ORIGINAL ARTICLE

AG-2021-136
doi.org/10.1590/S0004-2803.202200001-10

The prognosis of the different esophageal neuroendocrine carcinoma subtypes: a population-based study

Francisco **TUSTUMI**[1,2,3], Stefanie Sophie Buuck **MARQUES**[4], Esau Furini **BARROS**[4], Alexandre Cruz **HENRIQUES**[4], Jaques **WAISBERG**[4] and André Roncon **DIAS**[1]

Received: 29 June 2021
Accepted: 30 September 2021

ABSTRACT – Background – Neuroendocrine neoplasms are extremely rare and account for 0.4% to 2% of all malignant esophageal neoplasms. The burden of the neuroendocrine histological type on the patients' prognosis and survival is poorly debated. This study aimed to compare the survival rates of primary neuroendocrine neoplasms compared with adenocarcinoma and squamous cell carcinoma of the esophagus. **Methods –** This is a retrospective cohort from the Surveillance, Epidemiology, and End Results Program database. Overall survival and cancer-specific survival were evaluated with Kaplan-Meier curves and logrank tests. Proportional Cox regression models were used to evaluate variables related to overall survival. **Results –** After eligibility criteria, 66,528 patients were selected. The mean follow-up was 22.6 months (SD 35.6). Adenocarcinoma was predominant (62%), followed by squamous cell carcinoma (36%). Large cell carcinoma, small cell carcinoma, and mixed adenoneuroendocrine carcinoma each account for less than 1% each. On the long-term overall survival analysis, esophageal adenocarcinoma showed a better prognosis than all the other histologic types (*P*-value for logrank test <0.001). With adenocarcinoma as a reference, HR was 1.32 for large cell carcinoma (95%CI 1.2 to 1.45) and 1.37 for small cell carcinoma (95%CI 1.23 to 1.53). The HR was 1.22 for squamous cell carcinoma (95%CI: 1.2 to 1.24); and 1.3 for adenoneuroendocrine carcinoma (95%CI 1.01 to 1.66). For multivariate Cox regression analysis, besides age and stage, the neuroendocrine subtypes large cell carcinoma and small cell carcinoma were considered independent prognostic variables. **Conclusion –** In the esophagus, large cell carcinoma and small cell carcinoma show poorer long-term survival rates than squamous cell carcinoma and adenocarcinoma.

Keywords – Neuroendocrine tumors; neuroendocrine carcinoma; esophageal neoplasms.

INTRODUCTION

Adenocarcinoma and esophageal squamous cell carcinoma (ESCC) comprise 98% of the esophageal cancers histological types[1]. Neuroendocrine neoplasms (NENs) are extremely rare[2] and account for 0.4% to 2% of all malignant esophageal neoplasms[3-6]. These tumors are epithelial neoplasms with predominant neuroendocrine differentiation[3]. They originated from the peripheral neuroendocrine cell system[3]. Gastrointestinal NENs have shown an increased incidence rate over the last decades[7], but NENs are still far more common in the lungs[8], and a significant part of the knowledge of the disease, its presentation, classification, and therapeutic options are based on those utilized for neuroendocrine lung tumors[9].

The World Health Organization (WHO) 2019 classification[10] categorized in well-differentiated neuroendocrine tumors (NETs) and poorly differentiated neuroendocrine carcinomas (NECs). NETs can be subdivided into grades (G1, G2, and G3), according to the WHO grading system (G3 is defined as having a mitotic rate higher than 20/2 mm^2 or Ki67 higher than 20%)[10]. NECs are all considered high grades and can be subdivided into large-cell type (LCNEC) and small-cell type (SCNEC), according to the nucleus-cytoplasm ratio, and other variables such as cell shape, chromatin, nucleoli[11] besides, there are the mixed neoplasms, such as the mixed adenoneuroendocrine carcinomas (MANECs)[10].

In the esophageal neoplasms, the burden of the neuroendocrine histological type on the patients' prognosis and survival is poorly debated. This study aimed to compare the survival rates of primary esophageal NECs compared with adenocarcinoma and squamous cell carcinoma of the esophagus.

METHODS

Data source and studied population

This is a retrospective cohort from the Surveillance, Epidemiology, and End Results Program (SEER) database. Data were collected from 2000 to 2018. SEER database covers over one-third of the USA population. Patients submitted to esophagectomy were included. The specialized database "Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat database: incidence – SEER research data, 18 registries, Nov 2020 Sub (2000–2018) – linked to county attributes – time dependent (1990–2018) income/rurality, 1969–2019 counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2021, based on the

Declared conflict of interest of all authors: none
Disclosure of funding: no funding received
[1] Universidade de São Paulo, São Paulo, SP, Brasil. [2] Hospital Israelita Albert Einstein, São Paulo, SP, Brasil. [3] Centro Universitário Lusíada, Santos, SP, Brasil. [4] Faculdade de Medicina do ABC, Santo André, SP, Brasil.
Corresponding author: Francisco Tustumi. E-mail: franciscotustumi@gmail.com

November 2020 submission". Was applied to extract data using the SEER*Stat Software, version 8.3.5 (released on 6 March 2018). The staging was based on the SEER Summary Stage 2000, classifying the disease as localized (cancer does not extend beyond the primary organ); regional (cancer extends to adjacent organs, regional lymph nodes, or both); and distant (cancer with distant dissemination).

These data are publicly available, and we obtained access to the SEER data by signing the SEER Research Data Agreement. Consequently, local Ethics Committee waived informed consent. The study followed the Ethical Standards of the Brazilian Association of Research Companies (resolution 466/2012).

Data extraction

The following data were collected: 1) age; 2) sex; 3) follow-up; 4) overall and cancer-specific survival; 5) grade of cellular differentiation; and 6) histology. Only adenocarcinoma, ESCC, LCNEC, SCNEC, and MANEC were included. Esophageal carcinomas or neuroendocrine tumors with no information of the subtype of the tumor were excluded.

Statistical analysis

The statistical analysis was performed using STATA 16.1 software (StataCorp, College Station, Texas). A 95% confidence interval (95%CI) was adopted. Categorical variables were expressed as absolute numbers or percentages, and differences between groups were evaluated with the Person chi-squared test. Overall survival and cancer-specific survival were evaluated with Kaplan-Meier curves and logrank test. Proportional Cox regression models were used to evaluate variables related to overall survival. Hazard ratios (HRs) and their corresponding lower and upper 95%CI limits were informed for each independent variable. Only the preoperative clinical and histopathological data with *P*-value <0.05 in the univariate analysis were incorporated in the multivariate analysis.

RESULTS

Baseline characteristics

After applying inclusion criteria, 73,456 patients were selected. After excluding patients with no information regarding neuroendocrine subtype, carcinoma with no specification of the neuroendocrine subtype, and patients with no survival data, 66,528 patients were included (see flow diagram in FIGURE 1).

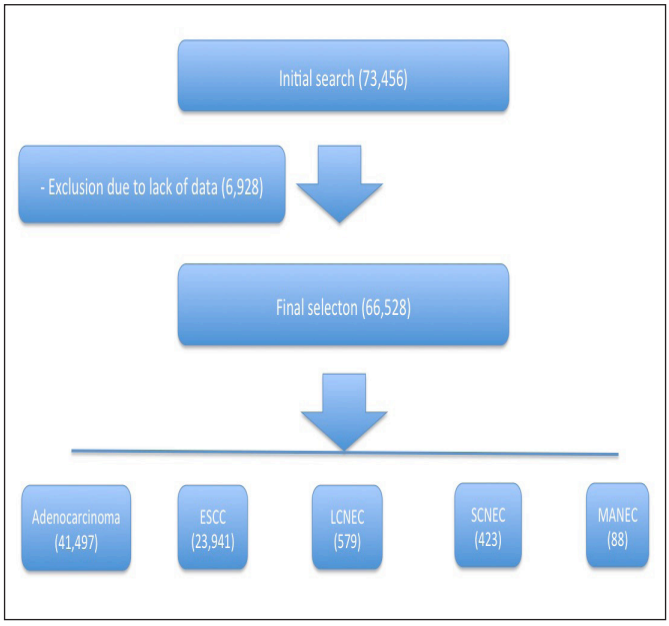

FIGURE 1. Flow diagram of the patients' selection.
ESCC: esophageal squamous cell carcinoma; LCNEC: large cell neuroendocrine; MANEC: mixed adenoneuroendocrine carcinoma; SCNEC: small cell neuroendocrine.

The mean follow-up was 22.6 months (SD 35.6). Adenocarcinoma was predominant (62.4%), followed by ESCC (36%). LCNEC, SCNEC, and MANEC account for less than 1% each. LCNEC and SCNEC presented a higher rate of elderly (>65 years old). Adenocarcinoma and MANEC had a higher proportion of men (86 and 80%, respectively) than the other subtypes. TABLE 1 shows the baseline characteristics of the patients according to the histology.

Survival analysis

On the long-term overall survival analysis, esophageal adenocarcinoma showed a better prognosis than all the other histologic types (*P*-value for logrank test <0.001). Overall survival Kaplan-Meier curves can be seen in FIGURE 2. For cancer-specific survival rates, similar findings were obtained (*P*-value for logrank test <0.001) (see FIGURE 3).

TABLE 1. Baseline characteristics.

	Adenocarcinoma	ESCC	LCNEC	MANEC	SC NEC	*P*-value
N (%)	41497 (62.4)	23941 (36)	579 (<1)	88 (<1)	423 (<1)	<0.001
Age						
>65 years (%)	58.8	58	62	55.7	61	<0.001
Male (%)	85.8	64.1	67.5	79.5	65	<0.001
Summary stage (%)						
Localized	25	25	22	9	15	<0.001
Regional	34	40	35	27	22	
Distant	41	35	43	64	63	
Grade of cellular differentiation						
I	17	10	0	0	0	0.413
II	47	50	0	0	0	
III	36	40	100	100	100	

ESCC: esophageal squamous cell carcinoma; LCNEC: large cell neuroendocrine; MANEC: mixed adenoneuroendocrine carcinoma; SCNEC: small cell neuroendocrine.

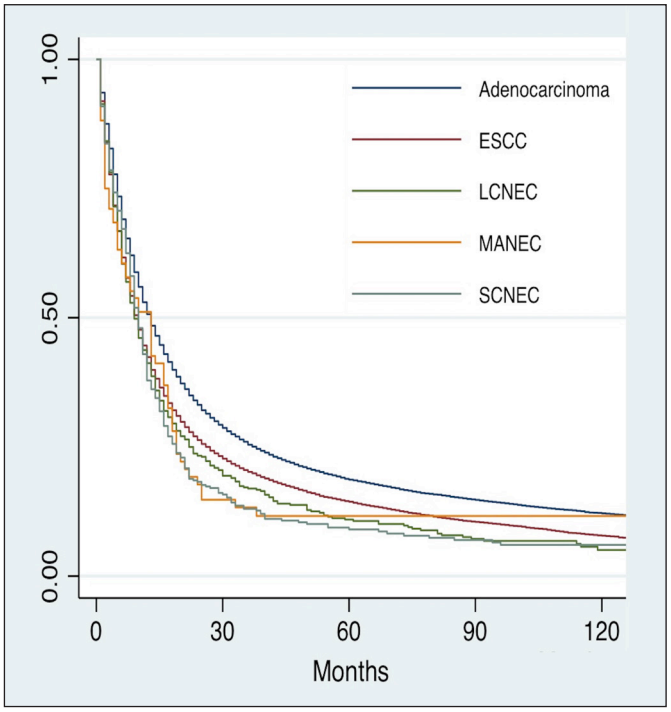

FIGURE 2. Overall survival Kaplan-Meier curves. *P*-value for logrank test <0.001.
ESCC: esophageal squamous cell ca=rcinoma; LCNEC: large cell neuroendocrine; MANEC: mixed adenoneuroendocrine carcinoma; SCNEC: small cell neuroendocrine.

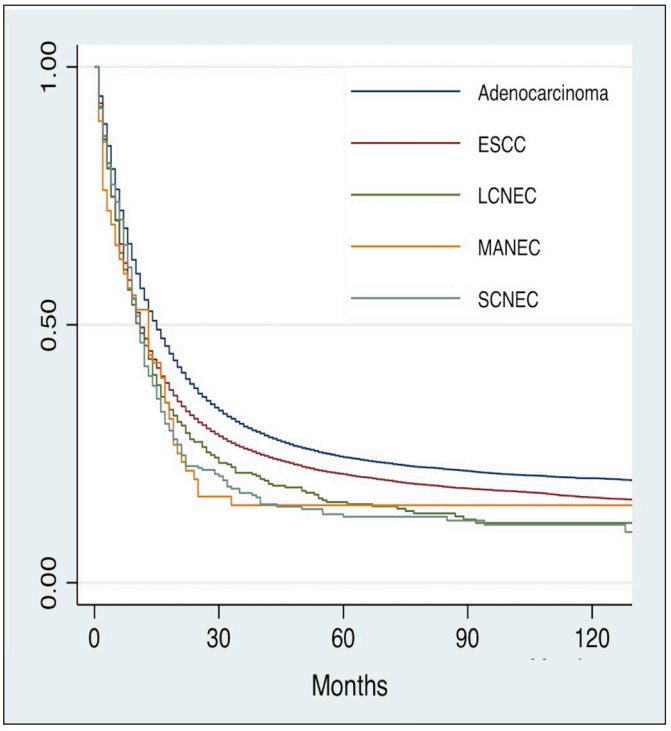

FIGURE 3. Cancer-specific survival Kaplan-Meier curves. *P*-value for logrank test <0.001.
ESCC: esophageal squamous cell carcinoma; LCNEC: large cell neuroendocrine; MANEC: mixed adenoneuroendocrine carcinoma; SCNEC: small cell neuroendocrine.

For pairwise multiple logrank comparisons for overall survival, adenocarcinoma showed a better prognosis than all the other studied subtypes (P<0.05). LCNEC and SCNEC showed equivalent overall survival rates (P=0.583). No significant difference was noted between MANEC and ESCC, LCNEC, and SCNEC (see TABLE 2).

TABLE 2. Pairwise multiple survival comparison with logrank test.

P-value for logrank	Adenocarcinoma	ESCC	LCNEC	SCNEC
Adenocarcinoma	x	x	x	x
ESCC	<0.001	x	x	x
LCNEC	<0.001	0.07	x	x
SCNEC	<0.001	0.03	0.583	x
MANEC	0.031	0.619	0.883	0.565

ESCC: esophageal squamous cell carcinoma; LCNEC: large cell neuroendocrine; MANEC: mixed adenoneuroendocrine carcinoma; SCNEC: small cell neuroendocrine.

The hazard for death for LCNEC and SCNEC was higher than the other histological subtypes. With adenocarcinoma as a reference, HR was 1.32 for LCNEC (95%CI 1.2 to 1.45) and 1.37 for SCNEC (95%CI 1.23 to 1.53). The HR was 1.22 for ESCC (95%CI: 1.2 to 1.24); and 1.3 for MANEC (95%CI 1.01 to 1.66). For multivariate Cox regression analysis, besides age and stage, the neuroendocrine subtypes LCNEC and SCNEC were considered independent prognostic variables (see TABLE 3).

DISCUSSION

The results of this population-based cohort showed that primary esophageal neuroendocrine carcinomas present poorer survival rates than adenocarcinoma and ESCC. Knowing the long-term survival outcomes for NECs subtypes helps stratify their risk and determine prognosis. The determination of the prognosis before deciding on any specific therapy is crucial to predict patient outcomes.

Currently, there is still no standardized treatment for NECs[3,6,12]. Most classification and therapeutic strategies are adapted from neuroendocrine lung cancer. The NECs subtypes were not contemplated in the 8th edition of the AJCC/UICC TNM staging system for esophageal cancer[13]. Consequently, the results of the present study fill a gap in the esophageal carcinoma staging system. The staging system has two main roles in esophageal cancer: decision-making and prognostication[13], and the present study helps stratify the prognosis of NEC of the esophagus. Clinicians should be aware that carcinomas with neuroendocrine differentiation have a poor long-term outcome, and consequently, an early and aggressive therapy should be considered.

The European Society for Medical Oncology[14] proposed a guideline for the management and risk assessment of neuroendocrine management. They recommend staging according to the adenocarcinoma criteria. Besides the traditional TNM staging and grade of cellular differentiation, they recommend evaluating the Ki-67 and mitotic index as prognostic histopathological variables. For evaluation of the disease extension, 68Ga/64Cu-SSTR-PET-CT and 18F-FDG PET/CT are complementary and should be used for

TABLE 3. Univariate and multivariate Cox proportional-hazards analysis for overall survival.

	Univariate					Multivariate				
	HR	SE	*P*	95%CI		HR	SE	*P*	95%CI	
				Lower	Upper				Lower	Upper
Age										
>65 years	1.259	0.011	<0.001	1.236	1.281	1.331	0.013	<0.001	1.306	1.356
Sex										
Female	1									
Male	0.996	0.011	0.696	0.975	1.017					
Summary stage										
Localized	1					1				
Regional	1.389	0.018	<0.001	1.354	1.425	1.406	0.018	<0.001	1.371	1.443
Distant	2.869	0.037	<0.001	2.796	2.943	2.98	0.388	<0.001	2.905	3.058
Histology						1				
Adenocarcinoma	1									
ESCC	1.218	0.011	<0.001	1.196	1.24	1.214	0.012	<0.001	1.19	1.238
LCNEC	1.322	0.061	<0.001	1.206	1.447	1.252	0.062	<0.001	1.135	1.38
MANEC	1.296	0.162	0.038	1.014	1.656	1.068	0.143	0.624	1.024	1.289
SCNEC	1.373	0.075	<0.001	1.233	1.528	1.149	0.068	0.018	1.024	1.289

ESCC: esophageal squamous cell carcinoma; LCNEC: large cell neuroendocrine; MANEC: mixed adenoneuroendocrine carcinoma; SCNEC: small cell neuroendocrine.

and 64% of disseminated disease at diagnosis, contributing to poor overall survival. Ku et al.[19], reporting their experience, showed that the most common sites of distant metastasis were lymph nodes, liver, lung, adrenal, and bone marrow. However, the Cox regression models in the present study demonstrated that independently of the extension of the disease, the LCNEC or SCNEC differentiation imposes a negative impact on long-term survival analysis. LCNEC and SCNEC have equally poor prospects.

Neuroendocrine carcinomas can also be associated with adenocarcinoma or squamous cell carcinoma subtypes[3]. Only 88 adenoneuroendocrine tumors were identified in the present cohort, limiting the statistical power of any of their analyses. These subtypes of neuroendocrine neoplasms represent a heterogeneous group, and thus, the prognosis of these tumors is probably poorly predictable. The proportion of neuroendocrine and adenocarcinoma or squamous cell carcinoma in the tumor (and, consequently, the prognosis) may vary in the mixed tumors. Also, chemoradiation response may depend if the neuroendocrine tumor is associated with squamous cell carcinoma or adenocarcinoma[21]. Besides, the site of lymph nodal and hematogenous metastasis may depend if the mixed tumor is associated with adenocarcinoma or squamous cell carcinoma[22].

The present cohort has some limitations. As with any population-based data, the present study is vulnerable to information bias and selection bias due to potential registry flaws[23,24]. Besides, esophageal cancer varies significantly worldwide, depending on the most frequent risk factors in each location. ESCC is the most common type in Asia and South America[25]. Tobacco and alcohol are the main risk factors in these places[25]. Adenocarcinoma is increasing its incidence, especially in developed countries, and obesity and gastroesophageal reflux disease are the main risk factors[25]. The SEER database covers the United States of America (USA) population, where adenocarcinoma is the most frequent histology[25]. In our analysis, adenocarcinoma covers 62.4% of the included patients. Knowing the expressive influences the environment imposes in esophageal cancer development, probably, NECs subtypes' incidence and causation factors may also be influenced according to each geographic location. Consequently, the external validity of the present results may be harmed.

Future studies evaluating populations other than the North-American are needed. These studies should also evaluate other potential prognostic variables, such as the molecular-based pre-treatment data, essential for the accurate risk stratification of neuroendocrine esophageal cancer.

CONCLUSION

Esophageal SCNEC, LCNEC, and MANEC have unique clinical features, including age, sex, and stage, and differ from the adenocarcinoma and squamous cell carcinoma regarding prognosis. This information should be taken into account in prognostication during the staging of esophageal cancer patients.

Statements

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. These data are publicly available, and we obtained access to the SEER data by signing the SEER Research Data Agreement.

Authors' contribution

Tustumi F: contributed to the conception and design of the work. Stefanie Marques SSB: contributed to the acquisition of the data. Barros EF: contributed to the analysis and interpretation of data for the work. Henriques AC: contributed to data analysis.

Waisberg J: contributed to data extraction. Dias AR: contributed to supervision. All authors contributed to this study and participated in the writing or critically revised it for relevant intellectual content. All authors have approved the final and submitted version to be published and assumed joint accountability for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Orcid

Francisco Tustumi: 0000-0001-6695-0496.
Stefanie Sophie Buuck Marques: 0000-0002-9076-093X.
Esau Furini Barros: 0000-0003-1122-9225.
Alexandre Cruz Henriques: 0000-0001-9611-7833.
Jaques Waisberg: 0000-0003-2775-8068.
André Roncon Dias: 0000-0003-3378-4916.

Tustumi F, Marques SSB, Barros EF, Henriques AC, Waisberg J, Dias AR. O prognóstico dos diferentes subtipos de carcinomas de esôfago neuroendócrinos: um estudo de base populacional. Arq Gastroenterol. 2022;59(1):53-7.

RESUMO – **Contexto –** As neoplasias neuroendócrinas são extremamente raras e representam 0,4% a 2% de todas as neoplasias malignas do esôfago. A determinação prognóstica e avaliação de sobrevida para o tipo histológico neuroendócrino é pouco debatida. Este estudo teve como objetivo comparar as taxas de sobrevida de neoplasias neuroendócrinas primárias comparadas com adenocarcinoma e carcinoma espinocelular de esôfago. **Métodos –** Este é um estudo coorte retrospectivo do banco de dados do *Surveillance, Epidemiology, and End Results Program*. A sobrevida global e a sobrevida específica do câncer foram avaliadas com curvas de Kaplan-Meier e testes de logrank. Modelos de regressão de Cox proporcional foram utilizados para avaliar as variáveis relacionadas à sobrevida global. **Resultados –** Após critérios de elegibilidade, foram selecionados 66,528 pacientes. O seguimento médio foi de 22,6 meses (DP 35,6). O adenocarcinoma foi predominante (62%), seguido pelo carcinoma espinocelular (36%). Carcinoma de grandes células, carcinoma de pequenas células e carcinoma adenoneuroendócrino misto representam menos de 1% cada. Na análise de sobrevida global, o adenocarcinoma de esôfago apresentou um prognóstico melhor do que todos os outros tipos histológicos (*P* valor para teste de logrank < 0,001). Com adenocarcinoma como referência, HR foi de 1,32 para carcinoma de grandes células (IC95% 1,2 a 1,45) e 1,37 para carcinoma de pequenas células (IC95% 1,23 a 1,53). O HR foi de 1,22 para carcinoma espinocelular (IC95%: 1,2 a 1,24); e 1,3 para carcinoma adenoneuroendócrino (IC95% 1,01 a 1,66). Para a análise multivariada da regressão de Cox, além da idade e do estadiamento, os subtipos neuroendócrinos carcinoma de grandes células e carcinoma de pequenas células foram considerados variáveis prognósticas independentes. **Conclusão –** No esôfago, o carcinoma de grandes células e o carcinoma de pequenas células apresentam menores taxas de sobrevida a longo prazo do que o carcinoma espinocelular e o adenocarcinoma.

Palavras-chave – Tumores neuroendócrinos; carcinoma neuroendócrino; neoplasias esofágicas.

REFERENCES

1. Tustumi F, Kimura CM, Takeda FR, Uema RH, Salum RA, Ribeiro-Junior U, et al. Prognostic factors and survival analysis in esophageal carcinoma. Arq Bras Cir Dig (São Paulo). 2016;29:138-41.
2. Huang Q, Wu H, Nie L, Shi J, Lebenthal A, Chen J, et al. Primary high-grade neuroendocrine carcinoma of the esophagus: a clinicopathologic and immunohistochemical study of 42 rese ction cases. Am J Surg Pathol. 2013;37: 467-83.
3. Ilett EE, Langer SW, Olsen IH, Federspiel B, Kjær A, Knigge U. Neuroendocrine carcinomas of the gastroenteropancreatic system: a comprehensive review. Diagnostics. 2015;5:119-76.
4. Egashira A, Morita M, Kumagai R, Taguchi KI, Ueda M, Yamaguchi S, et al. Neuroendocrine carcinoma of the esophagus: clinicopathological and immunohistochemical features of 14 cases. PLoS One. 2017;12:e0173501.
5. Yun JP, Zhang MF, Hou JH, Tian QH, Fu J, Liang XM, et al. Primary small cell carcinoma of the esophagus: clinicopathological and immunohistochemical features of 21 cases. BMC cancer. 2007;7:1-8.
6. Chen SB, Yang JS, Yang WP, Weng HR, Li H, Liu DT, et al. Treatment and prognosis of limited disease primary small cell carcinoma of esophagus. Dis Esophagus. 2011;24:114-9.
7. Modlin IM, Oberg K, Chung DC, Jensen RT, de Herder WW, Thakker RV, et al. Gastroenteropancreatic neuroendocrine tumours. Lancet Oncol. 2008;9:61-72.
8. Yao JC, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol. 2008;26:3063-72.
9. Brennan SM, Gregory DL, Stillie A, Herschtal A, Mac Manus M, Ball DL. Should extrapulmonary small cell cancer be managed like small cell lung cancer? Cancer. 2010;116:888-95.
10. Nagtegaal ID, Odze RD, Klimstra D, Paradis V, Rugge M, Schirmacher P, et al. The 2019 WHO classification of tumours of the digestive system. Histopathology. 2020;76:182-8.
11. Nicholson SA, Beasley MB, Brambilla E, Hasleton PS, Colby TV, Sheppard MN, et al. Small cell lung carcinoma (SCLC): a clinicopathologic study of 100 cases with surgical specimens. Am J Surg Pathol. 2002;26:1184-97.
12. Tanaka T, Matono S, Nagano T, Nishimura K, Murata K, Yamana H, et al. Surgical management for small cell carcinoma of the esophagus. Dis Esophagus. 2010;23:502-5.
13. Rice TW, Ishwaran H, Blackstone EH, Hofstetter WL, Kelsen DP, Apperson-Hansen C, Worldwide Esophageal Cancer Collaboration Investigators. Recommendations for clinical staging (cTNM) of cancer of the esophagus and esophagogastric junction for the 8th edition AJCC/UICC staging manuals. Dis Esophagus. 2016;29:913-9.
14. Pavel M, Öberg K, Falconi M, Krenning EP, Sundin A, Perren A, et al. Gastroenteropancreatic neuroendocrine neoplasms: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2020;31:844-60.
15. Xiaochuan L, Jiangyong Y, Ping Z, Xiaonan W, Lin L. Clinical characteristics and prognosis of pulmonary large cell carcinoma: A population-based retrospective study using SEER data. Thorac Cancer. 2020;11:1522-32.
16. Van Meerbeeck JP, Fennell DA, De Ruysscher DK. Small-cell lung cancer. Lancet. 2011;378:1741-55.
17. McKeown F. Oat-cell carcinoma of the oesophagus. J Pathol Bacteriol. 1952;64:889-91.
18. Giannetta E, Guarnotta V, Rota F, de Cicco F, Grillo F, Colao A, et al. A rare rarity: Neuroendocrine tumor of the esophagus. Crit Rev Oncol Hematol. 2019;137:92-107.
19. Ku GY, Minsky BD, Rusch VW, Bains M, Kelsen DP, Ilson DH. Small-cell carcinoma of the esophagus and gastroesophageal junction: review of the Memorial Sloan-Kettering experience. Ann Oncol. 2008;19:533-7.
20. Tustumi F, Takeda FR, Uema RH, Pereira GL, Sallum RA, Cecconello I. Primary neuroendocrine neoplasm of the esophagus–Report of 14 cases from a single institute and review of the literature. Arq Gastroenterol. 2017;54:4-10.
21. Takeda FR, Tustumi F, de Almeida Obregon C, Yogolare GG, Navarro YP, Segatelli V, et al. Prognostic value of tumor regression grade based on Ryan score in squamous cell carcinoma and adenocarcinoma of esophagus. Ann Surg Oncol. 2020;27:1241-7.
22. Tustumi F, Kimura CM, Takeda FR, Sallum RA, Ribeiro-Junior U, Cecconello I. Evaluation of lymphatic spread, visceral metastasis and tumoral local invasion in esophageal carcinomas. Arq Bras Cir Dig (São Paulo). 2016;29:215-7.
23. Szklo M. Population-based cohort studies. Epidemiol Rev. 1998;20:81-90.
24. Jacobsen SJ, Mahoney DW, Redfield MM, Bailey KR, Burnett Jr JC, Rodeheffer RJ. Participation bias in a population-based echocardiography study. Ann Epidemiol. 2004;14:579-84.
25. Cummings D, Wong J, Palm R, Hoffe S, Almhanna K, Vignesh S. Epidemiology, diagnosis, staging and multimodal therapy of esophageal and gastric tumors. Cancers. 2021;13:582.