future option treatment for SCEC. Other treatment approaches could target the interaction with the miR 224/PCSK9/glucocorticoid axis, which has been demonstrated to be involved in cell apoptosis, proliferation and invasion in pancreatic NETs (Bai et al., 2017).

5. Conclusions

Our results suggests that esophageal NETs deserve to be suspected mainly in men, but also in women, aged between 60 and 70 years, with smoking and/or alcohol abuse history, who have a symptomatology characterized by dysphagia, weight loss and/or appetite loss. The histotypes of esophageal NETs include a variety of possibilities and grade, even if the most common findings are the mixed neuroendocrine/non-neuroendocrine neoplasms. Esophageal NETs are typically a random finding on endoscopic examination, diagnosed through biopsy. Circulating markers should include CEA, NSE, SCC, CgA, and pro-GRP. Functional imaging combined with conventional CT or MRI contributes to the diagnosis and management.

Treatment approaches including surgery, chemotherapy, radiotherapy strictly depend on type, grade and stage of the tumor. The future perspectives in this area are to obtain a shared opinion on the management of these “rare NETs” and to orient the research in order to identify predictor of prognosis and of clinical response and target therapies, aiming to precision medicine also in this research field.

Declaration of interest

All authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Financial disclosure statement

None.

Author contributions

E.G., V.G., F.R. and F.D.C. selected the issue, researched studies from databases and independently extracted data on sample population (age, gender, clinical status, comorbidities), diagnostic assessment, histological features and treatment approaches. E.G. and A.F. performed quality control checks on extracted data. A.M.C. verified the analytic method and supervised the planned systemic review of literature. F.G. conceived Fig. 2 extracting images from her analysis of a case. E.G., V.G., F.R. F.D.C. and A.F. contributed to the final version of the manuscript.

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