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ORIGINAL ARTICLE

Design and validation of a prognostic survival nomogram in patients with primary neuroendocrine tumors of the cecal appendix

Diseño y validación de un nomograma pronóstico de supervivencia en pacientes con tumores neuroendocrinos primarios del apéndice cecal

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Abstract

Introduction. Neuroendocrine tumors of the appendix (NET-A) correspond to the most common appendicular neoplasia. Although they usually have a benign behavior, their potential for regional extension and metastasis makes it necessary to accurately determine the prognosis of each patient. The objective of the present study was to design and validate a prognostic nomogram to predict survival of patients with NET-A.

Methods. Retrospective cohort study, based on information from the surveillance, epidemiology, and outcomes database of the National Cancer Institute of the United States of America. Patients diagnosed with NET-A between 1978 and 2016 were included. Survival analysis was performed using a Cox regression model. With these results, nomograms for general and cancer-specific survival at one, two, three and five years were constructed. The analyzes were carried out in the statistical software R (v. 3.5.3).

Results. 3585 patients with a NET-A diagnosis were included, 55.8% were women, and the median age was 49 years. The most frequent histological subtype was the Mixed Histology Tumor (MHT). Age, histological subtype, size and tumor extension were the only variables independently associated with survival after multivariate analysis. The validated nomogram presented an outstanding discrimination capacity to predict both overall survival 0.81 (95% CI: 0.76-0.86) and cancer specific survival 0.88 (95% CI: 0.83 to 0.92).

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Discussion. The present study proposes a prognostic survival nomogram for patients with NET-A, taking into account the histological subtype, and achieves an outstanding discrimination capacity for the prediction of these outcomes. We highlight the poorer prognosis of patients with MHT, in addition to the similar survival between patients undergoing hemicolectomy and those undergoing appendectomy or resection of the cecum, after multivariate analysis. It is necessary to evaluate the role of adjuvant therapeutic modalities in the survival of these patients.

Keywords: nomogram; neuroendocrine tumors; neoplasms of the appendix; histology; prognosis; survival.

Resumen

Introducción. Los tumores neuroendocrinos apendiculares (TNE-A) corresponden a la neoplasia apendicular más común. Aunque habitualmente tienen un comportamiento benigno, su potencial de extensión regional y metástasis, hacen necesario determinar de manera precisa el pronóstico de cada paciente. El objetivo del presente estudio fue diseñar y validar un nomograma pronóstico para predecir la supervivencia de los pacientes con TNE-A.

Métodos. Estudio de cohorte retrospectiva, de acuerdo a la información de la base de datos de vigilancia, epidemiología y desenlaces del Instituto Nacional de Cáncer de los Estados Unidos de América. Se incluyeron los pacientes con diagnóstico de TNE-A entre 1978 y 2016. El análisis de supervivencia se realizó mediante un modelo de regresión de Cox. Con estos resultados se construyeron los nomogramas para la supervivencia general y específica de cáncer a uno, dos, tres y cinco años. Los análisis fueron realizados en el software estadístico R (v. 3.5.3).

Resultados. Se incluyeron 3585 pacientes con diagnóstico de TNE-A, el 55,8 % fueron mujeres, y la mediana de edad fue de 49 años. El subtipo histológico más frecuente fue el Tumor de Histología Mixta (MHT). La edad, el subtipo histológico, el tamaño y la extensión tumoral, fueron las únicas variables asociadas independientemente con la supervivencia después del análisis multivariado. El nomograma validado presentó una capacidad de discriminación sobresaliente para predecir tanto supervivencia general 0,81 ($IC_{95\%}$: 0,76-0,86), como específica a cáncer 0,88 ($IC_{95\%}$: 0,83 a 0,92).

Discusión. El presente estudio propone un nomograma pronóstico de supervivencia para pacientes con TNE-A, teniendo en cuenta el subtipo histológico, y alcanza una capacidad de discriminación sobresaliente para la predicción de estos desenlaces. Destacamos el peor pronóstico de los pacientes con MHT, además de la supervivencia similar entre los pacientes llevados a hemicolectomía y aquellos sometidos a apendicectomía o resección del ciego, luego del análisis multivariado. Se requiere evaluar el rol de modalidades terapéuticas adyuvantes en la supervivencia de estos pacientes.

Palabras clave: nomograma; tumores neuroendocrinos; neoplasias del apéndice; histología; pronóstico; supervivencia.

Introduction

Neuroendocrine tumors (NET) are neoplasms of varied clinical manifestation and behavior, which originate in cells of the diffuse neuroendocrine system [1]. Its place of presentation is associated with tissues derived from the primitive intestine, and 42% of these tumors are located in the middle intestine, including the small intestine and the appendix [2,3]. Although less frequent than other malignant neoplasms, its incidence and prevalence have progressively increased, which is attributed to the implementation of screening studies that allow the detection of the disease in earlier stages [4].

NET are the most common type of appendicular neoplasia and are usually found incidentally after appendectomies. Most appendicular neuroendocrine tumors (NET-A) are located at the tip of the appendix and are usually smaller than 2 cm in diameter [5]. Although these tumors are usually characterized by an indolent clinical course and benign behavior, they have the potential for regional extension (25-50%) and

distant metastases (10%), and the risk of lymph node metastases increases dramatically with larger tan 2 cm in tumor sizes and with the greatest depth of invasion [2,6]. In the appendix, in addition to NET, almost exclusively, tumors of mixed histology (MHT) can be found, which are characterized by containing both neuroendocrine and glandular elements. Within this histological subtype, goblet cell carcinoid tumor (GCCT) is the most common neoplasm. GCCT represent 14-19% of primary appendicular neoplasms and generally have a more aggressive behavior than other NET-A, which can vary according to the proportion of the glandular component within the tumor [7].

Due to the variety in the behavior of NET-A, it is necessary to determine the factors involved in the prognosis of patients with these neoplasms and their variants, and based on them, establish the individual prognosis of each patient, which allows defining the most appropriate surgical strategies and oncological procedures for each case.

A nomogram is a graphic representation of a statistical model that is used to predict prognosis in cancer patients, establishing the individual probability of a clinical event, by integrating various predictive variables [8]. To date, there are no prognostic nomograms for NET-A in the literature; therefore, our objective was to develop a clinicopathological nomogram in order to predict survival of these patients at 1, 2, 3, and 5 years.

Methods

This is a retrospective cohort study, in which the information available in the Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute of the United States of America is analyzed.

Database and eligibility criteria

To obtain the information in this study, we used the software SEER*Stat version 8.3.6.1 (https://seer.cancer.gov/seerstat/). It was initially filtered by primary tumor site, including only those originating from the cecal appendix, according to the codes according to the International Classification of Diseases (ICD): C18.1-Appendix. Subsequently, it was filtered according to the histopathological classification of the tumor, including those compatible with neuroendocrine tumors (ICD-O-3 Code: 8240/3: Carcinoid tumor, NOS, 8245/3: Adenocarcinoid tumor, 8243/3: Goblet cell carcinoid, 8244/3: Mixed adenoneuroendocrine carcinoma, 8013/3: Large cell neuroendocrine carcinoma, 8241/3: Enterochromaffin cell carcinoid, 8246/3: Neuroendocrine carcinoma, NOS, 8249/3: Atypical carcinoid tumor).

From the results obtained, only those registries with histopathological confirmation of the neoplasia, a complete follow-up, and the availability of the cause of death in the registry were included. Lastly, those patients in whom the neuroendocrine tumor of the cecal appendix did not represent the primary tumor, those in whom there were no data on the characteristics of the tumor (size, histological grade, or extension) and those who did not undergo surgery were excluded.

Variables evaluated

Clinicopathological variables were initially included, highlighting age at diagnosis, sex, race, histological subtype, degree of cell differentiation, size, and tumor stage. Additionally, the treatment received (chemotherapy, radiotherapy and surgical management), and survival data (survival in months and life outcome) were recorded.

The age at the time of diagnosis was classified as less than 53, 53-80 and 80 years or more, according to the results obtained by the X-tile software (see in the statistical analysis section). The race was classified as White, African American, and Other (American Indian / Alaska Native, Asian / Pacific Islander). The histological grade was classified taking into account the categories of the variable "Grade ICD-O-3", being divided into two groups: Grades I-II and III-IV. The size of the tumor was classified based on its longest axis (<1 cm, 1-2 cm, 2-5 cm, 5-10 cm, and >10 cm). The histological subtypes were assigned according to the WHO classification as well-differentiated neuroendocrine tumors (WDNET), poorly differentiated neuroendocrine carcinomas (PDNEC), and mixed histology tumors (MHT), as can be seen in Table 1.

The tumor stage was classified as localized, regional, and with distant involvement, accord-

Table 1. Demographic and clinical characteristics of patients with neuroendocrine tumors of the cecal appendix according to the study group.

	Validation group (n=1408)	Training group (n=2177)	Total (n=3585)	p-value
Age (years)				0.471
Media (SD)	46.6 (17.7)	47.0 (17.5)	46.8 (17.6)	
Median (Q1, Q3)	48 (33, 60)	49 (33, 60)	49 (33, 60)	
Min - Maximum	8.0 – 94.0	4.0 – 92.0	4.0 – 94.0	
No data	0	0	0	
Age (Categories)				0.845
0 - 52 years	867 (61.6%)	1329 (61.0%)	2196 (61.3%)	
53 - 80 years	511 (36.3%)	806 (37.0%)	1317 (36.7%)	
80 - 120 years	30 (2.1%)	42 (1.9%)	72 (2.0%)	
No data	0	0	0	
Sex				0.305
Female	771 (54.8%)	1230 (56.5%)	2001 (55.8%)	
Male	637 (45.2%)	947 (43.5%)	1584 (44.2%)	
No data	0	0	0	
Race				0.751
African American	107 (7.7%)	181 (8.4%)	288 (8.1%)	
White	1225 (88.2%)	1882 (87.5%)	3107 (87.8%)	
Other	57 (4.1%)	88 (4.1%)	145 (4.1%)	
No data	19	26	45	
Maritial status				0.606
Married	724 (54.4%)	1096 (53.5%)	1820 (53.8%)	
Single	607 (45.6%)	953 (46.5%)	1560 (46.2%)	
No data	77	128	205	
Histological grade				0.298
Grade I-II	698 (81.5%)	1022 (79.7%)	1720 (80.4%)	
Grade III-IV	158 (18.5%)	260 (20.3%)	418 (19.6%)	
No data	552	895	1447	
Histological subtype				0.102
WDNET	533 (43.8%)	789 (41.1%)	1322 (42.1%)	
MHT	617 (50.7%)	1017 (52.9%)	1634 (52.1%)	
PDNEC	68 (5.6%)	115 (6.0%)	183 (5.8%)	
No data	17	23	40	
Tumor size				0.275
< 1 cm	429 (33.5%)	682 (35.3%)	1111 (34.6%)	
1-2 cm	240 (18.7%)	324 (16.81%)	564 (17.6%)	
2-5 cm	524 (41.0%)	784 (40.6%)	1308 (40.8%)	
5-10 cm	77 (6.0%)	133 (6.9%)	210 (6.5%)	
> 10 cm	7 (0.7%)	4 (0.2%)	11 (0.4%)	
No data	371	574	945	

Table1 continued

	Validation group (n=1408)	Training group (n=2177)	Total (n=3585)	p-value
Extension				0.599
Distant	127 (9.1%)	178 (8.3%)	305 (8.6%)	
Regional	359 (25.8%)	546 (25.3%)	905 (25.5%)	
Local	906 (65.1%)	1431 (66.4%)	2337 (65.9%)	
No data	16	22	38	
Radiotherapy				0.843
No	1404 (99.7%)	2170 (99.7%)	3574 (99.7%)	
Yes	4 (0.3%)	7 (0.3%)	11 (0.3%)	
No data	0	0	0	
Chemotherapy				0.236
No	1266 (89.9%)	1930 (88.7%)	3196 (89.1%)	
Yes	142 (10.1%)	247 (11.3%)	389 (10.9%)	
No data	0	0	0	
Surgery				0.637
Appendectomy or cecum resection	838 (59.5%)	1263 (58.0%)	2101 (58.6%)	
Subtotal colectomy	523 (37.1%)	843 (38.7%)	1366 (38.1%)	
Total colectomy	47 (3.3%)	71 (3.3%)	118 (3.3%)	
No data	0	0	0	
Overall Mortality				0.554
No	1179 (83.7%)	1839 (84.5%)	3018 (84.2%)	
Yes	229 (16.3%)	338 (15.5%)	567 (15.8%)	
No data	0	0	0	
Cancer-Associated Mortality				0.494
No	1253 (89.0%)	1953 (89.7%)	3206 (89.4%)	
Yes	155 (11.0%)	224 (10.3%)	379 (10.6%)	
No data	0	0	0	

Abbreviations: WDNET: Well-differentiated neuroendocrine tumors; PDNEC: Poorly differentiated neuroendocrine carcinomas; MHT: Mixed histology tumors.

ing to the SEER classification, as described in the 2018 version of the summary stadium manual provided by SEER (https://seer.cancer.gov/tools/ssm/). Localized tumors were defined as those confined to the appendix, regional ones were defined as those that affected by direct extension to the abdominal wall, mesenteric or pericolic fat, retroperitoneal structures, small intestine or other organs, or with tumor involvement in regional lymph nodes. Finally, those with extension to distant organs (adrenal glands, bladder, diaphragm, fallopian tubes, skin, gallbladder, kidneys, liver, ovary, ureters, uterus, among others), to distant lymph nodes (inferior or superior mesenteric), or with evidence of peritoneal carcinomatosis, they were defined as tumors with distant involvement.

Statistic analysis

Using the dplyr package available from R Studio® (PBC, Boston, MA), NET-A patients who met the inclusion and exclusion criteria were randomly assigned to a training or validation group to construct and validate the nomograms, respectively. The quantitative variables were described as medians with their respective 25 and 75 quartiles, while the qualitative variables were described with their absolute and relative value with respect to the total group.

The Chi square test was used to compare the differences in clinical characteristics between the two groups. The age at the time of diagnosis was analyzed by the X-tile software in order to calculate the cutoff values based on the general survival information. A bivariate and multivariate Cox proportional hazards regression analysis with R Studio software (version 1.2.5042) was used to assess prognostic factors.

The variables were calculated using the hazard ratio (HR) and the corresponding 95% confidence interval. We chose two main outcomes: overall survival and cancer-specific survival. According to the results of the bivariate and multivariate Cox regression analysis, the nomograms were constructed for both specific and general survival at 1, 2, 3 and 5 years with the rms statistical package available in R (version 3.5.3). Meanwhile, internal and external validations of the prognostic nomograms were performed. The Harrell concordance index (C index) was used to evaluate their discrimination capacity. Calibration curves were constructed to compare the consistency between predicted and observed survivals.

In essence, the C index estimates the probability that the predicted results are consistent with the actual observed results, similar to that obtained by evaluating the area under the ROC curve. The C index can vary from 0.5 to 1.0, with a C index of 0.50 to 0.70 being classified as low precision, a C index of 0.71 to 0.90 as medium precision and finally those with a value greater than 0.90 as high precision [9].

Results

The SEER database search process allowed the identification of 15,128 patients diagnosed with neoplasms of the cecal appendix. Subsequently, the inclusion and exclusion criteria were applied, and 3585 patients were finally included (Figure 1).

Descriptive analysis

Of the total of 3585 individuals, 2177 patients were assigned in the model training cohort and 1408 patients in the validation group. The training group was used for the internal validation of the model, while the validation group was used for its external validation. In the training cohort, 338 (15.5%) deaths from any cause were reported, of which 224 (10.3%) had a cause related to appendicular neoplasia. On the other hand, in the validation cohort, 229 (16.3%) patients died, of which 155 (11%) died from complications associated with the study neoplasia. The main characteristics of the two study cohorts are summarized in Table 1. It should be noted that there were no significant differences in any evaluation variable between the two study groups.

Mixed histology tumors occurred in significantly older patients and more frequently in men, compared to the other histological subtypes of neuroendocrine tumors. Additionally, MHT tended to be larger and to affect regional and distant structures more often, being more frequently taken to colectomy-type surgical procedures and exhibiting a greater risk of mortality compared to their counterparts WDNET and PDNEC (Table 2 and Figure 2).

Prognostic factors for overall and cancer-specific survival

Multiple variables were significantly associated with the overall survival outcome in the bivariate analysis, as can be seen in table 2, however, only age, extension, histological subtype, and tumor size were independent predictors in the multivariate analysis. A higher risk of all-cause mortality was evidenced as age, extension, and tumor size increased. On the other hand, the mixed histological subtype was associated with a significantly higher risk of mortality from any cause, after multivariate adjustment (Table 2).

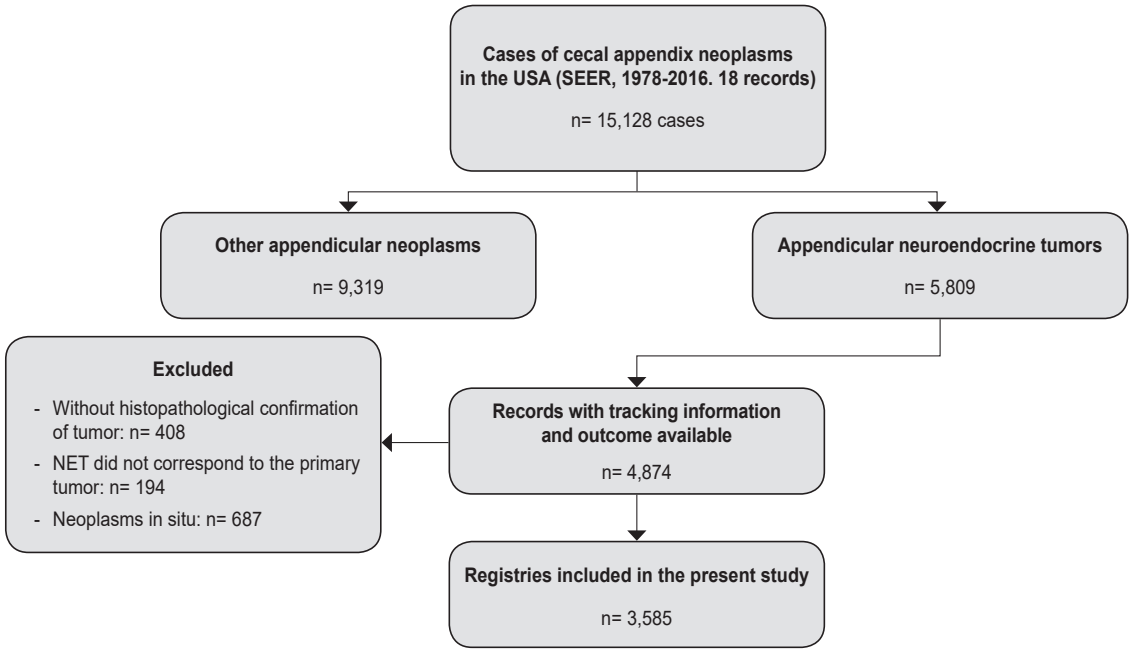

Figure 1. Flowchart that summarizes the selection process for cases of neuroendocrine tumors of the cecal appendix in the SEER database.

Table 2. Demographic and clinical characteristics of patients with appendicular neuroendocrine tumors according to histological subtype.

	MHT (n=1634)	PDNEC (n=183)	WDNET (n=1322)	Total (n=3139)	p-value
Age					< 0,001
Media (SD)	55.1 (13.0)	41.3 (17.0)	39.5 (17.9)	47.7 (17.3)	
Median (Q1, Q3)	55 (47, 63)	40 (27, 53.5)	37.5 (25, 53)	50 (35, 60)	
Min - Maximum	8 – 91	11 - 91	4 - 94	4 - 94	
No data	0	0	0	0	
Age (categories)					< 0,001
0 - 52 years	741 (45.3%)	137 (74.9%)	994 (75.2%)	1872 (59.6%)	
53 - 80 years	843 (51.6%)	44 (24%)	314 (23.8%)	1201 (38.3%)	
80 - 120 years	50 (3.1%)	2 (1.1%)	14 (1.1%)	66 (2.1%)	
No data	0	0	0	0	
Sex					< 0,001
Female	803 (49.1%)	107 (58.5%)	815 (61.6%)	1725 (55%)	
Male	831 (50.9%)	76 (41.5%)	507 (38.4%)	1414 (45%)	
No data	0	0	0	0	
Race					0,501
African American	145 (8.9%)	16 (8.9%)	93 (7.2%)	254 (8.2%)	
White	1415 (87.0%)	156 (86.7%)	1152 (89.0%)	2723 (87.8%)	
Other	66 (4.1%)	8 (4.4%)	49 (3.8%)	123 (4%)	
No data	8	3	28	39	
Tumor size					< 0,001
< 1 cm	137 (16.3%)	78 (50.3%)	716 (64.3%)	931 (44.2%)	

Table2 continued

	MHT (n=1634)	PDNEC (n=183)	WDNET (n=1322)	Total (n=3139)	p-value
1-2 cm	208 (24.8%)	34 (21.9%)	244 (21.9%)	486 (23.1%)	
2-5 cm	317 (37.8%)	29 (18.7%)	133 (11.9%)	479 (22.7%)	
5-10 cm	168 (20%)	14 (9%)	18 (1.6%)	200 (9.5%)	
> 10 cm	8 (1%)	0 (0%)	2 (0.2%)	10 (0.5%)	
Extension					< 0.001
Distant	237 (14.6%)	18 (9,8%)	26 (2%)	281 (9%)	
Regional	494 (30.5%)	42 (23%)	253 (19.3%)	789 (25.3%)	
Local	890 (54.9%)	123 (67.2%)	1031 (78.7%)	2044 (65.6%)	
No data	13	0	12	25	
Radiotherapy					0.085
No	1625 (99.4%)	182 (99.5%)	1321 (99.9%)	3128 (99.6%)	
Yes	9 (0.6%)	1 (0.5 %)	1 (0.1%)	11 (0.4%)	
No data	0	0	0	0	
Chemotherapy					< 0.001
No	1276 (78.1%)	171 (93.4%)	1310 (99.1%)	2757 (87.8%)	
Yes	358 (21.9%)	12 (6.6%)	12 (0.9%)	382 (12.2%)	
No data	0	0	0	0	
Surgery					< 0.001
Appendectomy or cecum resection	679 (41.6%)	133 (72.7%)	989 (74.8%)	1801 (57.4%)	
Colectomy	955 (58.4%)	50 (27.3%)	333 (25.2%)	1338 (42.6%)	
No data	0	0	0	0	
Overall Mortality					< 0.001
No	1160 (71%)	165 (90.2%)	1289 (97.5%)	2614 (83.3%)	
Yes	474 (29%)	18 (9.8%)	33 (2.5%)	525 (16.7%)	
Cancer-Associated Mortality					< 0.001
No	1299 (79.5%)	170 (92.9%)	1309 (99%)	2778 (88.5%)	
Yes	335 (20.5%)	13 (7.1%)	13 (1%)	361 (11.5%)	

*3585 patients were not included in the general analysis, since the histological subtype was not reported in 446 patients.
Abbreviations: WDNET: Well-differentiated neuroendocrine tumors; PDNEC: Poorly differentiated neuroendocrine carcinomas; MHT: Mixed histology tumors.

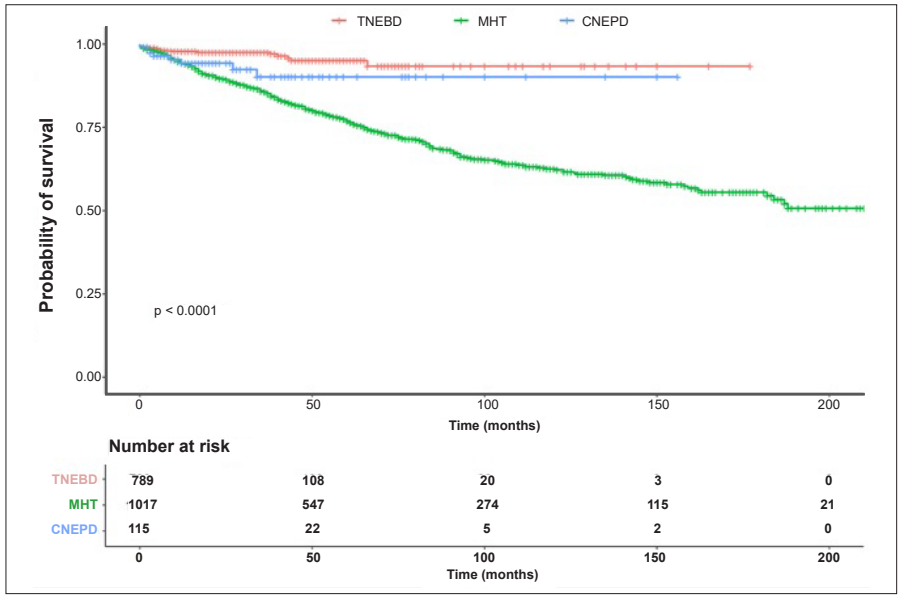

Figure 2. Kaplan-Meier graph showing the probability of survival in the follow-up of patients with neuroendocrine tumors of the cecal appendix according to the histological subtype.

Similarly, age, disease extent, tumor size, and histological subtype were identified as independent predictors of cancer-specific survival, even after multivariate analysis. The effect by category was similar to that observed for overall survival (Table 3).

Construction and validation of the prognostic nomogram

Once the independent predictor variables for general and cancer-specific survival were identified, prognostic nomograms were created to estimate survival values at 1, 2, 3, and 5 years. The resulting nomograms can be seen in figure 3. To put in context, the nomogram gives each prognosis variable a score on the top point scale. By adding these scores, the value in the total score of the scale will be located in the lower part, finally allowing to predict survival (either general or specific to cancer) by drawing a vertical line. Internal validation of the training cohort revealed a C-index of the global and cancer-specific survival nomograms of 0.80 (95% CI: 0.70–0.76) and 0.87 (95% CI: 0.73– 0.81), respectively. Similarly, the corresponding C index in the external validation cohort was 0.81 (95% CI: 0.76-0.86) and 0.88 (95% CI: 0.83-0.92). These results confirm that our prognostic nomograms are reasonably accurate. The calibration process (Figure 4) shows that the actual survival rate translates well with the prediction of the nomogram.

Discussion

Neuroendocrine tumors of the cecal appendix (NET-A) correspond to a group of neoplasms with heterogeneous behavior, susceptible to treatment, with more favorable results and an excellent prognosis, when compared with NET from other locations [10]. However, the great variety of NET-A subtypes requires an individualized approach to guide therapeutic strategies taking into account an estimated prognosis.

This study proposes a survival prognostic nomogram for patients with NET-A, taking into account their histological subtype, and found that age, disease extension, tumor size and histological subtype are independent prognostic factors for the survival of patients. these patients. Nomograms with these factors are presented, finding a C-index for global mortality of 0.81 and for cancer-specific mortality of 0.88, which shows their good performance for the discrimination of these outcomes.

In this study, age at diagnosis was an independent prognostic factor for global and specific mortality, an age greater than 80 years was associated with a worse prognosis in patients with neuroendocrine tumors of the appendix.

For the histological subtype, we used the latest WHO NET-A classification [11]. As in our study, research published in 2011 and 2017 demonstrated that, in addition to tumor size, the histological subtype is a determining factor for the risk of lymph node metastasis [12,13]. Although 20 mm was previously considered as the cut-off point to define a high risk of lymph node metastasis, Sarshekeh et al. observed that patients with WDNET and MHT had greater regional lymph node involvement when their size was greater than 10 mm, proposing this size as a new cut-off point to predict the risk of this outcome [13].

In the present study, no significant differences were found when the survival of those patients with tumors smaller than 1 cm was compared with those between 1 and 2 cm. When adjusting for the other independent factors, a greater impact on the prognosis of patients with a tumor size greater than 10 cm was evidenced.

The most identified histological subtype in our study was MHT, which occurred in older adults, with larger tumor size and with a higher percentage of regional and distant extension, more commonly requiring hemicolectomy and showing significantly worse survival compared to the other subtypes. Sarshekeh et al. also evidenced that MHT corresponded to the most frequent histological subtype, however, they found that PDNEC had the worst prognosis, this may be due to the limited number of patients with this histological subtype included in their analysis (132). Notably, they found a higher rate of lymph node metastatic involvement in patients with WDNET; however, this histological subtype was associated, as in our study and in previous studies, with a more favorable prognosis [12,14,15].

Table 3. Bivariate and multivariate Cox regression analysis of factors associated with overall survival in patients with neuroendocrine tumors of the cecal appendix.

Variables	Categories Modalities	n	Univariate HR (95% CI, p)	Multivariate HR (95% CI, p)
Age (categories)	0 - 52 years	1329	Reference	
	53 - 80 years	806	2.7 (2.1 – 3.3 p<0.001)	1.8 (1.2 – 2.5 p<0.001)
	80 - 120 years	42	9.8 (6.3 – 15.5 p<0.001)	6.3 (3.0 – 12.8 p<0.001)
Race	African American	181	Reference	
	White	1882	0.6 (0.4 – 0.9 p=0.021)	6.1 (3.0 – 12.6 p=0.691)
	Other	88	0.7 (0.4 – 1.4 p=0.461)	0.61 (0.1 – 1.8 p=0.348)
Sex	Female	1230	Reference	
	Male	947	1.0 (0.8 – 1.3 p=0.547)	
Marital status	Married	1096	Reference	
	Single	953	1.0 (0.8 – 1.3 p=0.458)	
Grade	Grade I-II	1022	Reference	
	Grade III-IV	260	1.1 (0.7 – 1.7 p=0.570)	
Histological subtype	MHT	1017	Reference	
	WDNET	789	0.4 (0.1 – 0.3 p<0.001)	0.4 (0.2 – 0.6 p<0.001)
	PDNEC	115	0.4 (0.2 – 0.9 p=0.049)	0.4 (0.1 – 0.9 p=0.046)
Extension	Distant	178	Reference	
	Regional	546	0.1 (0.1 – 0.1 p<0.001)	0.1 (0.1 – 0.2 p<0.001)
	Local	1431	0.0 (0.0 – 0.1 p<0.001)	0.1 (0.0 – 0.1 p<0.001)
Tumor size	< 1 cm	429	Reference	
	1-2 cm	240	1.4 (0.8 – 2.5 p=0.139)	0.8 (0.4 – 1.5 p=0.581)
	2-5 cm	524	3.2 (2.0 – 5.1 p<0.001)	1.1 (0.6 – 2.0 p=0.646)
	5-10 cm	77	5.5 (3.3 – 9.1 p<0.001)	1.2 (0.6 – 2.3 p=0.484)
	> 10 cm	7	22.9 (6.9 – 76.0 p<0.001)	7.7 (2.1 – 28.2 p<0.001)
Chemotherapy	No	1930	Reference	
	Yes	247	4.4 (3.5 – 5.5 p<0.001)	1.2 (0.7 – 1.9 p=0.382)
Radiotherapy	No	2170	Reference	
	Yes	7	6.2 (2.6 – 15.2 p<0.001)	2.8 (0.6 – 12.1 p=0.164)
Surgery	Appendectomy or cecum resection	1263	Reference	
	Colectomy	914	1.4 (1.1 – 1.7 p=0.002)	1.1 (0.8 – 1.6 p=0.452)

***** The total number of patients in the general analysis is not included, since there were individuals without data reported in some variables. The number of individuals with missing data per variable can be found in table 1.

Abbreviations: WDNET: Well-differentiated neuroendocrine tumors; PDNEC: Poorly differentiated neuroendocrine carcinomas; MHT: Mixed histology tumors.

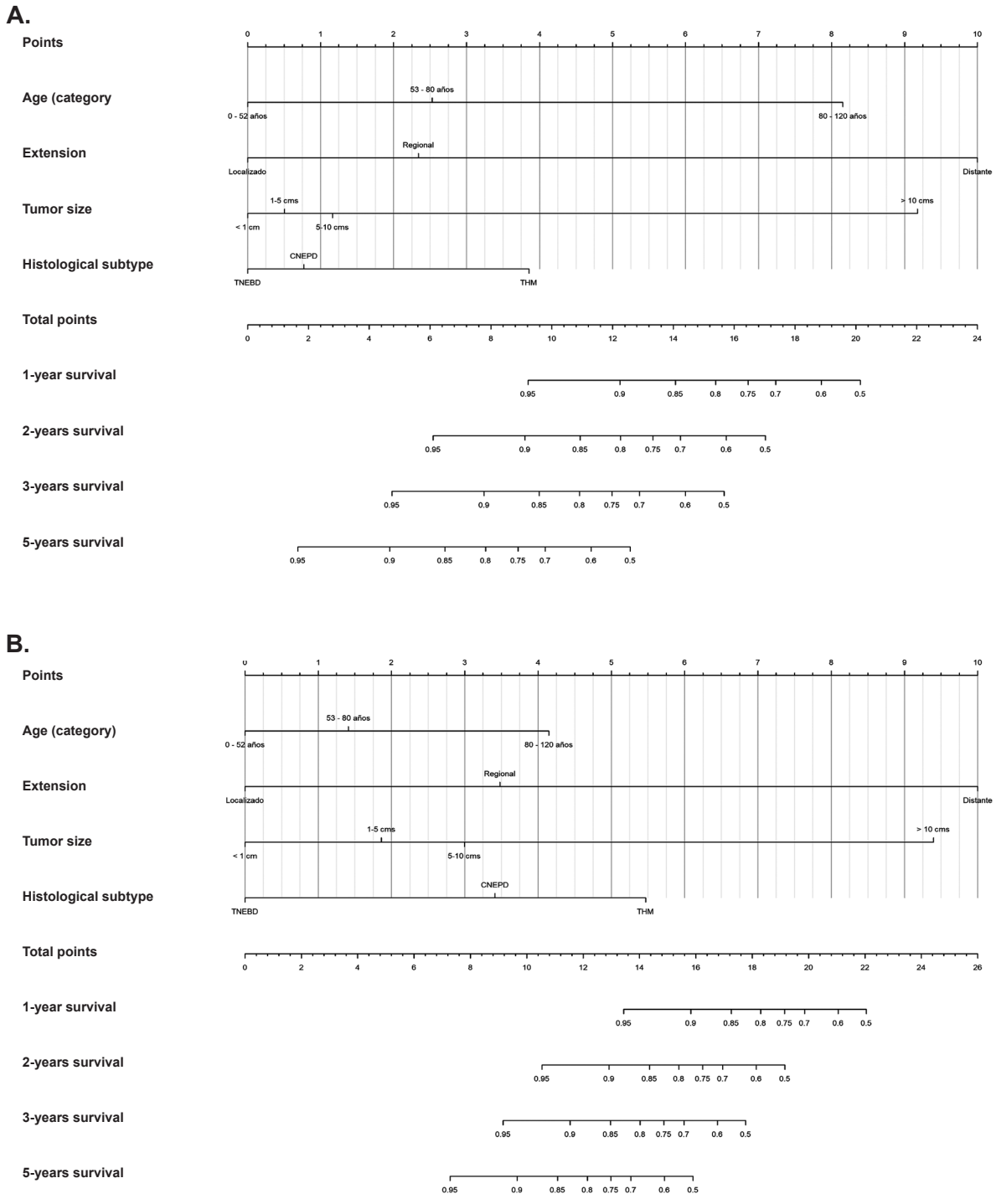

Figure 3. Prediction nomograms of general (Panel A) and cancer-specific (Panel B) survival at 1, 2, 3 and 5 years in appendicular neuroendocrine tumors (NET-A). Notes: The points for each variable are obtained by drawing a vertical line between each variable and the scale of points (upper). The predicted survival rate is obtained by adding the points obtained per variable and with the total points obtained, a vertical line is drawn from the total points scale to the overall survival scale for each year.
Abbreviations: WDNET: Well-differentiated neuroendocrine tumors; PDNEC: Poorly differentiated neuroendocrine carcinomas; MHT: Mixed histology tumors.

Table 4. Bivariate and multivariate Cox regression analysis of factors associated with cancer-specific survival in patients with neuroendocrine tumors of the cecal appendix.

Variables	Categories Modalities	n	Univariate HR (95% CI, p)	Multivariate HR (95% CI, p)
Age (category)	0 - 52 years	1329	Reference	
	53 - 80 years	806	2.2 (1.7 – 3.0 p<0.001)	1.4 (1.1 – 2.4 p=0.005)
	80 - 120 years	42	5.3 (2.7 – 10.3 p<0.001)	2.6 (1.7 – 8.6 p<0.001)
Race	African American	181	Reference	
	Other	88	0.7 (0.3 – 1.5 p=0.492)	0.6 (0.1 – 1,9 p=0.414)
	White	1882	0.58 (0.4 – 0.8 p=0.005)	0.6 (0.3 -1.2 p=0.193)
Sex	Female	1230	Reference	
	Male	947	0.8 (0.6 – 1.0 p=0.192)	
Marital status	Married	1096	Reference	
	Single	953	0.8 (0.6 – 1.1 p=0.216)	
Grade	Grade I-II	1022	Reference	
	Grade III-IV	260	1.33 (0.8 – 2.1 p=0.232)	
Histological subtype	MHT	1017	Reference	
	WDNET	789	8.9 (4.3 – 18.2 p<0.001)	0.1 (0.0 – 0.4 p<0.001)
	PDNEC	115	4.9 (1.8 – 13.7 p=0.002)	0.5 (0.2 – 1.3 p=0.186)
Extension	Distant	178	Reference	
	Local	1431	0.0 (0.0 – 0.0 p<0.001)	0.0 (0.0 – 0.0 p<0.001)
	Regional	546	0.1 (0.0 – 0.1 p<0.001)	0.1 (0.0 – 0.2 p<0.001)
Tumor size	< 1 cm	682	Reference	
	1-2 cm	240	2.5 (1,0 – 6,2 p=0.04)	1.1 (0.4 – 3.0 p=0.385)
	2-5 cm	524	8.8 (4.0 – 19.6 p<0.001)	2.1 (0.8 – 5.3 p=0.199)
	5-10 cm	133	19.1 (8.5 – 43.2 p<0.001)	2.6 (0.9 – 6.8 p=0.055)
	> 10 cm	4	80.0 (20.6 – 310.4 p<0.001)	17.8 (4.0 – 78.1 p<0.001)
Chemotherapy	No	1930	Reference	
	Yes	247	7.5 (5.8 – 9.8 p<0.001)	1.2 (0.7 – 2.1 p=0.367)
Radiotherapy	No	2170	Reference	
	Yes	7	9.3 (3.8 – 22.7 p<0.001)	2.5 (0.7 – 2.1 p=0.212)
Surgery	Appendectomy or cecum resection	1263	Reference	
	Colectomy	914	1.7 (1.3 – 2.2 p<0.001)	1.1 (0.7 – 1.7 p=0.561)

***** The total number of patients in the general analysis is not included, since there were individuals without data reported in some variables. The number of individuals with missing data per variable can be found in table 1.

Abbreviations: WDNET: Well-differentiated neuroendocrine tumors; PDNEC: Poorly differentiated neuroendocrine carcinomas; MHT: Mixed histology tumors.

As in previous studies, in this group of patients, surgical management (appendectomy vs. hemicolectomy) did not prove to be an independent prognostic factor for mortality when adjusting for age, extension, tumor size, and histological type. This may be due to the existence of clear guidelines by international consensus in which the extent of surgical management is specified according to tumor size, the compromise of the base and the resection margins and according to the depth of invasion of the mesoappendix [16,17,18].

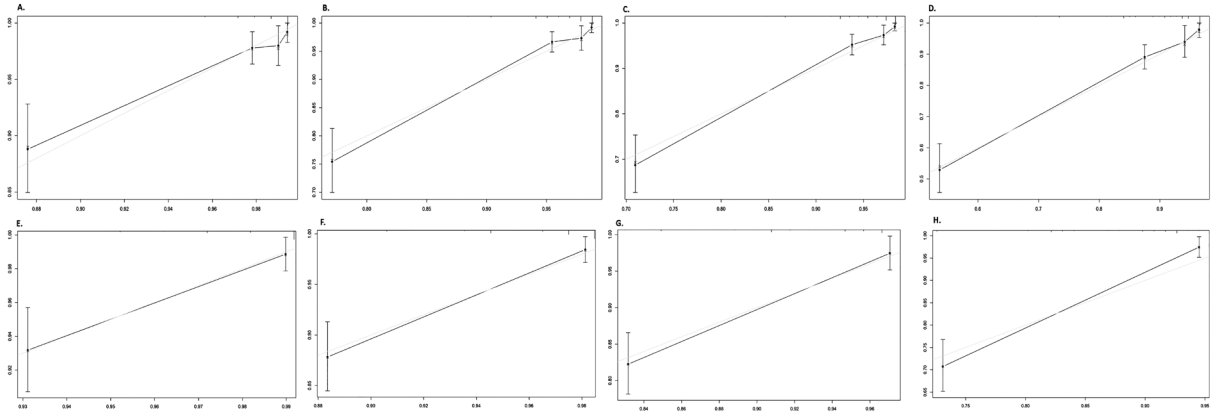

Figure 4. Calibration curves of the general survival nomogram at 1 year (A), 2 years (B), 3 years (C), and 5 years (D); Cancer-specific survival nomogram calibration curves at 1 year (E), 2 years (F), 3 years (G), and 5 years (H). Notes: The dashed line represents an excellent match between the actual survival result (Y-axis) and the predicted nomogram (X-axis). A closer distance between the dashed line and the dots indicates a higher prediction accuracy.

In patients undergoing hemicolectomy, it was found that the tumor size and extension were significantly greater than in those who underwent appendectomy, with hemicolectomy being more frequent in patients with MHT. Therefore, the similar prognostic result in patients managed with colectomy or with appendectomy could derive from these differences. However, it must be taken into account as a probable object of confusion that the SEER database, from which the figures for this analysis were obtained, includes segmental resections of the colon, cecum, ileum, or their combinations with the same. registration code of appendectomies.

The only nomogram previously performed for NET-A was developed by Mosquera et al. in 2017 [2]. The objective was to predict the risk of lymph node metastasis, taking into account the tumor size and the depth of invasion. An association was found between tumor size, depth of invasion and surgical management, with the incidence of lymph node metastases, obtaining an acceptable performance (AUC 0.89). In this study, high-grade NET and patients under 18 years of age were excluded.

The findings of this nomogram complement the results of the previous study, since, beyond evaluating only the risk of tumor progression, it allows predicting the survival of patients.

Strengths and limitations

The analysis of cases from a national registry such as SEER (which has recognized methodological and logistical strength) facilitated the extrapolation of the results obtained, given the large number of cases and their origin as real-life data. This also allowed for an adjustment by histological subtype, using the SEER histology codes according to the most recent WHO classification of appendicular tumors, so the behavior of these tumors was more clearly evaluated considering their heterogeneity.

This study had limitations, mainly derived from its retrospective nature and from the lack of clinical data, information on the recurrence of the disease and the type of chemotherapy used, among others, which significantly limits the evaluation of the factors associated with the survival. There is the possibility that, as they are usually considered benign, a significant proportion of NET-A has not been adequately reported in the SEER database.

Finally, the classification of procedures is also an important limitation, considering that the SEER database uses the same code for procedures such as appendectomies, cecum resections, and partial colectomies. Similarly, colectomies (hemicolectomies or total colectomies) were coded identically in the database, thus, in the present study, either of these two procedures was classified as colectomy.

Conclusion

The present study identified age, tumor size, histological subtype, and disease extension as the only independent predictors of global and cancer-specific survival in patients with neuroendocrine tumors of the appendix. From these, a practical nomogram was constructed with outstanding discrimination capacity for the prediction of these outcomes. Interestingly, colectomy-type procedures did not have a survival advantage in these patients compared to cecum appendectomy / resection. More studies are required to more clearly assess the role of the different surgical procedures in the survival of these patients, and the usefulness of the different adjuvant modalities in these settings.

Compliance with ethical standards

Informed consent: The present study did not require informed consent or approval by an ethics committee since it is based on data extracted from a freely accessible database. The authors have an authorized user to access the information, and the corresponding data management agreements were signed.

Conflict of interest: The authors declare that they have no conflicts of interest.

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Authors' contributions:

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